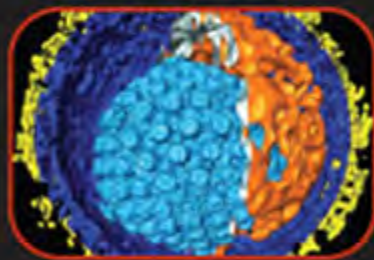
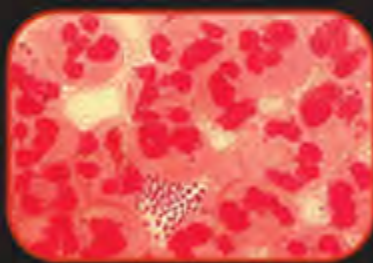
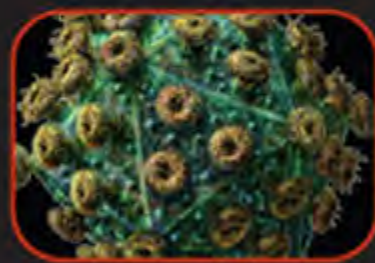


4TH EDITION

SEXUALLY TRANSMITTED DISEASES



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Sexually Transmitted Diseases

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INTRODUCTION AND OVERVIEW

CHANGES IN THE FOURTH EDITION

This edition welcomes new editors Myron Cohen, Larry Corey, and Heather Watts, and 119 new authors. The majority of the editors and many of the authors of this book have wide experience both with HIV/AIDS and with other STIs, facilitating our goal of integrating these two fields where possible throughout the text. We are very happy that the fourth edition is now produced in color and will be available online. Table 1 highlights 55 remarkable examples of recent developments—the good, the bad, and the ugly—in the STD/HIV field, during the 8 years since the third edition of this book was published. These and other recent developments in the epidemiology, pathogenesis, diagnosis, treatment, and prevention of STIs are discussed from different perspectives throughout the text. While many other areas of medicine and public health are also developing rapidly, the recent pace of change in the STI/HIV field has been quite remarkable, and perhaps unique. The 8-year gestation since the last edition helps account for the extensive changes required and the overall “weight” of the evidence presented in this fourth edition.

STD PATHOGENS AND SYNDROMES

The total number of distinct sexually transmitted or transmissible pathogens now exceeds 35 (Table 2). Many of these can be further categorized into multiple subtypes that may have differing clinical manifestations. For a few of these pathogens, sexual transmission is not yet well-defined, but seems quite likely on the basis of indirect clinical and epidemiologic evidence. Many of the clinical syndromes caused by infections with these pathogens are summarized in 10 important categories in Table 3. These syndromes can appear in every subspecialty of medicine, in any health-care setting. With the advent of phosphodiesterase-5 inhibitors for treatment of erectile dysfunction, even geriatrics providers can become increasingly involved in this field. The prevalence, of persistent vaginal and cervical infections are remarkably high in young women; and the incidence, and prevalence, of the chronic STIs are exceptionally high in adults, with seroprevalence increasing steadily with advancing age for infections caused by HIV, syphilis, hepatitis B, and especially, HSV-2 and the genital types of HPV. It is therefore, undoubtedly true that a very large proportion of patients seen by clinicians of all disciplines—perhaps the majority of all adults in the world—have one or more STIs.

IMPORTANCE OF STD FOR SPECIALISTS AS WELL AS FOR PRIMARY CARE CLINICIANS

The 25 years since the preparation of the first edition of this book began have seen extraordinary improvements in both the

quality and the quantity of new information concerning STDs. The qualifications and enthusiasm of professionals now entering the field are also higher than ever. STD clinical, research, teaching, and service or program activities have been reentering the academic mainstream after a long separation. This “mainstreaming” has been attributable to increasing recognition of both the magnitude and scope of the problems caused by various STDs, including the epidemic of sexually transmitted HIV/AIDS; to the availability of new tools and new disease prevention models to deal more effectively with them; and to the increasing concerns about STD/HIV in the fields of internal medicine (especially disciplines such as oncology, infectious diseases, hepatology and gastroenterology, neurology, dermatology, and rheumatology) and family medicine; reproductive health, gynecology, and urology; and pediatrics and adolescent medicine.

The organization of the academic discipline and of medical services for STD/HIV differ markedly across the world, especially when comparing developing and industrialized countries. Although the role of primary care clinicians in STD care is increasing in industrialized countries, various types of STD specialists see a high proportion of patients, and HIV/AIDS specialists provide care for a very high proportion of persons with HIV infection. In the United Kingdom, consultants in genitourinary medicine deal with STD, ambulatory care for HIV infection, and related genitourinary diseases. In much of Europe, including Eastern Europe, Africa, Latin America, and Asia, a varying proportion (small in Western Europe) of “dermatovenereologists” devote much of their time to clinical care, teaching, and research on STD. Many universities around the world now offer Graduate Certificates, Diplomas, Masters Degrees, predoctoral, or postdoctoral or professional training related to sexual health, and online training in sexual health, STDs, and HIV/AIDS is also now available from a number of programs.

In contrast, in most developing countries, where STDs and HIV are rampant and 90% of the world’s STD and HIV infections occur, the primary care clinician has the major role in providing services for STD and HIV care. In many parts of the developing world, nurses, pharmacists, and pharmacy workers or alternative care providers actually provide much of the frontline care, and specialists and physicians tend to see treatment failures or referrals, although special STD clinics may provide efficient care to a large proportion of men with STD and to sex workers in some urban settings and port cities. In developing countries, syndromic management of STDs is customary, supplemented by serologic screening for syphilis, microscopy, and increasingly by use of rapid, cheaper diagnostic tests, such as rapid HIV and syphilis serology.

Clinical management of HIV/AIDS in 2007 in developing countries still emphasizes first and second line antiretroviral

Table 1. Examples of Major Developments in the STI/HIV Field, 2000–2007

- **Clinical epidemiology**
 - Further globalization of the HIV epidemic, with an estimated 4.3 million new HIV infections in 2006.
 - Outbreaks of extremely drug-resistant TB in HIV-infected persons in South Africa in 2005; XDR-TB now documented on all continents. We need infection control, rapid diagnostics, new drugs for TB treatment.
 - Declining incidence and prevalence of curable STI (gonorrhea, syphilis, chancroid) in several developing countries, likely attributable both to widespread adoption of syndromic management, as well as to AIDS-related mortality and HIV/AIDS-related risk behavior reduction.
 - Reemergence of STD (syphilis, HIV/AIDS, HSV-2, other) in China and former Soviet Union; followed by improving control of syphilis and gonorrhea epidemics in Eastern Europe.
 - Shift from risk-avoidance by men who have sex with men (MSM) in industrialized countries, to serosorting, risk reduction, or sexual disinhibition with the advent of HAART, resulting in resurgent STD (syphilis, gonorrhea, chlamydial infection) in MSM.
 - Reemergence of LGV proctitis and proctocolitis in MSM (many of whom are HIV and/or HCV infected) in Europe, the United Kingdom, North America, Australia.
 - Declining HIV incidence in several countries in Eastern Africa, the Caribbean, Cambodia.
 - Despite earlier declines attributable to control programs, incidence of chlamydial infection appears to be rising in parts of North America and Nordic countries, with increasing rates of reinfection in British Columbia.
 - Global sexual risk reduction in young people.
 - Recent decline in HSV-2 seroprevalence in U.S. adolescents; continuing high prevalence in U.S. African American populations.
 - Rapid emergence of internet use for initiation of high risk sexual partnerships, especially among MSM, and among adolescents and young adults.
 - Rising proportions of newly diagnosed HIV infections in Europe and parts of North America involve immigrants from highly endemic developing countries.
 - Growing evidence that primary infection with HIV accounts for a substantial proportion of all HIV transmission.
 - Growing evidence for importance of sexual concurrency and highly connected sexual networks in promoting population-level transmission of STI.
 - Growing evidence for potential of infections such as malaria, HSV, and possibly TB and helminths to increase HIV viral load and thereby, possibly HIV progression and transmission.
 - Growing evidence that the frequency and severity of malaria are substantially increased in persons with HIV infection.
 - Neurosyphilis resurgence among HIV-infected MSM with early syphilis.
- **Etiology and pathogenesis**
 - *Mycoplasma genitalium*—recognized as a cause of NGU, and associated with mucopurulent endocervicitis and with upper genital tract disease in women. Quantity of cervical shedding of *M. genitalium* associated with HIV infection.
 - *Ureaplasma urealyticum*—divided into two species (*U. urealyticum* and *U. parvum*); only the former associated with NGU in some recent studies.
 - Bacterial vaginosis—newly recognized BV-associated bacteria identified, several not yet cultivated, including 3 species in the *Clostridiales* order.
 - Identification of the *tpr* gene family in *T. pallidum*. The family includes 12 *tpr* genes, designated *tprA* through *tprK*, belonging

Table 1. (Continued)

to subfamilies I, II, and III. *TprK* undergoes genetic variation during natural infection, with potential implications for treponemal adaptation to the immune response, and adaptation to varied microenvironments, and for vaccine development.

- Mechanism of variation in the *MgpB* and putative recombination with *MgPar* sequences discovered and characterized in *M. genitalium*; may also explain persistence through antigenic variation.
- Rapid, severe depletion of CD4 T lymphocytes from gut-associated lymphoid tissue during primary HIV infection.
- Growing evidence for cross-clade and within-clade HIV superinfection in high-risk cohorts: implications for HIV vaccine development?
- Phylogenetic and experimental evidence for coevolution of retroviruses and their primate hosts; the virus evolves rapidly to escape host defense mechanisms, while host resistance evolves over millenia to avoid the virus.
- **Diagnostics**
 - Household-based HIV counseling and testing (HBHCT) programs in Africa, demonstrating high acceptability, and very frequent HIV serodiscordance in affected couples, with major implications for HIV prevention and treatment strategies.
 - Increasing use of nucleic acid amplification tests (NAATs) for detecting *N. gonorrhoeae* and *C. trachomatis* infections.
 - Recognition and proliferation in Nordic countries of *C. trachomatis* strains with deletion of nucleotide target sequences for those NAATs that had been widely used.
 - Recognition that self-obtained vaginal swabs are suitable for detection of *N. gonorrhoeae* and *C. trachomatis* using certain of the currently available NAAT, and can be used for mailed-in specimens.
 - Serologic tests that are relatively specific for HSV-2 are now commercially available (e.g., the Kalon and Focus tests).
 - Rapid serologic tests for syphilis.
 - Emergence of web-based access to STI diagnostic testing
 - PCR testing of pooled sera to screen for acute HIV infection.
 - “Reflex testing” of liquid cervical cytology specimens for oncogenic HPV types by PCR (e.g., when Pap smears show Atypical Squamous Cells of Uncertain Significance [ASCUS]).
 - PCR testing provides more accurate diagnosis of genital herpes, other causes of genital ulcer disease.
- **Therapeutics**
 - Twenty-five antiretroviral drugs available in 2007, including several new ones since 2000 (including tipranavir, darunivir, fuseon, TMC125, and most recently HIV integrase inhibitor, raltegravir), for HIV treatment.
 - Global emergence of fluoroquinolone-resistance in *N. gonorrhoeae*.
 - Suppressive antiherpes therapy decreases HSV-2 transmission to HSV-2-uninfected sex partners.
 - Patient-delivered therapy for partners (i.e., expedited partner therapy or EPT) decreases repeat infection with gonorrhea or chlamydia (<http://www.cdc.gov/std/treatment/EPTFinalReport2006.pdf>).
 - Single-dose azithromycin effective for treating early syphilis in Africa; however, azithromycin-resistant strains of *T. pallidum* have rapidly emerged in North America and Ireland, attributable to point-mutations in the *23S rRNA* gene. This has usually been seen in MSM, and especially in areas where azithromycin was used widely to control syphilis outbreaks.
 - Suppressive therapy of HSV-2 infection reduces HIV viral load in plasma and mucosal secretions.
 - Comparable clinical and microbiologic responses to inpatient or outpatient therapy with cefoxitin plus doxycycline for PID (the PEACH study).

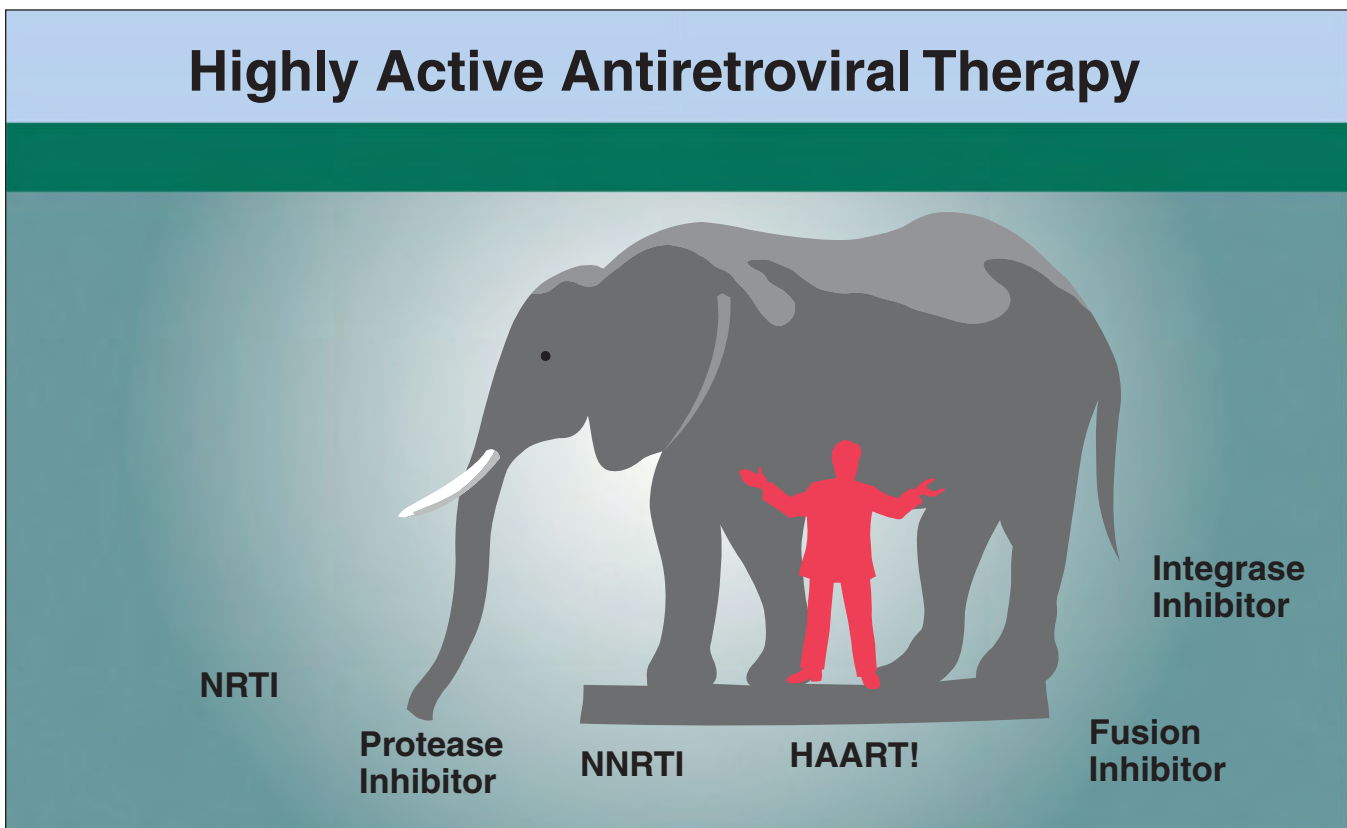
(continued)

Table 1. (Continued)

- 2006 U.S. and Canadian Guidelines for STD Treatment (www.cdc.gov/treatment). (See Appendix B for summary of U.S. CDC Guidelines.)
- Increasing resistance of head lice, and possibly of pubic lice, to pediculocides, including permethrin cream and pyrethrins.
- **Prevention**
 - Three randomized trials of male circumcision in Africa show approximately 60% protection against HIV acquisition. Scale-up of this intervention is a high priority.
 - Quadrivalent HPV vaccine (types 16, 18, 6, and 11) and bivalent HPV vaccine (types 16 and 18) both highly effective vs. infection with the HPV types included in these vaccines and vs. associated cervical and vaginal dysplasia. There is ongoing discussion of cost-effectiveness, policies requiring vaccination (analogous to requirements for HBV vaccine). Efficacy in men being studied.
 - U.S. Advisory Committee on Immunization Practice prohibits new guidelines recommending more aggressive HBV and HAV vaccine use in adults; and recommending HPV vaccine in females aged 9–26 years.
 - Cohort studies demonstrate condom effectiveness against STI acquisition, not only vs. HIV, but also vs. HSV, gonorrhea, and chlamydial and vaginal infections, and specifically against HPV infection—refuting earlier concerns that condoms did *not* prevent HPV acquisition.
 - Randomized clinical trials that did not reduce the risk of HIV acquisition: (a) *behavioral intervention in MSM*—the EXPLORE study did not have a statistically significant sustained impact on HIV acquisition, but did highlight the importance of comorbidities (e.g., depression, alcohol, drug use) as risk factors for HIV acquisition; (b) *vaginal microbicide trials*—cellulose sulphate, like Nonoxynol 9, actually may increase risk of HIV acquisition; SAWY trial stopped for futility; (c) *HIV vaccines*—GP120-based HIV vaccine trials demonstrated no efficacy in the U.S., the Netherlands, and Thailand; current emphasis is on clinical trials of HIV vaccines designed to produce a cytotoxic T-lymphocyte response; (d) *cervical diaphragm plus lubricating gel*—not associated with decreased risk of HIV acquisition in the MIRA trial; (e) *HSV-2 suppression with daily acyclovir*—did not reduce HIV acquisition in women in a small Tanzanian study with relatively low adherence to acyclovir therapy; (f) *structural intervention*—a microfinance program for women did not reduce HIV acquisition (the IMAGE trial).
 - Community-randomized trials of treatment of curable STIs in Mwanza, Tanzania (adults; school children); Rakai, Uganda; Masaka, Uganda, Manicaland, Zimbabwe have shown varying efficacy in reducing STI and HIV incidence. Comparative analyses suggest that STD treatment interventions have limited or no efficacy in reducing HIV transmission in generalized HIV epidemics where there is low STI incidence, as compared with the significant efficacy observed in the earlier Mwanza study, where the HIV epidemic was less widespread and STI prevalence was higher.
 - Serostatus-based approach to advancing HIV prevention, with greater emphasis on widespread testing, partner notification, and “prevention in positives.”
 - “Prevention in positives,” an early priority in a few European countries, is now becoming standard of care in North America; new CDC guidelines for “Prevention in Positives;” group level interventions among young minority HIV-infected women showed significant reduction in subsequent acquisition of other STIs (the WILLOW program).
 - A nonrandomized trial, but with comparison groups, found that a long-term school-based social development intervention (beginning in 5th grade) was associated with reduced teen pregnancy, and, in African American youth, with greatly reduced risk of self-reported STIs.

Table 1. (Continued)

- And finally, there is emerging consensus on need for multicomponent, integrated biomedical and behavioral effectiveness trials and programs for preventing HIV and other STI. Today, clinicians giving ART use a combination of at least 3 drugs in highly active antiretroviral therapy (HAART) and would not consider using a single drug (Fig. 1A). In contrast, in HIV prevention research and program, workers still tend to work in silos, constrained narrowly by their disciplines, and moral philosophies, advocating abstinence only, etc. (Fig. 1B). The limited impact so far of HIV prevention globally, coupled with growing evidence of the impact of various types of interventions, clearly warrants efforts to study the efficacy and implement and evaluate the effectiveness, of multicomponent preventive interventions, to achieve more highly active retrovirus prevention (HARP) (Fig. 1C). The potential for additive or synergistic effects is related in part to the differing non-duplicative mechanisms of action of various preventive interventions, to the existence of a multiplicity of HIV epidemics with differing characteristics and patterns of behavioral and other risk factors, each potentially presenting unique opportunities for differing preventive interventions.

**FIGURE 1A**

Use My Magic Bullet!

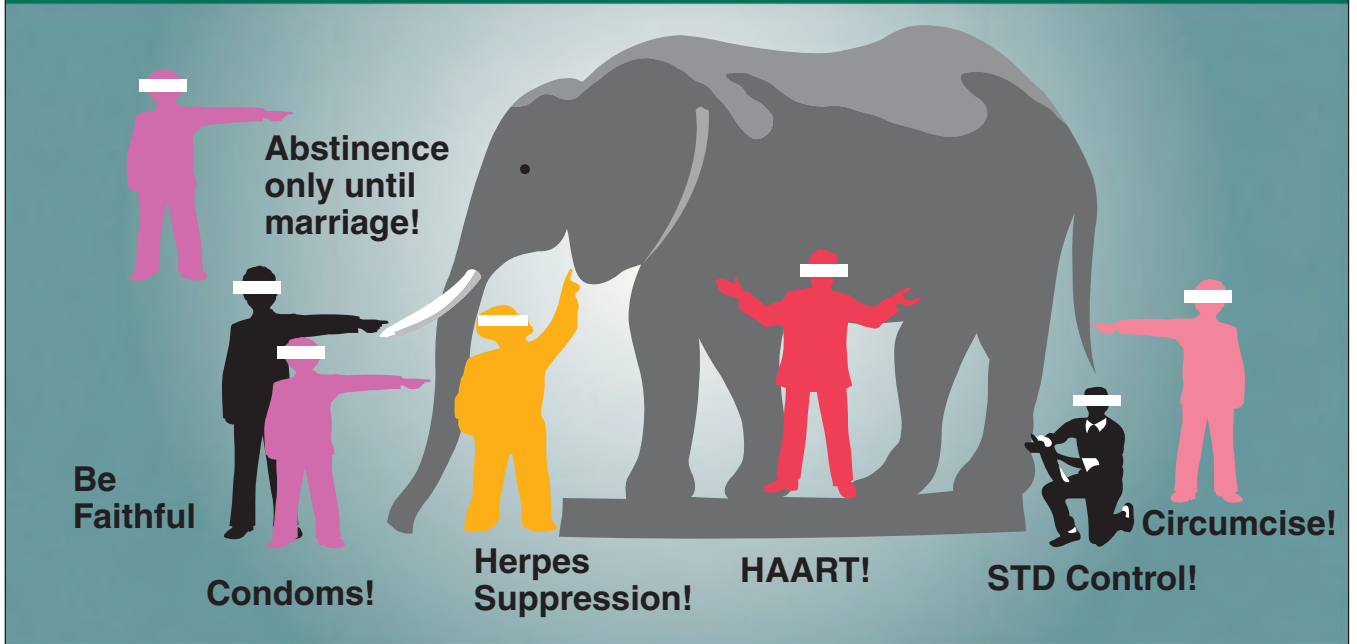


FIGURE 1B

Highly Active Retrovirus Prevention (HARP)

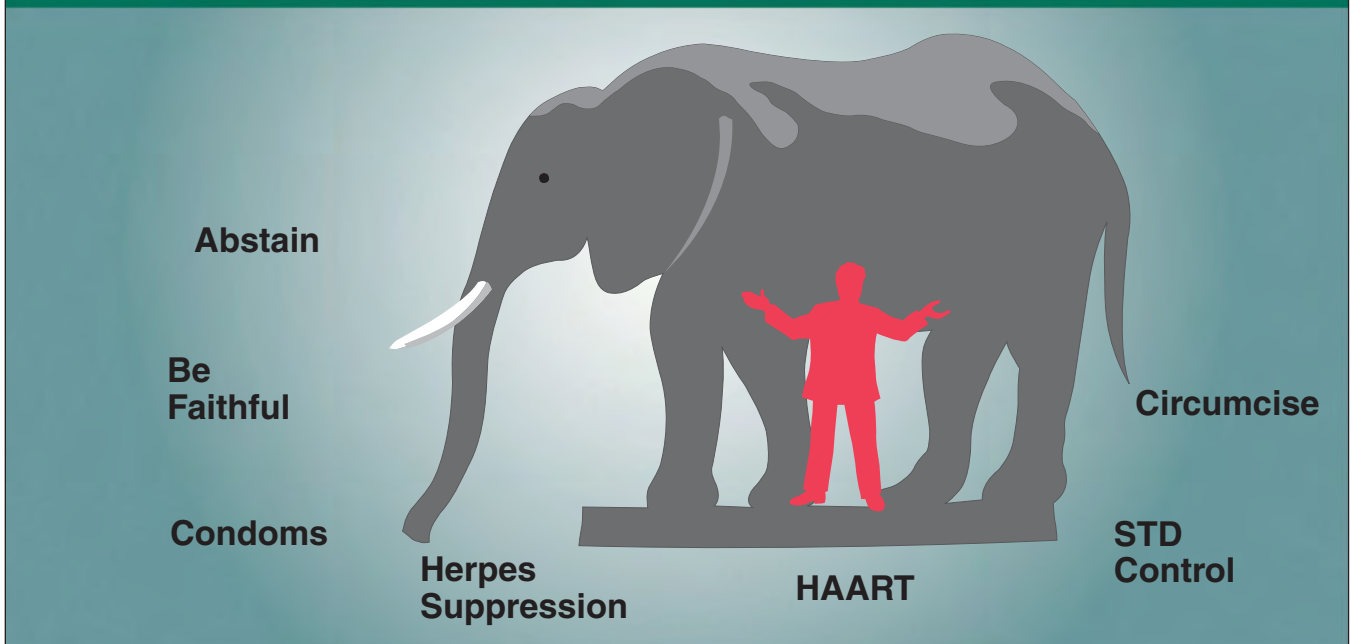


FIGURE 1C

Table 2. Sexually Transmitted and Sexually Transmissible Pathogens

Bacteria	Viruses	Protozoa, Ectoparasites, Fungi
<i>Transmitted in adults predominantly by sexual intercourse</i>		
<i>Neisseria gonorrhoeae</i>	HIV (types 1 and 2)	<i>Trichomonas vaginalis</i>
<i>Chlamydia trachomatis</i>	Human T cell lymphotropic virus type I	<i>Phthirus pubis</i>
<i>Treponema pallidum</i>		
<i>Haemophilus ducreyi</i>	Herpes simplex virus type 2	
<i>Calymmatobacterium granulomatis</i>	Human papillomavirus (multiple genotypes involved in genital infection)	
<i>Ureaplasma urealyticum</i>		
<i>Ureaplasma parvum</i>	Hepatitis B virus ^a	
	Molluscum contagiosum virus	
<i>Sexual transmission repeatedly described but not well defined or not the predominant mode</i>		
<i>Mycoplasma hominis</i>	Cytomegalovirus	<i>Candida albicans</i>
<i>Mycoplasma genitalium</i>	Human T cell lymphotropic virus type II	<i>Sarcoptes scabiei</i>
<i>Gardnerella vaginalis</i> and other vaginal bacteria	Hepatitis C, D viruses	
Group B <i>Streptococcus</i>	Herpes simplex virus type 1	
<i>Mobiluncus</i> spp.	Epstein-Barr virus	
<i>Helicobacter cinaedi</i>	Human herpesvirus type 8	
<i>Helicobacter fennelliae</i>		
<i>Transmitted by sexual contact involving oral-fecal exposure; of importance in homosexual men</i>		
<i>Shigella</i> spp.	Hepatitis A virus	<i>Giardia lamblia</i>
<i>Campylobacter</i> spp.		<i>Entamoeba histolytica</i>

^aAmong U.S. patients for whom a risk factor can be ascertained, most hepatitis B virus infections are transmitted sexually or by injection drug use.

therapy (ART), often initiated relatively late as HIV therapy has become available initially only to those with more advanced infection. Opportunistic infections (especially tuberculosis), and the immune reconstitution inflammatory syndrome (IRIS) after initiation of ART are much more common today in clinical practice in developing countries than in industrialized countries. In contrast, in industrialized countries, clinicians must place much greater emphasis on ARV-resistance phenotyping and genotyping, on viral load measurement, and on selection from a wide variety of newer ARVs.

At a policy and practice level, the field of STD has also become a more integral part of efforts to improve reproductive health both in developing countries and in the industrialized world. The explosion of new information on the impact of STD/HIV on reproductive health makes comprehensive knowledge of STD and HIV essential for reproductive health specialists.

Paradoxically, in industrialized countries, as STD has come under better control, and recurrent outbreaks of imported STD

emerge as major problems, the relative importance of the STD specialist has increased in public health settings best equipped to contain outbreaks of infection. Similarly, as the HIV epidemic comes under better control, and care has become more complex, the role of the HIV clinical specialist is increasing, even in the context of managed care.

This fourth edition of *Sexually Transmitted Diseases* aims to provide comprehensive and authoritative information on the clinical, microbiological, and public health aspects of STD including HIV infection, as an essential reference for the specialist as well as for the primary health care clinician. Authors of each chapter have been encouraged to address STD/HIV in developing countries as well as in industrialized countries, where appropriate.

EVOLUTION OF TERMINOLOGY: VD, STD, STI, AND RTI

The term *venereal* disease initially referred to the diseases syphilis, chancroid, and gonorrhea, later expanded to include

Table 3. Ten Major Categories of STD Syndromes and Related Sexually Transmitted Microbial Etiologies

Syndrome	Sexually Transmitted Microbial Etiologies
(1) AIDS	HIV types 1 and 2
(2) Genital tract infections: males	
Urethritis: males	<i>Neisseria gonorrhoeae</i> , <i>Chlamydia trachomatis</i> , <i>Mycoplasma genitalium</i> , <i>Ureaplasma urealyticum</i> , <i>Trichomonas vaginalis</i> , herpes simplex virus (HSV) types 1 and 2
Epididymitis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i>
(3) Genital tract infections: females	
Cystitis/urethritis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , HSV
Mucopurulent cervicitis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , <i>M. genitalium</i>
Vulvitis	<i>Candida albicans</i> , HSV
Vulvovaginitis	<i>C. albicans</i> , <i>T. vaginalis</i>
Bacterial vaginosis (BV)	BV-associated bacteria (see text)
Acute pelvic inflammatory disease	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , BV-associated bacteria, <i>M. genitalium</i> , group B streptococci
(4) Reproductive health	
Infertility	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , BV-associated bacteria
Complications of pregnancy/puerperium	Many STI pathogens have been implicated—especially HIV, HSV, <i>T. pallidum</i> , <i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , group B streptococci, BV-associated bacteria.
(5) Hepatology/gastroenterology	
Hepatitis	Hepatitis viruses, <i>T. pallidum</i> , CMV, HSV, EBV
Gastritis	<i>T. pallidum</i> (secondary syphilis)
Proctitis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , HSV, <i>T. pallidum</i>
Perihepatitis	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i>
Proctocolitis or enterocolitis	<i>Campylobacter</i> spp., <i>Shigella</i> spp., <i>Entamoeba histolytica</i> , other enteric pathogens
Enteritis	<i>Giardia lamblia</i>
(6) Acute arthritis with urogenital infection or viremia	<i>N. gonorrhoeae</i> (e.g., DGI), <i>C. trachomatis</i> (e.g., Reiter's syndrome), hepatitis B virus
(7) Hematology and oncology	
Mononucleosis syndrome	CMV, HIV, EBV
Squamous cell dysplasias and cancers of the cervix, anus, vulva, vagina, or penis	HPV (especially types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66)
Kaposi's sarcoma, body-cavity lymphomas	HHV-8
T-cell leukemia	HTLV-I
Hepatocellular carcinoma	HBV

Table 3. (Continued)

(8) Neurologic syndromes	
Myelitis, myelopathy, polyradiculopathy	<i>T. pallidum</i> , EBV, CMV, HTLV-I and II, HIV
Meningitis or encephalitis	<i>T. pallidum</i> , HIV, HSV, EBV, CMV
Peripheral neuropathy	<i>T. pallidum</i> , CMV, HSV, HIV, HTLV-I and II, HCV
Parenchymal mass	<i>T. pallidum</i> (gumma), EBV (lymphoma)
(9) Dermatology syndromes	
Ulcerative lesions of the genitalia	HSV-1, HSV-2, <i>Treponema pallidum</i> , <i>Haemophilus ducreyi</i> , <i>C. trachomatis</i> (LGV strains), <i>Calymmatobacterium granulomatis</i>
Scabies	<i>Sarcoptes scabiei</i>
Pubic lice	<i>Phthirus pubis</i>
Rash	<i>T. pallidum</i> , <i>N. gonorrhoeae</i> (DGI), <i>C. trachomatis</i> (Reiter's syndrome), HBV, EBV, HSV, HIV
Genital and anal warts	Human papillomavirus (90% of warts caused by types 6, 11)
(10) Neonatal syndromes	<i>T. pallidum</i> , HSV, CMV, Group B Streptococcus, <i>N. gonorrhoeae</i> , <i>C. trachomatis</i>

NOTE: HSV, herpes simplex virus; LGV, *lymphogranuloma venereum*; DGI, disseminated gonococcal infection; HPV, human papillomavirus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HTLV, human T cell lymphotropic virus; HHV-8, human herpesvirus type 8.

lymphogranuloma venereum and Donovanosis. As the number of diseases recognized to be sexually transmitted gradually grew to include nonspecific urethritis, trichomoniasis, genital herpes, genital warts, hepatitis B, and many others, the term sexually transmitted diseases came into more frequent use. What are the distinctions today between sexually transmitted diseases (STD), infections (STI), or pathogens? Between sexually transmitted and sexually transmissible diseases, infections, or pathogens? And between STI and reproductive tract infections (RTI, not to be confused with respiratory tract infections, also called RTI by pulmonologists)?

All these terms are used throughout this book. Some distinctions are evident: a pathogen causes infection, which may result in disease; a pathogen could be a sexually transmissible even when nonsexual routes of transmission predominate. Viruses like cytomegalovirus (CMV) and hepatitis B virus (HBV) may qualify as predominately sexually transmitted pathogens in adults but not in children. The term RTI is preferred by some in the reproductive health field to encompass conditions like bacterial vaginosis, for which the designation as an STD is debated; and to attempt to destigmatize such conditions.

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PART 1

History, Socioeconomic Impact, and Epidemiology of Sexually Transmitted Infections

1. Historical Perspectives on Sexually Transmitted Diseases: Challenges for Prevention and Control 3
2. An Economic Perspective on Sexually Transmitted Infections Including HIV in Developing Countries 13
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1

Historical Perspectives on Sexually Transmitted Diseases: Challenges for Prevention and Control

Laura J. McGough

METHODOLOGICAL ISSUES

■ PROBLEMS IN THE IDENTIFICATION OF DISEASES

Sexually transmitted diseases (STDs) are a broad modern category referring to a variety of pathogens, including viruses, bacteria, fungi, and protozoa, which manifest themselves in an equally wide variety of clinical symptoms (as subsequent chapters in this volume describe). The common factor is the mode of transmission and acquisition: sexual relations between human beings. Many of these pathogens, such as *Chlamydia* and human papillomavirus (HPV), have only been recently identified as part of the late twentieth-century expansion of biomedical research, thereby making the historical study of these pathogens challenging.

The problems that historians face in tracing the history of these diseases are twofold. First, it is difficult to identify modern disease entities based on the written historical record. Influenced by the work of cultural anthropologists, historians recognize that descriptions of disease symptoms are deeply influenced by changing cultural and social perceptions of disease. For example, late fifteenth- and early sixteenth-century Europeans emphasized the religious and moral dimensions of disease, often describing disease as God's punishment for sin. When an epidemic of a new disease was first described in Italy in 1496 after the French invasion and subsequent war on the Italian peninsula, the disease was often symbolically associated with the Biblical figure of Job, who suffered from ugly, incurable skin sores covering his body from head to toe. Italians called the new disease the "French disease" in reference to the French invasion. It is virtually impossible to disentangle the influence of this cultural tradition of interpreting disease according to Biblical traditions from the descriptions of the disease symptoms.¹ Produced during wartime, in a climate of heightened religious expectations of the imminent Second Coming of Christ, fifteenth-century Europeans did not write neutral, scientific accounts of a new disease. What we can learn from these descriptions about the natural history of modern venereal syphilis—the disease

that the historical French disease or pox is most commonly assumed to have been—is extremely limited.

Second, it is also difficult to identify specific pathogens from skeletal remains. *Treponema pallidum*, the pathogen responsible for modern venereal syphilis, causes certain distinctive malformations, especially to the central incisors (Hutchinson's teeth) and 6-year molars (mulberry molars), if the disease is acquired early in life, as in the case of congenital syphilis.² Other skeletal deformations are similar to those caused by the other treponemal diseases, such as yaws and pinta, thereby making precise identification of venereal syphilis difficult. Paleopathologists have examined skeletal remains from certain sites in both the Americas and Europe prior to the late fifteenth century to see if the pattern of malformations distinctive to venereal syphilis can be found in any of the remains. The implicit assumption is that syphilis, known as the "great imitator" because of its highly variable clinical presentations, exhibited the same pattern of skeletal malformation centuries ago that it does today. Although scientists have found evidence of the distinctive patterns of skeletal destruction associated with modern syphilis in bone remains carbon dated to before the fifteenth century in parts of the New World, specifically the present-day Dominican Republic where Columbus' ships landed in 1492,³ others will await more definitive proof by new methods in molecular genetics.

Even if scientists do find a method of identifying the pathogens that caused disease centuries ago, it will still be important to place that disease within its historical context in order to explain how people experienced and reacted toward disease. The laboratory revolution of the early twentieth century fundamentally changed the way people understood disease as resulting from a specific, underlying causal agent.⁴ When the French disease epidemic broke out in 1496, the disease was regarded as the result of an imbalance of humors in the body, which could be caused by changing climate, atmospheric conditions, diet, and daily habits. By placing descriptions of disease in their historical context, it becomes very clear why contemporary Europeans produced so many theories about the origins of what the majority perceived as a new disease or at least a new epidemic.

■ STORIES RELATED TO THE ORIGINS OF THE DISEASE

European reactions toward the French disease provide a marvelous case study of how societies react to the psychological, emotional, and societal stress provoked by a major new disease. Both physicians and popular writers produced numerous theories about the ultimate origins of this disease. By the 1530s, the theory that the French disease originated in the New World became popular, especially among the Spanish and those directly associated with the conquest. The Spanish physician, Roderico de Isla, who treated Columbus' sailors and claimed that they suffered from this new disease, did not write his account until 1539. Rather than focusing on whether his and other texts accurately represent a truthful account, it is more useful to examine the themes and symbols deployed in order to find out why this theory had such cultural resonance. Spanish writers described Indians as lascivious and promiscuous. Untouched by Christianity, Indians were portrayed as incestuous savages whose lack of sexual control produced disease. With this theory of disease origins, Spaniards successfully deflected blame for the spread of disease from them and projected it onto a distant people they hoped to conquer.⁵

Different cultures produced different accounts of the origins of syphilis to respond to the unique political, social, and even military conditions they faced. More than 50 years after the invasion of the Italian peninsula, Italian writers continued to locate the origins of the epidemic in the war that had brought the end of independence to most of the Italian city-states. One physician blamed the French army itself, which, as he claimed, resorted to cannibalism and thereby produced disease through this unnatural act⁶; another physician held an extremely beautiful prostitute, who served the French army, responsible for the origins of disease, thereby highlighting the dangers of the female body and the temptation of beauty.⁷

Non-European cultures share this tradition of placing syphilis origin stories within a broader political, economic, and social framework in order to deflect blame from them and toward an external "other." For example, while the city of Shanghai was still under European control during the early twentieth century, Chinese physicians wrote that although gonorrhea had existed in their country since antiquity, syphilis was a foreign import brought by the Portuguese in the sixteenth century.⁸ Whether the Chinese physicians' account is true is not the point of this analysis. Instead, it is important to recognize that disease origin stories are often explaining more than a biological event, but also the broader political, economic, and moral conditions that produced the disease. For the Chinese writing during the 1920s, the story of syphilis was a commentary on the evils of European colonialism and European influence, first experienced during the sixteenth century and again during the nineteenth and twentieth centuries. Similarly, modern-day stories of the origin of HIV/AIDS situate the disease within a wider geopolitical framework.⁹

■ TOWARD A SOCIAL, ECOLOGICAL HISTORY OF DISEASE

The two approaches to the history of disease just outlined—a history of modern pathogens versus a history of perceptions of disease—seem to have little in common. It would be useful, however, to combine the strengths of each approach and therefore produce a richer account of the interactions between human societies and their biological environment. The scientific accounts of *T. pallidum* have often ignored the social and political conditions that produce epidemics. For all of the problems with the sixteenth-century disease origin stories, they did nonetheless highlight the role of the Italian Wars (1494–1530), which brought mercenaries and soldiers from throughout the Europe for long-term liaisons between themselves and local women, in addition to the war's usual impact on rape and prostitution. Similarly, colonial rule brought European soldiers to Asia and Africa; these military units not only frequented local prostitutes, some of them even required that brothels be established in order to serve the sexual demands of European soldiers.¹⁰

On the other hand, historical accounts of disease perception often ignore the biological dimensions of disease, including their impact on the quality and duration of human life and on the reproductive success of populations. If historical pathogens can be identified, it would be useful to know how easily they were transmitted, how widespread they were, and what impact they had on human life. A social, ecological approach to the history of disease could build on the strengths of different disciplines and yield greater insights into the dynamic relationship between human populations and sexually transmitted pathogens. Although this approach has yet to be fully developed, historical research nonetheless provides many insights for present-day disease control, especially regarding the role of stigma, the problems associated with control of STDs among prostitutes and military personnel, ethical issues in research, the impact of effective medical therapy, and the roles of prevention and surveillance in STD control. This chapter provides a thematic survey of the history of STDs from the late fifteenth century until the early 1980s. Limitations in the availability of archival material for the last 20 years preclude a systematic history of the AIDS epidemic, but this chapter nonetheless provides valuable insights into the challenges of HIV/AIDS control as well as STD control.

STIGMA AND SHAME: ENDURING THEMES

■ SEXUAL TRANSMISSION AND SOCIAL INEQUALITY

The stigma and shame associated with STDs are one of the most enduring themes in their history. Although diseases such as leprosy had been associated with sexual activity in medieval Europe,¹¹ the idea of contagion (an ancient Greek

idea reinvigorated during the early sixteenth century by the work of Girolamo Fracastoro), and hence of sexual transmission, was newly accepted.¹² The idea of contagion coexisted with, rather than supplanted, other ideas about disease etiology that emphasized the role of climate, planetary influences, and imbalance of bodily humors. By the mid-sixteenth century, European physicians had reached a consensus that the French disease was a “thing” or “seed” that could be spread person-to-person through sexual activity, acquired at birth through mother’s milk, or occasionally transmitted through nonsexual skin-to-skin contact.¹ This expansive definition allowed some discretion to physicians to define “innocent” cases of the French disease.

Reactions to the French disease became closely linked to wider perceptions of sexuality. In sixteenth-century Italy, for example, church and city officials encouraged the “promiscuous” women (defined as a woman who had sexual relations outside of marriage), who contracted the disease, to repent and become nuns, while men were merely offered medical cures and spared the pressure to join a monastery.⁷ This sexual double standard persisted for centuries.

Stigma is embedded in wider social processes of power, domination, and social inequality.¹³ For example, as European society became more hierarchically differentiated at home during the nineteenth century, prejudices about class began to shape attitudes toward sexuality and venereal diseases (VDs). Throughout Europe, efforts to control VD by regulating prostitution gave widespread authority to police officers to arrest women merely on suspicion of prostitution. As the industrial revolution had produced a new class of factory workers and urban dwellers, who increasingly asserted their political power during the nineteenth century, the upper classes reacted by asserting class-based differences in intellectual and moral capacity. According to the upper classes, their social inferiors were akin to animals, unable to control their sexual impulses. Prostitution was an example of the degeneracy of working-class women, a hereditary vice. Consequently, virtually any working-class woman appearing in public alone was a suspect and could be forcibly detained, subjected to medical inspection, and humiliated in her neighborhood as a result of the arrest.^{14,15}

The nineteenth century also witnessed the expansion of European power in Asia and Africa, as well as the development of systematic racist ideologies. In South Africa, for example, white medical officers regarded Africans as incapable of controlling their sexual impulses and therefore unfit for health education about VD or its preventive measures.¹⁶

■ REPRODUCTION OF STIGMA THROUGH DISEASE CONTROL PROGRAMS

Historically, stigma has often been reproduced through disease control programs. Even when treatment has been offered

to the poor, it has seldom been offered on the same terms of voluntary, confidential treatment as it has been offered to the wealthy. In the eighteenth-century England, for example, a middle-class patient suffering from the “foul disease” could pay for confidential treatment from private physicians, while the poor had to make a public declaration of their disease in order to qualify for charitable treatment.¹⁷ In early twentieth-century Uganda, for example, colonial authorities carried out compulsory mass treatments with mercury injections for entire villages¹⁸; meanwhile, in Zimbabwe, public health officials had the power to destroy Africans’ homes as a disease prevention measure, while whites enjoyed voluntary treatment without punitive measures.¹⁹

■ SEXUALLY TRANSMITTED DISEASE AS SYMBOL

The stigma and shame attached to STDs made them powerful symbols in their own right. Because of their ability to evoke sexual immorality and decadence, they were used as metaphors in plays, novels, and poetry from sixteenth century onward.²⁰ Rather than facing the shame of a public diagnosis and subsequent loss of reputation, some eighteenth-century patients in London, for example, committed suicide.¹⁷ Allegations that certain individuals or groups had syphilis became one more weapon in the political struggles of the eighteenth century. The Enlightenment thinker and satirist Voltaire, for example, skewered the clergy and the nobility in his novel *Candide* with the suggestion that syphilis had been spread via a long line of heterosexual and homosexual contacts between nobility, clergy, and their servants.²¹ In an era of increased criticism of the power and privileges of the clergy and nobility, allegations of sexual misconduct and sexual disease were a means of bringing shame and dishonor to these groups. Because STDs were and are such powerful symbols, it is difficult to disentangle allegations about disease from reality, even today.

PROSTITUTION AND THE MILITARY: KEY TARGETS OF INTERVENTIONS

■ REGULATION VERSUS PROHIBITION OF PROSTITUTION

Public health officials consistently identified prostitution as one of the key problems in the spread of STDs. Policies have swung back and forth between periods of legalization and regulation of prostitution, complete with regular medical checkups for prostitutes, or abolition and criminalization of prostitution, in order to decrease the amount and frequency of commercial sexual relations. During the nineteenth and early twentieth centuries, neither policy was implemented in order to protect women (and men) involved in the sex trade from contracting disease, but rather to protect their clients. Under both systems,

legalization and decriminalization, repression of prostitutes rather than rehabilitation and assistance were the norms.

The French led the way in legalizing and regulating prostitution during the nineteenth century. The engineer who had designed Paris' sewage system tackled the problem of prostitution, which he defined as fundamentally similar. Prostitution was like excrement, unpleasant, but necessary to protect the social body from disease. To prevent the physical and moral contamination of rest of the society, prostitutes should remain under constant, lifelong surveillance, shuttling between brothel, hospital, and refuge, but never free to return to society.²² Other countries, such as Italy and Russia, adopted the French policies.^{14,23} Great Britain briefly experimented with the legalization and regulation of prostitution with the Contagious Diseases Acts of 1864, 1866, and 1869 in order to provide a “sexual outlet” for its army, whose enlisted men were not allowed to marry. As previously mentioned, these Acts gave the police substantial authority to arrest and detain working-class women on spurious grounds, while soldiers were not subjected to medical inspection. This sexual double standard provoked protests from an alliance of working- and middle-class women who succeeded in forcing the repeal of the Contagious Diseases Acts in 1886.¹⁵ World Wars I and II brought increased repression and prosecution of prostitution in Great Britain and in the United States in an effort to protect military personnel from disease.²⁴

■ CHANGING MILITARY POLICY

Closely allied to the control of prostitution is military policy toward STDs. As explained above, part of the reason for the nineteenth-century legalization of prostitution was to provide access to sexual relationships for military personnel, especially those stationed abroad in European-dominated parts of Asia and Africa. This policy provoked criticism abroad as well as at home. In India, for example, the National Congress in 1892 formally objected to state regulation of prostitution as part of its nationalist platform.²⁵

Partly under pressure from the social hygiene movement, which emphasized cleanliness and moral reform as bulwarks against disease, military policy in the United States and abroad changed during World War I. Not only did military officials discourage soldiers and sailors from patronizing prostitutes, but also the acquisition of an STD itself became a crime, subject to loss of pay. Medical officers grew concerned that this policy only worsened the health problems of the military forces, since soldiers and sailors avoided treatment as a means of escaping punishment. Political pressure by leading military commanders brought a change in American policy for World War II. Infected military personnel were no longer punished, and prevention and treatment were encouraged.²⁴

Before the advent of penicillin, wartime brought significant government attention, as well as increased resources, to

STD control. Because STDs affected precisely the demographic group (young men aged 18–25 years) needed to fight wars and caused significant loss of fighting days due to illness, governments changed their policies from peacetime neglect to active, comprehensive STD control. In the United States, Surgeon General Thomas Parran, already interested in reducing syphilis prevalence, seized on World War II as an opportunity to expand both military and civilian disease control efforts. Across the country, residential *rapid treatment centers* were opened for civilians. These centers provided free treatment, in addition to counseling, job training for wartime industries such as sheet metal work and riveting, and job placement following treatment.²⁶

The problem with past military approaches to STD control is that they have limited effectiveness as disease control measures for the population as a whole. The military's concern is, of course, with the health of military personnel and the short-term health and manpower needs related to waging war. Even with an unusually powerful public health leader such as Thomas Parran, American wartime STD prevention nonetheless focused on women as vectors of disease and male soldiers as victims. Racy posters of voluptuous scantily clad women with slogans such as “booby trap” disseminated fear-based messages about the dangers of women.²⁴ Wartime STD control thereby reinforced the idea that women, especially foreign women, spread disease, and it largely ignored the role that the overwhelmingly male military forces played in disease transmission. During the Vietnam War, this trend of blaming the “seductive” foreign female for STDs continued.²⁷

RESEARCH AND TREATMENT IN THE TWENTIETH CENTURY

■ THE TUSKEGEE STUDY

Wartime also provoked the expansion of research into the etiology of diseases and potential therapies. The early twentieth century had witnessed a significant expansion of biomedical research independent of wartime, as germ theory became widely accepted and wealthy philanthropists such as John D. Rockefeller supported research in disease control. During this period, however, some scientists participated in abuses of research ethics, such as the infamous Tuskegee syphilis study.

In 1972, when a journalist exposed the still ongoing 40-year study of untreated syphilis in African Americans in Macon County, AL, the public reacted with shock and outrage. Because many African Americans still cite this study as one of the reasons for their mistrust of the public health system, in particular AIDS prevention and treatment programs,²⁸ it is worth describing both the historical origins of the study in 1932, as well as its legacy. During the study's 40-year history, the United States Public Health Service

(USPHS) misled the study subjects, 399 poor African American men, that they were receiving treatment for a serious disease when in fact treatment was withheld. Given the current importance of establishing and maintaining ethical research studies in developing countries, the lessons of Tuskegee have relevance to a wider audience than just the American public.

Prior to and during World War II, standards for experimental research differed significantly from what they are today. Although most researchers insisted that research subjects agree voluntarily to their roles, occasional abuses occurred, especially in experiments on soldiers who could be forced to participate by their superiors. More commonly, however, the concept of “voluntary consent” was interpreted much more broadly than today, with fewer protections of subjects’ health and safety. A 1915 study on the causes of pellagra, for example, placed healthy male prisoners on a poor diet to determine if they would develop pellagra (and some did). The prisoners consented because they were offered pardons if they followed the diet for 6 months. A few critics argued that prisoners were in an inherently coercive situation in which they could not make independent decisions about participating in research, although the majority of people who knew about the study thought the conditions were fair or even generous. By today’s standards, other research studies exploited the economic vulnerability of the poor, especially in the Depression years, when participation in research studies constituted the only available form of employment for some destitute subjects.²⁹ These studies would not meet today’s standards of voluntary, informed consent and freedom from coercion.

Even for its time, however, the Tuskegee study pushed the boundaries of acceptable research ethics, given that the research subjects were under the impression that they were receiving treatment for “bad blood,” a vernacular term that covered a variety of conditions, and never told that they had syphilis and were not receiving treatment for this disease. The subjects could not give consent because they were never fully informed of what was happening.

How did this situation arise? Part of the answer lies in the fact that the study was originally conceived in 1929 as a treatment program to show that syphilis could be controlled in rural parts of the South where high disease burden, poverty, and the lack of roads and clinics made public health efforts particularly challenging. If public health officials could conquer syphilis in the rural South, then they thought that they could provide convincing evidence of their ability to control syphilis throughout the country.³⁰ Treatment at the time consisted of a series of painful intravenous injections of arsphenamine. With a charitable foundation on board to finance this massive treatment program, the initial work of testing blood began in 1930 in five counties in the rural South. By 1932, however, the Great Depression had wiped out the

financial reserves of many foundations, thereby making this ambitious treatment program unaffordable. In order to “salvage” the efforts that the USPHS had already directed toward blood testing and developing relationships with black churches and institutions, the USPHS leadership decided to convert the treatment program into a one-county research study, originally conceived as a 6-month to year-long project.³⁰

Race and class prejudice also played a role in the development of the study, since the researchers failed to treat their subjects as capable and competent adults. Furthermore, the subjects’ inadequate access to health care provided a further justification for research. At the beginning of the trial, medical facilities were so limited that none of the subjects would have been able to obtain treatment. The researchers thought that their study offered an improvement over existing conditions, since they provided hot meals, routine tonics, pain relievers such as aspirin, and \$50 toward burial costs. The subjects’ poverty served as a partial justification for the study.³¹ In a period of particularly brutal race relations characterized by public lynching and a resurgence of Ku Klux Klan activities,³² the researchers’ milder, paternalistic (but nonetheless insidious) form of racial prejudice no doubt seemed less “racist” at the time than the openly genocidal fantasies of some of their contemporaries.³⁰

The injustices of the original study were compounded and prolonged as the study was extended in time. Although penicillin became available in 1943, it was never offered to the study subjects. Worse yet, those who would have received penicillin because of their military service were denied treatment. The study was halted only after a journalist reported the story in 1972.³⁰

Because this story erupted during the civil rights movement, the Tuskegee study quickly became a symbol of the whole system of racial injustice that African Americans had suffered through during the previous century. African American mistrust of the medical profession and of the white society preceded the 1972 exposure of Tuskegee, based on a long and complex history of systematic racial exploitation. It is therefore important to understand African Americans’ reaction to Tuskegee not in terms of a single, isolated event, but in terms of its power to evoke the long, historical experience of injustice and abuse.³³ Because the Tuskegee study evokes such a powerful emotional response in the United States and beyond, it can, however, be used inappropriately to criticize ethical conduct in research studies that does not approximate the ethical abuses of Tuskegee.³⁴ It is important not to cry “Tuskegee” without carefully analyzing the conditions of a research study.

■ PENICILLIN REAPPRAISED

Early twentieth-century biomedical research also yielded one of the major triumphs of STD control: the discovery of

penicillin as an effective therapy for the syphilis and gonorrhea in 1943. Although treatment had existed since Paul Ehrlich's discovery of salvarsan (an organic arsenic compound) in 1909 and his development of a less toxic compound known as neosalvarsan in 1912, this treatment was complicated, lengthy, and often produced serious side effects. The outbreak of World War II contributed to the urgency of medical research, since, as previously mentioned, STDs accounted for a substantial amount of lost days of active duty. After finding successful results in the experimental treatment of penicillin on syphilitic rabbits, and then on one human subject, Dr. John Mahoney of USPHS announced the results of his research in September 1943. Within a year, 10,000 patients were being treated for early syphilis, with treatment success rates between 90% and 97%.²⁴

Initially, it was difficult to increase the production of penicillin rapidly enough to meet the demand. In the United States, priority of access to penicillin was given to the military to treat a variety of infections including syphilis and gonorrhea. Once the production of penicillin increased to cover military demand, a limited supply of the drug was released for civilian use under the strict control of an expert committee, called the Committee on Chemotherapeutic and Other Agents (COC), to make rationing decisions. The COC restricted access according to the proven efficacy of penicillin against a particular infection (such as staphylococci, sulfonamide-resistant streptococci, and gonococci), to the severity of infection (as long as it was responsive to penicillin), and occasionally to diseases that had research value, such as rare but potentially fatal diseases for which data regarding penicillin's efficacy did not yet exist. However, the need to ration penicillin caused some controversy among civilians. One former congressman complained that a worthy young civilian would die because he did not have access to the drug, while "careless" military personnel who had contracted syphilis or gonorrhea could obtain access to the drug.³⁵ The media hype about the new "wonder drugs" undoubtedly increased the demand for these medications.

Did the availability of penicillin make people more likely to engage in sexual activities than they would have before, simply because they were no longer afraid of STDs, as some have suggested? Rates of STD infection did in fact increase in Europe, the United States, and Australia between 1945 and 1948. It is difficult, however, to disaggregate the psychological effects of penicillin on behavior from other factors that influenced behavior during the same period. Most importantly, the end of war brought an end to heavy fighting which had been especially rigorous in 1944–1945. Few military personnel had the time or opportunity for sexual relations during the war's final years. During the postwar occupation, however, military personnel had leisure time to spare and disposable income. Meanwhile, occupied countries experienced extreme economic hardship that made casual prostitution or

relationships with soldiers one of the few economic opportunities for young women. In occupied postwar Germany, for example, despite an American official ban on fraternization with German citizens, 25% of American GIs spent at least 10 or more hours "talking" with German women every week. Given that few American GIs spoke German and few German women at the time spoke English, it is reasonable to speculate that activities other than talking occurred, especially given that the occupation army in postwar Germany had the highest rate of STDs of any American military unit during 1940s.³⁶ The situation was the same with Australian and British postwar occupation of Japan, where these troops contracted high rates of STDs.³⁷

It is difficult to determine whether soldiers' behavior was a reaction to the end of wartime, which brought expectations for "recreation," or a reaction to the introduction of penicillin, or both. It seems more likely to have been the former, however, because penicillin use was still not the first-line treatment choice for syphilis among British troops,³⁸ for example, who nonetheless displayed similar behavior to that of the Americans. Furthermore, penicillin was unavailable for civilians in occupied countries for several years after the war. In 1948, when civilians gained access to penicillin in Germany, rates of STDs began to decline.³⁹ In short, penicillin was introduced at the time of massive social upheaval, increased population mobility of displaced populations and movements of military personnel and civilians, as well as unequal power relations between occupying armies and occupied countries. The combined influences of these factors on sexual behavior and sexual networks make it difficult to attribute increased STD rates between 1945 and 1948 to the penicillin's effects on sexual behavior by itself.

One major effect of the introduction of penicillin, however, was loss of public health interest in STD control. Public spending on STD control declined throughout the world, and these diseases became a low priority.²⁴ For example, India developed the capacity to manufacture its own penicillin in 1954, after which the state governments of India turned their attention to other health problems.⁴⁰

One significant exception to this trend was China. Partly because the Chinese had blamed STDs on foreign occupation of China and foreign cultural decadence, the Communist government adopted STD control as one of its major policy initiatives immediately after its 1949 political victory. In a campaign that included widespread public relations efforts through plays, radio programs, and small discussion groups, the government undertook a massive screening and treatment program including vocational rehabilitation for former female sex workers. By 1964, the government claimed to have eliminated STDs, a statement that is impossible to verify but widely accepted as a general indication of a very low Chinese prevalence rate. The long-term effects of the campaign are, however, less clear. Because STDs were represented as a social evil and sign of decadence,

Chinese patients tried to avoid public hospitals, which charged STD patients to punish them for their having acquired these diseases. Social stigma became a major problem. Furthermore, the medical specialty of venereology was no longer practiced and taught after 1960s. With the liberalization of employment policies in 1989 and the subsequent development of an enormous migrant labor population (between 50 and 120 million people), rates of STDs began to increase, with insufficient medical resources and ability to respond.⁴¹

PREVENTION AND SURVEILLANCE

■ PREVENTION: THE NEGLECTED SCIENCE

Historically, prevention is the neglected aspect of STD control programs. Moral reformers have often asserted their control over prevention efforts by defining STD prevention as a problem of morality. Whether led by church groups themselves or by charitable organizations, these efforts focused on fear-based messages about the consequences of immorality (death, disfigurement, infertility, shame) along with representations of happy family life with abundant, healthy offspring as a consequence of correct moral choices.²⁴

This approach seldom focused on the structural factors which influence sexual behavior, such as long-term labor migration which keeps spouses separated, population displacement, and lack of economic opportunities for young females. In some cases, the content of the prevention messages themselves potentially undermined their effectiveness. For example, in 1919 the USPHS collaborated with the Young Men's Christian Association (YMCA) to produce an education campaign about the dangers of VD to present to American boys. Both white and black American boys viewed the same set of posters about the white man's responsibility to "lift up" inferior races by setting an example of moral behavior. It is unlikely that this educational campaign, built on assumptions about a racial hierarchy, was effective among African American boys.⁴²

Public health officials deliberately ignored prevention in much of sub-Saharan Africa during colonial rule. Racial prejudice informed these decisions, since whites claimed that the "inferior races" could not control their sexual impulses.^{16,18,19} Postcolonial African countries seldom possessed the resources to undertake major prevention efforts.

One of the major limiting factors in developing prevention activities has been the emphasis on medicines and technological interventions.²⁴ Furthermore, medical science could claim greater victories in disease control than the young field of behavioral sciences, thereby further reinforcing the emphasis on research and development of biomedical rather than behavioral interventions. As late as the 1970s and 1980s, prevention efforts worldwide, from San Francisco to Singapore,⁴³ focused on disseminating information about STDs on the (incorrect) assumption that information alone could produce

behavioral change. Not until the threat of HIV/AIDS emerged during the 1980s, when a fatal STD with no cure threatened the lives of millions, did governments begin to invest substantial resources into systematically studying behavioral science approaches to changing behavior.

■ SURVEILLANCE: A CENTURY OF CONTROVERSY

However neglected prevention and the behavioral sciences were, the same cannot be said of surveillance efforts, which, along with treatment, have formed the core of the STD control effort in the postantibiotic era, especially in the United States. Certain types of surveillance, such as contact tracing, sparked considerable, longstanding controversy over protection of individual privacy and rights versus protection of public health. During the early twentieth century in the United States, the majority of states treated STD patients differently than those with diseases such as measles and smallpox. Because of the social stigma attached to STDs, most states allowed cases to be reported by a patient's initials or a serial number rather than by full name in order to protect patients' privacy. This "shielded" reporting became standard public health practice until 1946, when efforts to find the "missing million" with syphilis were launched and later when laboratory-based reporting became widespread in the 1960s. Before 1946, public health officials had not known the names of the patients. Afterward, in order to contact patients based on laboratory reports and interview patients for names of sexual contacts, public health officials knew the names and other identifying information of STD patients. In order to protect patient privacy, public health officials did not release the name of the original patient to the contacts they later interviewed. Nonetheless, the definition of confidentiality and privacy had changed dramatically during the century so that after 1960s public health officials had access to information about patients that they had not previously possessed.⁴⁴

The fact that government employees (i.e., public health officials) had access to patients' names may have undermined efforts to build trust, especially with the groups suffering from government persecution. In 1947, for example, the U.S. Park police launched its "Pervert Elimination Campaign" to find and arrest gay men, which was followed by the McCarthy-inspired Federal Loyalty Program in which more than 1000 people lost their jobs because of allegations of homosexuality. Vice squad officers frequented gay bars and clubs, interviewed suspects' coworkers, and compiled the lists of "known" homosexuals.⁴⁵ Public health officials frequently complained about homosexual men's unwillingness to cooperate during interviews, but never connected their mistrust to the real risks that homosexual men faced from other local and federal government officials during 1950s and 1960s.

Contact tracing was less common in Europe than in the United States. Even a conservative country such as Scotland,

for example, was reluctant to pursue large-scale contact tracing out of fear that it was illegal under the Scots Laws, which protected citizens from slander or “injury done to feelings.” Consequently, only about 10% of patients were followed up for interviews and contact tracing.⁴⁶

Aside from contact tracing, surveillance efforts typically consisted of collecting data about patients who seek STD treatment, rather than more costly population-based screening. Governments have not always made effective use of the data from even limited surveillance efforts. For example, the government of Malaysia conducted a national survey of cases reported to the Ministry of Health in 1976. In response to the information that cases were primarily among young Malaysians (in their 20s), health workers advocated the introduction of an STD education program in schools and efforts to reduce stigma throughout the population. The government balked at what they considered a politically contentious program in a conservative Muslim society. Instead, the government focused screening and control efforts more narrowly on prostitutes than on the wider population of 20–30-year-olds.⁴⁷ Although surveillance was a central part of STD control during the late twentieth century, the information generated by surveillance efforts was not always used effectively. STD control programs often developed in response to political pressure rather than to actual trends in STD morbidity.

CONCLUSION: CHALLENGES FOR PREVENTION AND CONTROL

STD morbidity continues to remain a challenge, despite centuries of effort to prevent, treat, and control these diseases. Efforts to combat STD stigma have been rare and therefore remain a potential avenue of exploration. STD stigma needs to be recognized as part of a more complex social process than just its association with illicit sexuality, however, in order to develop an effective public health effort.

With the success of antibiotics, one of the major historical impetuses for STD control programs, wartime no longer activates public or government interest in STDs. The public has remained focused on the control of prostitution, but the historical record shows how difficult it is to create sustainable programs that control disease rather than punish prostitutes and further stigmatize these diseases. Prevention grounded in the behavioral sciences remains a marginal part of STD control programs, partly because these programs have often been separated from HIV/AIDS programs where much of the innovation in prevention occurred.

Although treatment has been the major focus of bacterial STD control programs, the viral STDs present a different story not yet adequately studied by historians. We know little historically about the impact of herpes and the success (or failure) of psychosocial support groups and little about the history of HPV. Furthermore, even a few of the bacterial

STDs, notably chlamydia, have been left out of this history. In particular, we do not know what the broader impact of the discovery of new STDs has been on public perceptions, availability of resources, and ability to build coordinated public health programs. The impact of the HIV/AIDS epidemic also demands further exploration, especially as the records of major government agencies during the 1980s and 1990s become available to researchers during the next 10 years. Is the history of these new and newly discovered STDs a history of synergy or of competing resources for new demands?

Finally, we still know little about the history of STDs and STD control outside of Europe and the United States. Most of the historical work on Asia and Africa has focused on the colonial period, while Latin America has been virtually ignored. Some of this historical research has been done, but is not available in English. Pre- and postcolonial histories could elucidate a wider range of public health efforts, as well as contribute to our knowledge about how perceptions of STDs vary according to changing historical conditions in different cultures. Even within the history of Europe and the United States—a history, which fully integrates the biological and social perspectives on STDs—a social, ecological approach has yet to be fully developed. By examining how social and biological conditions interact to facilitate or retard the spread of disease, it may be possible to come up with new ideas to prevent and control STDs.

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An Economic Perspective on Sexually Transmitted Infections Including HIV in Developing Countries

Stefano M. Bertozzi and Marjorie Opuni

INTRODUCTION

The burden of disease of sexually transmitted infections (STI) is large and it disproportionately affects developing countries.¹ As discussed elsewhere in this volume, the prevalence and incidence of STI other than the human immunodeficiency virus (HIV) are high in much of the developing world. Because diagnosis and treatment are often inaccessible, delayed, or inadequate, complications are common with their attendant high morbidity and mortality, especially affecting women and infants.¹ The morbidity and mortality impacts of these STIs are compounded since they also facilitate the sexual transmission of HIV, which continues its unrelenting spread predominantly in resource-poor settings and above all in sub-Saharan Africa.^{2,3} In countries heavily affected by the epidemic, HIV has had dramatic impacts on adult and child morbidity and mortality as well as population and family structure.⁴⁻⁸

In many developing countries, the scale of the STI epidemics, including HIV, requires that responses to them be based on multidisciplinary analysis, research, policymaking, and intervention development, which must include, but should not be limited to, the biomedical and epidemiological disciplines. Economics, the *science of choice*, is one discipline that has much to contribute to efforts to address the epidemics of STI/HIV in resource-poor settings. Economists have contributed to the analysis of the determinants of STI/HIV infection and to the impacts of STI/HIV on individuals, their households, their communities, production units and institutions, whole economic sectors, and in some cases entire national economies. These analyses have underscored the need for public intervention in the prevention and treatment of STI/HIV. Economics in conjunction with epidemiology also offers a set of tools that can assist in the evaluation and prioritization of STI/HIV interventions in contexts of limited resources.

The objective of this chapter is to provide an overview of some of the contributions that economists have made

regarding STI/HIV in developing countries. We focus on developing countries because, as discussed elsewhere in this volume, the epidemiology of STI epidemics in resource-poor settings and in wealthier countries differs substantially as do the impacts and the resources available for STI/HIV prevention and care. The chapter proceeds as follows: in the next section, we discuss briefly some key socioeconomic determinants of the spread of STI/HIV; we then describe the morbidity, mortality, and fertility impacts of STI/HIV and the economic impacts on individuals and their households that emanate from these, as well as the effects that result on the health sector. Finally, we review existing knowledge on the effectiveness, cost, efficiency, and cost-effectiveness of STI/HIV interventions in resource-poor settings and discuss the policy implications of this research.

SOCIOECONOMIC DETERMINANTS OF STI/HIV INFECTION

STI/HIV are not spread randomly. Unprotected sex with an infected partner is by far the most important risk factor for STI/HIV infection.^{1,9} This in turn is influenced by prevalence and distribution of infection in a population, as well as the behavior of an individual and his/her partners.

Economic deprivation, low education, economic inequality, and economically driven migration and mobility have all been found to be associated with the risk of STI/HIV infection.¹⁰⁻¹² With its key premise that the choices that people make are strategic decisions based on maximizing well-being given a set of constraints (e.g., income, education, information) within particular contexts, economics can provide a framework to help understand what underlies the behaviors associated with transmission of STI/HIV.

A number of studies suggest the possibility of a causal link between economic deprivation and risk of STI/HIV infection. This may be because the poor have less access to information about STI/HIV risks and are thus more likely to make their choices in the context of lack of information or

misinformation. Research in Cambodia, for example, shows that the poorest segments of society have much less knowledge of how HIV is transmitted and prevented and are more likely to engage in behaviors that put them at risk of STI/HIV infection.¹¹ The poor are also more likely to have sex at a younger age, they use condoms less frequently, and they are more likely to end up in activities that put them at high risk of STI/HIV infection.¹⁰ Poor women, for example, are more likely to turn to sex work than women who are better off economically.¹¹ In some cases, poor women are forced into sex work, into providing sexual favors without compensation or into providing sexual favors in return for money. As studies from Mexico, India, and the Philippines have shown, women in the sex-work industry may be willing to risk infection by not using condoms if they are adequately compensated—if they do not perceive the risk to be more significant than the other problems they face.^{13–15}

Related to economic deprivation, several studies have also shown an association between education and STI/HIV. Analysis of household data shows a strong correlation of both wealth and education with knowledge and condom use.¹⁶ Similarly, a recent study in Uganda showed that as the HIV epidemic has progressed, educated persons have been more responsive to prevention information campaigns.^{16,17} Education was found to be associated with lower risk of HIV infection.

Economic inequality is also likely to influence STI/HIV transmission.¹ Income inequality has been found to be a strong predictor of STI prevalence, even after controlling for gross national income (GNI) per capita. It is also a strong predictor of STI prevalence among key populations—populations at especially high risk of becoming infected or transmitting an infection, such as sex workers. A possible explanation given is that greater inequality creates more active markets for commercial and casual sex, as higher income men negotiate the sexual services of lower income sex workers.¹ A similar situation applies when tourists often have considerably more resources than local populations and may also be more likely to seek commercial sex away from their home environments.¹⁸ In many places, social inequality underpins this economic inequality. The education status of women is often lower than that of men, for example. They have fewer assets and fewer opportunities for employment.¹⁰

It should also be noted that processes associated with development such as increases in disposable income and increases in mobility among certain groups and not others are associated with increased risk.^{10,18} Professions involving high mobility and extended periods away from families, such as migrant labor, serving in the military, driving trucks, or working as sailors are also associated with augmented risk.

Finally, in many developing countries, inaccessible or low quality STI care services result in unnecessary complications from STI other than HIV and in preventable HIV infections.¹

Also, because of low levels of awareness regarding sexual health and associated stigma, health care seeking is frequently inadequate.¹ The care of opportunistic infections (OI) associated with HIV/AIDS and antiretroviral therapy are beyond the scope of this chapter. But clearly, resource constraints also limit access to health care, to antiretroviral therapy, and to social and legal support to combat discrimination for the millions of people living with HIV in resource-poor settings.

SOCIOECONOMIC IMPACT OF STI/HIV

The primary mechanisms through which STI/HIV affects the economic well-being of individuals and their households, communities, and countries are the impacts of the infections on morbidity and mortality. In countries heavily affected by HIV, this can lead to important changes in average household composition and population structure. Stigma and discrimination constitute a second burden for people living with and affected by STI/HIV and their effect on well-being is also partly mediated through economic mechanisms. Discrimination that limits access to education, employment, and/or housing affects a household's ability to generate income and/or its ability to use its income to purchase improved quality of life. Such “economic discrimination” is especially costly for the poor, exacerbating the impoverishment that results from lost income due to illness and the need to care for ill family members.

■ IMPACT OF STI OTHER THAN HIV ON MORBIDITY AND MORTALITY

Because diagnosis and treatment of STI other than HIV are often delayed or inadequate in resource-poor settings, the burden of morbidity in these countries is significant, especially among women. The most serious complications of pelvic inflammatory disease (PID), primarily associated with chlamydia and gonorrhea, include chronic pelvic pain and ectopic pregnancy.¹⁹ Complications of herpes simplex virus-2 (HSV-2) include severe primary disease, meningitis, and erythema multiforme. Infection with the human papillomavirus (HPV) is a prerequisite for the great majority of cervical cancers.²⁰ All of these STIs can have important impacts on the productivity of an affected individual.

STIs are also an important cause of reduced fertility among women and some STIs such as chlamydia can reduce fertility among men.^{20,21} This aspect of STI morbidity has not been adequately addressed by the health economics literature. Indeed, if one used a human capital approach to estimate the economic impact of STI-induced infertility, one might easily demonstrate that infertility was associated with greater labor market participation by both men and women, implying that infertility was economically beneficial. A better

approach would attempt to estimate the reduction in quality of life and its economic value, typically done by estimating people's willingness to pay to avoid infertility. However, even this approach is not simple, because only people who desire additional offspring have their quality of life reduced by infertility—after all, at any one time a larger proportion of the population is actively seeking temporary or permanent infertility (through contraception or sterilization) than seeking pregnancy.

STI other than HIV also have significant detrimental effects on the fetus and neonate of an infected woman. Adverse pregnancy outcomes include early abortion, premature births, low birth weight as well as congenital infections. Syphilis left untreated during pregnancy, for example, leads to fetal wastage and congenital syphilis.²² Most vaginally delivered neonates exposed to *Chlamydia* become infected, with a smaller proportion developing conjunctivitis or pneumonitis.²⁰ Complications of HSV-2 include neonatal herpes. Without appropriate diagnosis and antiviral therapy, over half of infected babies die and approximately half of surviving babies have lasting neurological complications.²³

■ IMPACT OF HIV ON MORBIDITY

As disease progresses in persons infected with HIV, with increasing viral load and decreasing CD4 count, the risk increases for OI such as tuberculosis, wasting syndrome, Kaposi's sarcoma, mucocutaneous HSV infection, cryptosporidial diarrhea, and esophageal candidiasis.^{24,25} All of these can also have important impacts on the productivity of an infected individual.

It is now well established that HIV/AIDS also has major impacts on fertility in highly affected countries. Studies in a number of countries in sub-Saharan Africa have shown that with the exception of the youngest age group, HIV-infected women have between 25% and 40% lower fertility than HIV-uninfected women.^{26,27}

These lower fertility rates are largely due to lower rates of conception. Women with HIV are more likely to have amenorrhea than are HIV-negative women; there may be repercussions for women's fertility from the decreased production of spermatozoa in their HIV-infected male partners, and there may be reductions in the frequency of sexual intercourse and/or increased contraception use resulting from knowledge or suspicion of own and/or partner infection.^{28–31} Another factor causing lower fertility rates among women with HIV is the increased rates of pregnancy loss (part of the increased loss may also be explained by the association between HIV infection and infection with other STI).^{28,29,32,33}

In addition, the epidemic is also likely to cause behavior changes in the general population. The HIV/AIDS epidemic appears to cause important changes in contraceptive use in the general population with an increase in the use of condoms

and the switching to condom use from other forms of contraception.²⁷ If condoms are used by couples who did not practice contraception previously, this will result in an overall decline in fertility. However, if they replace more effective methods of contraception with condoms, this will cause a slight increase in fertility. The epidemic is also having an impact on fertility by increasing women's age at first sex.^{34–36} Finally, changes in postpartum behavior, including reduction in breastfeeding or shortening of abstinence after the birth of a child to discourage a partner from seeking other partners that may be HIV-infected, would tend to increase fertility.²⁷

■ IMPACT OF HIV ON MORTALITY

The primary mechanism through which STI contribute to mortality is through mortality associated with HIV. And with an estimated median survival time, a little above 9 years from HIV infection to death in developing countries in the absence of antiretroviral therapy, HIV has had a dramatic impact on adult mortality.^{25,37} National data from the countries that have been most heavily affected by HIV indicate that mortality levels rose rapidly during the 1990s, and studies with information on the HIV serostatus of study participants in these countries provide evidence that HIV has been the major contributor to this increase in mortality.⁷

Demographic and Health Survey data suggest that in the countries most heavily affected by HIV, the probability of a 15-year old dying before reaching the age of 60 years increased from a range of 10–30% in the mid-1980s to a range of 30–60% at the end of the century.³⁸ More specifically, the probability of dying between the ages of 15 and 60 years in Kenya increased from 18% in the early 1990s to 28% by the end of the decade; in Malawi, while it was 30% in the early 1980s, it is now over 45%; in Zimbabwe, it increased from 33% for both women and men in 1985 to 50% and 65% for women and men, respectively, by 1997.^{4,39}

Several studies conducted in countries heavily affected by HIV with information on the HIV serostatus of study subjects provide evidence that HIV has been the major contributor to this increase in mortality. A recent review of these studies found that in regions with already fairly high background mortality, after standardizing for age, on average, the mortality rates of HIV-infected men were 9–16 times the mortality rates of uninfected men, while the mortality rates of HIV-infected women were 15–25 times those of uninfected women.⁷

Since mother-to-child transmission (MTCT) can occur before, during, and after delivery including during breastfeeding, HIV among children parallels that among women of reproductive age.⁶ And since most infected children, in absence of antiretroviral therapy, will develop AIDS and die before their fifth birthday, infant and child mortality increases in high HIV-prevalence countries as a result of AIDS.^{40,41}

It has been estimated that by 2002, in sub-Saharan Africa, 20% of all deaths among children under 5 years of age in the region could be attributable to HIV.⁶

■ ECONOMIC IMPACT OF HIV ON INDIVIDUALS AND THEIR HOUSEHOLDS

HIV/AIDS usually affects prime-age adults (age at which normal levels of morbidity and mortality are usually low) at the peak of their economically productive years and incapacitates them for significant periods of time before causing their death, typically with massively increased health costs compared to noninfected adults of similar age. Important economic impacts are therefore to be expected at the individual and household level. Moreover, though a detailed discussion of these is beyond the scope of this chapter, we should note that economists have also looked at how HIV impacts communities, production units and institutions, whole economic sectors, and in some cases entire national economies.^{41–61} However, determination of the macroeconomic impact of HIV/AIDS is extremely difficult since at any given time, one cannot determine how the economy would have functioned in the absence of HIV/AIDS. Numerous factors affect economic performance, and attributing changes in performance to one particular cause is difficult. It is therefore not surprising that predictions of the net macroeconomic impact of AIDS have varied widely and economists continue to debate the issue with some economists questioning the usefulness of placing too much emphasis on such studies and others continuing to place a great deal of emphasis on producing models of macroeconomic impact.

Economic research has therefore increasingly focused on assessing the impact of the epidemic on individuals and their households. The illness or death of young adults due to HIV/AIDS can result in changes in household composition; it can result in changed household labor allocations; it can lead to reductions in household income, assets, and savings; it can affect household consumption patterns; and it can affect the health and well-being of other household members.⁴²

Before turning to a brief review of key findings on these issues, we note that there are some limitations that characterize the research conducted on the impact of AIDS illness and death on households to date.⁴³ Much of the information that has been collected has been through anecdotes or through convenience samples, with people affected by HIV/AIDS identified through health centers or nongovernmental support organizations.^{44–56} The population-based study conducted by the World Bank in Kagera, Tanzania, is one exception and analysis of these data have provided a great deal of information.^{12,57–62} Another population based survey was conducted in Kenya more recently.⁶³ Economists have also used Demographic and Health Surveys as well as cohort studies in highly affected areas which include economic data

although unfortunately, the economic information included in these surveys is often limited.^{17,64}

There are also some methodological issues with some of the studies conducted to date. An AIDS death in a household is hypothesized to be a function at least in part of household and individual unobservable characteristics that differ across households and individuals. Moreover, economists are also concerned with the issue of simultaneity or reverse causality. It could be, for example, that it is not the occurrence of an AIDS death in a household that affects household labor allocation and income. Rather, it could be that households that have less stable membership or that include persons who have less stable employment are more likely to include persons that become infected with HIV. If the econometric analyses of the impact of AIDS deaths do not take these issues into account, any resulting estimates will be inconsistent and biased.

AIDS mortality and household composition

An AIDS death within a household clearly changes the composition of the household. In addition, it may also have a direct impact on household size although study results differ on whether such a death leads to an increase or a decrease in household size.^{12,65,66} In all studies, the dependency ratio in households affected by HIV/AIDS was higher on average following an adult death.

In the most extreme scenario, the change in household composition that results from a young adult death leads to the dissolution of the household. Analysis of data from rural Tanzania found that the death of a household head can result in household dissolution.⁶⁷ In a recent study conducted in KwaZulu-Natal, deaths of young adults were associated with a threefold increased risk of household dissolution compared with households without such a death.⁶⁸

The troubles of orphans and the grandparents caring for them have received a great deal of coverage in the media. This phenomenon does exist. In Kagera, statistically significant changes in household composition were found including a decrease in the percentage of elderly living in three-generation families and an increase in the percentage of living alone or with children only.⁶¹ But research conducted to date in South Africa and Uganda does not support the notion that these households are becoming the norm in areas where young adult mortality is high.^{65,69–71}

AIDS mortality and household labor allocations

One of the pathways through which AIDS-related illness and mortality is hypothesized to affect households is through changes in the own labor of other household members with particular concern raised regarding children leaving school to work or to care for the sick.¹² Most of the information on the impact of AIDS-related illness and death on household labor

allocations has consisted of anecdotal evidence or information gathered from convenience samples.^{45–47} Analysis of data on farm and chore hours of household members in Kagera, Tanzania, found small and insignificant changes in the labor supply of persons in households experiencing an adult death. This could be because where unemployment rates are high, as in rural Tanzania and other heavily affected countries, those providing care are often those who are themselves unemployed or participating in subsistence production.

AIDS mortality and household income and assets

Related to the issue of how AIDS-related illness and mortality affects the labor allocation of other household members is the issue of how it affects household income. Studies that have looked at the impact of AIDS-related illness and death on household income have generally found that young adult illness and death have a negative impact on income.^{44,48,54,63} This is largely due to the loss of income contributions from the ill or dead young adult. Recent analysis of panel data from Kenya found that only the death of a young adult male led to a statistically significant reduction in household off-farm income.⁶³

Selling assets, depleting savings, and incurring debt to meet augmented needs are also mechanisms that households have been found to use to cope with the impact of AIDS-related illness and death.^{12,44,48,51,55,62,63} For example, households in rural Kenya affected by a young adult death were found to be more likely to sell assets such as small animals and farm equipment to raise cash for medical care and funeral expenditures.⁶³

AIDS mortality and household consumption

Studies on the impact of AIDS-related illness and mortality on households have found that households that are affected tend to spend relatively less on certain categories of goods and services and more on other categories than do unaffected households.^{12,44,48,51,55,62} Affected households spend less on food, for example, and more on health and funerals. In Kagera, Tanzania, the expenditure on food by the poorest half of households affected by an adult death fell by 32% immediately following the death.⁶² Affected households spent one-third less on nonfood items such as clothing, soap, and batteries than did unaffected households. The share of total expenditure that households experiencing an adult death spent on medical care and funerals on average amounted to 16% and 5.4%, respectively, compared with 2.6% and 0.6% in households without an adult death.⁶²

However, few studies that have looked at household impact have been able to examine the medium- and long-term effects of such morbidity and mortality. This is likely to lead to two important biases. Household coping behaviors will be expected to compensate for the loss of income and for the

change in household composition such that short-term falls in income and consumption will likely be attenuated over time. This is consistent with the results from the Kagera study.^{12,62} The short-term impacts measured are likely to underestimate the long-term impact on human capital investments in children in affected households, as discussed below. This result is suggested by both the empirical work done by Gertler et al. in households suffering a non-AIDS-related young adult death in Indonesia as well as the modeling done by Bell et al. for Southern Africa.^{72,73}

AIDS mortality and the well-being of household members

Because AIDS deaths occur predominantly among prime-aged adults who are often parents, an estimated 15.2 million children aged 0–17 were estimated to have lost one or both parents at the end of 2005.³ This demographic trend has resulted in a growing body of research on the impact of young adult death on the well-being of children. Analysis of data from Uganda indicates that the presence of both parents in the household increase the odds of survival by 28%.⁷⁴ Analysis of panel data from Indonesia showed that children who had lost their mothers had worse measures of child health and nutritional status than other children.⁷⁵ In terms of education, the results of studies have been less consistent. A number of studies have concluded that “the orphan enrollment gap is dwarfed by the gap between children from richer and poorer households.”^{57,59,60} On the other hand, analysis of Demographic and Health Surveys from sub-Saharan Africa found that orphans were significantly less likely to be enrolled in school.⁶⁴ Moreover, analysis of data from Indonesia found that parental mortality doubled school dropout rates.⁷⁶

Though much more limited in scope, some economic analyses have also been conducted on the impact of young adult mortality on the well-being of older adults who often rely on their children and grandchildren for money, food, and other support. Analysis of data from Kagera found that the well-being of older adults as measured by body mass index (BMI) was negatively affected by the death of a prime-aged adult but that their BMI recovered over time and there did not appear to be a long-term association between prime-aged deaths and level of BMI.⁵⁸

ECONOMIC ANALYSIS TO PRIORITIZE INTERVENTIONS

Government and nongovernmental institutions in developing countries face resource constraints and many competing demands. With simply not enough resources to meet all demands, choices must be made and priorities set. Economics offers a set of tools that are useful in the prioritization of interventions.

The classical approach used by economists is to calculate the rate of return on competing interventions and to allocate funds to the investments that yield the highest return, followed by the next highest, until the budget is exhausted. Economists use cost-benefit and cost-effectiveness analyses to compare the benefits and opportunity costs of alternative investments. Cost-benefit analysis compares the benefits of an intervention to its costs with both evaluated in monetary terms. Cost-effectiveness analysis compares interventions using indicators, such as lives saved or disability adjusted life years gained that are not measured in monetary terms and costs that are measured in monetary terms. Many economists prefer cost-benefit analysis to cost-effectiveness analysis. The problem is that many assumptions are required to value the health benefits of an intervention in monetary terms. Because of this, cost-effectiveness analysis has dominated economic analyses in health, including STI/HIV.

In this discussion, we focus on interventions to reduce risk behavior as well as interventions to treat treatable STI. We do not address HIV/AIDS care and treatment interventions and refer readers interested in this issue to recent reviews on the subject.^{24,77}

■ EFFECTIVENESS

Details on the effectiveness of STI interventions are provided elsewhere in this volume. Here we highlight only that there are important differences in the data available regarding the effectiveness of biomedical interventions for STI/HIV prevention and STI treatment on the one hand and STI/HIV prevention interventions aimed at behavior change on the other. Biomedical interventions for STI prevention and treatment benefit from a large accumulated body of rigorous evaluation.⁷⁸ Likewise, the effectiveness of biomedical interventions for HIV prevention such as screening of blood for transfusion^{79–81} and the prevention of MTCT^{29,82–88} is well documented. While there is also an extensive body of literature on the effectiveness of behavior change interventions, that literature suffers from two important disadvantages. First, results of the studies are typically less translatable to different social, cultural, and economic settings. While there is no reason to believe that nevirapine would be more or less effective for MTCT in Guatemala than in Pakistan, there is every reason to question whether an HIV prevention school curriculum would be equally effective. Second, the interventions on average have been much less rigorous, often with insufficient or marginal statistical power, rarely incorporating biological endpoints and with even fewer that measure HIV incidence, something that the trials of biological interventions do routinely.

A number of issues make the evaluation of behavior change interventions particularly complex.²⁴ Counterfactual models (what would have happened in absence of the intervention) are difficult to estimate both because of the long delay from intervention implementation until a change in

prevalence can be observed and because historical controls are of limited utility in describing likely secular behavioral trends into the future. In addition, behavior change interventions are difficult to force into a typology that clearly distinguishes one intervention from another. Also, assessments of behavior change interventions have rarely incorporated well-defined control or comparison groups, in part because of a reluctance in the research community to fund prospective evaluations of large-scale, “real-life” programs rather than small pilot interventions. This absence of data on intervention effectiveness in different settings makes it difficult for policymakers to appropriately tailor packages of prevention interventions to diverse social, economic, and epidemiological settings, and for the varied subpopulations, in which STI/HIV transmission occurs.⁸⁹

Unfortunately, information about the effectiveness of different interventions in different settings/populations is not sufficient. It is also necessary to have information about the epidemiology of risk behavior and STI/HIV infections, as well as the relevant social and cultural characteristics from the countries where prevention programs will be implemented. Thus, the development and maintenance of a sound and reliable public health surveillance system is a prerequisite for an effective prevention response.⁸⁴ An understanding of HIV and STI prevalence and trends, as well as the prevalence and distribution of behaviors that contribute to the epidemic’s spread, should be supplemented by national monitoring systems that track sources and uses of funding to promote greater accountability. In addition, data are needed to identify and characterize key contextual issues that affect the feasibility and likely effectiveness of interventions.

To the extent that lack of effectiveness data and lack of data on local contexts result in the implementation of ineffective interventions and in the lack of implementation of effective ones, then prevention expenditures are wasteful and people are unnecessarily becoming infected. Without such data it is much more difficult to hold policymakers accountable for bad choices in the allocation of prevention resources, thus perpetuating prevention programs that reflect political expediency or discriminatory attitudes rather than the intent to prevent the maximal number of infections.

■ COST AND EFFICIENCY

Although the consensus among health economists favors analyses that use a societal perspective that considers all costs and benefits regardless of who incurs them, the most commonly used perspective in cost and cost-effectiveness analyses of STI/HIV interventions is that of the public sector, with the cost of an intervention often defined as total public sector expenditure attributable to that activity.¹ Total expenditure includes that for buildings, durable equipment, skilled and unskilled labor, and materials, including drugs.

The unit cost of an activity is defined as the total expenditure during a stated time period divided by the number of units of output during that same period.¹ Since the same activity can have several outputs, this definition can be ambiguous. While an intermediate output of the delivery of STI treatment services is the patient treated, a more final output is the patient cured. An even more complete measure of total output would include any secondary infections averted due to the cure of the primary infection.

Two reviews have recently been conducted of the literature on the unit costs of STI treatment and of STI/HIV prevention interventions in developing countries.^{1,24} This section and the ones following highlight some of the key findings from these reviews.

A partial list of the variables that determine the unit cost of STI treatment can be subdivided into epidemiological characteristics, supply side or provider characteristics, and demand-side or patient/client characteristics.¹ Epidemiological characteristics include prevalence and incidence of disease, transmission efficiency, and epidemic phase. Supply side characteristics include availability of appropriate diagnostic tools and availability of effective treatments with few side effects, the proportion of services delivered in the public versus the private sector, economies of scale, economies of scope, health system characteristics, resource combinations and input prices, incentives to deliver high quality and quantity of services, and discrimination. And finally, population composition and density, income, price, distance, education,

perceived stigma, perceived quality of services, and disutility of condom use, are all factors that can constrain demand and thus influence the unit cost of services.

A recent review of available studies in developing countries on the unit cost per cured or effectively managed STI case identified 35 studies.¹ Table 2-1 provides the average and standard deviation for the 42 unit cost estimates that could be interpreted and converted to 2001 US dollars by disease or syndrome and by type of output. The most notable characteristic is the extreme variability in the cost per unit of output across sites; variability that cannot be explained by variability in cost of the primary inputs (labor and drugs). These cost data suggest that very large gains in efficient use of resources stand to be made by more efficient production of services currently being delivered, something not contemplated in most discussions of efficiency in STI/HIV prevention which have typically focused on the relative cost-effectiveness of interventions and perhaps on heterogeneity of risk behavior and prevalence (exposure).

■ COST-EFFECTIVENESS

Data on cost-effectiveness are extremely limited and a function of the scarcity of both effectiveness and cost data. The best available data are for health facility-based interventions such as syndromic STI management, screening of blood for transfusion, and prevention of MTCT. The data on cost-effectiveness of behavioral, community, and structural interventions are far weaker.

Table 2-1. Average and Standard Deviation of Estimated Cost Per Unit Output, by Disease or Syndrome and by Type of Output

Disease or Syndrome	Treatment	Cure	Total
Syphilis	36.04 (5.91)	–	36.04 (5.91)
Urethral discharge	14.29 (20.68)	89.07 (0)	29.25 (37.94)
Genital ulcer	23.16 (21.73)	100.6 (83.74)	48.97 (59.56)
Venereal disease	25.47 (18.56)	82.65 (111.55)	31.83 (37.12)
Pelvic inflammatory disease	7.12 (3.09)	–	7.12 (3.09)
Vaginal discharge	48.23 (0)	102.92 (89.63)	81.04 (70.1)
Total	24.05 (19.04)	96.1 (73.44)	39.49 (47.23)

The figures in parenthesis are standard deviations.

Source: Aral S, Over M, Manhart L, Holmes KK. Sexually transmitted infections. In: Jamison D, Evans D, Alleyne G, et al., eds. *Disease Control Priorities in Developing Countries*. Washington, DC: World Bank and Oxford University Press, 2006.

Cost-effectiveness of interventions for prevention and care of STI other than HIV

The current state of the art was recently reviewed by Aral and Over in their chapter in the Disease Control Priorities in Developing Countries.¹ Even more so than in the prior review 13 years earlier, the position taken in the current chapter is that estimates of the cost-effectiveness of STI interventions are highly variable, reflecting both the great heterogeneity in environments as well as the great heterogeneity in the efficiency of service delivery:

The health benefit in terms of numbers of disability-adjusted, discounted, healthy life years saved by curing or preventing a case of syphilis varies from 3 years in a person who has ceased all sexual activity to as many as 161 years in a sex worker with two partners a day. The cost of treating that prostitute for syphilis varies from US\$ 5 to US\$ 100. Thus the cost per disability adjusted life year (DALY) of syphilis treatment can range from 100/3 or US\$ 33 per DALY to 5/161 or less than a US\$ 0.05 per DALY. As we learn more about the complexities of delivering STI treatment services and take into account the diversity of risk behavior, the ease with which STI

interventions can be ascribed a simple cost-effectiveness ratio has declined. If no easy way to summarize the experience to date with a simple cost effectiveness ratio is available, how should we proceed to analyze economic investments in STI treatment? We believe that the way forward is a better understanding of why STI treatment and other health services vary so much in terms of their efficiency and effectiveness from one setting to another. By studying the determinants of this variation, we should gain an improved understanding of the full costs of high-quality STI service delivery and its place in the health sector investment picture.

Cost-effectiveness of interventions for prevention of HIV

Several authors have recently reviewed estimates of cost-effectiveness for HIV prevention interventions.^{90–93} The paucity of studies (Table 2-2) of behavioral interventions is lamentable. The complete absence of studies of contextual and structural interventions or of interventions designed to reduce stigma and discrimination, despite 20 years of calls to action on all of these fronts, is worse than lamentable because it enables ineffectual action. However, the magnitude and growth path of the epidemic demand a massive response

Table 2-2. Cost-Effectiveness of HIV Prevention Interventions by Epidemic Profile

Intervention	Low-Level Epidemic	Concentrated Epidemic	Generalized Low-Level	Generalized High-Level
Blood safety	1 study found ⁹⁴	1 study found ⁹⁴	4 studies found ^{79,94–97}	2 studies found ^{94,96}
ART to reduce MTCT		2 studies found ^{98,99}	3 studies found ^{95,100}	3 studies found ^{101–103}
Sterile injection	1 study found ¹⁰⁴	2 studies found ¹⁰⁴	1 study found ¹⁰⁴	1 study found ¹⁰⁴
VCT		1 study found ⁹⁹	2 studies found ^{105,106}	
Peer-based programs		4 studies found ^{99,107,108}	4 studies found ^{95,109}	
STI treatment			3 studies found ^{95,110,111}	1 study found ¹¹²
School-based education		1 study found ⁹⁹		
Harm reduction for IDU		2 studies found ^{113,114}		
ART for prevention and postexposure prophylaxis		1 study found ¹¹⁵		
Condom promotion, distribution, and IEC				1 study found ¹¹⁶
Condom social marketing			1 study found ⁹⁵	
Surveillance				
IEC				
Abstinence education				
MTCT, feeding substitution				
Drug substitution for IDU		No cost-effectiveness studies found		
Universal precautions				
Vaccines				
Behavior change for those HIV+				

Source: Bertozzi S, Padian N, Wegbreit J, et al. HIV/AIDS prevention and treatment. In: Jamison D, Evans D, Alleyne G, et al., eds. *Disease Control Priorities in Developing Countries*. Washington, DC: World Bank and Oxford University Press, 2006.

however imperfect the cost and effectiveness data. The suggestions that follow are an attempt to synthesize the available evidence and apply it in the context of the world's very heterogeneous mix of epidemics. It is a far cry from guidance on relative funding levels for different interventions, but it does suggest how the top priority interventions are likely to change across epidemic types.

Prevention studies and national experiences over the past 20 years strongly suggest that prevention strategies are likely to be most effective when they are carefully tailored to the nature and stage of the epidemic in a specific country or community.²⁴ UNAIDS has developed epidemiological categories for characterizing individual epidemics based on the prevalence of infection in particular subpopulations and in the general population.

As a complement to guidance provided by the epidemic profile, Grassly and colleagues recommend assessing the prevalence of other STI, estimating the extent of mixing between high- and low-risk groups, for example, men who have sex with men who have sexual contact with female partners, and estimating the prevalence of high-risk sexual behaviors in the population, such as lack of condom use with casual partners.⁸⁹ They also cite two other critical contextual factors: the capacity of the health service and the social, economic, and legislative context, including social norms and attitudes about sexual and drug use behaviors and the acceptance of breastfeeding. Contextual factors that may play a role in the success of interventions include the status of women, the stigmatization of key populations, and the presence of armed conflict and social upheaval. Together, the epidemic profile and the context in which the epidemic occurs suggest various prevention strategies.

Almost by definition, there is more to be gained by changing the behavior of people with high levels of risk behavior than by changing that of an equivalent number of people with lower levels of risk behavior. However, the difference in the effectiveness between the two falls as epidemics become more generalized, such that in heavily affected countries prevention interventions are likely to become extremely cost-effective even when targeted to individuals with relatively low levels of risk behavior. Consequently, countries with low-level and concentrated epidemics should emphasize interventions that are targeted to individuals at especially high risk of becoming infected or transmitting the virus, whereas countries with generalized epidemics should also invest heavily in interventions that target entire populations or population subgroups. Thus, any determination of the likely effectiveness and cost-effectiveness of specific interventions in particular circumstances requires an accurate understanding of the stage and nature of the national epidemic.

Low-level epidemic. Providing widespread voluntary counseling and testing (VCT), screening for STIs, universal precautions, and postexposure prophylaxis may not be cost-effective in this setting. In a low-level epidemic, as in the Middle East and North Africa, HIV/AIDS control strategies should emphasize

- surveillance and individual-level interventions that target key populations such as sex workers, men who have sex with men, injecting drug users, and people living with HIV/AIDS;
- information, education, and counseling (IEC), including limited education via the mass media and sex education in schools;
- comprehensive prevention programs for people living with HIV/AIDS and harm reduction programs for IDUs;
- VCT that is available to key populations with the highest levels of risk behavior and infection;
- MTCT prevention to mothers known to be infected with HIV;
- screening all blood for transfusions and providing sterile injections;
- addressing market inefficiencies in condom procurement and distribution, including strategies like bulk purchases and incentives;
- addressing community attitudes that impede education and discussion about sexual activity, as these may thwart STI/HIV education efforts.

Concentrated epidemic. In a concentrated epidemic, as in the countries in East Asia and the Pacific, Europe and Central Asia, Latin America and the Caribbean, and South Asia, prevention priorities, in addition to those above, should include

- strengthened surveillance among key populations such as sex workers, men who have sex with men, and injecting drug users;
- subsidized VCT and promotion thereof among key populations;
- HIV screening of pregnant women, guided by individuals' risk profiles;
- peer-based programs for key populations to educate individuals at risk, promote safer behaviors, and distribute condoms;
- harm reduction for IDUs, including needle exchange and drug substitution programs;
- STI screening and treatment for key populations;
- targeted distribution and promotion of condoms to key populations, and condom distribution linked to VCT and STI care.

In addition, contextual factors, such as government rejection of needle exchange programs, the incarceration of drug users, the harassment of sex workers, and illegality of sex among men can be major impediments in the scaling up of effective prevention efforts. As HIV/AIDS is typically concentrated in socially and/or economically marginalized populations in countries with concentrated epidemics, attention to

socioeconomic factors and the stigmatization of key populations will also be vital to an effective response.

Generalized low-level epidemic. In a generalized low-level epidemic, as in many countries in sub-Saharan Africa, the emphasis on targeted interventions must be maintained or even strengthened, but interventions for broader populations must also be aggressively implemented. These prevention priorities should include

- surveillance of STI, risk behaviors, and HIV infections in the entire population, with a particular focus on young people;
- extending mass media IEC beyond basic education;
- routine voluntary and confidential HIV testing and STI screening and treatment promoted beyond key populations;
- subsidized and social marketing of condoms and strengthened distribution to ensure universal access;
- offering HIV screening to all pregnant women;
- broadening peer approaches and targeted IEC to include all populations with higher rates of STI and risk behavior.

Contextual factors remain critical to the success of prevention efforts in generalized low-level epidemics, but population-level factors now have greater priority. The most important of these is likely to be the status of women, especially with regard to their ability to control their sexual interactions, to negotiate condom use and VCT with their partner(s), to be protected from abuse, and to have property rights following the death of a spouse.

Generalized high-level epidemic. In a generalized high-level epidemic, such as in some countries in southern and eastern sub-Saharan Africa, an attack on all fronts is required. Prevention efforts should focus on broadly based population-level interventions that can mobilize an entire society so as to address prevention and care at all levels. Prevention should include

- mapping and surveillance of risk behaviors, STI, and HIV infection;
- routine universal HIV testing and universal promotion of STI screening and treatment;
- condom promotion and free distribution in all possible venues;
- VCT for couples seeking to have children;
- scaling up individual-level approaches to innovative mass strategies with accompanying evaluations of effectiveness;
- utilizing the mass media as a tool for mobilizing society and changing social norms;
- employing other channels to reach large numbers of people efficiently for a range of interventions including workplaces, transit venues, political rallies, schools and universities, and military camps;

- official institutional efforts to alter social norms on infant feeding, and harm reduction for IDUs.

In a generalized high-level epidemic, contextual factors, such as poverty and the fragility of the health care infrastructure, will dramatically affect service provision at every level. The status of women, an important factor in all epidemics, becomes an overriding concern in this setting, requiring priority action to radically alter gender norms and reduce the economic, social, legal, and physical vulnerability of girls and women.

CONCLUSION

The scale of the STI epidemics, including HIV, in many developing countries requires that responses to them be multidisciplinary and economics is one discipline that has much to contribute to efforts to address the epidemics of STI/HIV in resource-poor settings.

We reviewed the contributions made by economists to the analysis of the determinants of STI/HIV infection as well as their contributions to analysis of the impacts of STI/HIV on individuals and their households. Those data that are available underscore the need for public intervention in the prevention and treatment of STI/HIV. The review also highlights the need for additional data that is population-based as well as econometric analysis of these data to better assess the economic impact of young adult deaths on households.

Economics also offers a set of tools that can assist in the evaluation and prioritization of STI/HIV interventions in contexts of limited resources. This review highlights that each country needs data about its risk behaviors, its STI epidemics, and its responses. It also highlights the dearth of information on the effectiveness of interventions in different contexts. Without such data for planning, managing, and evaluation, billions of dollars will continue to be spent and far fewer deaths will be prevented than could be.

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3

The Transmission Dynamics of Sexually Transmitted Infections

Geoff P. Garnett

Epidemiology is the study of the patterns of disease and the risks leading to disease. For sexually transmitted disease (STD), in addition to identifying risk factors leading to the acquisition of infection and the development of disease, we can study the spread of infections through populations, i.e., the transmission dynamics of infection. Thus, in STD epidemiology we are concerned with patterns of risk at both the individual and the population level. The change in patterns of infection over time within the population can be described in mathematical models, which provide a framework for the analysis of data, generating testable predictions, and exploring the potential impact of interventions.¹ In this chapter, the key variables contributing to the spread of sexually transmitted infections (STIs) are reviewed within the theoretical framework provided by developing and analyzing mathematical models.

The spread of STIs is directly influenced by a limited number of biological and behavioral variables that could be called “proximate determinants.”² These in turn are influenced by a range of social, economic, demographic, and cultural factors of the individual and the population, which have to alter the proximate determinants to influence the spread of infection. The pattern of sexual contacts within the population is the same for each STI, but the ability of the infection to exploit these contacts will determine its distribution and depends upon its own biology. That biology is summarized in a description of our assumptions about the natural history of major STIs and the risks of transmission within sexual partnerships.

THE NATURAL HISTORY OF SEXUALLY TRANSMITTED INFECTIONS

The natural history of an infection is the relationship between that infection and disease and associated patterns of infectiousness. In understanding this natural history, individuals can be divided between mutually exclusive categories and the flows between them illustrated schematically in flow diagrams. [Figure 3-1](#) shows the assumptions frequently made about a range of the key STIs in such flow diagrams.

Chlamydia, gonorrhea, syphilis, chancroid, and trichomonas can be thought of as curable STDs, which as a group appear to be short-lived with a high transmission probability. On recovery from infection, either through an acute immune response, mechanical clearance, or treatment, the individual becomes susceptible to reinfection. This lack of acquired immunity maintains the pool of susceptibles facilitating the persistence of infection. Our ability to treat and cure the bacterial STDs and trichomonas provides a means of reducing the duration of infectiousness and controlling the spread of infections.³⁻⁶ Unfortunately, many infections remain asymptomatic, maintaining a reservoir of untreated infection within communities. This is particularly true of chlamydia and trichomonas infections where the majority often remain asymptomatic in women.^{5,6} Gonorrhea is also more likely asymptomatic in women than in men with only 5% of infection remaining asymptomatic in men.^{4,7} However, in population surveys a greater proportion of prevalent infections in men will be asymptomatic because of the long duration of asymptomatic compared with the more likely treated symptomatic infections.

The duration of infection, and infectiousness, in the absence of treatment determines the epidemiological success of STDs, but it cannot be measured because infections cannot ethically be allowed to continue untreated. Hence, we can only rely on historical records, with attendant problems of unreliable diagnosis and insensitivity to any evolution of the organisms, or on indirect estimates based on the prevalence of the infections and estimates of other parameters. Perhaps the best records are available for syphilis which is caused by slowly replicating spirochete *Treponema pallidum*. The natural history of this infection, which progresses through stages, can be pieced together from historical records of experimental inoculations, the observations of early venereologists, and a prospective observational cohort study in Oslo from the early twentieth century.⁸ The primary disease, a chancre at the site of infection emerges after about a month, resolves after around 2 weeks, but is followed about a month later by secondary disease that lasts on average for just under 4 months before resolving, with recurrences in 25% of cases. In

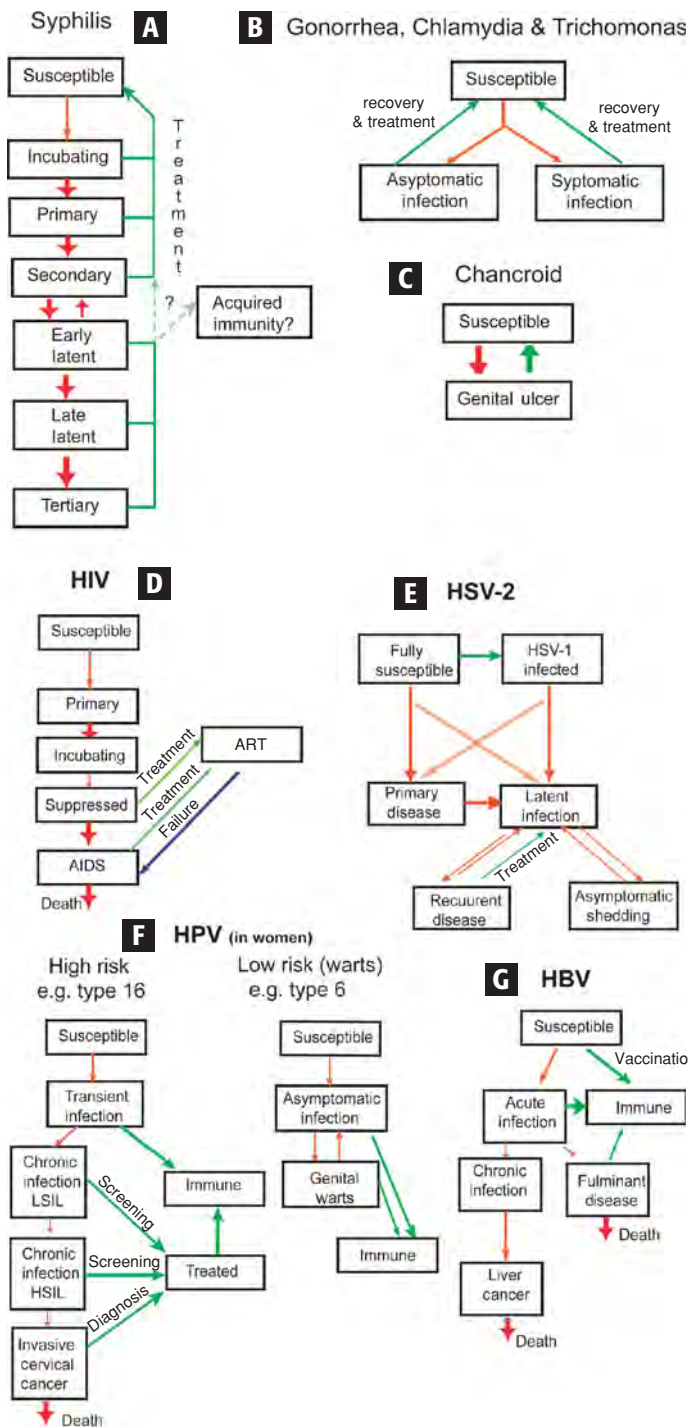


FIGURE 3-1. Flow diagrams illustrating the natural history of the major sexually transmitted infections. **A.** Syphilis; **B.** curable inflammatory STIs including gonorrhea, chlamydia, and trichomonas; **C.** chancroid; **D.** HIV; **E.** herpes simplex virus type 2; **F.** human papilloma virus; **G.** hepatitis B virus.

a follow up of 1940 patients infected between 1890 and 1910, 11% of 694 known deaths were attributable to syphilis, with 9% of men and 5% of women suffering neurosyphilis, 14% of men and 8% of women suffering cardiovascular syphilis, and 16% of men and 20% of women suffering benign late syphilis. Tertiary disease has since been almost eliminated due to the

widespread use of antibiotics, but congenital syphilis continues as a severe condition associated with syphilis epidemics.⁹ From records it is unclear when exactly syphilis is infectious, although transmission appears to be most closely associated with the early stages. Reinfection following treatment is possible, but there is evidence that long exposure to the bacteria can lead to acquired immunity. Such immunity, either acquired or concomitant in untreated cases provides a simple explanation for the regular cycles of approximately 10 years duration observed in syphilis case reports in the United States¹⁰ and has been invoked to explain increases in incidence following mass syphilis treatment.¹¹

The viral STDs appear to be much long-lasting with low transmission probabilities. Infection with genital herpes simplex virus type 2 (HSV-2) infection is more likely to lead to symptoms on infection in someone who has not previously been infected with the related HSV-1.¹² Disease cases take an average of 3 weeks to resolve and then, like initial asymptomatic infections, they enter a latent state from which recurrences of symptomatic lesions and episodes asymptomatic shedding occur with decreasing frequency over time.^{13,14} These recurrences create a long infectious period that can expose subsequent sexual partners to infection. A similar long asymptomatic infectious period is associated with HIV infection. Initially there can be symptoms associated with seroconversion, which are generally mild and resolve, then there is a period of on average a decade, before levels of CD4 positive T-helper cells fall to a level where the immune system fails.¹⁵ Treatment prevents viral replication and allows the immune system to recover, but it is not a cure and treatment failure is common.¹⁶ In contrast, human papilloma virus infections and hepatitis B virus infections are normally transient, but for each a fraction of cases become chronic and can progress to cause cancer.^{17,18} Human papilloma virus types are separated by a genetic difference of 10% or more and can be categorized as high risk, if they have oncogenic potential, or low risk.¹⁹ Some of the low-risk types, because of their cellular tropisms, are associated with genital warts, with infections sometimes moving repeated from asymptomatic infections to symptomatic lesions and back. HPV infection is a necessary but not sufficient cause of cervical cancer with HPV-16 associated with over 60% of cervical cancer cases.¹⁹ Transient infections become chronic with infections progressing either slowly or rapidly through stages of cytological abnormalities before becoming invasive cancer. It is these precancerous lesions that are detected in cervical cancer screening programs.²⁰ The illustrated categories of low-grade and high-grade squamous intraepithelial lesions are those used in the Bethesda System adopted in the United States. Elsewhere, cytological classifications of cervical intraepithelial neoplasias are classified as types 1, 2, and 3. It is questionable whether natural type restricted acquired immunity exists against HPV infections.²¹ The likelihood of hepatitis B becoming chronic

depends upon the age of infection, with chronic infection likely at the young ages of infection found when forces of infection are high.²² This creates a vicious cycle where a high prevalence of chronic and acute infection generates a high force of infection and more chronic cases. Once the force of infection can be lowered slightly increasing the age of infection, chronic infections become rare and the prevalence of hepatitis B should fall dramatically.²³

The natural history of the STDs determines patterns of disease associated with infection and the duration of infection, it also determines when infected individuals are infectious. Whether this infectiousness is translated into new cases of infection depends upon patterns of sexual contact and the risks of transmission to the contact.

TRANSMISSION OF INFECTION WITHIN SEXUAL PARTNERSHIPS

The relevant contact for the spread of STIs is sexual intercourse. If people distributed their sexual acts randomly through the population then the spread of STIs would likely be great. However, sex generally takes place within the context of sexual partnerships, limiting contacts to particular individuals. Each act of sexual intercourse between someone with an STI and someone susceptible exposes the susceptible to a risk of acquiring infection. Logically, the more sex acts there are, the greater the risk of transmission within the partnership; a relationship which can be described by a binomial model,²⁴ where the transmission probability per sex partnership (β_p) is a function of the probability per sex act (β_a) and the number of sex acts (n): $\beta_p = 1 - (1 - \beta_a)^n$. The explanation of this relationship is illustrated in Fig. 3-2A. Each act between the infectious and susceptible partner carries the risk (β_a) of infection being acquired and $(1 - \beta_a)$ of it not. At the next sex act only those remaining susceptible can still acquire the infection, so a fraction $(1 - \beta_a)$. β_a will acquire infection on this second act and $(1 - \beta_a)$. $(1 - \beta_a)$ will stay susceptible. This then leaves the cumulative fraction infected equal to one minus the fraction left susceptible.

The relationship saturates to one as the number of sex acts within the partnership increases and is illustrated for a wide range of transmission probabilities per act in Fig. 3-2B. For a high transmission probability per act, the risk of acquiring infection within the partnership soon becomes very high, whereas risk slowly accumulates with a low transmission probability per act. This very simple model relationship has been widely used in illustrating the potential impact of condoms within sexual partnerships^{25,26} with modifications to separate out acts with different transmission probabilities where, for example, a fraction f acts are protected by condoms with an efficacy e :

$$\beta_p = 1 - (1 - \beta_a)^{(1-f)n} (1 - (1 - e)\beta_a)^{fn}$$

Graph Figs. 3-2C and 3-2D illustrate for different underlying transmission probabilities the impact of condom use within a partnership where both the consistency and efficacy of condoms are varied. It can be seen that for a high number of acts and a high transmission probability, infrequent or inefficacious condom use has little or no effect. Only when condom use is consistent and efficacious does it reduce the transmission probability within the partnership. In a low transmission probability infection such as HSV-2, condoms can have a marked impact even if they are not consistently used or highly efficacious. The efficacy of condoms against both the bacterial and viral STIs has been demonstrated empirically.²⁷ Even for human papilloma virus, which can be transmitted without exposure of mucosal surfaces, condoms have been found to reduce the risk of acquisition by 70%.²⁸

The above arguments assume that the logically appropriate binomial model for transmission is valid. In the case of gonorrhea transmission from women to men, the model was confirmed in a study in which aircraft carrier personnel were screened for gonorrhea infection before and after shore leave, along with behavioral surveys and prevalence studies amongst women in bars on shore.²⁹ In contrast, studies of HIV transmission found little impact of number of sex acts on transmission except when small numbers of sex acts are involved.³⁰ A number of hypotheses are possible to explain this observation, including a large fraction of insusceptible people, a declining risk following initial exposure, possibly due to immunity acquired through exposure, or an extreme heterogeneity in transmission probability between partnerships.³¹ The latter (illustrated in Fig. 3-2E) is increasingly supported by data on the relationship between HIV viral load and transmission, which also reflects the course of HIV infection within the infected partner.³² This should have profound implications for HIV educational messages. The relevant risk of acquiring HIV in a sexual contact with an infectious individual is not the average risk of contact per act (estimated at 1 in a thousand), but more the risk per partnership since the chances of getting infected depend upon the partner's viral load more than the number of sex acts within the partnership. Additionally, condom use needs to be consistent within those partnerships with a high risk of transmission to substantially reduce the transmission probability per partnership.³³

Data for gonorrhea suggests that the transmission probability of STIs is greater from men to women than from women to men, which is readily explained anatomically.⁴ It also appears that the sex difference in prevalence of HSV-2 is a function of an asymmetric transmission probability with women at more risk from an infectious sex partner.³⁴ Estimates of heterosexual HIV transmission probabilities vary greatly between studies as the likelihood of transmission depends upon the presence of other STIs, the circumcision status of the man, and the stage of HIV infection in the infectious

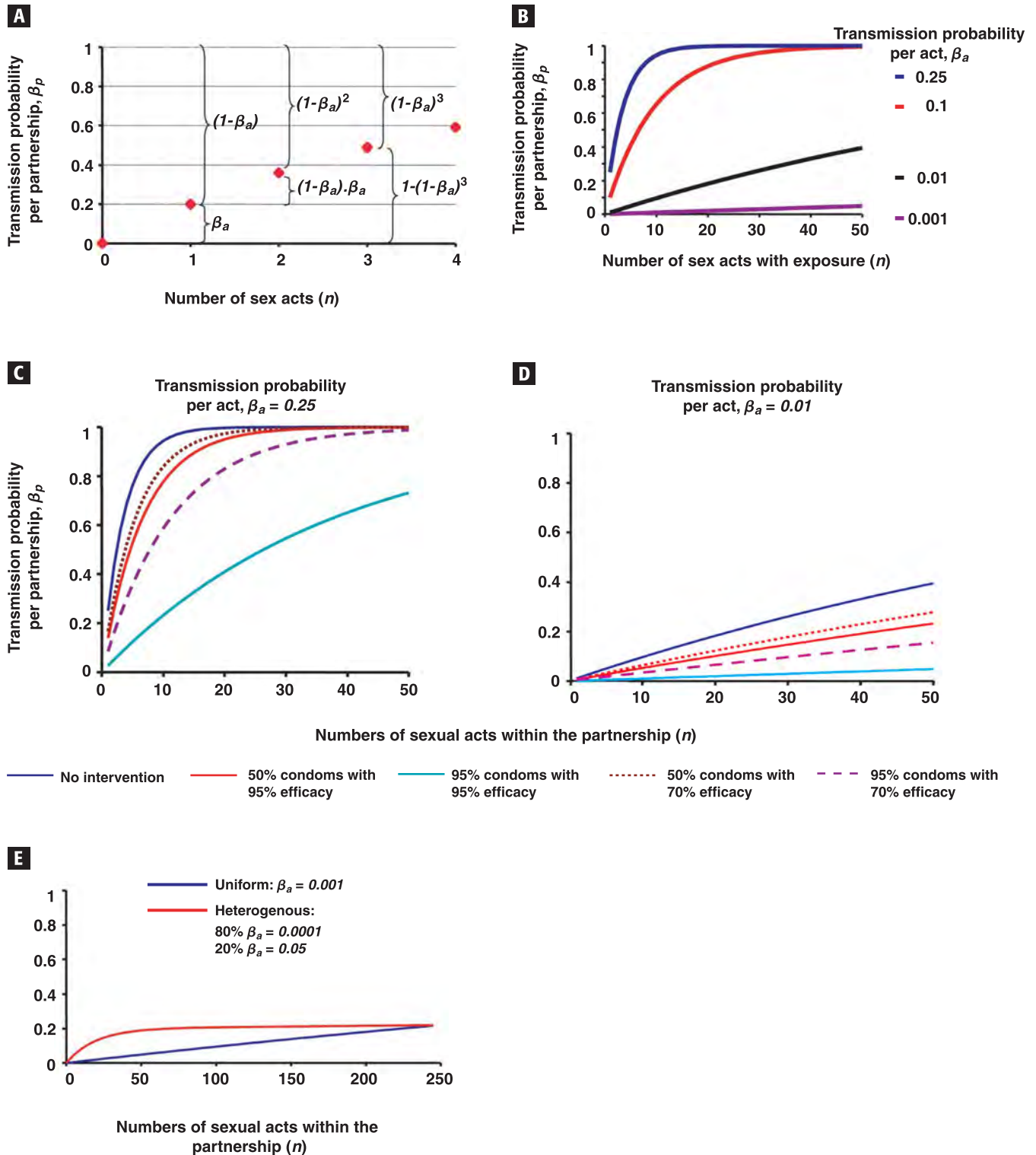


FIGURE 3-2. The transmission probability per sex partnership as a function of the number of sex acts. **A.** For a transmission probability per act (β_a) of 0.2 the probability of staying susceptible after 1 act is 0.8 ($1-\beta_a$); after 2 acts it is 0.64 ($1-\beta_a$)²; and after 3 acts it is 0.512 ($1-\beta_a$)³. **B.** The transmission probability per partnership as a function of the number of unprotected sexual acts for a range of transmission probabilities per act. **C.** The influence of condoms on the transmission probability per partnership as a function of the number of sex acts within the partnership with condoms used in 50% or 95% of sex acts with an efficacy of 95% or 70% when the transmission probability per unprotected sex act is 0.25. **D.** When the transmission probability per unprotected sex act is 0.01. **E.** The transmission probability per partnership as a function of number of unprotected sex acts comparing a homogeneous risk of 0.001 with a risk of 0.05 per act in 20% of partnerships and 0.0001 in the remaining 80% of partnerships.

partner. In more detailed studies in the United States and Western Europe, the transmission probability per partnership is around twofold greater from men to women than from women to men.^{30,35–37} This difference has not been observed in developing countries.^{38–40} The risk of transmission also appears greater amongst men who have sex with men (MSM) than heterosexuals.⁴¹

ESTIMATING TRANSMISSION PROBABILITIES

The risk of transmission of an STI cannot be estimated by simply determining the proportion of contacts of cases that are infected, as has sometimes been assumed.⁴² If we include contacts that were the original source of infection, this will lead to overestimation of the transmission probability. There are a number of ways around this problem. First, if it can be ascertained that the contacts had no other possible source of infection, we can assume that they could only be infected from the case and use the fraction infected as an estimate of the transmission probability.⁴³ A second method would be to sample all partnerships and determine the fraction where both are infected and where only one partner is infected. This requires a high prevalence, as partnerships have to be sampled randomly, irrespective of whether there is infection within the partnership. If partnerships are chosen on the basis of infection being present, partnerships where both are infected will more likely be sampled leading again to an overestimated transmission probability. In such studies of HIV transmission in sub-Saharan Africa, retrospective analyses have found higher transmission probabilities than observed when discordant couples are followed prospectively.³² This would be a product of a high early transmission probability associated with a high initial viral load leading to transmission in partnerships before they can be recruited into the study.

The biological characteristics of the STIs determine the relative influence of different sexual behaviors within populations. These behaviors have been explored in studies of those infected and in representative samples of the population as a whole.

RISK BEHAVIORS AND THE ACQUISITION OF STIs

In epidemiology, the normal method for identifying the role of risk behaviors is through comparisons between those with and without infection. However, the risks associated with a particular pattern of behavior depend upon the prevalence of infection within contacts, which in turn depends upon behaviors throughout the population. Thus, while the behaviors of infected individuals provide some indication of their role, we must also develop a theoretical as well as empirical understanding of the contact patterns.

In case control studies, subjects infected with STIs on average report more sexual contacts, but many of those infected can have low-risk behaviors^{44,45} (Fig. 3-3). Comparing populations, we might expect those with a higher incidence of STIs to have populations with higher aggregate numbers of sexual contacts. However, such a relationship can easily be confounded, for example, if there are different patterns of

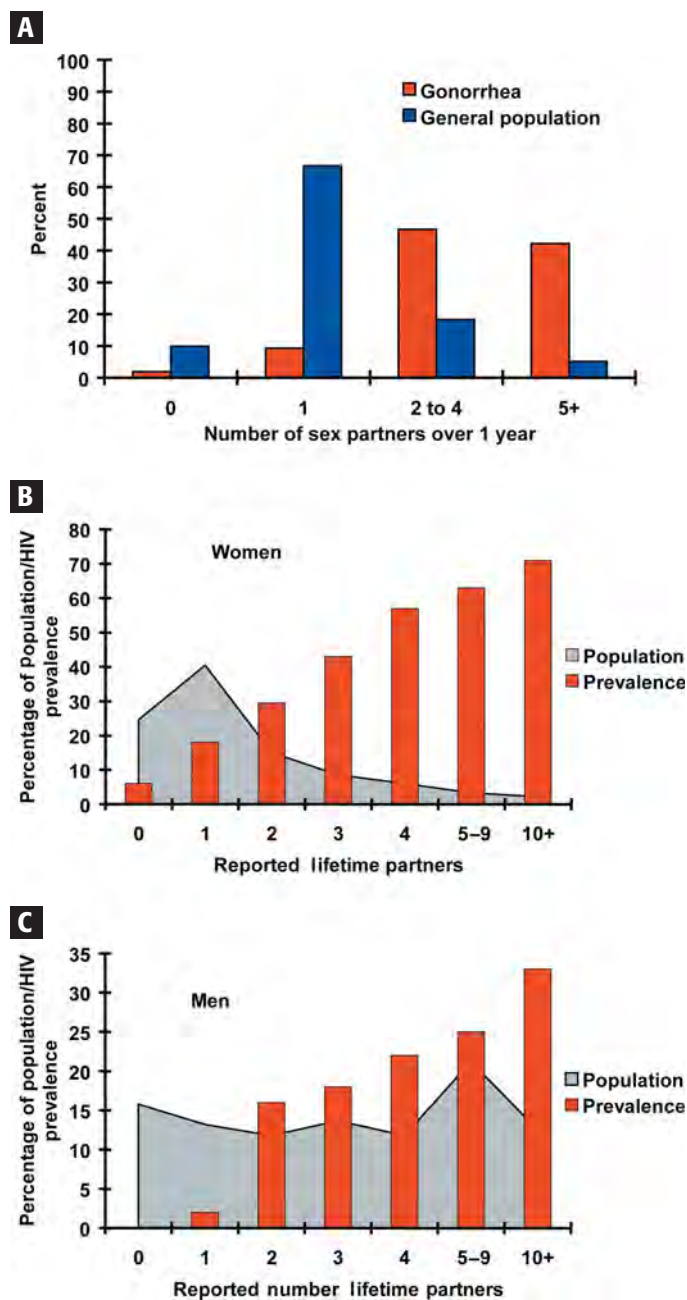


FIGURE 3-3. Reported numbers of sexual partnerships and the distribution of sexually transmitted infections: **A.** The distribution of men reporting a given number of sexual partners over a 1 year period from a household based representative sample in the United States and a sample of men with gonorrhea in Newark, New Jersey, USA.³⁸ The distribution of men, **B.**, and women, **C.**, reporting a given number of lifetime sex partners in a household based survey in rural Zimbabwe and the prevalence of HIV infection amongst them.³⁹

treatment seeking behavior or access to effective treatment, by the timing of an infection being introduced or by errors in reports of risk behavior. Additionally, the distribution of contacts can be as, or more, important than the average behavior. Studies of sexual behavior in representative samples of the population show that the reported number of sexual partners is extremely heterogeneous with some reporting many sexual partners and a minority very many sexual partners^{44–47} (Fig. 3-3).

Those with many sexual partners can drive the incidence of an STI in the population and have been described as a “core group”.⁴⁸ Axiomatically, for a sexually transmitted disease (STD) to exist there must be individuals with sufficient sexual partners to transmit infection to more than one other person.⁴⁹ If interventions could reliably prevent infection in these individuals, the STI could be eliminated. Studies of risk behaviors and the distribution of STIs have attempted to identify the characteristics of those within the core group as a target for interventions. This has led to the characterization of neighborhoods, or demographically defined groups, based on the prevalence of infection and those with repeated STIs as a core group.⁵⁰ Unfortunately, such grouping will inevitably miss some of those with a high risk, include many who are not at risk and can also lead to stigmatization.⁵⁰ Further definitions of the term “core group” have been broader, encompassing those with the social and cultural variables associated with high-risk behavior. This multiplicity of uses has led to confused debate about the role of core groups in the epidemiology of the infections.⁵¹

The lower the incidence of an STI in a population, the more it will be concentrated in those with higher risk behaviors. If the behaviors placing individuals at risk are similar then those most at risk of one STI would be the same as those most at risk of another infection. We would expect infections with a higher combined transmission probability and duration to not only be more widespread, but to also be found in those with STIs with a lower combined reproductive potential.⁵² If this is not the case as has been suggested in some observations,⁵³ potential explanations include the acquisition of immunity against one infection, different likelihoods of receiving treatment, and different risk behaviors placing individuals at risk. For example, we expect partner numbers over recent time to be more influential in the risk of having a short-lived STI like gonorrhea, and the lifetime number of sex partners to be more influential in the risk of having been infected with HIV.

■ MIXING PATTERNS

The choice of sexual partners of an individual will have a large influence on whether or not they are exposed to someone infected. The choice of sexual partners will depend upon the contexts in which potential couples meet, for instance,

schools, church groups, beer halls, and family gatherings and how they relate. Studies show that individuals tend to choose sexual partners, particularly spouses, who are similar with respect to social and demographic variables such as age, education and income.^{47,49} Such a choice will lead to assortative (like-with-like) sexual mixing within the population with respect to the specific variables. If no discrimination is made, mixing will be random, and if partners are chosen to be dissimilar then mixing will be disassortative (like-with-unlike). If individuals are grouped into categories, then a mixing matrix can describe the probabilities that when an individual from one group forms a sexual partnership, it will be with an individual from another group. These mixing matrices can be categorized on the basis of how assortative the mixing is^{54–56} (Fig. 3-4A). However, sexual behavior variables determine how likely an individual is to be infected with an STD and mixing according to risk behaviors determines how likely an STI is to spread. Theoretically, we can explore the influence of different patterns of mixing (Fig. 3-4B). Assortative mixing restricts the spread of STIs but helps maintain chains of infection within high-risk groups. Thus if mixing were assortative, an STI would be more likely to invade rapidly and persist within a population but would also be less likely to spread widely. In contrast, random mixing would spread infection from high- to low-risk individuals who are dead ends for the infection. Infection is less likely or slower to invade and persist, but if it did succeed, it would become more widespread.⁵⁷ Measuring the pattern of sexual partner formation according to sexual behavior variables is difficult and likely to be biased. If sexual behavior is strongly correlated with social and demographic variables then we would expect mixing to be assortative as similar partners to the individual are chosen on the basis of such variables. The choice of partners of those with high numbers of partners is most influential as it determines how widely an STI will spread through the population. Direct measures of mixing from egocentric data suggest that mixing is near random according to numbers of sexual partners over a short period, but with a few high-risk individuals who tend to have high-risk partners (Fig. 3-4C).⁵⁸ This is in agreement with the distribution of reported numbers of sexual partners in those with gonorrhea in the United States where the high proportion with low levels of risk would only be possible if mixing was toward the random end of the spectrum.⁴⁴

Sexual partner network structure: Small worlds, concurrency, and scale-free patterns of contact

The network of sexual contacts through which STIs spread is an example of a social network.⁵⁹ Sexual relationships provide the steps in paths linking individuals, with “components” made up of individuals connected through these paths. Recent advances in recording and analyzing social network structure have improved our general understanding of such

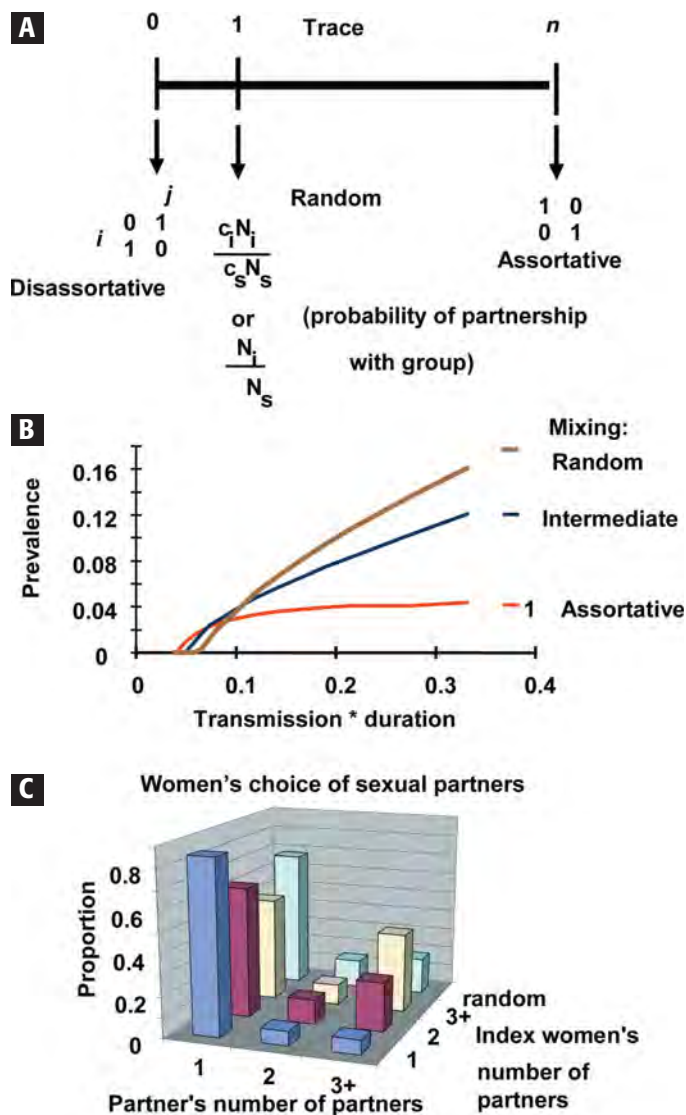


FIGURE 3-4. The influence of patterns of mixing according to sexual activity. **A.** The scale of mixing from fully disassortative through random to fully assortative with associated mixing matrices for two sexual activity groups. The trace is the sum of the values on the diagonal of the matrix which determine like-with-like mixing. Fully disassortative has no like-with-like partnerships, so the diagonal elements of the mixing matrix are zero. For random mixing, each element equals either the number of partnerships supplied by a group as a fraction of all partnerships supplied (where c_j is the rate of sexual partner change of the group j and N_j is the number in that group) or the number of people in the group as a fraction of the population of all potential partners. In both cases, the sum of the values on the diagonal equals 1. In fully assortative mixing, the values on the diagonal are all equal to the number of groups. **B.** The steady state prevalence of a bacterial STI which does not generate immunity in a two activity class model with a mean rate of sex partner change of 2 new partners per year. The prevalence as a function of the combined transmission probability per partnership and the mean duration of infectiousness per partnership is illustrated. Mixing is determined by a single parameter, with results shown for fully assortative, random, and half way between the two. **C.** The reported numbers of partner's partners over 3 months of index women with a bacterial STI as a function of the index women's number of partners from the Harborview STD clinic in Seattle compared with the distribution expected if mixing were random according to the number of partners reportedly "supplied" in household based survey across the United States.⁴⁷ Mixing is near random except for a high number of women with 3 or more partners whose partner also had 3 or more partners.

networks with insights often applied by analogy to sexual networks.⁶⁰ However, sexual relationships are likely less frequent than many other social contacts and will consequently generate sparser networks. An example is provided by the "small world" phenomena.⁶¹ Here geometric increases in the number of contacts connected through a given number of steps mean that very many people can be connected through a small number of steps. For example, if every new contact had on average 43 other novel contacts then over 6 billion people could be connected in only 6 steps. This assumes that each contact is novel and not already included in the component, which is unrealistic, as contacts are likely to be correlated, i.e., the acquaintances of one individual are also likely acquainted.⁶¹ Such correlations could prevent paths reaching across social and geographic space, except that a few longdistance contacts dramatically reduce path lengths creating a small world, where stepping through the network everyone is closely connected.⁶¹ This has been illustrated through the "6 degrees of separation" example, which has been shown to hold for many social networks, with a few people excluded.⁶¹ Such an extremely small world is unlikely to exist for sexual contacts, since if everyone has on average two partners then only 11 people would be connected to someone over six steps. Even if the average number of partners were increased to 10, this would only increase the maximum number of contacts to 664,299. There is the potential for the cumulative sexual network to be a small world, albeit with more than steps to connect individuals, but this needs to be empirically validated. Nonetheless, the concept of a few sexual partnerships linking sexual networks across social and geographic space is important.

Analysis of social networks tends to assume that networks are static with the network accumulated over time. Over time, sexual relationships form and dissolve creating a cumulative network which could be analyzed. However, the history of a relationship is obviously inadequate for the transmission of an STI where the sexual relationship has to be extant. The most relevant sexual network would be the one accumulated by individuals over the period they are infectious.⁶² For a long-lasting infection like HSV-2 (and potentially HIV and HPV), numbers of partners can accumulate over an extended period bringing many people into the network. With a short duration infection such as gonorrhea, the network has little time to build up and concurrent partnerships become important. Concurrent sexual partnerships create network components at one instant in time allowing the rapid spread of infection, both reducing the time before individuals become exposed to infection and negating any requirement for a correct sequence of sexual partnerships moving infection sequentially from infected to susceptible individuals.⁶³ As the average number of concurrent partnerships across a population increases it can pass a threshold where a giant component of connected individuals is formed, which would

allow the explosive spread of a highly transmissible STI.⁶⁴ Populations where this threshold has been passed are extremely vulnerable to STIs and such networks could have played a role in the rapid spread of HIV in sub-Saharan Africa. One study of four populations with different HIV epidemics did not find differences in patterns of concurrency.⁶⁵ However, retrospectively identifying the behaviors responsible for the spread of HIV is difficult, with a combination of factors increasing transmission probabilities and the density of contacts likely to matter.

The heterogeneity in the number of sex partners reported by individuals has also created interest amongst network analysts, because it provides an example of a scale-free distribution.⁶⁶ The distribution of individuals with respect to reported number of sexual partners does not reach a point with high numbers of partners where it rapidly falls away. This is illustrated for data from the UK in Fig. 3-5 in a log-log plot of the proportion of the population with a higher number of partners than indicated on the x-axis.⁶⁷ This illustrates the existence of some individuals reporting very many sex partners, but given the small numbers at the tail of the distribution there is debate over the statistical validity of rejecting non-scale-free distributions.⁶⁸ This is called scale free because as we move along the axis for number of partners, the pattern of decline in the fraction reporting a given number does not change. A mechanism called preferential attachment can generate such distributions, where those who already have more sex partners are also more likely to gain additional partners. With such distributions, as population sizes increase, there will always be a small number of people with very high numbers of sex partners and if the falloff in their numbers is slow then there will be no threshold transmission probability below which an STI cannot spread. While this might be theoretically interesting, it is important to note that this scale-free behavior has only been observed over a few

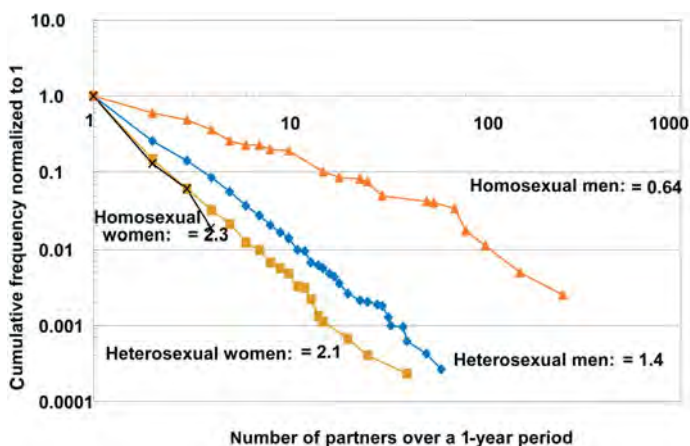


FIGURE 3-5. The distribution of individuals for the British Survey of Sexual Attitudes and Lifestyles from 2000 reporting more than a given number of sexual partners over 1 year logarithmic scales. The exponents show the rate of falloff in numbers which is slower for men, particularly men who have sex with men.

orders of magnitude, even when reports are for lifetime numbers of partners.⁶⁷ It is likely that if sample sizes increased in studies of sexual behavior, then we would quickly find a limit to the number of sexual partners an individual has.

INCIDENCE, PREVALENCE, AND THE COURSE OF AN EPIDEMIC

The basic reproductive number (R_0) is a measure of the potential for the spread of an infection and can be defined for STIs as the average number of infections caused by one infectious individual entering an entirely susceptible population.⁶⁹ The key components determining the value of the basic reproductive number are those discussed above: the transmission likelihood (β), the contact rate (c) and the duration of infectiousness (D), with, in a simple, illustrative model, the product of these three being the basic reproductive number: $R_0 = \beta c D$.⁶⁹ The value of R_0 determines: the chances of an epidemic when an infection enters a population; the rate of spread of the epidemic; the endemic level of infection, and the effort required to bring the infection under control. An important distinction has to be drawn between the *basic* reproductive number, R_0 , which measures the potential for spread in a naive population, and the *effective* reproductive number, R_t , which changes depending on the experience of infection in the population.⁷⁰ This effective reproductive number is the number of new infections caused by an average infection at a given time, t , which at time zero equals the basic reproductive number. Once some contacts are already infected or immune, the effective reproductive number is reduced and is the product of the basic reproductive number and the fraction of contacts remaining susceptible. When an infection successfully invades a population its prevalence will initially grow exponentially, until it saturates and the effective reproductive number falls. This is illustrated in Fig. 3-6. In Fig. 3-6A an infection with a long duration is represented, where prevalence will climb even once incidence has fallen, as infections accumulate. However, as infection is lost through death or recovery, prevalence could well fall. Where the prevalence saturates is a function of both the basic reproductive number and the distribution of risks within the population. When risks are evenly spread throughout the population the effective reproductive number is simply the basic reproductive number times the proportion of the population susceptible. At the endemic steady state each new infection on average causes one more infection ($R_t = 1$) and the proportion of the population susceptible is the inverse of the basic reproductive number. Consequently, the greater the value of R_0 , the higher predicted prevalence of infection and immunity. In the case of STIs, where there is heterogeneity of risk, contacts are concentrated in a small fraction of the population and infection saturates long before it would in a homogenous population.

In a randomly mixing population with heterogeneous behaviors, a good approximation for the basic reproductive number is the mean plus the variance to mean ratio of rate of sexual partner change.⁶⁹ More explicitly, the basic reproductive number for heterogeneous interacting groups can be calculated from a next generation matrix describing the number of new infection caused by the typical infection across the group.⁷¹ There will always be some imprecision in these calculations if individuals with different risk behaviors are included in the same group. More important though is to recognize that the value determines the rate of invasion and does not determine where the infection will saturate. When the value is large an epidemic is likely, as it falls close to one then chance events can prevent epidemics, and when the value is less than one a sustained epidemic is not possible. However, close to the value one moderately large outbreaks can occur infrequently as chains of infection grow by chance before fading away.⁷²

The pattern of spread of the epidemic and its subsequent progress to an endemic level depends upon the duration of infection and the role of acquired immunity as illustrated in Fig. 3-6 B. For a short-lived infection with no acquired immunity, such as gonorrhea, we can expect a steady state to be reached quickly. If death or acquired immunity reduces the susceptible pool, the prevalence of infection can fall until the resupply of susceptibles through newly susceptible individuals entering the population either balances the losses or builds up over time to cause new epidemics. The associated declines in prevalence could be confused for the impact of interventions but are the natural course of the epidemic. In the case of syphilis, acquired or concomitant immunity can explain the long-term cycles in incidence observed in US case reports.¹⁰ In the case of HIV, declines in prevalence can reflect earlier declines in incidence caused by saturation.⁷³

That a decline in prevalence is expected is not to say that declines in risk behavior do not occur, but that distinguishing between such prevention successes and the natural dynamics of infections requires careful analysis. It is possible to create null models that maximize the natural declines in prevalence expected following a peak in prevalence.⁷⁴ For HIV epidemics, the more concentrated the initial high incidence is before saturation, the shorter the period from infection to death, the shorter the average period of high-risk behavior in the life history of individuals and the less recruitment of high-risk individuals compensates for the removal of high-risk individuals through differential mortality, then the greater the postpeak decline in prevalence. Comparing such a null model with observed trends in HIV prevalence from consistently sampled sentinel antenatal clinic sites shows that HIV incidence has declined through changes in risk behavior in Uganda, Thailand, Zimbabwe, and urban Kenya and Haiti.⁷⁴

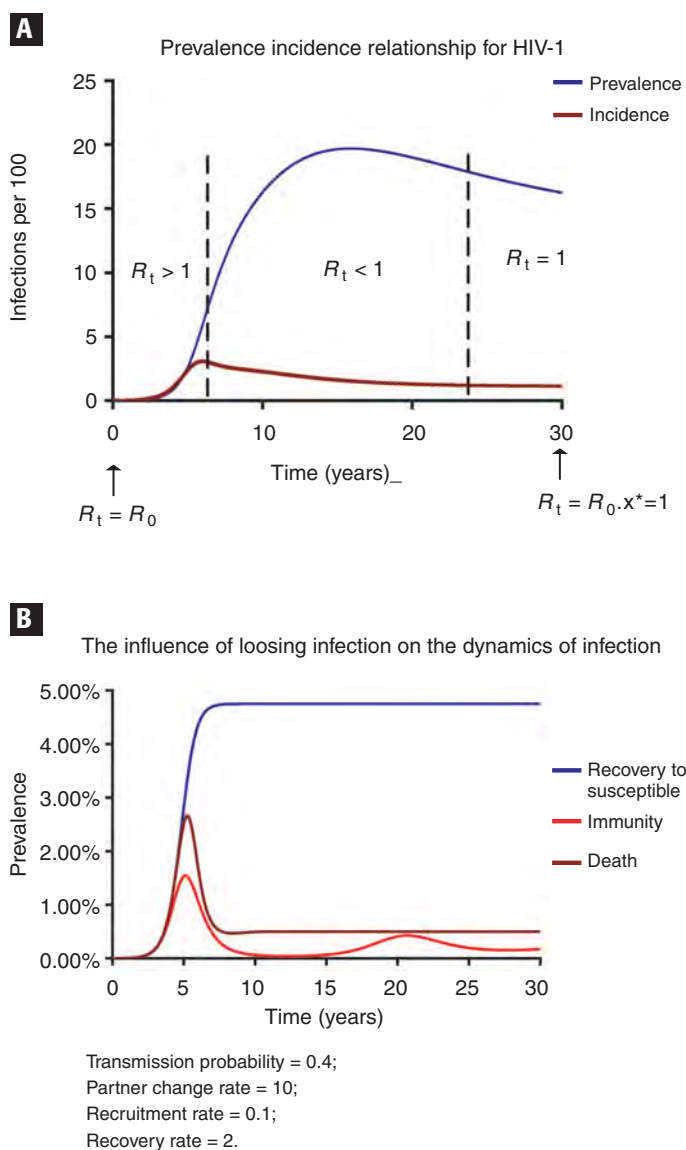


FIGURE 3-6. The predicted pattern of STD epidemics. **A.** The relationship between incidence and prevalence for HIV in a model of the spread of the virus. **B.** The predicted prevalence of an STD over time in a fraction of the population with a high risk of infection. The pattern when recovery is to the susceptible state is compared with recovery to an immune state and with loss of infection through death.

THE IMPACT OF INTERVENTIONS

To reduce the incidence of STI infection interventions must alter the reproductive potential of the infection. Shortening the infectious period, reducing the contact rate, or reducing the transmission probability, all reduce the basic reproductive number of infection, while introducing artificial immunity through vaccination would reduce the proportion of the population susceptible and thereby reduce the effective reproductive number. Reducing the basic reproductive number has a nonlinear impact on the endemic prevalence of infection, with reductions increasing as the threshold value of one is approached.⁶⁹ Thus, a small change in risk can have a dramatic

impact near the threshold, while it has very little impact at a high basic reproductive number (Fig. 3-7A). Vaccines on the other hand, if they offer complete protection, which is sometimes called “take” type protection, remove individuals from any risk of infection and linearly decrease prevalence (Fig. 3-7B).⁷⁵ If they offer partial protection reducing the risk per contact, termed “degree” type protection, then there is a return to a nonlinear decrease with reductions in exposure needed to reduce infection (Fig. 3-7B). These relationships apply to a homogenous population and might apply to interventions in a high-risk group. However, as we have seen heterogeneity in risk plays a key role in the epidemiology of STIs. In populations with a distribution of risk, small reductions in risk can have a large impact in a lower risk group while having little impact in higher risk groups.⁷⁵ Thus, initially interventions can have a large impact, but as their intensity is increased it generates diminishing returns, as infection is removed from low-risk

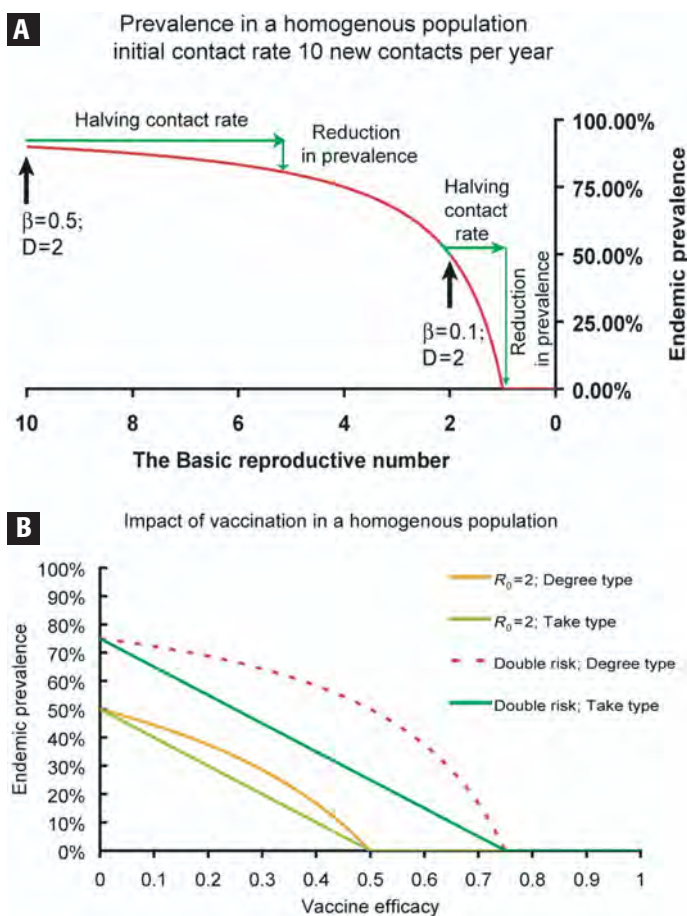


FIGURE 3-7. The predicted impact of interventions in a model of infection in a homogenous population. **A.** The endemic prevalence of infection as a function of the basic reproductive number and the impact of halving the contact rates at different starting points. **B.** The endemic prevalence as a function of vaccine efficacy with complete coverage. Two starting values of the basic reproductive number and two types of vaccine failure are compared. In take type protection, a fraction of individuals are protected, whereas in degree type protection individuals are protected from a fraction of challenges.

sections of the population and becomes more concentrated. This is illustrated for a model of treatment of symptomatic infections in and for a hypothetical HIV vaccine in (Fig. 3-8).⁷⁶

The introduction of effective treatment provides an opportunity both to relieve symptoms and reduce the duration of infectiousness of STIs. The impact of introducing rapid treatment of symptoms in a model is illustrated in Fig. 3-8A.⁴ The model assumes 40% of infections are asymptomatic which limit the impact of treating symptomatic disease. Screening to identify asymptomatic infections can reduce prevalence further. However, the rate of finding asymptomatic infections will likely be slower than is possible when symptoms lead patients to seek care. This suggests that repeated screening at short intervals is needed, which may be possible with high-risk individuals. The expected bounce back with rounds of screening or mass antimicrobial administration is illustrated in Fig. 3-8B for the same model with periodic rather than continuous screening. Here we see how quickly this short duration high transmission probability infection can regain its original prevalence in the absence of reductions in risk behavior.

Before the introduction of effective antimicrobials the incidence and prevalence of bacterial infections would have been greater. The relative success of different STIs is likely to have changed in response to treatment, with chancroid, syphilis, and gonorrhea becoming relatively less common if their symptoms are more likely to receive attention. Similarly within microbial populations, treatment is likely to provide a selective advantage to organisms that generate negligible symptoms, more so than organisms that have partial drug resistance. Over time, we might expect the pathogenicity of curable STIs to decline unless there is a correlation between symptoms and transmissibility, which is hypothetically likely if disease is associated with larger bacterial colonies and transmission depends upon the infectious dose of bacteria. However, if interventions through screening target both asymptomatic and symptomatic infections, then selection is likely to favor organisms that transmit more readily, with a concomitant shorter duration of infection in the absence of treatment.⁷⁷ Similarly, drug resistance becomes a better adaptive strategy if both symptomatic and asymptomatic infections are rapidly treated through active screening.

Although antivirals are now available to treat HIV, HSV, and HBV, these do not provide a cure to these persistent viral infections. Recent advances in the development of vaccines have seen the wide spread use of HBV vaccines and the development of highly effective HPV vaccines, less effective HSV-2 vaccines, and large investment into HIV vaccine development.^{73,21,34} The impact of a vaccine against an STI could have a large impact on the prevalence of infection, with the diminishing returns described above illustrated for hypothetical HIV vaccines in a model of the generalized spread of the virus (Fig. 3-8C).

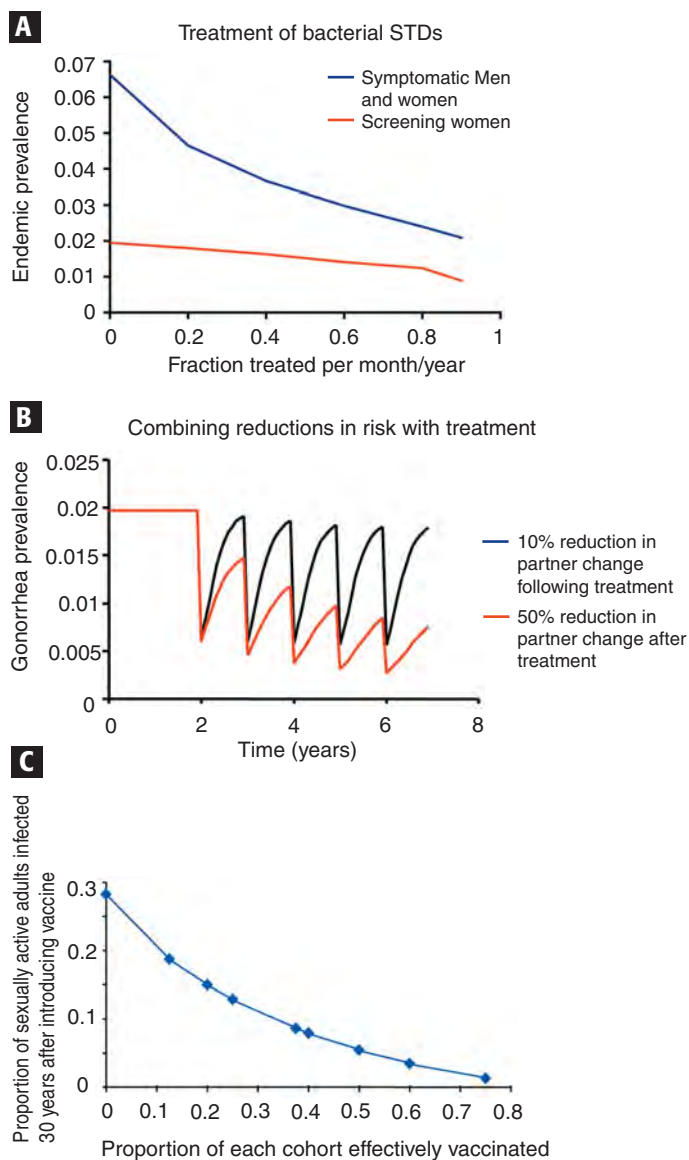


FIGURE 3-8. The population level impact of interventions. **A.** The impact of treatment for bacterial STDs in a model with three sexual activity classes, where 60% of infections lead to symptoms and infection lasts for an average of 6 months in the absence of treatment. One line illustrates the impact of treating 80% of the population for their symptomatic disease with a rate per month of seeking and receiving therapy. The lower line assumes the best symptomatic treatment and then adds screening for asymptomatic infections in 80% of the population. The screening is assumed to be continuous as would be the case with opportunistic screening. **B.** The impact over time of regular screening or mass treatment added to syndromic management of gonorrhea is illustrated, with a reduction in risk of 10% or 50% in those treated. **C.** The impact after 30 years on prevalence of a fully protective HIV vaccination in a sex, age, and sexual activity stratified model of HIV spread.

CONCLUSIONS

The theoretical framework provided by mathematical models allows us to integrate biological and behavioral data in understanding the distribution of STIs. Many aspects of sexual behavior are important in the spread of STIs, the rate of sexual partner change, concurrent partnerships, the pattern of

sexual partner choice, and the numbers of sex acts within partnerships all influence the spread of the different STIs. Studies of patterns of behavior have shown how heterogeneous these are within the same population, and understanding the cause of the patterns of behavior is key to understanding the spread of the infections and how to intervene.

Advances in treatments and vaccines have changed the landscape of STI epidemiology, altering the relative importance of the different STIs. However, understanding how to optimize the impact of treatment and change risk behaviors is a subject requiring both empirical and theoretical studies. Mathematical models can predict the impact of interventions, but more work is required to demonstrate at a population level which interventions can have an impact on the incidence of infection and disease. Unfortunately, the few community randomized trials of HIV interventions have been logistically difficult and slow in generating results, and most have shown little impact.⁷⁸ Understanding the transmission dynamics of STIs shows that we cannot rely on declines in prevalence alone to indicate intervention successes, but if we can compare observed and predicted declines and use supporting behavior then it is possible to see where interventions are working at a population level.

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The Global Epidemiology on HIV and AIDS

Karen A. Stanecki and Hein Marais

INTRODUCTION

In 2005, 40.3 million people (36.7–45.3 million) worldwide were living with HIV (Fig. 4-1).¹ That year, an estimated 4.9 million people (4.3–6.6 million) became newly infected with HIV. This is more than in any 1 year before. AIDS killed 3.1 million people (2.8–3.6 million) in 2005. Since the first AIDS case was diagnosed in 1981, more than 25 million people have died of AIDS.

This chapter describes the global epidemic by region, highlighting the changing dynamics of HIV transmission and the diverse patterns of infection found worldwide. The epidemic remains extremely dynamic, growing, and changing character as the virus exploits new opportunities for transmission. Virtually no country in the world remains unaffected. The number of people living with HIV has been rising in every region with the steepest recent increases occurring in East Asia and in Eastern Europe and Central Asia.

The number of AIDS deaths have nearly doubled in East Asia between 2003 and 2005, while a million more people are living with HIV in South and South East Asia in 2005 compared to 2003. In Eastern Europe and Central Asia, where the epidemic of injecting drug use among millions of young people is fuelling HIV transmission, the number of people living with HIV is estimated to be 1.6 million in 2005—a 20-fold increase in less than 10 years.

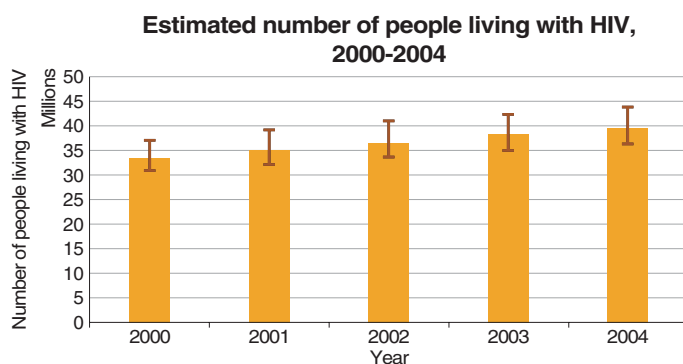


FIGURE 4-1. Estimated number of people living with HIV, 2000–2004.

Some industrialized countries that have let down their guard are seeing a rise in new infections, in part due to a dangerous myth fuelled by widespread access to antiretroviral medicines that AIDS has been defeated. In Asia, epidemics are evolving with the result that even countries that had mounted successful responses are now faced with having to shift gear to readdress emerging epidemics. In sub-Saharan Africa, the overall percentage of adults with HIV infection has remained stable in recent years, but the number of people living with HIV is still growing as populations expand.

The epidemic is not homogeneous within regions; some countries are more affected than others. Even at country level, most often there are wide variations in infection levels between different provinces, states, or districts, and between urban and rural areas. In reality, like the global epidemic, the national picture is made up of a series of epidemics with their own characteristics and dynamics.

SUB-SAHARAN AFRICA

Sub-Saharan Africa has just over 10% of the world’s population, but is home to more than 60% of all people living with HIV—some 25.8 million (23.8–28.9 million).¹ In 2005, an estimated 3.2 million (2.8–3.9 million) people in the region became newly infected, while 2.4 million (2.1–2.7 million) died of AIDS. The high HIV prevalence levels in several countries mean that even those that manage to reverse the epidemic’s course will have to contend with serious AIDS epidemics for many subsequent years.

The AIDS epidemic in this region is highly varied, both between and within subregions, making it inaccurate to speak of a single, “African” epidemic (Fig. 4-2). Southern Africa, the worst-affected part of the world, shows no sign yet of an overall, national decline. East Africa, though, boasts several examples of gradual, modest declines in median HIV prevalence among pregnant women in urban areas. Meanwhile, in West and Central Africa, infection levels are lower than elsewhere in the region and have stayed relatively stable for several years now.

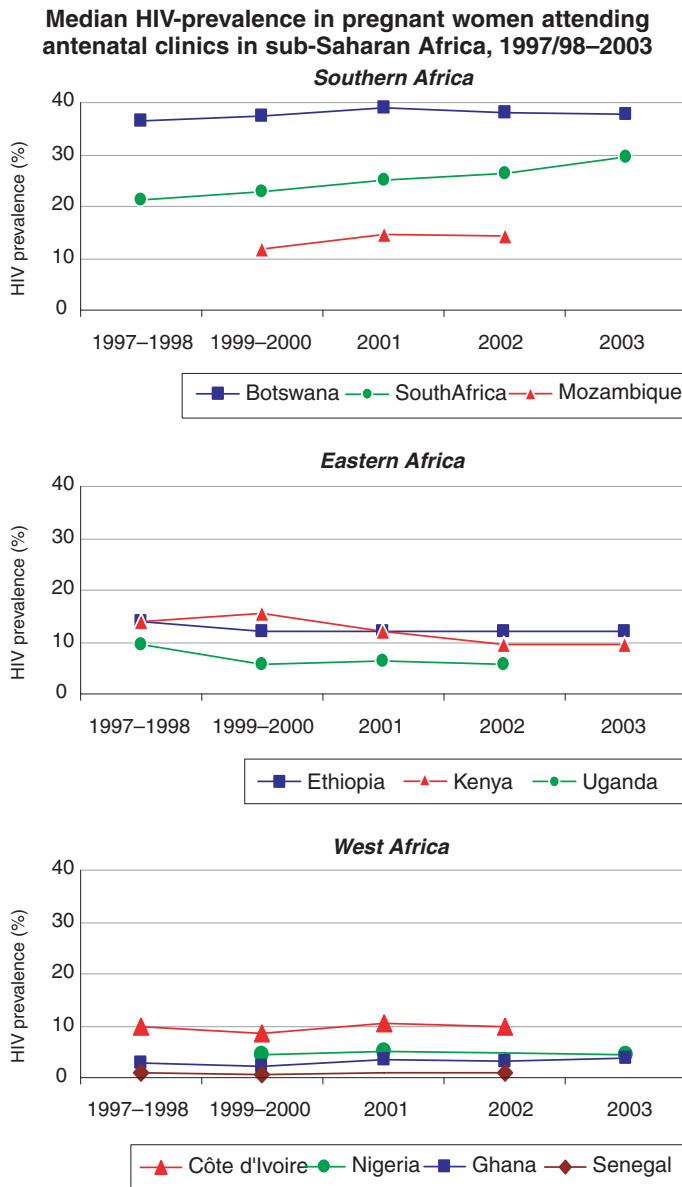


FIGURE 4-2. Median HIV-prevalence in pregnant women attending antenatal clinics in sub-Saharan Africa, 1997/98–2003. (Adapted from Asamoah-Odei E, Garcia-Calleja JM, Boerma T. HIV prevalence and trends in sub-Saharan Africa: No decline and large subregional differences. *Lancet* 2004; 364: 35–40. Data from consistently reporting antenatal clinics.)

Yet there are some striking consistencies, too. Firstly, adult HIV prevalence has been roughly stable in recent years in much of this region. This is not necessarily good news. Stabilization can disguise the worst phases of an epidemic—when roughly equally large numbers of people are being newly infected with HIV and are dying of AIDS. Secondly, throughout the region women are disproportionately affected by HIV, as Fig. 4-3 shows. On average, there are 13 women living with HIV for every 10 infected men and that gap continues to widen. The differences in infection levels between women and men are most evident among young people (aged 15–24 years). Recent population-based studies suggest that there are on average 36 young women living with HIV

HIV prevalence among 15–49-year-old men and women, in urban and rural areas, in selected sub-Saharan Africa countries, 2001–2003

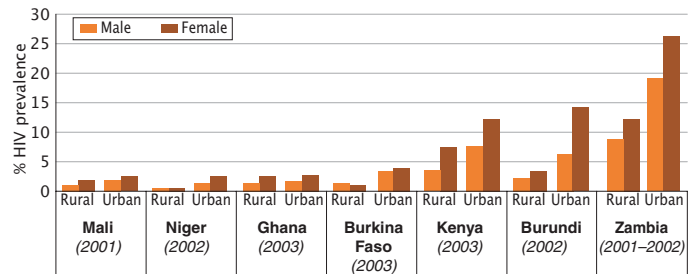


FIGURE 4-3. HIV prevalence among 15–49-year-old men and women, in urban and rural areas, in selected sub-Saharan African countries, 2001–2003. (Sources: Burkina Faso, Burkina Faso Enquête Démographique et de Santé 2003, Rapport Préliminaire; Burundi, Enquête Nationale de Séroprévalence de L'Infection par le VIH au Burundi, Bujumbura, Décembre 2002; Ghana, Ghana Demographic and Health Survey 2003, Preliminary Report; Kenya, Kenya Demographic and Health Survey 2003; Mali, Enquête Démographique et de Santé, Mali 2001; Niger, Enquête Nationale de Séroprévalence de L'Infection par le VIH dans la population générale âgée de 15 à 49 ans au Niger 2002; Zambia, Zambia Demographic and Health Survey 2001–2002.)

for every 10 young men in sub-Saharan Africa. In a study among women in Harare (Zimbabwe) and Durban and Soweto (South Africa), 66% reported having one lifetime partner, 79% had abstained from sex until at least their seventeenth birthday (roughly the average age of first sex in most countries in the world), and 79% said they used a condom. Yet, 40% of the young women were HIV-positive. Many women are being infected despite staying loyal to one partner.²

Delayed Pictures

Across sub-Saharan Africa, prevention and treatment efforts have grown manifold in the past 5 years in both scope and scale. HIV incidence data would sketch recent trends and offer clues to the possible impact of those efforts. However, there is no simple and reliable method to assess HIV incidence in sub-Saharan Africa. It is possible to estimate HIV prevalence levels, but these present a delayed picture of the epidemic since they reflect incidence patterns of several years previously. HIV *prevalence* describes the total number of people living with HIV, irrespective of when they were infected, while *incidence* refers to the number of people who became infected over a specific period, usually the previous year. The closest, though imperfect, proxy for HIV incidence would be HIV prevalence in 15–24-year-old pregnant women, most of whom would have been infected relatively recently. This indicator shows infection levels declining in that age group of women in some urban areas of East Africa. In southern Africa, though, it reveals little sign of change with the exception of South Africa, where infection levels have continued to increase in women of that age group.

An estimated 11.7 million (10.8–12.9 million) people are living with HIV in the nine hardest-hit southern African countries. Together those countries have 2% of the world's

population, yet they are home to almost 30% of the global number of people living with HIV.

South Africa continues to have the highest number of people living with HIV in the world. An estimated 5.3 million (4.5–6.2 million) people were living with HIV end-2003 in South Africa, 2.9 million (2.5–3.3 million) of them being women. Unfortunately, there is no sign yet of a decline in its epidemic. Prevalence levels among pregnant women aged 15–24 years, a possible indicator of recent trends in HIV incidence, have continued to rise, reaching 25.0% in 2004. Although levels of HIV prevalence among 15–19-year-olds has stabilized over the past few years, prevalence among 20–24-year old pregnant women continues to increase (Fig. 4-4). Overall HIV prevalence among pregnant women was 29.5% in 2004, compared with 26.5% in 2002 and 25% the year before.³

Very high HIV prevalence, often exceeding 30% among pregnant women, is still being recorded in Botswana, Lesotho, Namibia, and Swaziland. There, too, comparisons of prevalence levels at selected antenatal clinics have shown no evidence of a decline. Elsewhere, HIV infections in pregnant women appear to be stabilizing at lower levels—around 18% in Malawi (2003), 16% in Zambia (2003), and 25% in Zimbabwe (2003)—but there is little hint of an impending decline. Angola is an exception in this subregion. Available data suggest that nearly two generations probably slowed the spread of HIV there. Median HIV prevalence of approximately 3% has been measured at antenatal clinics in the capital, Luanda. As normal life resumes for millions of Angolans, there is every reason to fear much more widespread and rapid HIV transmission in their country.

In the Front Line

Effective prevention among young people is essential. Throughout southern Africa, HIV prevalence sharply increases once people reach their twenties. A recent study among young South Africans reports comparatively low HIV prevalence among 15–19-year-olds, at 4.8%.⁴ It is in the next age group, among 20–24-year-olds, that HIV prevalence soars, reaching 16.5%, with HIV infections massively concentrated among women. Almost 25% of the women surveyed were HIV-positive, compared to just under 8% of the men. Young women were found to be disproportionately at risk of HIV infection. Sexual aggression is common, with more than one-quarter (28%) of the women saying their first sexual experience was unwanted, and one in ten (10%) saying they had been forced to have sex. Almost half (49%) the young women who had had sex said they had been pregnant at some point, suggesting that condom use was not the norm.

A downward trend in HIV infection levels is most firmly established in Uganda, where national prevalence fell steeply in the mid- and late-1990s and has stayed at 5–6% since then. Kenya is on a similar path. There, median HIV prevalence

HIV prevalence among pregnant women at antenatal clinics in South Africa, by age group, 1991–2004

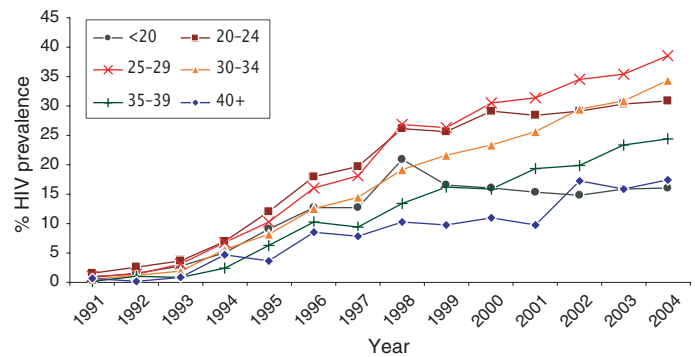


FIGURE 4-4. HIV prevalence among pregnant women at antenatal clinics in South Africa, by age group, 1991–2004. (Source: Department of Health, South Africa. *National HIV and Syphilis Antenatal Sero-Prevalence Survey in South Africa 2004.*)

among pregnant women decreased from 13.6% (12.2–27.1%) in 1997–1998 to 9.4% (6.6–14.3%) in 2002 and then stayed roughly the same in 2003. The declining HIV trend among pregnant women in Ethiopia’s capital, Addis Ababa, appears to be continuing, while information from Burundi also suggests a drop in HIV prevalence (though this is based on very limited data).⁵ It is much too early, though, to regard the declines as irrevocable reversals in these countries’ epidemics. Furthermore, the need for treatment, care and support will continue to increase for years to come.

Making a Difference

Although Tanzania shows no signs yet of nationwide HIV prevalence decline, some localities do offer proof that appropriate efforts prevention can make a difference. Mbeya region has been the focus of *intense* prevention work over the past 13 years. Condom use rose and treatment for sexually transmitted infections increased between 1994 and 2000, while a significant delay in age at first sex was also noted. HIV prevalence among 15–24-year-old women fell from 20.5% to 14.6% over the same period. In the urban parts of neighboring Rukwa region, by contrast, only sporadic prevention efforts were mounted. There, HIV prevalence in the same age group rose from 22.5% in 1994 to 30.2% in 1999.⁶ The specific kinds of interventions mounted in Mbeya probably helped drive down HIV prevalence there, whereas those in Rukwa did not inhibit the spread of HIV. Other research in Tanzania has revealed a marked lack of behavior change where *low-intensity* HIV prevention programs have been introduced. A standard, district HIV-prevention program operating since the mid-1990s in Mwanza, for example, appears to have made little headway against the epidemic. HIV prevalence rose gradually from 5.9% in 1994–1995 to 6.6% in 1996–1997 and 8.1% in 1999–2000. There was a small increase in condom use and in knowledge about the epidemic, but sexual risk behavior was unchanged and most people felt that they were not at risk of HIV infection.⁷ Low-cost, standard district and community-level prevention programs are not sufficient to change the course of the epidemic.

The epidemics in West Africa vary in scale and intensity, but appear to have stabilized in most countries. Median HIV prevalence measured among women in 112 antenatal clinics in the subregion remained at an average 3–4% between 1997 and 2002.⁵ Overall, HIV prevalence is lowest in the Sahel countries and highest in Burkina Faso, Côte d'Ivoire, and Nigeria—the latter having the third largest number of people living with HIV in the world (after South Africa and India). Nigeria's 2003 HIV sentinel survey put national HIV prevalence at 5%, a rise from 1.8% found in 1991 but roughly level with the 5.4% recorded in 1999. The apparent stabilization at national level hides significant regional differences in this vast and diverse country, with prevalence ranging from a low of 2.3% in the South West to a high of 7% in the North Central parts. This means that several, more or less distinct epidemics are underway in Nigeria.⁸

Côte d'Ivoire has continued to report the highest level of HIV prevalence in West Africa, although prevalence in the capital Abidjan in 2002 was the lowest it had been in 5 years, at 6.4% compared with 13% in 1999.⁵ National adult HIV prevalence in Togo has stayed roughly steady at around 4%⁹ while in neighboring Ghana and Benin prevalence is in the 2% to 4% range with little change noted over time.¹⁰ National HIV prevalence in Senegal, long-feted as an HIV success story, remains below 1% but slowly rising HIV levels have been detected among women who sell sex. In the capital, Dakar, prevalence stood at 14% in 2002, while among sex workers in other areas (such as Kaolack and Ziguinchor) it had risen to over 20% by the same year.¹¹

Serious epidemics are underway in Central Africa, with Cameroon, Central African Republic, and Gabon worst affected. Here, too, HIV prevalence among pregnant women appears to have stabilized but at high levels (of roughly 10%). In Congo, meanwhile, national adult prevalence has edged below 5%. Two recent rounds of HIV testing among pregnant women in the Democratic Republic of Congo showed prevalence ranging between 4.1% and 4.9%, but HIV levels varied considerably from as low as 1.8% in rural Mikalayi and roughly 3% in urban Bukavu and Bunia, to 6.3% and 7%, respectively, in the cities of Kisangani and Lubumbashi.⁵

LATIN AMERICA AND THE CARIBBEAN

More than 2.1 million (1.6–2.9 million) people are living with HIV in Latin America and the Caribbean, including 230,000 (150,000–440,000) adults and children who acquired the virus in 2005. An estimated 90,000 (68,000–130,000) people died of AIDS in the same year.¹

CARIBBEAN

With average adult HIV prevalence of 1.6% (1.1–2.7%) the Caribbean is the second worst affected region in the world.¹

As the epidemics in this region evolve, more women are being affected, and the number of new HIV infections among them now outstrips that among men. AIDS claimed an estimated 24,000 (16,000–40,000) lives in 2005 and has become the leading cause of death in the Caribbean among adults aged 15–44 years. On current trends, by 2010 life expectancy in several countries will be significantly lower than it would have been had AIDS not struck (Fig. 4-5).¹²

National adult HIV prevalence exceeds 2% in the Bahamas, Belize, Guyana, and Trinidad and Tobago, but is highest in Haiti which continues to have the largest number of people living with HIV in the Caribbean—some 280,000 at the end of 2003.¹³ The most recent data show HIV prevalence among pregnant women varying between 1.8% and almost 7% in different parts of Haiti. Although general AIDS knowledge is widespread, misconceptions about the virus continue to circulate, particularly among women. On the other half of Hispaniola Island, HIV prevalence among 15–24-year-old pregnant women in the Dominican Republic's capital, Santo Domingo, fell from around 3% in 1995 to below 1% in 2003. However, the same trend is not evident in the rest of the country, and HIV prevalence among pregnant women nationally was still higher than 2%.¹⁴

At an estimated 2.5% at the end of 2003, national adult HIV prevalence in Guyana was the second-highest in the region and there has been a steep rise in the numbers of HIV cases reported since mid-1990s. Jamaica, meanwhile, has the second-highest annual number of AIDS cases and deaths in the region and there is no evidence yet that its HIV epidemic is abating. HIV prevalence among pregnant women stood at 1.4% nationally in 2002 but was considerably higher in some parishes.

Life expectancy at birth with and without AIDS for selected Caribbean countries: 2010

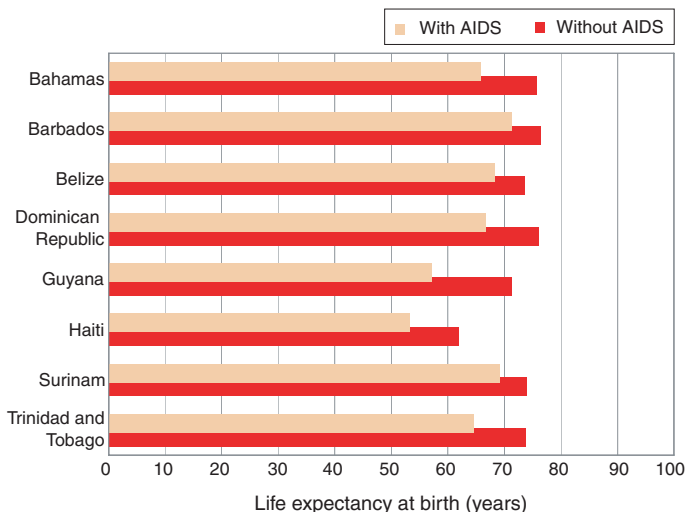


FIGURE 4-5. Life expectancy at birth with and without AIDS for selected Caribbean countries: 2010. (Source: U.S. Census Bureau, International Programs Center, International Data Base and unpublished tables.)

On the positive side, both the Bahamas and Barbados show signs that their boosted prevention efforts since the late 1990s could be forcing HIV-infection levels lower. In the Bahamas, HIV prevalence among pregnant women fell from 4.8% in 1993 and 3.6% in 1996 to 3% in the latest round of HIV surveillance in 2002 (Fig. 4-6). HIV levels among pregnant women in Barbados, which has a smaller epidemic, fell from 0.7% to 0.3% in 1999–2003. Mother-to-child transmission of HIV has been reduced since the expansion of voluntary counseling and testing services, and the provision of antiretroviral prevention regimens. In addition, the introduction in 2001 of antiretroviral treatment for people living with HIV halved the annual number of AIDS deaths between 1998 and 2003 and brought about a 42% drop in hospital admissions for treatment of opportunistic infections in the same period.

Cuba has been an exception in the region. Despite an increase in newly reported HIV cases since the late 1990s, HIV prevalence remains extremely low, while universal and free access to antiretroviral therapy has kept the number of AIDS cases and deaths to a minimum.

■ LATIN AMERICA

HIV prevalence in Latin American countries is lower than in the Caribbean and surpasses 1% in just two countries: Guatemala and Honduras. However, lower prevalence in other countries can hide serious, localized epidemics, for example, in Brazil, which has more than one-third of the people living with HIV in Latin America.¹³

Although national HIV prevalence among pregnant women in Brazil has stayed stable at below 1% for the past 5 years, higher levels have been found in some areas, for example, 3–6% among pregnant women in Rio Grande do Sul state who did not regularly attend antenatal clinics. Injecting drug use still features prominently in Brazil's epidemic, with drug injectors accounting for at least half of the AIDS cases in some regions. Harm reduction programs, though, are making a difference in some cities notably in Salvador where prevalence fell from 50% in 1996 to 7% in 2001. In the south of the country, though, HIV infection levels among injecting drug users remain high, indicating a need for more effective prevention programs.¹⁵

Several countries illustrate the epidemic's ability to "bridge" between apparently disparate sections of society. In the Andean area, HIV is spreading increasingly to the wives or girlfriends of sex worker clients and men who have sex with men. In Venezuela, which has one of the largest epidemics in the region,¹⁶ HIV is spreading mainly through unsafe sex, much of it between men, a significant proportion of whom also have sex with women. In Uruguay, where most registered HIV cases have been in or around the capital, Montevideo, there has been an alarming increase in the number of people living with HIV who are either injecting drug users or their sex partners.¹⁷ Argentina's epidemic is

Reported AIDS and HIV cases, Bahamas, 1985–2003

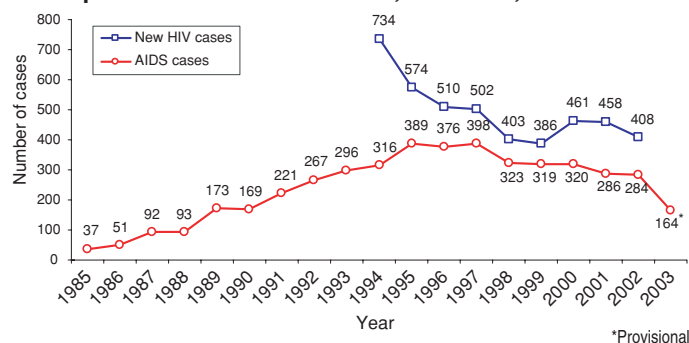


FIGURE 4-6. Reported AIDS and HIV cases, Bahamas, 1985–2003. (Sources: Caribbean Epidemiology Centre (CAREC)/PAHO/WHO. *Status and Trends Analysis of the Caribbean HIV/AIDS Epidemic 1982-2002*. Available at: <http://www.carec.org>)

powered mainly by unsafe drug injecting and is concentrated largely in the urban areas of Buenos Aires, Cordoba, and Santa Fe provinces. Sexual transmission of HIV, however, has become more prominent, with most new infections occurring among the poorest and least-educated urban inhabitants.¹⁸

In Central America, where the epidemic is also concentrated in urban areas, the numbers of HIV infections have been rising in several countries (including El Salvador, Nicaragua, and Panama) since the late 1990s. HIV prevalence is highest in Guatemala (1.1% at the end of 2003) and Honduras (1.8%).¹³ AIDS-related diseases are now estimated to be the second-leading cause of death in Honduras.¹⁹ Overall in Central America, HIV infection levels are highest among men who have sex with men and among female sex workers. To the north in Mexico, national prevalence in the adult population has remained well under 1% but shows some regional variance.²⁰

Turning a Blind Eye

Sex between men is a significant factor in most of the epidemics in Latin America and the Caribbean. More than half of Costa Rica's AIDS cases in 1998–2002 were among men who have sex with men, a significant percentage of whom also have sex with women. Studies in several countries have found high HIV levels in groups of men who have sex with men, ranging from 9% to 13% in Guatemala, Honduras, Nicaragua, and Panama to almost 18% in El Salvador. Large proportions of the men in those studies reported also having female sex partners. Therefore, bisexuality constitutes a significant bridge for HIV transmission into the wider population. Yet, widespread homophobia is providing an ideal climate for the spread of HIV, by driving men who have sex with men further away from the information, services, and security that can protect them against HIV. Moreover, particularly in Central America, prevention spending does not yet reflect the prominence of sex between men in countries' epidemics.

On the treatment front, Brazil continues to set an enviable example by offering all people living with HIV access to anti-retroviral drugs via its national health system when they need it. As a result, the survival time of AIDS patients has increased dramatically. AIDS cases and AIDS mortality have declined in several other countries including Argentina, Costa Rica, and Panama, after expansion of antiretroviral treatment access.

ASIA

The populations of many Asian countries are so large that even low national HIV prevalence means huge numbers of people are living with HIV. An estimated 8.3 million adults and children (5.4–12.0 million) in Asia were living with HIV at the end of 2005. Approximately 1.1 million (600,000–2.5 million) people acquired HIV in 2005, while 520,000 (330,000–780,000) people died of AIDS in the same year.¹

The nature, pace, and severity of the epidemics differ across the region. While some countries (notably Thailand and parts of India) were hit early, others (such as Indonesia and Nepal) are only now starting to experience rapidly expanding epidemics, and a few (including Bangladesh and Pakistan) are still seeing extremely low levels of HIV prevalence, even among people at high risk of exposure to HIV, and have golden opportunities to avoid serious outbreaks.²¹

In vast and populous India, serious epidemics are underway in several states, and latest estimates show about 5.1 million (2.5–8.5 million) people were living with HIV at the end of 2003.¹³ In each of Andhra Pradesh, Karnataka, Maharashtra, and Nagaland, HIV prevalence has crossed the 1% mark among pregnant women, while infection levels of 50% have been found among sex workers in Tamil Nadu. Manipur's maturing epidemic has already spread from drug injectors to the wider population. At antenatal clinics in the Manipur cities of Imphal and Churachand, HIV prevalence has risen from below 1% to over 5%; many of the women who test positive appear to be the sex partners of male drug injectors. Indeed, injecting drug use seems to be playing a bigger role in India's epidemics than previously thought—and not just in the north. In the southern city of Chennai, for example, 64% of drug injectors were found to be infected with HIV in 2003. The epidemic has ample scope for further growth if prevention efforts do not prevent onward transmission of HIV from drug injectors and the clients of sex workers to their other sex partners.²¹

The most ominous development in this region has been the swift emergence of an AIDS epidemic in the world's most populous country, China. Although moving at a varied pace, HIV has spread to all of China's 31 provinces, autonomous regions, and municipalities.²²

Much of the current spread of HIV in China is attributable to injecting drug use and paid sex (Fig. 4-7). HIV prevalence among drug injectors was measured at between 18% and

56% in six cities in the southern provinces of Guangdong and Guangxi in 2002, while in Yunnan province some 21% of injectors tested positive for HIV in 2003. Sexual transmission of HIV from injecting drug users to their sex partners looks certain to feature more prominently in China's fast-evolving epidemic. Harm-reduction programs can make a difference, as Sichuan province shows. There, reported reuse of nonsterile needles at last injection fell by almost half in 2002–2003, after the introduction of such programs.

Once HIV becomes well-established in commercial sex circuits, onward spread of the virus could be quite rapid unless current behavior trends alter. In 2003, almost one-quarter of surveyed sex workers in Guangxi said they never used condoms and about one-half used them only occasionally.

Women At Risk

Men who have unprotected sex with HIV-infected sex workers are at risk both of contracting HIV themselves and of passing it on to their other sex partners (including other sex workers). In a study in the southern Chinese city of Guangzhou, 72% of women with sexually transmitted infections said they had only had sex with their husband or regular partner in the previous 6 months—a clear sign that they were put at risk by their partners' behavior, not their own. Expressed in such ways are deeper social inequalities, not least the imbalances in men and women's social power, and the discrimination women face in earning and career opportunities in most countries of Asia (and, indeed, the world). Prevention efforts that neglect these wider dynamics are unlikely to achieve enduring, if any, success.

Recent steep rises in HIV infection among drug injectors have been followed by a rise in HIV among sex workers in parts of China, Indonesia, and Vietnam

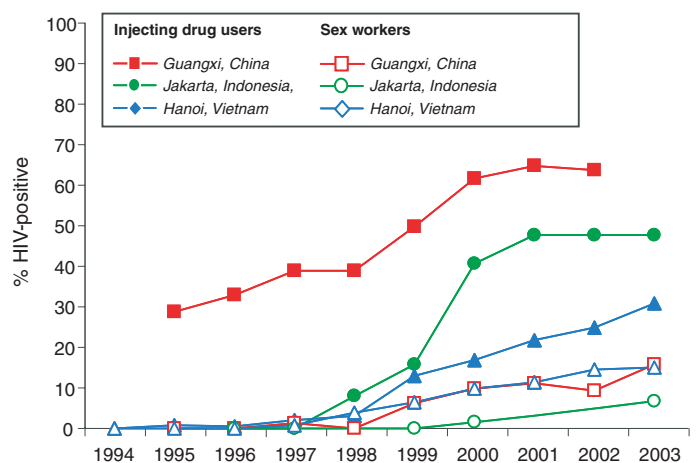


FIGURE 4-7. Recent steep rises in HIV infection among drug injectors have been followed by a rise in HIV among sex workers in parts of China, Indonesia, and Vietnam. (Sources: Lao People's Democratic Republic National Committee for the Control of AIDS Bureau 2001; Philippines Department of Health 2002 and national surveillance reports; Bangladesh National AIDS/STD program 2003; Pisani and Dili STI survey team 2004a.)

China can still shape the course of its epidemic, but it will have to act swiftly and with great resolve. Recent efforts to boost public knowledge about HIV appear to be yielding results, but there remains much room for improvement. Two in five Chinese men and women could not name a single way to protect themselves against infection, according to a 2003 survey, for example. In Sichuan province, more than one-third of sex workers (and a similar proportion of their clients) did not know that condoms offer good protection against HIV.

HIV now appears to be spreading freely in some of Vietnam's cities among groups that are at high risk of exposure to HIV. Widespread injecting drug use by sex workers makes Vietnam's epidemic particularly explosive (Fig. 4-7). In Ho Chi Minh City, 38% of almost 1000 surveyed sex workers injected drugs and almost half of those injecting sex workers were infected with HIV (compared with 8% of those who didn't use any drugs).

Wider epidemics are being "kick-started" in Indonesia and Nepal, where the sudden rises in HIV infection among drug injectors are now being followed by subsequent rises in infection among people who do not inject drugs but who have sexual risk behaviors. One in two injecting drug users in Indonesia's capital, Jakarta, now test positive for HIV, while in far-flung cities such as Pontianak (on the island of Borneo) more than 70% of drug injectors who request HIV tests are discovering that they are HIV-positive. Conditions favor HIV spread through sex work, where condom use ranges from irregular to rare.²¹

On the Move

Unsafe injecting drug use is the driving force of Nepal's epidemic, which also highlights the potential links between HIV infection and mobility. Injecting drug users from cities with low prevalence, but who had injected drugs elsewhere, have been found to be two to four times more likely to have acquired HIV than those who had remained in their home cities. Half of the sex workers surveyed in central Nepal and who said they had worked in Mumbai (India) were HIV-infected, compared with 1.2% of those who had never been to India.²¹

In Myanmar's older epidemic, HIV has already filtered from people with the highest-risk behaviors (such as nonsterile drug injection and unprotected commercial sex) to their regular sex partners. Between 45% and 80% of drug injectors have tested positive for HIV infection in sentinel surveillance each year between 1992 and 2003, while prevalence among sex workers leapt from around 5% to 31% over the same period. By 2003, HIV prevalence among pregnant women was above 2% at almost half the sentinel sites and exceeded 7% at one of them.²¹

Such trends can be avoided. Thailand continues to reap the benefits of the prevention effort it focused on sex work in the 1990s, with national adult HIV prevalence still edging lower. However, its epidemic is changing. It is estimated that as many as half of annual, new HIV infections have been occurring among cohabiting couples, as more women are infected by partners who are (or were) drug injectors or clients of sex workers. As a consequence, HIV infection levels among pregnant women are high in parts of the country, including the South (where they exceeded 2% in eight provinces in 2002). In addition, about one-fifth of new infections is occurring through unsafe injecting drug use. In the north, 30% of drug injectors are infected with HIV, while median HIV prevalence as high as 51% has been found in other parts of the country. Yet, scant prevention resources are deployed on that front. A renewed and pragmatic prevention effort is called for.²³

In Cambodia, large-scale prevention programs have brought reward, reducing sexual risk behavior and pushing HIV levels lower (Fig. 4-8). Fewer men now visit sex workers and more use condoms in commercial sex. The combined effect has been a steep drop in sexually transmitted infections and a steady decline in HIV prevalence.

Some countries still have a rare opportunity to prevent a significant epidemic from taking hold at all if they can provide prevention services to people most at risk of HIV infection. The Philippines, for example, has begun to take up that challenge. By following suit, Malaysia (where HIV infections are concentrated mainly among drug injectors and, possibly, sex workers) could avoid possibly serious HIV outbreaks.

HIV incidence rate among different groups, Cambodia, 1999–2002

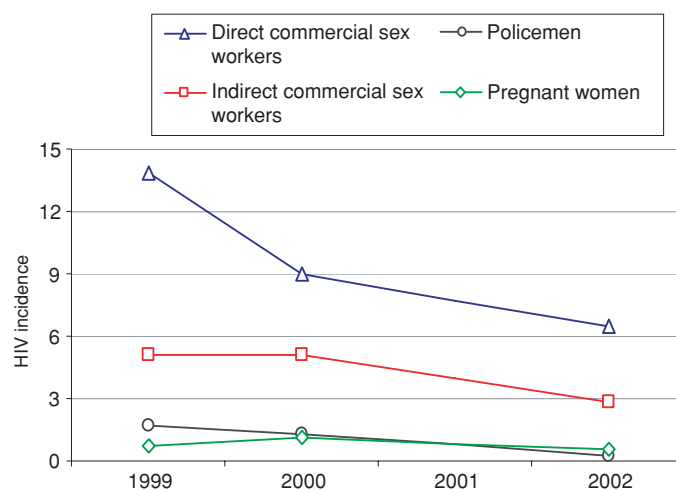


FIGURE 4-8. HIV incidence rate among different groups, Cambodia, 1999–2002. (Source: V. Saphon, et al. XV International AIDS Conference, 11–16 July 2004. Abstract No. ThOrC1424.)

Reaching Across Borders

Because AIDS epidemics crisscross national boundaries, joint efforts like the border area needle exchange program run by China and Vietnam since 2002 make sense. The program grew from the realization that the epidemics among injectors in China's Guangxi province and Vietnam's Quang Ninh and Langson provinces were closely linked. Outreach workers collect used syringes from drug injectors for safe disposal and provide them with vouchers that can be used to obtain new needles from participating pharmacies. The program is based on a successful trial that showed a drop in the use of nonsterile injecting equipment in the previous month from 61% to 30% among all injectors in Guangxi.

As the epidemics grow and mature in this region, treatment, care, and support have to move higher up the agenda. A few countries are taking up that challenge, with Thailand possibly on track to reach its target of providing 50,000 people with anti-retroviral treatment, while others have committed themselves to drastically expand treatment access, including India (which has pledged free treatment in several states) and Indonesia.

OCEANIA

In the Pacific, Papua New Guinea is home to a potentially explosive epidemic. There, HIV prevalence is higher than anywhere else in this region, with an estimated 0.6% (0.3–1.0%) of adults, roughly 16,000 (7800–28,000) of the 2.5 million adults in the country, living with HIV at the end of 2003.¹³ The annual number of new HIV infections detected in Papua New Guinea has been increasing progressively since the mid-1990s, exceeding 1000 in 2003, as Fig. 4-9 shows.²⁴ In the same year, 1.4% of pregnant women at antenatal clinics in the capital Port Moresby tested HIV-positive, while in Lae, in the central highlands, 2.5% of pregnant women were HIV-infected.

Many questions remain unanswered about Papua New Guinea's epidemic, but available information shows an epidemic that is spreading primarily through heterosexual intercourse, and against a backdrop of widespread violence against women. Urgent action is needed to improve HIV prevention and AIDS care services if Papua New Guinea is to avert a rampant epidemic.

Very low HIV-infection levels are being recorded in other parts of the Pacific, but the data are extremely limited. On remote islands, seafarers and their partners appear to be most at risk; on Kiribati, for example, 9% of seafarers included in a recent study had chlamydia and 3% syphilis, although HIV prevalence was still low (at 0.3%).²⁵ The high levels of other sexually transmitted infections detected on some other islands, including Vanuatu and Samoa, point to widespread unprotected sex that could enable rapid HIV spread once the virus acquires a presence in these tiny island nations.

Reported HIV infections by sex Papua New Guinea, 1987–2003

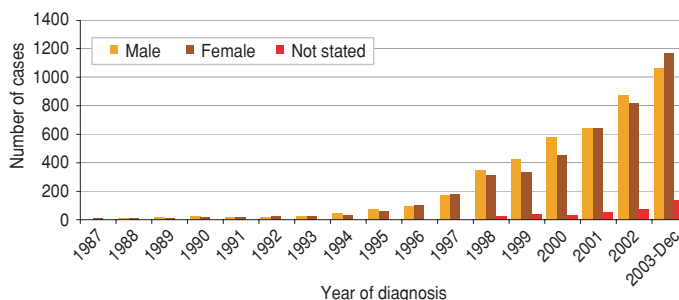


FIGURE 4-9. Reported HIV infections by sex, Papua New Guinea, 1987–2003. (Source: National AIDS Council and Department of Health Papua New Guinea. *HIV/AIDS Quarterly Report*. Boroko, Papua New Guinea, 2003.)

Prevention strategies that reduce and treat sexually transmitted infections and that quickly bolster AIDS knowledge among the population at-large are urgently needed.

EASTERN EUROPE AND CENTRAL ASIA

Diverse HIV epidemics are underway in Eastern Europe and Central Asia, where the number of people living with HIV has increased more than 20-fold in 10 years reaching an estimated 1.6 million (990,000–2.3 million) at the end of 2005.¹ The vast majority of them are young; more than 80% of the reported infections are being found among people below the age of 30 years (by comparison, in Western Europe some 30% of people with HIV fall in that age group). Some 270,000 (140,000–610,000) people were newly infected with HIV in 2005, while an estimated 62,000 (39,000–91,000) died of AIDS in the same year.

Research highlights a volatile mix of behaviors that could keep the region's epidemics flaring indefinitely. But most of the epidemics are still in their early stages, which means that timely, effective interventions can halt and reverse them. Arduous social and economic change serves as the context in which extraordinarily large number of young people are injecting drugs in this region. In countries with emerging epidemics, harm reduction programs among young people can prevent larger, more extensive HIV epidemics of the kind now taking hold in Russia and Ukraine. At the same time, sexual transmission of HIV is featuring increasingly in the most seriously affected countries—an indication that the epidemic has established itself in the wider population.

The most serious and firmly established epidemic is in Ukraine, which is experiencing a new surge of infections, while the Russian Federation is home to the largest epidemic in the entire region (indeed in all of Europe) and accounts for some 70% of all HIV infections officially registered in Eastern Europe and Central Asia. An estimated 860,000 (420,000–1.4 million) people were living with HIV in Russia at the end of 2003,¹³ fully 80% of them aged 15–29 years and more than one-third of them women. Although present

across the entire country, HIV is unevenly distributed in Russia, with about 60% of all HIV infections to date having been reported in just 10 of its 89 regions.²⁶ Much scope, therefore, exists for further expansion of Russia's epidemic alongside great opportunities to prevent such an outcome.

At the heart of Russia's epidemic are the extraordinarily large number of young people who inject drugs, many of who are sexually active and risk passing HIV to their partners. Between 1.5 and 3 million Russians are believed to inject drugs (1–2% of the entire population), and an estimated 30–40% of injecting drug users use nonsterile needles or syringes that massively boost the chances of HIV transmission. HIV prevalence among injecting drug users is very high in many parts of Russia. Recent studies have reported an estimated 65% of street drug injectors in Irkutsk were HIV-positive (90% of them still in their teens); in Tver, 55% were infected, in Ekaterinburg the figure was 34%, and in Samara 29%.²⁷

Sex and Drugs and HIV

The exchange of sex for drugs, or the use of sex to support drug habits acts functions as an ideal bridge for wider HIV spread. When commercial sex and injecting drug use connect, and when effective HIV-prevention services are absent, the effects can be devastating. In a recent St. Petersburg (Russian Federation) study, 81% of surveyed sex workers said they injected drugs daily, and 48% of the women were HIV-positive; among those aged 20–24 years, 64% were infected.²⁸

While some drug injectors buy or sell sex, many also have regular sex partners. According to studies in several Russian cities, upward of 70% drug injectors are sexually active. With safer sex not yet the norm, the epidemic's pattern in Russia has been shifting and the proportion of new, reported HIV infections acquired during heterosexual intercourse has grown dramatically from 5.3% in 2001 to just over 20% in 2003. This means that more women are being infected: the overall proportion of women among people living with the virus has increased to 38% in 2003, compared with 24% in 2001. As a result, more children are being born to HIV-positive mothers, making prevention of mother-to-child transmission an added priority (Fig. 4-10).

A similar trend is underway in Ukraine, where more than 40% of people with HIV infection are women, most of them in their peak reproductive years. There, however, efforts to expand programs to prevent mother-to-child transmission appear to be bearing fruit, with the proportion of HIV-infected babies born to infected mothers shrinking from 27% in 2001 to 12% in 2003.²⁹

Ukraine's epidemic continues to expand. Newly registered HIV infections increased by 7% in 2000, 13% in 2001, and 25% in 2002. Just 10 years ago, there were only 183 officially registered HIV cases in Ukraine; by mid-2004 more than 68,000 cases of HIV infection had been officially registered. These figures grossly understate the actual scale of the epi-

demical since they only measure infections among people who come in direct contact with the authorities and testing facilities.

The deadly combination of HIV and tuberculosis is a serious concern in Ukraine, where 10–15% of TB cases are estimated to be multidrug resistant. Tuberculosis has become the leading cause of death among people living with HIV. This underlines the need for a significant scaling up of access to antiretroviral treatment in Ukraine. Currently, just over 500 of the estimated 45,000 people who need antiretroviral treatment in Ukraine are receiving it, despite the fact that treatment access for all is guaranteed by Ukrainian law.

Hidden Epidemics?

There is a strong chance that HIV could be spreading largely undetected among men who have sex with men in many Eastern European and Central Asian countries. Studies are rare but networks of men who have sex with men have been documented in several countries and scattered surveys of sexual behavior (for example, in the Russian Federation and Ukraine) have pointed to high levels of unprotected sex. Men who have sex with men, like injecting drug users and sex workers, endure routine stigma and discrimination, both at the hands of officialdom and society at large. Reliable sentinel surveillance and appropriate prevention services for men who have sex with men could help limit the epidemic's spread through and beyond their ranks.³⁰

In the Baltic states, HIV transmission is occurring at a brisk rate, even if the overall numbers of infections remain low. The total number of HIV diagnoses in Latvia has risen at least fivefold since 1999, reaching more than 2500 in 2003. Just 4 years ago, Estonia reported 12 new HIV cases; in 2003, 840 people were newly diagnosed with the virus. In Lithuania, the 72 new HIV cases detected in 2001 increased more than fivefold the following year. In Belarus (where more than 5000 people had been officially diagnosed with HIV by

Newly registered HIV cases and HIV-seropositive children born to HIV-infected mothers, Ukraine, 1987–2003

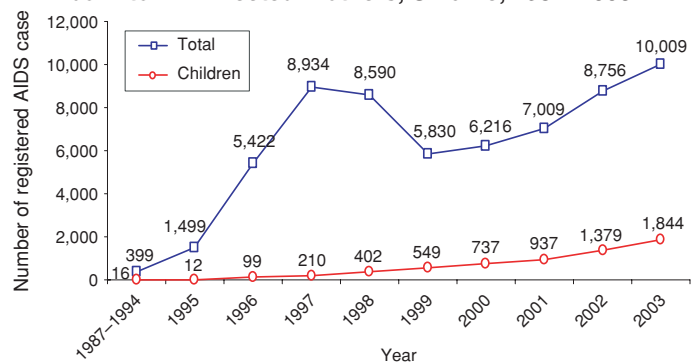


FIGURE 4-10. Newly registered HIV cases and HIV-seropositive children born to HIV-infected mothers, Ukraine, 1987–2003. (Source: Ukrainian Centre for HIV Prevention.)

mid-2003) and Moldova (where the figure stood at just under 1800), most infections are occurring among young drug injectors and their sexual partners.)⁹

HIV prevalence remains very low (less than 0.3%) in most of the Central Asian and Caucasian republics, but behavior patterns favor significant spread of the virus and the overall number of registered infections continues to rise formidably in Uzbekistan, which now hosts one of the youngest epidemics in the world (Fig. 4-11). Approximately 90% of all reported infections in Uzbekistan were diagnosed between 2001 and mid-2003, by which point more than 2500 HIV cases had already been reported. A total of 3600 HIV cases had been reported in Kazakhstan by mid-2003. In the Caucasus, significant HIV outbreaks are underway in Azerbaijan, where one in four street drug injectors in the capital, Baku, has been found to be HIV-positive, as were 11% of street-based sex workers).²⁹

In parts of south-eastern Europe (notably countries emerging from conflict and difficult transitions) drug injecting and sexual risk behavior appear to be on the increase, and rising numbers of HIV infections could follow. Relatively “young” epidemics such as these can be halted with prevention strategies that concentrate on reaching those who are currently most at risk of exposure to HIV.

There are many opportunities to improve the AIDS response. Surveys show that just 10% of sex workers, less than 8% of injecting drug users, and only 4% of men who have sex with men are being reached with prevention services. Just over 11% of people who need antiretroviral drugs currently are being treated, and for HIV-positive drug injectors, treatment access is still rare to nonexistent in the worst-affected countries. Although Russian law assures free, universal access to antiretroviral drugs for all citizens, current estimates suggest that fewer than 3000 people living with HIV are receiving antiretroviral medication, less than 5% of them injecting drug users in remission. In Ukraine, an estimated 13% of people in need of antiretroviral therapy are getting it, and treatment for drug injectors is not yet supported by substitution therapy.

MIDDLE EAST AND NORTH AFRICA

Latest estimates confirm that the Middle East and North Africa have not eluded the AIDS epidemic’s advance. Approximately 58,000 (25,000–145,000) people became infected with HIV in 2005, bringing to 510,000 (230,000–1.4 million) the total number of people living with the virus in this region.¹ AIDS killed an estimated 67,000 (35,000–200,000) people in 2005. With HIV being transmitted along diverse paths in this region, including paid sex, sex between men, and injecting drug use, there is considerable scope for further expansion of the epidemic.

Newly registered HIV cases in Uzbekistan, 1996–2003

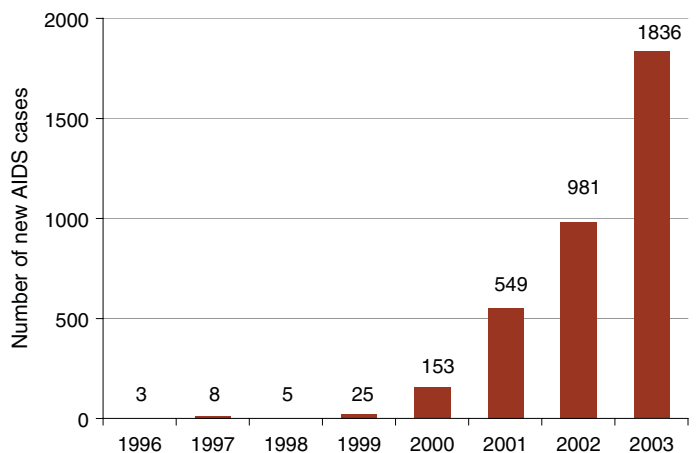


FIGURE 4-11. Newly registered HIV cases in Uzbekistan, 1996–2003. (Source: Republican AIDS Centre, 2003.)

Sudan is the region’s worst-affected country, with its epidemic concentrated largely in the south. The gradual cessation of conflict in parts of the country could accelerate HIV spread, as people resume their usual patterns of travel and trade.

In most other countries of the region, the epidemics are still in their early stages, which increase the chances that effective prevention efforts can limit the spread of HIV. However, inadequate HIV surveillance data in several countries could mean that significant HIV outbreaks in some populations (including men who have sex with men and injecting drug users) are being missed. Morocco, where the number of annual new HIV diagnoses in 2003 was almost 3 times higher than in 2001, could be a case in point.¹³

Libya’s epidemic has also been growing markedly, with almost 90% of its officially reported 5160 HIV infections (at end-2002) having occurred in 2000–2002 alone. Over 90% of those reported HIV cases are attributed to injecting drug use, much of it concentrated in the capital, Tripoli. Injecting drug use appears to be the main driver of HIV transmission in neighboring Tunisia, while a substantial share of HIV infections in Algeria, Bahrain, Kuwait, and Oman has been attributed to injecting drug use, highlighting an urgent need to expand and integrate HIV-prevention and AIDS-care services for drug injectors.

Iran has taken some positive steps in a bid to contain its epidemic, which has been growing in the wake of a dramatic rise in the overall number of people who inject drugs. About 15% of all HIV infections since the start of Iran’s epidemic were reported in 2003 alone, most of them among the country’s estimated 200,000 drug injectors.³¹ Unlike most other countries in the region, Iran has made needles and syringes available over the counter in pharmacies, a move which could be reducing the use of nonsterile needles by half. These moves need to be supplemented with prevention programs

that can limit HIV transmission from injecting drug users to their sex partners, given that research shows about half of drug injectors in Iran are married.

Meanwhile, in Yemen and in parts of Algeria, the epidemic appears to be centered on the sex-work industry. Sentinel surveillance conducted in Algeria in 2004 found 9% of the sex workers tested in Tamanrasset, compared to 1.7% just 4 years earlier.³² There and elsewhere in the region, more in-depth information is needed about patterns of HIV transmission and the possible role of sex work and sex between men in the epidemic.

Overall, more effective prevention efforts are needed across the region. Even basic steps such as condom promotion are largely absent and steps to defuse the social stigma and institutional discrimination experienced by vulnerable groups remain few and far between; so, too, education and communication to deepen public knowledge of the epidemic.

HIGH-INCOME COUNTRIES

An estimated 1.9 million people (1.3–2.6 million) are living with HIV in North America and in Western and Central Europe.

In high-income countries, where the great majority of people who need antiretroviral treatment do have access to it, people living with HIV are staying healthy and surviving longer than infected people elsewhere. Widespread access to life-extending antiretroviral treatment kept the number of AIDS deaths at between 19,000 and 42,000 in 2005. However, prevention efforts are not keeping pace with the changing epidemics in several countries. Sex between men is the most common route of infection in Australia, Canada, Denmark, Germany, Greece, and the United States. Patterns of HIV transmission are changing with an increasing proportion of people becoming infected through unprotected heterosexual intercourse. In Belgium, Norway, and the UK, the increase in heterosexually transmitted infections is dominated by people from countries with generalized epidemics, predominantly sub-Saharan Africa. In the United States, about half of newly reported infections are among African Americans who represent 12% of the population. Their HIV prevalence is 11 times higher than among whites. In New York City, over 1% of the city's adult population, and almost 2% of Manhattan's, was HIV-positive in 2001.

Drug injecting accounted for more than 10% of all reported HIV infections in Western Europe in 2002 (in Portugal it was responsible for over 50% of cases). In Canada and the United States, about 25% of HIV infections are attributed to drug injecting. Infections transmitted through contaminated injecting equipment are particularly frequent among indigenous people, who are often among the poorest and most marginalized inhabitants of the industrialized world.

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5

The Epidemiology of STIs and Their Social and Behavioral Determinants: Industrialized and Developing Countries

Sevgi O. Aral and King K. Holmes

INTRODUCTION

The incidence, prevalence, and population distribution of sexually transmitted infections (STIs) are largely determined by the complex interplay of dynamically changing demographic, economic, social, and behavioral forces and the response of the health system to emergent STI morbidity patterns. Over the past 3 decades, overall incidence and prevalence of bacterial STI, in particular gonorrhea, syphilis, chancroid, and chlamydial infections have declined in the United States, Western Europe, and many developing countries, to their lowest levels since World War II. Declines in bacterial STI in developing countries are attributed to the widespread implementation of syndromic management and to a large-scale shift to safer sexual behaviors in response to the HIV epidemic. Despite such remarkable declines, rates of some bacterial STI are still high and/or increasing in some subpopulations (e.g., adolescent African American women in the United States and homosexual men in Western Europe and the United States); and rates of some bacterial STI (e.g., chlamydial infections) seem to have plateaued. During the past decade prevalences of viral STI, particularly genital herpes infections (HSV), appear to have increased in many countries even though incidence of genital herpes infections has declined remarkably in the United States most recently. The increases in genital herpes and genital warts observed in many countries may be due to increased recognition. Absolute increases in genital herpes in developing countries, particularly in Africa, may be due to increased recurrent herpes caused by immunosuppression due to HIV infection; the relative increase in the proportion of genital ulcer disease (GUD) attributable to herpes also reflects declines in bacterial GUD. Diagnosis, management, and control of viral STIs have changed drastically over the past decade. The introduction of new diagnostic technologies has increased recognition of viral STI, improved sensitivity in identification of bacterial STI, and expanded the repertoire of usable specimens. The use of urine and vaginal swabs has greatly expanded coverage of

screening services and has led to the availability of true population-based estimates of the prevalences of STIs.¹ Implementation of integrated behavioral prevention interventions including “abstain,” “be faithful,” and “use condoms” (the ABC interventions) appears to have resulted in decreased transmission of STI including HIV in some countries like Uganda² raising optimistic expectations regarding STI prevention. However, the most recent surveillance data suggest that HIV incidence may again be increasing in Uganda.³ Introduction of therapeutic and prophylactic vaccines and suppressive therapies raises new behavioral concerns including issues of adherence and the potential for behavioral disinhibition; they also raise issues related to service delivery, technology dissemination, and acceptability. In fact, the simultaneous availability of new preventive and therapeutic interventions, including not only vaccines and suppressive therapy but also male circumcision, and perhaps effective microbicides, renders behavioral disinhibition a central issue. In contrast to overall declines in STI rates in industrialized countries, STIs among homosexual and other men who have sex with men (MSM) are again increasing. These increases further raise concerns about behavioral disinhibition, in this case, disinhibition, which may be related to antiretroviral therapy (ART). The increasing STI rates among MSM are observed consistently across the United States and Western Europe and in light of the global interconnectedness of MSM sexual networks,⁴ are expected to expand to other geographic regions.⁵ In all societies, for many reasons discussed in this chapter, STIs tend to concentrate in certain populations including urban, poor, and minority populations, with highest rates among sexually active adolescent females followed by adolescent and young adult men. This pattern is particularly pronounced in western industrialized countries where effective prevention and control efforts result in concentrated STI morbidity. During the past decade commercial sex has become an increasingly important factor in STI transmission^{6,7} in many areas of the world including the United States and Western Europe. Sex workers tend to include both local and

migrant women and men who move in response to supply and demand conditions and tend to have unstable contact with health-care providers. Social problems such as growing economic inequity between the rich and the poor, political instability, wars (including civil wars), unemployment, low education and low status of women, and globalization^{6,8} contribute to the expansion of commercial sex and mobility of sex workers; they also result in behaviors that fuel the hyperendemic transmission of STIs with continuing epidemic spread of HIV infection. Globalization also results in the interconnectedness of all sexual networks, through travel, and particularly of commercial sexual networks due to the mobility of sex workers and their clients.

EVOLVING CONCEPTS IN STI EPIDEMIOLOGY

The three direct determinants of the rate of spread of each sexually transmissible pathogen are: (1) probability of exposure of susceptible to infectious persons; (2) the mean efficiency of sexual transmission when such exposures occur; and (3) the mean duration of infectiousness of individuals who become infected. Efforts to understand the dynamics of transmission focus on the factors that influence these three component determinants of transmission.⁹

■ EXPOSURE OF SUSCEPTIBLE TO INFECTED PERSONS

National surveys of sexual behavior in a number of countries have revealed that, at any point in time, the great majority of the population does not engage in high-risk sexual behaviors, even though many individuals go through life stages during which they do. A recent review of sexual behavior data from 59 countries suggests substantial diversity in sexual behavior by region and sex.¹⁰ According to these data no recent universal trend toward earlier sexual intercourse has occurred, although the shift toward delayed marriage in most countries resulted in an increase in premarital sex; the prevalence of premarital sex is higher in developed countries compared to developing countries and among men compared to women. In all countries, monogamy is the dominant pattern; having had two or more sex partners in the past year is more common in industrialized compared to nonindustrialized countries and among men compared to women. Reported condom use has increased in most countries; however, rates remain low in many developing countries. Population-based studies including those in San Francisco, Uganda, and Thailand, have indicated, respectively, patterns of sexual mixing to be potential risk factors for HIV infection, concurrent partnerships (as apposed to sequential “serial monogamy”) to increase the rate of spread of STIs, and bridge populations to spread infection from high to low prevalence subgroups within a population^{11–14} (see Chapter 7).

■ EFFICIENCY OF TRANSMISSION PER EXPOSURE

Determinants of efficiency of sexual transmission include host susceptibility, the infectious virulence of the pathogen (e.g., the 50% infectious dose, or ID_{50} , assuming host susceptibility is held constant), and the amount or concentration of pathogens shed in semen or genital fluids, which in turn is related to the natural history of infection. The types of sexual exposure (i.e., sexual practices) also indirectly influence susceptibility, operating through host susceptibility, which varies according to the anatomic site exposed. Similarly, the “infectivity” of the infected person operates through the inoculum size delivered and the infectious virulence of the pathogen, both of which may vary in different stages of infection. In addition, recent research has indicated that male circumcision status influences the susceptibility and perhaps the infectivity status of a man.¹⁵

■ DURATION OF INFECTIVITY

The duration of infectivity is also based on the natural history of each type of infection, the effectiveness of the host immune response in controlling genital shedding or clearing the infection, as well as on the intrinsic efficacy and use-effectiveness (including population coverage, uptake, and adherence with the required dosage schedule) of antimicrobial therapy or immunity-enhancing approaches to shortening this duration.

Preventive interventions can operate on more than one of the preceding determinants of transmission. For example, vaccines or acquired immunity can produce absolute immunity to infection, thereby decreasing the number of susceptibles in the population and decreasing exposure of susceptibles to infected; can create partial immunity to infection, thereby decreasing the efficiency of transmission, especially for low inoculum exposures; or could simply attenuate infection, allowing infection to occur on exposure, but shortening the duration of infectivity, and perhaps decreasing the inoculum size and efficiency of subsequent transmission to a new partner.

■ TIMING, INTENSITY, AND TARGETING OF PREVENTIVE INTERVENTIONS

Increasingly, changes in STI rates and their determinants are understood within a framework of time-dependent mutual interaction between the spread of a specific STI and the efforts developed to prevent it. Very small but early beginnings can have large-scale impact both in the spread of STIs and in their prevention. Because the product of the three determinants of transmission must reach a critical threshold before an STI pathogen can spread within a population, even a trivial reduction in one or more of the determinants could, in theory, drop the reproductive rate of spread below that

threshold and ultimately eliminate the pathogen from the population. In the infected individual, the antimicrobial susceptibility of the pathogen, the rate at which the pathogen replicates itself, and the activity and half-life of the antibiotic, determine the choice, dose, and timing of antibiotic therapy. Similarly, in preventing spread of STIs in populations, the mean duration and mean efficiency of transmission of the infection, the density and interconnectedness of affected sexual networks, and the effectiveness of preventive interventions determine the intensity, mix, schedule, and target of preventive interventions required. Cost-effectiveness modeling repeatedly indicates that compared to interventions for the general population, targeted interventions that focus on core groups have greater impact and are most cost-effective.^{16–18} (Van Vliet C, et al. unpublished data)

The general inadequacy of STI health-care services in the United States suggests the contribution of inadequate STI services to STI morbidity in populations.¹⁹ Data now accumulating on STI-related health-care seeking indicate the role of health behaviors on duration of infectiousness, and hence, on STI epidemiology (see Chapter 92).

EMERGENT INSIGHTS ABOUT STI EPIDEMIOLOGY AND PREVENTION

Since the late 1990s, when the third version of this chapter was prepared, continued analyses of data from diverse areas have led to emergent insights about STI epidemiology and prevention, as briefly discussed below.

- Populations consist of many diverse subpopulations, and each population-level epidemic trajectory consists of many distinct subpopulation epidemic trajectories.²⁰ The epidemic trajectories of specific STIs differ depending on when and where the infection was introduced; the structure of sexual networks; the demographic, economic, social, and epidemiological context; and the state of the health system.¹
- Temporal dimensions are important in relation to STI epidemiology.²¹ At the individual level, concurrency of partnerships and short gaps between partnerships are risk factors for the acquisition and transmission of STIs.^{22–24} At the population level, investigators have described the evolution of STI epidemics through sometimes predictable phases, characterized by changing patterns in the distribution and transmission of STI pathogens within and between subpopulations.^{25,26}
- The timing of high and low levels of infectiousness during the natural history of infection further underscores the importance of the temporal dimension. At the individual level the possibility of infecting sex partners appears to be particularly high early during the natural history of infection, before the immune response begins to reduce genital shedding of STI pathogens; and then again, for HIV, late in the infection when plasma viral load and genital shedding again increase.^{27,28} Thus, concurrent partnerships and short gaps happen very early after acquiring an STI and very late during HIV infection; this would be particularly important in spreading disease. Interestingly, people may go through developmental phases of hypersexual mixing activity, (e.g., as steady partnerships dissolve and new partnerships are sought) when they engage in concurrent partnerships and may expose themselves or their partners to infection simultaneously. These developmental phases effectively link hypersexual activity with hyperinfectious, acute infections, creating short periods of heightened risk of transmission, when concordant partnerships and short gaps converge with acute STI and high levels of genital shedding of STI pathogens. As an STI is introduced and spreads through a population, cohorts with acute infections may move together through the stage of high infectiousness plus concurrent partnerships, accentuating increases in STI incidence.
- Sexual networks are important in the transmission dynamics of STIs at the population level, and position in a sexual network is important in the transmission and acquisition of STIs at the individual level²⁹ (see Chapter 7).
- Trajectories whereby STI epidemics evolve differ for different types of population–pathogen interactions.^{30–32} Whereas highly infectious, short duration bacterial STIs—for instance, gonorrhea—depend on the presence of core groups marked by multiple sex partnerships (often of short duration) for their spread, less infectious, long duration viral STIs—for example, herpes simplex virus (HSV) or human papillomavirus (HPV) infections—are less dependent on multiple partnerships of short duration or on short gaps between partnerships. Thus, the pattern of spatial and population distribution of various STIs differs markedly. Syphilis and gonorrhea tend to be concentrated in individuals with multiple partnerships and in populations with highly connected sexual networks; whereas genital chlamydial infections, genital herpes, and genital HPV infections are much more ecumenically, widely distributed across the entire population.³³
- Interactions among sexually transmitted pathogens affect STI epidemic trajectories at the population level.³⁴ The inconsistent findings of three landmark randomized community trials evaluating the effect of STI treatment on HIV transmission^{35–37} can be accounted for by the phase-specific nature of STI epidemics, with higher prevalences of HIV and declining levels of STI in the two Uganda studies that showed no impact of STI treatment.³⁸
- Epidemiologic, behavioral, and social context are highly important in determining the epidemiology of each STI and the potential impact of preventive interventions.

Prevalence, incidence, and distribution of infection(s) and interactions among sexually transmitted pathogens constitute the epidemiological context while the prevalence, incidence, and distribution of each risk and preventive behavior and interactions among distinct risk and preventive behaviors constitute the behavioral context. The impact of a condom use intervention on STI rates depends on the existing prevalence of condom use among high and low risk groups, on whether high or low risk groups receive the intervention, and on the prevalence, incidence, and distribution of infections. Social context includes societal determinants of risk and preventive behaviors and may determine whether or not behaviors can change in response to behavioral interventions. In the context of extreme poverty and/or extreme lack of power and of autonomy, behavioral elasticity (ability to change behaviors) may be close to zero. For example, women in many developing countries who cannot ask their husbands to use condoms, and drug-using sex workers who cannot negotiate condom use with clients for fear of losing them lack behavioral elasticity due to social context. Prevention program planning must be based on a detailed understanding of the local epidemiologic, behavioral, and social context.²⁰

- Most recent studies of STI epidemiology highlight the heterogeneity in affected populations, in epidemic trajectories, in social and behavioral contexts, in costs of STIs, and in cost-effectiveness of biomedical and behavioral interventions.³⁹
- The most common modality of STI intervention research to date has involved behavior change interventions. Recent reviews provide several insights into such research.⁴⁰ First, most evidence is on individual level interventions aimed at reducing STI acquisition, even though individual level interventions may be costly and difficult to sustain. Second, theory-based interventions did not show an effect more frequently than non-theory-based behavioral interventions. Third, behavioral interventions delivered in small group settings were as effective as those delivered to individuals. Fourth, the effect of a particular behavior change on STI risk depended on the type of STI. For example, one review suggested that the number of sex partners may be more predictive of risk for highly infectious STIs than for HIV, and the number of unprotected sex acts may be more predictive of risk for HIV than for highly infectious STI.⁴¹ The one exception to this generalization may be the initial stage of HIV infection—“the acute hyperinfectiousness” stage.²⁷ Available evidence suggests that during this initial stage of HIV infection (and during the final immunosuppressed stage) behavioral determinants of HIV infection may more closely resemble those of other highly infectious STIs. Finally, a number of intervention trials result in demonstrated declines in risk behavior and yet have no effect on STIs, or even result in

increases in STIs. This observation calls into question the use of behavioral outcome measures as indicators of biomedical outcomes.⁴²

- Unprecedented increases in travel and communication have had major impact on the global connectedness of sexual networks. Consequently, interconnected STI epidemics are increasingly observed in some populations. Recent outbreaks of syphilis among MSM in many areas of the United States, UK, Western Europe, and Australia are examples of the global connectedness of sexual networks.⁴
- Important methodological advances have taken place in the design, analysis, and interpretation of randomized trials—the gold standard in intervention research. Individual variation in response to medications has implications for the interpretation of individual randomized drug trials.^{43,44} The population level variations in cluster-randomized trials (CRTs), which are increasingly used to evaluate the impact of public health interventions have been the subject of considerable discussion. It is now clear that the matching or stratification of clusters and the number and size of the clusters to be randomized can affect the power of a CRT.⁴⁵ Moreover, the interdependency of individual outcomes within clusters must be accounted for. The role of cluster-level covariants requires careful consideration in the interpretation of CRT results.⁴⁶ An additional methodological advance, not surprisingly involves the increased emphasis on measuring “adherence” to the intervention for the analysis of results of prevention trials. Lack of adherence may be particularly problematic in intent-to-treat analyses.
- Finally, all preventive interventions may have unintended consequences that may modify their net impact. Behavioral disinhibition, the potential increase in unsafe sexual behaviors in response to the introduction of effective preventive and/or therapeutic STI/HIV interventions, is only one type of unintended consequence. Behavioral disinhibition (also euphemistically termed “risk compensation”) involves the perception of lowered risk by an individual or society, resulting in lessened perception of need for risk avoidance. Many other unintended consequences of interventions take place at the network and structural levels. For example, police raids to known sex work areas or bathhouses break down existing sexual networks and cause the formation of new networks, with altered probability of exposure between high-risk/infected persons and those who are low-risk/uninfected persons. Interventions that encouraged MSM to learn their HIV serostatus and avoid unprotected sex with serodiscordant partners may have unintentionally caused increases in syphilis incidence by increasing the practice of unprotected sexual intercourse between HIV seroconcordant MSM.⁵

DESCRIPTIVE EPIDEMIOLOGY OF SELECTED STIS AND SEXUALLY TRANSMITTED INFECTIONS

Subsequent chapters of this book describe the epidemiology of various STIs and STI pathogens in detail. This chapter focuses on cross-cutting comparisons that illustrate general or differing aspects of STI epidemiology. Not all STIs are reportable, and even reportable diseases are seldom reported completely or with complete specificity. Data from most of the world are sketchy, occasionally based on prospective cohort studies of incidence, or on serially repeated prevalence surveys but more often based on sporadic prevalence surveys, or solely on anecdotes. Populations sampled in developing societies have most often included sexually transmitted disease (STD) clinic patients or family planning clinic patients, who are not representative of the total population and have less often included prenatal or primary care clinics or other somewhat more representative population samples. Prenatal samples generally best represent sexually active, nonconceiving fertile married women of reproductive age who seek prenatal care, although they often underrepresent the single women who are at highest risk and underrepresent women rendered infertile or subfertile by past or present STIs, including HIV infection and they underrepresent women without access to acceptable hospital-based care. It is interesting that recent comparative assessments of HIV seroprevalence in antenatal women and in random household samples of the general populations in African

countries have shown significantly higher HIV prevalences in antenatal women. A detailed review of the descriptive epidemiology of STIs in individual developing countries is beyond the scope of this chapter.

The most recent updated estimates for prevalence and incidence of STIs globally are provided by the WHO.⁴⁷ These estimates suggest that of 340 million new cases of gonorrhea, syphilis, chlamydial infection, chancroid, and trichomoniasis STIs in 1999 under 10% occurred in North America and Western Europe; over 90% of new infections were in developing countries (Table 5-1). In 1999, the overall estimated number of new cases of chlamydia, gonorrhea, and syphilis infections among 15–49-year-old men and women totaled over 166 million with close to 92 million cases of chlamydial infection, 62.35 million cases of gonorrhea, and 11.76 million cases of syphilis (Table 5-2). In addition, there were an estimated 173.46 million cases of trichomoniasis.

In developing countries, passive surveillance of STI morbidity is particularly inadequate. However, in recent years the epidemiology of STIs in sub-Saharan Africa is better defined based on large population-based prevalence surveys. The results of these surveys have confirmed the high prevalences of STIs even in rural populations, for example, syphilis (5–10% of adults infected), vaginal trichomoniasis (20–30% of women), and bacterial vaginosis (up to 50% of women). Syphilis has been estimated to cause 490,000 stillbirths and neonatal deaths per year in Africa—a figure similar to the number of children dying of HIV/AIDS worldwide.⁴⁸

Table 5-1. Estimated Prevalence and Annual Incidence of Curable STDs by Region, 1999

Region	Adult Population (Millions) ¹	Infected Adults (Millions)	Infected Adults Per 1,000 Population	New Infections in 1999 (Millions)
North America	156	3	19	14
Western Europe	203	4	20	17
North Africa and Middle East	165	3.5	21	10
Eastern Europe and Central Europe	205	6	29	22
Sub-Saharan Africa	269	32	119	69
South and Southeast Asia	955	48	50	151
East Asia and Pacific	815	6	7	18
Australia and New Zealand	11	0.3	27	1
Latin America and Caribbean	260	18.5	71	38
Total	3040	116.5	–	340

Source: World Health Organization, "Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections Overview and Estimates 2001."

Table 5-2. Estimated New Cases of STI (in Millions) Among 15–49-Year-Olds During 1995 and 1999

Region	Chlamydial Infection						Gonorrhea					
	1995			1999			1995			1999		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
North America	1.64	2.34	3.99	1.77	2.16	3.93	0.83	0.92	1.75	0.72	0.84	1.56
Western Europe	2.30	3.20	5.50	2.28	2.94	5.22	0.60	0.63	1.23	0.49	0.63	1.11
North Africa & Middle Europe	1.67	1.28	2.95	1.71	1.44	3.15	0.77	0.77	1.54	0.79	0.68	1.47
Eastern Europe & Central Asia	2.15	2.92	5.07	2.72	3.25	5.97	1.17	1.16	2.32	1.50	1.81	3.31
Sub-Saharan Africa	6.96	8.44	15.40	7.65	8.24	15.89	7.30	8.38	15.67	8.19	8.84	17.03
South & South East Asia	20.20	20.28	40.48	18.93	23.96	42.89	14.56	14.55	29.11	12.12	15.09	27.20
East Asia & Pacific	2.70	2.63	5.33	2.56	2.74	5.30	1.80	1.47	3.27	1.59	1.68	3.27
Australia & New Zealand	0.12	0.17	0.30	0.14	0.17	0.30	0.06	0.07	0.13	0.06	0.06	0.12
Latin America & Caribbean	5.01	5.12	10.13	4.19	5.12	9.31	3.45	3.67	7.12	3.26	4.01	7.27
Total	42.77	46.38	89.15	41.95	50.03	91.98	30.54	31.61	62.15	28.70	33.65	62.35
Region	Syphilis						Trichomoniasis					
	1995			1999			1995			1999		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Totals
North America	0.07	0.07	0.14	0.054	0.0	3.93	4.23	3.78	8.01	4.29	3.90	8.19
Western Europe	0.10	0.10	0.20	0.069	0.066	0.136	5.76	5.30	11.06	5.52	5.09	10.61
North Africa & Middle Europe	0.28	0.33	0.62	0.167	0.197	0.364	2.22	2.32	4.54	2.25	2.35	4.60
Eastern Europe & Central Asia	0.05	0.05	0.10	0.053	0.052	0.105	5.17	4.90	10.07	6.75	6.36	13.11
Sub-Saharan Africa	1.56	1.97	3.53	1.683	2.144	3.828	15.35	15.07	30.42	16.19	15.93	32.12
South & South East Asia	2.66	3.13	5.79	1.851	2.187	4.038	35.87	39.56	75.43	36.36	40.06	76.42
East Asia & Pacific	0.26	0.30	0.56	0.112	0.132	0.244	4.53	4.83	9.36	4.61	4.91	9.52
Australia & New Zealand	0.01	0.01	0.02	0.004	0.004	0.008	0.32	0.29	0.61	0.32	0.29	0.61
Latin America & Caribbean	0.56	0.70	1.26	1.294	1.634	2.928	9.10	8.52	17.62	9.50	8.79	18.29
Total	5.55	6.67	12.22	5.29	6.47	11.76	82.55	84.57	167.12	85.78	87.68	173.47

Source: World Health Organization, "Global Prevalence and Incidence of Selected Curable Sexually Transmitted Infections Overview and Estimates 2001."

During the HIV/AIDS era, in areas where some form of active ongoing STI surveillance has been conducted, the incidence of gonorrhea, chancroid, and syphilis has declined markedly since the mid 1990s. This is likely related to reduction in risk behaviors during the HIV/AIDS era and to widespread promotion of STID syndromic management, especially for the curable bacterial genital ulcers, and for urethritis in men. Mortality among those who were at greatest sexual risk and acquired HIV infection early also likely has contributed. The fact that prospective data on trends in STI were collected predominantly in settings where STI programs were most strongly implemented—e.g., Thailand, Kenya, parts of South Africa and West Africa, the Caribbean—suggests that the available data are not necessarily widely generalizable.

In North America and many countries of Europe, as well as Australia and New Zealand, better data on reported STIs showed steady increases in the incidence of all STIs during the 1960s, with leveling off or decline of most of the bacterial STIs but continual increases in viral STIs and genital chlamydial infections during the 1970s and 1980s. The incidence of the best measured STIs, gonorrhea and syphilis, began to decline at different times, and declined at differing rates, in these industrialized countries but fell more rapidly, especially among MSM during the AIDS era, over the last quarter century. The sex ratio of males to females with bacterial STIs has declined for several decades. During the late 1980s and the 1990s, chlamydial infections began declining in Nordic countries and in the areas of the United States and Canada and wherever chlamydia control programs have been initiated. In contrast, some countries that underwent major

political change and opened their borders and/or allowed increasing mobility of their populations and saw rapid social changes, experienced explosive epidemics of bacterial STIs (e.g., China, Mongolia, and Russia and the newly independent states of the former USSR). Many countries in Eastern Europe, Southern Africa, and Asia have continued to experience epidemic increases in HIV infection.^{49–51}

Since the mid 1990s a number of the declining trends in the Northern Hemisphere have reversed themselves.⁵² Large-scale demographic changes in patterns of fertility, mortality, migration, marriage, and divorce have played an important role in the reemergence of selected STIs (see discussion in the section on the demographic, social, political, and technologic context). In the UK, Ireland, and Sweden diagnoses of gonorrhea more than doubled between 1995 and 2004. Similar increases have been observed in reported syphilis in Belgium, the UK, and Ireland (Table 5-3). Increases in reported gonorrhea and syphilis have been observed in Spain, Denmark, Austria, France, Finland, Netherlands, and Sweden. The increases have been most marked among MSM, since the advent of highly active ART in 1995, and also among young people, residents of major metropolitan areas, and migrant and ethnic minority communities. The reemergence of anorectal lymphogranuloma venereum among MSM after it had virtually disappeared in several European countries and in North America, is another striking example. Factors contributing to increases in incidence of curable STI include high prevalences of infection in countries of origin; higher prevalences of risk behaviors, often associated with increasing recreational drug use in some countries, such as the United

Table 5-3. Recent Trends in Reported Gonorrhea and Syphilis Among EU Countries

Country	Gonorrhea					Syphilis				
	1991	1995	2000	% Change 1991–1995	% Change 1995–2000	1991	1995	2000	% Change 1991–1995	% Change 1995–2000
Austria	1750	896	414	–48.8	–53.8	161	180	237	11.8	31.7
Belgium	267	130	145	–51.3	11.5	56	30	90	–46.4	200
Denmark	1,326	287	335	–78.4	16.7	62	42	54	–32.3	28.6
Finland	1,426	378	284	–73.5	–24.9	NA	138	198		43.5
Germany	NA	NA	NA	–	–	1,268	1,138	NA	–10.3	
Greece	118	117	98	–0.8	–16.2	NA	NA	NA		
Ireland	73	91	290	24.7	218.7	20	11	48	–45.0	336.4
The Netherlands	2,900	1,425	NA	–50.9		253	204	NA	–19.4	
Portugal	239	73	46	–69.5	–37	218	218	175	0.0	–19.7
Spain	11,428	4,599	1,045	–59.8	–77.3	1,509	1,010	700	–33.1	–36.7
Sweden	617	246	590	–60.1	139.8	118	69	99	–41.5	43.5
UK	17,666	10,598	21,131	–40.0	99.4	367	141	327	–61.6	131.9

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States; and poor access to acceptable prevention and treatment services. Changes in commercial sex patterns and networks (discussed later in the section on demographic social, political, and technologic context) have also contributed to increases in STI incidence.

The WHO categorizes the countries included in the European region into three geographic areas: West, Centre,

and East (Table 5-4). Patterns of STI transmission have changed over time and differ markedly between these geographic regions.⁵³ Although underreporting is common, and reported incidence data do not precisely reflect the numbers of new cases, they provide indicators of trends over time. Particularly noteworthy is the epidemics of syphilis and gonorrhea that spread throughout much of Eastern Europe soon

Table 5-4. Geographic Division of WHO European Region Member States

West	Centre	East
Andorra	Albania	Armenia
Austria	Bulgaria	Azerbaijan
Belgium	Croatia	Belarus
Denmark	Cyprus	Estonia
Finland	Czech Republic	Georgia
France	Hungary	Kazakhstan
Germany	Malta	Kyrgyzstan
Greece	Montenegro ^a	Latvia
Iceland	Poland	Lithuania
Israel	Romania	Republic of Moldova
Ireland	Serbia ^a	Russian Federation
Italy	Slovakia	Tajikistan
Lichtenstein	Slovenia	Turkmenistan
Luxembourg	The former Yugoslav	Ukraine
Monaco	Republic of Macedonia	Uzbekistan
The Netherlands	Turkey	
Norway		
Portugal		
San Marino		
Spain		
Sweden		
Switzerland		
United Kingdom		

^aThe data in this report were collected prior to 3 June 2006, when Montenegro voted for independence.

after the dissolution of the Soviet Union. The reported incidence of both diseases has subsequently declined throughout Eastern Europe, probably reflecting both HIV/AIDS-related behavior change and the intrinsic effectiveness of strengthened public health and clinical programs for control of these two STIs. Data from the WHO European Region Member States and from the United States are the most accessible and comprise the basis of discussions on specific STI below.

GONORRHEA

■ TRENDS IN INDUSTRIALIZED COUNTRIES

The major bacterial STIs include gonorrhea, chlamydial infection, syphilis, and in many developing countries, chancroid. In most European Union (EU) countries gonorrhea started declining in the 1970s and continued to decline at an accelerated rate during the second half of 1980s. The declines continued into the early 1990s. In many EU states, gonorrhea rates reached their lowest point in 1995. However, increases in reported cases and incidence rates of gonorrhea have been observed since the late 1990s. In Belgium, gonorrhea incidence increased starting in 1997. The incidence in 25–44-year-old men rose from 3 per 100,000 population in 1995 to 3.5 per 100,000 in 1997 and 5 per 100,000 in 1998.⁵² Gonorrhea diagnoses more than doubled between 1996 and 2001 in England and Wales and Northern Ireland; 40% of diagnoses among women occurred among those under 20 years of age. In Ireland, there was a 320% increase in reported gonorrhea cases between 1996 and 2001; 75.9% of cases in 2001 were among men. In Austria, the number of reported gonorrhea cases increased from 414 in 2000 to 995 in 2002; the increase was observed among both men and women. Some countries in Europe did report a continued decline in cases of gonorrhea during this period. In Spain, rates of reported gonorrhea declined from 18.6 per 100,000 population to 3.9 per 100,000 population between 1993 and 1999. In Norway, reported cases of gonorrhea decreased from 944 cases in 1990 to 175 in 1995, increased to 223 in 1996 but remained below 200 after 1996. In Sweden, gonorrhea cases increased between 1997 and 2000 but declined in 2001 and 2002 resulting in an infection rate of 5.6 per 100,000 population. However, cases increased during the first half of 2003 compared to the first half of 2002.⁵² As noted above, in many countries in the EU gonorrhea incidence is concentrated among the young, MSM, and in socioeconomically deprived communities.⁵²

In the United States, the rate of reported gonorrhea declined 74% from 1975 to 1997, then plateaued.⁵⁴ In 2005, 339,593 cases of gonorrhea were reported corresponding to a rate of 115.6 per 100,000 population—an increase from 2004 and vastly higher than in other industrialized countries; in fact, the annual incidence of gonorrhea per

100,000 population in the United States approached the total number of cases per country in several EU countries. As earlier, in 2005 the South had the highest gonorrhea rate in the United States. Interestingly, between 2001 and 2005 the gonorrhea rate in the South declined by 17.6% while that in the West has increased by 35.4% from 60.2 cases per 100,000 population to 81.5 cases in 2005. For the fourth year, the gonorrhea rate in women was slightly higher than that among men in 2005; 119.1 per 100,000 population and 111.5 per 100,000 population, respectively. Rates of gonorrhea are highest among 15–19-year-old women and among 20–24-year-old men. Although the gonorrhea rate among 15–19-year-olds has decreased in recent years, this rate increased 3.9% between 2004 and 2005 from 421.9 per 100,000 population to 438.2 per 100,000 population (Fig. 5-1). As before, in 2005, African American 15–19-year-old females had the highest gonorrhea rate among all age and race-ethnicity groups (2814 cases per 100,000 population). Gonorrhea rates among African American men and women did decline from 2001 to 2005 by 19.4% and 16.1%, respectively. Conversely, gonorrhea rates among white men and women increased from 2001 to 2005 by 18.9% and 20.4%, respectively (Figs 5-1 and 5-2).

■ INFLUENCE OF SOCIODEMOGRAPHIC FACTORS ON GONORRHEA MORBIDITY: MECHANISMS OF ACTION

Both socioeconomic status and racial ethnic background are highly correlated with gonorrhea morbidity in the United States and Western Europe.^{9,52,55} In the United States, gonorrhea ranked number one among notifiable diseases; racial disparities were greatest in 2002 with a black/white rate ratio of 24.2.⁵⁶ Moreover, racial differences in STIs persist after controlling for indicators of socioeconomic status (SES).^{57–59} Recent research has focused increasingly on the reasons for racial, ethnic, and socioeconomic disparities. Sexual mixing patterns are segregated by race and socioeconomic status.^{60,61} In addition, minorities are more likely to (sexually) mix with others from other risk groups than their own.⁶¹ The combination

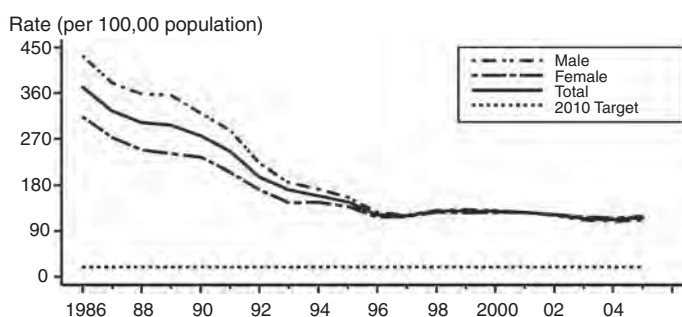


FIGURE 5-1. Gonorrhea rates: total and by sex: United States, 1986–2005 and the healthy people 2010 target. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance*, 2005. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

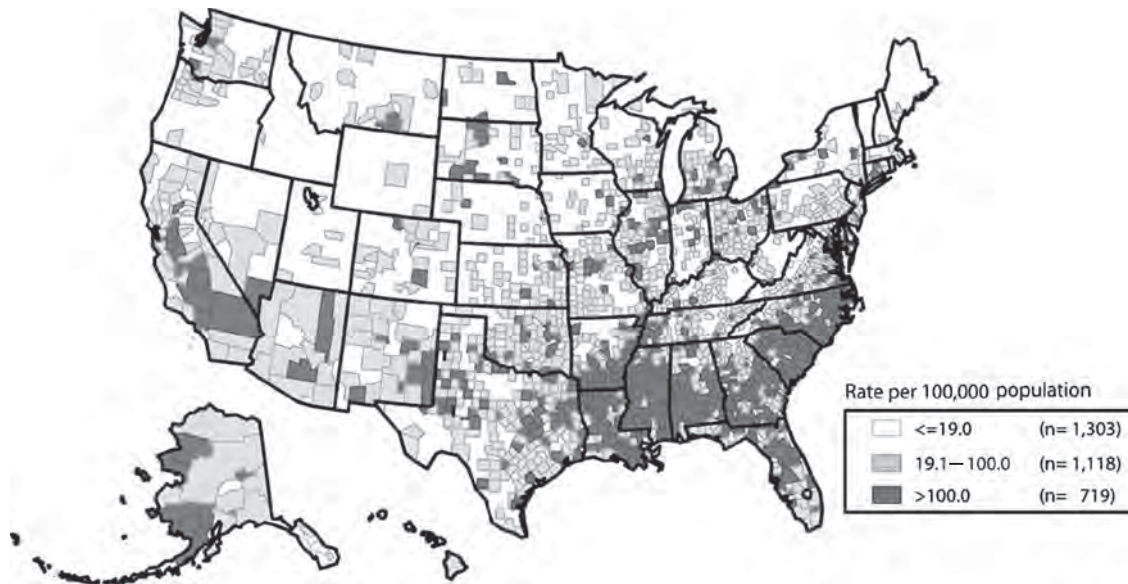


FIGURE 5-2. Gonorrhea rates by county: United States, 2005. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2005*. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

of assortative mixing by race (and probably socioeconomic status) and disassortative mixing by risk group may contribute to very high rates of all STIs including gonorrhea.⁵⁹ Individual behaviors do not account for the disparities; in the United States, while white young adults are at increased STI and HIV risk when they engage in high risk behaviors, black young adults are at high risk even when their behaviors are normative.⁵⁹ Interestingly, evidence suggests that socioeconomic status like risk behaviors, may be more strongly associated with STI among white populations compared to African American populations.^{58,61}

Residential segregation patterns may also contribute to sociodemographic disparities in gonorrhea and other STIs. In fact, segregation in sexual mixing patterns and residential patterns may interact so as to have a multiplicative impact on racial ethnic disparities in gonorrhea rates and rates of other STIs. The segregation of sexual networks is in part a function of the availability of sexual partners which has a significant geographic component that reflects patterns of social and residential interaction.^{62–66} Research that employs “cluster detection analysis” to identify critical STI transmission locations suggests that risks for gonorrhea are associated with definable sociogeographic spaces.⁶⁷ Statistically significant geographic clustering of reported gonorrhea cases in Baltimore was observed after adjustment for African American race/ethnicity. These findings suggest that both residential patterns and sex partner preferences may act as macroboundaries to sexual network formation. This pattern may apply to both racial-ethnic and socioeconomic characteristics and may help account for both types of disparities in rates of gonorrhea and other STIs.⁶⁷

Another potential explanation suggested for the strong association of race, ethnicity, and socioeconomic status with

gonorrhea is that deteriorated physical conditions of local neighborhoods may increase high-risk behaviors.⁶⁸ However, this association may not be causal.

Inadequate treatment can result in preventable onward transmission of gonorrhea, and a recent mathematical model demonstrated the importance of timely delivery of effective health care in preventing onward transmission of gonococcal infection.⁶⁹ Inadequate treatment capacity, as observed in the UK, or unacceptable services, as reported by African American men in the United States, can lead to disruptions and delays in the timely delivery of effective health care. This can lead to the establishment of “vicious circles” in the dynamics of further gonorrhea transmission.

As gonorrhea prevalence and incidence became concentrated in particular, separated populations, issues of “elimination, introduction, and reintroduction of infection” become important. Spatial bridging, sexual mixing between distant geographic areas, may represent an important mechanism of introduction and channel of transmission between geographic areas.⁷⁰ Since sexual mixing tends to be assortative with respect to race/ethnicity and socioeconomic status, spatial bridging may contribute to sociodemographic disparities in gonorrhea morbidity across local areas.

Increasing globalization, international trade, and travel have become increasingly important in the spread of new variants of sexually transmitted pathogens, such as fluoroquinolone-resistant gonococci. Molecular typing of *Neisseria gonorrhoeae* combined with contact tracing provides a unique and powerful approach to the identification of sexual networks in metropolitan areas,⁷¹ with potential for analyzing spatial and other types of bridging, sexual mixing, and introduction of distinct strains of gonorrhea into specific networks and local areas. Such approaches

could be usefully employed in the future to help understand the different patterns of spread of other communicable disease pathogens, such as specific strains of methicillin-resistant *staphylococcus aureus*, for example.

Gonorrhea incidence among MSM declined remarkably in response to the HIV epidemic during the 1980s but started increasing in discrete local areas in the United States in the early 1990s⁹ and subsequently in many European countries. In recent reports 17.4% of all gonorrhea diagnoses in men in England and Wales and Northern Ireland, were acquired through sex between men;⁵² 44.8% of the gonorrhea cases in Sweden in 2002 were among MSM; and in Denmark, MSM accounted for a disproportionately large burden of gonorrhea with highest incidence occurring in HIV-infected MSM (483.3 per 100,000 population per year). In Europe, there has been a strong association between gonococcal infection and overseas travel, highlighting the importance of spatial bridging in importing gonorrhea to Europe (with its relatively low rates of gonorrhea) from parts of the world with much higher rates.

Data from several U.S. cities and projects including the Gonococcal Isolate Surveillance Project (GISP) suggest that an increasing proportion of men with urethral gonococcal infection are MSM; and the incidences of syphilis and chlamydial infections involving MSM are also increasing.^{72–78} Data from Europe, Canada, United States and Australia suggest a substantial increase in high-risk sexual behaviors among MSM since 1996⁷⁹ perhaps leveling off in some cities as of 2006. The increase in STI acquisition appears to result in part from HIV “serosorting,” with unprotected sex among HIV seroconcordant men including the increased frequency of HIV seroconcordant sex partner recruitment, for unprotected sex, on the Internet. Serosorting reduces the risk of HIV transmission to uninfected individuals but does not decrease the risk of transmission of other STIs.⁷⁹ STDs and many of the sexual behaviors and patterns of sexual mixing associated with acquiring them increase the likelihood of acquiring and transmitting HIV infection; consequently, the rise in STIs among MSM may be associated with an increase in HIV incidence among MSM.^{80,81} Prospective data on STIs among MSM in the United States are provided by the MSM Prevalence Monitoring Project which includes data from six public STD clinics and three STD clinics in community-based gay men’s health clinics.⁸² From 1999 to 2005 the number of gonorrhea tests from all anatomic sites has increased in several cities, while the trend in the number of positive gonorrhea tests from all anatomic sites has varied by city (Fig. 5-3). In 2005, 78% of MSM were tested for urethral gonorrhea, 26% for rectal gonorrhea, and 26% for pharyngeal gonorrhea.⁸² In 2005, the median percentage of urethral tests that were positive for *N. gonorrhoeae* in MSM

was 11%, median rectal test positivity was 8%, and median pharyngeal test positivity was 7%.

RECENT TRENDS IN ANTIMICROBIAL RESISTANCE OF *N. GONORRHOEAE*

Data on gonococcal antimicrobial resistance across the EU are not comprehensive. Plasmid-mediated resistance to penicillin and tetracycline had increased in Europe during the early 1990s. Sporadic resistance to fluoroquinolones was also documented in the early 1990s, mainly imported from South East Asia.⁵² Resistance to third-generation cephalosporins was not observed at that time. By the mid 1990s, high rates of penicillinase-positive *Neisseria gonorrhoeae* (PPNG) were reported in many large metropolitan areas; prevalences were 13% in Sweden, 6% in Finland, 3% in England, 14% in France, and 15–30% in the Netherlands. Recently, increases in fluoroquinolone resistance have been reported in many countries in Europe. In Denmark, the laboratory-confirmed percentage of gonococci with fluoroquinolone resistance increased from 0% to 27% in 1999, 17% of the strains were resistant to both penicillin and fluoroquinolones.⁵² In Austria, reported resistance to ofloxacin increased from 0% to 52.3% between 1999 and 2002. The Gonococcal Resistance and Antimicrobials Surveillance Program (GRASP) in England and Wales also demonstrated increases in ciprofloxacin resistance from 2.1% in 2000 to 3.1% in 2001 and 9.8% in 2002. In Scotland, ciprofloxacin resistance increased from 2.8% in 2000 to 4% in 2001 and 11% in 2002.

In the United States, beta-lactamase-producing strains of *N. gonorrhoeae* were first isolated in 1976. Initially, the reported numbers of such strains remained stable at less than 100 cases per year and most cases were linked to overseas travel. In 1980, however, numbers of beta-lactamase-producing isolates started to increase, with reported cases exceeding 4500 by 1982. This may initially have reflected the spread of such strains within developing countries increasing importation into the United States from endemic areas such as Korea, the Philippines, and Africa and then increasing transmission within the United States. Eventually, beta-lactamase-producing gonococci became entrenched in some communities and the number of reported cases began to increase sharply after 1984.⁸³ This might have also been partly attributable to adaptive stabilization of beta-lactamase-encoding plasmids in *N. gonorrhoeae*. As the incidence of infections with beta-lactamase-producing strains of *N. gonorrhoeae* increased, the epidemiology changed: overseas travel and contact with female sex workers (FSWs) were identified as important risk factors in early outbreaks; but over time the distribution of these strains came to parallel that of endemic, antibiotic-sensitive gonococci, predominantly involving inner-city residents, members of ethnic minority groups, and heterosexuals.^{84,85}

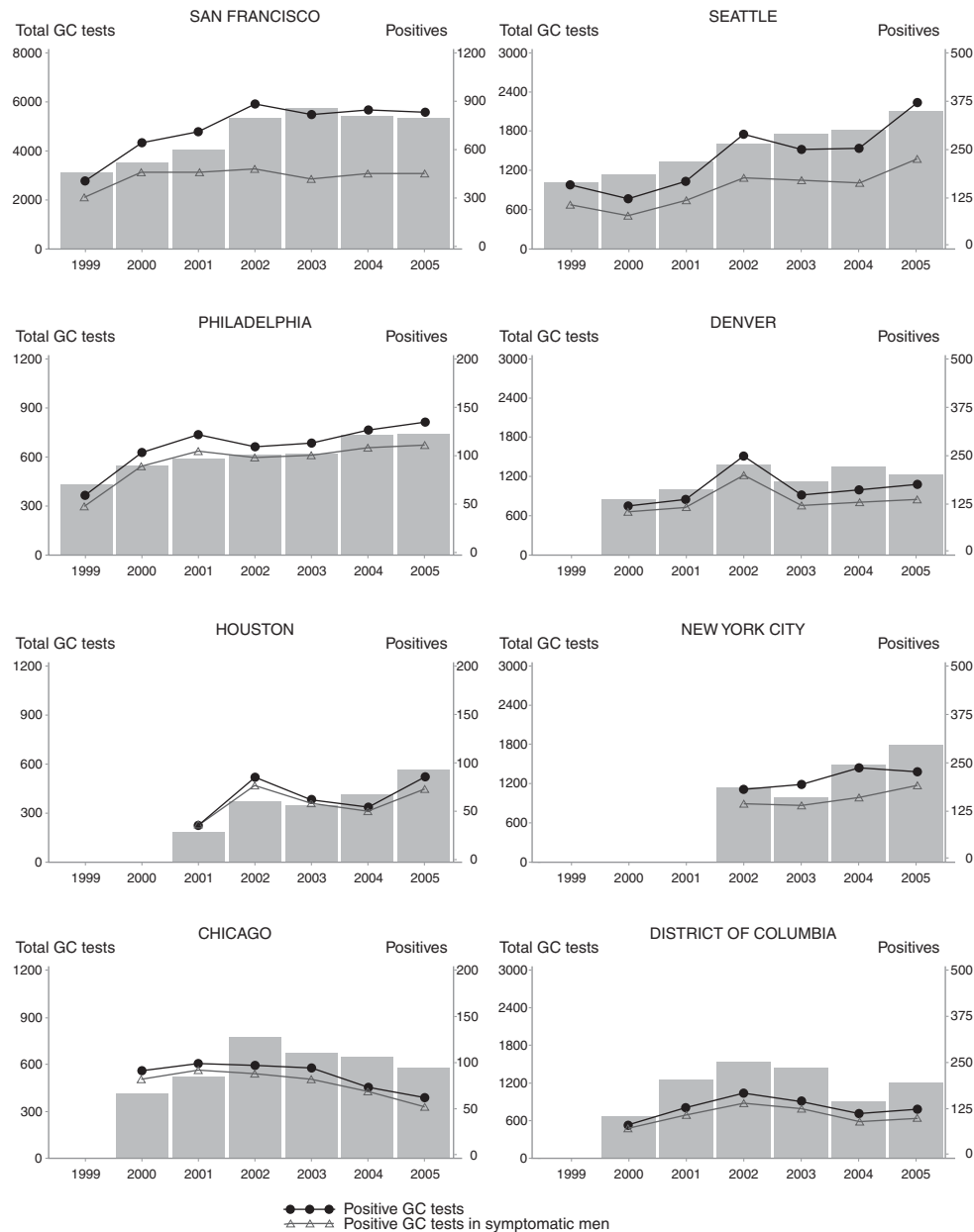


FIGURE 5-3. MSM prevalence monitoring project—number of gonorrhea tests and number of positive tests in men who have sex with men, STD clinics, 1999–2005. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2005*. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

During the 1990s, levels of gonococcal antimicrobial resistance in the United States were fairly stable, with about one-third of isolates resistant to penicillin or tetracycline, higher than in some other industrialized countries.³² The more rapid emergence of reduced susceptibility to ciprofloxacin since 1999 has been a concern.

By early 2004, fluoroquinolones were no longer recommended in the United States as first-line treatment for MSM, and by early 2007, were no longer recommended as first-line treatment of gonorrhea in any group.⁸⁶ As of 2006, there was considerable geographic variation in the prevalence of fluoroquinolone resistance in the United States for

heterosexuals, rates being highest in the west. In the GISP survey, the proportion of isolates that were resistant to ciprofloxacin increased steadily to 29% in MSM, while among heterosexuals the proportion of quinolone resistance *Neisseria gonorrhoea* (QRNG) had increased from 2.9% in 2004 to 3.8% in 2005 to 6.7% in 2006. (Figs 5-4 and 5-5) While fluoroquinolone resistant isolates were identified in 25 of the 27 GISP clinics, prevalence was highest in Western States.⁵⁴ To date, cephalosporin resistance has not been identified in GISP, and the proportion of GISP isolates demonstrating decreased susceptibility to ceftriaxone or cefixime has remained very low over time.^{87,54}

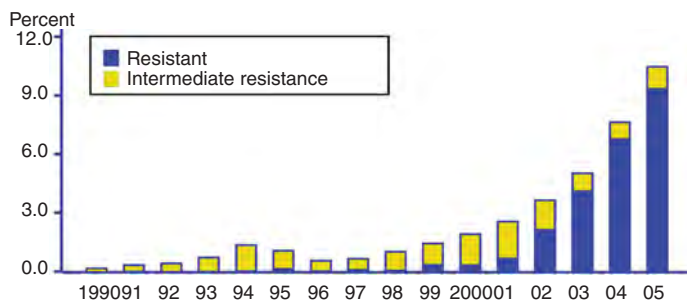


FIGURE 5-4. Gonococcal isolate surveillance project (GISP)—percent of *Neisseria gonorrhoeae* isolates with resistance or intermediate resistance to ciprofloxacin, 1990–2005. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2005*. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

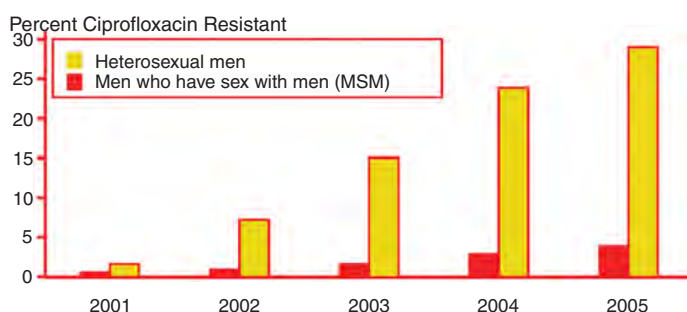


FIGURE 5-5. Gonococcal isolate surveillance project (GISP)—percent of *Neisseria gonorrhoeae* isolates with resistance to ciprofloxacin by sexual behavior. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2005*. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

SYPHILIS

■ TRENDS IN INDUSTRIALIZED AND DEVELOPING COUNTRIES

Globally, an estimated 12 million people are infected every year, and the majority of infections are believed to occur in sub-Saharan Africa and South East Asia.⁴⁸ While the majority of transmissions occur through heterosexual intercourse in these settings, vertical transmission remains a concern.⁸⁸ Recent estimates suggest that a million pregnancies are affected each year by syphilis.

Syphilis, gonorrhea, and chancroid may fluctuate in incidence somewhat more dramatically than other STIs such as HSV or HPV infections, as sexual behaviors change. In the United States and other industrialized countries, following World War I, the incidence of syphilis fell rapidly, coinciding with the increased availability of improved diagnostic tests and the arsenicals. After a brief rise in incidence during World War II, the incidence fell again, coinciding with the introduction of penicillin. The incidence rose again during the sexual revolution of the early 1960s, and unlike the incidence of gonorrhea, continued to increase after the 1970s, reflecting epidemic spread among MSM until the recognition

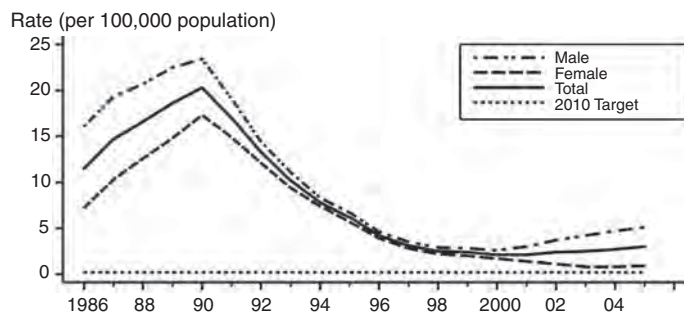


FIGURE 5-6. Primary and secondary syphilis rates: total and by sex: United States, 1986–2005 and the Health People 2010 target. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2005*. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

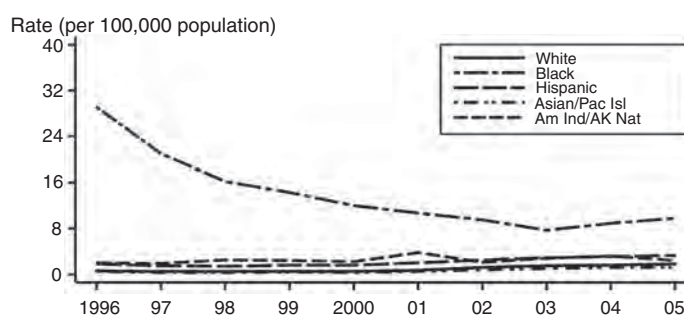


FIGURE 5-7. Primary and secondary syphilis—rates by race/ethnicity: United States, 1996–2005. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2005*. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

of AIDS in 1981. During the 1980s and early 1990s, with AIDS-related decreases in risk behaviors, rates of primary and secondary syphilis declined dramatically, particularly among MSM.⁹ Primary and secondary syphilis increased in the United States between 1986 and 1990 among minority heterosexual populations, concurrent with the crack cocaine epidemic. In the United States, rates of reported primary and secondary syphilis began to fall again after 1990, with the decreasing use of crack cocaine, and continued to fall until the year 2000, with the lowest incidence⁸⁹ of primary and secondary syphilis (since 1941, when reporting began) reached in the year 2000.⁵⁴ (Fig. 5-6) The low rate of infectious syphilis and the concentration of most syphilis cases in a very small proportion of geographic areas in the country led to the development of CDC's National plan to Eliminate Syphilis. The plan was first established in 1999 and was revised in 2006.⁹⁰

After implementation of the CDC's syphilis elimination plan, the incidence of primary and secondary syphilis did decline further among women, and among the black population, greatly decreasing the disparity between blacks and other racial-ethnic groups in syphilis incidence (Fig. 5-7). In 1997, the incidence of primary and secondary syphilis among African Americans was 44 times that among

non-Hispanic whites;⁹ in 2005, the incidence was 5.4 times higher among blacks than among non-Hispanic whites. However, unfortunately, this has been offset by a large resurgence of syphilis among MSM. In 2005, for the first time in over 10 years, the rate of primary and secondary syphilis among women also increased slightly, from 0.8 cases per 100,000 population in 2003 and 2004 to 0.9 cases per 100,000 population. In 2005, 8724 cases of primary and secondary syphilis were reported to CDC, up from 7980 in 2004, representing an increase of 9.3%; the corresponding incidence of primary and secondary syphilis per 100,000 population increased from 2.7 in 2004 to 3.0 in 2005—an increase of 11.1%. This increase involved most age groups.⁵⁴ In 2005, half of the total number of primary and secondary syphilis cases was reported from only 19 counties and two cities; 77.5% of the 3140 counties in the United States reported no cases of primary and secondary syphilis. One caution is that remarkable shift in the type of health-care facilities providing STI care in the United States may influence STI reporting: the proportion of primary and secondary syphilis cases reported from sources other than STD clinics increased from 25.6% in 1990 to 68.7% in 2005.

In 2005, the overall rate of congenital syphilis was 8 per 100,000 population in the United States. Between 1996 and 2005, the average yearly percentage decrease in the congenital syphilis rate was 14.1%.

Throughout much of Europe, following the emergence of HIV/AIDS, rates of infectious syphilis fell to their lowest levels in many countries by the early 1990s (Fig. 5-8A, 5-8B, 5-8C), although following 1990 and the end of the Soviet Union, syphilis increased dramatically in many of the former Soviet States. The declines in Western Europe were accompanied by reductions in the incidence of congenital syphilis and a continued fall in tertiary disease. In 1995 all countries of the EU except Germany, reported fewer than 300 cases of infectious syphilis.⁵² Most cases that did occur involved migrants from countries with a high prevalence of syphilis, or locals who were exposed to syphilis outside of Western Europe. In many Northern and Western European countries, syphilis incidence started to increase again in 1996.

Several outbreaks of infectious syphilis in the UK over the past decade⁹¹ have affected MSM, as well as heterosexual men and women, newborns, drug users, and sex workers.⁵² France, Belgium, the Netherlands, Denmark, Finland, and Austria all reported outbreaks of syphilis and increases in syphilis incidence. Syphilis incidence began to increase in large metropolitan German cities starting in 2000. Syphilis outbreaks and increased incidence of syphilis, mostly concentrated among MSM, have been reported in Ireland, Norway, and Sweden since 2000.

In Moscow, the prevalence of syphilis among pregnant women increased from 0.02% in 1990 to 1.10% in 1998⁹¹ and the number of babies infected with congenital syphilis in

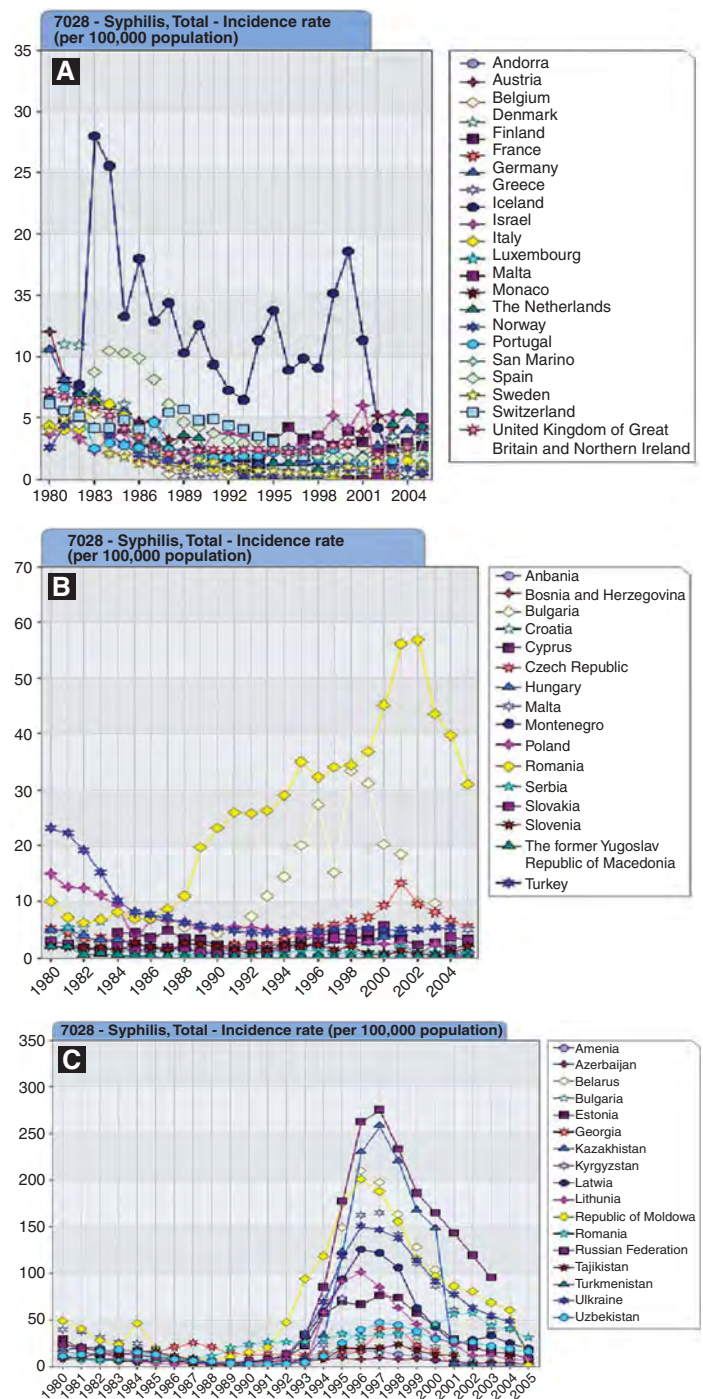


FIGURE 5-8 A. Syphilis, West, 1980–2005. (From Ulrich Laukamm-Josten, Division of Health Programmes, Communicable Diseases Section, World Health Organization Regional Office for Europe, Copenhagen.) **B.** Syphilis, Centre, 1980–2005. (From Ulrich Laukamm-Josten, Division of Health Programmes, Communicable Diseases Section, World Health Organization Regional Office for Europe, Copenhagen.) **C.** Syphilis, East, 1980–2005. (From Ulrich Laukamm-Josten, Division of Health Programmes, Communicable Diseases Section, World Health Organization Regional Office for Europe, Copenhagen.)

Russia increased from 15 in 1990 to 730 in 1999. The sharp increase in syphilis in former Soviet States during the 1990s, followed by declining incidence of syphilis in these States during the late 1990s and early part of this century,

provides an important case study, not fully explicated as yet, but probably reflecting multiple social and public health factors driving rates up after 1990, as discussed in the next section, followed by increased AIDS and related behavior change plus reinvigorated public health and clinical measures that are proving effective throughout the region.

In many developing countries, syphilis has remained very common, although in many regions where syndromic management of genital ulcers and urethral discharge were implemented, the incidence of syphilis has fallen dramatically. Reported prevalences of syphilis among pregnant women in recent years were 2.4% in Sudan, 3.0% in Morocco, 3.1% in Djibouti, 3.5% in Papua New Guinea, 4% in Cambodia, and 8% in the South Pacific Islands.⁹² In sub-Saharan Africa congenital syphilis was the most common cause of perinatal mortality in the 1990s, accounting for around 26% of stillbirths and 11% of neonatal deaths. A survey of 22 sub-Saharan African countries found that although universal screening of pregnant women for syphilis was recommended policy in 17 countries, only 38% of women attending antenatal clinics were actually screened and treated.⁹³

The recent history of syphilis epidemiology in China presents a unique pattern.^{94,95} After a massive syphilis epidemic during the first half of the twentieth century, syphilis was eliminated in China for 20 years between 1960 and 1980. Recent political and economic changes in Chinese society have been followed by a resurgence of STI epidemics. In 2005, the rate of reported primary and secondary syphilis was 5.7 cases per 100,000 persons compared to only 0.2 cases of all stages of syphilis per 100,000 population in 1993—a 25-fold increased risk.^{94,95} The rate of congenital syphilis increased from 0.01 cases per 100,000 live births in 1991 to 19.68 cases per 100,000 live births in 2005; an average yearly increase of 71.9%. Both biological and social factors may have contributed to the resurgence of syphilis in China. The control of syphilis may have created a population which was highly susceptible to infection.^{4,96} The country's explosive economic growth which brought with it increased economic inequality, increased internal and external migration and travel, with resurgent commercial sex work. The apparent absence of many STIs over a period of nearly 2 decades led to attrition of public health and clinical infrastructure for prevention and control of STIs, leaving the country ill-prepared to cope with resurgent spread of STIs.

■ INFLUENCES OF SOCIODEMOGRAPHIC FACTORS ON SYPHILIS MORBIDITY

In Europe, the resurgence of syphilis among MSM has been associated with increasing high-risk sexual behavior with development of new highly connected sexual networks, use of recreational drugs including ecstasy and gamma hydroxybutyrate,

sexual activity overseas, and HIV coinfection.^{97–99} Among heterosexuals risk factors have included migration from high prevalence countries, sexual activity overseas, contact with sex workers and illegal and recreational drug use.⁹⁷

In the United States, increases in syphilis among MSM have similarly been associated with high risk sexual behavior, recreational drug use, including methamphetamines, and high rates of HIV coinfection.^{100–105} Internet-based sex partner recruitment for unprotected sex has emerged as an important risk factor for syphilis transmission among MSM.^{106,107} Among heterosexuals, particularly in urban areas and in southern United States, syphilis has been associated with race-ethnicity assortative and risk group dissortative sexual mixing,⁶¹ incarceration,¹⁰⁸ concurrent partnerships,^{108,109} and perhaps culturally unacceptable prevention services. Societal parameters associated with syphilis in the past are undergoing worrisome trends. In 2000, 65% of black male high school dropouts in their twenties were jobless (unable to find work, not seeking work or incarcerated). By 2004, 72% of black male high school dropouts in their twenties were jobless compared to 34% of white and 19% of Hispanic dropouts. Incarceration rates have reached historic highs; in 2004, 21% of black men who did not attend college were incarcerated.¹¹⁰

■ THE ROLE OF IMMUNITY

Partial immunity to syphilis may influence trends in syphilis incidence.^{4,96,111} Mathematical modeling using data from cities in the United States over 50 years suggests that syphilis incidence may follow a natural cycle that peaks at 8–11 year intervals, possibly related to increasing and declining immunity in populations with particularly high rates of syphilis. The same work also revealed that since the early 1980s, syphilis rates in different cities have risen and fallen at the same time rather than varying independently, as they did earlier. This observation points to the emergence of spatially bridged sexual networks, at least among MSM.

CHLAMYDIA TRACHOMATIS INFECTIONS

Chlamydia trachomatis is still the most prevalent sexually transmitted bacterial infection in North America and Europe.^{52,54} It is difficult to describe temporal trends in the incidence of chlamydial infection because of the large proportion of asymptomatic infections; the increasing use of increasingly sensitive diagnostic tests, with expansion of chlamydia screening activities in Europe and the United States; the increased emphasis on case reporting by providers; and the improvements in the information systems for reporting. In many European countries, case reporting of genital chlamydial infections is not mandatory; consequently, relatively little information is available from national surveillance

sources. For example, in Ireland, the reported numbers of cases of chlamydial infection remained stable during the early 1990s at around 200 cases per year. In 1995, there was an increase of 84.2% compared to 1994. During the following 5 years there were an increasing number of cases reported each year reaching 1649 in 2001,⁵² still, undoubtedly, far fewer than the total number of new infections actually occurring. In Norway, reported chlamydia cases declined from a peak of 20,000 cases in 1988 to 12,500 cases in 1998. In Sweden, chlamydia incidence per 100,000 declined from 350 in 1989 to 160 per year from 1993 through 1997, then increasing to 276 in 2002—the same level of infection as 10 years earlier. In England, Wales, and Northern Ireland the number of uncomplicated chlamydia diagnoses in Genito Urinary Medicine clinics has risen steadily since the mid 1990s. Increases were also observed in Scotland and Vienna.⁵²

In the United States, by 2000, all 50 states and the District of Columbia had regulations requiring the reporting of chlamydia cases. From 1986 through 2005, the rates of reported chlamydia infection increased from 35.2 per 100,000 to 332.5 per 100,000 population. (Fig. 5-9) In 2005, the rate of reported chlamydia infection among women in the United States (496.5 cases per 100,000 women) was over 3 times higher than the rate among men (161.1 cases per 100,000 men) reflecting the greater number of women screened for chlamydia. However, use of nucleic acid amplification tests, particularly on urine, increasingly facilitates the identification of men with asymptomatic infection. From 2001 through 2005, the chlamydia infection incidence in men increased by 43.5% from 112.3 to 161.1 cases per 100,000 males. During the same period, rates per 100,000 women per year increased only by 15.6% from 429.6 to 496.5 cases.⁵⁴ Since 1996, chlamydia incidence has increased for all racial-ethnic groups. (Fig. 5-10) In 2005, the incidence of chlamydia among blacks was over 8 times higher than that of whites or Asian-Pacific Islanders; 1247.0 and 152.1 cases per 100,000, respectively. Incidence rates among American Indian/Alaska Natives (748.7 per 100,000) and Hispanics (459.0 per 100,000) were intermediate. In 2005, the highest incidence of reported chlamydia per 100,000 women was among 15–19-year-olds (2796.6) and 20–24-year olds (2,691.1). Age specific incidence per 100,000 men was highest in the 20–24-year age group (804.7). Initiated in 1988 and expanded in 1993, the chlamydia screening and prevalence-monitoring project provides chlamydia test positivity data for all 10 of the U.S. Health and Human Services regions. In 2005, the median state-specific chlamydia test positivity among 15–24-year-old women tested during visits to selected family planning clinics in all states and outlying areas was 6.3%. Chlamydia test positivity has remained stable within regions between 2001 and 2005 even after adjusting to account for use of increasingly sensitive laboratory test methods (Fig. 5-11).

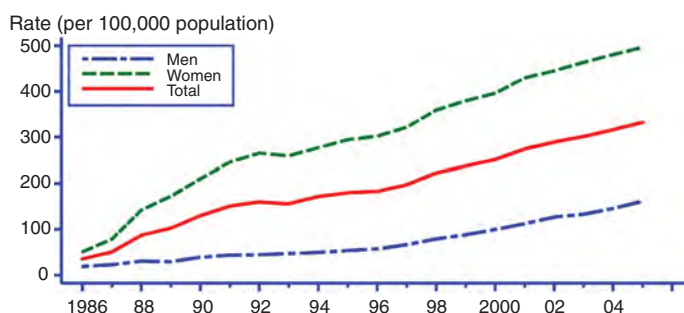


FIGURE 5-9. Chlamydia rates: total and by sex: United States, 1986–2005. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance*, 2005. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

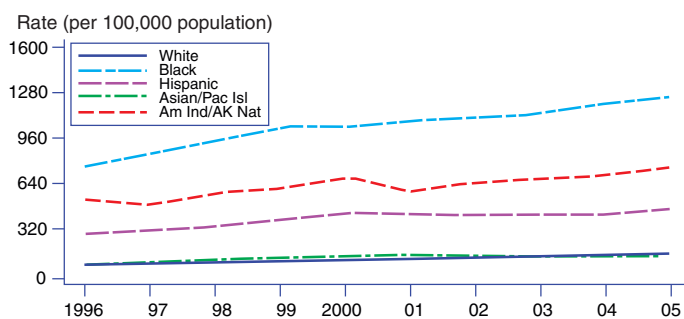
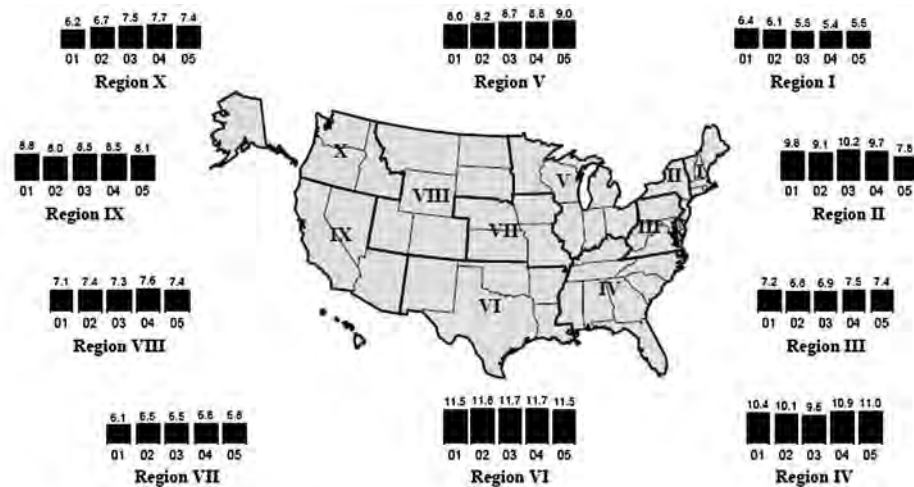


FIGURE 5-10. Chlamydia rates by race/ethnicity: United States, 1996–2005. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance*, 2005. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

Given the frequently asymptomatic nature of infections, our understanding of chlamydia epidemiology is greatly enhanced by population-based prevalence studies. In Britain in 2000, National Surveys of Sexual Attitudes and Lifestyles (NATSAL 2000) assessed the prevalence of *C. trachomatis* infection detected by urine testing.¹¹² Among 18–44-year-old men and women, *C. trachomatis* was found in 2.2% of men and 1.5% of women; age specific prevalence was highest among men aged 25–34 (3.1%) and women aged 16–24 years (3.0%). Nonmarried status, age, partner concurrency, or two or more partners in the previous year were independently associated with chlamydial infection. In the United States, data collected between 1999 and 2002 representing the noninstitutionalized civilian population between 14 and 39 years included urine samples tested for chlamydia using the ligase chain reaction assay. The prevalence of chlamydial infection was 2.2% and was similar for men and women. Among women the highest prevalence was among 14–19-year-olds (4.6%); among men the highest prevalence was among 20–29-year-olds (3.2%).¹¹³ Prevalence was higher among non-Hispanic blacks (6.4%) than among non-Hispanic whites (1.5%). Among non-Hispanic blacks 14–19 years of age, the prevalence of chlamydial infection was 11.1%. While overall chlamydia prevalence was similar in the British and



Note: Trends adjusted for changes in laboratory test method and associated increases in test sensitivity.

FIGURE 5-11. Chlamydia—Trends in positivity among 15- to 24-year-old women tested in family planning clinics by HHS region, 2001–2005. (From Regional Infertility Prevention Projects; Office of Population Affairs; Local and State STD Control Programs; Centers for Disease Control and Prevention.)

American samples, the prevalence was higher in men than in women in Britain but not in the United States. In another representative sample of 18–26-year-old U.S. men and women in 2001–2002, chlamydia prevalence was also measured using first-void urine specimens and ligase chain reaction assay.¹¹⁴ The overall prevalence of chlamydial infection was 4.19%. Women (4.74%) were more likely to be infected than men (3.67%). The prevalence of chlamydial infection was highest among black women (13.95%) and black men (11.12%) and lowest among Asian men (1.14%), white men (1.38%), and white women (2.52%). Prevalence was highest in the south (5.39%) and lowest in the northeast (2.39%).

Recently it has been hypothesized that immunity may play a role in the epidemiology of chlamydial infections^{115,116}—as has also been hypothesized for syphilis.⁴ In British Columbia, Canada, interventions to control chlamydial infections, including case identification, antibiotic treatment, and contact tracing have been undertaken since 1991. Rates of infection decreased from 1991 to 1996 but started increasing in 1998. In addition, the rate of reinfection with chlamydia has been increasing since 1991. Brunham et al. have suggested that screening and treatment in British Columbia have shortened the duration of chlamydial infections, attenuating the immune response, leading to increasing susceptibility to reinfection at the population level.¹¹⁵ This argument would be consistent with the stable or upward trend in the proportions of tests for chlamydial infection that are positive (after adjusting for changing test sensitivity) among women tested in the U.S. chlamydia screening project (Fig. 5-11). On the other hand, others argue that stable prevalences of chlamydial infection could reflect trends toward screening of higher risk women.

Moreover, there is evidence of inadequate patterns and coverage of screening and treatment delivered to females, not to mention males. Because screening and treatment represent the predominant intervention strategies employed for chlamydia control in the developed world, more direct testing of these hypotheses is very important.^{117–120}

■ CHANCROID

Once endemic in Europe and North America, chancroid began a steady decline early in the twentieth century, before the discovery of antibiotics. Social changes including changes in patterns of commercial sex may have disrupted the conditions necessary to sustain chancroid as an endemic disease. There is evidence that male circumcision reduces the risk of male acquisition of chancroid. Sporadic outbreaks can be easily controlled through effective curative and preventive services provided to sex workers and their clients. More recently, chancroid prevalence has declined in countries like the Philippines, Senegal, and Thailand.¹²¹ In the United States, since 1987, reported cases of chancroid declined steadily until 2001 when 38 cases were reported⁵⁴ (Fig. 5-12). In 2005, only 17 cases of chancroid were reported; only 10 states and one outlying area reported one or more cases of chancroid. Because *Haemophilus ducreyi*, the causative agent of chancroid, is difficult to culture and nucleic acid amplification tests for the pathogen are not widely available, chancroid cases may be underdiagnosed.

■ VAGINAL TRICHOMONIASIS AND OTHER VAGINAL INFECTIONS

Vaginal trichomoniasis and other vaginal infections are not reportable in the United States and Europe. In the United States, trend data are limited to estimates of initial visits to

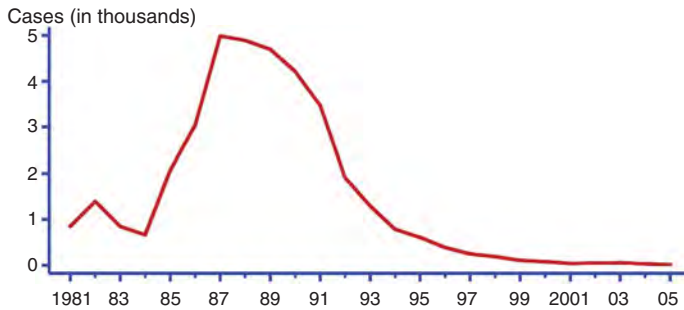


FIGURE 5-12. Chancroid—Reported cases: United States, 1981–2005. (From Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2005*. Atlanta, GA: US Department of Health and Human Services, Nov 2006.)

physicians' offices for these conditions from the National Disease and Therapeutic Index (NDTI).⁵⁴ These estimates suggest that incidence of trichomoniasis has declined from an estimated 579,000 in 1996 to 190,000 in 1988 and has remained relatively unchanged since then—there were 165,000 visits in 2005. (Fig. 5-13) These likely represent under estimates of incidence, as discussed below. During the same period initial visits for other vaginal infections of undefined etiology increased from an estimated 1,155,000 in 1966 to 4,474,000 in 1989, declined irregularly to 3,100,000 in 1997 but has been increasing irregularly since then—there were 4,071,000 visits in 2005.⁵⁴

In a recent study,¹²² U.S. women aged 14–49 participating in the National Health and Examination Survey (NHANES) cycles 2001–2004 provided self-collected vaginal swabs; vaginal fluids extracted from the swabs were evaluated for *Trichomonas vaginalis* using polymerase chain reaction (PCR). The overall prevalence of *T. vaginalis* was 3.1%; it was highest among non-Hispanic blacks (13.3%) and lower among Mexican Americans (1.8%) and non-Hispanic whites (1.3%). Factors associated with increased risk for *T. vaginalis* in multivariable analyses included non-Hispanic black race-ethnicity, being born in the United States, greater numbers of lifetime sex partners, increasing age, lower educational attainment, poverty, and douching.

Another recent study estimated the prevalence of trichomoniasis in young adults (mean age = 22 years) in the United States by testing urine specimens collected from men and women participating in the National Longitudinal Study of Adolescent Health.¹²³ In this study, the estimated overall prevalence of trichomoniasis was 2.3%. The prevalence was slightly higher in women (2.8%) than in men (1.7%). The prevalence increased with age and varied by region, with the South having the highest prevalence (2.8%). The prevalence was highest among black women (10.5%) and lowest among white women (1.1%). Among men, prevalence was highest among Native American (4.1%) and black men (3.3%) and lowest among white men (1.3%).¹²³

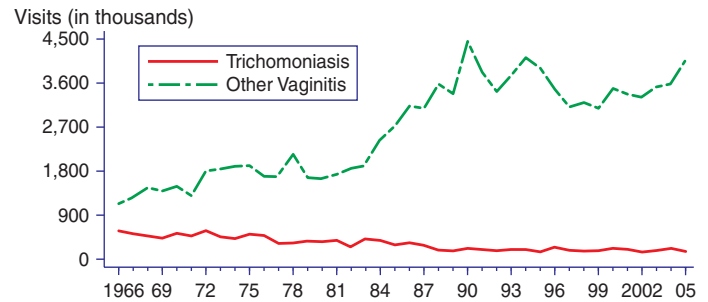


FIGURE 5-13. Trichomoniasis and other vaginal infections in women—Initial visits to physicians' offices: United States, 1966–2005. (From National Disease and Therapeutic Index (IMS Health).)

■ GENITAL HERPES

Viral STIs are not notifiable in most European countries and relatively limited temporal trend data have been published.⁵² Genital HSV infection is the most common ulcerative STI in the UK and the United States. However, many patients with genital herpes do not perceive or recognize symptoms of the infection, and clinical case-reports grossly underrepresent the true incidence of genital herpes as reflected by serologic testing for antibody to HSV-2. Increasing case recognition over time does, however, provide one indication of increasing incidence. Between 1972 and 2002, the number of genital HSV diagnoses made at GUM clinics in the UK increased twofold in males and ninefold in females. The number of diagnoses stabilized and fell briefly in the mid-1980s possibly because of changes in sexual behavior following extensive media coverage of AIDS. In 2002, 18,392 new cases were reported in England, Wales, and Northern Ireland. For females and males, highest rates were reported in the 20–24-year olds—2053 per 100,000 population and 93 per 100,000, respectively. In Ireland in 2001, notified cases of genital HSV increased by 23.0% on the previous year. HSV cases increased from 78 (2.2/100,000) in 1989 to 198 (5.5/100,000) in 1995 and 331 (8.5/100,000) in 2001. Between 1995 and 2001, the highest rates per 100,000 population were consistently in females and where age group was known, 20–29 year olds.⁵²

Virtually all seroepidemiological studies in Europe, the United States, and elsewhere show that HSV-2 seroprevalence increases with age (reflecting long-term persistence of antibody), and the number of partners during the previous year, and that HSV-2 seroprevalence is substantially higher in females than in males. An increasing proportion of first episodes of genital herpes has been attributed to HSV-1 rather than HSV-2 in several settings.

A recent review of published HSV type-specific seroepidemiologic surveys found striking variations in HSV-2 prevalence in Western Europe.

HSV-2 prevalence appears to be higher in Northern Europe and in North America than in Western and Southern

Europe. The highest prevalence of HSV-2 infection was found among women in Greenland, reaching 57% among 20–26-year olds and 74% in 25–39-year olds. In Scandinavia, HSV-2 prevalence was relatively higher than in other areas of Europe—15–35% among women between 25 and 35 years of age.¹²⁴ In Spain, HSV-2 prevalence was low, 2–6% in large samples of men and women between 14 and 45 years of age from different geographic areas. In Italy, HSV-2 prevalence was reportedly even lower; 0.1% in a national sample of male draftees 18–25 years of age and 1.1% among patients attending a hepatitis B immunization center (median age 26 years). In all studies conducted in the UK, HSV-2 seroprevalence was 9% for men and women of all ages.

In the United States, genital HSV infection spread rapidly from the mid-1960s until the onset of the AIDS epidemic. Initial patient consultations with private physicians in office practice for symptomatic genital herpes in the United States have been monitored since 1966 using data from the NDTI—a probability sample of private physician's practices carried out by IMS Health. The annual number of initial visits for genital herpes increased 12.5-fold from 18,000 in 1966, when it was also seen relatively infrequently in STD clinics, to over 235,000 visits in 1991; the annual number has fluctuated since then, with the highest estimated number of initial cases seen in 2004 (269,000 cases) and 2005 (266,000) (Fig. 5-14).



FIGURE 5-14. Genital herpes—Initial visits to physicians' offices: United States, 1966–2005. (From National Disease and Therapeutic Index (IMS Health).)

People 20–29 years of age had more office visits than other age groups. Women outnumbered men in genital herpes-related physician consultations, likely reflecting true gender differentials in genital herpes incidence based upon seroprevalence differences.

During the 1970s and 1980s, media attention may have increased both physicians' and patients' awareness of the signs and symptoms of genital herpes, increasing the proportions of patients with genital herpes who sought physician consultations and received a correct diagnosis.¹²⁵ The recent availability of more specific serologic tests for HSV-2 may also be increasing physician diagnoses of genital herpes. However, based on the percentage of adults with serum antibody, the true annual incidence of new HSV-2 infections in the United States clearly exceeds the number of physician consultations for newly diagnosed symptomatic genital infections by several-fold. (Fig. 5-14)

The most recent data on HSV-2 seroprevalence in the United States were collected in a stratified random sample of the United States population through the NHANES during 1988 through 1994 and 1999 through 2004.¹²⁶ Persons between ages 14 and 49 were included in the analyses. The overall age-adjusted HSV-2 seroprevalence was to 21.0% in the period 1988–1994, decreasing to 17.0% in 1999–2004, representing a relative decline of 19% between the two surveys. Decreases in HSV-2 seroprevalence were concentrated in persons aged 14–19 years between 1988 and 2004. In adolescents aged 17–19 and in young adults the decreases were significant even after adjusting for changes in sexual behaviors. The seroprevalence of HSV-1 also decreased from 62% to 57.7% between the two surveys—a relative decrease of 6.9%. HSV-2 seroprevalence was higher among women, non-Hispanic blacks, and 40–49-year olds (Fig. 5-15), as well as among the widowed and the divorced, those in greater poverty, those with higher education, those who reported ever using cocaine, and those who reported earlier age at sexual debut. HSV-2

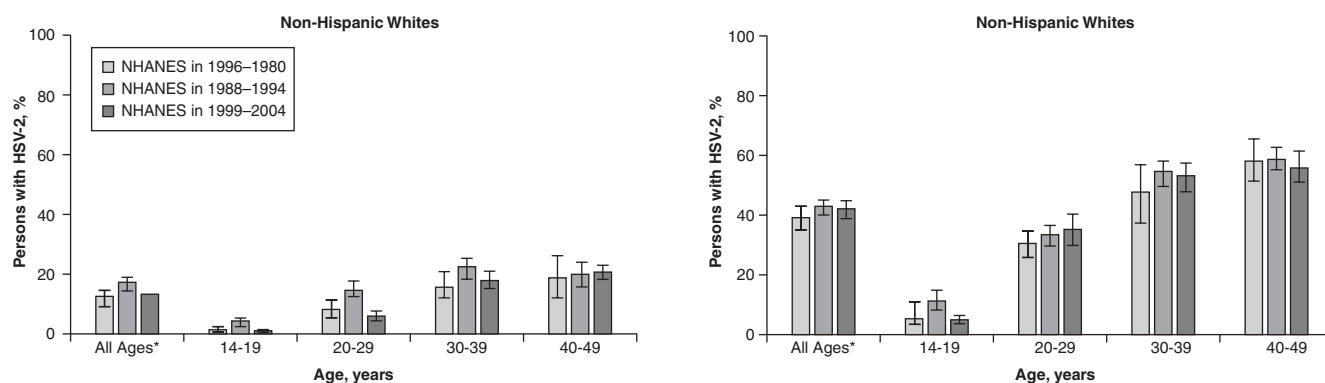


FIGURE 5-15. Herpes simplex virus type 2 seroprevalence in non-Hispanic whites and non-Hispanic blacks by age, on NHANES in 1976–1980, 1988–1994, and 1999–2004. (From Xu F, et al. *JAMA* 2006; 296(8): 971. Copyright© 2006. American Medical Association. All rights reserved.)

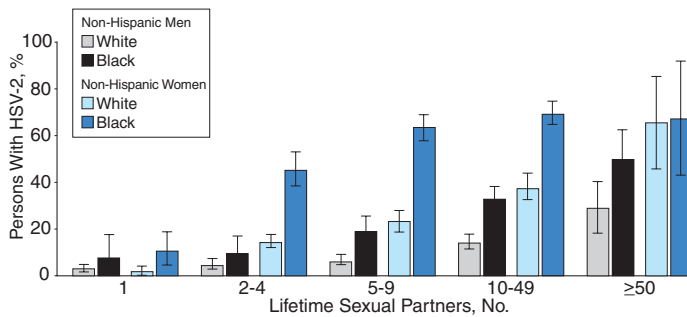


FIGURE 5-16. Age-adjusted herpes simplex virus type 2 seroprevalence according to the lifetime number of sex partners, by race/ethnicity and sex on NHANES in 1999–2004. (From Xu F, et al. *JAMA*. 2006; 296(8): 967.)

seroprevalence increased with reported number of lifetime sex partners. (Fig. 5-16) These findings may mark a reversal in the trajectory of increasing HSV-2 seroprevalence in the United States.

■ GENITAL HUMAN PAPILLOMAVIRUS INFECTIONS

The associations between certain types of genital or anal HPV infection and precancerous or invasive lesions of the cervix, vagina, vulva, and penis and anus have been clearly documented. Genital HPV infections are the most prevalent STIs in the United States and in the world. HPV infections other than those causing genital warts (usually types 6 and 11) are nearly always subclinical, not recognized by the infected individual. By screening for HPV DNA every 3 months, using PCR amplification tests, the cumulative incidence of genital HPV infections in one study was 43% over a 3-year period in one study of sexually active female University students¹²⁷ and 32% over a 2-year period in another.¹²⁸ Serologic tests for antibody to those types of HPV found in the genital tract help further define the epidemiology of genital HPV infection in the same way that serologic tests have elucidated the epidemiology of HSV-2 infection. Based on pooled data from 11 case-control studies of the association between cervical cancer and HPV infection from multiple countries, 15 HPV types have been classified as high risk for development of cervical cancer, three have been classified as probable high risk, 12 have been classified as low risk, and three as undetermined risk.¹²⁹ A recent pooled analysis showed the age standardized prevalence of all types of HPV infection to vary 20-fold among different regions of the world.¹³⁰ The prevalence of high risk types of the virus was 18% in sub-Saharan Africa, 5% in Asia, 10% in South America, and 4% in Europe. The prevalence of HPV infection is highest among young women and appears to drop-off with increasing age.¹³¹ However, some studies suggest a peak prevalence of HPV infection in women below age 25, a decrease among women between ages 35 and 54, and a second peak after age 55; the increase in the older age group may be attributable to a cohort effect or reactivation of latent virus. Cohort studies which looked at HPV seroprevalence

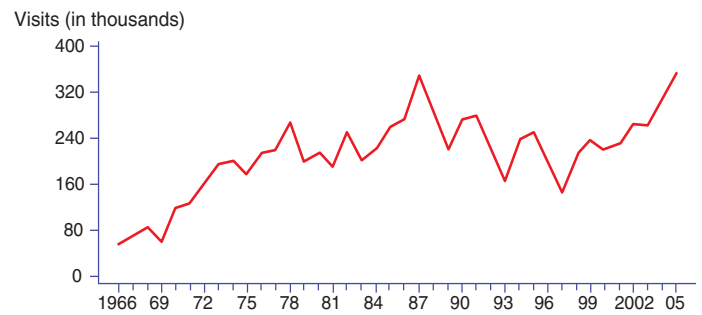


FIGURE 5-17. Genital warts—Initial visits to physicians' offices: United States, 1966–2005. (From National Disease and Therapeutic Index (IMS Health).)

suggest increases in the seroprevalence of some HPV types in Europe over the 1980s and 1990s.¹³¹ Risk factors for HPV infection include increased number of sex partners, increased number of male partners' lifetime partners, a short-time interval between meeting a partner and engaging in sexual intercourse, increased age difference between partners, and current smoking.¹²⁸

Because external genital warts are mostly caused by type 6 or 11 HPV, physician–patient consultations for this condition provide one indicator of trends in the incidence of genital infections by HPV types 6–11. Few European countries collect surveillance data on genital warts.⁵²

In the United States, the NDTI survey of physicians in private practice indicates that initial visits to physician offices for genital warts increased from 55,695 in 1966 to over 351,370 in 1987; declined irregularly from 1987 to 1997, and then increased irregularly to reach an all-time high of 357,000 visits in 2005. (Fig. 5-17) The extent to which this rise and fall represents the natural history of the spread of the epidemic of HPV 6 and 11 through the U.S. population versus changes in health-care seeking or diagnosis versus a rise and fall in risk-taking behaviors, remains undefined.

Among sexually active women, the prevalence of cervical HPV DNA has been highest for teenagers and those in the early twenties, and lower for older women. The natural history of genital HPV infection in men remains largely undefined, although the short-term natural history of incident genital infection by various HPV types has been defined in women by serial cervicovaginal PCR testing, cervical cytology, and by serologic studies^{127,128} and is now being studied in men. Type specific serum antibody detectable by current assays develops slowly over several months in the majority of infected women.

The natural history of genital and anal HPV infections is altered by HIV-related immunosuppression and other types of immunosuppression. HIV immunosuppression is associated with increased amount and longer durations of HPV shedding and a related increased risk of cervical and anal high grade squamous intraepithelial lesions.^{132,133}

Based on these preliminary findings from cohort studies, and together with data from national surveys of sexual behavior (see the following), it is not unlikely that the majority of adults in the United States, perhaps three-quarters, have been infected with one or more types of genital HPV. With the advent of multitype HPV vaccines that have proven highly effective in preventing HPV infections and cervical neoplasia lesions in women, future studies will be able to examine the impact of such vaccines on preventing HPV acquisition, on whether such vaccines protect men from penile or anal HPV infection, on population-level HPV transmission, and on defining whether there is cross-protection against types of HPV not included in the vaccines.

STIs IN SPECIAL POPULATIONS

Special populations are disproportionately affected by STI morbidity in countries all over the world. In Europe, MSM, migrants, young people, and HIV-positive men are recognized as special populations with high-risk behaviors and high prevalence and incidence of STI.⁵² In the United States, sex workers, homeless persons, adolescents and adults in detention, and migrant workers are among special populations with high STI morbidity. The Institute of Medicine report on STIs emphasized the importance of outreach to these special populations for STI control.¹³⁴ In general, the prevalence of cervical infection is highest during the first few years after beginning sex work and declines with age and immunity; whereas serologic evidence of past STIs or chronic viral STIs increases with age, time since sexual debut, or increasing duration of sex work, reflecting cumulative acquisition of infection. Consistent condom use protects sex workers against many of these infections, although commercial sex in areas of very high STI endemicity unfortunately leads to high cumulative rates of STIs, including HIV, even among women reporting consistent condom use.^{135–137} Among MSM who are sex workers, including transvestites and transsexuals, receptive anal intercourse is customary, carrying particularly high risk of certain STIs, including HIV infection. In industrialized countries, rates of STIs among FSWs and MSM are highest among those using illicit drugs, such as methamphetamines, heroin, and cocaine.

For example, among 227 street-recruited injection drug using MSM in San Francisco, California, between January 2000 and November 2001, 68% reported being paid by another man for sex and HIV prevalence was 12%.¹³⁸

Multiple studies have demonstrated a high prevalence of STIs among persons entering jails and juvenile detention facilities.^{139–142} In some locations a substantial proportion of all early syphilis cases are reported from correction facilities.¹⁴² Chlamydia and gonorrhea screening and treatment in jails may lead to reductions of chlamydia and gonorrhea in

the community.¹⁴³ In 2005, STI screening data from corrections facilities were reported from 32 states for chlamydia, 29 states for gonorrhea, and 13 states for syphilis as part of the Corrections STD Prevalence Monitoring Project.⁵⁴ Among adolescent females entering 57 juvenile corrections facilities, the median chlamydia positivity by facility was 14.2%, whereas among adolescent males entering 87 juvenile corrections facilities, the median chlamydia positivity was 6%. Among women entering 38 adult corrections facilities, the median positivity for chlamydia was 7.4%. Among men entering 41 adult corrections facilities, the median chlamydia positivity was 8.1%.

The median prevalence of gonorrhea for females entering 38 juvenile corrections facilities was 4.7% and was 1% for males entering 65 juvenile corrections facilities. The median prevalence of gonorrhea for women entering 33 adult facilities was 2.8%, and for men entering 35 adult corrections facilities, was 2.3%. These high positivity rates suggest that persons entering corrections facilities may comprise an important, special population for STI prevention interventions.

STIs including HIV infection are major health problems among migrant workers.^{144,145} Limited access to health care, language and cultural barriers, and limited economic resources, combined with sexual behaviors that expose migrant workers to high-risk partners tend to perpetuate high levels of STI morbidity among this group.^{146,147}

Finally, one assessment of STI among homeless adolescents showed the following baseline prevalences of chlamydia, 4.2% for males and 6.3% for females; HSV type 2, 5.73% for males and 12.5% for females; hepatitis B virus, 3.6%; hepatitis C virus 5.0%; and HIV seroprevalence, 0.3%. The annualized incidence of STIs was significantly higher among females (16.7%) than among males (9.8%) and was associated with inconsistent condom use, and for females, with number of partners and sex with older partners. Among females, the incidence of HSV-2 was over 25% and the incidence of chlamydial infection was 12%. Incident hepatitis B virus and hepatitis C virus infection rates were 3.4% and 6.6%, respectively, and both were associated with injection drug use.¹⁴⁸ Another assessment of homeless adolescents in Denver, Colorado, found a chlamydia prevalence of 11.6% and a gonorrhea prevalence of 2.7%. Among first testers, 13% were positive for chlamydia and 3.7% were positive for gonorrhea.¹⁴⁹

DIRECT AND INDIRECT DETERMINANTS OF POPULATION TRANSMISSION DYNAMICS

Each of the three determinants of the rate of spread of STIs in a population, rate of exposure, efficiency of transmission per exposure, and duration of infectivity, are driven by a complex set of factors.

■ DETERMINANTS OF EXPOSURE: TRENDS AND PATTERNS OF SEXUAL BEHAVIOR

Our understanding of the relevant components of sexual behavior that influence risk of STIs, including HIV infection, has evolved considerably over the past few decades. A better understanding of the epidemiology of specific STIs, and the greater need for preventive interventions to change sexual behavior in the context of increasing viral STIs, initiated such changes in the early 1980s. The AIDS epidemic has been the single most important factor to both highlight the need for more systematic information on sexual behavior and facilitate an unprecedented increase in infection-related studies of sexual behavior.

The term “sexual behavior” involves many components: sexual experience and activity, age at sexual debut or “coitarche,” current and lifetime number of sex partners, frequency of sexual intercourse, consistency of sexual activity, mode of recruitment of sexual partners and duration of sexual unions, and types of sexual practice.¹⁵⁰ Although the conjoint distribution of the component variables in the population determines aggregate exposure to the risk of STIs, the specific relationship between each of these variables and the risk of various STIs with differing natural histories, and the distribution of these variables across population subgroups, have by no means been fully defined.

The population at risk for STIs has often been very simply defined in terms of age groups, often assuming that those between ages 15 and 45 may engage in sexual intercourse with new partners. Further refinements of this concept have included the population at risk, only the sexually experienced, defined as persons who have ever had sexual intercourse.¹⁵¹ However, current sexual activity, rather than sexual experience per se, is a more accurate measure of current exposure to the risk of STIs.¹⁵²

During the past decade interest in sexual behavior has also focused on special populations, particularly persons who exchange sex for money, drugs, or other goods and services. Sexual services have always functioned as an economic good in human societies. However, the expansion of capitalism and globalization has led to a marked expansion in the volume of commercial sexual transactions.⁷ The mobility of goods, services, and capital that accompanies globalization⁸ has resulted in large numbers of men and women from distant areas and different cultures exchanging sex in many societies. This presence has important implications for changes in sexual networks and for the ability of the health system to provide coverage to sex workers for preventive, diagnostic, and therapeutic services.

■ TRENDS IN SEXUAL BEHAVIOR

Overall, sexual attitudes and behaviors became steadily more liberal in the industrialized countries throughout

most of the twentieth century—at least until the recognition of the genital herpes epidemic and then of the HIV/AIDS epidemic. With the antibiotic era came less fear of the curable STIs, and with oral contraception in the early 1960s came partial elimination of the double standard of sexual behavior of men and women. The sexual revolution extended to homosexual and bisexual men at the same time. During the 1970s and 1980s, an increasing percentage of young women had premarital intercourse, and recent birth cohorts have had more partners than earlier birth cohorts. During the AIDS era, gay men decreased risky sexual behaviors but some young gay men have since resumed such behaviors.

Globally, sexual behavior data from 59 countries show substantial diversity in sexual behavior by region and sex which highlights the importance of social and economic factors in shaping sexual behavior.¹⁰ Understanding social and economic determinants is essential in the interpretation of sexual behavior data and in the development of effective, high impact interventions. Sexual behavior changes in response to a variety of factors. During the past few decades there have been major socioeconomic changes affecting poverty and income disparities, education, and employment. Demographic changes have taken place in the age structure of populations, timing and frequency of marriage, and in the scale of mobility and migration between and within countries, including seasonal labor, rural-to-urban movement, and social disruption due to war and political instabilities. Many of these changes have affected developed as well as developing countries.

Even among industrialized societies heterogeneity in sexual behavior parameters is remarkable. Proportions of women who had sex before age 15 increased in France, Australia, Britain, Norway, and the United States between the late 1970s and late 1990s. During the same period proportions of men who had sex before age 15 increased in Italy, Switzerland, Britain, and Norway but declined in Australia and the United States.¹⁰ In most developing countries the time between first sexual intercourse and living with a partner is longer for men (3–6 years) than for women (0–2 years). In industrialized countries, the duration of this period is the same for both men and women (about 5 years). Monogamy is the dominant pattern in most regions of the world and most people report only one recent sex partner but the proportion reporting multiple partnerships is generally higher in industrialized countries (Fig. 5-18). Worldwide, more men than women report multiple partnerships except in some industrialized countries, where the proportions of men and women who report multiple partnerships are similar.¹⁰ The mean age difference between married men and women is lower in industrialized countries (1.9 in Australia and 2.2 in United States) than in developing countries; data are not available on age differences between sex partners. According

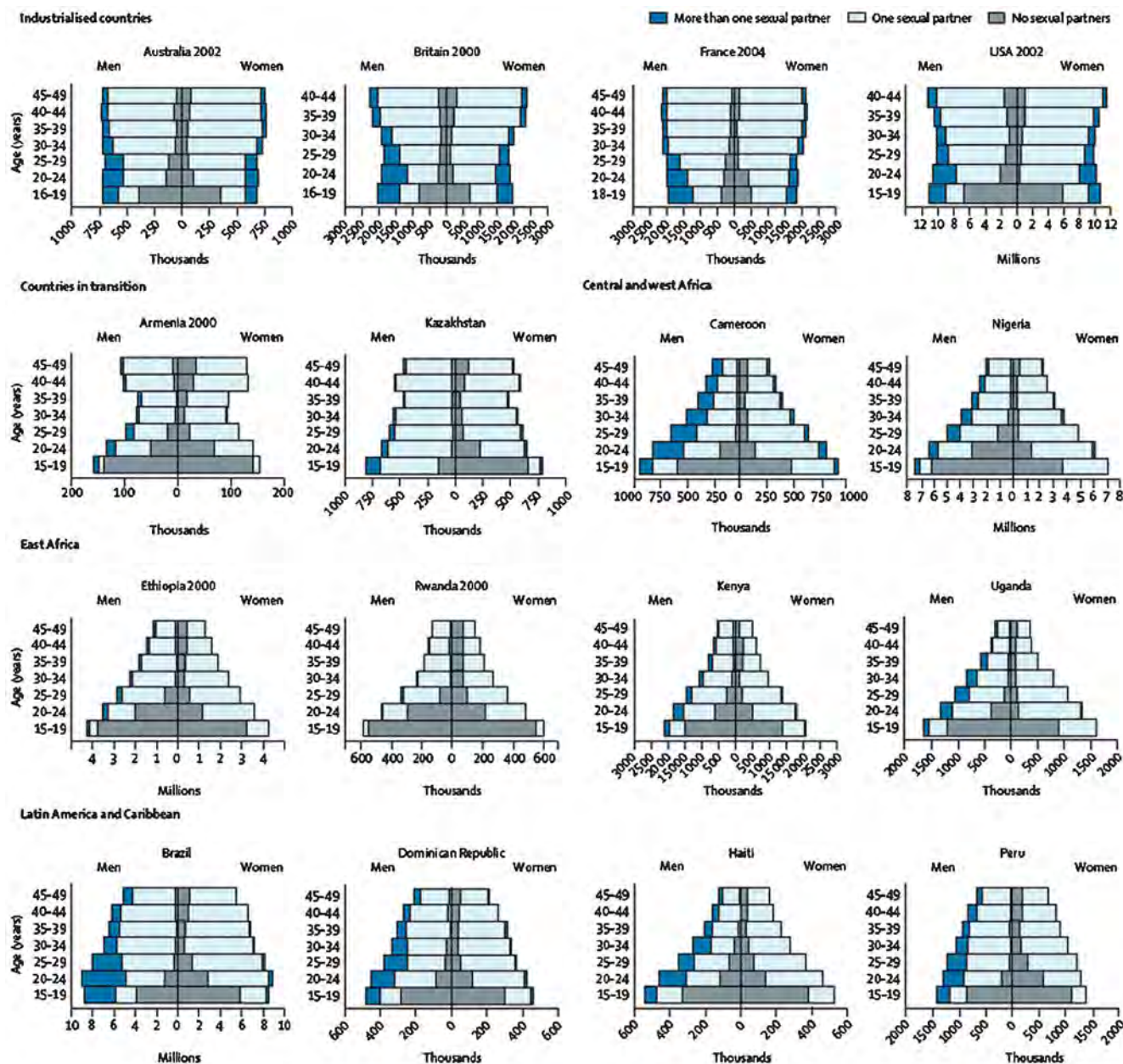


FIGURE 5-18. Population distribution by age and sex and number of sexual partners in the past year. (Reprinted from *The Lancet*, Vol. 368 (9548), Wellings K, et al. Sexual behaviour in context: a global perspective, pp.1707–1728, Copyright 2006, with permission from Elsevier.

to a recent review¹⁵³ of estimates of lifetime, prevalence of men having had sexual intercourse with other men is lower in industrialized countries (6% in the UK and 5% in France) than in most other regions of the world. Rates of condom use are generally higher in industrialized countries than in developing countries, especially in women.¹⁰ The increase in condom use in recent years has also often been more substantial in industrialized countries; the only exception to this pattern is France where women have reported declining condom use in more recent years. Global reviews of exchange of sex for money, drugs, or other goods report difficulties in estimating numbers of men and women who offer sexual services and their clients.¹⁵⁴

Two nationally representative surveys of sexual attitudes and life styles conducted in 1990–1991^{155–157} and 1999–2001¹⁵⁸ provide information on patterns of and temporal trends in sexual behavior of the general population in the UK.¹⁵⁸ The increased reporting of risky behaviors suggested by these data is consistent with changing cohabitation patterns and rising incidences of STIs. The comparison revealed increases over the 1990s in reporting of a wide range of behaviors including numbers of heterosexual partners, homosexual partnerships, concurrent partnerships, heterosexual anal sex, and payment for sex. For many of these parameters the magnitude of observed change was large. The number of heterosexual partners over the lifetime increased

from 8.6 to 12.7 for men and from 3.7 to 6.5 for women. The number of heterosexual partners over the past 5 years increased from 3.0 to 3.8 for men and from 1.7 to 2.4 for women.

The proportion reporting homosexual partnerships increased from 1.5% to 2.6% for men and from 0.8% to 2.6% for women. The proportion reporting concurrent partnerships increased from 11.4% to 14.6% among men and from 5.4% to 9.0% among women. Among men, the proportion reporting having paid for heterosexual or homosexual sex increased from 2.1% to 4.3%. The proportion of MSM who reported receptive anal intercourse in the past year also increased significantly.¹⁵⁸

In the United States, a survey of the general population in Seattle, WA, showed that between 1995 and 2004 the median number of lifetime sex partners increased from 7 to 8. Similarly, the proportion reporting any anal sex increased from 4.3% to 8.3% and those reporting any anal sex increased from 81.6% to 85.8%.¹⁵⁹ According to the National Survey of Family Growth, a nationally representative survey of sexual and reproductive behaviors, the proportion of 15–19-year-old men and women in the United States who have had sexual intercourse has declined between 1995 and 2002, from 49% to 45% for women and from 55% to 46% for men.¹⁶⁰

Trends in sexual behaviors of teenagers (15–19) in the United States are difficult to interpret. As of 2002, according to the National Survey of Family Growth, almost one in four teenagers who have *not* had sexual intercourse report having ever engaged in oral sex with an opposite sex partner (24% of males and 22% of females). Compared to published national analyses of oral sex among men in the 1995 National Survey of Adolescent Males,¹⁶¹ there has been no increase in oral sex practice among never married males aged 15–19 between 1995 and 2002. Overall, in 1995, 39% had ever given oral sex and 49% had ever received oral sex, compared with 38% and 51%, respectively, in 2002. However, in 2002, a greater proportion of never married teen males who had *not* had sexual intercourse reported ever receiving oral sex (21% in 2002 vs. 15% in 1995). Oral sex among never married teen males who had ever had sexual intercourse also increased from 1995 to 2002: 66% had ever given oral sex in 2002, compared with 61% in 1995; 84% had ever received oral sex in 2002, compared with 77% in 1995. Thus, the apparently stable overall trend in oral sex in part reflects the overall decline in the proportion of teenaged men who have had sexual intercourse. Trend data are not available for women.¹⁶² Older teens are more likely to report oral sex than younger teens. Interestingly, non-Hispanic black males are less likely than Hispanic and non-Hispanic white males to have ever given oral sex (21% vs. 37% and 45%). Among females, Hispanics are less likely than non-Hispanic whites to have oral sex experience (47% vs. 58%) and non-Hispanic white females are more likely than Hispanic and non-Hispanic black females to

have ever given oral sex (51% versus 34% vs. 25%). Finally, teens whose mothers have less education are less likely to report oral sex experience than those whose mothers have more education. Similarly, teens from families with higher incomes are more likely to report oral sex compared to those whose families have less income.¹⁶² These differences in patterns of oral sex practice by race-ethnicity and socioeconomic status may contribute to disparities in STI rates along these societal parameters. In addition, one in ten adolescent males and females had engaged in heterosexual anal sex.¹⁶³ There were no race-ethnicity differentials in this practice. The low prevalence of this practice may suggest that its patterns would not have much impact on sexual transmission at this time.

Oral and anal sex are prevalent among American adults. According to the 2002 National Survey of Family Growth (NSFG), overall, 30% of women and 34% of men had engaged in heterosexual anal sex.¹⁶³ The percentage of U.S. inhabitants who have ever had anal sex peaked among 30–34-year olds, with 44% of white women and 50% of African American men reporting that they had anal sex. Approximately, one-third of U.S. inhabitants aged 35–44 years reported having had anal sex; this reflects the fact that younger cohorts are more likely to engage in anal sex. As compared to anal sex, higher percentages of men and women reported ever receiving and giving oral sex—over 75%. Higher percentages of whites (84.8%) compared to Hispanics (64.2%) and non-Hispanic blacks (73.6%) reported ever receiving oral sex. Similarly, a higher proportion of whites (84.3%) compared to Hispanics (60.7%) reported ever giving oral sex. The proportion of non-Hispanic blacks who reported ever giving oral sex was lower (57.4%) compared to the other racial ethnic categories.¹⁶³ Only 6% of men and women used a condom at last oral sex; 25% of men and 16% of women reported condom use during last anal sex.

According to the 2002 NSFG, 69% of all reproductive age women reported having one sex partner over the past year; 20.8% reported no partners, 6.1% reported two partners, and 4.1% reported three or more partners. Racial ethnic differences in reported number of sex partners were small (Fig. 5-19).¹⁶³

In this group, 4.6% of Hispanic women, 10% of white women, and 9% of black women have had 15 or more male sex partners in their lifetimes. Among women 30–44 years of age, the median number of male sex partners in their lifetimes was about four.¹⁶⁴

Among 15–44-year-old men, 63.3% reported having one sex partner over the past year; 21.1% reported no partners; 7.7% reported 2 partners, 3.7% reported 3 partners, and 4.2% reported 4 or more partners (Fig. 5-20).¹⁶³ In this group, 18% of Hispanic men, 22% of white men, and 34% of black men have had 15 or more female sex partners in their lifetimes. Men 30–44 years of age reported an average (median) of 6–8 female sex partners in their lifetimes.¹⁶⁴

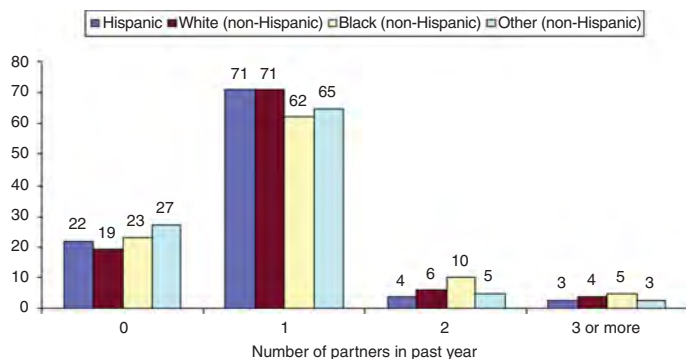


FIGURE 5-19. Number of sex partners in past year for women by ethnicity: 2002. (From Jami Leichliter, Centers for Disease Control and Prevention, Division of STD Prevention, Atlanta GA.)

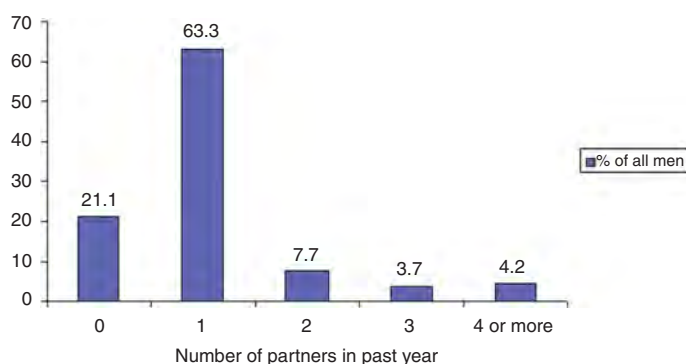


FIGURE 5-20. Percentage of males 15–44 years of age by number of sex partners in past year (overall): 2002. (From Jami Leichliter, Centers for Disease Control and Prevention, Division of STD Prevention, Atlanta GA.)

Preliminary analyses suggest some change in the number of sex partners over the past year reported by 15–44-year-old unmarried U.S. women between 1995 and 2002. The percentage of Hispanic women who reported two or more partners decreased from 13% in 1995 to 11.1% in 2002; percentages of black women who reported two or more partners declined from 23.8% in 1995 to 18.5% in 2002, while the percentage of white women who reported two or more partners increased slightly from 18.4% in 1995 to 19% in 2002. (Jami Leichliter, personal communication February 23, 2007) These findings suggest that except among whites, women may have decreased their number of sex partners while expanding their sexual repertoire.

Among reproductive age women in 2002, 11% reported any sexual activity ever with another female. The proportion of women who had a female sexual partner in the last 12 months was 4.4%; the proportion of women who had only female partners in the last 12 months was 1.3%. Among 15–44-year-old men, 5.7% reported having had oral sex with another male at some point in their lives; 3.7% reported having had anal sex with another male. Overall, 6% reported having had oral or anal sex with another male. Among men 2.9% reported having had a male sex partner over the previous 12 months; 16% had only male sex partners over the

previous 12 months. Approximately, 1% of men and 3% of women 15–44 years of age have had both male and female sex partners over the previous 12 months.¹⁶⁴

Among 15–44-year-old men who had at least one sex partner in the past year, 40% used a condom at their most recent sex; 65% of never married males and 24% of married males; 91% of men who ever had sex with another man and 36% of men who had never had sex with another man reported condom use during last sex.¹⁶⁴

The role of commercial sex in the epidemiology of STDs and sexual behavior, even though poorly understood, appears to be increasing. One study examined the epidemiology of female commercial sex contacts reported by men in the 1990 and 2000 National Surveys of Sexual Attitudes and Lifestyles (NATSAL) in the UK.¹⁶⁵ The proportion of men who reported paying women for sex in the previous 5 years increased from 2% in 1990 to 4.2% in 2000. Paying for sex was more frequent in men aged between 25 years and 34 years, who were never married, previously married, and lived in London in both surveys. There was no association between paying for sex and ethnicity, social class, homosexual contact, and injecting drug use. Men who paid for sex were more likely to report 10 or more sex partners in the previous 5 years but only 19.3% of their lifetime sex partners were commercial. Men who paid for sex were more likely to meet sex partners abroad and to report previous STIs. Only 15% among them reported having had an HIV test.¹⁶⁵ Prevalence of this behavior was higher among men attending a sexual health clinic in the UK.¹⁶⁶ A retrospective case note review showed that 10% of the male clinic attendees reported paid sex. The mean age was 34.7 years. The majority reported paying women, with 4.3% paying men for sex. Men reported paying for sex abroad (51%), locally (40%), elsewhere in the UK (11%), with only 1.7% paying for sex both in the UK and abroad. The majority (66%) had paid for sex within the previous 12 months. Almost half the men (43%) paid for sex while in another relationship.

In the United States, data on paid sex from a nationally representative sample are not available. Among a nationally representative U.S. sample of adolescents, 3.5% had ever exchanged sex for drugs or money.¹⁶⁷ In this nationally representative sample, among those who had so exchanged sex, 67.9% were boys. The odds of having ever exchanged sex were higher for African American youth (OR=1.75) and youth whose parents had high school education or less (OR=1.72). The elevated risk for STIs including HIV associated with exchange of sex for drugs or money may result from having more sex partners, riskier partners, and more unprotected sex.^{168,169} The exchange of sex for drugs, money, or other goods is observed among adults who use drugs, particularly crack cocaine.^{170–172} Among women who use crack cocaine, it is estimated that 70% have exchanged sex for drugs or money.¹⁷³ In a study of a nationally representative

sample of youths on the streets and a multicity sample of youths living in shelters in the United States, 28% and 10%, respectively, reported having ever exchanged sex for money or other things.¹⁷⁴

■ ROLE OF SEXUAL MIXING, SEXUAL NETWORKS, AND PARTNER CONCURRENCY

Some of the most important developments in our understanding of the role of sexual behavior in determining the probability of exposure between infected and uninfected persons (and thus the rate of spread of STIs in the population) in the 1990s have been in the understanding of patterns of partner mixing, sexual networks, and partner concurrency.^{175–181} Deterministic mathematical modeling has been used to describe how patterns of sex partner mixing, such as random, assortative (like with like), or disassortative, can influence the course of an HIV epidemic.¹⁷⁹ Concurrent partnerships, existence of “bridge” persons, who have sex both with members of high- and low-risk groups or with groups specifically found to have high STI prevalence and with groups with low STI prevalence all affect STI spread.^{61,182–188} High density sexual networks (i.e., those having a large number of sexual connections among all members of a group), variance in a population’s distribution of number of sex partners, and the extent to which so called “core groups” are embedded in the general population are all, in theory, associated with faster spread of STIs in the population, and higher STI rates.¹⁷⁷

In comparing sexual behaviors of African Americans and white Americans, available data from the National Health & Social Life Survey (NHSLs)¹⁸⁹ indicated infection may spread more extensively among African Americans because the African American core group (defined as those who have had four or more sex partners in the past 12 months, some concurrently) is significantly more likely to have contacts with its adjacent group (defined as those who had one or two partners in the past months, who had concurrent partners or who had been paid for sex, those who had three partners who may have been concurrent or not, and those who had four or more partners, none of whom were concurrent) than the white or Hispanic core groups do with their respective adjacent groups.¹⁸⁹ In addition, the percentage belonging to core and adjacent subgroups is higher for the African American subpopulation, (11 and 25%, respectively) than for the white subpopulation (5 and 14%, respectively). Of three racial/ethnic American subpopulations (white non-Hispanic, Hispanic, and African American), African Americans have the highest levels of assortative mixing, regardless of their level of sexual activity. Whites also express strong self-selection for their own racial/ethnic group, but the strength of this preference is weaker than it is for African Americans. On the other hand, the whites who are more sexually active

tend to be more race/ethnicity exclusive in their partner choice. Thus, in terms of transmission of infection, the two racial/ethnic groups tend to be somewhat isolated from each other; Hispanic Americans appear to contribute disproportionately to bridging between them.

The sexual mixing patterns by race/ethnicity and by region also suggest an explanation for the regional pattern of STI morbidity in the United States. The southern region of the United States has the highest rates of STD. According to the NHSLs 1992 data, in the southern region, which includes Arkansas, Tennessee, North Carolina, South Carolina, Georgia, Alabama, Mississippi, and Louisiana, the African American core group, perhaps because of its greater likelihood of rural residence, has a stronger tendency to have sexual partnerships outside of the core group than African American core groups in other census regions.¹⁸⁹

These developments comprise a paradigm shift in the behavioral epidemiology of STI. Historically, the predominant focus of STI epidemiology has been on the attributes and behaviors of individuals, and on the risk of acquiring, rather than of transmitting infection. This approach is consistent with the approaches of clinical medicine, chronic disease epidemiology, and psychology. However, when considered as the “sole” or “main” focus, it appears to be inconsistent with STI transmission dynamics¹⁹⁰ and it has been increasingly challenged in recent years. The new paradigm includes at least three principles: that one person’s health outcome is highly dependent on other person’s health outcomes;^{191,192} that transmission of infection and its prevention is at least as important and perhaps more important than acquisition of infection and its prevention—thus focusing attention on infected individuals and the role they play in the spread of infection; that characteristics of sex partners and partner selection processes are an important component of risk determination—thereby focusing on behaviors of sex partners as well.¹⁸⁶ Applications of this new paradigm have already been incorporated into the epidemiology of specific STDs.^{59,114} For specific examples, please see the earlier discussion on the epidemiology of gonorrhea and chlamydia in this chapter.

DETERMINANTS OF TRANSMISSION EFFICIENCY

Following the emergence of the AIDS epidemic, many studies have focused on the determinants of HIV transmission efficiency. Results of these studies also shed new light on our understanding of transmission efficiency of other STIs.

■ SUSCEPTIBILITY OF THE UNINFECTED HOST

Host susceptibility to invasive STI pathogens depends on entry of the pathogen into cells through one or more surface

receptors. Factors linked to inflammation or immune activation may influence susceptibility by altering number of susceptible target cells or the receptivity of these cells.¹⁹³ Microscopic erosions may allow the pathogen to enter the bloodstream directly. Factors that interfere with or facilitate the survival of the pathogenic organism on the genital skin or the genital, rectal, or oral mucosa may decrease or increase susceptibility. For example, the vaginal pH may affect the survival of HIV under some conditions; vaginal ecology, specifically, the absence of H₂O₂-producing lactobacilli has been associated with vaginal infections, as well as with acquisition of HIV infection.^{194,195}

Epidemiologic and molecular biologic data suggest that some hosts may have acquired immunity to HIV-1 infection.^{196,197} In addition, mutations or deletions in chemokine receptor genes, which serve as coreceptors (with CD4) for HIV-1, have been associated with inherited resistance to transmission or progression of HIV-1 infection.¹⁹⁸ Various related potential mechanisms for this type of resistance to infection include lack of expression of the abnormal coreceptor on the T-cell surface; in CCR5/CCR5 Δ 32 heterozygotes, decreased expression of the normal CCR5 receptor on the cell surface; and upregulations of C-C beta chemokines (RANTES, MIP-1 α , and MIP-1 β), which could inhibit viral attachment.¹⁹⁹ How host genetics plays a role in determining susceptibility to other STIs remains largely undefined.

Pre- or postexposure prophylaxis may potentially decrease susceptibility to STIs. The effect on susceptibility to infection of administering antiviral agents immediately after sexual exposure to HIV is not known although zidovudine administered following needle-stick injuries is associated with decreased risk of HIV infection.²⁰⁰ Commercial sex workers in many areas use continuous antibiotic therapy as prophylaxis against bacterial STIs. Whether or not this practice reduces susceptibility of the individual, it increases the likelihood of the emergence of resistant gonococci.²⁰¹

Several studies have given evidence that reproductive tract infections with other sexually transmitted pathogens increase both acquisition and transmission of HIV and through similar mechanisms, a given STI may increase susceptibility to other STIs as well. Conversely, prior HSV-1 infection decreases susceptibility to acquisition of HSV-2 infection. Acquired specific immunity to several STI pathogens also occurs. Strain-specific immunity to *C. trachomatis* and *N. gonorrhoeae* may be conferred by prior infection with antigenically related strains.^{202,203} Finally, specific immunity to HBV can of course be induced by hepatitis B immunoglobulin and hepatitis B vaccine, specific immunity to HPV by HPV vaccine, and partial protection of women who lack antibody to HSV-1 against HSV-2 by an HSV-2 vaccine not commercially available (see Chapter 24).

■ ANATOMICAL DETERMINANTS OF EFFICIENCY OF TRANSMISSION: MALE CIRCUMCISION AND CERVICAL ECTOPY

The weight of evidence indicates that male circumcision decreases host susceptibility to several STIs, particularly including chancroid, and HIV.²⁰⁴ The prevalence of HIV infection is 1.7–8.2 times as high in men with foreskins as in circumcised men and the incidence of infection is 8 times as high. Ecological comparisons have shown a striking geographic association between HIV seroprevalence and usual male circumcision practice in Africa.

A survey based on a national random sample of the U.S. population found no relationship of circumcision to STIs, but evidence for STIs was based only on self-reported history of STIs, rather than proven STIs.²⁰⁵ Several studies have found that uncircumcised men have increased risk of chancroid (or of undifferentiated genital ulcers in chancroid-endemic areas). Lack of circumcision has also been held to be a risk factor for penile cancer.^{204,206–208}

Biologically plausible hypotheses might explain the associations of STIs and HIV with having a foreskin. The recesses of the preputial sac, the mucosal surface, are less keratinized than the skin of the penis of a circumcised man that might predispose to secondary physical trauma, microbial infection, or balanitis.^{204,209} Similarly, balanitis per se might predispose to invasion by microbial pathogens. The less-keratinized mucosal surface of the prepuce appears to have a high concentration of Langerhans' cells that can serve to attach HIV and then present the virus to susceptible CD4 lymphocytes.^{209–211} The preputial sac might serve as a reservoir for STI pathogens acquired during intercourse, from which invasion of the urethra or squamous epithelium might proceed. Clinical manifestations of urethritis, warts, or genital ulcers might go undetected longer in an uncircumcised man, which could increase transmission or complications of STIs.

Over the past decade much attention has been focused on male circumcision as a preventive intervention to decrease HIV acquisition among men. A meta-analysis of data from observational studies suggested a sizable protective effect of male circumcision in the general population (Adj RR = 0.57; CI = 0.47–0.70) and an even greater protective effect (Adj RR=0.31; CI = 0.23–0.42) in high-risk populations.²¹² The Uganda discordant couples study also provided evidence of reduced transmission among circumcised heterosexual males especially at low viral loads (RR = 0.41; 95% CI = 0.1–1.1).²¹³ Three studies looked at the relationship between male circumcision and HIV among MSM; two of these found significant increased risk among uncircumcised men (OR = 2)^{214,215} and one found no effect.²¹⁶ Male circumcision has also been shown to be associated with chlamydia, chancroid, syphilis, HPV, and HSV.^{215,217} Evidence is

particularly strong on the association with HIV, syphilis, and chancroid.²¹⁸ Recent studies suggest a possible anatomical explanation for the epidemiologically observed protective effect of male circumcision.²¹⁰ Superficial Langerhans' cells on the inner aspect of the foreskin and frenulum are apparently poorly protected by keratin and thus may play an important role in primary male infection. Acceptability studies suggest that circumcision is highly acceptable to both men and women in noncircumcising communities as a preventive intervention.²¹⁹ Three randomized controlled trials of male circumcision for the prevention of HIV acquisition found a protective benefit against HIV infection of 50% in South Africa,²²⁰ 53% in Kenya,²²¹ and 51% in Uganda.²²² A simulation model based on the results of the randomized clinical trials (RCT) conducted in South Africa suggests that male circumcision could substantially reduce the burden of HIV in Africa, particularly in Southern Africa where prevalence of male circumcision is low and prevalence of HIV is high.²²³ While there is concern regarding potential risk compensation or behavioral disinhibition following circumcision, there is no strong evidence supporting this concern at this time.

A recent analysis of data from the NHANES suggests that in the United States the overall prevalence of male circumcision is 79% and it varies by race/ethnicity; 88% in non-Hispanic whites, 73% in non-Hispanic blacks, 42% in Mexican Americans, and 50% in others.²²⁴ The prevalence of circumcision peaked among those born in the 1970s (91%) and declined among those born in the 1980s (84%).

Cervical ectopy (the presence on the exposed face of the cervix of a single layer of columnar cells that are typically found inside the os) increases susceptibility to chlamydial infection, perhaps to gonorrhea, and to HIV infection.^{204,225,226} Cervical ectopy decreases with increasing age and smoking and increases with hormonal contraceptive use, and may partly mediate the association of early age at sexual debut and hormonal contraceptive use with increased risk for cervical infection, and perhaps the link seen in some studies between early sexual debut and cervical cancer. The increased risk for STIs, including HIV infection in young women because of cervical ectopy represents a powerful rationale for delaying sexual debut and for use of condoms for some time after sexual debut. One recent study found HIV infection not to be associated with cervical ectopy in multivariate analyses,²²⁷ but another found the adjusted odds ratio for cervical ectopy extending over >20% of the cervix was 2.18 (95% CI = 1.01–4.69).²²⁸

■ CONTRACEPTIVES, BARRIER METHODS, AND MICROBICIDES

A number of epidemiologic studies have looked at hormonal contraception as a potential risk factor for HIV infection among women of childbearing age. Study findings are mixed; some studies report a protective effect of hormonal

contraception while others find either no association or increased risk.^{229,230} A recent study of combined oral contraceptives and depot-medroxyprogesterone acetate found no association between hormonal contraceptive use and HIV acquisition overall.²²⁹ However, in this study, hormonal contraceptive users who were HSV-2 seronegative had increased risk of HIV acquisition—a finding which needs further explanation. The mechanisms by which hormonal contraception might facilitate HIV infection are not known but may involve cervical ectopy associated with combined oral contraceptive use,^{231,232} increased cervical chlamydial infection,^{231,233,234} and changes in vaginal ecology.²³⁵ Hormonal contraceptive use has also been associated with increased incidence of other STIs including chlamydial and gonococcal infections.^{231,233,234}

Use of barrier methods provides protection against the transmission of STIs including HIV. Best studied among the barrier methods is the male condom. Reported correct and consistent use of condoms is associated with protection against transmission of HIV,^{236,237} with meta-analysis suggesting 80–95% reduction in risk among HIV serodiscordant couples. Condom use is also protective against gonorrhea, chlamydial infection, and trichomoniasis in women²³⁸—a 62% reduction in risk of acquiring gonorrhea and a 26% reduction in risk of acquiring chlamydial infection. Consistent condom use is also protective against syphilis transmission,²³⁹ the transmission of HSV-2,^{240,241} and the male to female transmission of HPV infection.²⁴² In a longitudinal study of newly sexually active women, those whose partners used condoms for all instances of vaginal intercourse during the previous 8 months were 70% less likely to acquire a new infection than were women whose partners used condoms less than 5% of the time. Even women whose partners used condoms more than half the time had a 50% risk reduction compared to women whose partners used condoms less than 5% of the time.²⁴² It is difficult to properly measure the effectiveness of condoms. Overreporting of condom use resulting from social desirability bias may reduce both the point estimate of condom effectiveness and the power of the study to detect a protective effect of condom use.²⁴³ Failure to adjust for the improper use of condoms may also underestimate the effectiveness of proper use.²⁴⁴ Finally, it is important to restrict condom effectiveness analyses to participants with known exposure to infected partners in order to reduce confounding and obtain a more accurate measure of protective effects of condoms against STI.²⁴⁵ Efficacy of condoms in reducing STI acquisition and transmission is less of an issue at this point than their use effectiveness. Correct and consistent condom use appears difficult but possible for many to achieve.

During the past decade considerable effort and resources have been invested in the development of microbicides effective in preventing the acquisition of HIV and other STIs among women. However, to date study results have not been

encouraging; nonoxynol-9 has been found to increase HIV acquisition²⁴⁶ and more recently Phase III trials of cellulose sulfate have been halted after the Data Safety Monitoring Board found, during a routine check, an increased risk of HIV acquisition among women who used cellulose sulfate compared with women who used a placebo gel.²⁴⁷ Trials of a third topical microbicide, “Savvy,” were also recently stopped for futility (i.e., little hope for success). Nonetheless, other candidate products are being evaluated in Phase III trials.

■ SEXUAL PRACTICES

Clearly, unprotected receptive anorectal sex is a risk for acquiring HIV infection not only for men but also for women and for acquiring hepatitis B virus infection.²⁴⁸ During vaginal intercourse, women appear to be at somewhat higher risk than men of acquiring HIV infection and several other STIs as well, probably including HSV-2 infection, gonorrhea, chlamydia, and others. Sex during menstruation may increase a woman’s risk of acquiring HIV infection.²⁴⁹ Whether susceptibility to other STIs also increases during menstruation is not known.

■ INOCULUM SIZE: A DETERMINANT OF THE LEVEL OF INFECTIOUSNESS OF THE INFECTED HOST

From the standpoint of the pathogen, production of epithelial lesions and inflammatory exudates or diarrhea, and initially unfettered growth of the organism to high concentrations in genital fluids, represent strategies for transmission to new hosts and hence for self-propagation and persistence in the population. Thus, infections with HIV, like those with hepatitis B, HSV, *C. trachomatis*, *N. gonorrhoeae*, *Treponema pallidum*, and many other STI pathogens are probably most infectious in the early stage of infection, with infectivity increasing as the concentration of the organism in the genital tract increases, and decreasing as the pathogen-specific host immune response suppresses concentrations of the pathogen.^{250–252} To the extent that STIs are acquired during periods of rapid partner change, the pathogen benefits by achieving an early peak in transmissibility. Data on higher viral concentration in blood and semen with early HIV infection, on the correlation between an individual’s plasma viral load and probability of HIV infection in the partner, all generally support the association between stage of infection and transmission of HIV.^{213,253–256}

■ GENITAL ULCERS, INFLAMMATION, AND OTHER REPRODUCTIVE TRACT INFECTIONS

Inflammation and immune activation may affect the production of virus or bacteria and increase or decrease the level of infectiousness of the infected host. Similarly, factors that inhibit or facilitate survival of the pathogenic organism in or

on the oral, genital, or rectal mucosae may affect infectiousness of the infected host. For example, in theory, vaginal ecology may affect the concentration of a pathogen in the vagina of an infected host just as it affects susceptibility among the uninfected. Presence of other STIs increases HIV infectiousness. Seminal leukocytosis,²⁵⁷ gonococcal urethritis,^{258,259} and shedding of cytomegalovirus in semen²⁶⁰ are associated with increased detection of HIV in semen or urethral swab specimens. Treatment of urethritis diminishes detection of HIV in the urethra and the concentration of HIV in the semen.^{258,259} For women data are more limited but consistent with an influence of cervical infection, endometrial inflammation, and abnormal vaginal flora on cervical shedding of HIV.^{261–263} Similar data on the impact of genital inflammation or reproductive tract infection on shedding of other STIs are inconclusive.

■ DETERMINANTS OF DURATION OF INFECTIOUSNESS

As discussed in the preceding text, the primary determinant of duration of infectivity of any specific STI is the natural history of that infection. Access to effective treatment has become the most important factor in reducing the duration of infectiousness (and infection) of bacterial STIs. In some developing countries, inadequate clinical, laboratory, pharmacy, and public health infrastructure allow the duration of infectiousness for even the curable STIs to approach that of the natural history of infection. In the industrialized countries, antiviral therapies now may also influence the level of infectiousness of some of the viral STIs, making this parameter now relevant to both bacterial and viral STIs. Health-care seeking behaviors of the population, behaviors of health-care providers, and properties of the health-care system all influence the duration of infectiousness (and infection).

Even in the United States, the existing infrastructure for provision of STI care is woefully inadequate. The public STD clinics are unable to provide sufficient access to all persons seeking health care, and have generally not made hepatitis B vaccination available to high-risk groups to reduce spread of the first vaccine preventable STIs, or played a major role until recently in diagnostic testing and partner notification for *C. trachomatis* infection. The inadequacy of the STD health service infrastructure and the resulting preventable increment in duration of infectiousness is a major reason why the United States has the highest rates of STIs among developed countries.

■ PREVENTION TRIALS

Prevention trials targeting particular risk factors for STIs can help confirm the role of the risk factor, as well as guide preventive interventions that directly influence the epidemiology of STIs. The search for conclusive results in the evaluation of interventions to prevent STIs, including

HIV, has resulted in increasing numbers of controlled prevention trials in the past decade. Such trials are generally classified either as behavioral or biomedical intervention trials, although in reality, even those based on a biomedical intervention require supportive behavioral intervention components (e.g., to motivate vaccine acceptance and compliance, and prevent relapse to riskier behaviors by those who might otherwise feel safe after vaccination); and conversely, behavioral interventions benefit from biomedical outcome measures.

■ BEHAVIORAL PREVENTIVE INTERVENTION TRIALS

In STI and HIV prevention several specific issues need to be considered. First, the behaviors targeted for change (e.g., sexual behaviors) are difficult to measure objectively. Dependence on self-reports of behavior creates additional problems in that interventions may change reports of behavior without changing the behavior itself.²⁶⁴ Second, individuals who change one risk behavior often change other risk behaviors in a countervailing direction, necessitating use of summary measures that reflect the net effects of these changes.²⁶⁵ Third, the transmission dynamics of STIs are influenced not only by sexual behavior but also by additional factors, such as phase of the epidemic, population prevalence, transmission probability, duration of infectiousness, and specific characteristics of transmission networks, resulting in different trends in the incidence of various STIs in the same populations.^{266,267} Fourth, the nature of the relationship between sexual behavior and STI incidence varies across the phases of the epidemic. At the individual level, the magnitude of risk associated with particular behaviors depends on the infectiousness of the infected partner. Finally, whereas adjustments for confounding factors may be feasible in epidemiologic studies of etiologic factors, bias in adoption of behavior change (or in intervention assignment) is inherently part of the practice of medicine and public health, and the idea that such bias can be simply adjusted away may be wishful thinking.²⁶⁸ In this context, it is interesting to note that data sets from randomized controlled trials with null findings, when analyzed in the same manner as cohort studies with adjustment for confounding, can misleadingly indicate that the intervention was effective (Ward Cates and Ron Roddy, personal communication). This observation is congruent with earlier conclusions that the many advantages provided by randomization when subgroups are defined by baseline characteristics are lost when follow-up responses are used to define patient subgroups.²⁶⁹

In the light of all these considerations, it is obvious that in evaluating behavioral interventions to prevent STIs, and HIV, data from randomized controlled trials are particularly important, the choice of outcome measure is critical, and the outcome measure of choice is the appropriate biomedical measure of the STI or STIs of interest.^{264,270}

Most evaluations of behavioral interventions to date have employed less rigorous study designs and behavioral outcome measures. A systematic review of computerized abstracts from International AIDS conferences between 1989 and 1992 showed that only 10 of 15,946 abstracts reported on randomized controlled trials of behavioral interventions.²⁶⁴ Two subsequent critical reviews of behavioral interventions in general and behavioral interventions for young people reported similar findings.^{271,272} These reviews also indicated that many behavioral intervention studies focused only on determinants of behavior such as knowledge, beliefs, and attitudes as outcome measures.

Although the majority of behavioral intervention studies do not employ randomized controlled designs or biomedical outcome measures, some remarkably important studies that do have been completed. Among the most important of these, in terms of public health implications, is Project RESPECT. This project was designed to specifically evaluate the efficacy of individual HIV prevention counseling in changing high-risk behaviors and preventing new STIs. This study of high-risk heterosexuals was among the first randomized trials of HIV/STI prevention counseling.²⁷³ The study, conducted among HIV negative, heterosexual STD clinic patients enrolled from five United States inner-city STD clinics (Baltimore, Denver, Long Beach, Newark, San Francisco), compared (1) enhanced counseling (a four-session counseling intervention, each session of 1 hour duration) based on theories of behavioral science; social cognitive theory, and the theory of reasoned action, and aimed at changing attitudes, self-efficacy, and perception of risk regarding consistent condom use with all sex partners); (2) client-centered HIV Prevention counseling (two sessions of 20 minutes each), an intervention based on CDC's client-centered counseling model recommended for use with HIV testing, and aimed at increasing clients' perceptions of personal risk, exploring barriers and facilitators around risk reduction, and negotiating an incremental risk reduction plan that emphasized consistent condom use with all sex partners); and (3) HIV education (the control intervention that was purely informational, using two brief, didactic messages about HIV and STIs prevention that encouraged consistent condom use with all sex partners, similar to the type of prevention messages given at most STD clinics). The enhanced counseling and client-centered counseling interventions were significantly more effective than the HIV education intervention at decreasing high-risk behaviors and preventing new STIs. These findings were consistent across study sites and gender. Most of the STI reduction occurred in the first 6 months. At 12 months there were no differences across intervention and control groups in condom use, but a 20% reduction in new STIs for counseling interventions remained significant (although the 12-month difference was attributable to the reductions achieved during the first

6 months). The amount and duration of the effect of counseling in Project RESPECT were modest, but from the population perspective even modest changes in behaviors of high-risk STD clinic patients could have a substantial impact on STI and HIV transmission. Unfortunately, following its publication the RESPECT intervention was not widely implemented.

Another multisite randomized HIV prevention trial, coordinated by the National Institute of Mental Health (NIMH), developed and evaluated a seven-session intervention targeting sexual behavior change among low-income individuals at high-risk for HIV infection.^{274,275} Participants were largely recruited from STD clinics, with a smaller number from primary health-care settings. The intervention group experienced significant reductions in reported unprotected sexual exposures and lower rates of gonococcal infection in men (based on chart review), but urine ligase chain reaction (LCR) tests at 12 months showed no difference in prevalence of gonococcal or chlamydial infections. Taken together, Project RESPECT and the NIMH trial suggest an impact on behavior with transient reduction in bacterial STI incidence. The feasibility is lower for widescale implementation in public health settings of the seven-sessions intervention employed in the NIMH trial than for the two-session Project RESPECT intervention.

A third randomized controlled study, a culture and gender-specific risk-reduction intervention targeting African-American and Hispanic STD clinic patients in San Antonio, Texas, reduced reinfection rates with gonorrhea and chlamydia among high-risk minority women and these effects apparently persisted for 12 months.²⁷⁶ Further work on culture and gender specific behavioral interventions also showed declines in risk behaviors and bacterial STI incidence.²⁷⁷⁻²⁷⁹ One study focused on the efficacy of group sessions which emphasized race and gender pride, HIV knowledge, communication and condom skills, and healthy relationships in reducing risky behaviors and bacterial STIs. Significant reductions were reported in risky behaviors.²⁸⁰ Another study enrolled couples and randomized them to a six-session intervention provided to couples together versus the same intervention provided to the women alone; the results were not different in the two conditions.²⁸¹

Behavioral intervention trials that randomize groups or larger units are fewer in number. A study in Zimbabwe randomized work sites to an HIV-prevention health education intervention, women at the work sites that received the intervention reportedly experienced a subsequent significant reduction in HIV incidence, compared with the control work sites.²⁸² Persons with STI symptoms in developing countries often first seek treatment at pharmacies. Therefore, another study randomized 14 districts (total population nearly 4 million) in Lima, Peru, to receive either an intervention for pharmacy workers providing training and support for

management of STIs or to a control intervention providing training for management of diarrhea. Subsequent visits by simulated patients evaluated training outcome. The pharmacies that received training performed significantly better than control pharmacies in recognition of four STI syndromes, in recommendations for use of condoms, and for treatment of partners ($p < .05$ for 47/48 outcomes measured).²⁸³ In another effort researchers in the UK have conducted a four-school randomized trial to assess the feasibility of a large randomized controlled trial of peer-led sex education in schools.²⁸⁴ The findings suggest that evaluation of peer-led sex education through a randomized controlled trial is acceptable to schools, pupils, and parents. In general, pupils who received peer-led sex education responded more positively than those in control schools.

In the past 2 decades a number of behavioral intervention trials have been conducted including those mentioned above. Many of these studies showed efficacy in reducing risky behaviors, and a smaller number showed efficacy in reducing incidence of bacterial STI in study subjects. Interestingly, to date, no cluster randomized trial of behavioral interventions (where at least one arm of the study represented a behavioral intervention) has showed significant impact at the population level. Neither the MEMA kwa Vigana project (an adolescent health intervention)²⁸⁵ nor the behavioral arms of the Mwanza, Rakai, or Masaka trials have had significant outcomes. During an era of important declines in risky sexual behaviors in a number of countries,^{286,287} it is remarkable that intervention studies have failed to show statistically significant effects on risk behaviors and/or bacterial STIs. Reasons for this discrepancy need further explanation and may be related to issues of contamination, migration, or coverage/penetration.

■ BIOMEDICAL PREVENTIVE INTERVENTION TRIALS

A randomized controlled trial provided empirical evidence for the effectiveness of screening for cervical chlamydial infection followed by timely and appropriate treatment. This approach emerged as the key strategy for the prevention of pelvic inflammatory disease. Participants were unmarried female health maintenance organization enrollees 18–34 years of age with risk factors for chlamydial infection. They were randomized to receive chlamydia screening or routine care. In this study, cervical chlamydia screening led to a 56% reduction in the incidence of pelvic inflammatory disease during 1 year of follow-up.²⁸⁸

Considerable resources have been invested in the development and evaluation of microbicides that would prevent acquisition of HIV and other STIs. Unfortunately, to date results have not been encouraging. Four randomized trials of microbicides with HIV and STI end points have been stopped for safety concerns.^{246,247}

A landmark HIV prevention trial randomized communities to biomedical intervention and control conditions to assess the effect of the community level intervention. This community-randomized trial conducted in the Mwanza region of Tanzania was the first randomized trial to demonstrate an impact of a preventive intervention on HIV incidence in a general population. It showed that improved syndromic management of STIs at the primary health-care level reduced HIV incidence by about 38%.³⁵ HIV incidence was compared in six intervention communities and six pair-matched comparison communities. A random cohort of 1000 adults, 15–54 years of age, from each community was surveyed at baseline and at follow-up 2 years later. The intervention included establishment of an STD reference clinic, staff training in syndromic management, regular supervisory visits to health facilities, provision of antimicrobials, and general population health education about STIs and health-care seeking for STI symptoms.

A subsequent HIV-prevention trial in the Rakai district of Uganda randomized clusters of villages to mass treatment of STIs every 10 months versus antiparasitic treatment alone. Serologic screening and treatment for syphilis and syndromic management for STIs were offered both to intervention and control villages. The study showed no effect on HIV incidence but significant improvements in pregnancy outcomes.³⁷ The differences in outcome of the Mwanza and Rakai studies are intriguing. The Mwanza study focused on treatment of symptomatic STIs only, whereas the Rakai study provided antimicrobials to the entire population, some of whom had prevalent STIs. In the Mwanza trial, the intervention villages achieved a lower rate of seroconversion to active syphilis and of symptomatic urethritis in men. The Rakai study offered serologic screening and treatment for syphilis and syndromic management for STIs both in the intervention and the control communities. Thus, at the point the Rakai study was terminated, absolute differences between intervention and control groups in prevalence of STIs (other than trichomoniasis) were small: by the end of the study, there were no significant differences between intervention and control clusters in prevalence of gonorrhea, chlamydial infection, or bacterial vaginosis, or in frequency of reported genital ulcer disease, or in proportion seeking care for STI symptoms. The impact of systemic antimicrobial therapy on normal flora in uninfected individuals (e.g., transient suppression of potentially protective H₂O₂-producing lactobacilli or increasing vulvovaginal candidiasis, both potential risk factors for HIV acquisition), represents possible confounders of any beneficial impact of reduced STI prevalence.²⁸⁹ Differences in the relative prevalence of STIs and HIV in the Mwanza and Rakai districts (higher prevalence of HIV infection in Rakai) and basic differences in study design and in the nature of the interventions may also account for the differences in outcome. One paper provided a useful

methodologic overview of community randomization trials of STI/HIV preventive interventions.²⁹⁰

A third community randomized trial conducted in Masaka, Uganda, evaluated the efficacy of information, education, and communication coupled with improved STI case management and found no impact on HIV incidence.²⁹¹ Another cluster randomized trial conducted in Manicaland, Zimbabwe, failed to show significant differences between intervention and control communities.²⁹² The intervention included community-based peer education, free condom distribution, income-generating projects, and clinic-based STI treatment and counseling services.

These findings suggest that population level impact on STI/HIV morbidity is a function of a number of interrelated epidemiologic parameters including incidence and prevalence of infections, incidence and prevalence of risk, and preventive behaviors epidemic potential in the community and epidemic phase. In addition, volume of migration and turnover, penetration of the intervention into the subpopulation being targeted, and coverage of subpopulations that happen to drive the epidemic at a given point in time as well as sensitivity of measurements all affect the power of a study to demonstrate differences between intervention and control communities. These findings also have implications for STI prevention programs; they highlight the importance of strategic planning of programmatic activities including targeting, scale-up, coverage, maintenance, and continuous quality improvement of preventive interventions.

During the past decade remarkable advances were made in individual level biomedical interventions for STI prevention. Single-dose oral azithromycin has improved the treatment of several bacterial STIs.²⁹³ A major recent advance in STI prevention is the early success of a prophylactic, monovalent HPV type 16 vaccine;²⁹⁴ HPV vaccines may be able to help prevent genital and anal cancers in the foreseeable future. Researchers are evaluating multivalent vaccines for preventing moderate to severe cervical dysplasia as well²⁹⁵ and the use of suppressive therapy to reduce the transmission of genital herpes to regular partners.²⁹⁶ In a related development, a prophylactic vaccine against HSV type 2 (HSV-2) has shown limited efficacy in that it has proved partly effective for HSV-seronegative women but not for men or HSV type 1 (HSV-1) seropositive women.²⁹⁷

Finally, a recently published randomized, double blind, placebo-controlled trial of HSV suppressive therapy with valacyclovir (500 mg twice daily) among women who were seropositive for HIV-1 and HSV-2 in Burkina Faso showed that HSV suppressive therapy significantly reduces genital and plasma HIV-1 RNA levels in dually infected women.²⁹⁸ This finding has important implications for HIV control; combined with the results of the male circumcision trials discussed earlier, these findings provide reason for great optimism regarding HIV prevention in the near future.

Randomized controlled trials of HSV-2 suppression to prevent transmission and/or acquisition of HIV infection are ongoing.

■ ASSESSING EFFECTIVENESS OF POLICY INTERVENTIONS

Randomized controlled intervention trials at individual, group, or community levels provide the best empirical evidence for the effectiveness of preventive measures. However, preventive measures with the greatest impact include so-called structural interventions, often based on policy changes. Use of randomized controlled trials to assess the effects of policy interventions is usually not feasible; more creative approaches are needed for this purpose.

One well-known strategy is to combine information from many sources and check for consistency across data sets. A recent analysis assessing the impact of abstinence education on STI rates compared temporal trends in reported gonorrhea rates between 2001 and 2005 in those states that stressed abstinence education to rates in states which did not have a mandate to cover abstinence education and found no differences.²⁹⁹

Another approach has been used in demonstrating the effectiveness of alcohol taxation on reducing STI rates among youth.³⁰⁰ Between 1982 and 1994 there were 34 instances of a state beer tax increase in the United States. The investigators conducted a nonparametric quasiexperiment comparing the proportional changes in STI rates in states with and without a tax increase over the same period and employed a time series econometric analysis, evaluating the effect of the level of beer taxation on the proportional changes in STI rates, controlling for legal minimum drinking age, per capita income, and state and year differences. The results showed that in 26 (77%) of the states with an increase in beer tax, there was a greater proportional decrease in gonorrhea rates among males in both the 15–19 and the 20–24 age groups as compared to the proportional change among the states without a tax increase. Similar patterns were observed for females. It was estimated that a \$0.15 tax increase on a six-pack of beer would reduce gonorrhea incidence rates by roughly 10% among the 15–19 year age group. The feasibility, noninvasive nature, and relatively low cost of this study are remarkable, and of course its findings, not having been based on sample data, are completely generalizable to the study population. Nonobtrusive measures to assess the effectiveness of policy interventions to reduce STIs, including HIV, warrant further evaluation.

As indicated by comparisons of sexual lifestyles in the United States and the UK, the greater dispersion in sexual behavior in the United States than in the UK implies a need for strong public health policy, but that the same dispersion creates strong opinions about inappropriate sexual behavior that make implementation and evaluation of strong health policy decisions difficult.³⁰¹

THE DEMOGRAPHIC, SOCIAL, POLITICAL, AND TECHNOLOGICAL CONTEXT

The trends in STI prevalence and incidence, diagnostic, therapeutic, and vaccine developments and other preventive innovations are all embedded in historical demographic changes. The demographic shifts of the postindustrial era, known as the “second demographic transition,” are defined by an unexpected low level of fertility (below replacement); declining population size; and a compensatory trend in migration patterns. The demographic mechanisms of action involved in the second demographic transition are multiple and multidimensional. They include, in addition to large decreases in period and cohort fertility, decreases in the total first marriage rate, strong and large increases in mean age at marriage and childbearing, divorce and union dissolution, cohabitation, proportion of extramarital births, and maternal employment. In the second demographic transition, international migration plays an important role in redistributing population from low-income countries with high population growth to high-income countries with low or negative population growth. Migration into Western Europe and the United States has increased remarkably over the past 2 decades. During the same period the structure of marriage and the family and the values, attitudes, and expectations of men and women also changed.⁶ In Europe and the United States, many women choose not to marry; the number of children born to a woman declined; many people now live in a variety of household arrangements including single people with friends and children, gay couples and friends, and step families. Emphasis on values, such as individual autonomy, self-fulfillment, tolerance, democratic decision making, individual freedoms, and individual rights increased. Concurrently, women’s roles in society and their expectations also changed. Women are now less likely to endure abusive or unhappy marriages; they assume they have equal rights to education and work outside of the home and they expect an enjoyable sex life with control over their fertility. In industrialized countries, changes of the second demographic transition do not happen uniformly across socioeconomic strata. Changes involving increased freedoms, fulfillment, and autonomy are observed among higher socioeconomic strata while increased divorce and single parenthood are more frequent among lower social strata.⁶

The past few decades have also witnessed major political, technological, and economic shifts, all of which have the potential to impact sexual behavior, sexual networks, health-care infrastructure, and health service delivery. Included among these shifts are the breakdown of the Berlin Wall; the opening of China to the rest of the world; the establishment of democracy in South Africa; the demise of the former state socialist economies in Europe; and the information revolution and the emergence of the global economy (the globalization of

capitalism). Processes of globalization are driven by international corporations that move capital, goods, and technology across borders. Some aspects of globalization (e.g., globalization of knowledge, cultural globalization) have been welcomed throughout most of the world; however, economic globalization has created concern and controversy. Economic globalization involved the collapse of national regulatory frameworks; an increase in international trade and investment; increased production for export in developing countries; a decrease in public spending in many developing countries, particularly the poorest ones; and the disappearance of subsistence production. In the globalized system, capital is moved anywhere in the world to find the cheapest production costs. Consequently, in most areas of the world, the secure long-term employment that characterized the era since the second World War declined, job security is reduced markedly, more people work part-time and on temporary contracts, social welfare entitlements have been cut, and economic inequalities have increased.⁸ For example, in the United States in early 2005, there were multiple pension system defaults especially in the airline and steel industries and major changes have been proposed for the social security system. Such macrolevel changes in economic and social patterns can have major impact on the structure of sexual partnerships, sexual behaviors, and STD transmission patterns.²¹

Processes of globalization are reflected in the technologies that directly affect the diagnosis, management, and prevention of STI. The new and improved diagnostic tests and therapies, the newly developed vaccines, and medications that enhance sexual functioning such as Viagra and Cialis are researched, developed, and marketed globally, in accordance with the principles of minimized production costs and maximized profits, by increasingly merged global companies.

Processes of globalization are also reflected in the modified face of the sex industry which is an increasingly globally connected, multibillion dollar industry driven by international business concerns that move capital (women, young men, and children) and consumers (through sex tourism) across borders, sometimes illegally. Finally, globalization of capitalism and the market economy have resulted in the creation of new desire for ownership of consumer goods among young people in many developing countries such that they are willing to exchange sex for money in order to purchase consumer goods. Concurrently the market economy increases disposable income among men—a strong correlate of paying for sex. Moreover, there are very effective processes in place that efficiently bring the demand and supply for sexual transactions together. These processes include the flow of information through networks (e.g., sex worker client networks and pedophilic networks via websites) facilitated by the Internet; travel for business and tourism, sex tourism; economically motivated migrations some of which are for the purpose of buying and selling sex; politically motivated

migration; and trafficking of women and children for sex. Natural and man-made disasters such as earthquakes, hurricanes, tsunamis, economic collapse, civil wars, and wars between national states further fuel motivations and processes that govern commercial and quasicommercial sexual transactions.

Technological advances such as the Internet, cell phones, and other instant messaging devices facilitate efficient and low-cost hookups between potential sex partners and between buyers and sellers of sexual services. Numbers of cyber brothels easily accessible through the Internet; supply and demand for pornography, sex with children, sex toys, and sexual networking parties have all increased remarkably. As the volume of commercial sex increases and such transactions penetrate society, attitudes toward nonconventional sexual behavior change. Increased tolerance is associated with increased frequency of riskier sexual behaviors in the general population as observed in the United States and the UK.^{6,159}

Thus, the global topology of sexual transactions is changing radically. First, the volume of such transactions is growing. Second, societal acceptance of widely diverse transactions is growing; and third, due to the combined effect of the Internet, increased migration and increased travel, such transactions bring together increasingly diverse individuals—creating sexual network ties among geographically distant populations.

SUMMARY AND CONCLUSIONS

The past decade has been marked by continuing advances in STI/HIV prevention, diagnosis, and treatment. Improved understanding of the epidemiology of STIs including HIV can allow public health workers to make better use of the many available efficacious interventions to help prevent, identify, and treat STI including HIV. At the same time the gestalt of social determinants, public health systems, and risk and preventive behaviors are undergoing rapid transformation in the context of globalization, information technologies, and other social forces. Such transformation suggests that the near future may be marked by a further weakening of public health systems, important increases in risk behaviors, and resultant increases in STIs including HIV globally.

At this juncture, the science of STI/HIV prevention faces new, and perhaps, more difficult challenges. Moving efficacious interventions out of the randomized trial or experimental design context into effective everyday implementation in the community; moving effective interventions through appropriate targeting and scale-up to population level impact; and moving individual level interventions to implementation at the population level require both resources and specialized know-how. Recent experience with STI prevention programs such as screening for chlamydia and STI community randomized trials such as PREVEN and Manicaland suggest a number of new questions for which we

do not yet have answers. These include: How does the point in the epidemic at which an intervention is introduced affect the population level impact of the intervention? How do(es) the group(s) targeted by an intervention affect the population level impact of an epidemic? How do turnover (movement into and out of target groups) and spatial mobility affect coverage achieved during the implementation of an intervention and the resultant population level impact of the intervention? What is the effect of other interventions already being implemented on the population level impact of an intervention? Are there issues of diminishing incremental impact and saturation that need to be considered before implementing interventions? What are synergistic and redundant interactions among interventions that need to be considered in the choice of intervention packages? The current era will probably be marked by increased attention to the interactive dynamics among epidemiologic parameters, among intervention parameters, and the interaction between epidemiology and intervention.

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PART 2

Social and Psychological Dimensions of Sexuality

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6

Social Dimensions of Adolescent Sexuality

Katherine W. Stovel, Derek Kreager, and Megan A. Moreno

OVERVIEW

Most of us recall the awkwardness and immediacy of our early sexual development. With curiosity, excitement, and trepidation, adolescents watch as their bodies undergo the metamorphosis that accompanies puberty. In many ways, it is these changes that awaken adolescents' self-images as sexual beings, providing both the means and the desire for early sexual relationships.¹ But physiological maturation is insufficient for explaining early sexual development. For all youth, sexuality is equally shaped by the images, cues, and interactions that stem from lived environments. It is in negotiating a complex social landscape that adolescents fully come to understand their own sexual identities and subsequently learn to express themselves as sexual adults.

The purpose of this chapter is to explore the social contexts of adolescent sexuality and to present relevant research in this area. Doing so requires an ecological approach to adolescent sexuality and an acknowledgement that many social domains impact early sexual development and behavior. Youth not only have varying rates of physical maturation, but they also come from a multitude of economic, cultural, family, religious, and gendered backgrounds, while participating to varying degrees in age-graded tasks of education, work, peer affiliations, and home life. Therefore, we focus both on sociodemographic characteristics of youth (e.g., age, sex, race) and on various social structures and relationships that shape adolescents' sexual behavior, largely at the expense of the psychological and subjective aspects of adolescents' sexuality. Throughout the chapter, we examine factors that influence the onset and course of adolescents' sexual activities, and the related processes of partnership formation and dissolution. Discerning patterns in this intricate terrain—and relating these patterns to adolescent sexual development—is a challenging task.

For many years, methodological problems plagued research in this area, mainly because of selection effects, limited longitudinal data, small sample sizes, and lack of comparison samples. Recent efforts to understand the social

dimensions of adolescent sexuality have been substantially aided by federal investment in a comprehensive, nationally representative data set collected longitudinally since 1995 by the National Longitudinal Study of Adolescent Health (see Bearman² for design details). This project, frequently referred to as Add Health, includes survey and biological data from over 20,000 adolescents and young adults residing in 80 communities in the United States, as well as data from their parents and about their schools. Because Add Health was initially a school-based study, adolescents' peers and romantic partners are frequently also study participants—a design feature that allows for much more precise analysis of the multiple influences on adolescent behavior. Studies using Add Health data augment research on teen sexuality that relies on two other large nationally representative samples, the National Longitudinal Study of Youth (NLSY, 1997) and the ongoing National Survey of Family Growth (NSFG). Cumulatively, many published studies that use these data have broadened our understanding of adolescent romantic and sexual behavior; more generally, the availability of these data has reinvigorated this research area and stimulated even more research that seeks to illuminate an often tumultuous developmental stage.

RELATIONAL CONTEXTS OF ADOLESCENT SEXUALITY

■ PEER INFLUENCE

Peer influence has become the most actively researched area of adolescent sexuality. Interest in peer effects is partially explained by parental fears of children becoming lost to “youth culture.” However, it is also clear that the importance of peers increases substantially during the teenage years³ (see Giordano⁴ for a review). Contemporary age-graded societies typically place youth in a protracted period of educational attainment, where contacts with adults are limited and peer contacts greatly increase. This shift toward greater peer involvement fosters the highly complex and stratified

informal peer organizations found in most secondary schools.^{5,6} Situating oneself within local peer structures becomes a primary adolescent concern. Moreover, adolescents' lack of economic and political power heightens peer status as a means of attaining individual influence.⁷ At home and in school, youth have little control over their lives, but in evaluating and bestowing status on their peers, their power reigns supreme.

Peer relations take several forms, and over the life course different types of peer relations dominate.⁸ At the dyadic level are individual friendships or relationships; this type of peer relation first emerges during the toddler years and is frequent through all stages of life. Among adolescents, individual friendships are frequently same-sex, though most adolescents experiment with cross-sex friendships or romantic relationships at some point.

A second type of peer relation is the small group, which may be of same- or mixed sex. Small groups are identifiable among young school aged children, but rise in prominence during late childhood and adolescence. Frequently called cliques, small peer groups are composed of individual friendships of varying strength, duration, and intensity. Characteristically, small peer groups develop identities that distinguish them from other groups of adolescents, and contribute to adolescents' sense of "belonging." Some of these identities are considered prosocial by adults, while others are viewed as problematic or delinquent. However, adolescents who are isolated from these small groups may feel distressed and under some circumstances may engage in antisocial behavior.^{9,10}

Finally, a new source of peer group emerges in adolescence: the crowd.⁸ Adolescents in industrialized countries frequently become oriented toward large groups of other teens based upon shared interests, backgrounds, or styles. These crowd classifications exist even in the absence of specific relations linking adolescents together. The organization of schools, increased freedom of movement, and adolescents' emerging autonomy all contribute to a new cognitive orientation toward local youth cultures. In terms of relationships and sexual behavior, all three levels of peer influence are important, though scientific studies that disentangle the relative effects of each level are in their infancy.

■ PEER INFLUENCE ON SEXUAL BEHAVIOR

Peer relations at each level are widely believed to influence adolescent sexual behavior. However, in a recent review of the research literature, Brown and Theobald¹¹ conclude that peer influence on adolescent sexuality tends to be much more moderate than is often assumed. While parents, educators, and researchers observe a great deal of similarity among pairs or groups of adolescents and frequently interpret this as evidence of peer influence, in some cases adolescents with similar

interests or proclivities simply seek one another out. This process of selecting similar others is known as homophily.^{12,13} Thus an important concern in studying peer effects is identifying the distinction between the effects of selection and influence;⁴ because of these two confounding processes, it is surprisingly difficult to ascertain the extent and significance of peer influence.

Nevertheless, a review of the research suggests that the magnitude of peer influence varies across groups and developmental stages. With respect to age, both Berndt¹⁴ and Brown³ suggest that peer influence increases dramatically with the transition from childhood to early adolescence and slowly declines thereafter. Other studies document that girls and boys are differentially susceptible to peer influence and that effects differ among racial groups. In a longitudinal study of the effects of friends' sexual behavior on initiation of coitus, Billy and Udry find that peers exert a more powerful influence on whites than on blacks.¹⁵ The same study suggests that white females are more influenced by their male friends than by their female friends; for white males and black females these peer effects are insignificant. However, a recent longitudinal study of adolescents in the Philippines finds that having sexually active friends is associated with earlier sexual debut among both boys and girls, controlling for a variety of social and demographic factors.¹⁶

Peers are also important as an information source. Peer groups create and enforce group norms of behavior, which are particularly influential for adolescent behavior. Finally, peers may help create opportunities for adolescents, for example, by offering unsupervised venues that can be used to experiment with sexual and other nonnormative behavior.¹¹

Peer influence in these different forms may both encourage and discourage sexual risk taking. It is well documented that adolescents who believe that their friends are sexually active are more likely to become sexually active themselves,¹⁷ yet often teenagers must negotiate conflicting influences originating from different subgroups of their peer network (e.g., Haynie,¹⁸ Bearman and Brückner¹⁹). In this regard, the direction and magnitude of peer effects depend on the level of peer context and whether the friends are male or female. In an analysis of data from students attending high school in the United States, Bearman and Brückner¹⁹ find evidence of protective peer influence, especially among same-sex members of close friendship networks and larger peer groups. In fact, adolescents with no or very few friends are no less likely to become sexually active than are adolescents with average or large peer networks. However, the most popular girls in schools tend to experience sexual debut earlier than their less popular peers. On the other hand, these girls are significantly less likely to become pregnant.

Not surprisingly, the direction of influence depends on the kinds of peers to which an adolescent is connected. Bearman

and Brückner measured the risk status of peers based on a cross-classification of nonnormative behavior and academic orientation.¹⁹ They found that having peers with low risk status is negatively associated with sexual debut and pregnancy, while girls connected to peers who engage in higher-risk activities are at increased odds of both sexual debut and pregnancy. These relationships are illustrated in Table 6-1, which reports odds ratios for sexual debut and pregnancy among a representative sample of American girls aged 12–17 years.

Peer influence, whether via modeling, diffusion of information, norms, or opportunity structures, is not limited to direct peer pressure that flows through social relations between particular teens. Rather, adolescents' influence on one another may occur through intermediaries: friends of friends, or even others more distant. In fact, adolescents may change their behavior or norms as part of an attempt to fit in with a new crowd or to form new friendships.¹² For instance, the proportion of students in a school who are sexually active also strongly predicts sexual debut and pregnancy risk among female adolescents— independent of the behavior of particular friends.¹⁹ It is therefore not a simple matter to identify which peers are most relevant when studying peer effects. Focusing only on best friends or on the most popular peers (the “leading crowds”) may under- or overestimate peer effects.¹⁹ On the one hand, selection effects and reciprocity probably limit the influence of best friends, while on the other hand, adolescents may not necessarily like or trust the most popular peers in their school or neighborhood. Powers²⁰ has demonstrated that the behaviors of peers only indirectly tied to the focal individual (second step ties) influences white female sexual debut. Bearman and Brückner¹⁹ find the strongest and most consistent peer effects at the level of close friends and peer groups; in contrast to the fears of many parents, they find no evidence that the behavior of the most popular crowd in a school influences other adolescents' sexual activities.

These complex patterns of peer influence highlight the role of social networks among adolescents. However, the networks of social relations that underlie the peer influence process are often not readily apparent to adolescents themselves or to their parents and teachers. Studies that rely exclusively on adolescents' reports about their peers may miss significant sources of peer influence and therefore underestimate peer influences that operate through more subtle mechanisms than direct peer pressure. For example, Bearman, Moody, and Stovel used self-report data from all students attending a medium-sized high school in the Midwest to study the actual romantic and sexual network in this city²¹ (see Fig. 6-1). Their study found that many adolescents are initiated into romantic relations by partners who themselves have already had at least one romantic attachment. Equally as important, the structure of the overall sexual network was invisible to the students themselves, but provides the context for subsequent partnership formation through the emergence of subtle norms against sexual partnerships that close “short cycles” (i.e., sexual networks in which several sexual linkages occur between relatively small numbers of individuals—see Chapter 7). This apparent prohibition against short cycles among adolescents is important, since short cycles produce dense sexual networks—an important risk factor for the spread of sexually transmitted infection.

In light of these research findings, interventions that move beyond peer pressure resistance training are likely to be most effective at reducing adolescent sexual risk taking. Further, educational interventions that rely on peer leaders should make sure that adolescents chosen as leaders have credibility with their audience. Members of leading crowds or very popular adolescents might make for poor examples if they have high rates of sexual activity. In some cases, adults may actually have more credibility as sources of information.²²

Table 6-1. Summary of Effects for Peers' Risk Status Across Contexts¹⁹

	Sexual Debut		Pregnancy	
	Low Risk	High Risk	Low Risk	High Risk
Best male friend	1.09	1.29	0.61	1.36
Close friends (all)	0.63	1.12	0.42	1.26
Close female friends	0.74	1.20	0.50	1.08
Close male friends	0.68	0.73	0.93	2.19
Peer group	1.24	2.73	0.13	0.47

Numbers are odds ratios from logistic regressions, controlling for sociodemographic and individual characteristics.

Data from Bearman PS, Brückner H. *Power in Numbers: Peer Effects on Adolescent Girls' Sexual Debut and Pregnancy*. Washington, DC: National Campaign to Prevent Teen Pregnancy; Research Monographs; 1999.

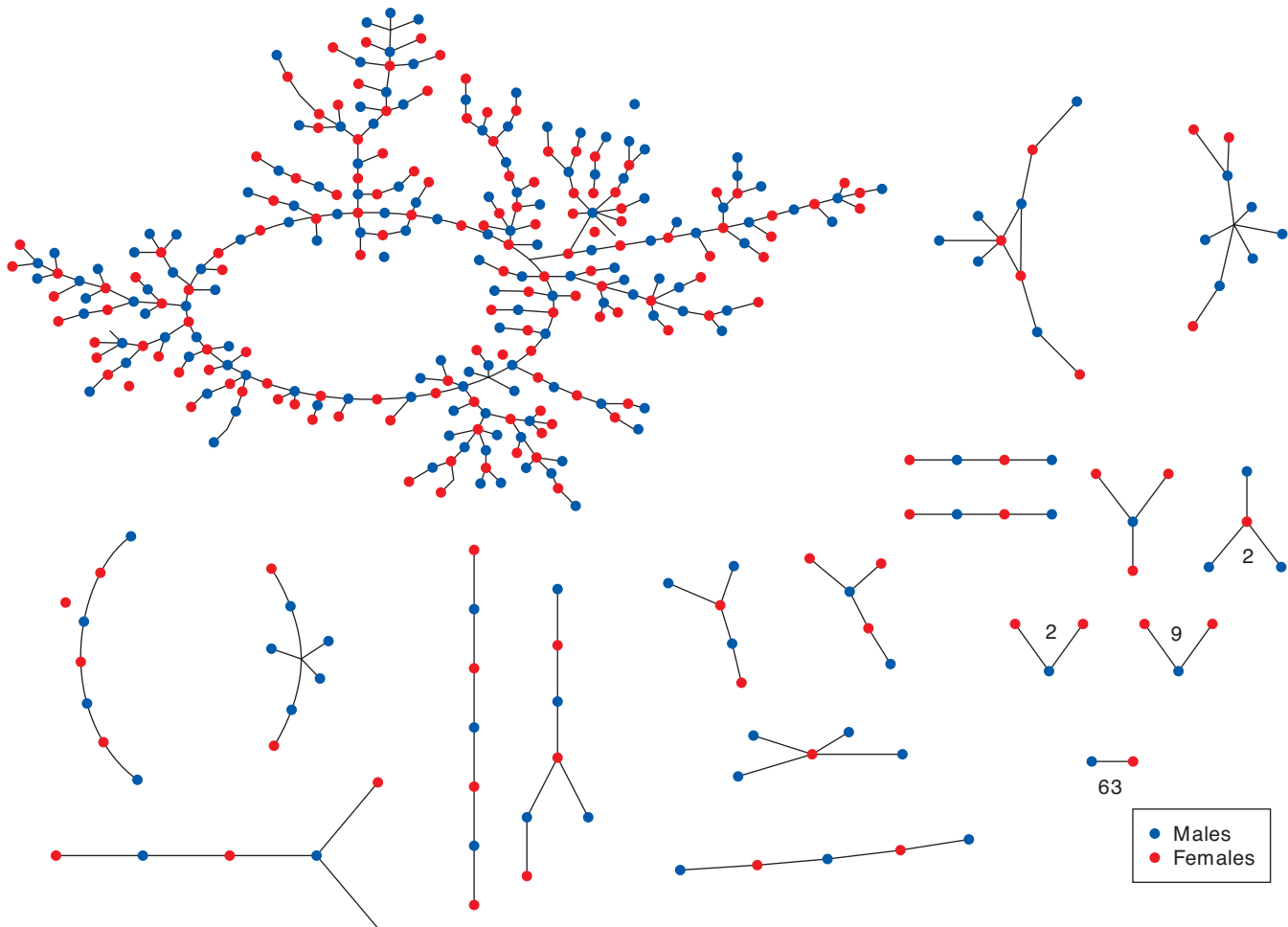


FIGURE 6-1. The structure of romantic and sexual relations at “Jefferson High School.” Each circle represents a student and lines connecting students represent romantic relations occurring within the 6 months preceding the interview. Numbers under the figure count the number of times that pattern was observed (i.e., we found 63 pairs unconnected to anyone else). (From Bearman P, Moody J, Stovel K. Chains of affection: The structure of adolescent romantic and sexual networks. *Am J Sociol* 2004; 110(1): 44–99.)

■ DATING PATTERNS AND SEXUAL BEHAVIOR

As mentioned above, adolescents’ opportunities for and interest in sexual relationships develop within a complex and dynamic social milieu. In late childhood, peer groups are predominantly monosexual and opposite-gender contacts are limited. During the middle-school years, boys and girls begin to congregate into group settings and heterosexual pairings emerge.¹¹ Continued allegiances to same-sex peer groups (along with uncertainties about interacting with the opposite sex) make most early “dating” incursions brief and superficial social displays rather than intimate friendships. Add Health data reveals that teens under age 14 typically report relationship durations of 5 months and teens aged 14–15 years report durations of 8 months.²³ Norms revolving around status symmetry, gender-appropriate behavior, fidelity, and peer valuation add to the scripted nature of early romantic experiences.¹⁰

As adolescents grow older, peer groups generally become smaller and more gender heterogeneous, making romantic partnerships highly visible structures within peer networks. For most adolescents, these changes correspond to increased

intimacy and trust in romantic partnerships, foreshadowing the longer-term relationships associated with adulthood. Accordingly, adolescents over age 16 report typical relationships of almost two years in duration.²³

The dominant pattern of adolescent relationships is “serial monogamy,”²⁴ in which teens date (and may be sexually active with) one partner, then select another partner following dissolution of the previous relationship. However, for those who remain embedded in highly gendered peer groups (e.g., athletics, gangs, etc.) or for whom status is a salient aspect of their identities, peer norms may impact these sexual behaviors and developmental trajectories.²⁵

For most adolescents, the first sexual experience takes place within the context of a romantic relationship.²⁶ More than three-quarters of adolescent girls report that their first sexual experience was with a steady boyfriend, a fiancé, a husband, or a cohabitating partner.²⁷ However, adolescent sexual activity is not always associated with a steady partner. A 1996 study surveyed 75 sexually experienced adolescents about types of sexual relationships and

found that teens classify sexual partners into three distinct groups: steady partners, casual partners/friends, and “one-night stands.”²⁸ Expectations about these relationships, as well as protective behaviors such as condom use, differed between these partnership types. Adolescents had lower expectations about the potential for long-term relationships and higher rates of condom use when they were involved in one-night stands, whereas steady partner relationships carried higher expectations and lowered condom use. These findings show that adolescents are well aware that not all sexual experiences are a part of, or result in, longer-term relationships. This study’s findings regarding condom use are also consistent with studies of adults showing that individuals frequently alter their contraceptive behavior depending on their assessment of risk and the future potential of the relationship.

OTHER CORRELATES OF SEXUAL ACTIVITY

■ AGE

Although peers have been the most studied social correlate of adolescent sexuality, recent research is broadening our understanding of the contexts of early romantic behaviors. Biological explanations are typically used to explain the strong correlation between age and sexual behavior.¹ Explaining variation in the age of sexual onset is one area where social researchers have gained additional insight. While children are physiologically capable of sexual arousal, it is with the onset of puberty that most become more curious and interested in pursuing their sexuality. However, as alluded to above, adolescents’ expressions of sexual interest are also functions of the social influences and behaviors of those around them.

National surveys show that a significant proportion of young adolescents (aged 12–14 years) report that they have been on a date or have had a romantic relationship, and approximately one in five adolescents have had sex before their 15th birthday.²⁹ Younger males are slightly more likely to be sexually active than younger females, though for both young boys and young girls, relationships tend to be short³⁰ and sex is likely to be sporadic.²⁹ However, partnerships linking young adolescents with older partners are significantly more likely to be sexual than relationships between young teens.³⁰

By late adolescence, the majority of adolescents, both male and female, have had sexual intercourse.^{27,31} In addition, most youth begin noninsertive sexual activities prior to first intercourse. Sexual exploration typically occurs in a stepwise fashion, with petting and oral sex commonly preceding vaginal sex. Teens report more “petting” (touching under clothing) and “heavy petting” or fondling (touching each other’s genitals) than sexual intercourse, with all behaviors increasing with age.²³ More than three-quarters of teenage males who have had vaginal intercourse report previous experience

with masturbation by a female.³² Moreover, one in five males who had never had vaginal intercourse reported having been masturbated by a female, and one in seven reported having received oral sex. A report from the Guttmacher Institute²⁷ estimated that 12% of teen males and 10% of teen females had experienced oral but not vaginal intercourse. Further studies of oral sex showed that for males between 15 and 19 years of age, roughly half had received oral sex and 39% had given oral sex.³² Additional evidence supporting the incremental model of sexual exploration is found in a study reporting that adolescents who intended to become sexually active in the next year had higher rates of petting and oral sex than peers who did not intend to become sexually active.³³ This suggests that teens who hope to have sexual intercourse may be more interested in experiencing other sexual activities as precursors.

Recent data from the National Survey of Family Growth shows that in 2002, the proportion of adolescents who had ever had vaginal intercourse rises steadily from approximately age 15 to 19 years (Fig. 6-2). Comparison with data from previous years shows that rates of sexual activity among younger adolescents have declined over the past decade, though older adolescents continue to become sexually active at comparable rates.³⁴

While petting and oral sex are common precursors to vaginal sex, less is known about adolescents’ engagement in anal sex. In most studies, adolescents report lower rates of anal sex than other sexual behaviors, though anal sex appears to become more common as adolescents age. In one of the few nationally representative studies of anal sex, Gates and Sonenstein³² report that 11% of males aged 15–19 years had had anal sex, while a study of college students found that 17% of males and 18% of females had engaged in anal sex.³⁵

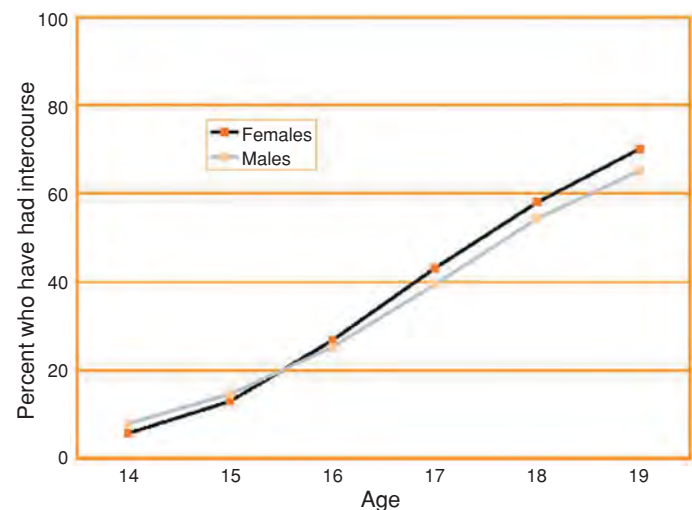


FIGURE 6-2. Percent who had intercourse. (From the Allan Guttmacher Institute, *Facts on American Teens’ Sexual and Reproductive Health*, 2006 (these data are from 2002, i.e., percent of males and females who have had intercourse, by age, 2002).)

Because anal sex is commonly associated with the homosexual male population, stigma surrounding this population may have impeded efforts to learn more about this particular practice among adolescents.³⁶

■ GENDER DIFFERENCES

Although the gender gap is narrowing, recent nationally representative data show that males continue to initiate sex at earlier ages than females^{31,37,38} and report that they have significantly more sexual partners than do girls.³¹ However, among sexually active adolescents, girls, particularly white girls, are more likely to report that they have had intercourse within the past 3 months.³¹

Some explain the overall decline in teenage sexuality over the last decade in terms of lowered rates of male intercourse.^{31,39} Risman and Schwartz³⁹ argue that increasing numbers of abstaining males result from girls having greater influence in romantic and sexual involvements. Girls are believed to have greater freedom and control over their sexuality within a romantic relationship, while at the same time fewer females are available for male nonromantic sexual activities. This shift in gendered romantic power could then explain lower rates of male sexual activity and level rates of female sexual activity, the latter resulting from offsetting rates of lowered nonromantic sexual activity and higher romantic sexual behavior.

Giordano et al.⁴⁰ provide support for Risman and Schwartz's³⁹ argument using data gathered from the Toledo Adolescent Relationship Study (TARS). They find that boys, more than girls, report that their partners are likely to have more power in a romantic relationship and are more likely to influence their behavior. Moreover, they find that boys are less likely than girls to show confidence in such relationships and are more likely to have difficulty communicating. They argue that their results support symbolic interactionist ideas about individual adaptations to problematic situations. Boys, more than girls, enter heterosexual dating with fewer emotional and social skills in reciprocal relationships. These deficits then leave them at a disadvantage in early romantic involvements. Interestingly, the authors found no significant gender differences in perceptions of "love" in adolescent romantic relationships. Boys were just as likely as girls to report loving feelings in these relationships.

Within gender, variation in biological development may also affect patterns of sexual development, particularly for girls. Girls with early or more advanced pubertal development have been shown to be at greater risk of delinquency^{41,42} and early sexual initiation.^{43,44} These patterns are typically explained as resulting from early-maturing girls being sought out by older (and likely more risk-taking) males.⁴² However, using Add Health, Haynie⁴¹ found that early-maturing girls were not more likely to be embedded in male or older peer

groups. Rather, she found that these girls were more likely to be involved in a romantic relationship, embedded in "party" groups, and spend more time with their peers. These results suggest that early development gains girls access to popular peer cliques that are characterized by precocious behavior, including sexual risk taking.

■ RACIAL DIFFERENCES

Several authors find that the behaviors and meanings of early romantic involvements differ by adolescents' racial characteristics. In a comparison of four nationally representative samples, Santelli et al.³¹ find that a higher proportion of African American adolescents aged 15–17 years have had sexual intercourse than white or Hispanic youth, though there is substantial variation in estimates of sexual activity level across surveys.³¹ Differences by race are also evident in data describing the proportion of teens that have had four or more lifetime partners: significantly more adolescent African Americans, particularly African American males, report multiple lifetime partners.³¹ Moreover, analyzing data from Add Health, Giordano et al.⁴⁵ find that even though African American and white youth are equally likely to be involved in a romantic relationship, African Americans are less likely to describe these relationships as intimate and intense. This difference is particularly significant between black and white girls. In addition, African American males are more likely than their white male counterparts to report having intercourse with their partners.

Giordano et al.'s⁴⁵ results have greater weight when added to other findings that black youth have lower marriage expectations compared to whites.^{46,47} Although the relationships between race, early dating experiences, and subsequent marriage rates are complex, observed patterns suggest important links between these factors.⁴⁸ Continued work in this area could distinguish structural, cultural, and developmental processes as they relate to racial dating experiences.

Another research area connecting race and adolescent romance looks at the experiences of young interracial relationships. Adolescent interracial couples are theoretically interesting because prominent racial scholars link interracial marriage rates to the erosion of racial barriers to social mobility.^{49,50} Adolescent cross-race relationships may therefore portend a less segregated future.⁵¹ However, even though attitudes toward these relationships are becoming more accommodating, young interracial couples remain infrequent. Looking at Add Health, Vaquera and Kao⁵² find that interracial couples are less likely than other daters to publicly and privately show affection. They assert that lower levels of intimacy in interracial romances result from continued social barriers and stigmatization of racially nonnormative relationships. The social isolation of minority communities⁵³ and the coercive acts of disapproving

peers and parents⁵⁴ likely contribute to the difficulties facing interracial couples.

■ SEXUAL ORIENTATION

For many adolescents, sexual development entails discovering their own sexual orientation. Sexual orientation refers to the direction of an individual's sexuality, usually in relation to the sex of one's preferred partner. Typically, researchers classify sexual orientation into three categories: exclusively heterosexual, predominantly heterosexual with some same-sex experience, and exclusively homosexual.⁵⁵ Classification is particularly slippery during adolescence, when the orientation of sexual preferences and sexual behaviors or experiences may not match.

Many studies reveal that adolescents frequently have same-sex romantic or sexual experiences, yet still consider themselves to be heterosexual (while others report having opposite-sex experiences but same-sex attractions). For instance, Add Health data show that the rate of same-sex attraction and behavior in the adolescent population ranges from 1% among younger teens to 15% among older adolescent girls who describe themselves as having a nonheterosexual identity.⁵⁶ A separate study of Swiss adolescents showed that 1.5% of girls and 2.5% of boys reported sexual behavior with a person of the same sex; however, 65% of these males and 80% of these females considered themselves to be heterosexual.⁵⁷ These data illustrate that sexual orientation cannot be simplified into "gay" and "straight" categories.

Researchers also investigate the life experiences of adolescents who are sexually oriented toward members of their own sex. Cumulatively, these studies show that adolescents with same-sex orientations are at elevated risk for a variety of social, emotional, and mental health problems.^{58,59} While some of these negative outcomes can be attributed to an exaggerated form of typical adolescent anxiety and alienation, particularly poor mental health and adverse social experiences may reflect, at least in part, homophobia of parents, teachers, and other adolescents.⁶⁰

■ SOCIOECONOMIC STATUS

Numerous studies have examined the links between family socioeconomic background and adolescent sexual behavior. By socioeconomic status, we mean the social and economic resources that an individual controls. Social scientists frequently measure socioeconomic status with a composite indicator that captures the highest level of education completed and a measure of income or occupation⁶¹; when studying adolescents, scholars typically use the socioeconomic status of adults in the household in which the adolescent resides.

Large-scale studies provide mixed results for the association between socioeconomic status and adolescent sexual activity. Some studies find no relationship between family

income or occupation and adolescent sexual behavior,^{26,62,63} while others find a negative relationship between socioeconomic status and sexual risk taking.^{64,65} Much of this divergence may be explained by the conflation of parent education and parent income/occupation in the measurement of family socioeconomic status.

Studies that disaggregate these concepts consistently find strong negative relationships between parent education and early sexual initiation,^{62,66,67} contraction of an STD,⁶⁸ teenage sexual intercourse,⁶³ and contraception use,^{66,69} but modest or null findings for income or occupation on these same behaviors. These findings suggest that educational opportunities and aspirations, more than financial resources, are important protective factors for adolescent sexual risk taking.

Robust findings that parental education is a protective factor against adolescent sexuality may also help explain socioeconomic status differences in teenage childbearing.⁶³ Teenage pregnancy and childbirth are strongly associated with poverty.⁷⁰ With low expectations for educational success or upward mobility, poor women may welcome young parenthood as a positive identity change and an opportunity to enter into supportive social networks.^{71,72} The paradox of parenthood among poor women is that the rewards of becoming a mother contrast sharply with the low likelihood of marriage and the increased risks of school dropout and welfare dependence. In an interview of 162 multiethnic, low-income mothers, Edin and Kefalas⁷² found that only 14% had ever been married, approximately 60% did not graduate from high school, and almost 50% were currently unemployed. This strong connection between urbanicity, poverty, and teenage parenthood remains a public health concern and contributes to the reproduction of social inequality.

■ OTHER RISK-TAKING BEHAVIORS

There is a well-documented association between adolescents' general level of risk taking and the likelihood that they will have sex or engage in risky sexual activities.⁷³ Most substantially, alcohol and drug use have both been linked to increased risk of having sex, having sex more often and with more partners, and pregnancy. Teens who use drugs are also less likely to use condoms, and more likely to contract an STD.⁷³ One explanation for these findings is that substance use itself may lower inhibitions and reduce adolescents' abilities to think clearly and take precautions.⁷³ However, other risk-taking activities, including aggression (such as physical fighting or carrying weapons) and delinquency, are also positively associated with sexual activity.⁷³

This pattern of empirical associations suggests that perhaps both risk-taking and unsafe sexual behavior are the result of a common cause—such as risky temperament, low socioeconomic status, or poor school performance.⁷³

ADDITIONAL SOURCES OF SOCIAL INFLUENCE

■ PARENTS

Relationships between parents and children have received substantial research attention (e.g., Youniss and Smollar⁷⁴). Few studies, however, have focused on the association between parenting and adolescent sexual development. This is somewhat surprising, given that a primary motivation for adolescents to date and initiate sexual encounters may be to separate themselves from their parents.⁷⁵ Lacking traditional rites of passage, modern adolescents are likely to turn to romantic involvements as assertions of adult status and autonomy from parents.

Even if romantic involvement serves a general developmental function during adolescence, significant variation remains in the timing and social correlates of teenage sexual activity. Some of this variation may be explained by relationships with parents before and during the adolescent period.

Studies consistently find that less cohesive family structures (e.g., single-parent households or families of divorce) are associated with earlier sexual initiation and higher risks of teen pregnancy.^{33,76–79} One explanation for this relationship is that disrupted families are less able to monitor children's behavior, increasing the probability that adolescents will deviate from parents' standards. In a longitudinal test of sexual initiation, Longmore et al.⁷⁷ found that parent monitoring during late childhood was the most significant parenting effect on the risk of adolescent first intercourse. Another study that measured both mother–child relations and family structure also found that qualities of the maternal relation are more important than family structure per se in predicting sexual initiation—except for adolescent girls in single-parent households.⁸⁰

A different explanation for the relationship between disrupted families and early sexual initiation is that the higher stress in these families results in coercive and authoritarian parenting. Children from overcontrolling families may respond by becoming more involved in unconventional peer groups and increase the risk of early sexual debut.⁸¹ In addition, the hostility associated with authoritarian parenting may influence the quality of adolescent romantic relationships.⁷⁵ Coercive and violent parenting, as well as violence in the parents' marital relationship, may be replicated in adolescent peer and romantic relationships.^{82,83}

The opposite is true of adolescents who are attached to supportive parents. Individuals from supportive families are more likely to communicate with their parents and share parents' (less permissive) sexual attitudes.^{84–86} Teens who live with both parents and enjoy close relationships with them are less likely to have sex or experience adverse sexual outcomes (e.g., pregnancy, STDs) if they do have sex.⁷³

The relationship between parenting and adolescent sexual development is also likely to differ by a child's gender. Parents

are more likely to monitor daughters' than sons' behaviors,^{87,88} and coercive parenting is more likely to apply to boys than girls.⁸⁹ These processes may contribute to gender differences in sexual development (see above) and parental responses to children's sexual activities.

■ NEIGHBORHOOD AND COMMUNITY

Communities provide important sources of informal social control,⁹⁰ as well as opportunity structures and normative contexts for early sexual development.³⁸ In concert with parents, a neighborhood's social networks may provide opportunities for monitoring and sanctioning that are likely to shape early romantic behaviors and prevent risky sexual activities. In addition, neighborhood characteristics may structure an adolescents' access to economic resources or adult role models and therefore affect the type and level of adolescent sexual behavior.⁹¹ Looking at Chicago neighborhoods, Browning et al.³⁸ recently showed that a community's trust, cohesion, and shared values (e.g., collective efficacy) condition the parental effects on adolescents' sexual debut. This study finds that community networks are particularly salient when parental monitoring is limited; this suggests that youth from disorganized communities who live in households with low levels of parental monitoring are at higher risk of early sexual intercourse.

■ RELIGION

The public debate over faith-based initiatives has galvanized research on religion and adolescent sexuality. Lowered rates of adolescent sexual intercourse are often attributed to greater adolescent religiosity, particularly among girls. Survey data shows that 44% of adolescent girls report religious or moral reasons for remaining abstinent,³⁷ while a review of longitudinal studies of the effect of religiosity on sexual initiation concludes that religiosity delays the onset of sexual activity for girls but not for boys.⁹²

Although empirical studies typically measure religious beliefs and affiliation at the individual or parent level, theoretical explanations commonly take an ecological approach to the religion–sexuality relationship, viewing religion's effects as occurring at the individual, family, peer, school, and community levels (see Rostosky et al.⁹² for a review). Ecological perspectives treat the contexts of religious affiliation as just as important as denominational beliefs and customs. In this vein, Bearman and Brückner⁶⁴ recently studied the effects of religiously based virginity pledges on adolescent sexual debut. They found that, net of controls, adolescents who take a virginity pledge initiate sexual intercourse at later ages than their peers. However, they also found that this effect varies substantially by peer context, with the virginity pledge being most effective when there is a minority

of pledgers in a school. They claim that pledging is more meaningful and central to an adolescent's identity when it is unusual and that this motivates adolescents to keep their pledges. When pledging is common, adolescents seem to take it less seriously. As a side note, Bearman and Brückner also found that pledgers who fail to keep their promise are less likely to use contraception than are their nonpledging peers. A follow-up study found that 5 years later, pledgers and nonpledgers had similar rates of STD (measured by nucleic acid amplification testing of urine specimens).⁹³

■ SCHOOL

Schools hold an important place in adolescent sexual development. Education is a primary adolescent task and most contemporary youth go to school for many years before becoming sexually active.⁹⁴ The concentrations of similarly aged youth within schools provide an important context for the development of romantic relationships. Moreover, the connection between education and the state makes schools important sites for policy interventions, such as sexual education programs and health clinic access.

Studies consistently find that adolescents who are more invested in school^{65,95} or who plan to attend college^{96,97} have later ages of sexual initiation and lower frequencies of risky sexual behavior. These findings are commonly explained using Hirschi's⁹⁸ social bonding theory of delinquency. For Hirschi,⁹⁸ adolescent bonds with schools and school-based adults and peers increase conventional behavior and reduce the risk of deviance, including risky sexual activity. Accordingly, strong bonds to school (1) commit youth to conventional lines of behavior because the cost of unwanted pregnancy or disease contraction could be foregone future opportunities, (2) build belief in a conventional order that discourages early sexual intercourse or childbearing, (3) increase the amount of time spent on conventional activities (e.g., homework, extracurricular activities) and reduce time spent in situations that promote risk taking, and (4) attach students to peers and teachers who encourage abstinence or safe sex.

Schvaneveldt et al.⁹⁹ provide a good summary of research connecting academic achievement and adolescent sexual behavior. They emphasize that this relationship may operate in both directions such that high academic aspirations and good grades may reduce sexual risk taking, while risk taking may simultaneously reduce academic aspirations and achievement. In longitudinal analyses using data from the National Survey of Children, they find evidence for both the effects: low educational goals and achievement correspond with lower ages of first sexual intercourse, while early intercourse also is associated with reduced future academic aspirations and achievement.

Although strong school bonds are clearly associated with reduced sexual risk taking among adolescents, evidence for

the effectiveness of school-based sex education courses and programs remains inconsistent and methodologically flawed.¹⁰⁰ There are currently no published studies that demonstrate that abstinence-only school programs delay sex.⁹⁴ However, Kirby (p. 29) notes that it is too early to judge these programs because "(a) abstinence-only programs are a very heterogeneous group of programs, (b) too few rigorous studies have been completed, and (c) there is some evidence that the abstinence pledge can lead to a delay in sex in some conditions and that one community-wide abstinence media campaign may have delayed sex among young teens."⁹⁴

The few studies that have examined the effects of sex education and HIV education in schools show mixed results, with some studies finding that such education delays sex, while others finding that they lower the age of sexual initiation (see Kirby⁹⁴). With regard to contraceptive use, studies show more consistent results in that sex education increases contraceptive use (see Kirby⁹⁴). Interestingly, the availability of condoms (from health clinics or free handouts) does not appear to increase their use or increase the frequency of adolescent sexual activity.⁹⁴ This is broadly consistent with the findings in a pair of longitudinal studies that use Add Health data to examine the consequences of early condom use. Shafii and her colleagues show that adolescents who use a condom at their sexual debut are more likely to use condoms subsequently¹⁰¹ and that over time, early condom users (1) continue to use condoms at higher rates than nonearly users, (2) have the same number of lifetime partners, and (3) have lower rates of sexually transmitted infections.¹⁰²

■ MEDIA

Today's adolescents are being raised in a multimedia environment that affects their social, academic, and romantic lives. Many theories describe the role that media can play in shaping people's perceptions and behaviors. Perhaps most salient, the Media Practice Model suggests that adolescents select and react to sexual media diets that speak to an emerging sense of themselves as sexual human beings.⁴⁴ Three prominent forms of media have been identified as influencing adolescents' sexual behaviors: music, television, and the Internet.

Though music's influence on teenage sexual behaviors has been suspected since Elvis Presley first swiveled his hips, the empirical evidence on this matter is thin. A recent study¹⁰³ interviewed teens between ages 12 and 17 years at baseline, one, and three years later. This survey asked about sexual behaviors and media use, including exposure to sexual content in music and found that even after controlling for multiple other factors, youth who listened to more degrading sexual content were more likely to subsequently initiate intercourse and to progress to more advanced levels of noncoital sexual activity. In contrast, exposure to music with nondegrading sexual content was unrelated to changes in participants' sexual behavior. Though this

study illustrates links between music and sexual activity, it is still somewhat unclear whether the association between sexually aggressive music and sexual activity is spurious.

The evidence with respect to television watching is more robust. For instance, a study using Add Health data found that among adolescents who report strong parental disapproval of sex, the number of hours of television watched is associated with higher rates of sexual activity.¹⁰⁴ However, the mechanism for influence is more complex than a simple exposure to suggestive content: the study found that higher rates of television watching and sexual activity were linked to lower parental monitoring of television watching, and thus the higher levels of sexual activity are—at least in part—a function of parental monitoring rather than simply the result of kids “getting ideas” from TV.

Subsequent studies have found that the relationship between adolescents’ television viewing and sexual experiences depends on the type of messages viewed, the sexual outcome considered, and the gender of the viewer.¹⁰⁵ Girls who frequently viewed portrayals of women attracting men by willingly making themselves sexual objects reported less sexual empowerment and had more sexual experience than other girls; girls who saw more portrayals of men shunning commitment in romantic relationships also reported less sexual empowerment. The study found few associations between males and television content. Another study examined four types of media—television, music, magazine, and movies—and found that exposure to sexual content in these forms of media was associated with earlier sexual debut in white, but not black, adolescents.⁴⁴

The evidence in these studies illustrates that the content of the media message is important and that the effects of media on adolescent sexuality may vary by sex and ethnicity. Thus while there is mounting evidence that television has an effect on shaping teen’s views and behavior, these effects are complex: program content, gender, and family circumstances all condition the relationship between media and adolescent sexual activity.

Over the past 5 years, the Internet has become a pervasive force in adolescents’ social lives. In fact, some observers have suggested that teens displace television watching with Internet-based activities.¹⁰⁶ Regardless, recent data show that that over 90% of American adolescents have Internet access, either at home or at school.^{107,108} Teens spend much of their time on the Internet communicating with other people, either through email, instant messaging (IM), or chat rooms.^{109–111} Just as the Internet has affected many other domains of life, it has shaped teens’ romantic lives by providing a venue for communication with partners and potential partners, as well as a way to seek out and meet new partners. For adolescents who spend a great deal of time online, this may make it easier to transition into, and out of, romantic relationships. Thus it is not surprising that many teens report using the Internet to ask someone out, as well as to break up with a current partner.¹¹²

Communicating via the Internet allows teens to seek companionship without the social pressure of encounters in person. Some have argued that the Internet provides an alternative venue for higher risk adolescents who have struggled to find satisfying face-to-face relationships.¹¹³ In support of this idea, a study of adolescents who were frequent chat-room users found a disproportionate number of teens who had run away from home, teens who were intrigued by risk, and teens who experimented with drugs and alcohol.¹¹⁴ This same study found that among ninth graders, those who were frequent Internet users were almost two times as likely to be sexually active than were peers who were not frequent Internet users.¹¹⁴

At present, there is evidence suggesting that seeking sexual partners through the Internet has risks. MacFarlane et al.¹¹⁵ found that young adults who found sexual partners online were at higher risk of acquiring STDs. This association is unlikely the result of the Internet itself triggering high-risk sexual behavior, however. More likely, it is the result of a selection process: since higher risk teens frequently use the Internet to find companionship, high-risk teens may find other high-risk teens on the Internet and share and spread STDs.

■ COMPARATIVE DATA

Adolescents in developed countries such as Canada, Great Britain, France, Sweden, and the United States have generally similar rates of sexual activity.⁷⁰ However, in spite of broad similarities, there are several respects in which American adolescents differ from their Canadian and European counterparts. Specifically, more adolescents in the United States have sexual intercourse before age 15. American teens also tend to have shorter and more sporadic relationships, and more relationship partners, than teens in other developed countries.

In addition to these small differences in relationship patterns, American adolescents experience far more adverse effects associated with their sexuality than do teens in Europe and Canada. Adolescents in the United States have higher rates of pregnancy, childbearing, and abortion than adolescents in other developed countries,^{116,117} and higher rates of STDs.¹¹⁶

The United States ranks among the top five countries in terms of teenage pregnancy rates.⁷⁰ Several factors influence the teen pregnancy rates in the United States, including negative societal attitudes toward teenage sexual relationships, restricted access to and high costs of reproductive health services, ambivalence toward contraceptive methods, and lack of motivation to avoid pregnancy.⁷⁰ The relatively high rates of STDs among American teens are associated with increased number of sexual partners, lower levels of condom use, and the structure of adolescents’ sexual networks.¹¹⁶

Countries with comparable rates of adolescent sexual activity but lower rates of adverse sexual outcomes are frequently described as being more accepting of teenage sexual relationships and more willing to provide access to contraception.¹⁷

The “pragmatic European approach” to adolescent sexuality¹¹⁸ refers to a set of interlocking norms and behaviors that support parents, schools, and health-care providers who link positive discussions about sexuality with clear information about how to prevent pregnancy and STDs within relationships.⁷⁰ Along these lines, Sweden’s success in reducing teenage pregnancy rates followed both improved sexuality education and enhanced provision of contraceptives to adolescents.¹¹⁹

SUMMARY

The social dimensions of adolescent sexuality are complex and intriguing. A recent systematic review found that one consistently strong predictor of adolescent sexual activity was the youth’s perceptions of social norms about sex.¹²⁰ Adolescents’ assessments of social norms, in turn, are strongly influenced by peer, partner, school, and parental values about sex. All of these groups influence teens by encouraging beliefs, modeling behaviors, and often by providing opportunities for behaviors to occur (or not to occur). Despite the common view of sexual activity as an intimate and personal topic, the decision to become sexually active is remarkably impacted by social influences.

Ecological approaches to understanding adolescent sexuality are aided by advances in data collection and methodology. Large-scale youth and parent surveys allow researchers to disentangle effects at the individual and contextual levels. With regard to sexual behaviors, these surveys provide clues to the impacts of self-selection, peer pressure, and community contexts on sexual initiation and early dating experiences. Moreover, multiple-school network data and emerging sociometric methods elaborate the structure of romantic ties and place these relationships within broader patterns of peer friendships and school contexts. Taken alongside longitudinal survey and relational data, social networks provide exciting opportunities to observe the development, maintenance, and dissolution of early romantic partnerships and sexual contacts. Such approaches hold the keys to future developmental research and move us past individualized conceptions of clearly social phenomena. By embedding youth in multiple and often overlapping social contexts, we are better able to understand the pushes and pulls that shape early sexual trajectories.

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7

Sexual Networks, Concurrency, and STD/HIV

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MOTIVATION

Over the past two decades, the HIV epidemic has challenged the epidemiological community to rethink the framework for understanding infectious disease transmission, both at the individual level and at the level of population transmission dynamics. Research has rapidly converged on the central importance of partnership networks. Systematic patterns in social networks have always served to channel infectious diseases—from the sequence of plagues in Europe and the introduction of European childhood infections into the Native American populations, to the polio epidemics of the early twentieth century and contemporary outbreaks of cholera and typhoid that attend mass movements of refugees.¹ The methodology for network data collection and analysis, however, is only now being developed.

Like other exchangeable goods, the diffusion of pathogens through a human population traces the structure of social networks. The pattern of spread is jointly determined by the biology of the pathogen and the social structure that can support it, so different kinds of diseases travel along different structural routes. The plague, for example, is spread by a mobile vector of rats and fleas. This makes for an efficient, long-lasting infectious vehicle, enabling spread via long-distance transportation and trade routes, so macroeconomic relations help to structure the diffusion path. For influenza and measles, by contrast, transmission requires casual or indirect personal contact in a relatively short period. The spread of these infections is structured by locations for frequent collective activity, like schools and supermarkets today, with transportation networks serving as potential bridges between communities, and sparsely settled or less traveled routes serving as buffers. Finally, there are infections that spread only by intimate or prolonged contact, and sexually transmitted infections (STIs) are a classic example. These diseases travel along the most selective forms of social networks, operating on what is comparatively a very sparse microstructure, with a typically modest duration of infectivity for several

STIs. The structure of sexual networks varies within and between societies, governed by local norms, power differentials, and oppositional subcultures. Here, as with other infectious diseases, the transmission network determines the potential for epidemics and the opportunities for prevention.

Network epidemiology offers a comprehensive way of thinking about individual sexual behavior and its consequences for STI. Unlike other health-related behaviors (e.g., smoking and seat belts), behaviors that transmit STI directly involve at least two people, and the links either of these persons might have to others. Understanding this process requires moving beyond the standard, individual-centered research paradigm. This has important implications for the analytic framework, data collection, and intervention planning.

The analytic framework must take a relational approach, integrating individual behavior into partnership contexts, and aggregating partnership configurations into networks. This is a marked departure from the standard approach to “behavioral research” that seeks to link individual attributes to individual outcomes. Data collection and statistical analysis need to be revised accordingly, making the partnership—rather than the individual—the primary sampling unit. While we know a lot about sampling individuals, we know much less about sampling partnerships and networks. Finally, analyzing the network data we collect requires different statistical methods, since the defining property of such data is that the units are not independent. Methods for analyzing dependent data are not unknown—spatial statistics, time series, and multilevel models provide a starting point—but the statistical tools needed to analyze networks have only recently been developed.

Given these difficulties, why bother taking a network approach? Why not simply focus on individual risk factors for acquisition of disease? The answer is that network epidemiology succeeds where more traditional epidemiological approaches have failed: explaining differentials in risk behavior, epidemic potential in low risk populations, and the persistent and substantial prevalence differentials

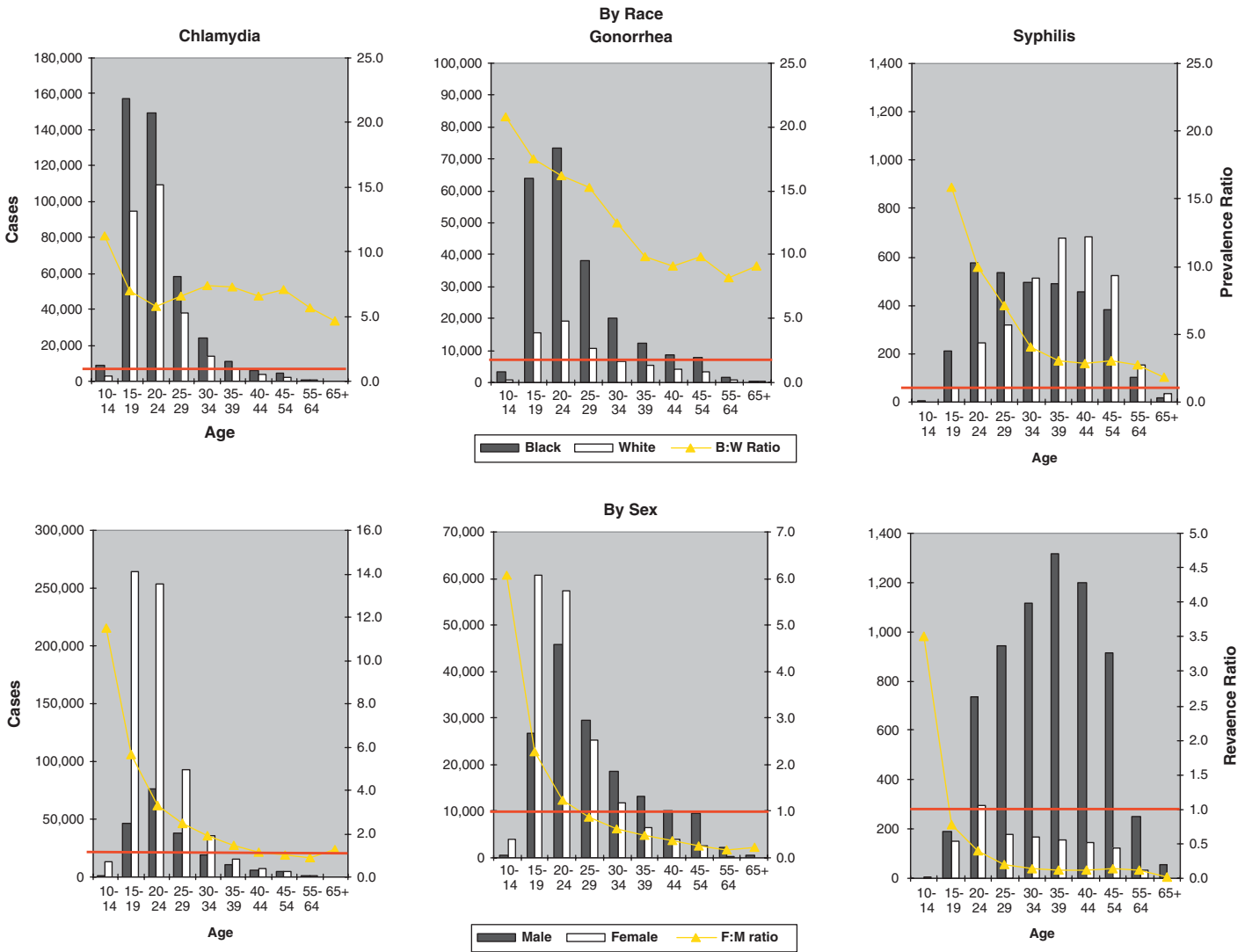


FIGURE 7-1. STI prevalence by age, race, and sex in the United States, 2004. The bars show the number of cases by age and group (on the left axis) and the yellow line shows the per capita prevalence ratio by group (on the right axis). The red line indicates a prevalence ratio of 1 (on the right axis).

across populations. An example of these differentials is the prevalence by age, race, and sex of reportable STI in the United States, shown in Fig. 7-1.

RACIAL DIFFERENTIALS IN STI PREVALENCE IN THE UNITED STATES

In one sense, a network explanation is almost tautological: individuals are infected by their partners, who are in turn infected by their partners—“networks” is just a term that describes this process. But the concept also has explanatory power and prevention implications, as it changes the focus from “what you do” to “whom you do it with.” This allows for behaviors to vary within, as well as between persons, and for the same individual behavior to lead to different infection outcomes in different contexts.

As a result, the network perspective changes the way we think about targeting concepts such as “risk groups” and “risk

behaviors.” The inadequacy of these concepts became clear as HIV prevalence rose among groups that do not engage in individually risky behavior, for example, monogamous married women.²⁻⁵ By the same token, a group of persons with extremely “risky” individual behavior may have little actual risk of STI exposure if their partners are uninfected, and not linked to the rest of the partnership network. It is not only individuals’ behaviors that define their risk, it is their partners’ behavior and (ultimately) their positions in a network.

The network perspective also changes the way we think about population-level risk factors: the key issue is not simply the mean number of partners but the connectivity of the network, and connectivity can be established even in low density networks. One of the primary ways in which this happens is through concurrent partnerships. Serial monogamy in sexual partnerships creates a highly segmented network with no links between each pair of persons at any moment in time. Relax this constraint, allowing people to have more

than one partner concurrently, and the network can become much more connected. The result is a large increase in the potential spread of STI, even at low levels of partnership formation.

Finally, the network perspective changes the way we think about behavior change. Because the relevant behavior occurs in the context of a partnership, individual knowledge, attitudes, and beliefs do not affect behavior directly. Instead, the impact of these individual-level variables is mediated by the relationship between the partners. A young woman who knows that condoms help prevent the sexual spread of HIV may be unable to convince her male partner to use one. It is not her knowledge that is deficient, but her control over joint behavior.

Networks thus determine the level of individual exposure, the population dynamics of spread, and the interactional context that constrains behavioral change. Taking this seriously represents a paradigm shift in the study of STI.

This chapter is organized into three sections: a brief overview of the origins of social network analysis and its applications to the epidemiology of STI, a review of the primary findings from the last 20 years of network-based STI research, and a discussion of the changes in research methodology needed for network-based studies.

■ NETWORKS AND EPIDEMIOLOGY: ORIGINS OF THE FIELD

The use of network analysis to understand population structures and their impact on diffusion processes is not new. The analysis of network structures has a relatively long history in the social sciences, which is where the most comprehensive methodology has been developed, and the study of diffusion through structured populations in epidemiology is also longstanding. In recent years, physicists have also begun to work on the epidemiology of diseases on networks.

Social science roots

Social network analysis is an established subfield in the social sciences, with a professional organization The International Network For Social Network Analysis (INSNA) holding an annual meeting (the “Sunbelt” social network conference, now in its 26th year) and a couple of journals (*Social Networks*, *Connections*). It is an interdisciplinary field, and it has developed a unique set of methodological tools.

What is a social network? The most common definition is a set of relations (links) among persons (nodes) where the relations can range from kinship and exchange, to affection or physical contact. Networks can also be defined on larger units, such as exchange networks among firms, or transportation networks among cities. Another form is the bipartite network (also called two-mode network), in which there are two distinct types of nodes (e.g., persons and places, or

men and women), and the links can only occur between types, not within.

The beginnings of the field are traced back to work by the social psychologist Jacob Moreno in the 1930s. Moreno developed the concept of “sociometry” for understanding the ways in which individuals are supported, constrained, and engaged by their network of ties to others. Sociometry became the name of the journal he started, and the name given to network measurement, delineating the nodes and links.

Early network analysts were interested in the social processes that generate networks, and the theories explicitly focused on how individual partner choices, guided by social norms, aggregate up to produce population-level network structures. For example, anthropologists and sociologists focused on how rules governing permissible exchange partners (e.g., gift giving or marriage) cumulate up to determine the overall structure and stability of an exchange system.^{6–9} Social psychologists and others explored the population-level impact of the norm of balance for positive and negative affect among three actors, e.g., my friend’s friend is my friend, my enemy’s friend is my enemy.^{10–12} The key findings from this period are that some simple rules of behavior at the local level may lead to overall network structures that display striking regularities, such as linear hierarchies, cliques, and stable cycles of exchange. Other rules do not produce such stable outcomes, and this distinction leads to an evolutionary hypothesis about the differential survival of rules over time.

For the last 25 years, social network analysts have been developing quantitative tools for empirical studies. There are two distinct approaches, defined by the type of data collected. The first is based on a network census—data collected on every node and link for a (typically small) population. This approach is largely descriptive and draws on mathematical graph theory and linear algebra for summary measures of network properties. Despite intense data requirements and unusual methods, this approach became the standard in social network analysis, providing a rich framework for thinking about networks and a wide range of summary measures to represent both the network position occupied by specific nodes and patterns in the overall network structure. Almost all of the classic network measures—paths, cycles, density, centrality, structural equivalence, cliques, blockmodels, role algebras, components, and bicomponents—owe their development to researchers working with these descriptive tools. The current textbooks and computer packages for social network analysis have these methods at their core.^{13,14} They have become the common language for network analysis, defining the basic features of networks and helping to develop our intuitions about the complex relational structures we seek to understand. Like linear regression, though, these are descriptive summaries, rather than generative models.

The second approach is based on sampled network data. Since a network census is often impractical, this approach

develops a statistical basis for network estimation and inference from a sample. The most well known of these is the local network (or egocentric) sample design: a sample of the nodes (egos), with a “name generator” in the questionnaire to obtain a roster of their partners (alters), and “name interpreters” to collect information on these partners. The beauty of this simple study design is that no attempt is made to identify or enroll the partners. Local network data collection costs about the same as a standard survey, is relatively easy to implement, and is less intrusive than complete network data collection. Early examples include the Detroit Area Study,^{15,16} the Northern California Communities Study,¹⁷ and the core discussion partners network module used in the General Social Survey.¹⁸ More recent methods rely on exponential random graph models that enable both estimation and simulation of networks from locally sampled data.^{19,20}

In between these two approaches lies a range of link tracing designs for collecting network data: snowball samples, random walks, and most recently, respondent driven sampling. The absence of methods for analyzing such data previously limited the use of this approach, but new methods are now available and becoming more common.^{21–24}

Epidemiology roots

Epidemiologists had a tradition of modeling infectious disease spread through “structured populations” well before the explicit connection was made to social network analysis. The spatial spread of infections was an early focus, with models for the dynamics of childhood disease transmission among families, neighborhoods, schools and playgroups,^{25,26} epidemics on islands,²⁷ and pandemics spreading through the network of airline routes.²⁸ Models for wildlife disease transmission, especially rabies, were built around small interacting subgroups connected by occasional long jump migrations,²⁹ anticipating the “small world” models in the recent physics literature.³⁰

Simple network-like models for sexually transmitted pathogens began to be developed in the late 1970s and early 1980s when, despite the relative availability of penicillin, gonorrhea and syphilis rates rose rapidly in the United States. Surveys of STI clinic patients in the late 1970s found that repeat cases contributed disproportionately to the total case-load: 3–7% of the infected persons accounted for about 30% of the cases.^{31,32} Simulation studies showed that this group can act as a “reservoir,” allowing an infection to persist in a population where the average level of activity was otherwise too low to allow for sustained transmission.^{33–35} This research led to the “core group” theory: if endemic persistence is due to this small core group, then all cases are caused directly or indirectly by the core. The core group thus came to be seen as the primary driving force in STIs and also as the locus for highly effective intervention targeting.^{36–38}

The heuristic of core groups continued to play an important role in early studies of HIV transmission, when the epidemic

was concentrated among men who have sex with men (MSM), injection drug users, and commercial sex workers. But concerns began to be raised about the limitations of the core group concept with the emergence of generalized epidemics in the countries of sub-Saharan Africa (see Ref. 39 for a critical review of this concept and literature).

Both the definition and the utility of the original core-group concept depend on high levels of reinfection—persons who contract an STI once are more likely to contract it again, contributing disproportionately to endemic persistence, and making it more cost-effective to rescreen them. In the case of HIV (and most other viral pathogens), there is no cure, and the role of reinfection remains uncertain, so repeat cases do not appear to drive the epidemic (though see Ref. 40). Core group theory explained endemic persistence in an otherwise infection-free population as the result of small highly active subgroups where transmission remained above the epidemic threshold. This model is consistent with the limited HIV spread in the United States and Western Europe but it cannot explain a generalized epidemic. There may be occasional “seeding” of the general population from a core group reservoir, but sustained spread outside the core is not possible since transmission outside the core is below the threshold. With HIV prevalence in some countries rising to 30 or 40%, it is clear that transmission is above the reproductive threshold in a large fraction of the population. Some kind of core group may have played a role in the initial outbreak of HIV here, but core groups are not responsible for generalized spread.

The first explicit link between social network methods and STI dynamics was made by Alden Klov Dahl in 1985.⁴¹ The paper was written before the virus that causes AIDS had been identified, and the mechanism of transmission had not been conclusively demonstrated. The paper included a sociogram of an MSM sexual network that linked many of the first known AIDS cases back to a single person (“patient 0”), providing strong evidence that this was an STI.

A large number of theoretical and empirical papers have since followed which use network concepts and methods to help understand the different patterns of HIV spread in different countries, the disparities in infection prevalence within countries, the behaviors that increase exposure risk, and the opportunities for prevention. At their best, network models help us understand the population-level implications of individual behavior—how the choices people make link together and aggregate up to create the partnership network that either inhibits or facilitates transmission.

WHAT HAVE WE LEARNED?

Using network analysis, researchers have identified two basic behavioral patterns that have a large impact on the STI transmission network: selective mixing and partnership timing. Selective mixing is about how we choose partners: the

population comprises several subgroups and the question is how many partnerships form within and between groups. Partnership timing is about the dynamics of relationships: monogamy requires partnerships to be strictly sequential, concurrency allows a new partnership to begin while an existing partnership is still active. Both are guided by norms that influence individual behavior, which in turn create partnership network structures that leave distinctive signatures on transmission dynamics and prevalence.

Partnership networks also have other structural features that can be important for STI spread. One example is closed cycles, e.g., the triangles and odd-numbered cycles that can emerge in same sex networks, and larger even-numbered cycles for heterosexual networks. Closed cycles have the effect of sequestering an infection and preventing further spread outside the cycle. A network with small closed cycles may have less potential for rapid spread if the cycles are not connected by other links. Another example is the “scale-free” model for the distribution for the number of sexual partners. These models use a single parameter to represent the shape of the upper tail in the partnership distribution and its impact on epidemic spread (scale-free models are discussed in a separate section below). The signature statistics from these models are typically employed as descriptive summaries for network structures, rather than generative models that link individual behavior to population level outcomes. But they do have epidemiological implications.

■ SELECTIVE MIXING

When choosing a sexual partner, people select on the basis of preferences and constraints. “Appropriate” partners are typically defined by attributes such as age, sex, sexual preference, race/ethnicity, social class, and marital status, and availability is dictated by geographic proximity and subgroup size. People also vary in their rates of partner change, and the mixing within and between activity levels is the focus of the classic “core group” model. At the population level, selective mixing can have a strong impact on the speed and direction of epidemic spread. Tight assortative (“like-with-like”) mixing can lead to multiple, decoupled epidemics in a population,⁴² with sequential waves of infection,⁴³ while disassortative mixing tends to generate slower-growing but larger epidemics in the long run.^{44–46} But the effect also depends on the attributes that define the mixing group boundaries: whether they are stable (like race/ethnicity) or change over time (like marital status), and whether they are correlated to levels of sexual risk behavior (like age). Mixing effects also depend on whether the groups are directly connected (males and females), or whether there are groups with no direct connection but only an indirect connection formed by a “bridge population” (women who are and women who are not commercial sex workers are

connected by their shared male partners). Selection thus occurs on many different kinds of attributes, with different but predictable outcomes on prevalence.

Race and ethnicity

This type of mixing is typically assortative and based on fixed attributes. An example is shown in [Table 7-1](#).

This assortative mixing leads to segregated networks which channel infection and can sustain long-term prevalence differentials like the persistent racial differentials in STI morbidity observed in the United States.⁴⁷ As shown in [Fig. 7-1](#), this differential peaks among young adults: rates of gonorrhea are 20 times greater among non-Hispanic blacks than among whites, rates of syphilis are 15 times greater,⁴⁸ rates of HIV infection are 20 times greater,⁴⁹ and chlamydial infection⁴⁸ and HSV-2 seropositivity⁵⁰ have significant (though smaller) racial disparities.

Race is a proxy for a number of factors that influence risk exposure: discrepancies in health care access, differences in sexual behavior, possible genetic differences, and the structure of partnership networks. But the stability of the race differential persists after controlling for socio-economic status⁵¹ and number of sexual partners⁵² remaining strong even among youth who enter juvenile detention facilities⁵³ and inject drugs.⁵⁴ This suggests that, while poverty and behavioral differentials may matter, they alone do not account for the race disparities in prevalence. While there has been some speculation that genetics may play a role, no mechanism by which genetic differences might influence susceptibility or infectivity has been proposed, and the consistent differences across a wide range of sexually transmitted pathogens suggest the transmission network is a more likely explanation.

Note that segregation alone cannot create a prevalence differential unless there is absolutely no direct or indirect contact between the groups. Segregation simply slows the rate of spread between groups. For STI differentials to persist over the long term, it is also necessary to have differential transmission rates within subgroups. This can be induced by different rates of partner change or of concurrency across groups.

■ AGE

Age mixing is generally assortative, but shows an asymmetry among heterosexual couples, with males typically older than their female partners. Age is also an attribute that changes over time. The net impact on transmission dynamics depends on whether the STI is curable or incurable. For curable STIs, prevalence will typically peak among youth, since rates of partner change are high in this group and partners are typically of similar ages, so the STI circulates rapidly within group. In the United States, for example, about 70% of all chlamydia cases and 60% of all gonorrhea cases are found among persons 15–24 years of age.⁴⁸ Age matching will lead

Table 7-1. Mixing by Race/Ethnicity in the National Health and Social Life Survey (NHSLs) and the Add Health Study for Heterosexual Partnerships

Women	Men				
	White ^a	Black ^a	Hispanic	Asian	Other
<i>NHSLs</i>					
White ^a	95.2	1.4	1.7	0.6	1.1
Black ^a	5.4	89.7	2.3		2.7
Hispanic	30.7	2.3	63.8	0.9	2.3
Asian ^a /PI	23.1	—	—	60.0	16.9
Other ^a	37.5	2.1	2.1	2.1	56.3
<i>Add Health Study</i>					
White ^a	84.9	3.6	5.8	1.8	4.0
Black ^a	8.4	80.2	6.0	0.7	4.6
Hispanic	22.4	7.6	63.0	2.6	4.5
Asian/PI	21.1	5.3	9.5	59.4	4.7
Other	34.4	14.4	24.0	5.6	21.6

The cells show the percent of reported partnerships among women in the row group that are with men in the column group

^aNon-Hispanic

to higher prevalence among youth in this case, as it intensifies the spread within this group. Incurable STI, by contrast, will accumulate with years of exposure, so higher prevalence should be found among older groups for these STIs. For example, in the United States, only 11% of persons living with HIV are in the 15–24-year-old age group.⁵⁵ In this case, assortative age mixing will (all else equal) protect youth by lowering their exposure to higher prevalence older partners.⁵⁶

Gender asymmetry in age-matching means that young women will be exposed to older men, and they will get infected earlier than their male age peers. This sex differential in prevalence by age is observed for HIV in many sub-Saharan African countries⁵⁷ and in the curable STI in the United States (as seen in Fig. 7-1). Biological mechanisms may contribute to this age differential, specifically cervical ectopy in young women, which gradually disappears as squamous epithelium replaces the ectopic cervical columnar epithelium of young women (see Chapter 55),^{58,59} though the evidence is inconsistent for HIV.⁶⁰ But young women with older male partners have consistently been found to have higher prevalence than young women with younger partners in empirical studies,^{61,62} with odd ratios ranging from 1.04 to 3.2 for age differences of 5 or more years. This suggests the transmission network, rather than some biological mechanism, is responsible.

For incurable lifelong infections, where prevalence rises with age, the gender asymmetry in age matching virtually ensures a strong intergenerational chain of transmission: a high-prevalence cohort of older males infects the newly active cohort of young females, who eventually pass it on to their male age-peers, who become the next cohort of older males, and so on.

Age mixing has been shown to influence the dynamics of spread among MSM, where young men with older partners are the leading edge of the epidemic in their cohort.^{63,64} An example below comes from the Longitudinal AIDS Impact Project, one of the early surveys of gay men at the beginning of the AIDS epidemic in New York City. The pattern of age matching in partnerships in which unsafe anal sex was reported is shown in the mixing matrix in Table 7-2.

The assortative bias in age-matching is relatively strong: about 40% more partnerships than expected are within group, and there is a steep falloff in partnerships as the age differential increases (stepping off the diagonal). Despite this, the fraction of the young cohorts' contacts that are with older cohorts is relatively high: about 60% of receptive partners are over 25, as are nearly 70% of insertive partners. The potential for spread from the older cohorts to the younger is still strong, though weaker than it would be without the assortative bias.

Table 7-2. Age-Mixing Matrix for Unsafe Anal Sex Partners from the Longitudinal AIDS Impact Project (LAIP), 1990–1991

	Receptive Partner				Pairs	Contact Rate
	18–24	25–34	35–44	45–54		
Insertive Partner						
18–24	6	8	2	1	17	1.04
25–34	9	38	18	6	71	0.95
35–44	3	21	25	7	56	0.91
45–54	1	7	7	5	20	1.08
Pairs	19	74	52	19	164	
Contact rate	1.25	0.97	0.85	1.03		0.96
Observed % within age group						45%
Expected % within age group under proportional mixing						33%
Ratio of observed/expected						1.4

The cells show the number of partnerships reported between insertive partners in the row age group and receptive partners in the column age group.

The effect of age-matching on individual risk was clear in the pattern of infection. Among those reporting any unsafe receptive sex, seroprevalence was 0 for those who reported no partners outside their own age group, and 44.4% for those who reported at least one partner over age 25. The pattern is the same for insertive anal sex: seroprevalence was 0 for those whose partners were all 25 or younger, and 15.3% for those who reported at least one partner over age 25.⁶³

SEXUAL ROLE BEHAVIOR AMONG MSM

For homosexual male anal intercourse, individual men can play either the insertive or receptive role. Some men consistently perform one or the other, while others perform both. This yields three role subgroups of men: insertive, receptive, and versatile as opposed to the two role categories of male and female in heterosexual intercourse. This changes population transmission dynamics, and the impact depends on the prevalence of each role and the relative transmission probabilities of insertive and receptive sex. If the prevalence of versatile role players is low, mixing between the other two role groups will be disassortative, which helps to ensure that the network is well connected. However, if receptive intercourse by an HIV-infected man with a seronegative insertive partner has a much lower probability of HIV transmission than does insertive intercourse with an HIV seronegative partner, spread will still be impeded, as receptives would be less likely to transmit once infected. As the

prevalence of versatile rises, they may either mix with the other two groups or segregate and mix primarily within group. Because they can transmit both ways, there is no biological brake on spread, so the parts of the network that include them will have higher prevalence. Unlike the biologically defined sex difference between men and women, sex roles are not fixed, so if norms change and the prevalence of the versatile role rises, the epidemic potential in the network can rise.

Simulation studies have shown that the effects of role separation on prevalence can be quite large.^{65–67} In a recent data-driven simulation, using data from Lima, Peru, Goodreau et al.⁶⁸ examined the impact of the prevalence and mixing of versatile men. The survey data showed that 67% of MSM reported segregated roles within their recent male partnerships. The simulation showed that a population of MSM with identical contact rates but complete role versatility would have had twice the HIV prevalence for the epidemic's first three decades. It also showed that versatility, while raising population prevalence, is not necessarily an individual risk factor; versatile remain less at risk than receptive-only men. This will not be true, however, if versatile men mix assortatively with other versatile men and role segregated men mix selectively (but disassortatively) with role-segregated men. In this case, the epidemic becomes concentrated among the versatile. Two studies have found higher HIV prevalence for role-versatile than for role-segregated men, which would be consistent with assortative mixing.^{69,70}

ACTIVITY LEVEL

Differences in rates of partner change, and mixing between more active and less active groups, was the first form of selective mixing explored by epidemiological modelers³³ and it remains a strong focus.^{71,72} Unlike most mixing by demographic attributes (with the notable exception of gender), mixing by activity level varies along the whole continuum from assortative to disassortative, depending on context. Assortative mixing by activity level might be found among gay men who participate in the bathhouse scene, or among younger heterosexuals as a byproduct of age-matching. Disassortative mixing by activity level is typically present in heterosexual partnerships, if norms encourage sexual conquest for men and sexual fidelity for women. Also, unlike demographic attributes, activity levels are not a physically observable feature. This makes it difficult for a person to know the activity levels of a potential or current partner and, therefore, lowers the direct selective impact of this attribute.

Tight assortative mixing by activity level generates the classic core group phenomenon—a reservoir of infection in the core, with limited spread beyond. Disassortative mixing by activity level leads to more generalized epidemics and a decoupling of individual behavior from risk of exposure. The classic example here is the monogamously partnered wife of a man who has had many partners.

GEOGRAPHIC BRIDGING

Sexual networks also have a spatial context, and research suggests that spatially mobile populations have played a key role in the initial spread of HIV, and, in some cases, to higher HIV prevalence. Travel has a wide variety of social origins, from working in the transport industry, seeking education or shopping, to military service, vacations, and involuntary displacement. Migration can be temporary, seasonal, or permanent. In all cases, travel increases the epidemic potential of the network by linking otherwise unconnected populations.

Truck drivers were among the first identified high-risk groups for HIV.⁷³ Military populations are also spatially mobile, and their tours of duty in both peacetime and war lead to both consensual and forced sexual interactions with sex workers and numerous local resident populations, including partners in their town of origin.^{74,75} In Uganda, both the spread of HIV infection in the 1980s and its 1990 spatial pattern, are significantly and positively correlated with ethnic patterns of recruitment into the Ugandan National Liberation Army after the overthrow of Idi Amin some 10 years earlier in 1979.⁷⁶ In this, HIV shows the classic association of war and disease.

Seasonal migration of laborers and traders also represents an important continuing vector for HIV transmission.^{77,78} Many who leave their homes in search of better employment

establish semipermanent homes and sexual relationships at the worksite, while maintaining regular sexual contact with spouses and other partners back home (i.e., concurrency). In a recent study in South Africa,⁷⁹ migrant couples were more likely than nonmigrant couples to have one or both partners infected (35 versus 19%) and to be HIV discordant (27 versus 15%). Using simulation based on these data, migrant men were 26 times more likely to be infected from outside their regular relationships than from inside, and nonmigrant men were 10 times more likely to be infected from outside. This pattern is also thought to have played a large role in establishing the high prevalence in countries like South Africa, Botswana, and Zaire.

Longer term international migration streams may also have contributed to the spread of HIV to developed countries but findings have varied by country. In England, HIV infections acquired overseas are mostly among overseas nationals now living in Britain, rather than in British citizens who travel. These imported infections are subsequently channeled by assortative sexual mixing and residential segregation by nationality within the UK, resulting in spread that is geographically and ethnically confined.⁸⁰ By contrast, a study in the Netherlands found disassortative sexual mixing by nationality. In one study, 50% of the partnerships reported by migrant men and 26% of those reported by migrant women were between members of different ethnic groups.⁸¹ In this case, bridges apparently exist for the spread of STIs from international travelers to the local population.

ATTRIBUTE-BASED BRIDGING

Selective mixing based on attributes can lead to the complete lack of direct contact between spatially integrated groups. Examples include prostitute and nonprostitute women, or (behaviorally defined) heterosexuals and homosexuals. Indirect exposure may still exist, however, if there is a bridge population that links the two groups.^{82–87}

The networks constructed by the sex industry provide a good example. Men who have both commercial and noncommercial sex partners play a critical bridging role for HIV transmission, linking a low prevalence population of female spouses and other noncommercial partners to a high prevalence population of sex workers.⁸⁸ A sexual network survey provided a quantitative estimate of the potential impact of this bridge in Thailand in 1993. About 17% of men reported both commercial and noncommercial partners during the past 6 months. As a result, 25 women were potentially exposed in the last 6 months for every 100 sexually active men, and an additional four women were potentially exposed in each successive 6-month interval.⁸⁴

The network approach taken in this study also identified the groups at risk with greater accuracy. While having a wife and a commercial partner was the most common pattern

reported by men, more nonspousal partners were exposed than wives because nonspousal partnerships turn over more rapidly. Younger men were more likely to expose nonspousal partners, and greater numbers of them, so younger unmarried women were at the highest exposure risk. In this case, simple local network data were able to provide substantial detail on the overall network structure, which in turn can help to refocus intervention strategies.

In recent theoretical studies, one of the most effective network structures for spreading infection was found to be the so-called “small world” network—largely separate groups with most of their contacts within group, connected by a small number of links between the groups.³⁰

■ PARTNERSHIP TIMING: MONOGAMY AND CONCURRENCY

The network connectivity that matters for STI transmission is also affected by the duration and sequence of partnerships. Duration affects the likelihood of transmission. Discordant partnerships of longer duration typically result in more sexual contacts and more chances for transmission. Sequence has its impact by changing the effective transmission structure of the network. Under serial monogamy, each partnership ends before the next begins. When this rule is not followed, partnerships can be active concurrently. The difference can be seen in Fig. 7-2.

The figure depicts two hypothetical partnership histories that a person might have. In both cases, the person has four partners over time, and in both cases, the lengths of each partnership are the same. The only difference is the sequence of start and end dates. Under serial monogamy, each partnership must end before the start of the next. With concurrency, more than one partnership can be active at one time.

In the earliest studies of partnership sequencing effects, researchers focused on monogamy and the duration of monogamous partnerships. Long-term monogamous pair formation slows down the rate of disease transmission, as concordant pairs provide no opportunity for spread, and discordant pairs remain together after transmission has occurred. Analytic findings support this intuition: increasing partnership duration raises the number of contacts needed to

reach the reproductive threshold, lowers the peak number infected, and increases the time to peak infection.^{89–92}

Attention then turned to the impact of concurrency, to understand the impact of relaxing the rule of monogamy.^{93–95} Concurrency has several consequences that lead to amplified transmission. First, as the earlier research showed, concurrency reduces the time between transmissions: the pathogen is not trapped in a partnership since there is another partner available for immediate subsequent transmission. Second, concurrency removes the protective effect of sequence. Under serial monogamy, earlier partners in the sequence are not exposed to infections that the index case acquires from later partners. Under concurrency, earlier partners lose this protection. In Fig. 7-2, partner 1 is indirectly exposed to partner 2, and partner 3 is exposed to partner 4. Not only does this expose two additional persons, it creates two new potential chains of infection from these persons to others.⁹⁶ Third, concurrent partnerships link individuals together to create large connected “components” in a network—if you have more than one partner, then your partner may have more than one partner, and so on. Such connected components function like a well-designed road network—they allow a pathogen to travel rapidly and efficiently to many destinations.

Concurrency increases the speed of STI transmission through a population. In some cases, this can raise transmission above the reproductive threshold: the difference between an infection dying out and sustained epidemic spread. This is particularly likely if the pathogen has a short window of peak infectivity. In this case, concurrency helps to ensure that recently infected hosts have an uninfected partner to transmit to within the constrained time frame.

It is important to note that none of these consequences imply more risk for the index case with concurrent partners; the index case simply has the risk associated with multiple partners, whether sequential or concurrent. Concurrency is instead a risk for the partners of index cases (at the individual level), and it raises the epidemic potential of the network (at the population level). If those with concurrent partners tend to choose partners who also have concurrent partners, then this is a form of assortative mixing. Under these conditions, a prevalence differential can develop, and one will observe a higher risk of infection among those with concurrent partners. This has important implications for empirical studies that seek to quantify the impact of concurrency, as discussed below.

■ SIMULATION AND ANALYTIC FINDINGS

Even small differences in partnership sequence can have a remarkably large impact on both network connectivity and epidemic spread. Two examples are shown below. In Fig. 7-3,

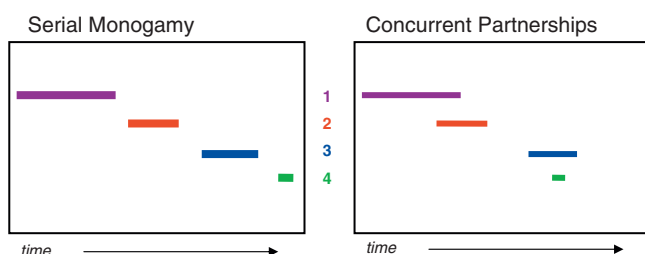


FIGURE 7-2. Definitions of serial monogamy and concurrency. The lines depict partnership intervals over time for a hypothetical person with four partners during the time period reviewed.

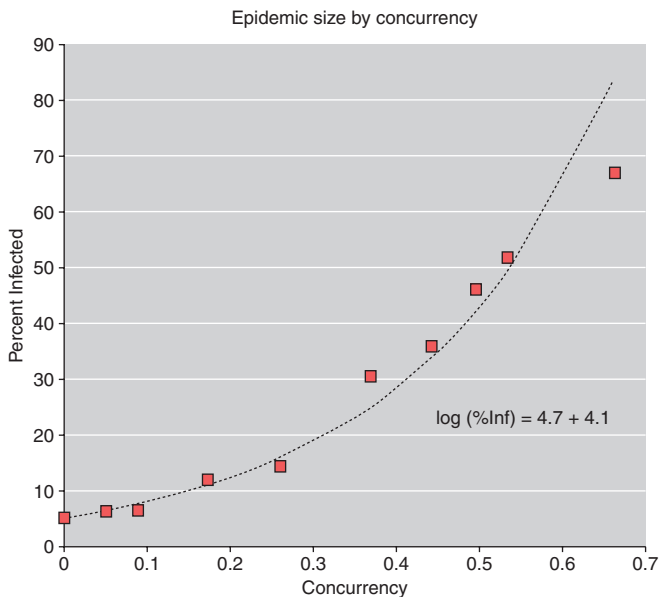


FIGURE 7-3. Impact of concurrency on prevalence. The graph shows the average percent infected at the end of the simulation (y axis) as concurrency was increased (x axis).

from an early paper in the field by Morris and Kretzschmar,⁹⁷ the plot shows the average prevalence of infection after several years (on the y axis) as a function of the level of concurrency in the population (on the x axis). The results are based on a fully stochastic dynamic simulation, with partnerships that form and dissolve over time, a fixed transmission probability per unit time in discordant partnerships, and no vital dynamics. The points on the graph represent the average of 100 simulations at that level of concurrency. Concurrency is measured as the mean degree of the “line graph” which can be interpreted roughly as the expected number of concurrent partnerships associated with each partnership in the population. In all simulations, the total number of persons and partnerships in the hypothetical population is the same, the infectivity of the pathogen is the same, and the number of years the simulation is run is the same; the only thing that varies is the level of concurrency. As concurrency rises, prevalence rises exponentially: with serial monogamy (concurrency = 0), final prevalence is approximately 5%, and by the time the measure of concurrency is 0.7 (7/10 of a concurrent partner for each partnership in the graph, or 7 out of 10 partnerships having a concurrent partnership), the final prevalence is nearly 70%. Since there is *no increase* in the number of partnerships (or the mean contact rate), the entire rise in prevalence here is due to relaxing the rule that partnerships be monogamous (the editorial that followed the original article was in error on this point⁹⁸). Data from Uganda in the early 1990s suggest that the concurrency measure was about 0.22, which would raise the expected number infected by a factor of 2 or 3 over serial monogamy.⁹⁹

One of the primary mechanisms that explains how concurrency amplifies spread is the increase in network connectivity. The intuition here is simple. Imagine if everyone had only two partners in their lifetime, but had them concurrently. Like a big circle of people holding hands, it is possible for the entire population to be connected, even though the contact rate is very low.

Concurrency can have a large impact on network connectivity, even in populations with low rates of partnership change. This is shown in Fig. 7-4.

Here, everyone in the population is constrained to have no more than three concurrent partners, and the majority have only one or two (we ignore persons with no partners for clarity here, since they do not matter for this example). As the mean of the concurrent partnership distribution rises from 1.68 to 1.84, a difference of less than 0.2 of a partner, the connectivity in the network rises dramatically; the fraction of the population in the largest connected component rises from 2% to over 60%. In addition, we observe the growth of a multiply connected component (the “bicomponent,” shown in red), where people are connected by at least two independent paths. Multiply connected components are an important feature of the network because they signal a more robust transmission system. It is harder to disrupt the chain of infection when multiple paths exist.

Concurrency has a number of variations. One is defined by its duration, the length of time that two partnerships overlap. Short overlaps provide less opportunity for transmission and less stable connectivity of the network, so are likely to have less impact on transmission. Another variation is defined by the sequencing of the overlapping partnerships: one partnership interval can be embedded in the other, or the overlap can be transitional, as one partnership ends and another begins. The transmission implications of these sequencing variations are not known but they do represent very different behavioral patterns, so their meaning and importance, culturally and individually, is likely to be quite different.¹⁰⁰

Formal mathematical analysis has shown that concurrency raises the fundamental measure of epidemic potential, R_0 .¹⁰¹ Other simulation studies show that the impact of concurrency is further amplified by “degree-based” mixing patterns, that is, when concurrency is itself a basis for mixing. Assortative mixing by degree might occur in a bathhouse setting, where those with multiple concurrent partners have sex with other multiply partnered persons, while outside the bathhouse monogamy tends to be mutual. This leads to more rapid short term spread, but lower prevalence in the long run, as the monogamous persons are protected by the segregation in mixing. Disassortative mixing by degree would be typical in heterosexual networks with the gender double standard, where multiply partnered men are paired with monogamously partnered women. This has a slower initial takeoff relative to assortative mixing, but leads to higher prevalence in the long term.⁶³

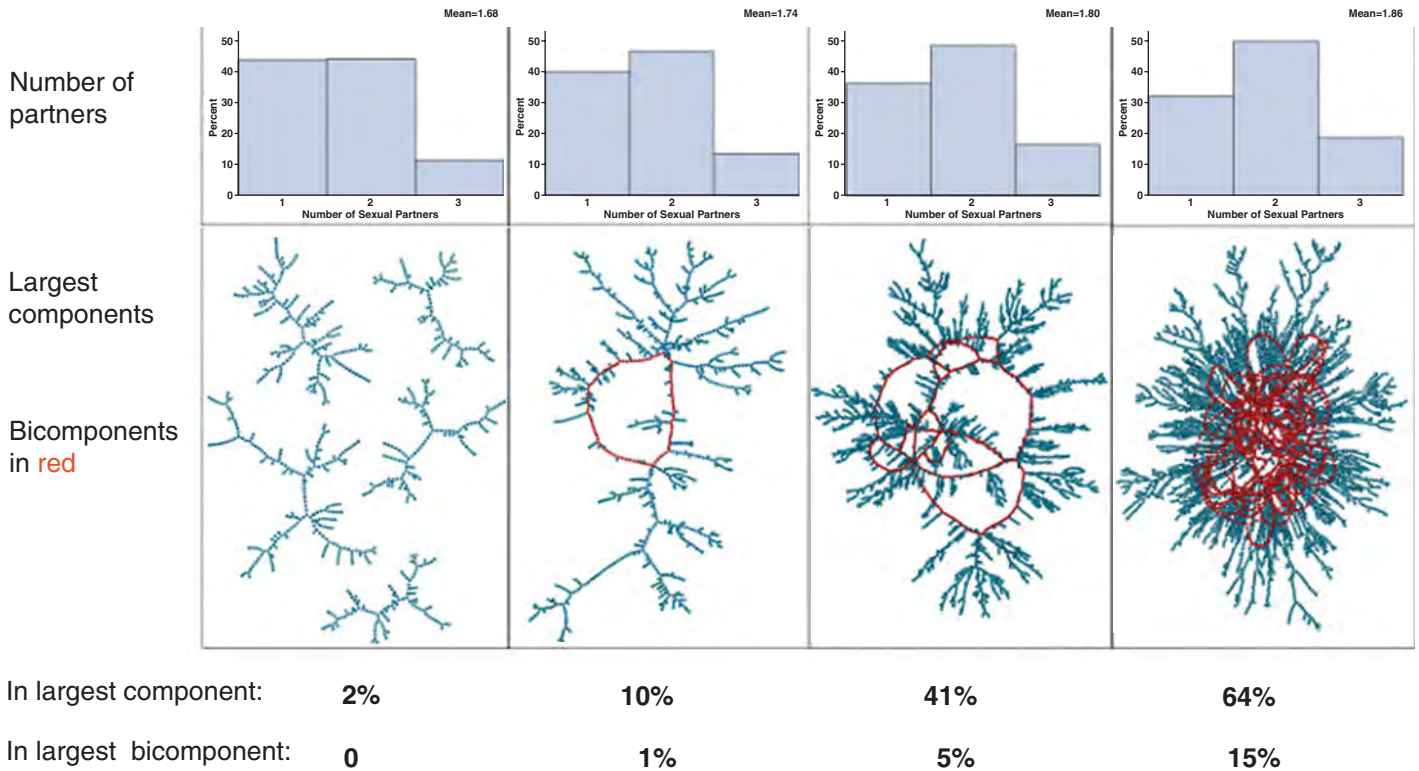


FIGURE 7-4. Impact of concurrency on network connectivity and robustness. The panels in the figure step through small changes in the level of concurrency (shown in the top panels) and its impact on the largest component and bicomponent in the network (in the bottom panels).

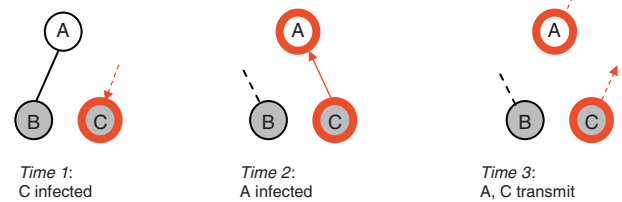
EMPIRICAL FINDINGS

Since these simulation studies in the early 1990s, a substantial number of studies have examined concurrency, and in general the findings have confirmed its importance for STI transmission. Empirical verification, however, turns out to be complicated. Concurrency has an impact at both the population level, by changing the network connectivity, and at the individual level, by changing the risk of transmission.

At the individual level the predicted effect of concurrency is to increase the chance of *transmitting* infection, since infection can now be passed to either partner, rather than just the later partner in the sequence, not the chance of *acquiring* infection.¹⁰² From an acquisition standpoint, two partners represent the same risk to the index case whether they are serial or concurrent. This can be seen in Fig. 7-5.

The difficulty is that epidemiological studies are typically designed to measure the risk of acquisition: data are collected on a sample of respondents, and analysis involves predicting the infection status of a respondent as a function of their individual risk factors. To demonstrate the impact of concurrency at the individual level, information on respondents *and* their partners would need to be collected, either by enrolling partners or by asking respondents to report on their partners' behavior. The former is difficult to execute, and the latter is vulnerable to reporting error. Despite this, studies have been done, and the findings generally confirm

Serial Monogamy



Concurrency

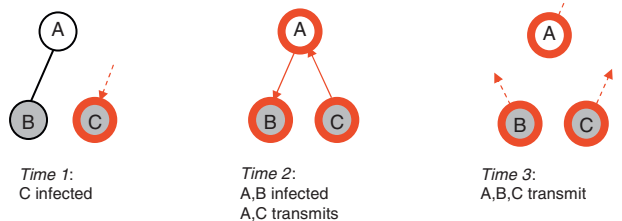


FIGURE 7-5. Concurrency effects at the individual level. The figure tracks an infection originally passed to partner C, under concurrency and serial monogamy. If A is the survey respondent, the effects of concurrency will not be observed in terms of A's infection status, which is the same in both scenarios, but in terms of A's transmission to B in time 2.

the importance of concurrency. The best evidence comes from careful contact tracing studies, which find that the adjusted odds of transmission are over three times higher for index cases with concurrent partnerships for both chlamydia¹⁰³ and syphilis.¹⁰⁴ Suggestive evidence comes

from a case-control study of pregnant women in Peru which enrolled the primary partners of the index cases. The HIV infection risk for the women was found to depend primarily on the number of partners their male partners reported.¹⁰⁵ Some studies have also found that respondents who report that their partner has other partners are more likely to be HIV+.^{106,107} Despite the fact that concurrency is not a risk for STI acquisition, several studies of clinic populations do find concurrency significantly associated with infection.^{108–110} This suggests that concurrency may be a marker for other forms of risk, such as being in a highly connected core of a network (for example, by assortatively choosing partners who also have concurrent partners).

At the population level, establishing the impact of concurrency requires estimates of the prevalence of concurrency and STI prevalence in many different populations. Note that this is not a traditional ecological correlation, since the effect is not hypothesized to operate at the individual level, it is a true population-level effect. But it is subject to the possibility of confounding, and it is complicated by variations in survey instruments and sampling schemes. A number of observational surveys have found higher rates of concurrency among populations with disproportionately high levels of STI and HIV in the United States.^{111–114} And in Uganda, survey data suggest the distribution of the number of partners is not that different from the distribution in the United States, but the rates of concurrency are much higher.¹¹⁵

The only exception to the findings linking concurrency to greater spread of STI is a comparative study of HIV based on five African cities.¹¹⁶ They find no evidence that concurrency influences transmission at the population level. While this is an exemplary survey, since the questionnaires and sampling strategy are largely consistent, the finding is weakened by the small size of the sample ($n = 5$ cities, and city is the relevant unit of analysis here) and timing discrepancies (the concurrency measure is based on reported behavior in the last year while HIV may have been acquired earlier). The city-specific prevalences of acute bacterial STIs do correlate well with the observed levels of concurrency in this study. This study also reported that there was no impact of concurrency at the individual level, but the analytic approach mistakenly sought to correlate concurrency of the index case with the HIV status of the index case, rather than the HIV status of their partners.

OTHER NETWORK PATTERNS

■ DETAILED NETWORK CONFIGURATIONS

The more fine-grained details of partnership network structure are not captured by selective mixing matrices. These additional details include cycles of transmission caused by closed network loops, the distribution of “component sizes”

(components are sets of connected individuals), the distribution of “path lengths” between persons (path lengths are the shortest number of steps between two individuals in a connected component), the centrality of individuals (centrality has several measures, “betweenness” centrality is the number of times an individual is on the shortest path between two other nodes), and the centralization of the overall network (the centralization of a network is the variance centrality of its members). (For an excellent review of network concepts and terminology, cf. Ref. 15.)

The data needed to map out these configurations are more difficult to collect, as they require either contact tracing or a census of the network. However, a number of studies have implemented this approach and the findings have been suggestive. In a comparison of two networks of high-risk persons, in Colorado Springs, CO, and Bushwick, NY, the prevalence differential was associated with the network positions of HIV+ subjects. The HIV+ subjects were found to be located in relatively smaller components of the network in Colorado, linked directly or indirectly to five or six other individuals.¹¹⁷ In New York City, HIV+ subjects were found to have much more central locations, linked to hundreds of others in a large connected component.¹¹⁸ Effective interventions in these two different network contexts would probably look quite different. In Colorado Springs, it would be sufficient to target the small, infected components intensively, while monitoring the incidence in the remainder of the network and responding to outbreaks as needed. In New York, the intervention challenge is much greater and would perhaps best be focused on “segmenting” the large, connected component and minimizing the links to newer (hopefully uninfected) users.

■ “SCALE-FREE” NETWORKS

One of the most well-known features of the partnership distribution is its long upper tail. It is the stuff of legend in U.S. popular culture—recall Wilt Chamberlain’s estimate of his 25,000–32,000 lifetime sexual partners—and a topic of serious study in STI epidemiology. An empirical example is shown in Fig. 7-6 based on reports of the number of lifetime sexual partners from a representative national survey of U.S. adults.

A hypothesis put forward in some recent studies with roots in the physics literature is that the long upper tail of the partnership distributions can be described by a “power law.”^{119,120} Power law distributions have an appealing simple form: the shape is determined by one parameter, which defines the rate at which the upper tail decreases. In mathematical terms, the relation is represented as:

$$p(R = x) \propto x^{-\alpha}$$

Or, the probability that a person’s number of partners (R) is equal to x is exponentially falling as x increases, at a rate of α .

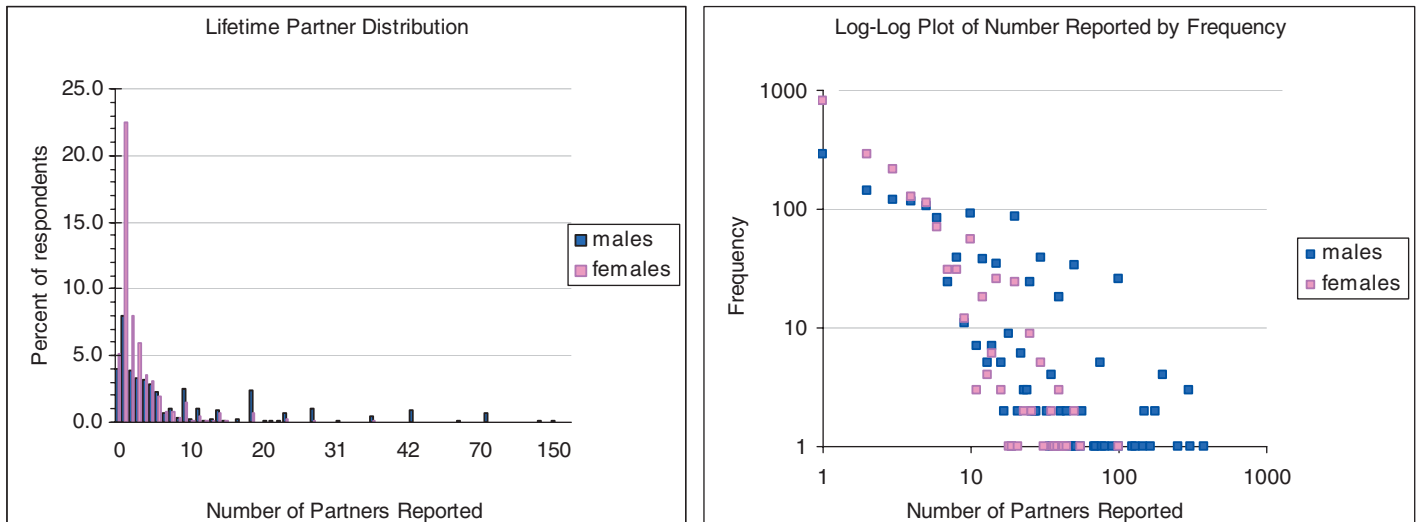


FIGURE 7-6. Distribution of lifetime sexual partners reported in the 1988 General Social Survey. The first plot shows the percent of male and female respondents reporting the number of partners shown on the x axis. The second plot shows the relationship between the number of partners reported and frequency of respondents reporting that number on a log-log scale.

A distribution with this property will reveal a linear relationship between the number reported and frequency of reports when plotted on a logarithmic scale. We show this logarithmic plot for our U.S. data in the second panel of Fig. 7-6.

The power law distribution has arisen independently in many scientific fields and is also commonly known as a “Zipf” or “Pareto” distribution.¹²¹ It has been used to represent the distribution of many different phenomena, from income and the frequency of word usage to earthquake magnitudes. In the context of sexual behavior, the power law model defines a distribution where a small number of persons have a very large number of partners. These “superspreaders” serve as hubs in the transmission network.

The epidemiologically interesting behavior of the model occurs when the value of the exponent α is below 3. In this case, the (theoretical) variance of the distribution is infinite, and the R_0 for an infection in such a population would also be infinite. Distributions with this property are sometimes called “scale free.” In a scale-free network, the hubs connect such a large fraction of the population that they alone determine the dynamics of epidemic spread. General population interventions that seek to reduce transmissibility will have little impact: there is no transmission threshold, and no critical vaccination fraction or “herd immunity,” so the only effective intervention is to remove the hubs.

The most commonly proposed behavioral mechanism that would lead to a power law distribution of contacts at the population level is the “preferential attachment” process.¹²² This process implies that people choose sexual partners with a probability proportional to the number of partners that person already has. In some limited contexts, this may be plausible but as a general model of sexual partnership formation, this seems questionable.

Empirically, the support for scale-free networks is not strong. Early studies that claimed to find such evidence were based on simple regression line fits to a log-log plot of the partnership density function, often to the top tail of the data only, making no effort to assess the goodness of fit, or to test alternative models. Where more rigorous statistical methods have been used, the results suggest sexual partnership distributions are not scale free.¹²³

While the theoretical implications of this model are striking, its relevance for STI is probably limited to specific settings like commercial sex and bathhouses. The simplicity that makes this model appealing also limits its realism. Partner selection based on the various attributes noted above, race, age, geography, etc., will segment the network and constrain the impact of any particular hub. Concurrency can create connectivity that is robust to the removal of hubs.

In any particular population, a range of different network structures may be present, arising from the culturally determined mix of behavioral rules that guide partner selection. The epidemic potential of a sexual network determined by the cumulative structural impact of many rules can vary dramatically. There is no one-model-fits-all rule for sexual networks. There are, instead, basic structural regularities that must be assessed empirically.

FUTURE DIRECTIONS

A lot has been learned about the impact of sexual networks on STI transmission, but there have also been some systematic obstacles to progress, especially for empirical research. The major obstacle to the empirical study of networks, in epidemiology as in other fields, has been methodological. The traditional methods of social network analysis required a network census: data on every node and every link in the

population of interest. That approach is clearly infeasible for epidemiological research on sexual networks. What is needed is a statistical framework for sampling networks and for estimating the epidemiologically relevant properties of the network from the sampled data.

Rapid progress is being made now in the development of methodology for network analysis. Methods have been developed to handle networks sampled with egocentric^{119,124} and link-tracing designs.^{125–128} Statistical theory is being developed for estimation and inference, which is complicated for networks given the dependent data and nonlinear threshold effects.^{129,130} The class of models being developed can represent an arbitrarily complex network structure but can also test the goodness of fit of simple parsimonious models to data. A computer package has been released that allows researchers to use these methods for network analysis.¹³¹ It turns out that the algorithm used for network estimation in this package can also be used for simulation. So, for the first time, researchers can simulate networks using models and parameters that have been derived from data and statistically evaluated for goodness of fit.

The promise of these new methods is the potential for parsimony and rapid assessment: explaining the population network structure with a small number of partnership formation rules. If this can be done, it will radically simplify data collection needs and give network analysis a central place in the tools of STI research and intervention.

The research of the previous decade has suggested that mixing and concurrency have a large impact on network structure and transmission dynamics. Now we can ask whether these are the only features that matter. On the one hand, there is a good theoretical basis for this hypothesis. It seems reasonable to presume that people make decisions about which partners to choose based on preferences and norms that operate at the local level. That is, we choose partners because they are the right sex, age, race, and status, and we often care if we (or they) have other partners. It is unlikely that people form partnerships thinking, “if I choose this partner I can increase my eigenvector centrality” or “I’d like to reduce my path length to a randomly chosen person on the west coast.” This may seem obvious at one level, but the implications are quite striking. If simple local rules govern partner selection, then these also determine the aggregate structure in the network; what looks like an unfathomably complicated system is, in fact, produced by a few key local organizing principles. By extension, these simple local rules are also, therefore, the key behavioral determinants of disease transmission dynamics on the network.

There are also important practical implications if this is true. Both mixing and concurrency are network properties that can be measured with local (egocentric) network sampling strategies. If it turns out that these two local rules explain most of the variation in network structure that is relevant to

disease spread, then we have a simple inexpensive way to rapidly assess network vulnerability for public health surveillance and some simple behavioral rules that people can be taught to recognize and change.

IMPLICATIONS FOR PREVENTION

A number of implications follow from the body of simulation studies and empirical findings on sexual networks and STI transmission that have accumulated since the early 1990s.

First, despite the popular fascination with “superspreaders,” it is not necessary to have highly active persons to create the potential for epidemic spread in a network. A modest amount of concurrency can provide the connectivity needed for sustained transmission. This is particularly true for generalized epidemics, which may have started in a traditional core group, but are being sustained in a less active population. In this context there is probably little to be gained by urging people to have fewer partners. Intervention instead should be focused on breaking up the network formed by concurrency. A good intervention message would be: “one partner at a time.” Moreover, a good intervention research program would focus on the socioeconomic and cultural roots of concurrent partnerships.

Second, small differences in the pattern of contacts can have huge effects on the transmission network structure. Near the threshold, an average increase of less than 0.2 concurrent partners can be enough to fundamentally change the connectivity of a network and create a robust connected network core. This is important to remember when evaluating the significance of empirical differences in sample survey data. Most samples are not large enough to detect a difference this small as statistically significant, but the difference may still be substantively important.

Finally, persistent prevalence disparities across populations for a wide range of STIs are a signal that the underlying transmission network is probably the cause. A combination of processes may be at work: assortative mixing (which segregates populations), and small variations in concurrent partnerships (which differentially raise the spread in some groups). The disparities that can be sustained in such networks can be surprisingly large, even when the behaviors do not appear to differ much by group. While this may look like a puzzle, it may be an indication that prevention is close at hand. Just as small changes may be enough to push transmission above the epidemic threshold in some groups, small changes may be all that are needed to bring transmission down below that threshold. For this reason, it is important that we have an accurate empirical picture of the key aspects of the transmission network. We need to know who needs to change behavior, what behaviors need to change, and the relevant cultural contexts, so that our intervention efforts can be properly targeted and maximally effective.

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8

Sexual Partnership Effects on STIs/HIV Transmission

Pamina M. Gorbach and King K. Holmes

INTRODUCTION

Individuals throughout the world establish and maintain different types of sexual partnerships over their life course. While sexually transmitted infections (STIs) including HIV infection occur for individuals in all types of partnerships, risk of acquisition is determined more by the behaviors practiced with each sex act than by the type of partnership being maintained. The prevalence of STIs as well as relevant risk behaviors such as having a concurrent partner and sex without condoms vary with physical, social, and emotional factors within each partnership. The risk of STI/HIV transmission appears to vary across types of concurrent partnerships according to the differing dynamics within them.¹ Previous research on partnership dynamics has improved our understanding of the multidimensional aspects of sexual partnering, and of how these aspects of sexual partnering interact and increase risks for STIs. Therefore, recognizing within-person variation of sexual behaviors across types of partnerships can enhance the ability of STI practitioners to develop successful counseling approaches and enable public health practitioners to anticipate risk and plan programs to manage the level of disease within a population. Greater understanding of the distribution of different types of risk within populations will also enable program planners to assess the scope and progress of STI epidemics.

In this chapter, we discuss how our understanding of sexual partnerships among heterosexuals and among men who have sex with men (MSM) enhances our understanding of how STIs continue to be propagated through populations. The partnerships of women who have sex with women are not discussed in this chapter not because STIs are not transmitted within such partnerships, but because STI transmission and prevalences in such partnerships are at lower levels than for the partnerships of heterosexuals and MSM. Culture and norms about gender and sexuality play a significant role in determining partnership types and gender-specific sexual behaviors; therefore, this chapter is also limited to discussing

partnerships and types within Western countries including the United States and those in Europe. One framework cannot serve all cultures equally; nevertheless, a conceptual framework is developed that reflects how individual and partner characteristics influence partnership dynamics that in turn influence risk behaviors, such as concurrency and not using condoms, and influence associated risks for STIs and HIV. It is hoped that such a framework that includes negotiated safety agreements and discordance of partnership characteristics will be of use to those studying partnerships in other cultural contexts.

DESCRIPTIONS OF PARTNERSHIP TYPES

The types of partnership classifications most often studied in STI/HIV research are “main partner” or “regular partner” versus “casual partner,” with few attempts to define what is meant by these types. Even for the clearest designations of a type of partner, the respondents often have some latitude in defining partner type. For example, when asked to describe a “new partner,” the length of time that a partner is classified as “new” is not standardized and is often left to be defined by respondents. The benchmark study of sexuality in the United States, the National Health and Social Life Survey (NHSL), described only four types of sexual partnerships: marriage, cohabitation, the intention of one or both partners to pursue the relationship further, and the explicit view by the partners of the relationship as short term.² An expanded list of partnership types allows for a greater variation of types with potential for a more nuanced understanding of differences in behaviors across types. For example, [Table 8-1](#) presents an expanded list of seven different types of partners, for both heterosexuals and MSM, with definitions provided for each. The inclusion of the list in a study of MSM recently infected with HIV revealed a large distribution in the types of partnerships reported³ and revealed changes in numbers of such partners and in the practice of risk behaviors within these partnerships following the diagnosis of HIV.⁴

Table 8-1. Definitions of Types of Sex Partners for Men Who Have Sex with Men and Heterosexuals⁴

Main: Someone who is your primary sexual partner; this might be your only sex partner or the partner you consider to be most important if you have more than one partner
Regular: Someone who you have sex with on a regular basis but who is not your main partner or primary partner
Friend: Someone you have had sexual contact with more than once, but not on a regular basis, and you normally socialize with
Acquaintance: Someone you have had sexual contact with more than once, but not on a regular basis, and who you don't socialize with
Onetime: Someone you had sexual contact with only one time but could find again if necessary
Unknown: Someone that you had never met before you had had sexual contact and never plan to see again
Trade: Someone who you gave sex to for money or other goods or someone who gave you sex for money or other goods

Data from Gorbach PM, Drumright LN, Daar ES, Little SJ. Transmission behaviors of recently HIV infected men who have sex with men. *J Acquir Immune Defic Syndr*, 2006; 42(1): 80–85.

Most research on partnership types has classified types according to a single aspect of relationships such as duration or exclusivity (or concurrency) and have looked for variations in behaviors by few domains such as emotional closeness (intimacy), communication, and power. Few if any studies have examined these dynamics simultaneously. Scales for measuring dynamics within established couples such as the Dyadic Adjustment Scale^{5,6} are not designed for nonmain partnerships. Below we review the literature on three such domains and existing measures for them.

■ EMOTIONAL CLOSENESS OR INTIMACY

Within some partnerships, increased intimacy can make condom use more likely because it suggests greater comfort in negotiating behaviors. Condom use and partnership factors (mutual partner support and emotional closeness) have been associated with the likelihood that women would attempt to use condoms with main partners; the belief that condoms build trust was also associated with long-term consistent condom use.⁷ However, intimacy may also function as a barrier to condom use. For those in ongoing partnerships, nonuse of condoms has been associated with greater perceived relational intimacy⁸ and greater commitment has been associated with lower condom use.⁹ Among female adolescents, a higher score on a perceived relationship quality scale (a measure of intimacy) of primary partnerships was associated with not using condoms.¹⁰ Clearly, intimacy operates along with other partnership dynamics to influence condom use; however, the relationship between the level of intimacy in a partnership and STI or HIV acquisition is complex.

Partnership discordance by differing intentions to terminate the partnership, another emotional dimension of partnerships, has been associated with STI in heterosexual young adult partners.¹¹ This might happen when one partner is contemplating termination and the other partner is striving to hold on to the partnership, condoms might not be used to

counteract diminishing emotional concordance by enhancing the intimacy during sexual activity. Measurement of emotional discordance in partnerships requires comparison of intentions of each partner to continue the partnership and can benefit from longitudinal assessments of the same partnership.

Measures used to assess emotional closeness or intimacy include the Passionate Love Scale,¹² Miller's Social Intimacy Scale,¹³ and the Dyadic Sexual Communication Scale.¹⁴

■ COMMUNICATION

Research on communication between partners and risk of STI has focused mostly on communication about condom use but has rarely considered how communication affects other measures of sexual risk. One scale often used to measure communication in partnerships, the Health Protective Communication Scale,¹⁵ has been predictive of condom use and measures partners' discussions of past sexual history in relation to condom use. Higher communication with new partners has been associated with higher condom use among Hispanic women.¹⁶ Communication has been positively associated with consistent condom use among incarcerated adolescents,¹⁷ although no significant difference in levels of reported condom use was found between respondents who reported talking about past sexual histories and those who talked specifically about HIV/AIDS protection.¹⁸ It has also been suggested that belief in one's ability to communicate (communication self-efficacy) may increase the likelihood of condom use.¹⁹ Finally, poor communication in a partnership (both general sexual communication and health-protective communication) has been associated with higher numbers of partners among adolescents.¹⁸ In the studies cited above, communication within partnerships was studied at one point in time and did not consider how communication patterns may evolve as intimacy grows in a partnership or, conversely, as it dissolves. Communication skills, measured

more generally as ability to discuss feelings and concerns within the partnership, need to be considered more fully in relation to other sexual risk behaviors.

■ POWER DYNAMICS

Power differentials in heterosexual partnerships have been related in part to gender.²⁰ Physical abuse and economic dependence are related to power dynamics in partnerships and may also decrease an individual's ability to adopt risk avoidance behaviors that protect against STI/HIV. Gender differences in power are thought to increase women's risk for HIV, especially among minorities and women who are economically and socially marginalized. Among Latina women with a primary sexual partner, low relationship power accounted for about half the risk of consistent condom use in one study,²¹ and with increased HIV risk behaviors (i.e., having multiple partners, not using condoms with new partners, having partners who may use drugs) in another study.²²

Because insistence on condom use by economically vulnerable minority women may jeopardize their continued financial support by male partners, their immediate financial needs may outweigh the perceived risk of HIV infection.²³ The threat of domestic violence may also deter women from participating in STI/HIV control efforts such as partner notification.²⁴ Among young African American women, those in abusive relationships were less likely than others to use condoms, were more fearful of asking their partners to use condoms, worried more about acquiring HIV, felt more isolated, and were more likely to experience verbal abuse, emotional abuse, or threats of physical abuse when they discussed condoms than were the women not in abusive partnerships.²⁵ Of note, few studies have considered how males' economic dependence on female partners or on other males in homosexual relationships may affect condom use, as the assumption thus far appears to have been that it is females, not males, who are vulnerable to relationship power differentials.

One psychometric instrument used to assess power in partnerships is the Sexual Relationship Power Scale,²¹ developed for minority women based on the Theory of Gender and Power²⁰ and the Social Exchange Theory.²⁶ This instrument is used for assessing associations between relationship power and consistent condom use. Locus of control has also been used to assess power in relationships.²²

BEHAVIORS MOST ASSOCIATED WITH RISK OF STI ACQUISITION

■ CONDOM USE

In general, among U.S. adults, more men than women report using a condom at last intercourse (40% vs. 22%

respectively), and condom use is more likely among those who are younger and never married.²⁷ Condoms are about half as likely to be used with an ongoing or steady partner than with other partners,^{28–30} for example, among sexually active U.S. adults, 17.5% of those with an ongoing partner versus 44% with a other sexual partner reported condom use at last sex.²⁹ Condom negotiation and use are reported more often by individuals with new partners than with ongoing partners; for college students, especially males, perception of positive individual and relational outcomes, such as believing the partner was more deserving of respect, less likely to have an STI, and more caring about them, were reported more often for new partners who insisted on condom use than for those who did not.⁸ For those at high risk for STI such as patients in a STD clinic, this pattern holds. For example, in a prospective study of women in STD clinics, condom use was more common with new partners and casual partners than with regular partners; even among women with multiple partners, condoms were still reportedly used more often with new and casual partners than with regular partners.³¹

Within ongoing partnerships, condom use may be less frequent. A population-based survey of U.S. adults found after examining the type of relationship risk (i.e., IDU, MSM, or HIV-infected partner), only 22% of persons at increased risk for HIV used condoms during last intercourse within an ongoing relationship, suggesting a substantial risk of unprotected exposure to HIV.³² Why condom use is less likely in ongoing partnerships appears influenced by perceptions of the partners' attitudes. Among STD clinic patients, intentions for condom use with casual partners were influenced more by social norms for women and by personal attributes for men, but in steady partnerships, both men and women perceived their steady partners as less likely than casual partners to favor condoms. They seemed more concerned about steady partner's norms concerning condoms than about casual partner's norms.³³ An important consideration is that partners may not agree with each other on the type of partnership they are in. Among 162 partnership pairs at an STD clinic, there was poor agreement between partners on whether their partnership was regular or casual, despite fair agreement on whether the partnership was new.³⁴

Condom use patterns within partnerships cannot be assumed to be static because partnerships themselves change over time. It appears that condom use is more likely to lapse than to be adopted as a partnership continues.^{35–37} Among the few female STD clinic patients followed prospectively, whose relationship with a new partner evolved to the point where that partner was considered a regular partner, consistency of condom use decreased significantly.³¹ Among adolescents, condoms also have been used more often in new than in established partnerships (66% vs. 54%), but among new partnerships, condom use declined rapidly over time, so that within 3 weeks after the establishment of the new

partnership levels of condom use were similar to the levels measured among already established partnerships.³⁵ Adolescent females have also been found to have increased coital frequency along with less condom use as the duration of their sexual relationships increases, resulting in greater potential risk of acquisition if they are exposed to STIs within the relationship.³⁶ Therefore, risk of STI acquisition may persist even as partnership duration is prolonged.

■ CONCURRENCY AND BRIDGING

The concurrent partnership or partner overlap is defined as a sexual partnership in which one or more of the partnership members have other sexual partners while continuing sexual activity with the original partner.³⁸ Concurrency has been shown to play a fundamental role in potentiating the spread of STIs such as chlamydial infections,³⁹ gonorrhea,⁴⁰ and syphilis,³⁸ and HIV infection.^{28,41,42} Mathematical modeling has indicated that concurrent partnerships are as important as multiple partners and cofactor infections in the spread of HIV,²⁸ not only influencing the rapidity of the spread of HIV in the initial epidemic phase but also the total number of individuals who become infected.⁴² Prevalences of reported concurrent partnerships have ranged from 32% to 54% among adolescents^{43,44} and 12% to 40% among adults^{45–47} in different regions of the United States. In the National Survey of Family Growth, approximately 25% of U.S. women 15–44 years of age who reported a lifetime number of ≥ 2 partners and 12% of all women, reported concurrent sex partners.⁴⁶ Prevalence of concurrency reported by African American women has been higher than that of white and Hispanic women in national surveys.⁴⁸ Concurrency has been reported more often by males than by females within the same heterosexual study population.⁴⁹

An individual's practice of having concurrent partners (individual's concurrency) has been associated with higher prevalence of STIs⁵⁰ including *Chlamydia trachomatis* in the United States,⁵¹ *Neisseria gonorrhoeae* in Trinidad,⁵² and bacterial STIs in adolescents⁴⁴ even after adjusting for the individual's number of partners. Essentially having more than one sex partner at one time has appeared more risky than having had the same number of sex partners serially over a somewhat longer period, and has been associated with greater risk of having a bacterial STI at that time. Not surprisingly, among individuals with comparable numbers of recent sex partners, those who have partners with concurrent sexual partners (partner's concurrency) are also at increased risk of acquiring an STI^{38,44,49,52} and those whose partners have concurrent partners are also more likely to be transmitters of syphilis (defined as having a partner at an earlier stage of syphilis than oneself) than those who do not report partner's concurrency.³⁸

Thus, concurrency has been associated not only with rate of spread and prevalence of STI at the population level but

also at the individual and partnership level. Moreover, concurrency and partnership discordance (a difference between members of a partnership with respect to characteristics such as age, ethnicity, geographic residence, or rate of sex partner acquisition) have been found to coexist.¹¹ Discordance between sexual partners (disassortative mixing) may represent a proxy measure for sexual bridging between two sexual networks, since sexual networks tend to be composed of individuals concordant for geographic residence, age, ethnicity, and sexual activity level.^{2,53} This combination of concurrency and bridging may enhance the spread of STI both within and across sexual networks. Bridging alone can bring STI from higher STI prevalence populations to lower STI prevalence populations; and concurrency alone links individuals into clusters of concurrent sexual connections at one point in time,⁵⁴ increasing the probability of STI spread to many members of the network within a short period. These two scenarios increase the spread of STI in different ways. Thus if two populations (or networks) were bridged by individuals having concurrent partners, the increase in STI would be at least additive, if not multiplicative in nature. Of course STI transmission within or across networks will only be observed if concurrency or bridging occurs within or across networks in which STI already exists or is introduced. Measuring concurrency and STI prevalences among both members of a partnership, or ideally, among members of sexual networks, would allow for a more complete understanding of the interaction between concurrency and bridging, while quantifying the contribution of both to an individual's risk of STI.⁵⁵

As noted above, sexual bridging between higher-risk and lower-risk sexual networks contributes to the movement of STI/HIV from those with high-risk behaviors to those with lower risks. Among STD patients in the United States who practiced sexual-bridging behaviors, "active bridgers" were defined as those infected with an STI, and "potential bridgers" were defined as those who were uninfected.⁵⁶ Concurrent partnerships may involve either assortative mixing (e.g., partners have similar characteristic or behaviors) or disassortative mixing (e.g., sex partners have dissimilar characteristics or behaviors). When a person has concurrent partnerships involving unprotected intercourse with individuals from different sexual networks, that person becomes a particularly efficient bridge for potentially carrying STIs between groups. There are few data on the proportion of concurrent partnerships that involve bridging of networks or on the proportions of potential bridgers who have concurrent partnerships (as opposed to serial partnerships) with members of different sexual networks.⁵¹ Partnerships that involve discordance as described above, as well as concurrent partners, have the potential to rapidly accelerate the spread of STIs/HIV in a population. Such discordance per se may be associated with STI acquisition because it can be a marker for bridging between high and low STI prevalence groups.^{2,53,56–59} Partner

discordance for number of recent partners, for example, may represent a connection between high and low STI prevalence populations. When such discordance in partnerships was considered by using data from both individuals in one partnership (i.e., using the partnership as a unit of analysis), partnerships discordant by number of lifetime partners were more likely to have STI than partnerships that were concordant for number of partners, regardless of the actual numbers of partners. Having a sex partner from a network with a level of partner change higher than the level of one's own network presents a greater risk for STI than having a partner from a network with less partner change or similar to one's own network, again emphasizing how an individual's STI risk may not only be a result of an individual's behavior and network but of the partner's behavior and network as well.^{11,55}

To the extent ethnicity is associated with STI, partnership discordance by ethnic group may be another proxy for bridging between higher and lower STI prevalence populations, and such discordance has been associated with current STI.^{53,57–59} Additionally, ethnic discordance has been shown to be associated with decreased condom use among adolescent partnerships,⁵⁹ which may contribute to increased risk of STI in adolescence. Yet, ethnic concordance between partners does not necessarily mean these partners reside in the same sexual networks. For example, among African Americans the smaller population size and high level of assortative mixing by ethnicity among African American women result in African American women having partners who are concordant with them for ethnicity, but these partners are often discordant for sexual activity.^{53,58}

A taxonomy of concurrent partnerships among heterosexuals¹ and a longitudinal study assessing the interrelationships between partnership formation and dissolution, condom use, concurrency, and STI incidence within partnerships^{11,55} indicate how the efficiency of HIV/STI transmission can vary according to the differing partnership dynamics and patterns of concurrency.

■ PARTNERSHIP TYPES INVOLVING MSM

Less research has been done on the partnerships of MSM than on those of heterosexuals; research that has been done has tended to focus on the numbers of sexual partners among MSM who acquire or who are at risk for STIs including HIV rather than on partnership types. While many MSM have short-term partnerships, a substantial proportion of which are even anonymous, these types of partnerships have often been lumped into one category termed “casual.” The sexual partnerships of MSM are often identified by the venues where men meet partners or have sex, such as circuit parties,⁶⁰ or public sex and commercial sex environments,⁶¹ and not by the more substantive or structural features of the partnerships. Partnership type has also come to be identified for

MSM by HIV serostatus of the partner, i.e., HIV serostatus concordant positive or negative, or serostatus discordant (one positive, one negative), or serostatus unknown, again ignoring the dynamics within these partnerships. Another characteristic of MSM as individuals and as partners that strongly influences risk of STI/HIV acquisition or transmission is the nature of the sexual behavior, i.e., anorectal insertive, anorectal receptive, or both. Prevalences of such behaviors appear to have differed between countries and regions and have changed over time.

Many MSM establish main or primary partnerships, with 68% of U.S. MSM reporting having a main partner in the past year⁶²; and many such partnerships do have long duration. However, a notable characteristic of MSM primary partnerships is the preponderance of nonmonogamy within these partnerships⁶³ reportedly involving around half of those with main partners in one survey.⁶⁴ While nonmonogamy often exists in the context of explicit agreements as to what can be practiced and the need to tell the main partner of the practice, this is not always the case. Moreover, MSM in partnerships they define as monogamous but in which one or more partners report recent nonmonogamy have expressed less satisfaction with their partnerships than those who are openly nonmonogamous or strictly monogamous.⁶⁵

MSM tend to have a variety of different partnership types and continue to accumulate new partners over their life course, and these partnerships are very often concurrent, even though they may have a long-term main or primary partner. Table 8-1 provides illustrative definitions of some of the variety of partner types that exist for MSM and for heterosexuals; these terms and definitions may be useful for sexual behavior research and surveys. It should be noted that while different types of concurrent partnerships have been described for heterosexuals,¹ this remains a topic yet to be tackled for concurrent partnerships of MSM. While sexual behaviors have been compared by partnership type, there is less research examining factors such as communication, power dynamics, and intimacy across partnership types for MSM than for heterosexuals.

HIV INFECTION AS A PARTNERSHIP ISSUE FOR MSM

Given the high prevalence of HIV among MSM in many large cities, averaging about 25% in the United States but ranging by city from 18 to 40%,⁶⁶ HIV infection per se has become a very salient issue for MSM partnerships. The likelihood of being in a partnership, albeit of short or long duration, with someone having HIV infection is much more likely for MSM than it is for heterosexuals. This makes discussion of HIV status a particularly important dynamic for MSM within their partnerships. Disclosure of HIV status remains a challenge for HIV-positive MSM; among those

reporting unprotected sex, almost half^{67,68} reported not disclosing their HIV status to prospective sex partners prior to having unprotected sex, and even fewer report disclosing within their casual partnerships.⁶⁹ Within more intimate partnerships there is a tension between facing fear of rejection from a partner and wanting to share the information with that partner, often resulting in a delay of the discussion.⁷⁰ Unprotected intercourse occurs frequently within serodiscordant regular partnerships regardless of whether HIV has been disclosed by the positive partner; as reported above, condoms are less likely to be used with main or regular partners than with other partners. This leads to a higher probability of HIV transmission within such regular partnerships than in nonregular serodiscordant partnerships.⁷¹ Nevertheless, MSM more often report practicing unprotected anal intercourse (UAI) in seroconcordant partnerships than in serodiscordant partnerships, particularly if the seroconcordant partner is also a steady partner.⁷² When total numbers of recent sex acts are considered, more than half of those reported by HIV-positive MSM occurred with seroconcordant partners and 82% of those with serodiscordant partners were protected.⁷³ Not knowing the status of a partner is associated more often with risky sex than when the partner is known to be serodiscordant. For sex with non-main partners, HIV-positive MSM more often report unprotected sex with partners of unknown serostatus than with HIV-negative partners.⁷⁴ There may also be the misguided expectation that the HIV-negative individual should inquire about the HIV status of his partner, and that if that negative individual does not ask, then an HIV-positive partner may either assume that the individual is also positive or does not care about the risk of acquisition.⁷⁰ While HIV-positive MSM clearly struggle with disclosure and many do practice unprotected sex with partners of unknown or serodiscordant status, there are many who either use condoms with such partners or avoid sex with them to reduce transmission risks.

Some evidence suggests that after a diagnosis of HIV infection, men seek partners who are also HIV infected (i.e., sorting themselves by serostatus to establish seroconcordant partnerships).⁷⁵ Some, but not all, HIV-infected individuals may also intentionally modify their sexual behavior to reduce the risk of transmission to others,⁷⁶ but other HIV-positive MSM may continue risky behavior following their HIV diagnoses.^{77–80} Comparisons of reported risk behaviors over time have not shown increased risk taking among HIV-positive MSM.^{81,82} However, the rising rates of STIs such as gonorrhea, syphilis, and chlamydial infection among MSM, including HIV-positive MSM, may be explained either by increasing risk taking in general or by increasing rates of unprotected sex in HIV-seroconcordant partners, which could offer some protection against acquisition or transmission of HIV but not of other STIs.

■ USE AND NONUSE OF PROTECTIVE BEHAVIORS

Condom use by MSM has long been promoted as the fundamental way to prevent STI/HIV transmission among MSM, yet is still far from a universal behavior even with partners who are not regular partners. For example, among MSM in 17 U.S. cities, about half reported UAI in the past year, 58% with a main male partner (defined in the study as someone with whom the participant had sex and to whom he felt most committed, e.g., a boyfriend, spouse, significant other, or life partner), and by 36% with a casual male partner (defined as someone with whom the participant had sex but who was not considered a main partner).⁶² The pattern is similar for young MSM, with even fewer always using condoms with steady partners than with nonsteady partners.⁸³ Findings are similar in Britain; in their National Survey of Sexual Attitudes and Lifestyles, 60% of MSM who reported anal intercourse in the past year reported UAI in the same period; condoms were used at last intercourse by about one-third, with either a regular or not regular partner.⁸⁴

Similar to heterosexuals, MSM may practice protected sexual activity (condom use) with new and short-term partners more frequently than with ongoing partners, making longer-term partnerships risky for HIV transmission between serodiscordant partners or nonmonogamous partners. Among HIV-positive MSM more report practicing UAI in stable or main partnerships than in shorter term or less intimate partnerships.^{85–87} Moreover, condom use is often discontinued early on (within the first 3 months) and without previous discussion in these partnerships.⁸⁸ Such behaviors have been responsible for a substantial proportion of HIV acquisition; an ongoing or primary partner was reported to be the source in 50% of cases of seroconversion in a cohort of young men in Amsterdam.⁸⁹ However, no independent confirmation of the source of infection was obtained and many seroconverters reported multiple partners. Seronegative MSM have been found to use condoms significantly less often if they are in a primary relationship with a single partner known or thought to be HIV-seronegative than with other partners⁹⁰ whereas seropositive MSM reported significantly less unprotected insertive anal intercourse (IAI) with seronegative partners than with seropositive partners.⁹¹

“Barebacking” or “raw sex” (slang terms for anal sex without condoms) has been defined as a phenomenon in which some MSM seek unprotected anal sex in spite of and sometimes because of the risk of acquiring HIV.⁹² Barebacking has been construed as anal intercourse without condoms with intention, to be contrasted with just the behavior of anal sex without a condom, and that those who bareback share a social identity.⁹³ Barebacking has been reported more often by HIV-positive MSM than by HIV-negative MSM, who often reported barebacking with seroconcordant partners.⁹⁴ Up to one-third of HIV-positive MSM in a survey in two

large cities identified themselves as “barebackers”; among those 42% reported only barebacking other HIV-positive men and were more likely to also have IAI with HIV-positive men than with HIV-negative men or men whose serostatus was unknown.⁹³ This suggests some reduction in transmission risk that may accompany the barebacking practiced by some HIV-positive MSM. When not considering the intention involved in unprotected sex, studies have reported that HIV-positive MSM continue risk behavior following their diagnoses,⁹⁵ and unprotected sex with casual partners has been especially common among MSM on highly active antiretroviral therapy (HAART) although also observed among men with high HIV-1 RNA levels and not receiving HAART.⁹⁶ Among MSM in HIV-discordant partnerships^{97,98} using condoms can signify lack of closeness and trust.

■ NEGOTIATED SAFETY

UAI does not always represent risk within a partnership if it occurs within a “negotiated safety” (NS) agreement in which both men are seronegative and comply with an arrangement in which they only have UAI with each other.⁹⁹ Such agreements are relatively common, reported by 50% of HIV-negative men in partnerships of ≥ 6 months duration in one study.¹⁰⁰ However, because compliance with such negotiated agreements is not consistent, e.g., up to 40% of those with NS agreements reporting recent violations of the agreement,¹⁰⁰ risk may not be static and may not remain low.¹⁰¹ In the San Francisco Men’s Health Study, HIV-positive men in a primary relationship were less likely to be monogamous than HIV-negative men.¹⁰² Management of this risk within the partnership requires both partners knowing and sharing their HIV status with each other; however, many MSM do not know their own or partners’ status—even those in primary relationships. In one large study in Switzerland, only 52% of steady partners knew each other’s status.¹⁰³ Another study found that although the men with primary partners reported higher frequencies of UAI than men without primary partners, only a quarter of those primary partnerships were reported monogamous.¹⁰⁴ Compliance with such negotiated safety agreements may be affected by the same partnership dynamics over time as those described above for heterosexuals.

■ SEXUAL POSITIONING

The practice in which HIV-positive men report opting to be receptive with HIV-negative or HIV-status unknown partners is known as “selective” or “strategic” positioning.¹⁰⁵ Some HIV-positive MSM report choosing lower-risk sexual positions to avoid disclosing their serostatus.⁷⁰ Overall, the evidence to support the intentional practice of sexual positioning by HIV-positive MSM as a method of reducing risk

of HIV transmission is mixed. While there is some evidence from Australia that MSM in regular serodiscordant partnerships practice sexual positioning to reduce transmission risk¹⁰⁶ the choice of positions did not seem to be consistent among HIV-positive men with serodiscordant or serostatus unknown partners when studied in two large U.S. cities. Moreover, the latter U.S. study did not find positioning practiced in a consistent manner across partner types, although HIV-positive MSM did report more risk behaviors such as IAI with other HIV-positive partners.⁷⁴ Thus, while some HIV-positive MSM report using this approach, this has not yet become a normative behavior.

Among HIV-negative MSM sexual positioning is also a strategy being employed to reduce risk of acquiring HIV. There is some evidence that HIV-negative MSM in the United States practice unprotected IAI slightly more often than receptive anal intercourse (55% vs. 48%).¹⁰⁷ Clearly both for HIV-negative and HIV-positive MSM, there is awareness of sexual positioning as a strategy to reduce transmission, but not for a large majority of MSM. This may be because of the influence of partnership type, and of other factors such as substance use during sexual activity, and also because this alone is likely a much less reliable strategy than consistent condom use. Finally, positioning is not widely promoted by public health authorities as an effective method for preventing HIV transmission among MSM.

■ A FRAMEWORK

Partnership dynamics have been assessed largely as predictors of condom use and less often as predictors of other risk behaviors, such as having other partners in an ongoing partnership. In Fig. 8-1 we offer a conceptual framework for individual and partner characteristics which influence partnership dynamics, which in turn influence risk behaviors

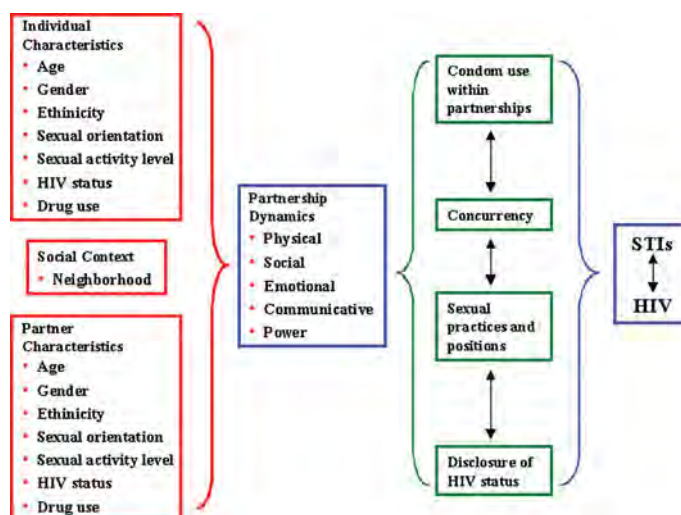


FIGURE 8-1. Expanded framework of how partnership dynamics affect STI/HIV transmission.

such as the practice of certain sexual behaviors and positions (such as anal sex itself or practice of either receptive or insertive anal sex, or both), concurrency and condom use, for all of which there may be explicit agreements in a negotiated safety agreement, and which are all ultimately associated with some risk of HIV and other STIs.

CONCLUSIONS

Measures of sexual risk within partnerships (i.e., amount of sexual contact and sexual practices including condom use) have not been incorporated into sexual network models. Sexual networks are instead usually described by their density, i.e., by the number of partnerships within them and the number of those that are concurrent. Yet just as the differing natural histories of various STIs have received little attention as yet in transmission models, the potential contribution of sexual networks to STI/HIV transmission can also benefit from a further advanced approach; transmission may vary not only by network size but also by other sexual behaviors occurring within the network. Therefore, network studies could be advanced by research that includes in-depth descriptions of partnership types and risk behaviors within networks, while measuring and characterizing numbers of sexual contacts. One example of this is research on “bridge” persons who have sex both with members of high-risk and of low-risk groups, or with individuals from groups that have high and low STI/HIV prevalences, respectively.¹⁰⁸ Transmission in some networks could be accelerated when such bridging occurs within concurrent sex partnerships.

Partnership level analysis can also expand the concept of risk for researchers who focus on individual level analysis in assessing associations between behavior and disease. The individual’s risk of acquiring an STI stemming from his or her concurrency resides not only in the individual’s own behavior via increased exposure to additional sexual partners over a short period but also particularly in the individual’s partner’s practice of concurrency. These partners may reside in high STI/HIV prevalence sexual networks thereby drawing an individual unknowingly into further exposure,⁵⁴ Risk varies both across partnership types and within partnerships over time; however, the associations between such variation and STI/HIV acquisition have not yet been well defined. To improve the understanding of transmission dynamics driving STI/HIV epidemics, there is a need to move beyond reports of sexual behaviors to include the measures of partnership dynamics cited in Fig. 8-1 such as level of communication, intimacy, and power dynamics as well as concurrency and condom use. To further the understanding of behavioral epidemiology on STI/HIV, we need a better understanding of how partnerships vary within sexual networks, how risk behaviors vary within partnership types, and how the

intersection of risky partnership types and sexual networks is associated with disease transmission.

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9

Psychological Perspectives on Sexuality and Sexually Transmissible Diseases and HIV Infection

Michael W. Ross

INTRODUCTION

Psychological variables are closely associated with sexually transmissible infections (STIs) in both immediate (social psychology of situational pressures to engage in sex, which may lead to higher risk of infection) and more distant (personality styles or attitudes to sex and sexuality, which may put an individual at greater risk of STI) senses. Psychological aspects of sexuality may affect both risk of STI (precursors of STI risk) and presentation for, and response to, treatment (consequences of STI). Maladaptive or psychopathological responses to infection (or fear of infection) may also occur. However, psychological precursors to STI risk largely operate where power over sexual behavior resides in the individual and not the situation.^{1,2} Where the individual is largely powerless to avoid sex or unsafe sex, or would be at risk of consequent violence or discrimination (as in younger age, female gender, sex workers, or other dependent positions), psychological *determinants* of STI risk behaviors (although not psychological *consequences* of STIs and risk behaviors, which may even be exacerbated by powerlessness) may be of minimal importance.

PSYCHOLOGICAL THEORIES OF HUMAN SEXUALITY

Sexual behavior is considered an inborn drive in humans: even infants show signs of sexual behavior. Sex drive may be markedly modified by cultural, social, and interpersonal factors. Freud termed the energy of sex the libido, and believed that along with hostility and aggression it accounted for most of the motivation behind human behavior. Freud postulated that the individual was born potentially able to respond to any individual sexually but that socialization through a series of stages directed the sexual urge toward heterosexual contact. Freud's stages included the oral stage, the anal stage, the genital stage, the latency stage, and the reawakening of sexual impulses at puberty. Major studies of children's sexual thinking³ show that sexual understanding follows three Piagetian stages of nonsexual, transitional sexual,

and fully sexual stages of cognition rather than Freud's psychoanalytic stages, and these depend strongly upon the cultural and educational information on sexuality available to children and adolescents.

There is general agreement that a fundamental propensity to act sexually exists but that it may be modified by learning. Ford and Beach⁴ note that cultural conditioning accounts for the extent and type of sexual expression but falls short of accounting for what is biologically possible in humans. The psychological process of moulding sexual expression is through conditioning. Modeling, in which individuals learn roles or behaviors through observing the behavior of others, is also involved.⁵ Nevertheless, little is understood about the specific development of heterosexual or homosexual behavior, which probably results from the interaction of biological and social factors. Sexuality has a number of different aspects and meanings depending on variation in person, time, culture, age, and situation. Ross⁶ has noted that multiple meanings of sexual expression are learned. These multiple meanings of sexual behavior can include, in addition to reproduction, the symbolism of union, religious meanings, love, release of sexual urges, pleasure, meeting survival or financial needs, as ritual, as experimentation, dominance or ownership, developmental or normative in a particular peer group, dynastic, in the context of mentoring, or the excitement of the forbidden. Some of these meanings may have significance in particular cultural or historical contexts, not necessarily in Western or twenty first century situations. Sexuality is not a unitary phenomenon but part of social interaction and best explained by opportunity and contingencies of reinforcement acting upon a basic biological drive. For people in all cultures, sex is multidetermined but most commonly associated with seeking comfort, finding pleasure, and survival.⁷ Racial, ethnic, and cultural groups may be differentiated by a wide range of social, psychological, and demographic factors that influence both STI transmission and reaction to STIs, and it is important to specifically distinguish these rather than to assume that they are "cultural" just because they covary with particular racial or ethnic identities.⁸

PSYCHOLOGICAL VARIABLES ASSOCIATED WITH RISK OF STI

The psychological variables associated with increased risk of contracting STIs include those associated with behaviors that carry an increased risk of infection. In addition to specific behaviors such as high partner numbers, specific sexual practices (including condom use), and the context in which the sex occurs, I generally review the variables that have been associated with STI. Where psychosocial factors are associated with risk of STI, this provides a possibility of modifying such factors to decrease the probability of infection as well as to develop information on which intervention strategies may be based. Psychosocial factors may vary across phases of development and be profoundly influenced by experiences in childhood and adolescence.

DEVELOPMENTAL ASPECTS OF HIV RISK

■ IMPACT OF SEXUAL ABUSE

In a cross-sectional study of adult African American women, adult rape survivors were 6 times more likely to have reported >10 partners, 3 times more likely to report not using condoms, and 3.3 times more likely to report not using condoms consistently, in the past 3 months.⁹ In Australia, Pitzner et al.¹⁰ using STD clinic attendees and a matched (age, gender) community sample reported that abuse was significantly more prevalent in the STD sample, with the effects being stronger in females than males. In a large psychiatric treatment sample in the United States, Brown et al.¹¹ indicated that abused versus nonabused adolescents were significantly more likely to report higher rates of STIs: also associated with abuse were less condom self-efficacy, less condom use, and less impulse control. In the UK, Petrak et al.¹², studying female STD clinic attendees, found that 26% of women reported sexual childhood abuse, with similar overlapping proportions reporting emotional and physical childhood abuse. Abuse was very significantly associated with multiple previous STIs. While confidence in using condoms with a partner was not associated with a history of abuse, anticipating negative reactions from partners to suggested condom use was. In a sample of native American women, child physical/emotional abuse was associated with a five times greater risk of having had an STI than found in nonabused women. This risk was higher than the risk for a history of sexual abuse.¹³ Minority (Mexican and African American) women with a laboratory-diagnosed STI who reported a history of abuse (sexual, physical, and psychological) were found to report a larger number of measures of psychological distress than a nonabused comparison group.¹⁴ Champion et al.¹⁴ also noted that for a majority this abuse was experienced from a boyfriend or friend/acquaintance, and that in this population an STI diagnosis mandates the inclusion of violence histories in STI treatment and its inclusion

in prevention campaigns. In a population of child and adolescent (aged <16) survivors of sexual assaults/rapes in the UK, Kawsar et al.¹⁵ found an STI prevalence of 26%, while one-third gave a history of previous sexual or other abuse. Over 80% gave a history of current psychological problems with a wide range of multiple mental health and social difficulties. Bartholow et al.¹⁶ in a study of over a thousand adult homosexual/bisexual men attending an STD clinic, found that a history of being sexually abused was associated with STI and HIV risk behaviors. Sexual abuse was also found to be associated with mental health problems, psychoactive substance use, and injecting drug use, suggesting that abuse may produce mental health problems which may in turn lead to drug and STI risk behaviors. The data on history of sexual and other abuse in childhood are consistent in predicting later risk for both STI/HIV risk behaviors and mental health problems. Similarly, recent sexual abuse is associated with more immediate risk of STIs and with multiple mental health problems.

ADOLESCENCE AND PSYCHOLOGICAL ASPECTS OF STI

Adolescence is a time of discovery of sexuality and often sexual experimentation. Rosenthal et al.¹⁷ looked at coping strategies in adolescent girls but found no differences in coping strategies between those who had had an STI and those who had not (wishful thinking was used by most of the subjects). Subsequently, Rosenthal et al.¹⁸ and Baker and Rosenthal¹⁹ reported that older females were more likely to report STIs, lifetime partner numbers, and less negative feelings about STI acquisition (with feelings of control over fate being associated with level of development and cultural norms). Problem solving was used less often, and self-blame more often, for STI acquisition in girls when compared with a recent interpersonal stressor.²⁰ In a longitudinal study of predictors of STI/HIV-related sexual-risk behavior in African American adolescent females, DiClemente et al.²¹ found that those with psychological distress at baseline were more likely to perceive barriers to condom use, to be fearful of negative consequences of condom use, to have experienced dating violence, and feel less efficacy in condom negotiation with a new partner. These data suggest that even moderate emotional distress in adolescent African American females may be predictive of STI risk and that clinicians should be vigilant for this. In a study of minority females,²² symptoms of depression, conduct problems, and substance use were associated with younger teens' STI-related risk behaviors, and negative emotional reactions to intercourse (discomfort, feeling bad about or angry after sex) were also associated with STI in young adults. Taken together, these data suggest that lack of control and negative experiences surrounding sex in adolescents and young adults may be associated with lessened power to negotiate sex or safer sex.

■ PERSONALITY AND ATTITUDINAL VARIABLES

Hart²³ has argued not only that there is increasing recognition of venereal disease as a behavioral disease, but that psychological variables implicated in venereal disease may be primarily related to the personality of the individual. He reported for his heterosexual sample that an increase in extroversion, and to a lesser extent neuroticism as measured by the Eysenck Personality Inventory,²⁴ were associated with increased STI. Similar findings are reported by other researchers: Eysenck found that extroverts will have intercourse earlier, more frequently, with more different partners and in more different positions than introverts: they will also engage in more varied sexual behavior outside intercourse and engage in longer foreplay.²⁵ Measuring attitudes on Eysenck's Sexual Attitudes Inventory (ESAI), Fulford et al.²⁶ found STD clinic subjects to be less interested than Eysenck's controls in physical sex and pornography, to have less sexual excitement, greater prudishness, sexual disgust, and neurotic sexual attitudes; homosexual patients did not differ from heterosexual patients in these respects, and bisexual patients accounted for most of the differences which were found. Familial variables have also been implicated: Hart²⁷ has reported soldiers coming from large (four or more children) families as significantly more at risk for STI, and Ross^{28,29} reported that the extremes of rejecting and overly supportive parental relationships were among the significant predictors of multiple STI infections in the four western countries he studied.

Personality and attitudinal variables may be associated with increased risk of STI in men. Ross³⁰ found that beliefs about the meaning of sexuality and its social and political implications predicted sexual behaviors in Swedish homosexual men. Eysenck²⁵ found that high psychoticism scorers (those who tend to be isolated, affectless, and aggressive) were also more sexually curious, more accepting of premarital sex, more promiscuous, and more hostile. Extroverts scored as more promiscuous and less sexually nervous, while high scorers on the neuroticism scale had significantly lower scores on sexual satisfaction and significantly higher scores on excitement, nervousness, sexual hostility, sexual guilt, and sexual inhibition. High neuroticism scores are also closely associated with "venereoneurosis."²³

Fulford et al.²⁶ used the ESAI and found that neuroticism correlated positively with syphilis and gonorrhea infections, and extroversion correlated negatively with the diagnosis of syphilis. Ross³⁰ refactored the ESAI after rewording it to make it appropriate for homosexual men and derived nine interpretable dimensions. He found that, as anticipated, sexual attitudes did underlie sexual behaviors. In fact, six of the nine scales were predictors of partner numbers, five were predictors of particular sexual practices, and six were predictors of places of partner contact. All of these scales were related in a curvilinear rather than a linear fashion to partner numbers,

with those with zero and high partner numbers having greater sexual prudishness, fear of sexual relationships and lower interest in pornography, degree of sexual excitability, and sexual permissiveness. Those with higher partner numbers were highest on the scale measuring lack of control of libido.

Sensation seeking has more recently been implicated in STI including HIV-related risk behaviors. Kalichman et al.³¹ found that it predicted HIV-risk behavior in homosexual men, and even with substance use controlled for, sexual adventurousness and sensation seeking were major predictors of unsafe sexual behavior. This has also been confirmed in heterosexual men: Bogaert and Fisher³² were able to predict a significant proportion of the variance of partner numbers using sensation-seeking measures. It appears that there is a constellation of disinhibition, including Eysenck's psychoticism and extroversion, and sensation seeking, significantly related both to safety and to partner numbers. Kalichman et al.³³ reported that sensation-seeking was related to engaging in unprotected sex with casual partners, and that it was also associated with expectancies that alcohol would enhance sex. Subsequently, in a prospective cohort of STD clinic attendees, Kalichman and Cain³⁴ showed that sensation-seeking predicted unprotected intercourse 6 months later, as well as alcohol use in sexual contexts, which in turn also predicted unprotected sex.

■ ROMANTIC LOVE AND STD ACQUISITION

The association between romantic love, conceptualized as a possibly biologically programmed urge to fall in love, that intellectually blinds the individual, and STD acquisition, is reviewed by Goldmeier and Richardson.³⁵ They see romantic love as akin to an obsessional condition in which euphoric mental states override the rational aspects of a decision to have sex or safer sex. Goldmeier and Richardson note research³⁶ shows that people "in love" differed from controls in having reduced serotonin transporter sites (measured in platelets, and perhaps reflecting a putative "altered serotonergic tone,") and that being "in love" is associated with raised cortisol levels until the initial throes of love dissipate in 12–24 months. They argue that these data support the contention that romantic love produces a "deterministic and nonlogical response to have sex and thus acquire an STI" and that biological states produced by being "in love" may drive some STI-related risk behaviors.

■ PSYCHOSOCIAL VARIABLES

The environmental stresses of war and immigration produce behavior patterns, which many would not otherwise experience.^{23,37} During the 1960s in the UK, half of the men with gonorrhea were immigrants. Single migrants may have numerous sexual encounters until they settle into their new cultural backgrounds.³⁸ This holds for nonwestern societies:

Hart³⁹ reported that in single laborers and married immigrants in Papua New Guinea, recourse to prostitutes and, to a lesser extent, homosexual behavior, are more common outlets and venereal disease a prominent sequel. STI incidence rates in immigrants and soldiers are increased markedly (in comparison to baseline rates before immigration or war) and instability and insecurity are associated with lack of discrimination and increase in frequency of sexual contacts. Kelus⁴⁰ took random samples of STD clinic attenders and inhabitants in a Polish town and found no differences between inhabitants and patients apart from a tendency for patients to be more urbanized and less religious. However, Hooker⁴¹ has suggested that for some, the seeking of sexual contacts is an activity that is isolated from all other aspects of their lives. We cannot assume that psychological factors that influence sexual contacts will be obvious in other areas of the individual's life.

■ PSYCHOLOGICAL CONCOMITANTS OF PARTNER NUMBERS

Partner numbers are an important determinant of STI, as they can increase (depending on STI prevalence) the probability of infection. If sexual practices that do not transfer body fluids are utilized, partner numbers are immaterial, and if all partners are mutually monogamous and uninfected, there is no risk. Ross⁴² found that partner numbers were not invariably associated with risk of STI in homosexual men. Schofield⁴³ reports that there is little if any evidence that individuals with high partner numbers have personality defects, are emotionally damaged, or come from a less than adequate social milieu. Goode and Troiden⁴⁴ found that homosexual men with higher partner numbers tended to prefer emotionally superficial sex and were less well educated. Partner numbers can be depressed during dysphoric mood states (confusion, fatigue, and distress).³⁰ High partner numbers may also protect from psychological decompensation through their effect on increasing self-esteem. It was reported that depression increased in homosexual men who reduced their risk of contracting HIV,⁴⁵ which suggests that there is some association between mood and partner numbers. Beck et al.⁴⁶ found that clinical measures of depression were associated with STI-related risk behavior, and depression was itself associated with perceptions of the uncontrollability of risk and perceived lack of control over sexual practices and fidelity.

Bogaert and Fisher³² found that number of sexual partners of heterosexual men were best predicted by hypermasculinity and sensation-seeking. A personality construct they labeled "disinhibition" (sensation-seeking, hypermasculinity, Eysenck's psychoticism,²⁵ and erotophilia) accounted for a substantial proportion of variance in partner numbers. In one cross-cultural study, the homosexual male with high partner numbers sees himself as conventionally masculine,

prefers a more feminine partner, and has high alcohol consumption. He may have had a more negative parental rearing pattern and be under less stress than men with low partner numbers, be more involved in the homosexual subculture, see his homosexuality as more central to his lifestyle, and have had more STIs.³⁰ These data illustrate the multifactorial nature of the variables associated with high partner numbers in white, western cultures.

■ PSYCHOLOGICAL CONCOMITANTS OF PARTICULAR SEXUAL PRACTICES

Practices that involve the transmission of body fluids, including unprotected anal or vaginal intercourse, brachioproctic ("fist fornication") activities, and fellatio may transmit pathogens; mutual masturbation and frottage (rubbing bodies together) will not. Haist and Hewitt⁴⁷ noted that homosexual men who preferred the anal insertee role also tended to prefer the oral insertee role in fellatio. However, Hooker⁴⁸ reported no relationship between sexual activity preferences and sex role. Preference for insertee and insertee roles in both fellatio and anal intercourse in homosexual men appeared to be strongly related to conventional masculine and feminine sex roles, and activities such as full-body contact and mutual masturbation appear to be nonsex role related.³⁰ These last two activities appear to occur when there is emphasis on emotional as well as physical closeness and they are associated with decreased frequencies of STI. Ross's data also suggest that sexual socialization into homosexual subcultures and, to a lesser extent, parental and peer models, have a major influence on the type of sexual activities undertaken: increased time and degree of socialization into the homosexual subculture increase preference for specific roles, as does degree of organization of the homosexual subculture within which that socialization occurs. Preference for particular practices does appear to be a function of increasing sexual experience, although the influence of masculine and feminine sex roles is significant. Acculturation to the norms of a subculture, depending on whether they support or reduce safer sex, also influences risk of STD/HIV acquisition.⁴⁹ Safe (or safer) sex involves protection by use of male or female condoms. Psychological characteristics associated with use of condoms have included more assertive personality styles and lower depression and dysphoric mood in both cross-sectional and longitudinal studies.^{50,51}

■ PSYCHOLOGICAL CONCOMITANTS OF PARTNER ANONYMITY AND PLACES OF SEXUAL CONTACT

Partner anonymity and place of sexual contact play an important part in STI; the links are threefold. First, the possibility of partner notification of anonymous partners is virtually impossible. Second, in some places of anonymous contact such as gay

bathhouses, there are opportunities for multiple contacts with multiple partners within a short time span. Third, such places may generate their own demands, which may lead to person–situation interactions in which the effect of being in the situation is significant. However, different motives and interests may attract people to similar physical contexts. The now-classic study of Humphreys⁵² classified men using public toilets as places for sexual gratification into four groups: “trade,” ambisexuals, gays, and closet queens. Humphreys’ “trade” group comprised working-class married men. Two-thirds took an inserter role in fellatio in sexual encounters. Ambisexuals were married men with high income: two-thirds of this group were insertees in fellatio and saw themselves as bisexual. The gay group was individuals who were unmarried, had no preference for sexual roles, and who had independent occupations, while the “closet queens” were also unmarried but in lower middle class occupations in which they were dependent on others for employment, and they avoided the homosexual subculture. They preferred to play the inserter role, at least until they lost their attractiveness.

Ross³⁰ noted few differences between those preferring particular places of meeting sexual partners. Those meeting partners through cruising reported more positive mood states and higher self-esteem than others, and were markedly different from those who frequented bathhouses, who appear to be more depressed and avoided close emotional contacts. It appears that psychological variables, particularly mood states, are strongly associated with the drive for partners and the context in which they are sought, with a relationship between mood and partner-seeking.

■ PSYCHOLOGICAL CONCOMITANTS OF STD PREVENTION BEHAVIORS

The psychological aspects of response to STI/HIV prevention activities are important in preventing infection. Following indications from national campaigns in which fear was the central principal in HIV prevention^{53–55} there has been considerable focus on what constitutes an effective message. In a comprehensive theoretical review, Ruiter et al.⁵⁶ noted that implicit assumptions that prevention will be activated or enhanced by fear arousal are not necessarily supported by the scientific literature. Fear may simply increase denial, and while threat perception may be inherent to fear arousal, they are not necessarily linked. Fear appeals, Ruiter et al. show, provide two types of information: first, fear is aroused by presenting a threat (STI or HIV infection); second, a search for safe conditions is prompted by recommending protective action (e.g., condom use). Ruiter et al. indicate the data suggest that people with low self-esteem seem primarily concerned with fear control and turn to danger control only when fear has been reduced. Those with high self-esteem are more likely to act directly on controlling the threat through preventive

action. Moderately fearful individuals are only likely to process information about a recommended response if they expect the information to reassure them.

Using multiracial female samples of both STD clinic and community samples, Nyamathi et al.⁵⁷ examined the predictive value of recent STI and return for test results. Emotion-based (as opposed to problem-based) coping strategies were associated with increased STI risk and were in turn predicted by lower self-esteem and more perceived social support. They report that emotion-based coping strategies were more common in their sample of African American women than in homeless Latina women. Osborn et al.⁵⁸ noted that patients rated by staff as more psychologically disturbed were more likely to return for follow-up, and Pitts et al.⁵⁹ monitored STD patients in Australia and found that 19% returned within 2 years with a new infection; however, reattenders did not differ significantly from the remainder of the cohort on demographic, sexual, or psychological variables.

Several studies have noted psychological variables associated with condom use. Personality variables associated with increased condom use in homosexual men include increased scores on the dominance and aggression scales of the adjective check list and decreased scores on the abasement and deference scales.⁵⁰ Longitudinally, mood states as measured by the Profile of Mood States that were associated with a move to safer sex included lower depression, anger and hostility, fatigue, confusion, and total dysphoric mood scores⁵¹. These data suggest that assertiveness and lack of dysphoric mood are both associated with increased condom use. In a comparative study of heterosexual and homosexual men, Treffke et al.⁶⁰ found that attitudes toward condoms were strongly associated with both general assertiveness and condom assertiveness in heterosexual men, but that there was no such association in homosexual men. Data on psychological concomitants of condom use may not generalize across sexual orientation, and probably not across gender.

THE PSYCHOLOGY OF STI

The second area of importance in considering psychological aspects of STIs is the psychological aspects of infection as such, such as reactions and abnormal behavior in those infected. This section considers the presentation and management of the psychosocial manifestations and psychopathology of STIs. Psychological sequelae of STI exposure are poorly understood, frequently unrecognized, and inadequately managed despite being among the most common conditions encountered in STD practice.²³ Psychological and psychiatric problems in STD practice may be divided into three categories: the normal range of psychological reactions to STIs; abnormal reactions to STI (or to believe one is infected); and sexual dysfunctions which may become apparent in the course of consultation or present initially to STD clinics.

■ PSYCHOSOCIAL RESPONSES TO STD INFECTION

Over 40% of patients attending public STD clinics have been classified as having psychiatric problems on the basis of screening tests.⁶¹ A subsequent study noted that the anxiety caused by the presenting problem was probably the cause of such a high figure, since less than 5% had a sufficiently abnormal level of distress to justify calling it psychopathological.⁶² Another study reported that less than 5% of STD patients required psychiatric referral,⁶³ although Barczak et al.⁶⁴ reported that 31% had anxiety and depression not affected by the physical symptoms of STIs, and that these were significantly more prevalent in females. Significant life events in the past 6 months were related to presence of physical symptoms, and in the absence of major life events in this time frame, a psychiatric diagnosis was more likely (this relationship may be related to increase in sexual activity following traumatic life events). Osborn et al.⁵⁸ studied over 900 STD clinic patients on the Hospital Anxiety and Depression Scale and reported that 51% scored above normal threshold, whereas clinic staff rated 20% of the patients as “having psychological problems.” These latter patients were 1.9 times more likely to attend for follow-up. It is therefore important to differentiate the normal range of reactions to STI from psychopathological ones.

Ross³⁰ has postulated a model of the meaning of STIs to the individual, which explains the beliefs underlying psychological reactions to STIs and the reasons for psychopathology when it occurs. In discussing the meaning of STDs to the individual, there are at least four separate attributions as follows:

1. STIs are a deserved outcome of indiscriminate sexual behavior and punishment for sexual sins.
2. STIs are a consequence of individual inadequacy that leads to sexually indiscriminate behavior.
3. STIs are a consequence of a breakdown in traditional social values and rapid social change.
4. STIs are solely the result of an individual coming into intimate contact with a virulent pathogen and no blame attaches to this.

There is a hierarchy of decreasing blame from attributions 1 to 4, based on the degree to which individuals see themselves responsible for the infection. The degree to which there is a psychological investment in sexual behavior is also important. The meaning of STIs to the patient and to a lesser degree to the attending health professional will affect not only the compliance with treatment but also the psychological sequelae and the subsequent risks of exposure to STIs.

A qualitative study of the experiences of STD clinic attenders who received an STI diagnosis⁶⁵ Holgate and Longman, reported that some experienced feelings of anxiety, stigma,

and isolation. Providers should ascertain their own positions and make some estimate of the position of their patients before seeking to educate or to modify risky behaviors.

Reactions to STI may arise from any of the four attributions toward STIs noted above, and vary by culture, degree of control, and gender. In Zimbabwe, Pitts et al.⁶⁶ Studied psychosocial and gender issues related to multiple STIs within the context of marriage, through in-depth interviews with 60 men and women attending an STD clinic. Major differences between men and women were found, with gender differences in reactions to various STIs (men can discuss it with friends, while women are shamed and isolated by it). Male STI-related risk behaviors may often be seen as a culturally-sanctioned norm toward male promiscuity. Women's lack of power to negotiate safe sex within marriage, and lack of social support networks for infected women were consistently found.

Reactions to STIs may be further classified into *abnormal illness behavior and venereoneuroses*. Psychotic reactions that are either triggered by STI or have major venereological components are recognizable by such classic psychotic features as delusional thought patterns and the inability of patients to be convinced by rational discussion. Such patients with psychotic reactions will generally also have a history of psychotic illness.

■ ABNORMAL ILLNESS BEHAVIOR

Abnormal illness behavior has important implications for treatment. In the case of individuals with an erroneous conviction that they have an STI, there is abnormal illness behavior in terms of both general hypochondriasis and a strong disease conviction without demonstrable pathology. There may also be an indication that patients believe they “deserve” the infection, as noted above. Perhaps more common is the refusal to see STI as an illness but perhaps only as a minor nonsignificant risk of a particular lifestyle. In the case of the absence of any illness behavior, patients may frequently compromise treatment by discontinuing medication after symptoms have resolved, continuing sexual activity after symptom resolution but before clearance, or not returning for proof of cure. Thus, both extreme illness behavior and lack of illness behavior can be abnormal and may have implications for the management of STIs.

Ross⁶⁷ found that it was the repeated STD clinic attenders rather than the first attenders who displayed the greatest anxiety and hypochondriasis over STI. Those with higher previous numbers of infections also more often tended to deny life

The interaction between patients and physicians who hold conflicting attributions for STIs may lead to tension, anger, transference and countertransference issues, and resistance to taking advice, treatment or prevention, particularly where more divergent attributions are held.

stresses and attribute their problems solely to the episode of illness. Such individuals also displayed significantly higher disease conviction and symptom preoccupation and higher levels of symptom exaggeration. In comparison, first attenders more often tended to deny that an STI was an illness (denial of acquisition of a stigmatizing illness). Compared to other illnesses, in which there may be substantial secondary gain through sympathy, illness behavior would appear to differ for STIs and to develop as a function of repeated infections. STI tends to be seen as a chance event until after several infections when it becomes perceived not only as an illness but also as a result of particular behaviors. Ross also found that there were few differences between heterosexual and homosexual men in illness behavior with STIs, apart from the fact that there is a less negative reaction to STI among gay men. The STD clinic population was closer in illness behavior scores to a psychiatric outpatient population than to a general practice population. It is unclear whether the disturbance was a function of having a stigmatized illness such as an STI or inherent in STD clinic attenders.

Ross⁶⁸ also found that acknowledgment of homosexuality in STD clinics varied significantly between countries (20–52% of homosexually active men did not acknowledge being homosexual) although not between private and public clinics. The variables predictive of whether the respondent reveals his homosexual orientation when presenting to an STD clinic or medical practitioner are coherent. Nonrevealers are likely to conceal their homosexuality from most people, to expect the most negative social reaction to their homosexuality from significant others and society in general, and to believe in much more rigid and conservative sex roles for men and women. Compared with those who reveal homosexual contact, nonrevealers are more likely to report themselves as being more bisexual than exclusively homosexual, to have had no previous STI, and to have had poor relationships with their mother during adolescence. They are also more likely to be unassertive.

The lack of previous STIs in nonrevealers suggests that the clinic situation will be a new and potentially frightening one in which condemnation is expected: in subsequent visits to a clinic, the patient will tend to be more open if the clinician's approach has been nonjudgmental. When clinicians take histories in a manner that implies that any sexual contact was a heterosexual one, the patient may not have the courage to make a correction. These data do suggest that there are significant and consistent psychological factors operating to prevent some homosexual men from revealing same-sex contacts in the context of STD clinics. However, these psychological factors will clearly operate in interaction with environmental factors such as the clinic, the clinician, the stigma, and the legal and social climate regarding homosexuality. The imposition of shame and guilt upon sexual interactions by religious and other traditional moralities is the single most important cause of stigma and consequent psychological problems in STI

treatment, and if the physician is able to assess and deal with this early in the treatment process, many difficulties may be prevented or minimized. To fail to do so may even introduce or reinforce shame or guilt and produce an iatrogenically strengthened psychopathology. A high index of suspicion for psychosocial problems attendant on having an STI or reported exposure to STI is mandatory to ensure maximal compliance with treatment, partner notification, and preventive education, and the possible contribution of psychosocial factors to relapse or reinfection should not be underestimated.

■ COMMON RESPONSES TO STIS

There is a large literature on the response to genital herpes infection, reviewed by Longo and Koehn.⁶⁹ They note that much of the research on the impact of genital herpes is neither longitudinal in comparing with the premorbid psychological state, nor comparative with other curable STIs. Nevertheless, some elements of response are common across studies. For people who have had genital herpes for less than a year, negative life events, depression, anxiety, anger, and social alienation predict herpes simplex virus (HSV) recurrences; after a year, high levels of depression and low self-esteem are consistently associated with more frequent HSV recurrences. It is important to note that *responses* to infection may lead to these states, thus setting up a cycle of response and recurrence. Stronks et al.⁷⁰ compared people with genital herpes both to a control group with gonorrhoea and to their reported premorbid adjustment, and found that while there was no difference in outcome for those with HSV or gonorrhoea, both had significantly increased anxiety, sexual inhibition, bitterness toward sexual partners, and increased psychological complaints compared to a control group with no STI. There was a significant interaction between premorbid state and morbid change, however, with the HSV group increasing markedly in psychological complaints and the gonorrhoea group increasing minimally. Carney et al.,⁷¹ in a longitudinal study, found that the first episode of genital herpes had a substantially negative psychological impact, with over 60% meeting screening criteria for being a psychiatric case as measured by the General Health Questionnaire. However, two-thirds of these became noncases if there were no recurrences of disease: if there were recurrences, the level of psychiatric case classification stayed high. A clinical study⁷² found that the majority of people with genital HSV report that infection made them less capable of physical warmth and intimacy, enjoy sex less, and feel less sexually desirable. This extended outside sexual contacts: all reported that work performance was also hampered. A majority reported disturbance of affect, feeling that genital HSV is incompatible with happiness, and feeling pessimistic about the future course of the illness. Depression was also reported by 84%. Sexual dysfunctions including reduced interest, reduced ability to

achieve orgasm, avoidance of intimacy, and reduced enjoyment of sex, as well as feeling repugnant to others (over 30% of Americans said they would not associate with someone who has genital HSV⁷³) were reported. Mindel⁷⁴ notes that emotional problems in genital herpes patients are worse for patients with first episodes of genital herpes than for other STD clinic attenders, and likely to be more severe in females than males. Mindel also indicates that cognitive coping strategies and social support from a partner appear to be positive predictors of adjustment.

In a longitudinal study of people with no known history of genital herpes, Rosenthal et al.⁷⁵ (2005) note that cross-sectional studies suggest that there is transient distress, concerns about relationship implications, and fear of transmitting the virus but no substantial, negative psychological reaction to HSV-2 infection. Their study compared those diagnosed with HSV-2 with matched controls found to be uninfected; reevaluation using a genital herpes quality of life measure 3 months after diagnosis found that the infected reported intrusive emotional thoughts about herpes and concern about infecting others, but little lasting psychological distress. Significant predictors of distress on infection were greater baseline interpersonal sensitivity, lower social support, and lower perceived quality of sex. These data suggest that the pain and discomfort of the disease itself may be one of the most important aspects of psychological sequelae of HSV-2, and that premonitory functioning is one of the best predictors of poorer psychological outcome. These findings emphasize the importance of anticipating and addressing concerns of newly diagnosed patients, and particularly anticipating problems in those whose feelings are easily hurt. In clinical practice, brief probing as to how a patient might react to a positive diagnosis may usefully anticipate subsequent psychological problems when the patient is given a positive diagnosis. The interaction between pain and discomfort and psychological sequelae underscores the interactions between physical and psychological aspects of STIs.

■ VENEREONEUROSES

Venereoneuroses may be divided into those neuroses that manifest with exposure to infection and include overreaction to infection, and venereophobias and abnormal disease convictions, as well as factitious STIs and AIDS.

Veneral overreaction and hypochondriasis

Hart²³ notes that individuals may be abnormally preoccupied with bodily processes, manifesting as a genitally-focused hypochondriasis. Irrational concern is focused on urethral, anal, or vaginal discharge or the appearance and sensations of the genitalia. There may be an obsessional element to these, or compulsive genital examination that may itself cause irritation or discharge. Acceptance of these symptoms (or the

patient's description of these symptoms) without objective evidence of infection or relapse may promote venereoneurosis and aggravation of the neurotic tendencies of the patient. Hart²³ has also reported that penile manipulation to produce discharge (often including their vigorous squeezing of the glans and shaft, in contrast to the more usual cautious manipulation) is a feature of some patients. In other manifestations, abnormal attention may be paid to irregularities in pigmentation or skin surface, skin tags, sebaceous cysts and hair follicles, and pearly penile papules. Demands for treatment, in the absence of demonstrable infection or pathology, are one indication of the presence of venereoneurosis, and Hart believes that such patients tend to be more severely disturbed.

Miller et al.⁷⁶ have reported that in the case of HIV infection, individuals will focus on the nonspecific nature of the symptoms of HIV infection, and attend for minor changes in skin pigmentation which they believe is Kaposi's sarcoma, or for minor changes in respiratory function which they believe is indicative of an opportunistic pulmonary infection. In some cases, obsessional palpation of cervical and axillary lymph nodes will lead to local irritation that may be interpreted as lymphadenopathy. Management involves discussing the patient's specific anxieties, and an opportunity to talk about these may in itself provide considerable relief. In the case of concern over AIDS in those who have been infected with HIV, it is important to focus on the patient's specific concerns, including fear of exposure, stigmatization, pain, death, and the uncertainty associated with the diagnosis of HIV infection and likelihood of progression.

Venereophobias

Venereophobias have been recognized for most of this century, with syphilophobia as the earliest manifestation reported.⁷⁷ At present, AIDS phobias are more commonly reported,⁷⁸ probably because of the increase in publicity surrounding AIDS and the mortality and morbidity associated with it. In syphilo- and AIDS-phobias, individuals at no or low risk of contracting the disease believe that they are infected. While more accurately described as an abnormal disease conviction than a phobia, in some cases there will also be irrational precautions to avoid catching AIDS and fear or avoidance of situations in which there is a perceived risk of catching AIDS. AIDS phobic patients differ from venereoneurotics in that symptoms are not usually genitally focused and often cannot be traced to a specific sexual episode. Ross⁷⁸ has also reported that underlying conflicts and life stresses are likely to be major contributors, and that such presentations are usually associated with guilt over sexual behavior (commonly bisexual or homosexual contact or sexual activity outside a primary relationship). The trigger is usually life stresses, often relationship-related, or media publicity on AIDS. The belief in infection may sometimes be near delusional in quality, with patients refusing to believe the results of HIV tests or

going from clinic to clinic in search of a test result that confirms their worst fears.

Management of venereophobias must encompass more than just reassurance of noninfection, which the patient may interpret as not being taken seriously. Excessive physical intervention, beyond that necessary to exclude disease, reinforces the patient's belief in the existence of disease. Taking a brief sexual history, history of current concerns and stresses, and recent conflicts will frequently bring out the underlying issues of guilt or concern over moral self-image or sexual orientation. Brief interpretive counseling focusing on the conflicts underlying the phobia and on the stresses which promote such conflicts, with emphasis on giving the patient a degree of insight into the processes leading them to present with an abnormal disease conviction, will often resolve the problem. However, referral to appropriate mental health professionals should be considered and not delayed if resolution does not occur.

Not all improbable cases will be evidence of psychopathology. Bodsworth et al.⁷⁹ examined the medical records of over 30 male and female virgins attending an STD clinic and reported that most attendances represented recognition of STD clinics as appropriate centers for a wide range of genital and sexual problems: only 10% presented with genital symptoms as part of a previously diagnosed psychosis.

Symptoms without objective signs or microbiological evidence of infection in many women presenting at gynecology or STD clinics, those with vaginal symptoms but no signs or microbiologic evidence of bacterial vaginosis or vaginal infection did not differ from women without symptoms or signs or from women with both symptoms and signs with respect to life stress, sex guilt, or global personality function. However, these symptomatic but otherwise normal women indicated significantly lower marital satisfaction and thought that their relationship was less sexually satisfying to their partner. McGuire et al.⁸⁰ suggested that preoccupation with vaginal symptomatology might reconcile for these women the difference between the objective and subjective evaluations of their sexual relationships.

Factitious illness

Several cases of factitious AIDS have been reported.^{81–83} Individuals may present stating that they have been diagnosed as having AIDS at another center but findings on examination do not accord with this. Immediate professional consultation with the center of previous treatment usually confirms that the claim of illness is incorrect. Individuals confirmed to have factitious AIDS may be either seeking the secondary gain of sympathy and hospitalization, or seeking to come to terms with the death of a significant other from AIDS. In the few cases reported, individuals usually strongly deny the diagnosis of factitious illness (“Munchausen syndrome”) and may present in the future with other factitious

illnesses with substituted symptoms. Such individuals are frequently quite medically sophisticated and may present plausible histories. Referral for psychiatric assessment is strongly recommended in such cases.

ACQUIRED IMMUNE DEFICIENCY SYNDROME AND HIV INFECTION

Reactions to HIV infection may be more extreme than reactions to other STIs for four reasons. First, the fully developed disease is usually fatal, although HAART (highly active antiretroviral therapy), where available, has somewhat mitigated this concern, especially in more developed countries. Second, in western societies AIDS is commonly associated with stigmatized minority groups (homosexual and bisexual men, illicit injecting drug users, and prostitutes) and a substantial component of attitudes toward AIDS comprises stigmatization, anti-homosexual and antiminority beliefs, and attribution of blame.⁸⁴ Third, such attitudes may be internalized in those infected and may lead to guilt and self-blame. Fourth, medical attendants may also contribute to stigmatization through overprecautions or avoidance of contact.⁸⁵ Consequently, the emotional impact on the patient of informing them they are infected with HIV is not significantly different from the news they have AIDS-related symptoms or full AIDS.⁸⁶

Psychological complications of HIV infection may be exogenous or endogenous. Exogenous complications arise from the psychosocial stresses resulting from negative societal and interpersonal reactions to AIDS. Faulstich⁸⁷ notes that the “worried well” (whether infected or not) may exhibit generalized anxiety and panic attacks, along with excessive somatic preoccupation and fear of the disease. On diagnosis of HIV infection or AIDS, individuals may exhibit disbelief and denial, followed by depressive and anxiety symptoms. Emotional distress may commonly lead to adjustment disorders with depressed mood or major depression. Recurrent psychological themes include uncertainty about disease progression, social isolation (imposed or adopted), dealing with terminal illness, and guilt or blame over lifestyle. Suicidal ideation may be present. The advent of HAART may have lowered the intensity of the psychological impact of HIV infection in places where HAART is accessible, as can medical feedback about success or failure of treatment regimens.⁸⁸

Endogenous complications result from the neuropsychiatric sequelae of HIV infection, either from the direct effect of HIV infection, on the central nervous system (CNS), opportunistic CNS infections, or CNS neoplasia. Up to half of patients with AIDS in the absence of HAART may present signs and symptoms of CNS infection, including subacute encephalitis characterized by malaise, social withdrawal, lethargy, and reduced sexual drive (these may also be signs and symptoms of depressed mood, or of systemic disease).

Subsequently, signs of progressive dementia may appear. Neuropsychiatric deficits resulting from HIV may typically involve impaired language, memory and integrative abilities, and occasionally depressed mood, and their insidious onset makes it important to maintain a high index of suspicion that psychological symptoms may indicate onset of CNS involvement. Although rarer, tertiary syphilis may also involve the CNS and include psychological symptoms.

The potential for depressive reactions, sexual acting out, and further discrimination and stigmatization and loss of social supports make informed consent and adequate pre- and post-HIV test counseling mandatory.⁸⁹ Where individuals are infected with HIV, frequent psychological support (or referral to appropriate agencies) and attention to patient's genuine fears of exposure, pain, discrimination, abandonment, and death is indicated, rather than general reassurance that may be interpreted as being dismissive. In cases of chronic depressed mood, pharmacotherapy or referral for psychotherapeutic treatment is indicated.

Longer-term psychological adjustment to HIV was studied in a longitudinal cohort of 38 gay men in psychotherapy over a decade.⁹⁰ They noted that HIV disease is like many other chronic and terminal illnesses in its emphasis on it being seen as an attack on the self, raising issues of time, and boundaries between chronic and terminal disease, illness and health, and hope and despair. While this study involved HIV in gay men, feelings of persecution, the dilemma of who to disclose to and possible consequent discrimination or rejection, issues of avoiding intimacy, multiple loss (especially in the pre-HAART era), and dilemmas about having sex and its associated risks of (re)infection, with both HIV and STIs may not be unique to this group. Nilsson Schönnesson and Ross⁹⁰ found that psychological adaptation occurs but as the disease enters each new phase (asymptomatic, mild symptomatic, severe, and terminal), psychologic symptoms reoccur. Mood states in the asymptomatic and mild symptomatic phase typically included anger, whereas disappointment, sense of violation, and feelings of aloneness characterized the terminal phase, with powerlessness and helplessness being expressed in all phases. They also report that a central psychological issue in HIV disease across time is existential: the need to provide a meaning for the infection. As Sontag⁹¹ notes, "Nothing is more punitive than to give disease a meaning—that meaning being invariably a moralistic one."

■ PSYCHOSEXUAL PROBLEMS

Studies in Europe and India^{61,92} and clinical experience in Africa have noted that sexual dysfunctions may present to STD clinics or be detected in STD clinics. In some countries, the clinical specialty of andrology serves men with STIs, psychosexual problems, as well as infertility and various urological disorders. Over 13% of STD clinic presentations are for sexual

dysfunctions in India, compared with only 4% in psychiatric clinics. Of these, over 80% are males with concerns over the effect of masturbation, erectile dysfunction, and premature ejaculation. Generally, presenting dysfunctions in males will include premature ejaculation, retarded ejaculation, and erectile dysfunction ("impotence"); in females, anorgasmia and general dysfunction ("frigidity") and rarely, vaginismus (spasm of the muscles of the vaginal introitus preventing penetration). Psychosexual problems usually occur in STD patients secondary to pain from infection or trauma, or from fear of infection, reinfection, or of infecting others. Patients or clinicians also sometimes may ascribe sexual dysfunction to STI in the absence of objective evidence of STI, and some clinicians offer therapy for a nonexistent STI in an effort to relieve sexual dysfunction.

In the case of mild or transient dysfunctions, the STD clinician can provide reassurance that such transient dysfunctions are not unusual and are often limited to particular partners, situations, and times, and information or education to correct misapprehensions which affect sexual performance is appropriate. However, chronic psychosexual problems which are not a result of physical pathology warrant referral to sex therapists. It is not uncommon to detect psychosexual dysfunctions in the course of history taking or treatment, and for some individuals the STD clinic will be the first point of consultation for this problem. While the majority of sexual dysfunctions are probably mild and transient and may resolve with adequate information and encouragement, the major dysfunctions in males and females listed above require more specific therapy from specialists in psychosexual dysfunctions.

In summary, psychological variables may be determinants of STD infection, and psychological problems are commonly associated with acquisition of STDs. The physician should be aware of the range, nature, and presentations of these disorders that may adversely affect attendance, compliance, and treatment as well as the psychological state of the individual.

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PART 3

Profiles of Vulnerable Populations

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Anne Buvé, Catherine Gourbin, and Marie Laga

There are important differences in the way sexually transmitted infections (STIs) affect men and women. These differences are not only determined by biological factors (“sex”), such as susceptibility to infections and complications, but also by gender. “Gender” is a social construct distinct from the biological determinism implied by the word “sex” and refers to the socially and culturally prescribed roles of men and women.¹ Gender includes social status, responsibilities, and behavioral patterns of men and women. The different roles men and women have in society result in a hierarchy of positions occupied by men and women, and a power inequality that usually favors men.^{2,3}

GENDER DIFFERENCES IN SEXUAL BEHAVIOR

Social norms determine the importance that is attached to virginity and fertility, and the relationships within which sexual intercourse is permitted. As such they determine, to a large extent, the sexual behavior of men and women. Social norms regarding sexuality evolve over time and there are large differences between different populations. But in many, if not most societies, norms regarding appropriate sexual behavior are different for men and women, usually being less restrictive for men than for women. Restrictive norms regarding women’s sexuality not only limit women’s sexual freedom but also restrict their access to information about sexuality and, as such, undermine their negotiation position in sexual relations. In addition, the power inequality between men and women extends into sexual relationships and lack of economic independence may prevent women from leaving a relationship that puts them at risk of acquiring an STI. In many settings, even in a stable union, wives have little control over marital sexuality, and women’s ability to negotiate safer sexual practices, particularly condom use, is practically nil. The lack of control over their own sexuality makes women not only vulnerable to STIs and their complications, but also affects their health-seeking behavior for STIs.

SEXUAL DEBUT, MARRIAGE, AND EXTRAMARITAL RELATIONSHIPS

Sexual debut has always been considered an important step in a person’s life, everywhere in the world. Circumstances of first sexual intercourse have a big influence on sexual behavior and sexual health later in life. Young age at first sexual intercourse has been found to be associated with higher number of lifetime sex partners, even when allowing for more years of sexual activity, and higher risk behavior later in life, especially in men.⁴ In women, younger age at first sexual intercourse is often associated with younger age at marriage.⁴ However, young women are also more often coerced into their first sexual experience than young men,⁵ and coercion is associated with a younger age at sexual debut. In addition, forced first sexual intercourse is associated with a large age difference with the male partner, lower use of condom, or other contraceptives and higher risk of STIs.^{5–8}

While traditionally first sexual intercourse, especially for women, is closely associated with marriage, in industrialized countries social norms regarding sexuality have relaxed in the latter half of the twentieth century and this has been accompanied by a decrease in age at first sexual intercourse, which was more marked in women than in men.⁹ Nowadays there is only a small difference in age at first sex in the younger generation of men and women in most industrialized countries.⁹ In contrast, in many developing countries there is a tendency for age at first sexual intercourse to decrease for men and to increase for women; e.g., in sub-Saharan Africa, men born in 1975 started their sexual activity roughly 1 year earlier than men born in 1950, while women born in 1975 had their first sexual intercourse about 0.5 years later than women born in 1950.^{10,11} In both men and women age at first marriage is delayed.^{10,11} In women, in all regions in the world, delay of marriage is associated with better education.¹² A delay of marriage can increase sexual activity and rate of sex partner change if the time period between first sexual intercourse and marriage is extended.

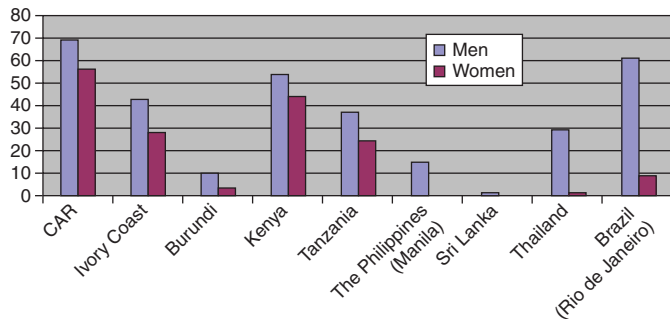


FIGURE 10-1. The proportion of never married men and women 15–19 years-old who reported sexual activity in the previous 12 months. (Source: Caraël M. Sexual behaviour. In Cleland J, Ferry B, eds. *Sexual Behaviour and AIDS in the Developing World*. London: Taylor & Francis on behalf of the World Health Organization, 1995: 80).

Premarital sexual activity of women varies from one population to another and is highly dependent on social norms regarding virginity, as is illustrated in (Fig. 10-1).¹³ In most industrialized countries and in sub-Saharan Africa, a high proportion of never married young women are sexually active. Other societies maintain strict control over young women's sexual behavior. In these societies, women usually have their first sexual experience with their husband, while men, for whom norms are less strict, often have their first sexual experience with a commercial sex worker. For instance, in many European countries visiting a female sex worker used to be a common way for young men to initiate sexual activity, but since norms on sexuality have relaxed commercial sexual activity has become rather marginal in most European countries.¹⁴ Whether or not women have sexual relations outside marriage has important implications for their exposure to STIs and for prevention interventions. For instance, in populations where the majority of women are only sexually active within a marital relationship, interventions aimed at changing sexual behavior of women in the general population are quite meaningless. Interventions should then rather focus on men and the women with whom they have sex outside marriage, including commercial sex workers.

■ SEXUAL BEHAVIOR AS REPORTED BY MEN AND BY WOMEN

A major problem when assessing the risk of men and women of contracting an STI, is the differential reporting of sexual behavior between men and women. It is believed that women tend to underreport sexual activity, whereas men tend to overreport. This has been highlighted by studies assessing changes in reported age at first sexual intercourse between successive birth cohorts¹⁵ and by studies that compared the numbers of sex partners reported by men and by women.^{10,13,16–18} Several explanations have been put forward for these differences in reporting of sexual activity. Women may only report partner-

ships that mattered to them and omit relationships that were traumatic. Moreover, social desirability bias may operate in opposite directions for men and women with respect to sexual behavior so that women underreport partners while men overreport.

GENDER AND RISK OF SEXUALLY TRANSMITTED INFECTIONS

■ PREVALENCE OF STIs IN MEN AND IN WOMEN

There is widespread agreement that women are more frequently and severely affected by STIs than men. However, population-based studies that permit comparison of STI prevalence in men and women are limited. There are several such studies from sub-Saharan Africa and the National Health and Nutrition Examination Surveys (NHANES) in the United States. In the studies in the general population that have assessed the prevalence of gonorrhea, chlamydial infection, and active syphilis, the prevalence was generally higher in women than in men (Table 10-1), with differences in prevalence being more marked in the younger age groups. *Trichomonas vaginalis* is the most common curable STI worldwide,¹⁹ but this STI has been studied primarily in women. In the studies in Table 10-1, for instance, prevalence of trichomoniasis has been assessed in women only, mainly because of the logistical difficulties of obtaining and processing samples for culture for *T. vaginalis* in men. One of the few population-based studies on *T. vaginalis* infection in men has been conducted in the Mwanza region of Tanzania. It found a prevalence of 11% in the age group 15–54 years,²⁰ whereas in this region the prevalence of trichomoniasis in women was 25.6%.

The difference in prevalence of HSV-2 infection between men and women is much more marked than the difference in prevalence of most curable STIs (Fig. 10-2). HIV infection is also strikingly more prevalent in women than in men in most populations where the predominant mode of transmission is heterosexual intercourse and where the HIV epidemic is mature (Fig. 10-3A). This is particularly apparent in the younger age groups (Fig. 10-3B). In the age group 15–49 years, the ratio of the HIV prevalence in women to the HIV prevalence in men ranges between 1 and 1.5. However, in young people 15–20 years the prevalence in girls may be 5–7 times higher than in boys.

■ MALE-TO-FEMALE AND FEMALE-TO-MALE STI TRANSMISSION PROBABILITY

Several factors can explain differences in STI prevalence between men and women, including differences in sexual behavior; differences in per sex act transmission probability; and differences in the natural course of the infection and health

Table 10-1. Prevalence of Sexually Transmitted Infections in Women and in Men as Assessed in Population-Based Studies

STI	Population (Ref)	Age Group	Prevalence in Women (%)	Prevalence in Men (%)
Gonorrhea	<i>Sub-saharan Africa</i>			
	Cotonou, Benin ¹	15–49	0.9	1.1
	Yaoundé, Cameroon ¹	15–49	2.7	1.6
	Kisumu, Kenya ¹	15–49	0.9	0
	Ndola, Zambia ¹	15–49	2.3	0.6
	Rakai, Uganda ²	15–39	1.6	0.9
	Masaka, Uganda ²	15–39	1.5	0.8
	Carletonville, South Africa (sexually active individuals) ³	14–24	10.9	2.9
	<i>China</i> ⁴	20–64	0.08	0.02
Chlamydial infection	<i>Sub-saharan Africa</i>			
	Cotonou, Benin ¹	15–49	1.3	2.3
	Yaoundé, Cameroon ¹	15–49	9.4	5.9
	Kisumu, Kenya ¹	15–49	4.5	2.6
	Ndola, Zambia ¹	15–49	2.9	2.1
	Rakai, Uganda ²	15–39	2.7	2.4
	Masaka, Uganda ²	15–39	1.4	1.9
	Carletonville, South Africa (sexually active individuals) ³	14–24	14.6	4.8
	<i>United States</i>			
	NHANES: non-Hispanic whites ⁵	12–39	2.3	0.9
	NHANES: non-Hispanic blacks ⁵	12–39	7.5	6.3
	NHANES: Mexican Americans ⁵	12–39	4.7	1.7
	Add Health ⁶	18–26	4.7	3.7
	<i>Europe</i>			
	UK ⁷	18–44	1.5	2.2
The Netherlands ⁸	15–29	2.5	1.5	
	<i>China</i> ⁴	20–64	2.6	2.1
Syphilis ^a	<i>Sub-saharan Africa</i>			
	Cotonou, Benin ¹	15–49	1.2	1.8
	Yaoundé, Cameroon ¹	15–49	5.6	6.0
	Kisumu, Kenya ¹	15–49	3.9	3.1
	Ndola, Zambia ¹	15–49	14.0	11.3
	Rakai, Uganda ²	15–54	9.9	9.6
	Masaka, Uganda ²	15–54	11.3	11.3
Mwanza, Tanzania ²	15–54	8.9	7.3	

(Continued)

Table 10-1. (Continued)

STI	Population (Ref)	Age Group	Prevalence in Women (%)	Prevalence in Men (%)	
Trichomoniasis	Carletonville, South Africa (sexually active individuals) ³	14–24	4.5	1.8	
	<i>Sub-saharan Africa</i>				
	Cotonou, Benin ¹	15–49	3.2	–	
	Yaoundé, Cameroon ¹	15–49	17.5	–	
	Kisumu, Kenya ¹	15–49	29.3	–	
	Ndola, Zambia ¹	15–49	34.3	–	
	Rakai, Uganda ²	15–49	24.3	–	
Mwanza, Tanzania ²	15–49	25.6	–		

^aSerology positive for active syphilis.

Sources: Buvé A, Caraël M, Hayes RJ, et al. Multicentre study on factors determining differences in rate of spread of HIV in sub-Saharan Africa: summary and conclusions. *AIDS* 2001; (suppl 4): S127–S131; Orroth KK, Korenromp EL, White RG, et al. Comparison of STD prevalences in the Mwanza, Rakai, and Masaka trials populations: the role of selection bias and diagnostic errors. *Sex Transm Infect* 2003; 79: 98–105; Auvert B, Ballard R, Campbell C, et al. HIV infection among youth in a South African mining town is associated with herpes simplex virus-2 seropositivity and sexual behaviour. *AIDS* 2001; 15: 885–898; Parish WL, Laumann EO, Cohen MS, et al. Population-based study of chlamydial infection in China. A hidden epidemic. *JAMA* 2003; 289(10): 1265–1273; Mertz KJ, McQuillan GM, Levine WC, et al. A pilot study of the prevalence of chlamydial infection in a national household survey. *Sex Transm Dis* 1998; 25: 225–228; Miller WC, Ford CA, Morris M, et al. Prevalence of chlamydial and gonococcal infections among young adults in the United States. *JAMA* 2004; 291(18): 2229–2236; Fenton KA, Korovessis C, Johnson AM, et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital *Chlamydia trachomatis* infection. *Lancet* 2001; 358: 1851–1854; van Bergen J, Götz HM, Richardus JH, et al. Prevalence of urogenital *Chlamydia trachomatis* increases significantly with level of urbanization and suggests targeted screening approaches: results from the first national population based study in the Netherlands. *Sex Transm Infect* 2005; 81: 17–23.)

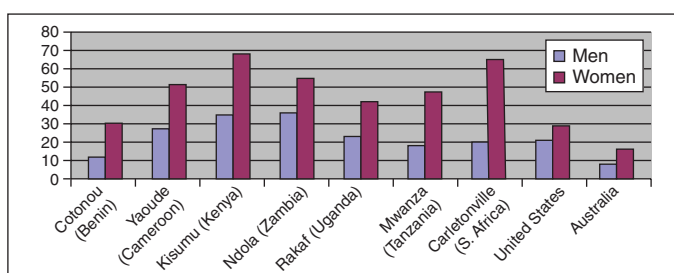


FIGURE 10-2. Prevalence of HSV-2 infection in men and in women as assessed in selected population based studies. (*Sources:* Weiss HA, Buvé A, Robinson NJ, et al. The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations. *AIDS* 2001; 15(suppl 4): S97–S108; Orroth KK, Korenromp EL, White RG, et al. Comparison of STD prevalences in the Mwanza, Rakai, and Masaka trials populations: the role of selection bias and diagnostic errors. *Sex Transm Infect* 2003;79:98–105; Auvert B, Ballard R, Campbell C, et al. HIV infection among youth in a South African mining town is associated with herpes simplex virus-2 seropositivity and sexual behaviour. *AIDS* 2001; 15: 885–898; McQuillan GM, Kruszon-Moran D, Kottiri BJ, et al. Racial and ethnic differences in the seroprevalence of 6 infectious diseases in the United States: Data from NHANES III, 1988–1994. *Am J Public Health* 2004; 94: 1952–1958; Mindel A, Taylor R, Taylor J, et al. *Prevalence of Infection with Herpes Simplex Virus Type 1 and 2 in Australia: A Nationwide Population-Based Survey.* Oral presentation, abstract n° MO-601, at the 16th Biennial meeting of the International Society of Sexually Transmitted Diseases Research, Amsterdam, 10–13 July, 2005.)

seeking behavior. It is generally accepted that the male-to-female transmission of STI pathogens is more efficient than female-to-male transmission. The large mucosal surface of the vagina and the cervix compared to the urethral meatus in men makes it biologically plausible that women are more susceptible than men to STIs that infect these sites. In addition, the mucosa of the genital tract of women has more prolonged exposure to infected semen thus increasing probability of infection.

Attempts have been made to assess the male-to-female and female-to-male transmission of gonorrhea and chlamydial infection by studying sexual partners of patients with confirmed gonococcal and/ or chlamydial infection.^{21–23} Data from some of those studies do suggest that male-to-female transmission of gonorrhea and chlamydial infection is more efficient than female-to-male transmission.^{21,22} However, deriving conclusions about transmission probabilities of STIs from cross-sectional data obtained from contacts of patients with STIs is fraught with problems, as it cannot be established with sufficient certainty who was the infecting partner.²⁴

The first data suggestive of a difference in male-to-female and female-to-male transmission probability of HIV-1, also came from studies of partners of HIV-1 infected index cases. These cross-sectional studies strongly suggested that male-to-female

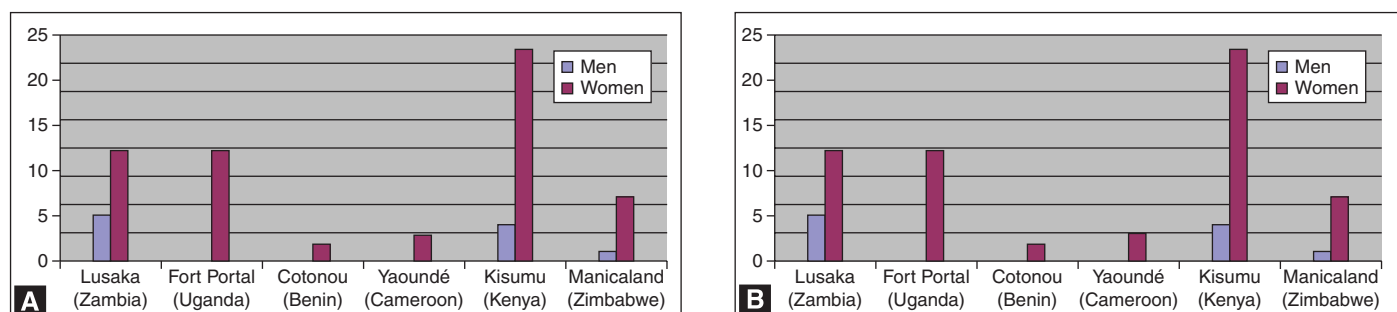


FIGURE 10-3. A. Prevalence of HIV infection in men and in women as assessed in selected population-based studies. **B.** Prevalence of HIV infection in men and in women 15–20 years as assessed in selected population based studies. (Sources: Fylkesnes K, Ndhlovu Z, Kasumba K, et al. Studying dynamics of the HIV epidemic: population-based data compared with sentinel surveillance in Zambia. *AIDS* 1998; 12: 1227–1234; Kilian AHD, Gregson S, Ndyabangi B, et al. Reductions in risk behaviour provide the most consistent explanation for declining HIV-1 prevalence in Uganda. *AIDS* 1999; 13:391–398; Buvé A, Caraël M, Hayes RJ, et al. Multicentre study on factors determining differences in rate of spread of HIV in sub-Saharan Africa: methods and prevalence of HIV infection. *AIDS* 2001; (suppl 4):S5–S14; Gregson S, Terceira N, Kakowa M, et al. Study of bias in antenatal clinic HIV-1 surveillance data in a high contraceptive prevalence population in sub-Saharan Africa. *AIDS* 2002; 16: 643–652.)

transmission is more efficient than female-to-male transmission.^{25–27} Follow-up studies of HIV discordant couples allowed for more direct estimates of the transmission probability of HIV-1. (Table 10-2) summarizes the major prospective studies on HIV-1 discordant couples that allowed comparison of the male-to-female and female-to-male transmission probabilities. Several studies found a higher male-to-female than female-to-male transmission but other studies could not confirm this. There are several possible explanations for these discrepancies. The studies did not all control for the same confounding variables. For instance, in the earlier studies it was not possible to control for viral load of the index patient. Also, many studies did not objectively assess circumcision status of the male partner, which may substantially alter female-to-male transmission rates.²⁸ Furthermore, not all studies could reliably establish infection within the partnership as opposed to infection by sexual relations outside the regular partnership. This is a problem especially for those studies of discordant couples that have been conducted in high HIV prevalence populations. In the study from the Democratic Republic of Congo, for instance, seronegative men had more extramarital relationships once the positive serostatus of their spouse became known,²⁹ suggesting that a number of men who seroconverted actually became infected through an extramarital relationship. Lastly, there is mounting evidence for some acquired immunity against HIV-1 infection in individuals who are repeatedly exposed to the virus.³⁰ At the time of identification, HIV-1 discordant couples already have a history of unprotected sexual intercourse, and discordant couples may have features that distinguish them from HIV-1 concordant couples. Ideally, one would like to recruit HIV-1 discordant couples before they initiate sexual relations but for obvious reason this is not possible.

Data on male-to-female and female-to-male transmission of HSV-2 are also available from prospective studies of HSV-2 discordant couples. In a randomized controlled trial of the

effect of suppressive therapy with valacyclovir, 7.4% of female partners of the HSV-2 infected men in the control group became infected with HSV-2, whereas only 1.2% of male partners of HSV-2 infected women seroconverted.³¹

■ RISK FACTORS FOR GENDER-SPECIFIC DIFFERENTIALS IN HIV PREVALENCE

The difference in prevalence of STIs between men and women is especially marked in young people under the age of 25 (Table 10-1). In industrialized countries also, the incidence of syphilis, gonorrhea, and chlamydial infection is considerably higher in young women aged 15–19 years than in young men.³² The female-to-male ratio for reported syphilis cases ranged between 0.96 and 3.00; for gonorrhea the ratio was between 0.96 and 3.09 and for chlamydial infection between 3.9 and 69.7. However, the latter high ratios for reported cases of chlamydial infection can, in part, be explained by screening programs that target young women. The discrepancies in prevalence of STIs between young men and young women cannot only be explained by more efficient transmission from men to women than from women to men. The high vulnerability to STIs of young women compared to young men is the result of an interplay between psychological, sociocultural, and biological factors.³³

Usually, women do not start sexual activity at an earlier age than men, so differences in age at first sexual intercourse cannot explain differences in STI prevalence.³⁴ Young women do not have more sex partners than young men, but women mostly have partners who are older than themselves, whereas men usually have partners who are younger. As such, young women are more likely to encounter a sex partner who is more experienced and may be infected with an STI. Older age of the sexual partner has indeed been found to increase the risk of HIV-1 infection in young women in Zimbabwe.³⁵ In addition, the power imbalance between men and women is

Table 10-2. Main Cohort Studies of HIV-1 Discordant Couples

Geographic Area (Ref)	Parameter Used to Assess Transmission	No. of Discordant Couples	Male-to-Female Transmission	Female-to-Male Transmission
Europe ¹	Cumulative rate of seroconversions in couples not using condoms	121	13.4%	11.4%
Haiti ²	Seroconversions per 100 person years	177	4.8	7.6
DRC ³	Seroconversions per 100 person years	178	3.7	6.8
Tanzania ⁴	Seroconversions per 100 person years	43	10	5
Zambia ⁵	Seroconversions per 100 person years	1022	8.9	8.2
Linked infections only			7.8	6.2
Uganda ⁶	Seroconversions per 100 person years	121	10.1	5.5
Uganda ⁷	Per sex act transmission probability	174	0.0009	0.0013

Sources: de Vicenzi et al. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. *N Engl J Med* 1994; 331: 341–346; Deschamps M-M, Pape JW, Hafner A, et al. Heterosexual transmission of HIV in Haiti. *Ann Intern Med* 1996; 125: 324–330; Ryder RW, Kamenga C, Jingu M, et al. Pregnancy and HIV-1 incidence in 178 married couples with discordant HIV-1 serostatus: additional experience at an HIV-1 counselling centre in the Democratic Republic of the Congo. *Trop Med Int Health* 2000; 5: 482–487; Hugonnet S, Mosha F, Todd J, et al. Incidence of HIV infection in stable sexual partnerships: A retrospective cohort study of 1802 couples in Mwanza Region, Tanzania. *J Acquir Immune Defic Syndr* 2002;30: 73–80; Fideli US, Allen SA, Musonda R, et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. *AIDS Res Hum Retroviruses* 2001; 17: 901–910; Carpenter L, Kamali A, Ruberantwari A, et al. Rates of HIV-1 transmission within marriage in rural Uganda in relation to the HIV sero-status of the partners. *AIDS* 1999; 13: 1083–1089; Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1 discordant couples in Rakai, Uganda. *Lancet* 2001; 357: 1149–1153.

more marked in relationships between young women and older men. Young women have low social status and may be economically dependent on men. As a result, they find themselves in a weaker position to negotiate safe sex or to refuse sexual intercourse. They may not even have the knowledge and skills to avoid unwanted pregnancies and STIs if prevailing norms about virginity and “proper” sexual behavior of women limit women’s access to information.³⁶

Biological factors that may explain the high vulnerability of young women to STIs include trauma from defloration, cervical ectopy, and other features of the immature female genital tract. Defloration and the associated trauma have been suggested as a risk factor for heterosexual transmission of HIV.³⁷ Cervical ectopy, a zone of columnar epithelium on the ectocervix, is a feature of the immature cervix of young adolescents that is replaced by squamous epithelium in adult women. The columnar epithelium is thin, vascularized, and contains target cells for several STIs, including gonorrhea and chlamydial infection. Therefore, ectopy may increase adolescents’

vulnerability to STIs. Ectopy, however, disappears with sexual activity and other irritation of the cervix. As such, any inverse association that is found between ectopy and STIs in adolescent girls may be confounded by sexual behavior.³⁸ The cervical mucus produced during adolescence is more easily penetrable to microorganisms and sperm than the mucus produced by more mature women. Adolescent girls are also immunologically naïve and it is believed that this is an explanation for the higher rates of chlamydial infection found in young women compared to older, more sexually experienced women.³⁹ Lastly, infection with one or more STIs that go unnoticed may increase susceptibility to another STI, in particular HIV infection. There is, for instance, mounting evidence that HSV-2 infection is an important factor that may explain the high vulnerability to HIV infection of young women.³⁴ HSV-2 infection has been found to be associated with increased risk of HIV acquisition, and in studies from sub-Saharan Africa prevalence rates of HSV-2 infection in young women aged 15–19 years ranged between 9% and 39%.^{40–42}

■ CHANGES IN STI SUSCEPTIBILITY OVER THE LIFECYCLE

In women, variations in susceptibility to STIs and their complications have been quite well studied in relation to physiological, hormonal, and immunological changes, but less is known about changes in the male genital tract and how they affect risk of STIs. Sexual intercourse during menses has been associated with higher self-reported history of an STI.⁴³ The risk of upper genital tract infections associated with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and/or bacterial vaginosis has been associated with the woman being in the first week of her menstrual cycle.⁴⁴ This is in keeping with the finding that sexual intercourse during menses has been associated with PID.⁴⁵ Sexual intercourse during menses, however, does not seem to increase the risk of acquisition of HIV in women, but to increase the risk for the male partner, because of a higher viral load in genital secretions.^{26,46,47} Pregnancy appears to be protective against most common STIs. However, gonorrhea and chlamydial infection that remain undetected during pregnancy increase the risk of endometritis after childbirth. Recent evidence suggests that risk of HIV infection may be increased during pregnancy.⁴⁸ Also, the period immediately postpartum seems to be a period very vulnerable for women to acquire HIV infection, though it is not clear whether the high incidence is due to increased vulnerability of the vagina and cervix immediately after birth, or due to the fact that many male partners have sex with other women during pregnancy, and with recently acquired HIV, are highly infectious.^{49,50}

The effects of contraception on risk of STIs have been extensively studied. Cervical ectopy associated with hormonal contraceptive use has been put forward as a plausible explanation for an increased susceptibility to STIs. Studies on the effects of oral contraceptive use on acquisition of STIs revealed conflicting results.⁵¹ But the evidence for an association between the use of depo-medroxyprogesterone acetate and increased susceptibility to cervical infections, including chlamydial infection and gonorrhea, and HIV infection appeared to be more consistent.^{52–55} A large scale multicenter prospective study, however, could not confirm an increase in risk of chlamydial infection, gonorrhea, and HIV infection associated with hormonal contraception in the overall population, though use of hormonal contraception by HSV-2 negative women appeared to increase their risk of HIV acquisition.⁵⁶ Hormonal contraception has also been explored as a risk factor for cervical cancer. It appears that use of oral contraception does not increase the risk of infection with human papilloma virus, but that long-term use of oral contraceptives is associated with an increased risk of cervical carcinoma in women who are HPV DNA positive.⁵⁷ The possibility that contraception increases the risk of acquiring STIs, especially HIV infection, was a cause for concern for several years, as it

could have posed a difficult dilemma between prevention of adverse reproductive health outcomes associated with pregnancies and increased transmission of HIV. Recent evidence suggests that oral contraceptives, as well as IUD, are safe. It is now accepted that the IUD can be inserted safely in women at low risk for an STI, but that women at high risk for an STI should be tested and/or receive a prophylactic antibiotic prior to insertion.

Worldwide, large numbers of older adults are affected by STIs, especially HIV infection. The role older women play in mitigating the impact of the HIV epidemic, as caregivers of patients and/or as guardians of orphaned children, is well documented. But older people also appear to be directly affected by STIs. In the United States, the numbers of AIDS cases in people over age 50 years have quintupled between 1990 and 2001.⁵⁸ Part of this increase is due to the longer life expectancy of people living with HIV as a result of highly active antiretroviral treatment. But there is also some evidence to suggest that postmenopausal women are at increased risk of acquiring HIV infection and HTLV-1 infection through sexual intercourse.^{59–61} It has been suggested that this may be due to a thinning of the vaginal epithelium in postmenopausal women.⁶⁰ In general, however, we know little about the risk of STIs and their complications in older people. Sexual activity decreases with age and unsafe sexual behavior is not expected of older people. Nevertheless, a number of contextual factors have been identified that may increase older women's vulnerability to STIs.⁶² Longer life expectancy, widowhood, and divorce may push older women to seek out new sexual partnerships. Postmenopausal women do not have to worry anymore about unwanted pregnancy and they may not think of using a barrier method to protect against STIs. In addition, older women seem less assertive in negotiating safe sex than younger women, and old people in general are less knowledgeable about protective behavior and are less aware about the risks they run. Finally, care providers may be less likely to ask about sexual activity or provide risk reduction counseling to older patients.

GENDER DIFFERENCES IN NATURAL HISTORY AND COMPLICATIONS OF STIs

■ COMPLICATIONS OF CURABLE STIs

Both men and women are at risk of serious, even life threatening, complications of STIs although the frequency and severity of complications is generally greater in women than in men. Complications of curable STIs, i.e., STIs caused by bacteria or protozoa, can be avoided if infected persons promptly seek care and are managed appropriately. However, a prerequisite to seeking care is that infected persons are aware that they are infected and that they seek treatment.⁶³ A high

proportion of men and of women infected with *N. gonorrhoeae*, *C. trachomatis*, or *T. vaginalis*, however, never experience symptoms. Women are asymptomatic more often than men. It has been estimated that 55% of episodes of gonorrhea in men and 86% of episodes in women remain asymptomatic; 89% of men with chlamydial infection remain asymptomatic and 94% of women.⁶⁴ For chlamydial infection, it has been well documented that serious complications, including infertility due to tubal occlusion, can occur in the absence of a history of symptoms of pelvic inflammatory disease.⁶⁵

Complications of gonorrhea and of chlamydial infection in men include epididymitis and urethra stricture. Epididymitis can lead to infertility in the extremely rare instances when it is bilateral. Urethra stricture as a complication of gonococcal urethritis was not uncommon in the pre-antibiotic era, but is considered a very rare complication nowadays, at least in industrialized countries.⁶⁶ However, in many parts of the world efficacious treatment of gonorrhea may not be readily accessible and in such contexts severe, incapacitating complications of gonorrhea in men may not be all that uncommon.^{67–69}

There is, however, the general consensus that women carry the heaviest burden of complications from curable STIs. The most dramatic complication of gonococcal and chlamydial infection in women is ectopic pregnancy. Not all ectopic pregnancies are due to gonorrhea or chlamydial infection but the most important risk factor is PID associated with STI. Ectopic pregnancy carries a high case fatality rate. In the United States and the UK, the case fatality rate has been estimated at 0.03–0.04%.^{70,71} Hospital-based studies from Africa reported much higher case fatality rates, in the range of 1–3%.⁷² In the United States, ruptured ectopic pregnancy is the leading cause of maternal mortality in the first trimester of pregnancy and accounts for 10–15% of all maternal deaths.⁷⁰ In developing countries, the contribution of ectopic pregnancy to overall maternal mortality is smaller.⁷² It was, for instance, responsible for about 1% of maternal deaths in Jamaica in 1993–1995, but the maternal mortality in these countries is much higher than in industrialized countries.⁷³ As a result, ectopic pregnancy is a nonnegligible cause of mortality among women of reproductive age in developing countries.

The most common, serious complications of bacterial STIs in women are impaired fertility and adverse pregnancy outcomes. In the cohort study of Lund, Sweden, 8% of women who had a single episode of PID subsequently developed tubal infertility. Among women with two and three episodes the prevalence of tubal infertility was between 19.5% and 40%, respectively.⁷⁴ A study conducted by WHO among infertile couples in 33 medical centers in different continents, found that the proportion of women with bilateral tubal occlusion ranged between 11% in industrialized countries and 49% in Africa.⁷⁵ Psychiatric morbidity associated with

fertility problems appears to be more frequent in women than in men, and low self-esteem, guilt, and blame are common.^{76,77} In societies where fertility is the principal reason for couple formation, infertility constitutes a major social handicap for men as well as for women and may lead to social isolation for the latter. However, when a couple is infertile, it is usually the woman who is blamed, while male factors are rarely considered. A study from India found that the blame for infertility lies entirely with the female partner.⁷⁸ In some societies, infertile women are accused of having had multiple partners and induced abortions.⁷⁹ Infertility is associated with marital instability and constitutes a major cause of early dissolution of the marriage.⁸⁰ Women lose the support of their family and may even be subjected to physical and psychological violence.^{81–83} Infertility may push men and women into sexual relationships outside marriage, hoping for conception and offspring. They may thereby increase their risk of acquiring an STI. Several studies have documented a higher HIV prevalence in women who are infertile compared to women who are fertile, but it cannot always be established with certainty whether the infertility preceded the HIV infection or the other way round.⁸⁴

■ HUMAN PAPILLOMAVIRUS INFECTION

Anogenital human papilloma virus (HPV) infection is one of the most common STIs. In the United States, it has been estimated that 4.6 million young men and women, aged 15–24 years, became newly infected with HPV in 2000.⁸⁵

The epidemiology and natural history of HPV infection have been well studied in women, but we lack data on the natural history of HPV infection in men. Only a few studies have compared the prevalence and incidence of HPV infection in men and women of the same age and population subgroup. These studies suggest that the prevalence and incidence of HPV infection in men and women are similar, but there is some evidence to suggest that persistence of HPV infection is more common in women than in men.⁸⁶ It is well established that morbidity and mortality related to HPV infection are more frequent in women than in men. Persistent infection with oncogenic types of HPV is found in nearly all cases of cervical cancer, the second most common malignancy in women worldwide. In 2002, there were an estimated 493,000 new cases of cervical cancer and 274,000 deaths.⁸⁷ The incidence ranged between 5.8 per 100,000 in Western Asia and 42.7 per 100,000 in Eastern Africa. In industrialized countries, the incidence of cervical cancer used to be in the range of the current incidence in developing countries, but since the introduction of screening programs in the 1960s and 1970s, the incidence has decreased to levels below 15 per 100,000.⁸⁷ Anal cancer and penile cancer are relatively rare, especially compared to cervical cancer. However, the incidence of anal cancer has been increasing in the United

States since the early 1970s.⁸⁸ The increase is more marked in men than in women and is attributed to the HIV epidemic and the increased incidence of anal cancer among men who have sex with men.

In both men and women there is interaction between HIV infection and HPV infection. Prevalence of HPV infection is higher in HIV infected persons than in HIV uninfected men and women. This is partly explained by the fact that both viruses are sexually transmitted, but HPV infection also persists longer in HIV infected individuals, thereby increasing their risk of developing anogenital cancers.^{86,89–94}

■ HIV INFECTION IN MEN AND WOMEN

In industrialized countries, the HIV epidemic initially disproportionately affected men, including homosexual men and intravenous drug users. As a consequence, the first studies on the natural history of HIV infection were in men. When drugs for HIV infection became available, the first trials were also conducted mainly in men, not only because in industrialized countries more men were affected than women but also because there were legitimate concerns about testing novel drugs in women who could become pregnant. Since the early 1990s, studies have been published that addressed sex differences in progression of HIV infection in industrialized countries.⁹⁵ Women appear to have lower viral load levels than men even after adjusting for CD4 count and time since seroconversion,^{96,97} but it is still not clear whether these sex differences persist throughout infection.⁹⁵ Also CD4 counts are higher in women than in men.⁹⁵ In the era before highly active antiretroviral treatment (HAART), given equal access to care, progression to AIDS and death was slightly slower in women than in men. This was found in industrialized countries and in one general population cohort in Uganda.^{95,98} With HAART there does not seem to be any difference between men and women in response to treatment and outcome, after adjusting for transmission route, initial viral load and CD4 count, and age.⁹⁹

There is no evidence that pregnancy alters the course of HIV infection substantially,^{100–102} but the majority of studies have been conducted in industrialized countries and it is not certain whether the results of those studies can be extrapolated to developing countries.⁹⁵ HIV infection in pregnant women, however, increases the risk of obstetric complications and pregnancy related mortality.^{103–106} Whether HIV epidemics increase maternal mortality at a population level, thereby obliterating gains in maternal health achieved by safe motherhood programs in developing countries, is still unclear. Some studies have found an increase in maternal mortality, whereas other studies did not find evidence for an increase.^{107,108} A possible explanation for discrepancies in findings is that increases in pregnancy-related mortality associated with HIV infection may be offset by lower fertility of HIV infected women, especially in the later stages of disease.¹⁰⁹

In industrialized countries, the proportion of HIV infected women who become pregnant and keep the pregnancy has increased in the 1990s, in part because of improvements in care and access to antiretroviral treatment.^{110–113} In many developing countries, women have less control over their lives and are under pressure from relatives and their environment to have children, even if access to prevention of mother-to-child transmission (MTCT) of HIV is not assured.¹¹⁴ However, women who have access to programs of prevention of MTCT often are not able to make full use of the opportunities offered to them to prevent their newborn baby from becoming HIV infected. In many programs, uptake of voluntary counseling and testing (VCT) at antenatal clinic is low because of the stigma attached to HIV infection and the inability or reluctance of women to disclose their HIV status to their partner and relatives.^{115,116} For the same reason, women cannot use bottle feeding if the norm is breastfeeding. In such contexts, the probability is high that the woman bears a child who is HIV infected or becomes HIV infected through breastfeeding. This is not only a cause of grief but may also be associated with feelings of guilt and being inadequate as a wife and mother.¹¹⁷

GENDER DIFFERENCES IN CARE AND PREVENTION OF STIs

Just as prompt diagnosis and treatment of curable STIs can interrupt transmission and prevent serious complications, early diagnosis and management of viral STIs, including genital herpes and HIV infection, may interrupt transmission and result in better health outcomes. There are more opportunities for women to be screened for STIs than for men, including family planning clinics and antenatal clinics. In the latter setting, however, the main rationale for STI screening used to be the prevention of adverse pregnancy outcome and infection in the newborn infant, while the health of the woman was a secondary consideration. Because of the high costs of treatment of PID and its sequelae, extensive screening programs for chlamydial infection have been set up in several industrialized countries. In these programs, far more women are screened than men with resulting declines in chlamydial infection and even ectopic pregnancy rates.^{118,119} In recent years, however, it was noted that the decline did not continue and this was attributed, at least in part, to lack of screening among men.^{118,120}

Stigma and shame associated with STIs are powerful barriers for promptly seeking effective treatment for STIs, for both men and women.^{121–123} However, women appear to face more obstacles than men. In general, women in developing countries have more limited access to proper information and health services than men.^{124,125} They may not be in a position to decide themselves to seek care but depend on decisions made by the partner and/ or relatives. Female seclusion can

prevent women from utilizing services outside the home unless she is accompanied by a male relative.¹²⁶ Furthermore, women may not have the financial means to seek treatment or may be too busy caring for children to attend a health service. In societies where childbearing is highly valued, women may place the health of their children above their own health needs and this can lead to an unequal utilization of health services within the family.¹²⁶ Women may also not recognize STI symptoms as serious enough to seek care and may not have sufficient knowledge about their reproductive functions and STI symptoms.^{127–129} If societal norms regarding extramarital sexual relations are more restrictive for women than for men, the psychological and social impact of a diagnosis of an STI is felt more strongly by women than by men.¹³⁰ Women may feel too embarrassed to seek care for STI-related symptoms if staff attitudes are (perceived to be) discriminatory or moralizing.^{122,131} This is a fortiori the case for young, unmarried women.¹²¹ Several studies from developing countries, conducted in the community and in health services, suggest that women less often seek treatment for STIs than men or have symptoms for a longer period before coming for treatment.^{127,132–134}

The notification and management of sexual partners of patients diagnosed with an STI, is an essential component of STI control programs.¹³⁵ The aim of partner services, including notification of partners, treatment, and counseling, is to prevent reinfection of the index patient and to interrupt transmission to other men or women. Whatever the strategy that is employed to contact sexual partners, provider initiated or patient initiated, partner notification is often a painful process. Patients find it difficult to reveal the identity of their sexual partners and/or to inform their sexual partners, and partner notification may even be a reason for not seeking care in the public health sector.¹²¹ In societies where women have low social status and are economically dependent on men and where communication about sexual matters between partners is poor, women, in particular, face huge difficulties informing their sexual partner(s).^{130,136,137} Apart from embarrassment there is also the fear of rejection or, even worse, violence. In settings where the management of STIs relies on syndromic management, the potential negative consequences of partner notification for women have to be considered against the risk of reinfection because syndromic management of discharge syndromes has a very low specificity for the detection of STIs in women.

The establishment of the causal association between HPV infection and cervical cancer has given impetus to the search for a prophylactic vaccine for the prevention of HPV infection. Two vaccines have been tested in phase III trials in young women and have been found to be effective in preventing incident and persistent HPV infection.^{138–141} However, there are still a number of questions about the best way to scale up use of the vaccines in programs and the resulting

impact on the incidence of anogenital cancers.¹⁴² There are no data on the efficacy of the vaccines in (young) men, but phase III trials are underway. If the results of these trials are positive, the question remains whether vaccination of men will be cost-effective.^{142,143} The added benefits of vaccinating young men in the prevention of cervical cancer may be limited, but vaccination would be an important strategy in the prevention of anal cancer, especially in men who have sex with men.

HIV infection used to be a deadly infection and is now a chronic disease, requiring lifelong treatment with antiretroviral drugs. However, the stigma and fear associated with HIV infection continue to be enormous obstacles for care and prevention, especially for women.^{144,145} Stigma surrounding HIV infection affects women more than men. In many societies women have low social status and are blamed for the spread of HIV infection, posing enormous challenges for partner notification by HIV infected women. Fear of being abandoned, which may also mean loss of financial support, and of being subjected to domestic violence, prevents many women from informing their partner, even if this partner is the only person who could have transmitted the infection to them.^{116,146,147} Without the support of other persons in the household, compliance with antiretroviral treatment becomes nearly impossible. In many prevention of mother-to-child transmission (PMTCT) programs uptake of HIV-test results and prophylactic treatment with antiretroviral drugs remains low, despite the known benefits of testing and treatment during pregnancy.^{148,149} Fear of stigma also prevents mothers in developing countries from using formula feeding instead of breast feeding, even if they are aware that they expose their baby to HIV infection via breast milk. Nevertheless six out of 10 HIV infected patients in sub-Saharan Africa who were on HAART in 2004–2005, were women.^{150,151} The high proportion of women among patients on HAART reflects the epidemiological reality of HIV infection in Africa where more women are infected than men. But it could also be explained by the fact that women have more opportunities for HIV screening than men, for instance at antenatal clinics.

CONCLUSIONS AND IMPLICATIONS FOR STI CONTROL: IT TAKES TWO TO TANGO

Unsafe sex ranks fifth among global risk factors for mortality and is the second global risk factor for burden of disease. Mortality and disease burden attributable to this risk factor are higher in women than in men.¹⁵² Part of the excess mortality and disease burden attributable to STIs in women is due to biological factors, but the power imbalance between men and women also plays a critical role in increasing women's vulnerability to STIs and their complications. Several interventions that aim to empower women, especially young women,

have been shown to have health benefits for women.¹⁵³ These include improved access to education for girls and the creation of economic opportunities for women.

STI control is, par excellence, an issue that affects both men and women. In recent years, the idea that men should be more involved in reproductive health programs has gained ground. For instance, some successes have been reported with interventions that appeal to men's sense of responsibility for the health of their unborn child.¹⁵⁴ It is clear that men and women have a responsibility in preserving each other's reproductive health. As the experience with screening programs for chlamydial infection has demonstrated, interventions to control STIs have to target both sexes. This does not mean, however, that both sexes have to be approached in an identical manner. Intervention programs have to be sensitive to the context of gender relations and the type of risks men and women encounter.

Eventually, however, norms in society have to change. Redressing the power imbalance between men and women will also benefit men. Norms about masculinity may prevent men from seeking information because they are supposed "to know it all," whereas their female sex partners cannot ask questions because they are "not supposed to know." The same norms may put men under pressure to have multiple sex partners and lead to discrimination against gay men. Yet norms concerning female and male roles are part of the collective consciousness of a society dealing with the meaning of masculinity and femininity and the exercise of power by men.¹⁵⁵ Deeply rooted gender norms may also be a factor contributing to sexual coercion in childhood and adolescence.¹⁵⁶ Reproductive health programs may, therefore, lead more significantly to changes in discourse than in behavior. Gender equity and equality, including in sexual education and reproductive health decisions, should be mainstreamed throughout the educational curriculum, starting from primary school. Last but not the least, advocacy among public opinion leaders should be pursued as a complement to individual education.

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Stuart M. Berman and Jonathan M. Ellen

Making the transition from childhood to being healthy sexual adults is one of the major tasks and challenges faced by young people. A successful transition implies forming intimate relationships while avoiding the acquisition of sexually transmitted diseases (STDs). Yet it is apparent from the current data that around the world, for a combination of reasons involving biology, psychology, ambient culture, and changing mores, adolescents who have had sexual intercourse have the highest rates of STDs—including HIV in some locales—of any age group. As stated by one researcher, “the challenge lies in getting teenagers to view their relationships in a more realistic light without destroying the positive ways in which these (relationships) may also add to their lives.”¹ This chapter describes the magnitude of the STD and HIV problem among adolescents, the factors that contribute to their risk of infection, considerations such as sexual network structure that underlie that risk,² and the STD/HIV prevention activities which reflect this understanding and are effective among these young people.

EPIDEMIOLOGY OF STDs AND HIV AMONG ADOLESCENTS

Most population-based STD rates underestimate risk for sexually active adolescents because the rate is inappropriately expressed as cases of disease divided by the number of individuals in this age group. Yet only those who have had intercourse are truly at risk for STDs. *For rates to reflect risk among those who are sexually experienced, appropriate denominators should include only the number of individuals in the demographic group who have had sexual intercourse.* In 2002, whereas 87% of 20–24-year-old women had had sexual intercourse, this was true of only 53% of women 15–19-years old.^{3,4} This underestimation of rates is greatest among the youngest adolescents, since only a small proportion of them have had sex. In general, when rates are corrected for those who are sexually active, the youngest adolescents have the highest STD rates of any age group.⁵

■ CHLAMYDIA

Chlamydia trachomatis infection is the STD most strongly associated with adolescents. Early studies in family planning clinics demonstrated that prevalence of cervical chlamydia is greatest among sexually active individuals under 20 years of age, being approximately twice that found among older individuals.^{6–8} Such findings are consistent with more recent data and with results from population-based assessments. It is also clear that prevalence of chlamydia among males is also substantial, if somewhat less than prevalence among women.

Population-based prevalence data are available from several sources. As part of the 1999–2002 National Health and Nutrition Examination Survey (NHANES), urine specimens among women 15–39 years of age were tested for chlamydia and almost 5% of those 14–19 years of age were infected; prevalence was under 2% for older women. African American women (with prevalence exceeding 10% among those 14–19 years of age) and women with 12 years of education or less were also at greater risk of infection.⁹ Comparable results were obtained in follow-up of the National Longitudinal Study of Adolescent Health (AddHealth) cohort at 18–26 years of age; overall prevalence among females was 4.7% and rates were substantially higher among blacks than whites, but in this survey prevalence varied less by age.¹⁰

Chlamydia prevalence data among males are available from multiple settings, including clinical facility based,^{11–13} detention-based,^{13,14} and community-based venues,¹⁵ as well as from schools¹⁶ and population-based surveys.^{9,10,17} As would be expected, prevalence among young males is lower in suburban clinical settings (0.9%),¹¹ and higher in general clinical settings (4%),¹² and among detainees (3.2–8.0%).¹⁴ Data from the 1999–2002 NHANES indicated that just over 2% of males 14–19 years of age and over 3% of those 20–29 years had chlamydia; prevalence was approximately three times greater among African American males than among whites and low among males 30–39 years of age (prevalence under 0.7%).⁹ Data from the AddHealth cohort and the National Survey of Adolescent Males were consistent,

finding a somewhat lower prevalence among adolescent males than that among young adult males¹⁷ and documenting substantial racial disparity.¹⁰ However, these data were not adjusted for sexual activity.

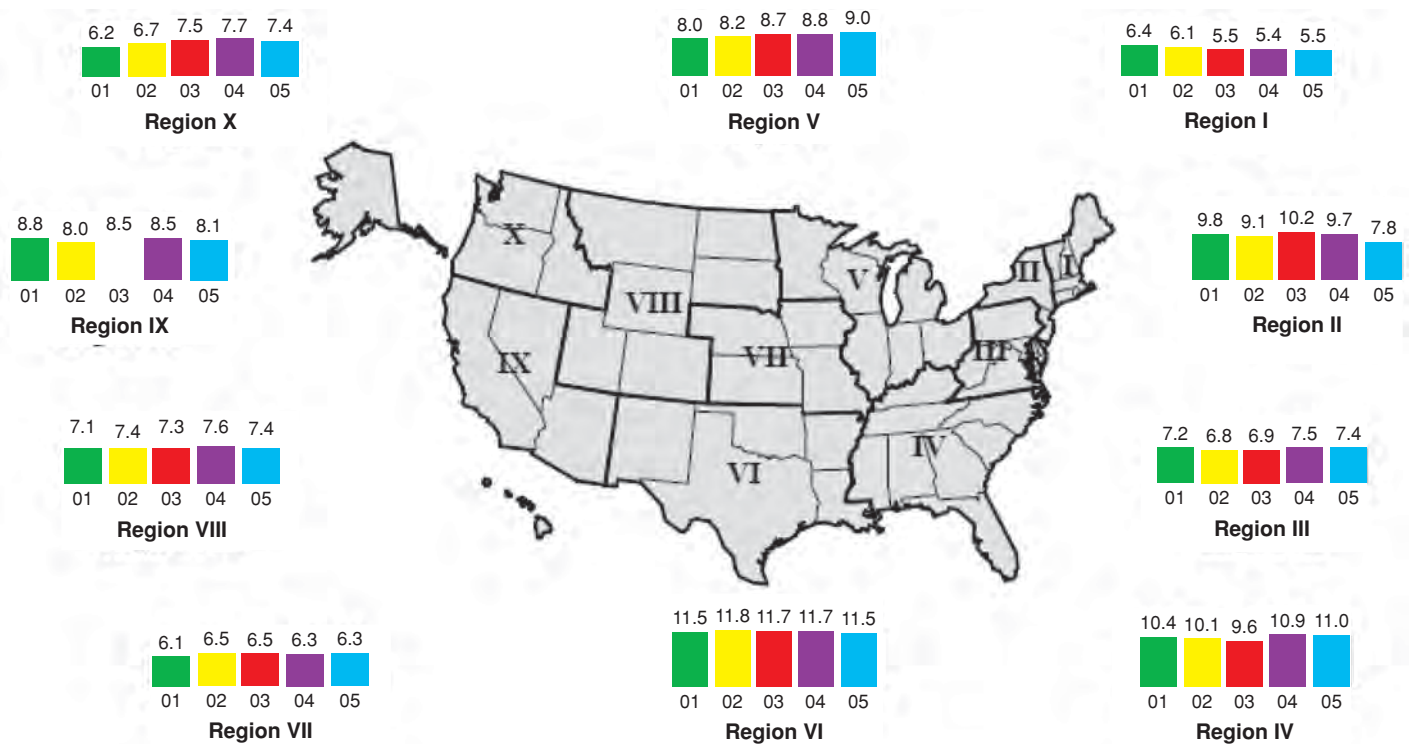
In the United States, CDC first implemented chlamydia screening among family planning attendees in 1988 in the Northwest, and in all 50 states by 1995. Although prevalence among 15–19-year-old women in family planning clinics in the Northwest (Alaska, Idaho, Oregon, and Washington) decreased from 17.8% in 1988 to 5.7% in 1997, prevalence increased to 8.5% by 2005¹⁸ (Fig. 11-1). The increase was not associated with changes in clients' risk profile, or demographics, or explained by use of tests with greater sensitivity (i.e., NAATs).¹⁹ Although elsewhere in the United States, prevalence among 15–19-year-olds in family clinics was essentially unchanged from 2000–2005, increases in chlamydia have been noted in several other countries, such as Finland, Norway, Denmark, Sweden, and Canada.^{20–22} In some countries, increased risk behavior has been noted (i.e., Finland), while in other areas low screening coverage is thought responsible (e.g., Sweden),²³ or increases in chlamydia have been accompanied increases in other bacterial STDs.²² Others believe that the answer is more complicated, and that in areas such as British Columbia, with widespread chlamydia screening, duration of infection was sufficiently shortened to reduce population levels of immunity, allowing

an increase in incidence.²⁴ This is a critical question, requiring ongoing research. Further complicating the issue is the fact that in the United States, from 1998 to 2004, chlamydia prevalence decreased from 11.7% to 10.3% among 16–24-year-old female enrollees in a national training program for disadvantaged and out-of-school youth (formerly the Job Corps).²⁵ However, the prevalence in this high-risk group remains substantial (see Fig. 11-2).

Chlamydia prevalence among adolescents in other countries has been found to be comparable to that in the United States.^{26–32}

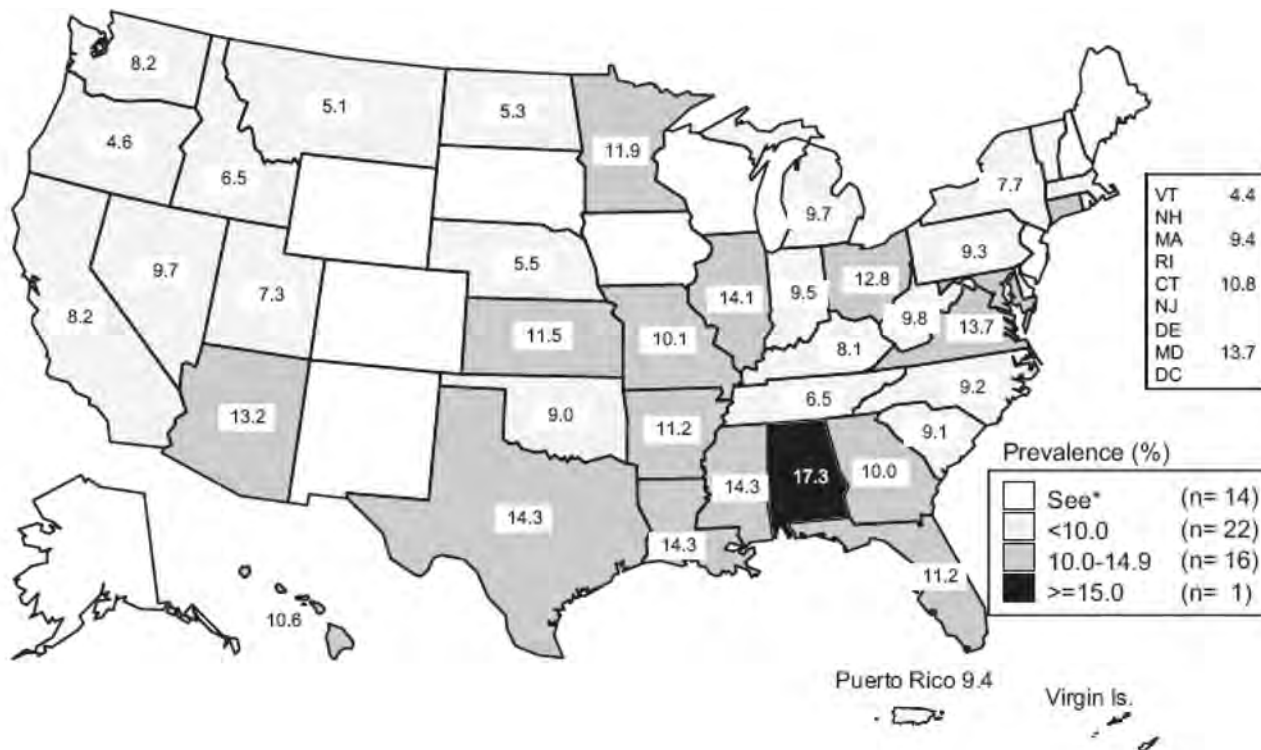
Cumulative risk of chlamydial infection is substantial among adolescents. Among female adolescents tested at least twice in family planning clinics in Washington, Oregon, Idaho, and Alaska from 1988 through 1991, 22% were found to be infected on at least one visit.³³ Similar findings were produced by a population-based study in Umea, Sweden, which evaluated cumulative risk of chlamydia by serologic tests.³⁴ The prevalence of *C. trachomatis*, identified by culture, among 19-year-old women was 5.5% (3/55).³⁵ However, 29.1% of these women and 18.0% of 21-year-old women (*n* = 139) showed serologic evidence of previous chlamydial infection.

Recurrent infection may be particularly worrisome, since such infections may be more likely to be associated with significant damage to the fallopian tubes than is primary



Note: Trends adjusted for changes in laboratory test method and associated increases in test sensitivity.

FIGURE 11-1. Trends in chlamydia positivity among 15–24-year-old women tested in family planning clinics by HHS regions, 2001–2005.¹⁸ (Source: Regional Infertility Prevention Projects; Office of Population Affairs; Local and State STD Control Programs; Centers for Disease Control and Prevention.)



*Fewer than 100 women residing in these states/areas and entering the National Job Training Program were screened for chlamydia in 2004.

Note: The overall chlamydia prevalence among female students entering the National Job Training Program in 2004 was 10.3%.

FIGURE 11-2. Chlamydia prevalence among 16–24-year-old women entering the National Job Training Program by state of residence: United States, 2005.¹⁸

infection. The risk of recurrent infection is higher among adolescents compared with older women,^{36–38} with several studies finding that among women treated for chlamydia, at least 10% had infection identified again within 4–6 months after treatment.^{37–39} Recurrent or persistent infections have been associated with the continuing presence of an untreated sex partner^{40,41} and with treatment failure.³⁷ Clearly, more information is needed concerning factors responsible for chlamydial persistence after treatment among young women.

■ GONORRHEA

Gonorrhea rates in the United States fell by almost 75%, from a peak of 467 cases per 100,000 in 1975 to 120 cases per 100,000 in 1997; subsequently, decreases have been smaller and less consistent. Rates among adolescents have also fallen, although not entirely in sync with overall rates. For example, from 1981 to 1991, although the overall gonorrhea rate among males declined by 46%, the rate among 15–19-year-old males did not decline at all. From 1985 to 1995, while the overall rate among females decreased by 53%, rates among 15–19-year-old females decreased by 39%. In contrast, from 1995 to 2005, overall rates of gonorrhea decreased less than 23%, while rates among 15–19-year-olds declined over 34%.¹⁸ Rates among females

15–19 years of age have been the highest of any age group since 1984.

In the United States, as of 2006, rates of reported gonorrhea among African American adolescents are over 17-fold higher than that among their white counterparts.¹⁸ Over the past 10 years, the disparity has decreased somewhat; in 1995 there was a 25-fold difference. These differences are comparable to results of a population-based survey among the cohort enrolled in the AddHealth, which was age 18–26 years at evaluation. Prevalence of gonorrhea among black males and females (approximately 2% for both men and women) was 36 and 14 times greater than that among white men and women, respectively. Reasons for such racial inequalities are beginning to be understood, and involve structural causes⁴² as well as sexual mixing patterns.⁴³

Gonorrhea screening among sexually active women is a major component of the national prevention program, and recent recommendations acknowledge that women under 25 years of age are at increased risk.⁴⁴ However, it is not clear that young age is a sufficient criterion for screening (as it is for chlamydia), since prevalence is so variable across some populations, and closely related to factors such as race⁹ and geography⁴⁵; indeed, the median state-specific prevalence of gonorrhea among 15–24-year females attending selected family planning clinics was 0.9%,¹⁸ while that among females admitted to juvenile detention centers was

almost 6%,¹⁴ highlighting the importance of screening in such venues.

Recently, gonorrhea rates have been increasing in several locales and countries (France, Denmark, England, Denver) typically related to increases among MSM,^{46–49} but have not appeared to involve adolescents to any extent. However, increases in Sweden⁵⁰ and Canada have involved young women,⁵¹ although the reasons for such increases are unclear.

Gonorrhea rates in much of the developing world are still very high, based upon prevalence in antenatal or family planning clinics, or village surveys.^{52,53} When age-specific data are reported, prevalence is usually highest among adolescents.^{54,55} Population-based prevalence data for gonorrhea from South Africa²⁶ suggest that approximately 3–4% of young females (15–24 years) and males (20–24 years) were infected; prevalence was lower among younger males (i.e., 15–19 years). Results from elsewhere in Africa (Mwanza, Tanzania, Masaka, and Rakai, Uganda) were comparable, although prevalence among males was somewhat lower than the rates cited above in the two Ugandan locales, as was prevalence among 15–19 females.⁵⁶

■ SYPHILIS

Adolescents are not a prime risk group for syphilis, and in the United States, with changes in the epidemiology of syphilis, the risk for adolescents has declined. Following decreases throughout the 1990s, syphilis rates have increased during 2000–2005¹⁸ primarily among older MSM,⁵⁷ often with high prevalence of HIV coinfection.^{58–60} However, rates of P&S syphilis among 15–19-year-olds in the United States declined throughout the 1990s and were stable during the early 2000s. As a result, the rate of P&S syphilis among 15–19-year-olds in 2005 (2.1 per 100,000) was about one-eighth the rate in 1993 (17.0 per 100,000). Of note, although among 15–19-year-olds the rate of syphilis is typically lower among males than females, in 2005, the M:F ratio for P&S rates was above 1 (i.e., 1.3); this is consistent with the national trend of increasing M:F rate ratios (in 2005, over 5:1), reflecting the burden of disease among MSM. The extent of the burden among adolescent MSM is unknown.¹⁸

Not surprisingly, even among high-risk populations, syphilis seropositivity among adolescents is less than that among older populations; median seropositivity among admittees to juvenile detention facilities (females, 0.7%; males, 0.5%) was less than that among admittees to adult corrections (females, 5.3%; males, 2.7%).¹⁸

Although syphilis is still quite prevalent in the developing world (2–16% among antenatal attendees),^{52,61} adolescents are at substantial, if somewhat lower, risk than older populations. Population-based surveys in Mwanza, Masaka, and Rakai have found that prevalence of syphilis among 15–19-year-old females can be over 5% in some places (Mwanza), and 2–4% in the other locales. As expected, prevalence among

older populations was consistently greater.⁵⁶ Elsewhere, adolescents have not been spared when syphilis has increased; as syphilis exploded in Russia between 1987 and 1998, with rates increasing over 60-fold during that time, rates among adolescents—though lower than that among older individuals—increased proportionately.⁶²

■ HUMAN PAPILLOMAVIRUS

More than 6 million new human papillomavirus infections (HPV) occur each year in the United States,⁶³ and prevalence is highest among adolescents and young adults.⁶⁴ Although there is variation in method of detection and which HPV types were looked for, a large number of clinical studies in a variety of venues^{65–67} documented that prevalence among young women was consistently greater than 20–25%, and that most have infection with one of the high-risk types.⁶⁸ The prevalence of HPV among males is harder to assess, since there is less agreement about the appropriate method of and site for specimen collection. Nevertheless, prevalence of HPV infection among heterosexual males has ranged from 16% to 45%⁶⁸ and is not so clearly associated with young age.^{69,70}

These findings are similar to results from analyses of population-based data, obtained from the AddHealth cohort (18–25 years), with HPV prevalence assessed on first catch urine. Overall, almost 27% of women were infected, over 70% of time involving high-risk HPV types. HPV prevalence was highest among those 18–21 years of age (approximately 30%), and then decreased with age.⁷¹

Risk for HPV acquisition is underestimated by determinations of point prevalence. In a longitudinal study of 15–19-year-old females, cumulative incidence of HPV infection over 5 years was 60%.⁷² In other studies, cumulative incidence was as high as 82%.⁷³

Although risk of HPV acquisition increases with number of partners,^{67,74,75} prevalence of infection is substantial even with limited sexual exposure. Numerous clinic-based studies,^{76,77} supported by population-based data, indicate that HPV prevalence typically exceeds 10% among young women with only one or two partners.⁷¹

In addition, infection appears to be acquired soon after sexual debut. Winer et al. followed college students soon after they became sexually active and found that 20% were infected within 6 months after first intercourse.⁷⁸

Although adolescents and young women are at highest risk for HPV, they appear to clear the infection promptly in the vast majority of instances, since 70% of new HPV infections are no longer detectable within 1 year, and up to 91% within 2 years.⁶⁸ Younger women (i.e., ≤25 years) are more likely to clear infection than women who are older.⁷⁹ Importantly, persistent cervical infection is a critical predictor of dysplastic changes.⁸⁰ Although changes consistent with cervical cancer may not develop for several decades, among young

women with incident HPV infection, dysplasia may appear quite soon; the 36-month cumulative incidence of CIN 2/3 was found to exceed 11%.⁷⁸

Low-grade squamous intraepithelial lesions (LSILs), associated with acute HPV infection, are the findings typically associated with and common among adolescents and young women.⁸¹ In their longitudinal study of college-age women, Winer et al. found that approximately 50% developed cervical LSILs within 3 years from the detection of an incident HPV infection.⁷⁸ Such lesions tend to resolve quickly and without need for intervention; Moscicki found, in 36 months follow-up, that 91% of LSILs regressed among an adolescent cohort,⁸² findings similar to those of Winer et al. who evaluated college-age women and found that 86% of such lesions cleared in a median of 5.5 months.⁷⁸ These findings suggest that incident LSILs among young women have a different natural history than prevalent LSILs among older women, which are more likely to be associated with persistent infection.⁷⁸ Of note, an evaluation of prevalent LSILs among adolescents found that 31% had progressed, and only 62% had regressed by 36 months, results similar to those among adult women.⁸³

The availability of effective HPV vaccines is expected to have substantial impact on genital warts, cervical cancer, and cancer precursors^{84,85} given vaccine effectiveness.^{86,87} In June 2006, the FDA licensed a quadrivalent HPV vaccine that protects against types 6/11/16/18 for use among females, ages 9–26 years. (There is another HPV vaccine expected to be licensed during 2008 that protects against types 16/18). In 2006, The Advisory Committee on Immunization Practices (ACIP) recommended that the quadrivalent vaccine be offered to 11–12-year-old females, with catch-up vaccination recommended for females 13–26 years who had not been previously vaccinated. The factors that influenced the recommendation included age distribution of sexual debut (HPV acquisition occurs soon thereafter and immunization should occur prior to exposure); evidence of a vigorous antibody response among preadolescents to vaccination; and age at which adolescents are scheduled to receive other vaccines.⁸⁸ Studies have demonstrated that parents and providers are quite accepting of the provision of an STD vaccine to preadolescents,^{89–92} although there has been controversy with regard to making HPV vaccination mandatory for young girls.⁹³ HPV vaccines may also have major impact on cervical cancer screening recommendations for adolescents in the United States; with HPV vaccination against HPV types 16/18, it is more cost-effective to begin screening at 25 years of age than during adolescence (i.e., by 21 years of age), which is when most agencies and organizations (i.e., United States Preventive Task Force, American Cancer Society, American College of Obstetricians-Gynecologists) currently recommend that screening begin.⁹⁴

■ HERPES SIMPLEX

Few individuals with herpes simplex virus type 2 (HSV-2) infection have recognized symptoms or signs.⁹⁵ Population-based serologic data are available from analyses of specimens obtained in 1976–1980, 1988–1994, and 1999–2002 from nationally representative samples of the U.S. population, in the NHANES. Consistent findings from these surveys are that cumulative risk for HSV-2 infection rises with age,⁹⁶ that seroprevalence is higher among females than males, and that prevalence is substantially greater among African Americans than whites.^{96–98} However, overall seroprevalence fluctuated across these surveys; seroprevalence was 16.0%, 20.8%, and 17.5% in 1976–80, 1988–94, and 1999–2002, respectively. Importantly, both the increases noted from the first to the second survey (i.e., 1976–80 to 1988–94) and the subsequent decreases from the second survey to the third (i.e., from 1988–94 to 1999–02) were concentrated in younger ages.^{97,98} Between these last two surveys, HSV-2 seroprevalence among 14–19-year-olds in the United States decreased from 5.8% to 1.7%, essentially returning to the level seen in the 1976–80 survey⁸ (Table 11-1). These decreases occurred among males and females and all race/ethnicity groups. The changes may reflect the delay in onset of sexual activity and other behavioral changes reported among adolescents in the last decade.⁹⁹

Although genital herpes is typically associated with HSV-2, there is evidence in several countries (i.e., Australia, Israel, Norway)^{100–102} that HSV-1 is responsible for an increasing proportion of genital herpes; one study among students at a U.S. college found that that the proportion of genital herpes that was HSV-1 increased from 31% in 1993 to 78% in 2001.¹⁰³ In general, this changing epidemiology affects primarily adolescents and young adults.^{103,104} There are several factors that may be contributing to this. For one, it is possible that a greater proportion of adolescents are susceptible to HSV-1 as they become sexually active; with increasing affluence, acquisition of HSV-1 in childhood decreases.¹⁰⁵ In addition, HSV-1 genital herpes has been associated with receptive oral sex,¹⁰⁶ and recent data indicate that over 50% of 15–19-year-olds have received oral sex (49.6% females; 51.5% males).⁴

However, the issue of genital herpes and adolescents may be most critical in the developing world—in particular those areas hardest hit by HIV/AIDS. The evidence that HSV-2 is an important risk factor for HIV acquisition and transmission is extensive.^{107–109} Indeed, HSV-2 seroprevalence has been identified as one of the critical factors that may determine HIV population prevalence.¹¹⁰ This can be seen by looking at HIV prevalence among women 20–24 years, and HSV-2 prevalence among those 15–19 years in four African cities.¹¹¹ Compare Cotonou, Benin (HSV 9%, HIV 3.8%), and Yaounde, Cameroon (HSV 14%, HIV 9.3%), with Ndola, Zambia (HSV 41.8%, HIV 23%), and Kisumu, Kenya (HSV 39%, HIV 38.3%).

Table 11-1. HSV-2 Seroprevalence by Age, NHANES II, NHANES III, NHANES 1999–2000, by Race⁹⁸

Non-Hispanic whites			
Age	NHANES II (%) 1976–1980	NHANES III (%) 1988–1994	NHANES (%) 1999–2000
All ages ^a	12	17	14
14–19	1	4	1
20–29	8	15	7
Non-Hispanic blacks			
Age	NHANES II (%) 1976–1980	NHANES III (%) 1988–1994	NHANES (%) 1999–2000
All ages ^a	39	43	42
14–19	7	11	5
20–29	30	33	37

^a14–49 years; 2000 US Census civilian noninstitutionalized population is standard.

Data from Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. *JAMA* 2006; 23; 296: 964–973.

■ PELVIC INFLAMMATORY DISEASE

Since pelvic inflammatory disease (PID) is usually caused by either gonorrhea or chlamydia, and since these infections are most prevalent among sexually active adolescent females, this group is also at substantial risk for PID. In 1980, the estimated risk of PID among sexually active 15-year-olds in Sweden was 12.5%, and among sexually active 16-year-olds it was 10%, with progressive decreases with increasing age.¹¹² The investigators calculated that the risk of developing salpingitis for those with chlamydial infection was approximately 70% greater among women between 15 and 19 than among women between 20 and 24 years old; among those with gonorrhea, the risk for 15–19-year-olds was about 20% less than that among the 20–24-year-olds.¹¹³

Although monitoring PID is a challenge,¹¹⁴ available data suggest U.S. rates of PID have been declining overall, and also among adolescents. In the United States, although hospitalization rates for acute PID decreased over the decade of the 1980s, decline was least among 15–19-year-olds.¹¹⁵ A recent analysis of data for 1985–2001 found overall hospitalization rates for acute PID declining 68% (1985–2001), but rates among adolescents decreasing somewhat less (53%) than rates among either 20–24- (77%), or 25–29-year-old (68%) women.¹¹⁶ nevertheless, when average annual rates of PID for 1995–2001 were analyzed, PID hospitalization rate was lower among women aged 15–19 years than among those 20–25 years, but greater than among women 25–29 years, findings which are comparable to those from England and Wales.¹¹⁴ In the United States, occurrence of outpatient PID

was lower among 15–19-year-old women than among women 20–24 or 25–29 years of age¹¹⁶—important to note since hospitalization accounts for less than 10% of diagnosed PID cases.^{116,117} However, if rates were based only among those adolescents who had ever had intercourse, the risk for hospitalization with PID among sexually active 15–19-year-olds would be the highest of any age group.

A study in Philadelphia found that adolescent females diagnosed with PID sought care an average of 7.8 days after the onset of symptoms compared with 5.6 days for adults.¹¹⁸ Such behavior is of particular importance given the finding that the risk of impaired fertility or ectopic pregnancy increases significantly with increasing delay between onset of symptoms and receipt of care.¹¹⁹ Nevertheless, recent data indicate that women less than 26 years of age are no more likely to suffer chronic pelvic pain after PID than older women; delay of care was not significantly associated with chronic pain.¹²⁰

■ HUMAN IMMUNODEFICIENCY VIRUS

HIV is a great problem for many of the world's adolescents. It has become clear that in several sub-Saharan countries with the highest rates of HIV, the risk of HIV acquisition among women increases dramatically in the adolescent and early adult years. In a recent population-based survey among young people in South Africa, HIV prevalence among 15–19-year-old females was 7.3%, but 2.5% for males of the same age; among those 20–24 years, 24.5% of women were infected, compared with 7.6% of males.¹²¹ Similar results have been noted elsewhere.¹²² Overall, 26% of individuals in Kisumu and 28% in Ndola were HIV-positive. In both

sites, HIV prevalence in women was six times that in men among sexually active 15–19-year-olds (with rates as high as 23% in Kisumu)¹¹¹ and three times that in men among 20–24-year-olds, but equal to that in men among 25–49-year-olds; young women were at similarly increased risk compared to males in Zimbabwe (age-adjusted odds ratio 4.6).¹²³ Although several factors, such as cervical immaturity, and increased prevalence of STDs contribute, the major factor associated with the increased risk for young women appears to be having older male partners¹²³ (Fig. 11-3). While young men typically have sexual relations with partners who are of same age or younger, it is common for young women to have male partners 5–10 years older, as was found in Zimbabwe¹²³ and elsewhere.¹²² Young women prefer older males in large part for economic reasons; unfortunately, they are less likely to use condoms with such partners, who frequently have had relations with commercial sex workers and who view the young women as “safe” and unlikely to be HIV-infected.

In the United States, there have been few recent HIV-prevalence studies among adolescents. Older U.S. studies have demonstrated that prevalence of HIV infection was appreciable in several populations of adolescents. Prevalence exceeding 1% was documented among adolescents seen at STD clinics, among those at shelters for homeless and runaway youth, and among those in correctional facilities. Many of these young people have had sex in exchange for drugs, shelter, or food (“survival sex”).¹²⁴

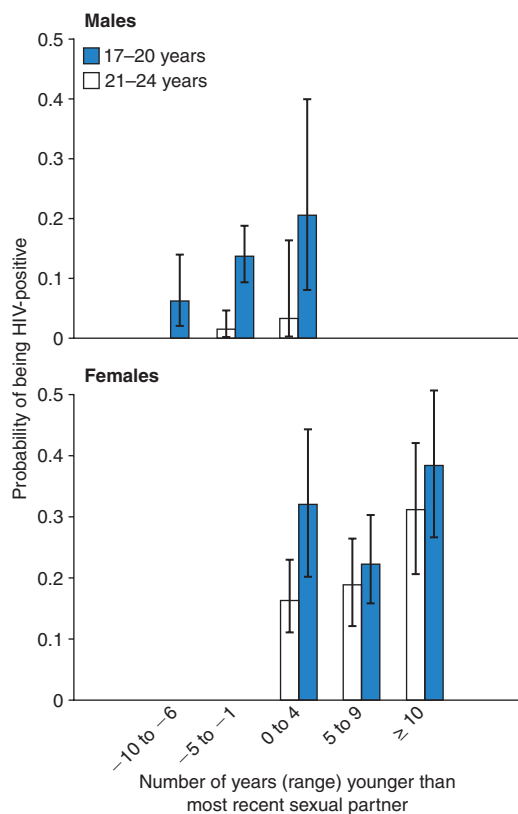


FIGURE 11-3. Probability of being infected with HIV by age and age difference with most recent sexual partner, rural Zimbabwe. (Modified from Gregson S, Nyamukapa CA, Garnett GP, et al. Sexual mixing patterns and sex-differentials in teenage exposure to HIV infection in rural Zimbabwe. *Lancet* 2002; 359: 1896–1903.)

African American youth are disproportionately affected, accounting for 56% of HIV infections reported among those aged 13–24 years.¹²⁵

National HIV surveillance data, using name-based reporting, revealed that, from 1994 to 2003, cases among females 13–24 years of age decreased slightly. A different pattern was seen among males; from 1994 to 1999 male cases decreased substantially, but increased from 1999 to 2004.¹²⁶ This increase occurred primarily among 20–24-year-old MSM, and involved all races, with increases greatest among blacks. Such findings are consistent with other reports of high rates of HIV prevalence among young MSM (14% among those 18–24 years).¹²⁷ Among those MSM with HIV, young MSM were most likely to have unrecognized infection (79%).

DETERMINANTS OF STD/HIV RISK AMONG ADOLESCENTS

Adolescence is a unique time of life, when societal, biologic, behavioral, and developmental factors all act in concert to increase the likelihood of STD/HIV acquisition.

■ BIOLOGICAL FACTORS

Several aspects of physical development may be relevant to the high risk of STDs among sexually active adolescents. The histology of the cervix and vagina undergo dramatic changes from childhood through puberty and into adulthood. Newborns show effects of exposure to maternal estrogen, which produces the squamous epithelium lining of the vagina as seen in adults. Soon after birth, these squamous cells are replaced with columnar epithelium. At puberty, estrogen exposure causes the vaginal lining to thicken again with layers of squamous epithelium. Such epithelial changes may be particularly important at the cervix, since the persistence of cervical columnar epithelium in young women appears to significantly increase their vulnerability to STDs. Although cervical columnar epithelium eventually recedes completely, to be replaced with squamous epithelium, this replacement is a gradual process, continuing well into adulthood. Typically, the cervix in the adolescent still displays areas of exposed columnar epithelium,¹²⁸ a condition often referred to as *ectopy*. This is significant because *C. trachomatis* infects columnar, not squamous, epithelium and thus ectopy may increase exposure of susceptible mucosa to infection.¹²⁹

The presence of ectopy has repeatedly been associated with chlamydial infection, even after adjusting for sexual behavior and other confounders.^{130,131} Although it may be that chlamydial infection causes the appearance of columnar epithelium on the cervix,¹²⁸ longitudinal studies have demonstrated that ectopy is associated with increased risk of subsequent infection.^{132,133} However, whether ectopy facilitates the detection of chlamydia is still a question.¹²⁹

The presence of ectopy also appears to increase the risk for other STDs and their adverse outcomes. *Neisseria gonorrhoeae* attaches preferentially to columnar epithelium rather than squamous tissue. In addition, there is some evidence that ectopy may contribute to HIV acquisition^{134,135} and HIV shedding.¹³⁶ The vasculature found with the columnar epithelium associated with ectopy is more superficial and more easily traumatized than that of squamous epithelium, theoretically permitting HIV-infected cellular elements from the circulation to gain access to the mucosal surface, and infected monocytes and lymphocytes to reach the circulation. Ectopy may partially account for the high incidence of HIV among adolescent women by increasing susceptibility; the implications of possibly increased infectivity, associated with HIV shedding, are unknown. However, some studies have not found an association between HIV and ectopy.^{137,138} The vaginal flora also changes during puberty. The appearance of *Lactobacillus* spp results in reduction of the high vaginal pH levels of childhood to the more acidic pH associated with adulthood. The higher vaginal pH of early adolescence may be associated with a lower prevalence of hydrogen peroxide-producing organisms. However, causal links between these anatomic or physiologic changes and STD acquisition have not yet been demonstrated.

Changes in mucosal anatomy produce changes in mucus production, which is minimal in childhood. Mucus production is greatly increased in early puberty, but the mucus is thinner than that found in older adolescents or adult women. Thinner mucus may permit organisms to penetrate more easily and to attach to mucosal sites or gain access to the upper tract.

Research has suggested that adolescent females experience a greater decline in IgG levels in cervical secretions during menstrual cycles than adult women,¹³⁹ but the implications of such a finding for disease acquisition is unknown. There are many aspects of immune protection of the female reproductive tract, such as expression of chemokines or cytokines, or expressions of CCR5 and CXCR4 receptors, that may function differently among young women, but such differences have not yet been documented and need to be elucidated.

Unfortunately, there is very little information about how development in males affects their risk of STD acquisition or transmission.

■ PSYCHOLOGICAL AND COGNITIVE DEVELOPMENT

The stages of adolescence have been arbitrarily categorized as “early,” “middle,” and “late,” and have been considered in terms of psychologic, physiologic, and social development (Table 11-2). Development in each of these areas is not necessarily parallel. Individuals are often advanced in some categories, but slower than their age-matched peers in others. Furthermore, growth in some of the cognitive areas is strongly influenced by the quality of teaching or role-modeling individuals’ experience.¹⁴⁰ This is particularly relevant for STD prevention, where adults may use indirect methods of educating or rely on “scare tactics” rather than using skills training. Several characteristics of adolescents, particularly in early or middle stages of development, may have important implications for STD risk and prevention. Younger

Table 11-2. Highlights of Adolescent Development Stages²⁵⁴

Early Adolescence Females ages 9–13 Males ages 11–15	Middle Adolescence Females ages 12–16 Males ages 14–17	Late Adolescence Females ages 16 and older Males ages 17 and older
<ul style="list-style-type: none"> • Puberty as hallmark • Adjusting to puberty such as secondary sexual characteristics • Concern with body image • Beginning of separation from family, increased parent-child conflict • Presence of social group cliques • Concentration on relationships with peers • Concrete thinking but beginning of exploration of new ability to abstract 	<ul style="list-style-type: none"> • Increased independence from family • Increased importance of peer group • Experimentation with relationships and sexual behaviors • Increased abstract thinking 	<ul style="list-style-type: none"> • Autonomy nearly secured • Body image and gender role definition nearly secured • Empathetic relationships • Attainment of abstract thinking • Defining of adult roles • Transition to adult roles • Greater intimacy skills • Sexual orientation nearly secured

adolescents frequently use a concrete style of reasoning, focusing on the present time, and until they reach middle or late adolescence are unable to conceptualize the long-term impact that current actions may have. Since some STDs (e.g., HIV or chlamydia) may have adverse effects that are not experienced for a decade or more, it should not be surprising that younger adolescents may not take actions needed to avoid such consequences. Furthermore, adolescents may have difficulty correctly implementing complex tasks (such as condom use) involving a series of steps that must be accomplished in a certain sequence to be effective.

These findings are consistent with ongoing research concerning cognitive development.¹⁴¹ Significant structural changes in the brain continue into the later teenage years,¹⁴² and the development of an “executive suite” of upper level decision-making functions is a lengthy process, requiring time and experience. Pubertal development and its attendant hormonal milieu appear to fire romantic motivations and an appetite for risk taking, independent of chronological age. However, self-regulation and competent decision making while under emotional stress (i.e., in the throes of adolescent passion) develop slowly and continue well after puberty.¹⁴³ The occurrence of puberty at younger ages is, as described by one researcher, like starting a car engine with an inexperienced driver at the wheel.¹⁴¹ The fact that adolescents are not fully prepared to handle the situations they find themselves in is a reason why it is important to provide appropriate “social scaffolding,”¹⁴³ and may explain why parental monitoring appears to be an effective prevention strategy.

Finally, many parents, educators, and health-care workers do not teach about STD risk or even details of pubertal development until long after many adolescents are at risk for STDs. Therefore, these youths do not have even the basic information to make informed choices.

SEXUAL BEHAVIOR

Over the last century, sociocultural and behavioral changes have combined with changes in aspects of the developmental physiology of adolescents to increase the risk of STDs among these young people. Biologically, the average age at menarche has decreased (although it has been stable over the last generation). At the same time, societal changes have resulted in increases in the average age at which young men and women marry. As a result, while 100 years ago young men in the United States spent approximately 7 years between maturation and marriage, more recently the interval was 13 years, and increasing; for young women, the interval between menarche and marriage has increased from 8 years to 14. For this reason alone, it should be expected that premarital sex in the United States has increased¹⁴⁴ (Fig. 11-4).

Changes in sexual behavior have placed adolescents at increased risk of STDs, with the longstanding trend to earlier age

at first intercourse occurring worldwide.^{145–148} However, in the United States, several ongoing, population-based surveys that provide information about the sexual behavior of adolescents show that during the past decade, the proportion of teenagers that have experienced premarital sexual intercourse has declined.^{4,149} This change in behavior reverses the trend seen over the previous several decades in the United States, in which the age of first intercourse had steadily decreased. In 1970, only 5% of women in United States had had premarital intercourse by age 15, whereas in 1988, 26% had engaged in intercourse by this age. However, in 1988, 37% of never married 15–17-year-olds had engaged in intercourse but in 2002, only 30% had. Comparable data from males demonstrated even greater declines—50% of never married 15–17-year-olds reported having had intercourse in 1988, compared with only 31% in 2002⁹⁹ (Fig. 11-5). Consistent with these U.S. data, between 1991 and 2000, the pregnancy rate among U.S. females (15–17 years) declined by 33%.¹⁵⁰ Similarly, the percentage of 9–12th grade students who reported having had four or more sexual partners also declined from 19% in 1993 to 14% in 2003.¹⁴⁹ This trend is not universal; no such decline was reported in Sweden.¹⁵¹

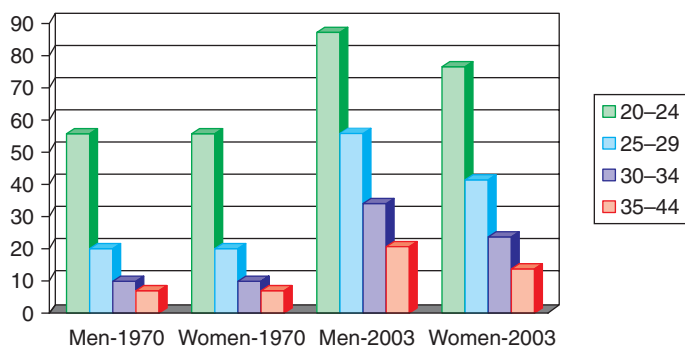


FIGURE 11-4. Percentage of men and women who had never married, by age, 1970, 2003. (Source: Census Bureau, 2003)

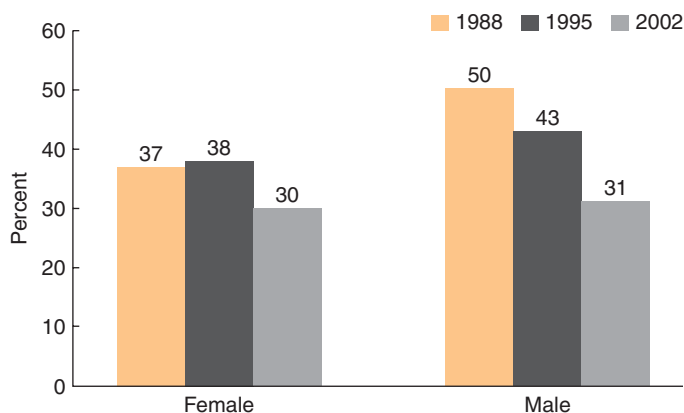


FIGURE 11-5. Percent of never married females and males 15–17 years of age who have ever had sexual intercourse: United States, 1988–2002.⁹⁹

Younger age of sexual “debut” is associated with a greater number of sexual partners—an important determinant of STD risk.¹⁵² In 1988, among American women 15–24 years of age who were sexually active for the same length of time (less than 24 months), over 40% of 15–19-year-olds had had two or more partners, compared with only 26% of women 20 years of age or older.¹⁵³ Younger age of sexual debut (below age 18) is also associated with ongoing sexual risk among unmarried women, with an increased likelihood of having two or more recent partners.¹⁵⁴ Adolescent relationships are of shorter duration than those of older individuals. Duration on average is only 15 months, and many relationships are less than 4 months.¹⁵⁵ It is becoming clear that determinants of STD risk at both an individual and population level include other factors such as concurrency¹⁵⁶ and sexual mixing patterns,⁴³ which involve assessment of sexual network structure^{157,158} and should be considered regarding adolescent STD risk. Nevertheless, partner acquisition tends to follow a pattern of serial monogamy, with one study finding that fewer than 10% of sexually active adolescents having more than one partner within a 3-month period.¹⁵² In another study, among adolescents reporting activity in the previous 18 months, over 85% indicated that they had either a single or sequential relationships. However, among serially monogamous females of all ages, adolescents are quicker to acquire a new partner than older women; in a national survey, mean gap between partners was 8 months for serially monogamous 15–19-year-old women, compared with 11 months and 18 months for 20–29- and 30–44-year-old women, respectively.¹⁵⁹ (Some smaller studies among higher risk cohorts of

adolescents have found mean interval between old and new partners to be as short as 21 days.¹⁶⁰) It should be noted, however, that among those adolescents who had more than one partner, concurrency is rather frequent; among adolescents who reported more than one partner in the previous 18 months, over 40% had overlapping sexual relationships.¹⁶¹

Although concurrency is expected to have population level effects, implications for individual risk are less clear, since concurrency may^{162,163} or may not^{45,63} be associated with increased individual STD risk. Furthermore, risk for the individual adolescent may be affected by the likelihood that one’s partner has concurrent partners,⁴⁵ which appears related to whether one lives in a high-risk community or not.⁴⁵

Recent studies provide some insight into sexual (and romantic) network structures among adolescents. As part of the AddHealth, data were obtained from all students in a large high school and all the romantic and sexual relationships among those students were identified. The relationship structure was described by the researchers as a “spanning tree,” similar to “rural phone lines running from a long trunk to individual houses.”¹⁶⁴ Such a structure does not reflect random partner selection, but rather a situation in which there are rules about who can be involved with whom. In addition, although there were few “short cycles” (i.e., cyclical pattern which promptly leads back to the same individual), there was a large network component that linked over half of the adolescents involved in romantic relationships (Fig. 11-6). Such a structure would allow efficient spread of an STD across the network, and, as the authors point out, demonstrates that STD risk is not simply

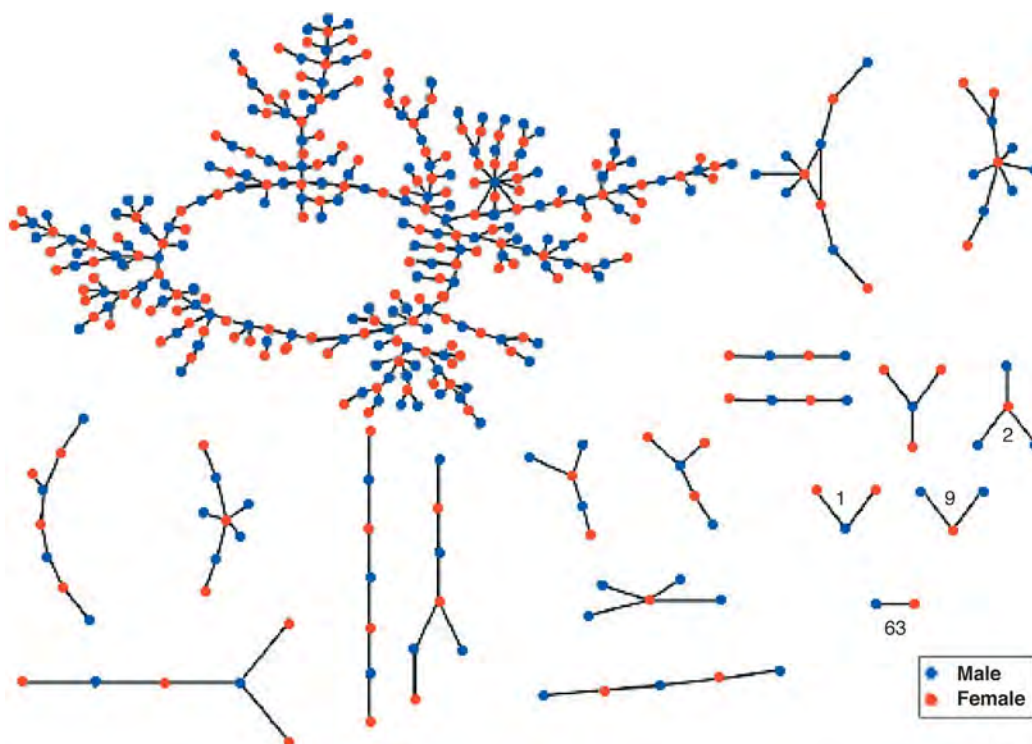


FIGURE 11-6. Direct relationship structure at an American High School. (Modified from Bearman PS, Moody J, Stovel K. Chains of affection: The structure of adolescent romantic and sexual networks. *Am J Sociol* 2004; 110: 44–9111.)

defined by the number of partners. Moreover, the structure has implications for STD prevention. Given the existence of a “spanning tree” network, effective prevention efforts need not target individuals in the “core.” A prevention approach that reaches all adolescents—and thus breaks the “spanning tree” into smaller, unconnected clusters—might be even more effective. Of course, this is a single study, performed in a middle-sized town, in the Midwest among working-class population, with limited diversity; and the network analysis did not include individuals who were not high-school attendees; therefore the extent to which its results are generalizable is unknown.

Population-based data demonstrate that condom use has increased substantially in the United States, but that use is not consistent. Surveys indicate that adolescents are more likely to use condoms than older individuals. In 2002, 66% of male teens reported using condoms at last intercourse compared with 53%, 45%, and 29% of males 20–24 years, 25–29 years, and 30–44 years, respectively.⁹⁹ In addition, 67% of U.S. women reported condom use at first intercourse if it occurred during 1990–2002, while only 36% of women 15–44 years of age reported condom use at first intercourse that occurred before 1990⁴ (see Table 11-3). Condom use among adolescents in general has increased. In 2002, among never married sexually active 15–19-year-old females, 54% used condoms at last intercourse, compared to 38% and 31% in 1995 and 1988, respectively.⁴ Similar increases are reported by adolescent males; in 2002, 71% of sexually active, never married 15–19-year-old males reported use of condoms at last intercourse, compared with 64% and 53% in 1995 and 1988, respectively.⁴

However, follow-up data indicate that as males get older and as the duration of the existing relationship increases, condoms are likely to be replaced by forms of contraception that offer less protection against STDs, particularly oral contraceptives.¹⁶⁵ This pattern has also been reported from other countries, such as Australia,¹⁶⁶ Canada,¹⁶⁷ and New Zealand.¹⁶⁸ It is noteworthy that the combined effect of serial monogamy and diminishing use of condoms over the duration of a relationship may be particularly important in exposure to and ongoing transmission of organisms such as HSV-2, chlamydia, HPV, and HIV, which are associated with chronic and often asymptomatic infection.

Although more people are using condoms, few people, including adolescents, use them consistently. Among unmarried U.S. women, 28% of 15–19-year-olds report using condoms consistently (i.e., all the time) over the past 12 months⁴; 48% of 15–19-year-old males report doing so. Not surprisingly, both teenagers and older individuals use condoms less frequently with partners in an ongoing relationship, than in sexual encounters outside that relationship.¹⁶⁹ Furthermore, the young people most at risk for STDs appear to use condoms least.¹⁷⁰ A survey among adolescent males indicated that those who were substance abusers or had paid for sex were among the least likely to have used condoms at last intercourse.¹⁷¹ Young males were less likely than older males to use condoms at first intercourse with

Table 11-3. Percent of Males and Females Who Used Condoms at First Sexual Intercourse, by Year of First Intercourse, United States^{4a}

Year of First Intercourse	% Used Condoms
Males	
1999–2002	73.0
1995–98	70.9
1990–94	58.6
1980–89	44.3
Before 1980	21.7
Females	
1999–2002	67.2
1995–98	61.7
1990–94	58.0
1980–89	38.1
Before 1980	21.7

^a2002 NSFG.

partners they perceived to be at higher STD risk.¹⁶⁵ Among young people with two or more partners, individuals with a greater numbers of partners were less likely to use condoms consistently with either primary or secondary partners.¹⁷² A similar pattern has been observed in other countries.¹⁷³

Use of condoms is a complex behavior, but we can make some generalizations about determinants of condom use upon which to base prevention strategies; most parallel determinants noted among adults. Many studies,^{174,175} but not all,^{176,177} indicate that use is associated with perceived risk of HIV infection. Youths who think their peers use condoms are more likely to use them,^{176,178–180} as are adolescents who feel that their partner would support their use,^{170,181,182} and adolescent males who are more able to communicate with their parents and with peers.¹⁸³ Adolescents are often mistaken about what their partners believe, however, with females overestimating the resistance and negative attitudes that males have about condom use.¹⁸⁴ In addition, when condoms are used, adolescents frequently experience errors in their use. In one study, among adolescent females who used condoms in the prior 3 months, at least one condom error was reported by 71%.¹⁸⁵ National survey data indicate that misconceptions about condom use (i.e., need for space at tip; use of Vaseline; protection with lambskin vs. latex condoms) are quite prevalent, with up to 50% of adolescents being mistaken about some of these issues.¹⁸⁶

Studies have noted that self-efficacy, perceived risk, and partner support are important factors in increased condom use.^{180,187} However, many young females who feel confident that they could get their partner to use condoms, are not motivated to use them. An important factor appears to be the extent to which young people underestimate their partners' risk of infection. Young homosexual males¹⁸⁸ believe that they are safe if they have sex with younger partners. Heterosexual females often feel that they have little or no risk of acquiring HIV from their male partners and believe their boyfriends' statements of fidelity, often despite having a history of STD themselves.¹ Another major concern is the belief that their partners, particularly their steady partners, would view the request to use a condom as indicating a lack of trust. Conversely, if the request for use is made by the male, the female may assume he is dating outside the relationship. Approaches to reconciling these issues are complex and require skillful and practiced communication, as well as interventions suitable for sexually active adolescents who are in the formative phases of social skill development. Other barriers to condom use that are unique to adolescents include lack of ready availability.¹⁷⁵ Embarrassment about purchasing condoms may be a particular obstacle for girls.¹⁸⁹

LEGAL AND ETHICAL ISSUES

Adolescents have unique legal status with regard to the provision of health care. Legally they are accorded more rights than children, but in some matters they may have rights that differ from those of adults. These issues are addressed by state minor consent laws that may allow minors to give their own consent for health care. These laws differ by state. However, in all states, adolescents who are at least 14-years-old can be diagnosed and treated for STDs without parental consent or knowledge, and some states have specific provisions regarding testing for and treating HIV infection. Beyond STD diagnosis and treatment, there are some basic issues providers confront in dealing with adolescents¹⁹⁰:

1. Is the adolescent who is under 14 years of age old enough to have the authority to consent to care without parental involvement? Must the provider request any specific evidence of age?
2. Does the adolescent have the authority to release or prevent release of confidential information (particularly to parents)?
3. Is the adolescent or another source responsible for payment for services rendered? Can adolescents insist that parents not be contacted for health insurance coverage or payments?

In the United States, the answers vary by state^{190,191}; however, some generalizations are possible. First, it should be noted that in most states the age of majority is 18, but in three states (Alabama, Nebraska, and Wyoming) it is 19, and elsewhere 21

(Mississippi, and District of Columbia). However, as stated, all states either have specific statutes or otherwise permit the diagnosis and treatment of "venereal disease" (the usual terminology) without parental consent.

■ CONSENT

Although all states and the District of Columbia permit a minor to consent to STD care without parental consent, some states identify an age criterion. In five states (Alabama, California, Delaware, Illinois, and Vermont), minors must be at least 12 years old to consent to STD-related care, and in five states (Hawaii, Idaho, New Hampshire, North Dakota, and Washington) they must be 14-years-old. Laws may also address the extent to which providers can, in "good faith," rely on information provided by the minor about his or her ability to consent. Over a dozen states have such a statement (Alabama, Alaska, Colorado, Delaware, District of Columbia, Indiana, Maine, Massachusetts, Minnesota, Missouri, Oklahoma, Pennsylvania, and Texas).

■ PARENTAL NOTIFICATION

In general, providers are obligated to maintain confidentiality, although communication with parents is sometimes addressed specifically. The Health Insurance Portability and Accountability Act of 1996 (HIPAA) suggests statutory protection, by indicating that when minors consent to their own care without parental consent, parents do not necessarily have the right to the information related to that care. However, it is state law that determines the specific protections that are applicable (i.e., medical privacy laws, state minor consent laws, etc.).¹⁹² In several states, laws indicate that the information is confidential, and thus parents cannot be informed without the minor's consent (e.g., California, Connecticut, Delaware, Florida, Hawaii, Iowa, Massachusetts), although exceptions are made if life or limb are in danger (Massachusetts), or if the adolescent is found to have HIV (Delaware, Iowa). Other states either permit the provider to notify parents, indicate that providers are not obligated to notify parents, or do not address the issue.

■ LIABILITY

Most states have not specifically addressed this issue. However, in several states (Connecticut, District of Columbia, Maine, Minnesota, and Oklahoma, and also in the Montana), depending upon ability to pay, the minor who seeks STD care is liable for costs. In many others it is stated that the parents are *not* liable, and therefore cost recovery would not be a reason to contact them.

The specific issue of a minor consenting for care relating to HIV/AIDS has been addressed by a majority of states.¹⁹⁰ Many states have statutes that permit emancipated minors in "special

circumstances”—those who are married, are themselves parents of children, or are living apart from their parents—to consent to care, including diagnosis and treatment of HIV infection. In addition, many states have laws specifically authorizing minors to give consent for HIV testing. Furthermore, several other states indirectly authorize minors to consent to diagnosis and treatment of HIV infection by either (1) stating that HIV/AIDS is an STD and permitting minors to consent to diagnosis and treatment of STDs, or (2) stating that HIV/AIDS is a reportable, infectious, or communicable disease and minors are authorized to give consent for the diagnosis and treatment of such conditions. As a result, adolescents in well over half of the states can consent to diagnosis and treatment of HIV infection, although some laws may limit the care to testing.

Clinicians caring for adolescents should know the laws regarding medical treatment of minors in their locale. Some health-care workers may feel a conflict between the desire to honor a minor's right to confidentiality and the desire to involve a parent or other adult. In addition to being aware of laws supporting an adolescent's right to confidential care for STDs, providers should realize that by disclosing confidential information they may undermine the ability of any provider to care for the adolescent in the future, particularly with regard to these sensitive issues.

HEALTH-CARE UTILIZATION, CONFIDENTIALITY, AND COMPLIANCE

The data suggest that U.S. adolescents obtain health care for all types of problems less often than older or younger individuals. In 1985, U.S. adolescents 10–18 years of age made an average of 1.6 visits to private, office-based physicians, compared with the national average of 2.7 for all ages.¹⁹³ Barriers to care relate to adolescents' stage of development. They may wish to arrange care on their own but lack knowledge of or transportation to available services. Since their parents usually have the insurance or Medicaid information, adolescents may be unable to document coverage, and they usually cannot pay for their care themselves. They may be put off by child-oriented waiting rooms or feel unwelcome in facilities that are geared to adults. When adolescents do obtain care, they may be seen by clinicians poorly trained in adolescent issues. From the adolescents' perspective, information about services or the services themselves may be unavailable. As a result, adolescents and young adults have more limited access to health care than other individuals, with 15% of adolescents unable to identify a routine source of care.¹⁹⁴ Obtaining STD-related health care presents even more problems for young people. Over 37% of tenth-grade students did not know where to get treated for STDs and over 40% would be embarrassed to ask a doctor about symptoms related to the genitourinary tract.¹⁹⁵ Adolescents are very concerned about confidentiality and claim that they would not seek care for problems

relating to sexuality if they believed their parents would find out.¹⁹⁶ This is particularly true for sensitive issues, such as STDs.¹⁹⁷ In one large national survey, one-quarter of those in middle/high schools indicated they had not sought needed care, and the reason in 35% of cases was that they did not want to tell their parents.¹⁹⁸ In another such survey, one-half of single women less than 18 years of age who were receiving family planning services indicated they would stop using the clinic if their parents were notified about their use of contraception and an additional 12% would not use services such as STD care; however, only 1% indicated they would stop having sex.¹⁹⁹ To some extent, this observation speaks to the anticipated effect of recent attempts to mandate parental notification.²⁰⁰ Likewise, it is worrisome that over one-third of tenth-graders in a national survey thought that the health department would inform parents about STDs and that most clinics required parental consent to treat STDs.¹⁹⁵ Furthermore, over half of sexually active 15–17-year-olds indicated that they would like more information about where to go to get tested for HIV or other STDs.²⁰¹ The general lack of knowledge about STDs among adolescents is a serious concern and undoubtedly influences health-care seeking. In the same survey among sexually active 15–17-year-olds, 20% believed that STDs can only be spread when symptoms are present; 25% did not know that STDs can cause problems with fertility; and of those sexually active teens who had not been tested for STDs, 53% thought they were not at risk and 33% did not know where to go to get tested.²⁰²

Either because they are not sufficiently trained or they are unaware of or unwilling to address the needs and desires of their young clients, physicians frequently are not useful sources of STD information for adolescents. Although many young people are concerned about STDs²⁰³ and would like more information from their doctors, a survey among college freshmen found that 79% had never received counseling about STDs.²⁰⁴ A 1997 survey among a school-based sample of adolescent boys and girls found that among those who had made a health-care visit in the past year, 61% wanted to discuss STDs, 65% to discuss drugs, and 59% wanted to discuss smoking and other issues. Unfortunately, a third never discussed any of these topics with the provider.²⁰⁵

In many countries STD treatment for females is seen in the most stigmatizing terms,²⁰⁶ and unmarried young women are too ashamed to access care, such as family planning services, where needed STD treatment can also be obtained. Despite the attention and education concerning HIV infection, adolescents, particularly females, are not informed about STD symptoms. A population-based study in Ethiopia found that 90% of young females had untreated symptoms such as discharge and irritation that warranted care but which the women accepted as normal.²⁰⁷

In the United States, improvement in STD and HIV services for adolescents may require that managed care organizations

address the unique situations posed by and facing young people. Fee-for-service providers or primary-care providers who function as the “gateway” to the system may not be well attuned to the needs of adolescents. School-based clinics with a full range of services are among the few sources of accessible, affordable, and comprehensive care for adolescents.²⁰⁸ Many such clinics provide reproductive health services that include counseling, gynecologic examinations, and the diagnosis and treatment of STDs. However, such clinics are available to only 2% of the nation’s students²⁰⁹ and are threatened by unstable financing.²¹⁰

Contrary to “conventional wisdom,” young people and adults adhere to prescribed regimens equally well,^{211,212} although compliance with HIV treatment has been a challenge for adolescents.²¹³ Compliance is often dependent upon provider behavior and can improve when clinicians explain the rationale for treatment. Providers tend to underestimate adolescents’ knowledge and the obstacles that adolescents face in implementing medical instructions. Studies suggest that extra efforts on the part of providers can greatly improve compliance.²¹⁴

Advances in STD treatments and diagnosis may be particularly helpful in improving care for adolescents. Convenient, effective treatment regimens such as azithromycin permit single-dose treatment of chlamydia. DNA amplification tests for chlamydia performed on urine or self-collected vaginal swabs expand access for adolescents by allowing specimens to be obtained in street settings,²¹⁵ in school clinics,²¹⁶ at other community locations,¹⁵ and from general school populations.^{16,217} Specimens can even be mailed in.^{218,219}

CURRENT AND FUTURE DIRECTIONS TO IMPROVE STD PREVENTION AMONG ADOLESCENTS

In the United States, over the past decade, there has been a trend toward decreased acceptance of teenage sexuality.²²⁰ Fewer high school students have had sex and those who had sex began at a later age and use condoms more consistently,¹⁴⁹ suggesting that changes in societal norms may have had an impact on adolescent sexual behavior.

However, despite these positive behavioral trends, STDs remain endemic among adolescents and young adults, and the arsenal of prevention strategies is limited. Most successful programs have focused on modifying individual behaviors associated with acquiring HIV and have not emphasized factors associated with transmission (i.e., targeting core groups and networks). Similarly, there have been barriers to the dissemination of efficacious programs and limited data on their effectiveness when taken to scale.²²¹ In addition, few studies have focused on addressing broader structural determinants of risk that exist at the community level such as the lack of economic opportunities and

social support for youth who reside in the most affected communities.²²²

In this section, we will describe what has worked, where there are challenges, and promising new approaches in areas of behavior and treatment. We will leave discussion regarding vaccines for the other chapters (see Chapters 99 and 100).

■ BEHAVIORS

Individual-level cognitive behavioral interventions

Over the past 20 years, several cognitive-behavioral interventions to reduce adolescents sexual risk behaviors have been developed and evaluated. These interventions have focused on outcomes that include delayed onset of sexual intercourse, abstinence, consistent condom use, and the number of sexual partners. Empirical evidence suggests that such programs can achieve their desired behavioral outcome,²²³ and recent data indicate that some have been associated with decreased STD incidence.^{224,225} Several interventions (but not all²²⁶), tested in randomized trials, were effective in reducing risk among youth accessed in school, clinic-based settings or in the community,^{227–229} and among runaway youth in shelters.²³⁰ Internet and computer programs are now being developed and tested that may more cost-effectively deliver these interventions.²³¹ Further enhancements to these interventions have included the addition of a component to enhance parental monitoring.^{232,233} Parental monitoring has gained attention as an intervention because of its association with delay of sexual onset and discouraging selection of high-risk sex partners. Despite these successes, the dissemination of these efficacious programs has not occurred at the level they merit, perhaps due to costs and competing social values about adolescent sexuality.

In the United States, not only is there a failure to implement and scale-up programs with demonstrable efficacy, but also, as a result of political and cultural forces, so-called “abstinence-only” curricula have been adopted by an increasing number of states and locales. Such curricula lack evidence of effectiveness²³⁴ and have few of the characteristics of those programs that have been shown to be efficacious.^{223,235} As a result of the changes in the curricula that have been presented, fewer adolescents in 2002 indicated they had instruction in use of birth control than in 1995.²³⁶ Early analyses from the AddHealth cohort had, in fact, suggested the promise of an abstinence-only approach, since those students who had given “virginity pledges” were more likely to delay onset of sexual activity. However, follow-up evaluation of the cohort indicated that STDs were at least as prevalent among the individuals who had given those pledges as among those who had not. Disturbingly, those who had pledged were also less likely to have tested previously for STDs and were less likely to use condoms when they had initiate intercourse.²³⁷

Social marketing intervention

The use of mass media has been effective in disseminating information and, in at least one instance, promoting a specific sexual behavior change among young people. In countries such as Zaire and Ghana, mass media campaigns were associated with increases in knowledge and awareness of HIV among adolescents,²³⁸ and a Swiss multimedia campaign significantly increased condom use among adolescents and young adults,²³⁹ although neither the number of partners reported nor the percentage of adolescents who reported being sexually active decreased. To further focus prevention efforts, some health information campaigns addressing HIV prevention among adolescents have used principles from social marketing, and tailored messages to specific audiences; Kennedy et al. demonstrated that increasing adolescents' exposure to STD-related risk reduction messages with a program that included public service announcements, posters, small media, and peer outreach was associated with greater likelihood of condom use with main partners.²⁴⁰

Promising new approaches

Youth development interventions. Observational studies have identified those community assets or resources available for youth that are associated with better developmental outcomes. Studies have also shown that youth who feel connected to other individuals, schools, families, or peers have more favorable developmental outcomes.²⁴¹ One strategy for STD/HIV prevention, which has been evaluated primarily for pregnancy prevention,^{242–244} is to harness the power of the youth development perspective to reduce STD/HIV risk. Potential mechanisms of action could range from less frequent sexual behavior, to safer sexual behavior, to selection of less risky partners. This has also been used in the United States for prevention of adolescent substance abuse.²⁴⁵

Structural intervention

School- or community-level policies, practices, or programs can have a profound effect on STD/HIV risk. These structural determinants of risk operate outside the control of the individual, but nonetheless may shape behavior and individual risk. Examples of structural determinants include school policies on condom distribution. Some schools have tried to overcome the barriers adolescents encounter in obtaining condoms. In the United States, over 400 schools have condom availability programs.²⁴⁶ In this controversial approach,^{247,248} most of the schools make condoms available through school personnel, with only a few making condoms available through peers, baskets, bowls, or vending machines—the latter approaches being the more effective in increasing availability.

Partner and networks intervention

Over the past decade, studies have revealed the importance of sexual partners and networks on risk of exposure to STD/HIV. Currently there are no interventions that leverage this information to prevent STDs in adolescents. However, there is no doubt that interventions will be developed that will influence individual partner selection or network structure, composition, and STD prevalence.

■ EARLY DETECTION AND TREATMENT

The strategies to increase early detection and treatment can be divided into (1) alternative-site STD/HIV testing; (2) increasing adolescent care seeking; and (3) improved quality of care.

Alternative-site testing

The advent of NAAT and their use for urine-based STD screening have made testing in nontraditional settings possible, including schools, jails, street, CBOs, home (with Internet-mediated mail-in), and other social venues.²⁴⁹ This strategy is particularly useful for asymptomatic infections and especially those in men. The lack of symptoms delays care seeking. Many women may be tested for asymptomatic STDs because they seek care for family planning services. However, men are less likely to seek care and thus alternative-site testing is essential if asymptomatic men are a target.

Care seeking

Studies have shown that many youth fail to access STD services despite their risk of infections. Adolescents are relatively limited in their knowledge about chlamydia and gonorrhea. Although they report that they are infections that can be transmitted sexually, they are often unaware of their asymptomatic nature and their link to infertility.²⁵⁰ As such, interventions are necessary to increase youths' STD care seeking. One such program, the YUTHE project, was developed, implemented, and evaluated by the San Francisco Department of Public Health and targeted African American youth residing in a high-morbidity area of the city.²⁵¹ Peer staff engaged in street-based counseling and referral and distributed informational materials about testing. The evaluation of the intervention showed that exposure to the program was associated with greater likelihood of being tested for STDs.

A critical issue affecting care seeking for adolescents is the perceived confidentiality of services and existence of local laws that permit adolescents to consent for their reproductive- and STD-related care, without parental permission. Adolescents rate privacy and confidentiality as integral to their decisions about when and where to seek care. Adolescent consent laws represent a structural facilitator of care seeking for youth.

Clinical care

Clinic-based services to diagnose and treat STDs can make a significant difference in prevalence of disease. Many providers do not screen at-risk youth because of their discomfort with sexuality, lack of skills with genitourinary examinations, and time constraints. While NAAT tests have increased the acceptability of screening by providers and adolescents by eliminating genitourinary examinations and reducing time, they fail to address the discomfort issues. Training programs are focused on increasing provider comfort with adolescent sexuality. Systems level quality improvement interventions also have greatest promise for increasing STD testing in clinical settings. Shafer et al. conducted a clinical practice improvement intervention designed to increase chlamydia screening using urine-based tests for sexually active adolescent girls during routine checkup visits. They demonstrated that, by 16–18 months, the intervention clinics screened a higher percentage of girls compared to control facilities.²⁵²

In summary, there are effective strategies which, if coordinated and implemented broadly, should result in healthier behavior and lower rates of STDs among adolescents. Effective health education messages can be provided with consistency across the different levels of social context of adolescents' lives,²⁵³ and educational and health service activities can be systematically linked across schools, media, community organizations, and health-care settings. Clinicians can be trained in effective techniques for communicating with young people and their parents. Providers, together with adolescents, can conduct a meaningful assessment of STD risk with appropriate counseling and treatment. Prevention and care for adolescents must be accessible, affordable, and comprehensive, and it must be provided by professionals who are knowledgeable and committed to caring for young people, in communities and cultures attentive to young people's needs.

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Female Sex Workers and Their Clients in the Epidemiology and Control of Sexually Transmitted Diseases

James F. Blanchard and Stephen Moses

INTRODUCTION

Sex work entails the provision of sexual services for money or its equivalent, and female sex workers (FSWs) are those women who engage in such work. Clients are those who purchase sex from FSWs. Reducing the transmission of STDs, including HIV, in the context of sex work is a global public health imperative due to the obligation to protect and promote the health of FSWs and clients, and to the strategic importance of interrupting transmission to and from these subpopulations as a means of controlling STD and HIV epidemics.^{1–4} Sex workers are generally at high risk of acquiring STDs because they often have many sexual partners^{5–13} and many of those partners also have multiple partners.^{14–18} Moreover, FSWs are often in highly vulnerable situations or environments that impede their ability to reduce their risk of acquiring STDs and to seek treatment to shorten the duration of STD episodes. Economic needs and the exploitative working environments experienced by many FSWs reduce their freedom to choose the number and types of clients and other sexual partners, and impede their ability to negotiate the use of condoms.^{10,19–23} The vulnerability of FSWs is exacerbated by the fact that they are highly stigmatized in many societies, and sex work is criminalized in many countries.^{24,25} This often hinders the provision of programs and services and reduces the ability of sex workers to access them.

The strategic importance of STD prevention in the context of female sex work is due to the fact that FSWs and their clients are often at the center of important sexual networks that greatly influence the overall transmission dynamics and epidemiology of STDs. Although the relative epidemiologic importance of sex work interventions in controlling STD epidemics varies according to the pathogen, the prevailing sexual network patterns, and the phase of the epidemic, in many locations these interventions form perhaps the single most important STD control strategy.^{26–29}

In this chapter, we provide an overview of the general dimensions and contours of female sex work organization and practice, with an emphasis on the aspects that relate to

the epidemiology and control of STDs in the sex work setting. In so doing, we recognize that the complex social, cultural, gender, and public health issues related to STD control in female sex work defy generalization. Moreover, the organization and practice of sex work is highly diverse and in many locations, it is evolving rapidly. Therefore, STD control strategies should be tailored to the local social, cultural, and epidemiological setting.

TYOLOGY AND SOCIAL CONTEXT OF FEMALE SEX WORK

Sex work, broadly defined, exists in all societies. However, the extent, typology, and organization of sex work are highly variable between and within countries. An assessment of four cities in Africa found that the estimated number of FSWs varied between 10.1 and 19.1 per 1000 men.³⁰ A high variability in sex work volume was also found in Saratov Oblast, Russia, where the estimated number of sex work contacts in different cities ranged from 32,800 to 730,000 per 100,000 population per year.³¹ A recent review article summarized studies estimating the relative size of the FSW population and estimated the proportion of urban adult females engaging in sex work in different global regions as follows: 0.4–4.3% in sub-Saharan Africa cities, 0.2–2.6% in Asia (national estimates), 0.1–1.5% in ex-Russian Federation, 0.4–1.4% in East Europe, 0.1–1.4% in West Europe, and 0.2–7.4% in Latin America.³² Some variability in these estimates can be attributed to differences in how sex work is defined and on estimation methods.

Different approaches have been used to classify sex work typology.^{33,34} At a general level, sex work has been classified as being either “direct” or “indirect.”³³ According to this classification, “direct” sex work refers to those circumstances where the exchange of sex for a fee is clearly the primary purpose of the interaction. This includes sex work that occurs at venues which are explicitly maintained for this purpose, such as brothels, and circumstances where solicitation for paid sex occurs in less formal settings, such as on the street, in bars

and pubs, or by telephone contact. For women engaged in indirect sex work, the provision of sex for a fee is generally opportunistic and more often a source of supplemental income than among direct sex workers.^{19,35,36} Examples include women who work in massage parlors or as dancers in clubs and will also accept money for sex from some patrons.^{19,37} Another classification divides sex work and sex workers into “formal” and “informal” types.³⁴ In this rubric, “formal” sex work refers to situations wherein FSWs are connected to a formal structure that facilitates the commercial transactions, usually at specific locations such as brothels, lodges, or private homes. In contrast, “informal” sex workers tend to work alone and from nonspecific locations, such as on the street, at market places, and sites where clients can be encountered such as bars, truck stops, and at bus and train stations.^{38–42}

While these high-level classifications encompass a broad spectrum of sex work, there is often considerable overlap between categories, and individual FSWs often do not clearly fit into one category or move between these categories periodically. Moreover, such broad classifications do not provide a sufficient basis for understanding the social organization of sex work or the level of vulnerability and risk experienced by sex workers in the local context, which is necessary for planning appropriate programmatic responses. For that purpose, a framework that is structured around the diverse factors that shape the social organization of sex work is helpful. Here we present a conceptual framework that links the various societal, local environmental, and individual characteristics of sex workers to the various ways in which sex work is organized and practised (Fig. 12-1). Societal factors include the broad economic environment, along with social and cultural norms, including gender roles and expectations. These societal level factors influence both the demand for sex work (i.e., proportion of men seeking paid sex) and the supply and characteristics of sex workers. For example, the dramatic changes in the political, social, and economic circumstances in the former Soviet Union and Eastern Europe during the 1990s resulted in an upsurge in the number of FSWs.^{31,43,44} Similarly, broad economic and social changes in China, including increasing numbers of mobile and migrant male laborers and the ballooning male:female sex ratio, have influenced the volume and patterns of sex work.^{42,45} The local environment in which sex work exists includes the local level of tolerance or suppression, the level of criminalization of sex work, the size and nature of the client population, and the presence of local organizers or controllers of the sex work structure. These factors have a more proximal influence on the individual sociodemographic characteristics of those who enter into sex work and how sex work is organized and controlled locally. For example, longstanding social and cultural traditions and contemporary economic deprivation in parts of rural India have fostered the emergence of a large number

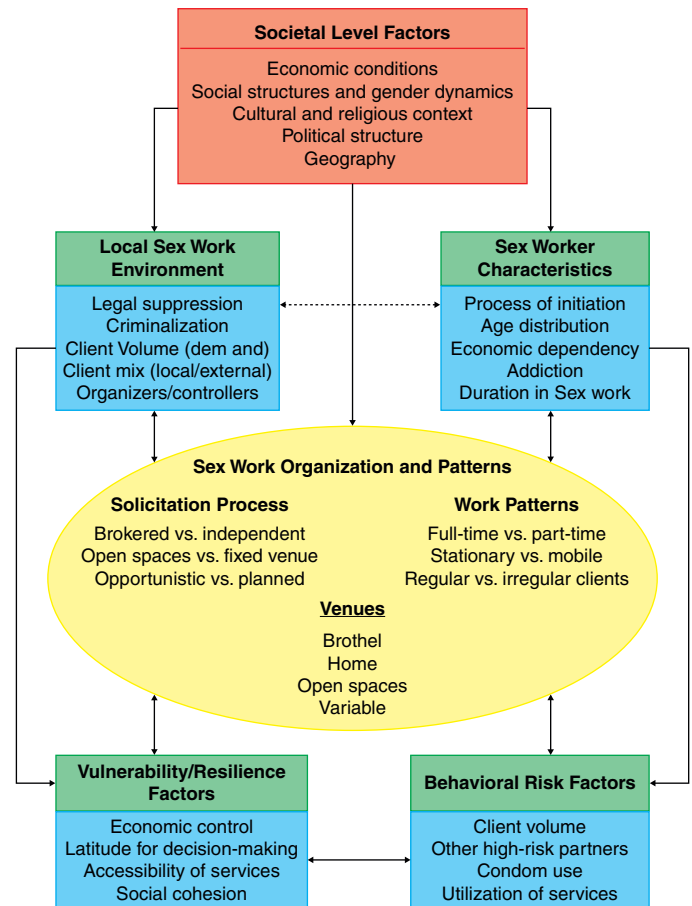


FIGURE 12-1. Conceptual framework for describing the relationship between determinants and patterns of sex work in a population.

of rural FSWs, many of whom migrate to large cities for economic gain.^{46,47} Local social and economic factors, including the presence of criminal organizations, have played a major role in shaping the nature of the sex worker population and the organization of sex work in parts of Russia as well.^{31,44} At the individual level, the sociodemographic characteristics of FSWs also contribute to the typology and organization of sex work within an area. For example, in some locales, it has been observed that FSWs who have insufficient income from other employment and dependent children are inclined to work as FSWs part-time, and less often work in brothels or other established sex work venues.^{35,46}

Together, these factors shape the basic organization and practice of sex work within a particular environment, and are relevant for the STD epidemiology and transmission dynamics and for the design of program responses. There are three important considerations in describing the organization and patterns of sex work. The first is the solicitation process, which describes the way in which FSWs and client populations encounter each other (see Table 12-1 for examples). In some cases, this process is not much under the control of the FSW, but rather is controlled by others such as madams, pimps, or other brokers. In other circumstances, sex workers

Table 12-1. Selected Examples of Different Processes for Client Solicitation

Solicitation Processes	
Brokered	Independent
<p>"Falang xiaojie" ("beauty parlour girl") in South China are highly controlled by managers or "pimps" who often determine how many and which clients are to be entertained⁴⁸</p> <p>Sex work concentrated in "tochkas" along major thoroughfares in Moscow, Russia, where pimps, guards, and drivers largely determine client–sex worker interactions for clusters of 15–25 sex workers⁴⁴</p>	<p>"Roadside girls" in Zhengzhou, China, solicit clients independently and entertain them at "mini-motels"⁹</p> <p>Individual sex workers, many of whom are drug users, who work as "freelancers" in Balakovo, Russia³¹</p>
<p>Solicit in Open Spaces</p> <p>Street-based sex workers in Milan, Italy, most of whom are immigrants from other European countries¹¹</p> <p>Street-based sex workers in towns and cities of Andhra Pradesh state of South India, mostly local⁸</p>	<p>Solicit at Fixed Locations</p> <p>Brothel-based sex workers in Cotonou, Bénin, with lower income than other sex workers³⁰</p> <p>Large registered brothel in Daulatdia, Bangladesh²²</p>
<p>Opportunistic Client Solicitation</p> <p>Homeless sex workers in Miami, FL, who intermittently sell or trade sex, often to obtain shelter, food, or drugs¹⁰</p> <p>"Indirect" sex workers in Zhengzhou, China, who work in hair salons and massage parlors and occasionally provide sexual services for clients⁹</p>	<p>Planned/Organized Solicitation</p> <p>Brothel-based sex workers in Kolkata, India, who work in Sonagachi, a large and well-known "red light" area⁴⁹</p> <p>Home-based sex workers in rural India, many of whom own and work out of their own home⁴⁶</p>

operate as free agents and largely decide where to find clients and which clients they will choose. Some solicitation occurs in open spaces such as street corners, parks, bus stands, and markets, whereas in other circumstances, the solicitation occurs in a fixed venue such as a brothel or hotel. This is relevant because solicitation that occurs in an open setting can leave FSWs more vulnerable to harassment and intimidation by a variety of individuals, including the police and local "goons." Finally, some solicitation is planned, in the sense that the FSW has a specific intent to seek clients at a particular time and place and can prepare accordingly, including ensuring that she has condoms in case the client does not. In other circumstances, FSWs will be solicited in a more ad hoc way, which can leave them more vulnerable to high-risk sexual encounters. There is also variability in sex work patterns (see Table 12-2 for examples). In some locations, there is a high proportion of part-time FSWs who tend to have fewer clients, whereas in other locations a high proportion of FSWs are full-time and have a high client volume. Many FSWs are highly mobile and therefore often working in unfamiliar surroundings, which can be a source of vulnerability. Some FSWs have a relatively high proportion of their contacts with regular clients, whereas others almost never have repeat clients. There is some evidence that over time, condom use with regular clients decreases, perhaps due to an enhanced level of trust.⁵⁴ Altogether, the organization and patterns of

sex work interact with the local environmental conditions and the individual FSW characteristics to influence the level of vulnerability and risk experienced by sex workers (Fig. 12-1). For example, FSWs who are in new environments where there is extensive control exerted over client volume and choice have less latitude for decision making and will be more prone to high-risk sexual encounters. Conversely, FSWs who are in a familiar environment with a high degree of social cohesion will be in a much stronger position to choose the number, type, and circumstances of their client encounters, and will also be in a stronger negotiating position if the client is reluctant to use a condom.

SEX WORK AND STD/HIV TRANSMISSION DYNAMICS

Prevention of STD and HIV transmission to and from FSWs is often critical to limiting the establishment and expansion of these epidemics at the population level. The role of sex-worker and client groups in the epidemiology of a particular STD depends upon the frequency and nature of commercial sex transactions and the transmission dynamics of the STD.⁵⁵ It has been noted that in the absence of effective treatment and prevention programs, the transmission efficiency and duration of infectivity are relatively stable characteristics of STD pathogens.⁵⁶ The frequency of interaction between an

Table 12-2. Selected Examples of Different Work Patterns of Female Sex Workers

Work Patterns	
Part-Time	Full-Time
Sex workers in a suburb of Mombasa, Kenya, the majority of whom also earn money from small businesses such as selling foodstuffs ³⁵	Sex workers in the port city of Diego-Suarez, Madagascar, many of whom work full time and are registered with an association of sex workers ⁵⁰
“Indirect” sex workers in Nha Trang City, Vietnam, who often work in entertainment venues and are more likely to entertain foreign clients than direct sex workers ⁵	
Stationary	Mobile
Street-based sex workers in South India, most of whom live in the same district where they solicit clients ⁴⁶	Migrant sex workers in Madrid, Spain, many of whom have migrated from South America ⁵¹
Local sex workers in a Ugandan trading town who tend to be impoverished and work in back-street bars serving poor local men ¹⁹	Rajasthani rural traditional FSWs who move from their rural villages to large urban centers, predominantly to Mumbai ⁴⁷
Regular Clients	Irregular Clients
Some traditional <i>Devadasi</i> sex workers in rural parts of Karnataka state in South India who often have one or more regular clients ⁴⁷	Sex workers in Cotonou, Bénin, who do not have many repeat clients ³
Sex workers in Nyanza, Kenya, who often have multiple long-term regular clients ⁵²	Sex workers at truck stop in KwaZulu-Natal Province, South Africa, who report that many of their clients were truckers from other African countries ⁵³

infected individual and a new susceptible is therefore the critical determinant of the reproductive rates of STDs. Sex workers and their clients, because of their high rates of partner change, are therefore important in the transmission dynamics of all STDs, including HIV infection. However, it is also important to consider that the centrality of sexual networks involving FSWs will differ according to the STD pathogen. Garnett has pointed out that epidemics of STD pathogens that are highly infectious, but have over a relatively short duration, such as syphilis, gonorrhea, and chancroid, are particularly dependent on subpopulations with high rates of partner change.⁵⁷ As STD treatment and prevention programs improve in quality and expand in scope, the duration of infectiousness and perhaps transmission efficiency of the targeted STDs should decrease.⁵⁸ As a result, these STDs will increasingly become concentrated in networks where there is a high rate of partner change, including FSWs and their clients. Furthermore, because these groups often experience stigmatization, discrimination, and marginalization, their access to STD-related health care may be limited, resulting in increased durations of infectiousness. Therefore, it is anticipated that control of such epidemics would depend greatly on effective interventions in FSW populations.

FSWs and their clients can also be important for the spread and persistence of HIV infection. However,

compared with most curable STDs, HIV is less easily transmitted, but has a longer duration of infectiousness. Therefore, the centrality of subpopulations with high rates of partner change, including FSWs, is less predictable, particularly in more advanced HIV epidemics in which most new infections occur in longer-term, stable partnerships. Mathematical models suggest that an HIV control strategy that achieves condom use in 75% of FSW–client sexual contacts could be sufficient to control the HIV epidemic in India.²⁸ Similarly, empirical data and mathematical models have shown that the HIV epidemic in Cotonou, Bénin, is still largely dependent on transmission chains that include FSWs.³ There is also at least anecdotal evidence that programs that achieve a relatively high level of condom use in FSW–client contacts have been associated with a reduction in HIV prevalence in the general population in diverse settings such as Nairobi, Kenya,⁵⁹ Kolkata, India,⁶⁰ and Thailand.⁶¹ However, the contribution of sexual transmission related to sex work to new HIV infections appears to have changed over time in Kenya and Cambodia.⁶² Mathematical modeling has indicated that the introduction of a single intervention that reduced transmission to and from FSW populations, while very effective in controlling HIV in a setting like India, would not have as substantial an impact in Botswana,²⁸ largely because of the high HIV

prevalence in the general population and the higher frequency of concurrent partnerships outside of sex work. Another study that modeled HIV transmission for a population in rural Uganda showed that transmission in sex work settings was very important early in the epidemic, but declined substantially over time as HIV prevalence in the population rose.⁶³

Another key strategic consideration relates to the epidemiologic synergy between HIV and other STD pathogens. Since other STDs, especially those which cause genital ulcers, greatly facilitate the transmission of HIV, reducing the incidence and prevalence of these pathogens in a population is an important component of HIV control.⁶⁴ This is particularly true at phases of an HIV epidemic when much of the HIV transmission is occurring in short-duration partnerships. When such circumstances exist, programs that reduce STD transmission in FSW populations are likely to be of critical strategic importance.

In addition to the general importance of sex workers and clients in the transmission of STDs, mathematical modeling suggests that the particular patterns of sex worker–client sexual partnerships also influence the expansion and persistence of STDs in a population. Recent work by Ghani and Aral suggests that STD persistence and prevalence are greater if clients tend to visit different sex workers, rather than repeatedly visiting the same FSWs, since the more random sex worker–client partnership patterns result in denser sexual networks.²⁹

SEX WORK AND THE EPIDEMIOLOGY OF SPECIFIC STDs

■ GONOCOCCAL AND CHLAMYDIAL INFECTIONS

In 1959, Rosenthal and Vandow, finding a decline in the prevalence of gonorrhea among FSWs arrested for soliciting in New York City (from 23.6% in 1946 to 5.2% in 1956), stated that “the prostitute is no longer the major vector of venereal disease” and that “the promiscuous amateur” was filling the role.⁶⁵ In fact, the prevalences of *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infection among FSWs have been found to be highly variable and to depend, among other things, upon the frequency and nature of sexual encounters, characteristics of clients, levels of condom use, interactions with HIV infection, and frequency of medical examinations.¹ More recent examples of prevalence levels in a variety of sex worker populations in developing countries are shown in [Table 12-3](#).^{35,36,66–73} Lower prevalence of gonorrhea and chlamydial infection is generally reported from developed countries than from developing countries,^{25,74,75,76} but this is not always the case. Among sex workers attending clinical services in London, England, the prevalence of gonorrhea declined from 4.5% in 1985–1992 to 1.1% in 1996–2002.²⁵ During the same time period, the prevalence of chlamydia declined from 10.7% to 4.8%. The relationship with HIV infection is also quite variable. For example, very low rates of gonorrhea and

Table 12-3. Prevalence of *N. gonorrhoeae* and *C. trachomatis* Infections in Populations of Female Sex Workers in Developing Countries

Location	Year of Publication	<i>N. gonorrhoeae</i> Prevalence	<i>C. trachomatis</i> Prevalence	Ref. No.
Asia				
Dhaka, Bangladesh	2005	18%	16%	7
Yunnan, China	2005	38%	59%	66
Surat, India	2003	17%	9%	62
Kupang, Indonesia	2003	31%	24%	63
Papua New Guinea	2005	21%	19%	59
Vietnam (border provinces)	2005	11%	12%	64
Africa				
Mombasa, Kenya	2002	2%	4%	35
Nairobi, Kenya	2004	10%	9%	60
Dakar, Senegal	2003	22%	20%	61
Mbeya, Tanzania	2003	22%	12%	36
Mashonaland West, Zimbabwe	2005	2%	2%	26
North America				
Chiapas, Mexico	2003	12%	15%	65

chlamydial infection have been reported from sex worker populations in Zimbabwe²⁶ and Mombasa, Kenya,³⁵ where HIV prevalence is very high, and high rates of gonorrhea and chlamydial infection have been reported from sex worker populations in Bangladesh⁷ and Indonesia,⁷⁰ where HIV rates are very low. The interactions are complex, and each context must be evaluated individually.

The incidence of gonorrhea and chlamydial infection is also variable. Very high incidences have been reported from developing countries in sex workers of lower socioeconomic strata, for example, in Nairobi an 11% weekly incidence of gonococcal cervicitis⁷⁷ and in Bangkok 31.7 new gonococcal infections and 43.1 new *C. trachomatis* infections per 100 woman-months of observation.⁷⁸ A case-control study among predominantly African American gonorrhea patients in San Francisco in 1988 found that 32% of the female patients and none of the controls had received money or drugs in exchange for sex.⁷⁹ In Fresno, California,⁸⁰ and Colorado Springs, Colorado,⁸¹ programs of screening or mass treatment for gonococcal infection in FSWs resulted in declines in the incidence of gonococcal infections in the general community. These data suggest that in some areas of the world and in certain subgroups, sizable fractions of gonococcal and chlamydial transmission are attributable to sex workers and their clients. Since, in addition, many non-sex worker acquired infections are likely secondary to sex worker acquired infections, successful intervention in sex worker/client core groups is crucial to the control of gonorrhea and chlamydial infection.

■ GENITAL ULCER DISEASES

The STDs that cause genital ulceration are particularly important because of their strong association with risk for HIV infection.⁶⁴ Syphilis and sex work have long been associated. At the height of the U.S. syphilis epidemic in the early twentieth century, 25% of all cases of syphilis were estimated to have been transmitted through commercial sex.⁸² Sex work linked with crack cocaine use has been identified as an important contributor to syphilis transmission in the United States.⁸³ North American epidemics of syphilis in heterosexuals have been described in Fresno, CA,⁸⁰ Winnipeg, MB,⁸⁴ Edmonton, AB,⁸⁵ Baltimore, MD,⁸⁶ and Vancouver, BC.⁸⁷ Each of these outbreaks has been associated with sex work in urban core areas. In Amsterdam, FSWs who use “hard” drugs have been identified as being at high risk for syphilis.⁸⁸ Since the prevalence of syphilis in the general heterosexual population is extremely low, it seems plausible that a large proportion of the heterosexual transmission of syphilis cases in North America and Europe is attributable to FSWs and their clients.

Syphilis is also highly prevalent among FSWs in developing countries. In studies from Honduras,⁸⁹ Senegal,⁶⁸ Madagascar,⁹⁰ India,⁶⁹ Cambodia,⁶ and Papua New Guinea,⁶⁶

over 18% of sex worker populations sampled were found to have syphilis prevalences of over 18%. These data suggest that in developing countries as well, commercial sex plays an important role in the spread of syphilis.

Chancroid has been highly associated with FSWs and their clients, particularly those in lower socioeconomic strata, in virtually every major North American outbreak that has been reported. In several modern epidemics of chancroid (Winnipeg, MB,⁹¹ Orange County, CA,⁹² South Florida,⁹³ New York City,⁹⁴ and New Orleans⁹⁵), sex work has been linked with much of chancroid transmission, often in association with drug use and the sale of sex for drugs. In Nairobi, an area of high chancroid endemicity in the 1980s, 66% of men with chancroid attending an STD clinic reported a paid sex partner as the source contact.⁹⁶ In a study among one group of Nairobi sex workers during the same time period, the prevalence of culture-proven chancroid was 13%.⁹⁷ However, as STD control programs have improved in developing countries, chancroid rates have declined, and chancroid now represents a much smaller proportion of genital ulcer disease.⁹⁸

The reasons for the association between chancroid and lower-socioeconomic-stratum sex work are not entirely clear. As the epidemiology of chancroid is understood, most female transmitters of *Haemophilus ducreyi* have clinical genital ulceration.⁹⁶ It may be that poor women, in need of income and with restricted access to health care, ignore ulcer symptoms rather than forgo income for several days. In addition, because of chancroid's relatively short duration of infectivity (compared to other STDs), chancroid epidemics can only be maintained in populations that have very high rates of partner change,⁹⁹ such as those seen typically among lower-socioeconomic-stratum FSWs.

Infection with herpes simplex type 2 (HSV-2) is extremely common among FSWs, and because HSV-2 infection increases the likelihood of both HIV acquisition in HIV-uninfected individuals, and HIV transmission in HIV-infected individuals, HSV-2 infection plays a key role in HIV transmission dynamics.¹⁰⁰ Studies of FSWs in Kenya,⁶⁷ South Africa,¹⁰¹ Tanzania,³⁶ and Mexico⁷² have found HSV-2 prevalences ranging from 70% to over 80%. In a prospective study of HIV seronegative FSWs in Nairobi, Kenya, 72.7% were HSV-2 seropositive at baseline.⁶⁷ Over the course of over two years of observation, HIV seroincidence was approximately 4 per 100 person-years, and HSV-2 seropositive FSWs were over six times more likely to acquire HIV infection than women who were HSV-2 seronegative. In a prospective study of HIV seronegative FSWs in Kwazulu Natal, South Africa, 84% were HSV-2 seropositive at baseline.¹⁰¹ When HSV-2 seroconversion was analyzed as a time-dependent covariate, the risk of HIV seroconversion was six times higher among women with incident HSV-2 infection compared to those with prevalent HSV-2 infection. Ongoing clinical trials will elucidate the role of HSV-2 suppressive therapy in

reducing the risk of both acquisition and transmission of HIV infection.

■ HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Human immunodeficiency virus infection is, of course, the most important STD associated with sex work. FSWs and their clients are major groups at risk of acquiring and transmitting HIV. The first evidence that FSWs were at risk for HIV infection came from a study reporting lymphadenopathy and altered T-cell subset ratios among FSWs in New York City.¹⁰² FSWs in Africa were first identified as a risk group for HIV infection in the mid-1980s, when several studies found an extremely high prevalence of HIV infection in women selling sex. The HIV prevalence among FSWs in an early study in Kigali, Rwanda, was 88%.⁷⁰ At about the same time in Nairobi, the HIV prevalence was 66% among lower-socioeconomic-stratum FSWs and 31% among higher-socioeconomic-stratum FSWs.¹⁰³ Subsequent studies in Uganda and Zaire yielded similar results.^{104,105} In the early years of the HIV/AIDS epidemic, high HIV prevalences and incidences were also observed in some Asian countries. In national HIV surveillance conducted in Thailand in 1993, the median HIV prevalence among FSWs was approximately 30%.¹⁰⁶ Annual HIV incidence among FSWs in Thailand was also very high, ranging from 24% to 29%.¹⁰⁷ The high prevalence of other STDs among FSWs, as noted above, is also an important factor facilitating HIV transmission. Genital tract infections and inflammation probably increase HIV shedding in the female genital tract, rendering a woman more infectious to a sexual partner.^{108,109} Thus, FSWs are likely more efficient transmitters of HIV because of their high prevalence of genital ulcers and other STDs.¹¹⁰

In many developing countries, commercial sex is an important factor in HIV transmission. The concentration of HIV infection in urban areas and along major overland trucking and trade routes has indirectly implicated sex work in the spread of HIV through East Africa.^{111,112} In a Kenyan study, male STD clinic patients in Nairobi who reported frequent contact with FSWs, as well as past and current genital ulcer disease (both of which are highly sex work associated), were more likely to be HIV infected.¹¹³ In the same population, an HIV incidence of 8% was estimated to have followed a single sexual encounter with an HIV-infected FSW.¹¹⁴ More recent data from the state of Karnataka in southern India suggest that HIV prevalence in rural areas is associated with the volume of sex work, both in terms of numbers of identified sex workers and reported contacts by clients.¹¹⁵ However, as with gonorrhea and chlamydial infection, there is wide variability in reports of HIV prevalence among FSW populations in developing countries. In recent studies, these have ranged from 0% prevalence among FSW populations in Papua New Guinea,⁶⁶ Pakistan,¹¹⁶ and Indonesia⁷⁰; under 1%

among FSWs in Madagascar,¹¹⁷ Colombia,¹¹⁸ and Mexico⁷²; 6–14% in Senegal⁶⁸ and the Democratic Republic of the Congo¹¹⁹; and 30–68% in Kenya,³⁵ South Africa,¹⁰¹ Tanzania,³⁶ Zimbabwe,³⁵ Cambodia,¹²⁰ and India.⁶⁹ Reasons for these wide variations in risk are unclear, but may be due to a variety of factors, including differences in exposure (numbers and types of sexual partners, degree of condom use), as well as differences in rates of other STDs, and perhaps the interplay of other biological factors, such as male circumcision practices.

The prevalence of HIV infection has also been studied in North American and European FSWs. Early studies found relatively low HIV prevalence rates.^{121,122,123} The prevalence of HIV infection is higher, however, among intravenous-drug-using sex workers. HIV prevalences of over 50% have been found among intravenous as well as non-intravenous (crack cocaine) drug using FSWs in New York and New Jersey.¹²⁴ In Amsterdam, 30% of drug-using FSWs have been found to be infected with HIV, and other STDs were also highly prevalent in this group.¹²⁵ In European countries, as well as in North America, FSWs frequently acquire HIV infection through intravenous drug use or from intravenous-drug-using sex partners.¹²⁶ In North America, the crack cocaine epidemic, with its accompanying sex-for-drugs phenomenon, is probably also responsible for a large proportion of sex-work-associated HIV infections.¹²⁷ The substantial number of FSWs infected with HIV suggests potential for transmission of the virus to the general heterosexual population. That this has not already occurred to a greater extent may be a result of high levels of condom use, the use of nonpenetrative sex, the relative absence of other cofactors such as genital ulcer disease, and sexual mixing patterns.

CLIENTS OF SEX WORKERS

Clients play a large role in determining the volume and organization of sex work and the epidemiology of STDs. However, there has been a relative paucity of research to better understand client behaviors and the epidemiology of STDs in client populations. Surveys in Asia found that 6% of men in the Philippines reported buying sex in the previous 6 months, whereas 7% of men in Myanmar and 16% of men in central Thailand reported buying sex in the previous year.¹²⁸ One study found that approximately 75% of men in northern Thailand reported having ever visited a sex worker,¹²⁹ but this level of client behavior appears to be uncommon in Asia and elsewhere. A survey in Hong Kong found that 12% of men reported visiting FSWs in the past 6 months.¹³⁰ In Africa, estimates of the proportion of men visiting a sex worker in the past 12 months from population-based surveys are highly variable, ranging from 1% to almost 30% of adult males.¹³¹ In Nairobi, Kenya, one study found that almost 15% of a sample of men residing in an urban slum reported having purchased

sex from a FSW at least once during the previous 3 months.¹³² However, other focused studies have indicated that there is variability between different regions of Africa. A survey of FSWs in four African cities estimated that the number of client–sex worker contacts varied considerably, ranging from 960 to more than 3300 contacts per 1000 men per year.³⁰ Surveys in the UK¹³³ and New Zealand¹³⁴ found that approximately 7% of men reported ever paying for sex. A more recent telephone survey in Australia found that almost 16% of men reported having ever paid for sex, with 1.9% reporting that they had paid for sex in the past 12 months.¹³⁵ Two national surveys in Britain found that the proportion of men who reported paying women for sex in the previous 5 years increased from 2.0% in 1990 to 4.2% in 2000.¹⁴ A recent review article summarizing the findings of various surveys in different global regions found that the median proportion of men who reported “exchanging gifts or money for sex” in the past 12 months was approximately 9–10%, whereas the proportion of men reporting who engaged in “paid sex” or sex with a sex worker was 2–3%.¹³⁶ This review also found that there were substantial regional differences, with the median estimates for proportion of men “exchanging money or gifts for sex” of 13–15% in Central Africa, 10–11% in Eastern and Southern Africa, and 5–7% in Asia and Latin America. For “paid sex,” regional estimates ranged from 7% in the South African region to 1% in Asia and West Africa. Interpretation of these estimates and the regional differences is constrained by variability in the definitions of payment for sex, and also the likelihood of differential levels of social desirability biases such that men in some regions might be much less likely to report paying for sex than others. This likelihood is supported by the fact that regional differences in the proportion of men who report paying for sex appear much larger than the variability in regional estimates in the relative size of the FSW population.³²

As discussed above, in addition to the volume of client–FSW contacts, the pattern by which clients select FSW partners will also affect the transmission dynamics of STDs. In particular, when clients tend to visit the same FSW, or the same type of FSWs, the resulting high-risk sexual networks are less conducive to widespread dissemination of STDs, including HIV. For example, a study in the Netherlands found that almost half of the clients frequented only one type of FSW (club, brothel, window, street, home, or escort), and only 3% of clients reported having unprotected sex with more than one type of sex worker in the past 12 months.⁵⁴ In Nyanza, Kenya, clients tended to have more steady FSW partnerships,⁵² whereas clients in Cotonou, Bénin, did not tend to visit the same FSW, and 10–20% of clients reported having FSW partners both in Cotonou and outside of the city.³

A few client studies have also suggested that sexual risk behaviors depend on the circumstances, location, and type of sex worker being visited. For example, clients from Hong Kong who visited FSWs in mainland China, or both mainland

China and other places, reported less consistent condom use than Hong Kong clients who only visited FSWs in Hong Kong.¹⁷ It is not clear whether these differences are due to differences in the characteristics of the client groups, differences in the protective behaviors of FSWs, or both. A study of clients in the Netherlands found that the proportion of client–FSW contacts in which a condom was not used varied by the type of sex work, ranging from 3.7% of brothel-based contacts to 23.6% of contacts with escort FSWs.⁵⁴

There has been a paucity of research into the prevalence of specific STDs among clients of sex workers, but the available evidence indicates that clients have a substantial risk of STDs and HIV. A study in Bénin found a relatively high prevalence of gonorrhea (5.4%) and chlamydial infection (2.7%) among clients of FSWs.¹³⁷ HIV prevalence was 8.4%, and approximately 2% of the clients had genital ulcers on physical examination. The prevalences of both HIV and gonorrhea among clients were several-fold higher than that found in a general population-based survey of men. Interestingly, HIV prevalence (16.1%), but not gonorrhea or chlamydia prevalence, was higher among the boyfriends of FSWs than among clients. A study in rural Zimbabwe found that men who reported visiting an FSW were three times more likely to report a genital ulcer in the past 6 months.²⁷ A study of truckers who visited FSWs at five truck stops in South Africa found that the HIV prevalence was 56%.⁵³

STD PREVENTION AND CONTROL PROGRAMS IN SEX WORK

From a strategic perspective, the objectives of STD and HIV prevention and control programs in sex work are the same as in other settings: (1) to reduce the number of high-risk sexual encounters in which STDs and HIV can be transmitted and (2) to shorten the effective duration of infectiousness among those who are infected. There are many examples of successful programs in a variety of settings.^{34,49} In many cases, consistent condom use in client–sex worker contacts has increased to more than 80%, and there have been substantial declines in the prevalence of STDs in some sex worker and client populations.^{3,59} Given the diverse factors that contribute to the vulnerability of FSWs to STDs and HIV, successful programs cannot focus solely on individual/cognitive interventions for behavior change. Instead, the importance of structural–environmental interventions to complement individual level approaches has been recognized.^{138,139,140,141,142} Accordingly, Bourcier et al. have adapted the concept of “risk causation” developed by Sweat and Denison¹⁴¹ to formulate a framework for sex work program development. In this context, they specify four levels of risk causation in sex work: (1) societal (super structural); (2) community (structural);

(3) institutional (infrastructure/environment); and (4) individual.³⁴ Similarly, Overs has categorized sex work intervention strategies at three levels: (1) individual/cognitive; (2) participation and empowerment; and (3) structural and environmental.¹⁴³ This approach emphasizes the importance of incorporating program elements that address both individual level and structural and environmental factors to reduce the vulnerability of FSWs. A key principle in the development of sex work programs is the empowerment of FSWs to take a leadership role in all aspects of program design, delivery, and monitoring. Doing so promotes the development of programs and services that meet the specific requirements of FSWs in a particular location. Moreover, it often contributes to a reduction in stigma and discrimination that prevent FSWs from accessing needed prevention and treatment services. The following sections give a brief overview of four key elements of STD/HIV prevention and control programs in the context of sex work: peer outreach and education; provision of STD clinical management and other health services; promotion of participation and empowerment; and structural interventions to create an enabling environment.

■ PEER OUTREACH AND EDUCATION

To reduce the risk of STD and HIV transmission, FSWs require the knowledge and skills to negotiate condom use and lower-risk sexual acts (i.e., nonpenetrative sex) with their clients. Therefore, it is essential that programs ensure that there are mechanisms to reach individual FSWs and provide them with the necessary education and training in risk reduction techniques. To achieve this, a central component of most effective programs is peer-led outreach and education. This entails the training of FSWs as peer educators or guides and giving them the responsibility to reach and educate other FSWs, who are part of their social network or work in similar geographic locations.^{49,144,145,147} In addition to providing education and building skills, peers are often responsible for ensuring that FSWs in their sphere of work have an adequate supply of condoms, either through direct distribution or through fixed locations (“condom depots”) where FSWs can easily access condoms. Peers also often provide direct education to other FSWs on how to negotiate and use condoms with clients. To be effective, peer outreach programs must be tailored to the local sex work environment. In particular, consideration should be given to the diversity of the social networks of FSWs and the different typologies of sex work in selecting and assigning peers.

■ PROMOTING PARTICIPATION AND EMPOWERMENT

In addition to individual level interventions, effective programs promote participation and empowerment of FSWs.

This entails activities such as the organization of social events that promote social cohesion among FSWs. Other programs have effectively promoted participation and empowerment by addressing some of the broader social needs of FSWs with program components such as literacy classes and skills training for FSWs, and child care for their children.¹⁴⁷ Some programs support FSWs to develop skills to earn money from non-sex work sources as a way of reducing their dependence on sex work income, and thereby increase their latitude for decision making with clients. One such project found that those who earned additional income were more likely to increase their condom use with clients and to reduce their number of clients.¹⁴⁸ Other successful programs have fostered the development of self-help groups and collectives of FSWs. These function as a forum for socialization, a structure for promoting greater economic security through collective savings, and an organization that can take collective action to ensure access to social entitlement programs and protect the rights of FSWs.^{49,149} There is some evidence that participation in these collectives results in increased knowledge about STD and HIV prevention, and increased condom usage.¹⁴⁹ Although this association might not be causal, it is reasonable to conclude that enhanced social cohesion and increased access to a wider pool of knowledge and skills render FSWs who participate in such groups less vulnerable than those who are socially isolated.

■ CLINICAL SERVICES

Many FSWs experience a high degree of marginalization and discrimination by health-care providers and therefore do not have adequate access to health services. Moreover, many FSWs are poor, creating a financial barrier to accessing health care. Therefore, providing access to health services, especially for reproductive health, and including STD treatment, is another cornerstone of effective STD/HIV prevention programs for FSWs. Access to such services can be a key motivator for many FSWs to interact with program staff and to participate in program activities.¹⁴⁷ It is important to ensure that health services, and particularly those for STD management, are configured so that they are easily accessible and acceptable to FSWs. This often means establishing clinics in locations that are convenient and ensuring that they are open at times when FSWs are most able to visit them. In locations where there are diverse types of FSWs, different service configurations might be required. For example, full-time street-based FSWs might prefer a fixed and dedicated clinic site close to where they work, whereas part-time home-based FSWs might prefer the option of visiting clinics that are not exclusively and explicitly for FSWs. Regardless of the type of clinic, it is important to ensure that doctors and other health workers at the clinic are both competent and sensitive to the particular concerns and needs of FSWs.

■ STRUCTURAL INTERVENTIONS

Structural interventions focus on changing the societal level factors that influence the organization of sex work and the prevailing behavioral norms. Perhaps the most notable examples of this approach are the 100% condom campaign instituted in Thailand⁶¹ and the Sonagachi project in Kolkata, India.⁴⁹ The Thailand program focused substantially on changing behavioral norms, largely through a policy of enforcement of condom use in brothels. By so doing, there was less reliance on individual FSWs to use condoms and to convince their clients to do so. Instead, a behavioral norm was established and ultimately 90% or more of brothel-based FSWs consistently used condoms with their clients.⁶¹ In contrast, the Sonagachi project focused substantially on changing the perspectives and actions of those who influence the sex trade in the area, including madams, police, and pimps. In so doing, an enabling environment was created whereby FSWs could take an increasing role in program leadership and in advocating for the rights of FSWs. This empowerment, along with the extensive capacity building of the FSW community, resulted in substantial increases in consistent condom use and stabilization of HIV prevalence among sex workers. It has been noted that such structural interventions have not been as successful when tried elsewhere. It is not clear whether the variations in the results are due to differences in the organization of sex work (i.e., controlling structures) and the prevailing political and economic situation, the social and cultural characteristics of the FSWs, the implementation process, or a combination of these factors.^{150,151,152} Nonetheless, it has been observed that the most successful programs for FSWs incorporate a substantial focus on addressing the structural barriers to the empowerment of FSWs and the adoption of safer behaviors.³⁴

■ CLIENT INTERVENTIONS

Despite their centrality in STD/HIV transmission dynamics, clients of FSWs have seldom been the focus of targeted prevention programs.^{137,153} In general, client interventions have focused on particular client groups such as truckers¹⁰¹ and miners.¹⁵⁴ However, in many countries these groups form a small minority of all clients; therefore targeting these specific occupational or sociodemographic groups is not a sufficient strategy. Another approach is to develop specific outreach and education services for men at or near sex work locations, for men who live or work near such locations, or who seek sex there.¹³⁷ This approach takes advantage of the fact that sex work often has geographic specificity.¹⁵⁵ To motivate men to engage with the outreach team, on-site STD treatment can be offered after testing with a leukocyte esterase dipstick test. Such approaches hold some promise, but more applied research is required to develop effective strategies for male clients.

MANAGEMENT OF SEXUALLY TRANSMITTED DISEASES

As noted above, it is important for STDs among FSWs to be treated promptly and effectively, both because of the health benefits for the FSW and to reduce STD transmission to clients and other partners. In addition to reducing STD transmission, STD treatment may be important in reducing HIV transmission,⁶⁴ although randomized community trials of STD treatment for HIV prevention conducted in Tanzania and Uganda have had conflicting results in this regard.^{156,157,158} It may be that STD treatment is more important in reducing HIV infectivity among HIV positive individuals with an STD than in reducing HIV susceptibility among uninfected persons.⁶⁷ As indicated in the section above, STD rates are often extremely high among FSWs because of their high levels of exposure, and STD control among FSWs and clients can have considerable impact in reducing STD transmission in the general population.¹⁴⁵ However, because of the stigma associated with sex work, FSWs are often marginalized and have limited access to health care. It is important, therefore, to reach FSWs and clients with effective STD treatment and preventive services, which must be accessible, user-friendly, and available at convenient hours.

A review by Steen and Dallabetta has identified three main specific sexually transmitted infection (STI) treatment strategies involving sex workers¹⁵⁹: diagnosis of symptomatic sex workers, using either etiologic or clinical/syndromic approaches; regular screening of sex workers (regardless of symptoms) with clinical examination and possibly laboratory tests; and periodic presumptive treatment (PPT). Syndromic case management for STIs is most frequently employed for the treatment of symptomatic infections in developing country settings, ideally using evidence-based treatment guidelines. STI services developed and implemented for FSWs in Madagascar include syphilis screening and treatment; presumptive treatment for gonorrhea, chlamydia, and trichomoniasis/bacterial vaginosis during initial visits, and individual risk-based treatment during follow-up visits; and speculum exams, with treatment for genital ulcers, if present.¹¹⁷ A program of services for FSWs developed in India follows similar guidelines, but presumptive treatment is provided only for gonorrhea and chlamydia, and vaginal infections are treated only when symptoms are present.¹⁶⁰ A study from Bénin has shown that syndromic diagnosis is preferable to laboratory diagnosis of cervical infections (and much less expensive) in this context, even in the presence of high levels of asymptomatic infection, because of low patient follow-up rates.¹⁶¹ A study from Ghana has suggested that Gram-stained genital smears in FSWs without clinical symptoms or signs can improve diagnostic accuracy for cervical infections.¹⁶² As FSWs are exposed frequently to STIs, examination and treatment must often be repeated. The frequency with which

examinations should occur is unclear, but 3-month intervals would seem to be a minimum and visits should perhaps be even more frequent. In a program in South Africa, FSWs were offered clinic visits at monthly intervals for examination and counseling, and were provided presumptive treatment with one gram of azithromycin at each visit. Significant declines in the prevalences of gonorrhea, chlamydial infection, and genital ulcer disease were observed over time, both among the women themselves and among miners in the intervention area, who largely formed the client population for the FSWs.¹⁶³

Because the detection of asymptomatic cervical infections in FSWs is problematic, even with the use of risk-based algorithms and simple laboratory tests,¹⁶⁴ increasing interest is being accorded to presumptive treatment, either one-time or PPT. Most commonly, antibiotics (usually azithromycin, at times with the addition of cefixime or other drugs) are provided regularly, often at monthly intervals, for the presumptive treatment of gonococcal and/or chlamydial cervical infection, but PPT has also been used in the context of syphilis and chancroid control. In addition to reducing disease burden among sex workers, PPT should have an impact on the bridging populations that interact with FSWs, such as male clients, but the effectiveness of PPT in reducing STD transmission will depend upon the levels of treatable STDs in the FSW and bridging groups, and the rapidity with which STD prevalence rates are reestablished following treatment. PPT has been used over the past several decades with varying degrees of success to control gonorrhea and chlamydial infections among sex workers in the Philippines, South Africa, Madagascar, Kenya, Bénin, Ghana, and Zimbabwe; and to control syphilis and chancroid infections in Indonesia, United States, Canada, South Africa, and Madagascar.^{158,164}

There have been only three reported randomized trials involving PPT in sex worker populations. A trial in Kenya showed significant reductions in gonorrhea and chlamydial infection, as well as trichomoniasis, among FSWs provided a monthly dose of 1 g azithromycin (but no impact on HIV incidence), compared to controls receiving a placebo.⁶⁷ A trial in Zimbabwe compared PPT regimens of single doses of 1 g azithromycin and 2 g of metronidazole, with or without 500 mg of ciprofloxacin.²⁶ Declines were observed in both the groups in the prevalences of gonorrhea, chlamydial infection, and trichomoniasis after 1 month of follow-up among FSWs provided with one dose of PPT, but rates rose to pretreatment levels after 3 months, and the prevalence of gonorrhea and chlamydial infection were both very low in general. A placebo-controlled clinical trial in Bénin and Ghana compared women randomly assigned to receive 1 g azithromycin at month 1 and 500 mg of ciprofloxacin at months 2 and 3 in 3-month cycles. No impact of PPT was found on gonorrhea or chlamydial infection prevalence overall, but there was a decline in gonorrhea prevalence among HIV seronegative FSWs.¹⁶⁵ Thus, PPT administration appears to be associated with reductions in the

prevalence of bacterial STDs and trichomoniasis, but not HIV infection. For PPT to be considered as an intervention in sex worker populations, the prevalence of bacterial STDs must be high, and this usually occurs in relatively early stages of STD and HIV epidemics, when preventive and curative services are being established. PPT should be considered where bacterial STD rates are high, and should be integrated with other clinical STD services, such as condom promotion, syndromic case management, risk assessment, and other screening services, such as syphilis screening and HIV voluntary counseling and testing.¹⁶⁶ Important issues that should be studied further include the levels of STD prevalence needed for initiating PPT, the optimum periodicity of PPT, under what circumstances PPT should be discontinued, and what risk groups are most suitable for programs involving PPT.

SUMMARY AND CONCLUSIONS

FSWs and their clients remain central to the transmission dynamics of STDs including HIV in many regions globally. Over the past two decades, much has been learned about how to design and implement programs that are effective in reducing STD and HIV transmission in sex work settings. In fact, adequate programs have almost invariably resulted in substantial increases in safer sex behavior and reduced STD rates among FSWs. However, despite the public health importance and evident success of such programs, there remain unacceptable gaps in the coverage globally so that too many FSWs and their clients still lack the basic information, resources, and services to reduce their risk of STDs. Clearly more resources and greater policy and program focus are required in many countries. But, more resources and determined policy, although necessary, are not likely to be sufficient. The organization and patterns of sex work are already highly complex. Rapid development in many countries and globalization are altering the context and organization of sex work, often more quickly than programs can adapt. Therefore, researchers and those who develop and implement programs from different regions must share, summarize, and analyze their observations so that new strategies can be developed to respond to emerging needs. If widespread control of STDs and HIV can be achieved among sex workers and their clients, that would be a major global public health achievement.

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Homosexual and Bisexual Behavior in Men in Relation to STDs and HIV Infection

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INTRODUCTION

Male homosexual behavior has been denounced in the Old Testament and extolled by classical Greek poets like Hesiod, underscoring the longstanding awareness that these behaviors have been commonly expressed since the beginning of human civilization, and demonstrating the ways that diverse cultures have grappled with deviations from the heterosexual norm.¹ Although the Bible recommended that men and women who engaged in homosexual intercourse be put to death, justifying this as a crime against nature, these behaviors were also associated with sacred rituals of local polytheistic cultures, suggesting that neighboring peoples were able to accept homosexuality. Although many famous personalities in history—e.g., Alexander the Great, Tchaikovsky, Walt Whitman—were known to prefer homosexual partners, until the landmark studies of Kinsey and colleagues, very little was known about the natural history and prevalence of male homosexual behavior.² Kinsey et al. examined the life histories of more than 6300 males and found that 2/3 had engaged in some homoerotic play as preadolescents, but only 15% of the events involved oral or anal–genital contact. Although the finding that 37% of the males had at least one postpubertal homosexual experience is higher than the rates reported in subsequent studies. The majority of respondents described self-limited experiences, and subsequently identified as heterosexual males for the rest of their lives. The Kinsey group developed a scale from 0 to 6 for the respondents to indicate their sexual preference, with 6 being for those whose sexual attraction was exclusively homosexual. About 18% of the men rated themselves between 3 (equally attracted to both sexes) and 6 for at least 3 consecutive years, but only 4% rated themselves as exclusively homosexual for all of their lives, similar to more recent estimates (see below).

Because of legal and social sanctions against the public expression of homosexuality until the advent of the sexual revolution of the past 40 years, earlier records of sexually transmitted disease (STD) epidemics, such as the spread of syphilis in the late fifteenth century, are generally not enlightening

with regard to the extent that male homosexual behavior abetted the spread of specific STD pathogens. However, the increased social acceptance of homosexuality in developed countries in the late 1960s and 1970s was associated with the development of a subculture that accepted intimacy with multiple partners as a normative behavioral pattern.³ Increased ease of travel also facilitated the spread of STDs through male homosexual behavior, both because of the ability of men to travel widely, contracting infections that could subsequently be efficiently introduced into new settings, and because of the migration of men who wanted sex with men into major metropolitan areas, such as New York and San Francisco, creating “gay ghettos” and the economic environments that could support sexual venues like bath houses, in which sexually transmitted infections could be most readily disseminated.

DEFINITIONS

Current epidemiological reports, especially those dealing with HIV and AIDS, include “men who have sex with men” (MSM) in the breakdown of populations affected by the epidemic. MSM is a nomenclature coined in the mid 1980s in an attempt to find an umbrella term to describe a variety of men who have sex with other men, and thereby may transmit or acquire HIV or other STDs, but do not necessarily share the same sexual orientation, sexual identity, or gender identity. What do these terms mean? Although there is no consensus on specific definitions, there are common uses.

Biological sexuality refers to the genetic determinants of sexual expression. Although the external genitalia are usually considered the most obvious phenotypic indication of biological sex, this is not always unequivocal. Maternal use of estrogens during pregnancy or a variety of endocrine abnormalities may result in children born with underdeveloped external genitals and testis that have not descended, who therefore were thought to be girls and treated as such until adolescence, when suddenly they developed secondary male sexual characteristics. Therefore, chromosomes are the ultimate indicator of biological sex.³

Gender refers to the social traits and characteristics associated with each biological sex. The terms “masculine” and “feminine” are generally used to refer to gender, e.g., “the masculine demeanor of Marlon Brando.” It should be noted that gender is a social construct and that what is considered masculine or feminine varies significantly from culture to culture. Bolton,⁴ in his book *Bravehearts, Men in Skirts*, exemplified this issue by focusing on the clothing men wear in different cultures and signaling that a man wearing a pleated skirt would be considered effeminate in many western societies but not in others—e.g., kilts among the Scots, or skirts worn by the Evzones of the Greek Presidential Guard. Not only dress codes but also behavioral patterns may be judged differently in various cultural milieus—e.g., holding hands among men is considered effeminate in Western nations, but not so in the Arab world.

Biological men who adopt gender traits generally associated with women and vice versa, or individuals who feel they are “trapped in the wrong body,” are frequently referred to as transgender persons.

Sexual orientation refers to the erotic and/or affectional disposition to the same and/or opposite sex. “Orientation” rather than “preference” is used because most individuals do not experience having ever had a choice about being attracted to women or men. The terms most commonly employed to refer to sexual orientation are heterosexual, homosexual, and bisexual. This “western” nomenclature is not necessarily shared by all cultures, there being not only different words but also different cultural constructs about what sexual orientation is. For example, whereas in the United States a man who has sex with another man is likely to be labeled homosexual, in many Latin American countries it is not the sex of the partner but the behavior that takes place with that partner that determines such label.^{5,6} Thus, a man who always takes the insertive and never the receptive role in anal sex with another man may be considered hypermasculine rather than homosexual.⁷ Among Indian men, their roles as husbands and fathers may define men’s status much more than the kind of sexual behavior they engage in so that same-sex sexual behavior can occur without necessarily raising the question of sexual orientation for those who engage in the behavior. In some communities in India, male homosexual behavior may be seen as play, a way of dealing with sexual “needs,” or maintaining the social norms that restrict sex with women for purposes other than procreation.⁸

Sexual self-identification refers to the way people choose to describe themselves in terms of their sexual orientation. Words like “gay,” “lesbian,” “straight,” and others are used for self-identification. Controversy exists concerning the role culture plays in the reification of such identities, with a school of social criticism, called “queer theory”⁹ underscoring the natural sexual plasticity of human beings. Just like gender traits that may not necessarily coincide with genes, sexual orientation, self-identity, and sexual behavior are not always directly related. For example,

there are individuals with exclusively same sex orientation and behavior who do not consider themselves gay, and gay-identified individuals who have female sexual partners. Thus, the term MSM is often used to describe male homosexual behavior in a way that is inclusive of the different terms that males may use to identify themselves, while engaging in same-sex practices. The recent phenomenon of African American MSM who do not self-identify as gay, stating that they are “on the down-low,” or DL, has been noted in other racial/ethnic communities.¹⁰ This term has been defined as the term referring to men who have sex with other men in secret while maintaining heterosexual relations for public consumption. Williams states that “above all, men on the DL do not think of themselves, much less present themselves to others, as gay.”¹⁰

Distinctions can also be made among behavior, fantasy, and attraction, as famously stated by Kinsey et al.²: “Nature rarely deals with discrete categories. Only the human mind invents categories and tries to force facts into separated pigeon-holes. The living world is a continuum in each and every one of its aspects. The sooner we learn this concerning human sexual behavior, the sooner we will reach some understanding of the realities of sex.”

PREVALENCE OF MALE HOMOSEXUAL BEHAVIOR

The estimates of the prevalence of same-sex intimate behaviors among men are controversial, fraught with methodological problems, ranging from limitations in the ability to extrapolate from limited (often convenience) samples to disagreements about the appropriateness of inclusion of diverse individuals within a cohort (e.g., men who are situationally homosexual in prison, vs. self-actualized men who are “out,” and exclusively homosexual). Laumann and colleagues¹¹ wrote in their comprehensive monograph, *The National Health and Sexual Life Survey*, “Estimating a single number for the prevalence of homosexuality is a futile exercise because it presupposes assumptions that are patently false, that homosexuality is a uniform attribute across individuals, that it is stable over time, and that it can be easily measured.” The prevalence of male homosexual behavior in modern, industrialized societies has been estimated as ranging from 1% to 10%, depending on the sampling interval (e.g., lifetime experience vs. recent contact, or only measuring activities undertaken as an adult) and the behaviors that are considered (e.g., is arousal without physical contact included?).^{12,13} Estimates of recent sexual behaviors of adults suggest that 3–7% of men had a homosexual experience within the past year.^{14–16}

There are no central repositories that provide comparative data about the prevalence of sexual behaviors in diverse subcultures, and only a handful of countries have comprehensive statistics. Sex research, where it exists, tends to be fertility related, rather than sexuality oriented. Often, even definitions

vary regarding these sensitive topics.¹⁷ In societies where the social expression of homosexuality is more constrained because of the implicit assumption that all men must marry, male homosexual behavior may be common, but difficult to address with Western-oriented prevention messages, based on assumptions of the existence of a coherent subculture. For example, one study in rural India found that 10% of single men and 3% of married men reported anal intercourse with another man within the past year.¹⁸

ETIOLOGY OF MALE HOMOSEXUAL BEHAVIOR

Two fundamental theories, essentialism and social constructionism, have been posited to explain the etiology of sexual orientation.¹⁹ Essentialism originated with Plato,²⁰ whose proponents posited that the world is constituted by a finite number of unchanging forms. Modern essentialism implies a belief that certain phenomena are natural, inevitable, universal, and biologically determined. By contrast, social constructionism asserts that reality is ordered by society and everyday reality is shared, with common views of reality becoming institutionalized. Knowledge may be institutionalized at the level of society or within subgroups. *Essentialist theories* underlie many studies that have attempted to find the biological origins of homosexuality.²⁰ For example, Bailey and Pillard²¹ studied identical twin brothers and sisters and found that they have a 52–48% concordance rate of homosexuality; yet, since this observation did not demonstrate 100% concordance, other factors must also be involved. Although LeVay²² found differences in the size of the hypothalamuses of autopsied homosexual men compared to those of heterosexual men and women, a disproportionate percent of the MSM had died of AIDS, raising methodological concerns.

Studies have found no major hormonal differences between male homosexuals and heterosexuals without endocrine disorders.²³ In congenital adrenal hyperplasia, high levels of androgens are produced. Girls with this disease are genetically female and have female reproductive organs but are born with masculinized external genitalia. When raised as boys, these genetic girls usually adopt a male gender identity and role (showing that the Y chromosome is not necessary for gender development in a male direction). When raised as girls from birth, they develop a female gender identity in spite of their prenatal androgenization. The reverse case is androgen insensitivity syndrome, when tissues do not respond to male sex hormones. Genetic boys have genitals that look like female genitals. If raised like girls, they develop a female gender identity in spite of the presence of the Y chromosome. These studies provide strong evidence that gender roles and sexual identities may be more significantly determined by psychological rather than biological factors. Although hormones may not influence gender

identity, they may influence social roles: Girls with congenital adrenal hyperplasia are more likely to be characterized as “tomboys.” Money²⁴ believed that prenatal sex hormones play some part in the development of later sexual orientation, but that whether the individual will be identified as homosexual, heterosexual, or bisexual is strongly dependent on postnatal experience. It is invariably difficult to separate hormonal and environmental influences.²³

Other studies have focused on birth order, suggesting that gay men are more often born later than their male siblings.²⁵ According to Cantor et al.,²⁶ each additional brother increases the odds of homosexuality by approximately 33%. However, only one gay man in seven may have his sexual orientation related to the so-called “fraternal birth effect.” One developmental theory that may explain this effect posits that it might be a by product of a biological mechanism that shifts personalities more in the “feminine” (word used by the author) direction in the later born sons, reducing the probability of these sons engaging in unproductive mating competition with each other.²⁷

Social Constructionism theorizes that sexuality is not expressed identically in all times and cultures, concluding that sexuality is created by culture that defines some relationships as sexual and creates behavioral scripts.²⁸ Foucault²⁹ surmised that sexuality’s meaning is derived from how specific behaviors and actors are described. As a consequence of some of these ideas, a whole new area of study appeared, referred to as Queer Theory. It questioned the very idea of identity and its grounds for looking at sexuality and sexual orientation. One of the main characteristics of the gay movement was that it assumed that sexual orientation provided a common ground for a group of people that shared such orientation, as well as other aspects of their personality and lives.³⁰ One of the main goals of the movement was affirming a presumably stable gay identity, which could be accepted and integrated within mainstream culture, which institutionalized and normalized the establishment of an identity based on (homo)sexual desire. This process created a socially accepted minority status for homosexuals, publicly recognized with rights similar to those of racial or ethnic minority groups. This was done, however, at the expense of excluding marginal manifestations of sexuality. Dissatisfaction with the dominant concept of “gayness” and the emergence of new fractured and dissident kinds of sexual expression led to the development of the idea of “queer,” as an alternative. Queer theorists criticized the essentialist idea of the self as a basic and stable entity⁹ and posited that sex, gender, and sexual orientation evolve over life. None of these are permanently defined at birth (contradicting the famous Freudian principle according to which “biology is destiny”) and can change, be shaped, and evolve, not being constrained by standards of normality imposed by society.³¹

■ CULTURAL CONTEXT OF HOMOSEXUALITY

Aldrich³² wrote that ever since the time of ancient Athens and the Biblical Sodom and Gomorrah, organized homosexual activity has been associated with the city. The migration of homosexual men from rural areas to urban centers has been well known for many years, and the appearance of gay neighborhoods in large cities gave rise to the application of the word “ghetto” in the 1970s to such concentrations. Gay ghettos, like Chelsea in New York or the Castro in San Francisco, are distinctive for the visibility of gay men in public spaces and an abundance of establishments that cater to them. Furthermore, some of the men who live in these areas may adopt a common look, from clothes to haircuts to body types, sometimes being referred to derisively as “clones.” By contrast, many ethnic minority MSM who live in big cities but not in the gay ghettos may adopt different looks, language, and even lifestyle.³³ Therefore, location, socioeconomic level, ethnicity, and value systems may characterize different groups of MSM. Of course, the boundaries between these groups are not rigid and there is interaction between members of different groups, and some men may move between groups over time. Some MSM who are not city dwellers have found Internet as a very efficient tool to feel less isolated. Recent studies³⁴ have used the Internet to recruit MSM in rural areas and have started to shed light on this population. The lack of social supports provided by living in an urban environment has often forced rural MSM to be more covert about their sexual orientation, and to feel more isolated, sometimes resulting in substance use and other manifestations of psychosocial distress.

SEXUAL PRACTICES AND STD/HIV TRANSMISSION

MSM may engage in sexual practices that put them at risk for specific STDs, particularly HIV. Because of logistical and ethical issues, the relative efficiency of STD/HIV transmission per discrete sexual act is difficult to define with precision.³⁴ The majority of studies that document these behaviors tend to follow large cohorts of MSM periodically and infer from participant reports of sexual behaviors the relative transmission risks among the men who become newly infected. Thus, precise estimates of per contact risks are generally not feasible. Unprotected anal intercourse has been generally shown to be most efficient for sexual HIV transmission with an 8.2/1000 contact risk for unprotected receptive anal intercourse with a known HIV-infected partner, and 0.6/1000 contact risk for unprotected insertive anal sex with a known HIV-infected partner.³⁵ The relative risks of HIV transmission with partners whose status is unknown will reflect the background HIV prevalence in specific communities and cultural milieus.

The relative efficiency of fellatio in transmitting HIV is unclear (partially because of the preponderance of at-risk

men also engaging in anal intercourse), but animal data has established biological plausibility.³⁶ Among 2915 MSM followed in the Multicenter AIDS Cohort Study with 9330 person-years of follow-up, 2 men who only engaged in receptive oral intercourse and no anal intercourse were identified among the 232 seroconverters.³⁷ Vittinghoff³⁵ and colleagues estimated the per contact risk of unprotected oral exposure to the ejaculate of HIV-infected or status unknown partners to be 0.4/1000, which was comparable to their estimate of the risk from unprotected insertive anal sex. The role of cofactors may be extremely important in determining the relative efficiency of specific sexual practices for HIV transmission. In a multivariate analysis of factors associated with HIV seroconversion in MSM in a multinational study, Page-Shafer et al.³⁸ found that although oral sex was modestly, but independently, associated with increased risk of becoming HIV-infected (OR: 1.01), the presence of an intercurrent STD (OR: 3.39) and amphetamine use (OR: 2.55) were much more potent independent predictors for HIV seroconversion.

One of the major variables associated with the efficiency of heterosexual HIV transmission is the plasma HIV RNA level of the infected partner.³⁹ Although in a study in Uganda, untreated HIV-infected individuals with lower plasma viral loads were less likely than those with higher viral loads to transmit HIV to their discordant partners, suppressing plasma HIV RNA with antiretroviral medications in patients with longstanding HIV infection has not yet been shown to eliminate HIV transmission. In the United States, although the majority of HIV-infected MSM who meet criteria for initiating treatment are on highly active antiretroviral therapy (HAART), USPHS estimates suggest that HIV incidence is increasing in some subgroups of MSM.^{40,41} Despite the effects of HAART in lowering HIV concentrations in different compartments, HIV RNA has been detected in the semen,⁴² rectal secretions,⁴³ and pharyngeal samples⁴³ of MSM on suppressive antiretroviral therapy.⁴⁴ Reports of increase in sexually transmitted, drug-resistant HIV⁴⁵ also suggest that HAART alone will not necessarily prevent new infections from occurring in MSM. Other cofactors associated with increased HIV transmission among MSM include the use of volatile inhaled nitrates and being uncircumcised.⁴⁶

Other STDs are also efficiently transmitted by anal intercourse, including syphilis, gonorrhea, chlamydia infection, *herpes simplex virus*, and hepatitis B. Many of these pathogens may also be more efficiently transmitted through fellatio than HIV.⁴⁷ Human papillomavirus (HPV) is readily transmitted without anal penetration, and may be autoinoculated from the penis to the rectum in sexually active MSM. Other nontraditional STDs may be readily transmitted by specific MSM practices, e.g., enteropathogens like *Shigella* or *Salmonella* may be spread by oral–anal intercourse (“rimming”) or digital–anal contact (“fisting”) because of the low pathogen inoculum needed to cause infection.

STD TRENDS AMONG MSM

Although the incidence of STDs among MSM initially declined as MSM increasingly practiced safer sex with the advent of the AIDS epidemic,⁴⁸ since the late 1990s STD rates have markedly increased in urban epicenters in the United States (Figs. 13-1 to 13-4), as well as other industrialized nations.^{49,50} Studies have suggested a combination of factors at play, including the perception, with the widespread availability of HAART that HIV infection is not as dire as at the outset of the AIDS epidemic,⁵¹⁻⁵³ lack of engagement with current prevention messages, the increasing popularity of different nonprescription drugs (including methamphetamines, volatile nitrates, known as poppers, and erectile dysfunction drugs) in some subgroups,⁵⁴ and the coming of age of a generation of young MSM who did not witness the devastation of AIDS in the 1980s.

CDC surveillance studies have suggested that recent increases in sexually transmitted infections have been most pronounced among MSM from communities of color, but the secular trends demonstrate STD increases among all subgroups of MSM, independent of race/ethnicity or geographic location.^{55,56} Additional concerns about the increases of STDs in MSM include the potential for epidemiological synergy,^{57,58} increasing incidence of new HIV infections among at-risk MSM, and the risks that untreated STDs could compromise the health of HIV-infected MSM. Specific STD trends are reviewed below.

■ SYPHILIS

Although national syphilis elimination efforts have proven very successful in many communities in recent years,⁵⁹ reports of increasing rates of new infections among MSM continue to occur,⁶⁰ with disproportionate numbers of newly diagnosed syphilis patients being HIV coinfecting.⁶¹ Almost one-quarter (23%) of HIV-infected MSM accessing services at an STD clinic participating in the U.S. Gonorrhea Isolate Surveillance Program (GISP) had a reactive syphilis serology compared to 8% of MSM who were HIV uninfected or whose serostatus was unknown.⁵⁶ Overall, seroreactivity ranged from 4% to 11% by clinic location. The male-to-female primary and secondary syphilis rate ratio increased from 1.2 in 1996 to 5.7 in 2005 (Fig. 13-5), primarily due to the resurgence of syphilis among MSM.⁵⁵ Furthermore, CDC data reveal almost a tripling in median syphilis seropositivity from 4% in 1999 to 11% in 2005 among MSM visiting the STD clinics participating in the national MSM prevalence monitoring project.⁵⁵ However, sustained increases were documented in only 3% of the sites. Syphilis may upregulate HIV expression and replication⁶² as well as CCR5 coreceptor prevalence,⁶³ enhancing HIV transmission to susceptible hosts. The increased prevalence of syphilis in HIV-coinfecting MSM may also reflect “serosorting,” i.e., careful selection by HIV-infected MSM of other infected partners with whom they can have unprotected sex and/or increased

susceptibility to syphilis among HIV-infected patients. Since oropharyngeal chancres may transmit infectious syphilis to insertive partners engaging in oral sex, this practice that is considered safe in relation to HIV transmission may result in new syphilis infections, and safer sex education should take this risk when prevention messages are developed for MSM.

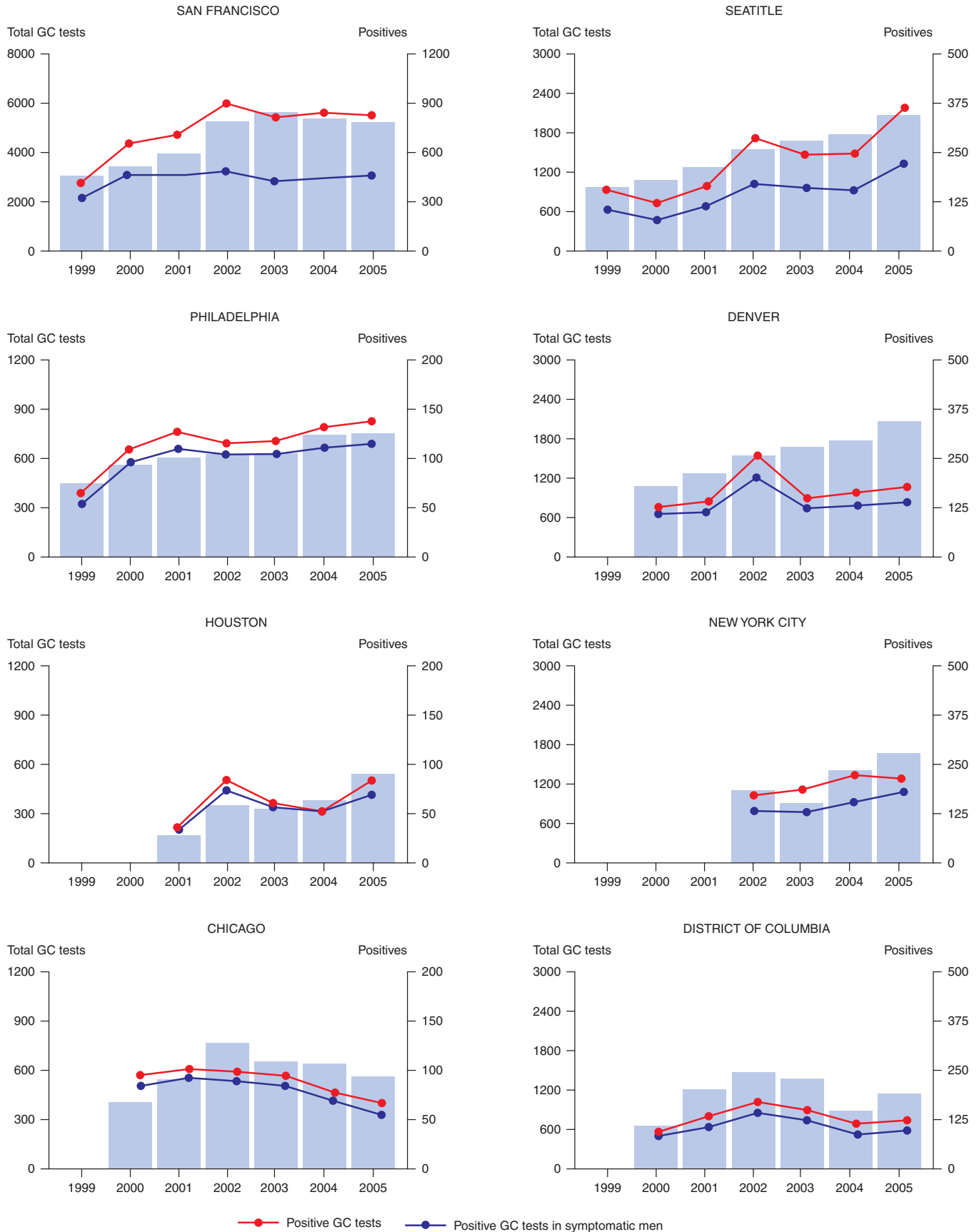
■ GONORRHEA

Gonorrhea rates have also increased in recent years among urban MSM in developed countries, paralleling the rises seen with syphilis.^{64,65} Gonorrhea may be transmitted by fellatio, as well as insertive or receptive anal intercourse, although anal sex is the most efficient means of transmission.⁶⁶ According to the GISP, the proportion of positive test results for MSM increased from 4% in 1988 to more than 20% in 2005.⁵⁵ Between 1999 and 2005, the overall number of gonorrhea test performed from all anatomical sites for MSM increased at GISP clinics, with the majority being done because of symptomatic complaints.⁵⁶ The median clinic test positivity rate was 11% for urethral gonorrhea, 8% for rectal gonorrhea, and 7% for pharyngeal gonorrhea (Fig. 13-6). MSM have accounted for a substantial number of all new gonococcal infections diagnosed at surveillance sites across the country in recent years, particularly on the West Coast (Fig. 13-7).

Increases in unprotected anal intercourse have been paralleled by increases in rectal gonorrhea rates in San Francisco,⁶⁷ which have been postulated to be at least partially responsible for the increased HIV incidence noted by the local health department in the years immediately after the introduction of HAART.⁶⁸ Although some studies of MSM have suggested that gonococcal infection was associated with increased risk of HIV acquisition,⁶⁹ studies from heterosexual cohorts in Africa have not demonstrated such a clear association.^{70,71} However, this may be due to the low prevalence of anal intercourse in these populations. In any event, gonococcal urethritis has been demonstrated to increase seminal HIV shedding eightfold in coinfecting men, with 0.7 log HIV RNA/mL decreases when men were treated with effective antibiotics.⁷² Quinolone-resistant gonococci have been increasingly isolated from MSM, constituting 29% of specimens from MSM in CDC's GISP in 2005 and necessitating the use of expanded spectrum cephalosporins for the treatment of gonococcal infections in MSM, and the recommendation that quinolones no longer be used to treat any gonococcal infection in MSM.^{55,73}

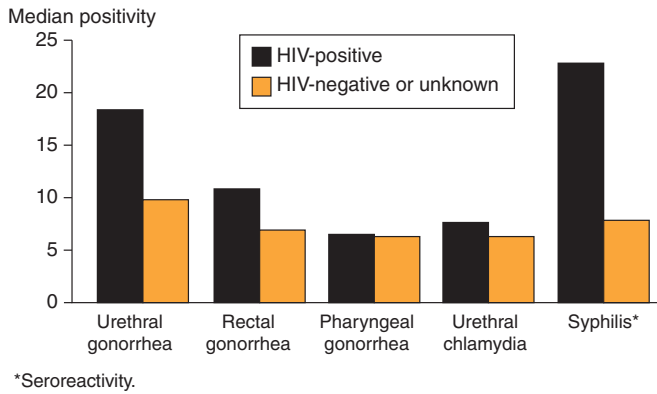
■ CHLAMYDIA INFECTION

Although nongonococcal urethritis (NGU) in MSM may be due to *Trichomonas vaginalis*, *Ureaplasma urealyticum*, and *Mycoplasma genitalium*, *Chlamydia trachomatis* is still responsible for the largest number of cases^{74,75} and also for most cases of nongonococcal proctitis.^{76,77} In 2005, between 5% and 8% of MSM accessing STD services at one of the GISP



Note: The bars represent the number of GC tests at all anatomic sites (pharyngeal, rectal, and urethral) each year. The scales on the left and right axis differ. The bar graphs use the scale on the left. The line graphs use the scale on the right.

FIGURE 13-1. W.MSM Prevalence Monitoring Project—Number of gonorrhea tests and number of positive tests in MSM, STD clinics, 1999–2005.



*Seroreactivity.

FIGURE 13-2. MSM Prevalence Monitoring Project—Test positivity for gonorrhea and chlamydia and syphilis seroreactivity among MSM, by HIV status, STD clinics, 2005.

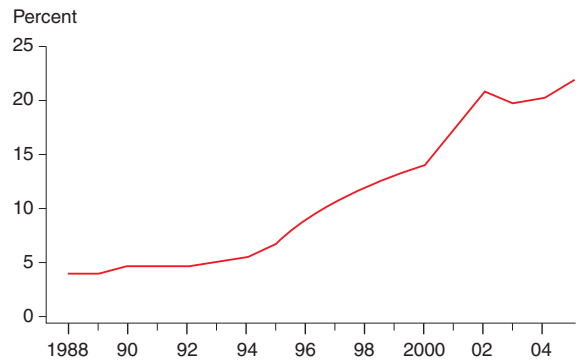


FIGURE 13-3. Gonococcal Isolate Surveillance Project—Percent of urethral *Neisseria gonorrhoeae* isolates obtained from MSM, attending STD clinics, 1988–2005.

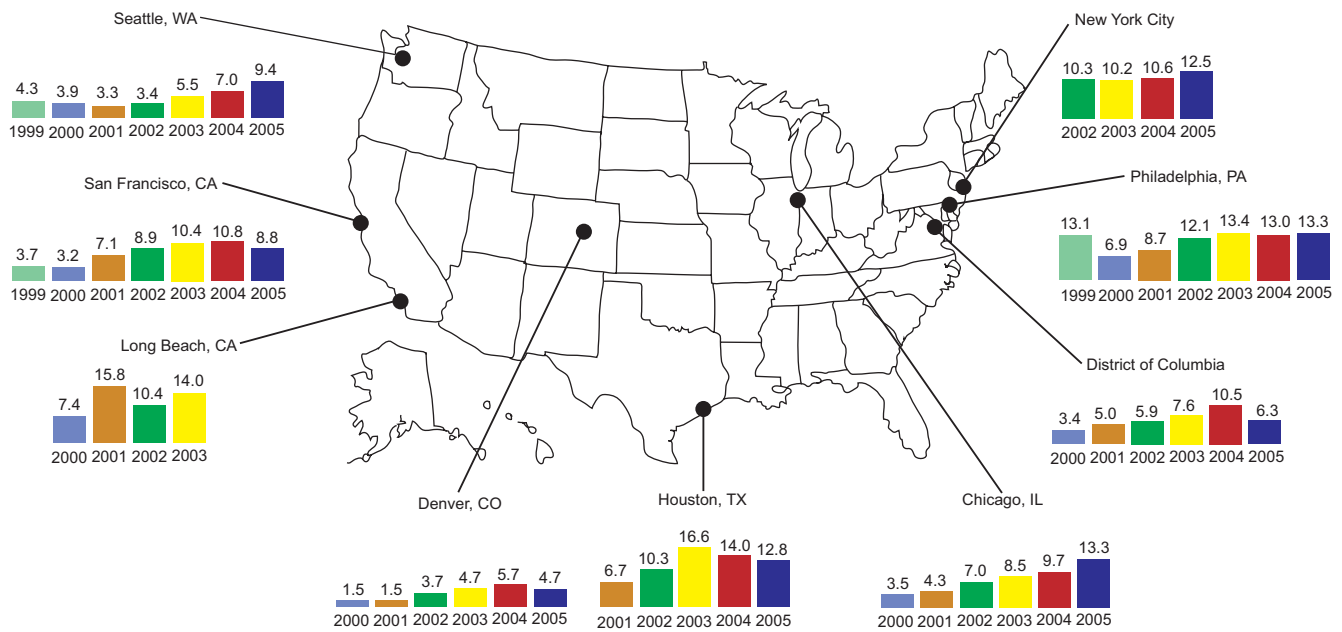


FIGURE 13-4. MSM Prevalence Monitoring Project—Syphilis serologic reactivity among MSM, STD clinics, 1999–2005.

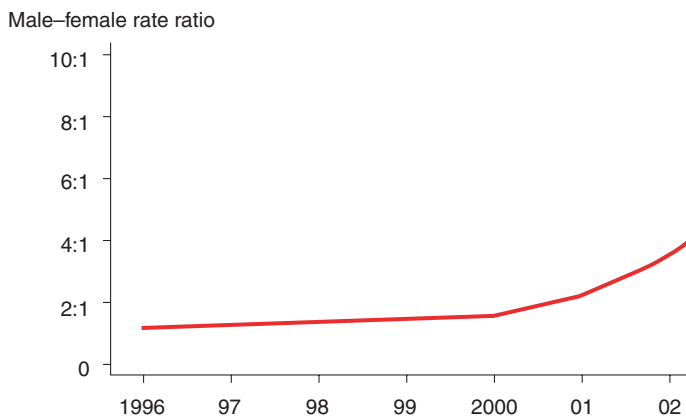
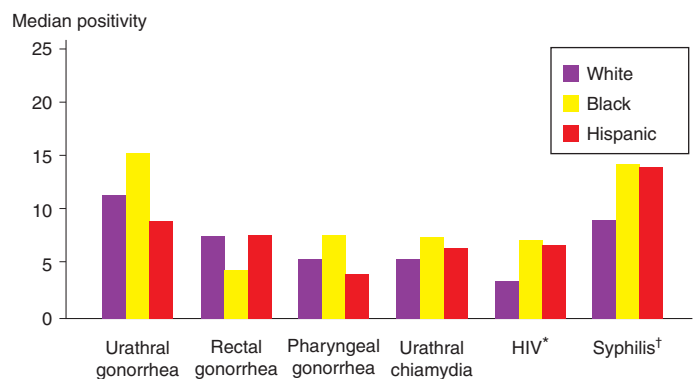


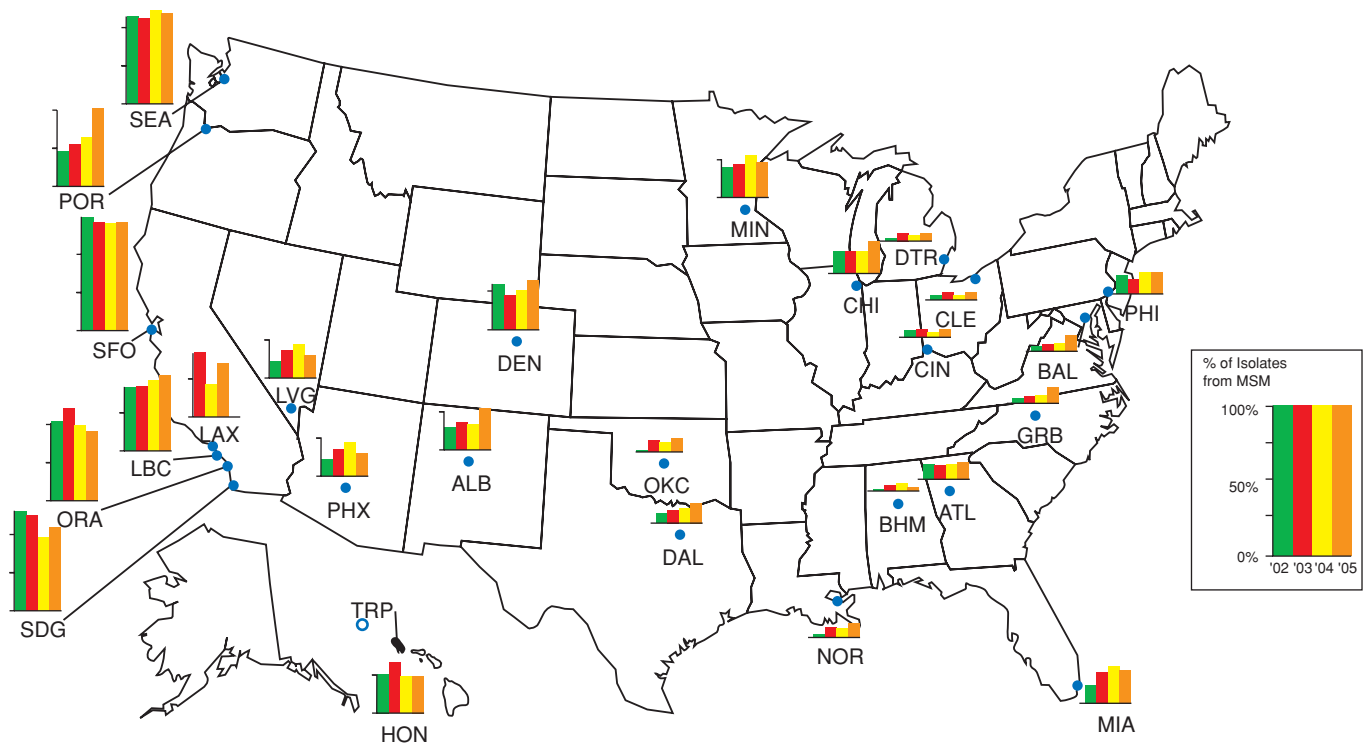
FIGURE 13-5. Primary and secondary syphilis—Male-to-female ratios, United States, 1996–2005.



*Excludes persons previously known to be HIV-positive.

†Seroreactivity.

FIGURE 13-6. MSM Prevalence Monitoring Project—Test positivity for gonorrhea, chlamydia, and HIV and seroreactivity to syphilis among MSM, by race/ethnicity, STD clinics, 2005.



Note: Not all clinics participated in GISP for the last 4 years. Clinics include: ALB = Albuquerque, NM; ATL = Atlanta, GA; BAL = Baltimore, MD; BHM = Birmingham, AL; CHI = Chicago, IL; CIN = Cincinnati, OH; CLE = Cleveland, OH; DAL = Dallas, TX; DEN = Denver, CO; DTR = Detroit, MI; HON = Honolulu, HI; LAX = Los Angeles, CA; LBC = Long Beach, CA; LVG = Las Vegas, NV; MIA = Miami, FL; MIN = Minneapolis, MN; GRB = Greensboro, NC; NOR = New Orleans, LA; OKC = Oklahoma City, OK; ORA = Orange County, CA; PHI = Philadelphia, PA; PHX = Phoenix, AZ; POR = Portland, OR; SDG = San Diego, CA; SEA = Seattle, WA; SFO = San Francisco, CA; and TRP = Tripler Army Medical Center, HI (does not provide sexual risk behavior data).

FIGURE 13-7. Gonococcal Isolate Surveillance Project—Percent of *N. gonorrhoeae* isolates obtained from MSM, attending STD clinics, 2002–2005.

clinics tested positive for urethral gonorrhea.⁵⁵ NGU has been associated with increased seminal HIV RNA shedding in coinfected men^{78,79} and has been associated with increased risk for HIV acquisition in heterosexual cohorts,^{70,71} and thus may be reasonably considered a potentiator of HIV transmission and acquisition among MSM. In 2005, the median chlamydia positivity rate among MSM in CDC's MSM prevalence monitoring project was 6% (range 5–8%).⁵⁵

■ OTHER AGENTS ASSOCIATED WITH NGU

Although the data are scant in MSM, *T. vaginalis* has increasingly been associated with NGU and increased HIV transmission.^{80,81} *U. urealyticum* and *M. genitalium* have also been identified as common causes of NGU.^{82–85} The increased prevalence of genital mycoplasmas and ureaplasmas in HIV-infected patients may reflect their increased immunosuppression, or increase sexual activity prior to HIV acquisition, but may also serve to upregulate genital tract HIV and potentiate its transmission.⁸⁶

■ LYMPHOGRANULOMA VENEREUM

LGV proctitis was first described in MSM more than 60 years ago⁸⁷—a distinctly different syndrome than LGV infection of

the genitourinary tract, which has most often been associated with inguinal adenopathy with draining buboes. LGV proctitis was also described just prior to the onset of the AIDS epidemic among U.S. MSM,^{88,89} suggesting that the increasing recent recognition of this syndrome^{90,91} may reflect the increasing unprotected anal sex among MSM with the wider propagation of an endemic STD pathogen.⁹² In a prospective study of rectal swabs of MSM presenting for STD screening in San Francisco, 7% of 205 men had positive nucleic acid amplification tests for chlamydia infection and 36% of those specimens were LGV.⁹³ Because of the potential for unrecognized LGV to cause ulcerative proctitis with serious sequelae, recommendations have been made for increased surveillance to establish the incidence of LGV among at-risk MSM to inform optimal standards of clinical care.⁹²

■ HERPES SIMPLEX VIRUS TYPE 2

Herpes simplex virus type 2 (HSV-2) is extremely prevalent in the general population worldwide,^{94–96} with more than one-fifth of the U.S. population being infected with HSV-2.^{97,98} The prevalence is much greater in sexually active MSM, with more than half of any survey of MSM demonstrating seroreactivity.⁹⁹ HIV has been readily detected by PCR from HSV-related

male genital ulcers of 70% of a certified cohort in one series,¹⁰⁰ consistent with data supporting its role in potentiating HIV transmission.¹⁰¹ Large public health trials are underway to assess whether the ongoing use of acyclovir—an HSV-2 thymidine kinase inhibitor—can protect HSV-2-infected, HIV-uninfected high-risk individuals from HIV acquisition, or decrease the likelihood of HIV transmission by HIV-1/HSV-2 coinfecting individuals.

■ HUMAN PAPILLOMAVIRUS

HPV is thought to be the most common STD in the United States and other developed countries,¹⁰² with more than 85% of HIV-infected MSM being HPV coinfecting^{103–105} and the prevalence of HPV in HIV-uninfected MSM being consistently greater than 50%.^{105,106} HPV is primarily spread between male sexual partners through insertive or receptive anal intercourse,¹⁰⁷ but may also be transmitted by oral sex,¹⁰⁸ digital–rectal contact,^{109,110} and scrotal contact.¹¹⁰ Reports of anal cancer in HPV-infected MSM have led to suggestions that routine anal screening for atypia and proactive management of precancerous lesions should be part of the primary care of MSM engaging in anal intercourse.^{111,112}

HIV TRENDS AMONG MSM

Since the first cases of AIDS were reported in the United States in 1981, MSM have been disproportionately affected by this epidemic, with about two-third of the men living with AIDS in 2002, having reported male homosexual intercourse as their route of infection,⁴⁰ despite MSM comprising less than 10% of adult U.S. males.^{15,16} More than half a million MSM in the United States have been diagnosed with AIDS, and more than 200,000 have died since the start of the epidemic.⁴⁰ With the advent of HAART, deaths related to AIDS decreased dramatically in the mid 1990s. However, approximately 40,000 Americans continue to be newly infected with HIV every year.⁴⁰ HIV incidence had initially increased among MSM in San Francisco, despite wide utilization of HAART, because of increased sexual risk taking and increased rates of STDs.⁶⁸ Although rates seem to have subsequently stabilized in Massachusetts, recent figures from the Department of Public Health indicate that 10% of all cases of HIV were newly diagnosed within the past year, and almost half of them were among the MSM.¹¹³

Because larger numbers of HIV-infected MSM are living longer and feeling healthier on HAART, they may be engaging in risky sexual practices. Their providers need to assist them in developing the skills to negotiate complex social issues, including the development of behavioral changes that will prevent HIV transmission to their sexual partners.^{114,115} These secondary prevention efforts are critical for curtailing new infections.¹¹⁶ Several studies have shown that 20–30%

of HIV-infected MSM engage in risky sexual practices frequently and consistently.^{117–119} Kalichman and colleagues¹²⁰ found that 23% of their sample of HIV-infected MSM reported three or more sexual encounters involving unprotected anal intercourse within the past month. Marks and colleagues¹²¹ found similar results in their large sample of HIV-infected MSM. Twenty percent of their cohort engaged in unprotected anal intercourse within the previous 2 months, representing an increase in unprotected anal intercourse in a comparable cohort of HIV-infected MSM they followed from 1996–2000. Rates of unprotected anal intercourse appeared stable between 1996 and 1998, but then increased nearly 50% between 1998 and 2000 after the advent of HAART. In this study, the cumulative probability of a participant engaging in insertive, unprotected anal intercourse with an HIV-uninfected or unknown partner increased from 13% in 1996 to 25% in 2000. Unprotected anal intercourse also appears to be increasing among HIV-uninfected MSM.¹²² In a sample of 13,415 MSM in Seattle, rates of unprotected anal intercourse increased nearly 20% over 3 years, with greater rates of unprotected sex among young men and men of color.

The advent of HAART has not eliminated the AIDS epidemic among MSM. HIV-infected MSM are clearly living longer due to HAART, but the increasing therapeutic armamentarium may result in morbidity for some.¹²³ Although people with lower plasma HIV RNA concentrations may be less likely to transmit HIV to their partners,³⁹ HIV can replicate independently in the genital tract. The increasing rates of transmission of drug-resistant HIV to newly infected people⁴⁵ suggests that ongoing behavioral research will be needed to optimize biological approaches to HIV prevention. Additional concerns include the possibility of HIV superinfection and viral recombination when HIV concordant couples engage in unprotected intercourse,¹²⁴ and therefore prevention messages need to apprise HIV-infected persons of the desirability of safer sex to protect themselves, as well as their partners, independent of HIV status.

FACTORS THAT POTENTIATE TRANSMISSION

Despite a collective understanding and knowledge about the modes of HIV transmission, HIV rates are on the rise. The potential causes are complex and unique to each individual. The conventional wisdom that MSM are optimistic about current HIV treatments or that “prevention fatigue” has caused increased sexual risk taking has yielded mixed results when subject to empirical scrutiny.^{125–128} Factors consistently shown to be associated with increased risk taking include a lack of willingness to change one’s sexual behaviors,¹²⁰ emotional distress,¹²⁹ ongoing substance use,¹²⁰ past sexual abuse,¹³⁰ sex with familiar partners,¹³¹ a diminished sense of sexual control,^{132,133} and sexual compulsivity.¹³⁴

Fenton and Imrie¹³⁵ attempted to account for recent increases in rates of STDs among MSM in Western Europe and the United States. The authors discuss individual level factors, infectious agents, sociocultural environment, and biomedical environment. Within individual level factors, they mention demographic changes (increases in the proportion of men reporting same-sex experiences and intercourse, increased survival of MSM because of HAART, and increases in HIV-positive MSM populations), sexual risk behaviors (increases in unsafe sex, sex partner change rates, sex partner concurrency, serosorting, and payment for sex), and proximal determinants of sexual risk behavior (recreational drug use, drug abuse, and mental illness). Among the factors related to infectious agents, the authors include resistance and the interaction between STDs (antimicrobial and antiretroviral resistance, interaction between HIV and bacterial STDs, and epidemiologic synergy). Among sociocultural environment factors, the authors list the growth in the sexual marketplace (Internet, sex on premises venues, circuit and sex parties, and sex tourism), socioeconomic status (lower socioeconomic status and lower educational attainment), and changing cultural environments that facilitate high-risk behavior (barebacking, discrimination, homophobia, and HAART optimism). Finally, among factors related to the biomedical environment, they point out the inability of health services to effectively intervene (e.g., MSM seek care in the private sector which may be less amenable or accessible to STD prevention interventions, public health department staff may be less used to dealing with MSM issues or clients, and effectiveness of traditional disease control interventions—e.g., partner notification—with MSM may be reduced because of high proportions of anonymous partners). In sum, there is a wide range of factors that may potentiate each and facilitate sexual risk behavior. This analysis highlights the need to intervene at the personal, interpersonal, community, and structural level if durable decreases in MSM STDs are to be achieved.

INTERVENTIONS TO REDUCE STD/HIV TRANSMISSION IN MSM

Several theoretical models developed in the past two decades have attempted to organize diverse research findings into coherent and comprehensive behavioral models. Some of these have been tested empirically through randomized controlled trials, and for other models, different levels of support were found for their effectiveness in modifying risk behavior.¹³⁶ Yet, the studies did not have the statistical power or long-term follow-up required to show intervention effects on HIV incidence, itself. Three of the most common psychosocial models that have been employed to explain HIV risk taking are the health belief model, the theory of reasoned action, and social cognitive

theory.^{137,138} Health belief models emphasize the role of perceived benefits and barriers to condom use and perceived vulnerability to and consequences of getting HIV infection.¹³⁹ In the theory of reasoned action,^{140,141} health behavior, such as condom use, is a function of intentions to use condoms and, in turn, intentions to use condoms are a function of variables such as attitudes and norms regarding HIV and condom use. Social cognitive models explain condom use as a function of individuals' knowledge about HIV, their expectations about the outcomes of using condoms (i.e., pleasure reduction vs. disease prevention), and their own self-efficacy or capability to use a condom in different sexual situations.^{142,143} These psychosocial models of HIV risk-related behavior have been tested both cross-sectionally and longitudinally in a variety of populations, including HIV-infected individuals.

In a recent meta-analytic review,¹⁴⁴ Herbst et al. searched published and unpublished English language reports of HIV behavioral interventions to reduce sexual risk behavior of MSM. The authors found data from 33 studies described in 65 reports available as of July 2003. After careful comparisons of all reports that offered sufficient data to calculate effect sizes, the authors concluded that there was evidence that the reported interventions were associated with significant decreases in unprotected anal intercourse and number of sexual partners, and with a significant increase in condom use during anal intercourse. Furthermore, the authors found that interventions successful in reducing risky sexual behavior were based on theoretical models, included interpersonal skills training, incorporated several delivery methods, and were delivered over multiple sessions spanning a minimum of 3 weeks. A prior systematic review¹⁴⁵ had also found that interventions that had been evaluated through rigorously controlled trials had shown a reduction in the proportion of men engaging in unprotected anal intercourse. These authors pointed out that the most clearly favorable effects were observed among interventions that promoted interpersonal skills, were delivered in community-level formats, or focused on younger populations or those at higher behavioral risk.

The CDC has compiled a Compendium of HIV Prevention Interventions with Evidence of Effectiveness,¹⁴⁶ which has included five interventions specifically designed for MSM that had been rigorously evaluated and proven effective. Of the community-level interventions, the Popular Opinion Leader program¹⁴⁷ was developed first and conducted in one small city with two other cities used for comparison. The intervention was based on theories of peer influence, social and behavioral norms, and diffusion of innovation and was composed of two parts. The first consisted of a four-session intervention with persons who were popular with others that focused on HIV education and communication strategies. In the second part, these

participants committed to having conversations with 14 peers regarding HIV risk reduction. Before and after this intervention, surveys were conducted among men patronizing gay clubs in the intervention and comparison cities to assess for high-risk sexual behavior. The authors found that the intervention was effective in reducing the proportion of men in those cities who engaged in high-risk activities as well as in increasing the precautions taken by this population. This intervention is currently being evaluated in a multicenter randomized controlled trials involving cities in China, India, Peru, Russia, and Zimbabwe.

The Mpowerment Project,¹⁴⁸ building on the diffusion of innovation components of the POLs intervention, focused on young gay men and was conducted during an 8-month period in Eugene, OR, with Santa Barbara, CA, serving as a comparison city. The intervention had three components: peer outreach aimed at diffusing the safer sex message through the community, small groups of gay men focusing on factors that contributed to unsafe sex among young men, and a publicity campaign which aimed to establish the program in the community and urge the participation of young gay men. A survey assessing sexual behavior, psychosocial factors, and exposure to intervention activities was conducted before and after the intervention to young gay men in both cities. The authors found a significant reduction in the proportion of men in the experimental community reporting unprotected anal intercourse during the previous 2 months, across different types of partners.

The CDC AIDS Community Demonstration Projects¹⁴⁹ tested a community-level intervention aimed at different high-risk groups, including intravenous drug users, their female partners, sex workers, high-risk youth, and non-gay-identified men who have sex with men. The intervention consisted of theoretically based role model stories that were distributed along with condoms and bleach by community members who also encouraged behavior change. The outcome measures focused on movement on the Stages of Change continuum for condom and bleach use, exposure to the intervention, and condom carrying. The authors reported that the intervention led to significant progress in adopting HIV risk-reduction behaviors. However, the assessment of condom use during anal sex with nonmain partners, which was of particular importance in assessing the impact of the intervention among MSM, is still part of an ongoing study.

Results from the two small-group-based interventions were reported in close proximity. The experimental group in the Behavioral Self-management and Assertion Skills intervention received 12 weekly group sessions of 75–90 minute duration which covered the areas of AIDS risk-reduction, behavioral self-management, assertion skills training, relationship skills and social support development, and risk-reduction review.¹⁵⁰ Measures for the study included

a risk history, a risk-behavior monitoring journal, self-report inventories, AIDS risk knowledge test, and sexual assertiveness role plays. The intervention produced a reduction in risk behavior among the experimental group that was not replicated in the control group. While not all risk behavior changed, a significant reduction in unprotected anal intercourse among the experimental group was seen. Furthermore, the experimental group experienced increased assertiveness skills in relation to HIV risk behavior, as well as increased AIDS risk knowledge.

In contrast to the other interventions discussed,¹⁵¹ Valdiserri and colleagues compared the effectiveness of two small group interventions, both providing an educational component, but only one incorporating a skills training component. The outcome variables focused on self-reported sexual behavior, particularly on condom use for insertive and receptive anal intercourse. The educational intervention, which lasted 60–90 minutes, covered HIV transmission and infection, clinical outcomes of HIV infection, risks of specific sexual practices, appropriate use of condoms, importance of “safer sex,” and the interpretation of HIV test results. The enhanced intervention, lasting 140 minutes, consisted of this exact educational material plus the use of role plays, psychodrama, and group process as part of skills training aimed at promoting acceptability of safer sex, and facilitate the modification of high-risk behaviors. Participants were randomized into one of the interventions. Results revealed that skills training increased condom use for insertive anal intercourse, but no change was seen in relation to receptive anal intercourse.

Two more recent HIV-prevention interventions focused on MSM are the Project Explore study and the Seropositive Urban Men’s Intervention Trial (SUMIT). Blending components of motivational interviewing, the Project Explore information-motivation-behavioral skills model, and social learning theory, the intervention consisted of 10 one-on-one sessions followed with maintenance sessions every 3 months, with the primary outcome being HIV seroconversion.^{149,152} The study, carried out in six U.S. cities, enrolled 4295 MSM. The results from Project Explore demonstrated a modest benefit in HIV risk-taking behavior among men in the intervention arm compared to controls, but the difference in HIV incidence rates was small, and suggested that the intervention would not be sufficient to curb the continued HIV epidemic among MSM.¹⁵³ The annualized HIV incidence among all study participants was 2.1%, underscoring the need to develop more robust prevention interventions.

SUMIT¹⁵⁴ was based on the findings of the Seropositive Urban Men’s Study (SUMS) and was conducted in New York City and San Francisco. HIV-infected MSM participants were randomized into either a single-session educational session or an enhanced six-session intervention,

which included group activities aimed at promoting the adoption of safer sex practices with uninfected partners, and the disclosure of HIV status. Preliminary results indicate that the intervention was not effective in reducing transmission risks over time or in improving rates of HIV disclosure, underscoring the need for more effective interventions in this population, as well.

Interventions for HIV-infected patients in care have shown some efficacy in decreasing HIV risk-taking among MSM.^{155,156} The Options Project¹⁵⁵ involved training providers to deliver prevention messages to their patients via a “prevention prescription,” while the Partnership for Health involved provider training and the use of diverse printed materials, including posters and educational materials that patients could read in the waiting room or at home. These interventions and other modest steps that providers can use to help promote safer sex among MSM are discussed in recent publications by the CDC.^{40,146,157}

Despite the success reported for some interventions in promoting safer sexual practices among MSM, rates of high-risk sexual behavior are increasing among MSM in important urban centers in the developed world. Speculating on why this is the case, Elford and Hart¹⁵⁸ pointed out that it is uncertain whether experimental behavioral interventions shown to be effective in one setting, place, or moment can be generalized to another. They concluded that investigators need to develop programs of research addressing the transferability, sustainability, and effectiveness of sexual health promotion among MSM.

Kippax and Race¹⁵⁹ argued that a successful response to the epidemic among gay men—and drug users as well—is dependent on their being positioned, and positioning themselves, as responsible agents in charge of their own lives and the well being of their communities. They suggested that the medical encounter could be used to augment the prevention efforts and rather than apposing treatments with prevention, treatment can be in entry point for many prevention interventions, both by creating a trusting environment, where prevention education may be readily accepted (an “educable moment”) and by enabling the provider to address some of the underlying issues (ranging from depression to active substance use) that enhance the likelihood of persisting risky sexual practices.

PUBLIC HEALTH PRACTICE AND MSM

Several investigators have called attention to the need for structural and environmental interventions to promote safer sexual practices among MSM,^{160,161} focusing on economic issues (e.g., poverty); mobility, including migration, seasonal work, and social disruption due to war and political instability; gender inequalities; and the effects of particular governmental and intergovernmental policies in

increasing or diminishing HIV vulnerability and transmission. Ameliorating problems that may enhance risk taking (e.g., economic necessity) may help to reduce sexual risk taking in some cases, but innate sexual desires may not be amenable to change despite improvement in standards of living for many MSM.

There are no definitive public health data that demonstrate that specific local structural interventions, such as closing gay bathhouses, have led to reductions in rates of STDs. However, it may be argued that criminalization of homosexual behavior has never eradicated the desire to engage in specific practices. Punitive legal constraints and homophobic social environments could serve to drive such activity underground, making it harder for public health officials to identify sexual contacts. Some have argued for a model of sexual harm reduction, which uses places where risky sexual practices occur, like bathhouses, as sites where STD screening and HIV rapid testing may be performed in for the most appropriate MSM populations.^{162,163} Others have suggested that decriminalization of homosexuality and the promotion of stable same-sex relationships through the promulgation of civil unions or homosexual marriage might help to normalize monogamy among MSM and lead to a decrease in STD acquisition and transmission. The governments of several European countries, Canada, and Australia have been able to work with the gay community to create culturally sensitive legal and public-health environments, allowing for the effective detection and treatment of STDs and HIV infection; however, none has seen a diminution in the recent increases in new infections among MSM. It is possible that many of the social changes that allow for the general society to accept homosexual behavior have happened so recently that their effects on community norms and individual behavior will not be discernable for several years. It is also feasible that other societal changes, ranging from the decline in heterosexual marriage, the high rates of divorce, and the advent of meeting partners on the Internet, and other private venues, may mean that for at least a subset of MSM, there will be minimal cultural inducements toward monogamy.

If for the foreseeable future, a subset of MSM continue to engage in risky sexual practices, then optimal public health practice must be to educate them and their providers about the prevalence, signs, symptoms, and clinical consequences of STDs and HIV infection. The U.S. Public Health Service has developed guidelines for routine screening for MSM for STD and HIV (Table 13-1).¹⁶⁴ Interventions to motivate busy providers to pay increased attention to public-health recommendations are needed, as well as intensified efforts in alerting and educating at-risk MSM, if the disturbing trends in high HIV and STD prevalence and incidence among MSM are to be reversed.

Table 13-1. CDC Recommendations for STD Screening for Men Who Have Sex with Men^a**Annual screening of sexually active MSM for**

- HIV serology, if HIV seronegative or not tested within the previous year
- Syphilis serology
- A test for urethral infection with *N. gonorrhoeae* and *C. trachomatis* in men who have engaged in insertive intercourse^a during the preceding year
- A test for rectal infection^b with *N. gonorrhoeae* and *C. trachomatis* in men who have had receptive anal intercourse^a during the preceding year
- A test for pharyngeal infection^b with *N. gonorrhoeae* and *C. trachomatis* in men who have acknowledged participation in receptive oral intercourse^c during the preceding year; testing for *C. trachomatis* pharyngeal infection is not recommended
- Some specialists would consider type-specific serologic tests for HSV-2, if infection status is unknown
- Routine testing for anal cytologic abnormalities or anal HPV infection is not recommended until more data are available on the reliability of screening methods, the safety of and response to treatment, and programmatic considerations
- More frequent STD screening (i.e., at 3–6 month intervals) is indicated for MSM who have multiple or anonymous partners, have sex in conjunction with nonprescription or nonmedically indicated drug use, or whose sex partners participate in these activities

^aAdapted from Sexually Transmitted Disease Guidelines, *MMWR* 2006; 55 (RR-11): 1–100.

^bProviders should use a culture or nucleic acid amplification test that has been cleared by the FDA, or locally verified in accordance with applicable statutes.

^cRegardless of history of condom use during exposure.

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Lesbian Sexual Behavior in Relation to STDs and HIV Infection

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INTRODUCTION

The term “lesbian” derives from the Greek island of Lesbos, home to the famous Greek poetess Sappho (c 600 BC), whose erotic tributes to both male and female lovers continue to undergo fresh translation into the twenty-first century.¹ The Oxford English Dictionary defines the term as both an adjective (“of a woman: homosexual, characterized by a sexual interest in other women. Also, of or pertaining to homosexual relations between women”) and a noun (“a female homosexual”).² Because of the relatively wide implications of these definitions, the use of the term in the scientific literature has given rise to considerable debate and confusion. The term has been used variably, and often carelessly, to convey information about each of three distinct axes of sexuality (orientation, behavior, and identity, discussed further below). Many authors (and readers) assume that use of this term conveys relevant information about all three axes. This confusion has been compounded by a relatively widespread assumption that women who self-identify as lesbian presumably do not have a history of sex with men, and certainly, are not still sexually active with men. Unfortunately, imprecise terminology, assumptions about sexual practices and previous sexual history, and general ignorance of the complexity of women’s sexuality have all contributed to the relative lack of sophisticated, long-term data on the sexual practices, preferences, and history of a highly diverse group of women. Moreover, it can be difficult to compare data derived from studying this group over time, as relevant social and sexual mores (for example, acceptance of public discussion of homosexuality in the popular media) can evolve rapidly.³

To compound these challenges, the availability of the term “lesbian” has been problematic for researchers seeking a convenient and accurate way to refer to the population of women who report sex with other women. Some investigators have used the term to convey a description of sexual contact between women, leaving aside entirely the question of whether subjects identify as lesbian. Others have simply assumed that self-identification as a lesbian connotes current

sexual practice with women. Some authors now use the term *lesbian and bisexual women* to (often vaguely) account for all possibilities, while others have adopted “women who have sex with women (WSW)” for studies that have emphasized outcomes focused on sexual behaviors (as a parallel to men who have sex with men, or MSM). The use of the term WSW has evoked a range of responses in the literature, from perplexity to hostility; some have derided the term for its unwieldiness, “political correctness,” or insensitivity to the rich nature of sexual identity.^{4,5} Interestingly, no such reaction was reported immediately pursuant to the increasingly widespread use of “MSM.”

For ease of reference, in this chapter we use the term *lesbian* as a function of sexual behavior: to define women who have sex with other women. When appropriate, the term “bisexual” will be used to imply sexual behavior with men and women. When referring specifically to the axis of sexual identity, these terms will be prefaced with the phrase “self-identified.”

EPIDEMIOLOGY OF LESBIAN AND BISEXUAL BEHAVIOR

Data to describe the population of women who practice sex with other women, whether or not they self-identify as lesbian, are limited for several reasons. The challenges of terminology are noted above. Moreover, while the social stigma associated with disclosure of homosexuality has lessened markedly in the last two decades, many individuals may still be reluctant to disclose these behaviors or feelings, even in the context of a supposedly anonymous or confidential survey, for fear of exposure and negative consequences. This may be particularly true for lesbians who live outside of major urban areas, which have traditionally provided a relative safe haven for gay people. Critically, lesbians have been invisible in the data collected as part of the national disease surveillance systems and major national women’s health studies. The Women’s Health Initiative did not begin to collect information on same-sex behavior or sexual identity

until 1998, and the Nurses' Health Study began to do so in 1995.⁶ These omissions allowed the loss of valuable opportunities to prospectively compare important long-term health outcomes for lesbians and heterosexual women. Critically, among 350 subjects participating in a pilot questionnaire to assess disclosure of sexual orientation and response rates in the Nurses' Health Study II, disclosure rates were similar to the 91,654 subjects participating in the larger cohort study; the investigators concluded that questions on sexual orientation could be added to large studies of women without affecting response rates.⁷

In 2000, the U.S. Census for the first time collected and reported information referent to households in which two unmarried adults reported being the same sex and had a close personal relationship with each other.⁸ Although these data do not specifically focus on sexual behavior, they provide an indirect and necessarily incomplete window into the prevalence of females who cohabit. With data enumerated from 105.5 million households in the United States, 297,061 women indicated that they were unmarried partners living in same-sex households at the time of the survey. Other investigators subsequently indicated that this value may underestimate the total population of lesbians living in same-sex households by as much as 72%.⁹ Importantly, 15% of all (male and female) cohabitating same-sex couples who responded to the census resided in rural settings. As noted by O'Hanlon, if one assumes a prevalence of 2% of lesbians among the 146,707,720 adult women estimated to reside in the United States by these census data, the U.S. population of lesbians is approximately 3 million.¹⁰ This number is close to the 2.3 million U.S. women previously estimated to identify as lesbians.¹¹ Aaron and colleagues employed a methodology used in estimating numbers of rare wildlife species to get at the population estimation problem in a different way.¹² Using identifying data for a county in Pennsylvania and a "capture-recapture" approach with log-linear modeling, they estimated that lesbians comprised 1.87% (95% CI, 1.56–2.28%) of the total county population. Other investigators have used area probability sampling, facilitated by U.S. census tracking, to enhance the proportion of lesbian respondents within the methodologic confines of a population-based approach.¹³

Very few large-scale surveys in which sexual behavior was specifically assessed have reported on the frequency or nature of same-sex behavior among women, or assessed measures of self-identity as lesbian. Those that have done so have employed different recruitment methodologies and, critically, have asked relevant questions in different ways. Directly comparing findings from different surveys is further complicated by the fact that large temporal gaps often exist between them. These gaps may have encompassed major shifts in social norms regarding homosexuality, which significantly impact practices about disclosure.

For example, the National Health and Social Life Survey, an area probability sample of 3432 U.S. adults aged 18–59 interviewed in 1992, found that 4.3% of women surveyed reported same-gender sex since puberty and that 8.3% demonstrated at least one of the three components of homosexuality: desire, identity, or behavior.¹⁴ The investigators in that study interviewed subjects face-to-face. More recently, investigators reported findings from the National Survey of Family Growth (NSFG), which collected report of sexual behavior using audio computer-assisted self-interviewing (A-CASI) in a national sample of 12,571 males and females in the household population of the United States.¹⁵ As detailed in [Table 14-1](#), in 2002, among women 15–44 years old, the percentage reporting same-sex behavior during their lifetime was 11% and, during the last year, 4.4%. Interestingly, among women 18–44-years-old, of the 10% who did not think of themselves as heterosexual, the breakdown was 1.3% "homosexual," 2.8% "bisexual," 3.8% "something else," and 1.8% with no answer. The fact that the majority of women who did not classify themselves as heterosexual called themselves "something else," and that this category was cited much less frequently by nonheterosexual male respondents than by the corresponding female group, emphasizes the need for further study regarding research on women's self-defined sexual identity. The NSFG percentages translate to 2.29 million U.S. women 18–44 years of age who self-identify as either homosexual or bisexual.

Findings from a large population-based survey of sexual behavior in adults in the UK have recently been reported.¹⁶ The National Survey of Sexual Attitudes and Lifestyles (NATSAL) 2000 study was a probability sample survey of 11,161 respondents aged 16–44 years who were resident in Britain, with intentional oversampling of London residents.¹⁷ Respondents were interviewed by CASI for the sexual history portion of the assessment, and "WSW" was defined liberally as any woman reporting at least one female sex partner in the past 5 years. Of all female respondents, 4.9% reported any same-sex experience involving genital contact, with 2.8% reporting that this had occurred in the last year. In accord with other surveys, most of the WSW thus defined (98%) reported prior sex with men, with 85% reporting that this had occurred in the past 5 years.

Although the data above are incomplete and do not provide an in-depth picture of the true prevalence of same-sex behavior among women, the most recent estimates are surprisingly consistent, indicating that approximately 2–2.8% of the adult U.S. and UK populations may be lesbian. Apart from the general caveats regarding the conclusions of these surveys, it is important to emphasize that ensuring a representative population-based sample may still not obviate variability in successfully eliciting disclosure of same-sex behavior from women of different cultures and

Table 14-1. Number of Females 15–44 Years of Age and Percentage Reporting any Same-Sex Sexual Contact in the Year Prior to Interview and in Lifetime, by Selected Characteristics: National Survey of Family Growth, U.S., 2002

Characteristic	No. in Thousands	Lifetime(%)	Last Year(%)
All respondents 15–44 years of age	61,561	11.2	4.4
Age (years)			
15–19	9,834	10.6	7.7
20–24	9,840	14.2	5.8
25–44	41,887	10.7	3.4
25–29	9,249	14.1	3.6
30–34	10,272	9.1	3.0
35–39	10,853	12.3	4.5
40–44	11,512	7.8	2.4
Residence			
Metropolitan, central city of 12 largest MSAs	8,538	14.1	5.6
Metropolitan, central city of other MSAs	14,082	12.7	5.2
Metropolitan, suburb of 12 largest MSAs	13,981	9.6	4.5
Metropolitan, suburb of other MSAs	14,079	11.4	3.8
Nonmetropolitan	10,880	8.9	3.3

MSA, metropolitan statistical area.

With permission from Mosher WD, Chandra A, Jones J. Sexual behavior and selected health measures: Men and women 15–44 years of age, United States, 2002. *Advance Data from Vital and Health Statistics*, Vol. 362. Hyattsville, MD: National Center for Health Statistics, 2005.

ethnicities within the larger populations, and from adolescents.¹⁸ The likelihood of reporting sensitive behaviors such as sexual practices could be markedly modified by membership in some of these groups. For example, analysis of eight school-based adolescent health surveys in the United States and Canada from 1986 through 1999 revealed that nonresponse rates for questions about sexual orientation (but not for other comparable variables) were higher for younger students, immigrants, and students with learning disabilities.¹⁹ In a related analysis, self-report of both sexual orientation and sexual behavior revealed significantly higher prevalence of homosexual, bisexual, and unsure responses among 12,978 reservation-based American-Indian adolescents compared to 11,356 Anglo-American adolescents, but the nonresponse rate for these questions was also significantly higher among the former group.²⁰ Further, no systematically collected data on same-sex behavior are available from women in non-Western or developing countries. Alternative approaches will be required to fully characterize

the spectrum of same-sex behavior among women of diverse ethnic backgrounds and geographic regions, particularly because health outcomes themselves are likely adversely affected by “dual” minority status (race and sexual orientation).²¹

SEXUAL IDENTITY, RISK BEHAVIORS, AND PREGNANCY-RELATED OUTCOMES AMONG WSW

In all published studies that have queried lesbians about their lifetime sexual history, the majority of respondents (typically between 80% and 95%) report prior sex with at least one male partner and often report risky sexual behaviors. Diamant and colleagues surveyed 6935 self-identified lesbians solicited through a survey printed in *The Advocate*, a national news magazine aimed at gay men and lesbians. The majority of women (77.3%) reported one or more lifetime male sex partners, with 17.2% reporting ever having had anal intercourse

and 5.7% reporting having had a male sex partner during the past year.²² Sexual activity with male partners likely begins in adolescence.²³ Female adolescents who have sex with other females may be especially likely to engage in unprotected sex with both male and female partners or to report sexual abuse.^{24,25} Among 182 self-identified bisexual or homosexual adolescents in one study, girls younger than 15 years were more likely than their older counterparts to report an earlier age at onset of sexual intercourse with males.²⁶ In a subsample of 3816 students who completed the 1987 Minnesota Adolescent Health Survey, bisexual or lesbian respondents were as likely as heterosexual women ever to have had intercourse (33% and 29%, respectively), but reported a significantly higher prevalence of pregnancy (12%) and physical or sexual abuse (19–22%) than heterosexuals or adolescents who were “unsure” about their sexuality.²⁷ Among sexually experienced respondents, bisexual or lesbian respondents were most likely to have frequent intercourse (22%, compared with 15–17% in the other groups). Among all who were sexually experienced and those who had ever been pregnant, bisexual or lesbian women were the most likely to have engaged in prostitution during the previous year.²⁷

Thus, many lesbians report lifetime reproductive outcomes including pregnancy, childbirth, and induced abortion. Lifetime prevalence of reported pregnancy in the few studies that have addressed this issue ranges from 23% to 35%.^{28–30} Among participants in the Women’s Health Initiative, ever use of oral contraceptives was similar between lesbians and heterosexual women, and 35% reported ever having been pregnant.²⁹ Among 392 lesbians who participated in the Seattle Lesbian Health Study (1998–2001; median age of all subjects, 28 years), reports of prior pregnancy, oral contraceptive use, and induced abortion were common.³⁰ Overall, 25% of women had been pregnant at least once and 16% had had an abortion. Over half of all subjects had used oral contraceptives (mean duration, 40 months). The majority of women (63%) who had ever been pregnant had had at least one abortion. One-fifth of the subjects who specifically self-identified as lesbian had been pregnant at least once, 12% had had an induced abortion, and almost half had ever used oral contraceptives. The most common pregnancy outcome for women who became pregnant at age less than 25 years was induced abortion, which occurred in 59% of these pregnancies. Of related importance, the number of reported lifetime male sex partners did not differ by whether women identified as lesbian or bisexual. The overall age-adjusted rate of abortions was comparable to the estimated rate reported for U.S. women overall in the NSFG.³¹ The authors concluded that self-identification as lesbian did not consistently preclude prior use of oral contraceptives or pregnancy-related outcomes, with the implication that providers should address these issues with all adult women patients, regardless of stated sexual identity or behavior. These findings may be particularly important for clinics

with a traditional “family planning” focus, as these may serve as the primary entry point of care for many lesbians, particularly those with limited resources.

Finally, lesbians who are also currently sexually active with men may, in some settings, demonstrate increased sexual risk-taking behavior.³² Among women attending STD clinics, reports of sex with women as well as with men has been associated with a markedly increased prevalence of HIV-related risk behaviors, including sex with gay or bisexual men, use of injection drugs and crack cocaine, and exchange of sex for drugs or money.^{33–35} In the 1997 College Alcohol Study, comprised of 14,251 randomly selected U.S. college students, women reporting sex with both men and women were more likely to report multiple sex partners than peers with only opposite-sex partners.³⁶ In a large, cross-sectional, community-based study of sociometric networks among intravenous drug users, Friedman found that a report of same-sex behavior by female respondents was associated with a twofold increase in the likelihood of HIV infection.³⁷ Koh successfully recruited 1304 lesbians from 33 outpatient primary care settings across the United States.³⁸ In order to enrich the study population with lesbians, the investigators used a sampling scheme that took into consideration the proportion of lesbian patients (>30% as estimated by lead clinicians) served by contributing sites. They used an extensive questionnaire (98 items) with good response rate (>50%). Respondents were mostly white, highly educated, and had relatively high income. Although most were in a stable relationship (71%), many (23%) reported substance use while having sex or sex with a gay or bisexual man (6%) in the past year. Among women who recently had sex with men ($N = 600$), 51% reported ever using condoms. Bisexual women reported substance use during sex at a higher rate than lesbians or heterosexual women. While lesbians more frequently reported sex with bisexual men and injection drug users, they also reported using condoms more frequently than did bisexual or heterosexual women. Notably, lesbians who participated believed that their risk for HIV infection was high, yet few reported ever having had tests for non-HIV STDs, which are considerably more likely than HIV infection in this group. Why were lesbians employing risk reduction measures? Proximity to the issue of HIV/AIDS in the MSM community may inform this choice (although this might not be consistent with the inverse relationship between age and report of condom use in this subgroup). It could also relate to lesbians’ choice of MSM as partners when they do choose to have sex with men. Of great interest is that among women who reported sex with men in the prior year, lesbians reported a higher number of male sex partners than either heterosexual or bisexual women. This finding was modified by age, with younger women tending to report this behavior more commonly. The data collected on heterosexual women’s condom use are valuable because of the paucity of data for women whom most primary care providers might categorize

as “low risk”; variations in the frequency of condom use by income and age in heterosexual women deserve further scrutiny.

In the UK some of the findings on risk behaviors from the NATSAL 2000 Study were unexpected.¹⁶ First, two-thirds of female respondents reported only one female partner in the past 5 years and 42% of WSW (as defined in this study, described above) did not report any female partners in the past year. Second, relative to exclusively heterosexual women respondents, WSW reported significantly larger numbers of male partners in the past 5 years (Fig. 14-1), ever, and in the past year (all $P < 0.001$). Third, relative to exclusively heterosexual women, WSW reporting male partners were significantly more likely to report potentially high-risk heterosexual behaviors including anal sex (AOR (age-adjusted odds ratio for WSW relative to women reporting exclusively heterosexual partners) 2.46 [95% CI 1.58–3.85, $P < 0.001$]), most recent partner described as “not regular” (AOR 1.74 [95% CI 1.07–2.82, $P = 0.02$]), initiating sex less than 24 hours after meeting most recent partner (AOR 2.48 [95% CI 1.44–4.27, $P = 0.001$]), and unsafe sex (two or more heterosexual partners in the past 4 weeks with inconsistent condom use; AOR 7.17 [95% CI 3.25–15.8, $P < 0.001$]). WSW respondents were significantly more likely to report seeking care at an STD clinic, getting an HIV test, being diagnosed with any STD, and having had an induced abortion ($P < 0.001$ for each relative to heterosexual respondents). While some of these findings raise questions about the nature of the WSW respondent population, and the generalizability of the study’s findings, they do highlight the marked diversity within groups of women who engage in same-sex behavior.

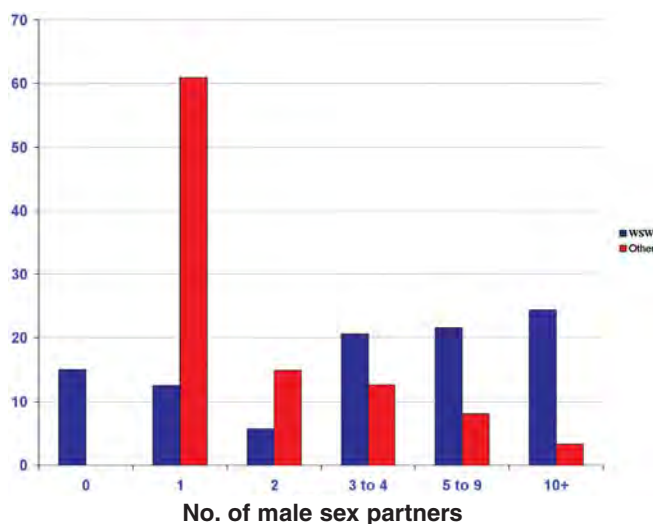


FIGURE 14-1. Number of male sex partners reported in the past 5 years among women who reported sex with other women and among those who reported exclusively male partners. (With permission from Mercer CH, Bailey JV, Johnson AM, et al. Women who report having sex with women: British national probability data on prevalence, sexual behaviors, and health outcomes. *Am J Public Health* 2007; 97:1126–1133.)

Finally, French investigators used data from a national phone survey that focused on domestic violence in France in 2000 to compare female respondents who reported at least one female sex partner ($N = 78$) to heterosexual women ($N = 6332$).³⁹ Lesbians in this survey reported a younger age at sexual debut, a higher number of lifetime male partners, more frequent report of STD diagnoses and prior HIV testing, and, importantly, more frequently experiencing domestic violence as adults.

EPIDEMIOLOGY OF STDs AND HIV INFECTION AMONG WSW

Despite the considerable numbers of women who engage in same-sex behavior, relatively little data are available on health outcomes related to STD, or to the attributable risk of STDs from sexual practices in which lesbians engage. In its 1999 report “Lesbian Health: Current Assessment and Directions for the Future,” the Institute of Medicine emphasized that more data on STDs, Pap smear screening, and risk of cervical cancer in lesbians were needed.¹¹ Attempts to use national or local surveillance data to estimate the risk of STD transmission between women are limited by the fact that virtually all risk classification schemes have either excluded same-gender sex among women or subsumed it under a hierarchy of other behaviors viewed as higher risk. Moreover, few if any state or local STD reporting systems routinely collect information on same-sex behavior among women. The available data are derived from two sources: small studies that have directly measured the prevalence of common STDs, usually among clinic attendees or self-referred study volunteers, and surveys that have queried lesbians about their self-reported STD history. Many of these studies have also assessed lesbians’ self-report of sexual practices. Taken as a whole, these data—limited as they are—indicate that the risk of STD transmission between women depends on two major factors: (1) the specific STD under consideration and (2) the sexual practices in which lesbians engage.

Some sexual practices, including oral–genital sex, vaginal or anal sex using hands, fingers, or penetrative sex toys, and oral–anal sex, are practiced commonly between female sex partners (Table 14-2).^{35,40,41} Oral sex, in particular, appears to be extremely common, and is probably practiced more frequently than among heterosexual women. Other sexual practices include digital–vaginal or digital–anal contact, particularly with shared penetrative sex toys. These sexual practices present a plausible means for transmission of infected cervicovaginal secretions, although the frequency of transmission associated with these practices is not well documented. Transmission of common viral STD, especially human papillomavirus (HPV) and herpes simplex virus (HSV), and of *Treponema pallidum*, the causative agent of

Table 14-2. Sexual Practices Among Lesbians: Frequency and Associated STD Risk

Practice	Description & Vernacular Terms	Estimated Frequency ^a	Factors Modifying Risk of STD ^b
Oral–vulvovaginal contact (cunnilingus)	<ul style="list-style-type: none"> - “Going down” - Top = performing partner - Bottom = receiving partner 	Very common (>95%)	<ul style="list-style-type: none"> - Presence of oral lesions in top partner (herpes, syphilis, possibly gonorrhea) (+) - Use of barriers (plastic wrap, dental dams, condoms)
Digital–vaginal contact	<ul style="list-style-type: none"> - Range of penetration, from “finger-fucking” to “fisting” 	Very common (>85%)	<ul style="list-style-type: none"> - Sharing of infected cervicovaginal secretions (trichomoniasis, <i>C. trachomatis</i>, gonorrhea, HPV, herpes) (+) - Use of gloves (-)
Digital–anal contact	<ul style="list-style-type: none"> - Range of penetration, from “finger-fucking” to “fisting” 	Common (25%)	<ul style="list-style-type: none"> - Sharing of infected anorectal secretions (hepatitis A, enteric pathogens, gonorrhea, HPV, herpes) (+) - Use of gloves (-)
Insertive sex objects (vagina or anus)	Toys, dildos	Very common vaginally (60%) Common anally (25%)	<ul style="list-style-type: none"> - Sharing of infected cervicovaginal or anal fluid (trichomoniasis, <i>C. trachomatis</i>, gonorrhea, HPV, herpes) (+) - Use of condoms with sex toys (-) - Sharing insertive toys without cleansing prior to use (+)
Oral–anal contact	“Rimming”	(Common 35%)	<ul style="list-style-type: none"> - Presence of oral infection in performing partner (syphilis, genital herpes) (+) - Presence of anorectal infection in receiving partner (hepatitis A, enteric pathogens) (+) - Use of barriers (-)
Direct genital to genital contact	<ul style="list-style-type: none"> - Tribadism 	Very common (>95%)	<ul style="list-style-type: none"> - Direct contact of susceptible skin/mucosa (HPV, herpes, syphilis)(+) - May involve use of interposed devices, such as vibrators, which can cause mechanical vulvar irritation
Sadomasochism	Bondage, “BDSM”	Unknown; probably uncommon (<2%)	Sharing of blood (hepatitis B, hepatitis C, HIV) (+)

^aRefs. 35, 40, and 41.

^bPlus sign (+) denotes factor likely to enhance risk of STD transmission or acquisition; minus sign (-) denotes factor with probable protective effect.

syphilis, requires only skin to skin or mucosa contact which can easily occur in the context of sex between women. As discussed above, most lesbians (53–99%) have had sex with men, and many (21–30%) continue to do so²²; they may acquire viral STDs from men and subsequently transmit

them to female partners. Among 6146 respondents in the National Lesbian and Bi Women’s Health Survey conducted in the early 1990s, women reported contracting an STD from a female partner (including herpes in 135, chlamydia in 102, genital warts in 100, gonorrhea in 16, hepatitis in 9, and HIV

in 1).⁴² Although self-report of STD history is often inaccurate (as is attribution of STD to a specific source partner), these data indicate that while transmission of some STDs is relatively inefficient between female sex partners, these respondents sought care for perceived genitourinary abnormalities, and received a diagnosis that indicated the provider had reason to suspect a specific STD.

■ GENITAL HUMAN PAPILLOMAVIRUS

Genital infection with specific types of HPV causes genital warts and the majority of cervical cancer. In addition to case reports,^{43,44} two studies that enrolled self-referred lesbians in Seattle have detected HPV DNA by PCR-based methods in 13–30% of subjects.^{40,45} In both of these studies, samples obtained from the cervix, vagina, and vulva all demonstrated HPV DNA and no one anatomic site accounted for the majority of infections. Among 150 women in the earlier of these two studies (1995–1997), HPV DNA was present in 30% of all subjects and in 19% who reported no prior sex with men.⁴⁰ In multivariate analysis, current but not prior cigarette smoking was an independent predictor of the presence of HPV DNA (OR 3.4; 95% CI, 1.2, 9.6), as was time to last sex with a male partner ($P = 0.002$). Among all subjects with detectable HPV DNA, 29 (69%) had unclassified types only, 9 (21%) had HPV-31/33/35/39, 8 (19%) had HPV-16, and 1 (2%) had HPV-6/11. Twenty-eight (62%) of these women had HPV DNA detected in the specimens obtained from the cervix, 26 (58%) from the vagina, and 32 (71%) from the vulva; 24 (53%) had HPV DNA in specimens from more than one site. Among the 41 women with HPV DNA who reported prior sex with men, 21 (51%) had not had sex with a male partner in over a year (range, 1–18 years; median, 2 years). In their sexual practices with female partners, women who had detectable HPV DNA did not differ from those who had no detectable HPV DNA. With male partners, women with detectable HPV DNA were more likely to report a history of receptive oral sex ($P = 0.05$). In the subsequent Seattle Lesbian Health Study (1998–2001), HPV DNA was measured in 248 women and detected in 31 (13%), including 7 with HPV type 16 and 15 with other oncogenic types.⁴⁵ Twelve (39%) had nononcogenic types (6/11, 40/42/53/54). Among the 28 women with HPV DNA who reported prior sex with men, 14 (50%) had not had sex with a male partner in over a year (range, 1–11 years; median, 2 years).

Capture enzyme-linked immunoabsorbent assay (ELISA) was used in the earlier study to measure type-specific antibodies to HPV and 47% of 133 subjects were seropositive for antibodies to HPV-16 and 62% for HPV-6; 54% had antibodies to both.⁴⁰ Among 19 subjects reporting never having had sex with a man, 5 (26%) had antibodies to HPV-16 and 8 (42%) had antibodies to HPV-6. Antibodies

to HPV-6 or -16 were detected in 8 (42%) of 19 women reporting no prior sex with men and in 84 (74%) of 114 women reporting prior sex with men. Subjects who were seropositive to either HPV-6 or HPV-16 were older than seronegative subjects (mean age, 34 years vs. 30 years, respectively; $P = 0.01$), but did not differ significantly from seronegative subjects in time to last sex with a male partner, lifetime number of male or female partners, or detection of HPV DNA.

Importantly, both high- and low-grade squamous intraepithelial lesions (SIL) were detected on Pap smear testing in both of these studies, including among women who reported no prior sex with men. In the first study, 13 of the 150 subjects (6% of all subjects) had abnormal Pap smears. Three of these women reported no history of sex with men and three reported having had female sex partners with genital warts. SIL was detected in 2 of 21 women (10%) who had never had sex with men, in 2 (2%) of 93 women who had had sex with a man >1 year previously, and in 2 (6%) of 35 women who reported sex with men during the last year (not significant). HPV DNA was detected in 5 of the 6 women with SIL; HPV type 31/33/35/39 was found in both cases of SIL that occurred in women without a history of sex with men. Among 248 women enrolled in the second study, 7 of the 11 SIL detected occurred in women who reported never having had sex with men, or sex with men >1 year previously. Twenty-five women (10% of all subjects) had abnormal Pap smears. Four women had high-grade and 7 had low-grade SIL detected; 7 of these lesions occurred in women who reported either never having had sex with men or sex with men more than one year prior to testing. HPV DNA was detected in 7 of the 11 women with SIL (HPV-16 in 3 women and other oncogenic types in 4 women). In a large study reporting Pap smear data for lesbians and heterosexual controls in an STD clinic in Melbourne, abnormal Pap smears occurred equally frequently in both groups.³⁵

There are fewer data available for the clinical diagnosis of genital warts among lesbians, but this condition has been reported among lesbians who denied prior sex with men in several studies, primarily from STD clinics.⁴⁶ In STD clinics that have reported data from lesbian clients, a diagnosis of genital warts was relatively uncommon in London, occurring in 1.6% of 708 lesbians,⁴⁷ but more common in Melbourne (8% of 1408 lesbians) (Table 14–3).³⁵ While genital HPV and associated conditions are most common among women who report increasing numbers of lifetime male sex partners, the data above and the fact that SIL has been observed in women who reported no prior sex with men indicate that high-risk and low-risk genital HPV types are sexually transmitted between women and that lesbians should undergo Pap smear screening using current national guidelines, as recommended in the 2006 Sexually

Table 14-3. Demographics, STD Detected at Clinic Visit, and Risk Behavior Among Lesbians and Heterosexual Control Women at a Sexual Health (STD) Clinic in Melbourne, Australia^a

	Lesbian (N = 1408)	Heterosexual (N = 1423)	OR (95% CI) ^b	P
Median age, yr (range)	27 (14–78)	26 (16–56)		
Bacterial vaginosis	111 (8%)	69 (5%)	1.7 (1.2–2.3)	0.001
Genital warts	106 (8%)	158 (11%)	0.7 (0.5–0.9)	0.001
Genital herpes	133 (9%)	136 (9%)		0.95
Gonorrhea	4/958 (<1%)	7 (<1%)		0.39
Chlamydia	28/830 (3%)	31/747 (4%)		0.34
Hepatitis C	73 (5%)	10 (<1%)	7.7 (3.9–16.0)	<0.001
Hepatitis B	73 (5%)	36 (3%)	2.1 (1.4–3.2)	<0.001
HIV	5 (<1%)	3 (<1%)		0.51
Abnormal Pap smear	69/356 (19%)	28/286 (20%)		0.78
Past history of STD ^c	616 (44%)	459 (32%)	1.6 (1.1–2.0)	<0.001
Sex with gay or bisexual male (ever)	206/1347 (15%)	68/1343 (5%)	3.4 (2.5–4.6)	<0.001
Sex with heterosexual man with multiple partners (ever)	273 (19%)	244 (17%)		0.13
Sex with injecting drug user (ever)	288/1353 (21%)	81/1346 (6%)	4.2 (3.2–5.5)	<0.001
Injecting drug use (ever)	316/1398 (23%)	49/1387 (4%)	8.0 (5.6–11.3)	<0.001
Current sex work	235/1089 (22%)	114/1061 (11%)	2.3 (1.8–2.9)	<0.001
Termination of pregnancy (ever)	537 (38%)	380 (27%)	1.7 (1.4–2.0)	<0.001

^aLesbian defined as woman who reported ever having had sex with another woman. Controls defined as women who reported never having had sex with another woman. A nested analysis of 283 women reporting sex exclusively with women in the year prior to clinic visit showed that these women were still significantly more likely than controls to report >50 lifetime male sex partners (4% vs. 2%; OR 2.8, $P = 0.003$). The risk behavior profile of this group was otherwise similar to “all” lesbians as depicted in this table. All denominators for percentages are total group numbers as listed at top of column unless otherwise specified. (With permission from Fethers K, Marks C, Mindel A, Estcourt CS. Sexually transmitted infections and risk behaviours in women who have sex with women. *Sex Transm Infect* 2000; 76: 345–349.)

^bOR, odds ratio for detection of characteristic in lesbian group; CI, confidence interval.

^cSelf-reported history of chlamydia, gonorrhea, bacterial vaginosis, syphilis, genital herpes, or genital warts.

Transmitted Disease Treatment Guidelines from the Centers for Disease Control and Prevention.⁴⁸

■ GENITAL HERPES

The majority of genital herpes is caused by HSV type-2 (HSV-2), although recent reports indicate a consistent trend towards more HSV-1 related genital disease.⁴⁹ Using the Western blot assay to detect type-specific antibodies among 392 women in the Seattle Lesbian Health Study, antibodies to

HSV-1 were detected in 46% and to HSV-2 in 8% (Fig. 14-2).⁵⁰ HSV-1 seroprevalence increased significantly with increasing number of female partners (Fig. 14-3; also discussed below). Increasing age predicted higher seroprevalence to both HSV types, and HSV-2 seropositivity was associated with a reported history of having had a male partner with genital herpes (but not with prior number of male sex partners). Of 78 women reporting no prior sex with men, 3% were HSV-2 seropositive. Seropositivity to HSV-2 was also associated with report of prior trichomoniasis, gonorrhea, and pelvic

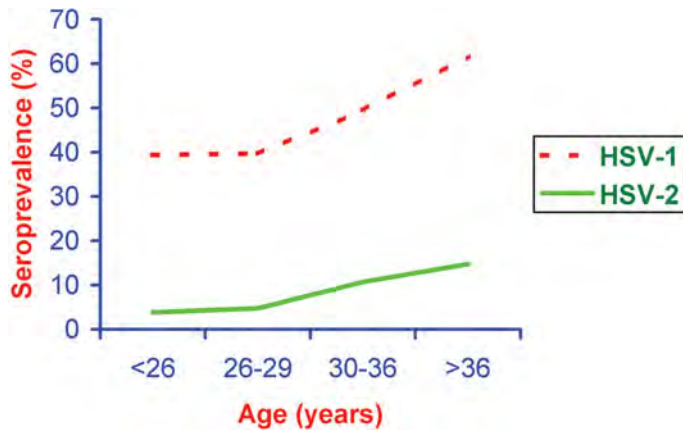
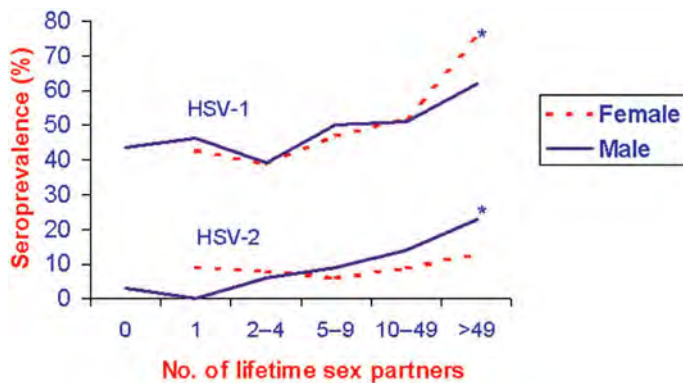


FIGURE 14-2. Age-specific seroprevalence of herpes simplex virus types 1 and 2 among 392 lesbians tested in 1998–2001 by Western Blot. (With permission from Marrazzo JM, Stine K, Wald A. Prevalence and risk factors for infection with herpes simplex virus type-1 and -2 among lesbians. *Sex Transm Dis* 2003; 30: 890–895.)



* $P < 0.05$, chi-square test for linear trend

FIGURE 14-3. Seroprevalence of herpes simplex virus type 1 and 2 by number of lifetime sex partners. (With permission from Marrazzo JM, Stine K, Wald A. Prevalence and risk factors for infection with herpes simplex virus type-1 and -2 among lesbians. *Sex Transm Dis* 2003; 30: 890–895.)

inflammatory disease. As has been demonstrated in other studies, most HSV-2 seropositive subjects (71%) reported no history of genital herpes; only 6.1% of all subjects gave such a history. The seroprevalence of HSV-2 among women in this study was approximately half that reported among white women in the National Health and Nutrition Examination Survey (NHANES) study, which tested sera obtained during the years 1999–2004.⁵¹ Data on the sexual orientation of the women in these studies was not reported, but most were presumably heterosexual. In the NHANES population, HSV-2 seroprevalence among women aged 20–29 years old—the subgroup most comparable to the Seattle study population—was 15.6% (95% CI, 13.1–18.5). Possible reasons for the lower HSV-2 seroprevalence among the Seattle lesbian subjects include the potential for less efficient genital transmission of HSV-2 in the absence of penile–vaginal sex, the fact that many subjects were part of monogamous partnerships, frequently of

long duration, and subjects' predominantly white race. In all HSV-2 serosurveys performed to date, blacks have been more likely than other racial or ethnic groups to be infected with HSV-2, and also experienced significantly higher rates of new HSV-2 infections in one prospective study.⁵² Further, risk factors for infection with HSV-2 may vary across populations studied. In the NHANES study, predictors of HSV-2 infection were race, age, lifetime number of sex partners (gender not specified), and marital status, but fewer years of formal education, income below the poverty level, and ever having used cocaine were also independently associated. Of these characteristics, only increasing age independently predicted higher seroprevalence to HSV-2 in the Seattle Lesbian Health Study.

Many studies have suggested that the incidence of genital infection with HSV-1 is increasing^{53–57} and that new genital HSV-1 infections are as common as oropharyngeal HSV-1 infections.⁵² Further, report of receptive oral sex in the absence of vaginal intercourse increased the risk of HSV-1 seroconversion among 1207 heterosexual women prospectively assessed in Pittsburgh (9.8 vs. 1.2 cases per 100 woman-years of follow-up; $P = 0.04$).⁵⁸ The majority of the subjects (54%) in the Seattle Lesbian Health Study lacked serum antibody to HSV-1, a percentage even lower than that of baseline seroprevalence among women enrolled in the Pittsburgh study (62%). Because genital infection with HSV-1 is most likely acquired during receipt of oral sex,⁵³ a behavior commonly practiced by lesbians, a substantial proportion of lesbians engaging in receptive oral sex are probably at risk for genital acquisition of HSV-1. In fact, the Seattle data demonstrated a more prominent association between number of lifetime female sex partners and HSV-1 infection than that reported for male sex partners among the women studied in the NHANES III Study.⁵⁹ Other investigators have suggested that decreasing HSV-1 seroprevalence among young adults may place these individuals at higher risk for subsequent genital HSV-1 acquisition, and have suggested a need for increased education about the risks of orogenital sex.^{56,57} Counseling about susceptibility to genital herpes infection may be enhanced by the recent availability of less expensive, type-specific HSV serologic assays that identify persons at risk.⁶⁰

While no other studies have measured lesbians' HSV seroprevalence, others have assessed lesbians' self-report of genital herpes. Most have used self-referred, volunteer samples and reported a lifetime prevalence of 3.3–7.4%.^{22,61,62} However, as noted above, self-reports of genital herpes substantially underestimate prevalence as measured by type-specific HSV serology. Among 27 lesbians seen at an STD clinic in London in the late 1980s, genital herpes was diagnosed by culture in 3 women (11%).⁶³ More recently, 1.1% of 708 new patients attending a clinic for lesbians in London and 9% of 1408 lesbians seen in a Melbourne (Australia) STD clinic were diagnosed with genital herpes by culture, including women who reported no prior sex with men (Table 14-3).^{35,47}

■ HUMAN IMMUNODEFICIENCY VIRUS

While sexual transmission of HIV between women has been reported,^{64–68} the likelihood of transmission in this setting is unknown. It is probably strongly modified by the extent to which female partners share cervicovaginal secretions, particularly if menstrual blood is involved or if activities involving vaginal or anal penetration are vigorous enough to abrade mucosa or cause bleeding. Recently, Kwakwa detailed a convincing case of a 20-year-old woman with documented HIV acquisition during the course of a monogamous relationship with an HIV-infected female partner.⁶⁹ The viral strains were genotypically identical, providing strong supporting evidence that the female partner was the source. These women denied having sex during menses, but reported using vaginal sex toys as well as digital penetration, with associated exchange of blood-tinged vaginal fluid. Raiteri followed approximately 18 discordant lesbian couples for HIV transmission over several years without observing any transmission.⁷⁰

In addition to behaviors that transmit these potentially infected secretions, lesbians' participation in sexual networks that involve gay or bisexual men or their own IDU could place them at increased risk of HIV acquisition, but this has not been extensively studied. Chu used national surveillance for reported AIDS cases from 1980 to 1989 to characterize the 79 women who reported sex with another woman in these data; 95% also reported IDU.⁷¹ The HIV Epidemiologic Research Study, which required that women report IDU, sex with 5 or more partners in the prior 5 years, prior sex with a male at risk for HIV, or exchange of sex for drugs or money in order to be eligible for enrollment, reported that 67 of 871 subjects (8%) had had sex with a woman during the 3½ years of the prospective follow-up.⁷² Most (82%) had a history of IDU. Subjects reported frequent practice of sexual behaviors that could potentially transmit infected secretions without concomitant barrier use, but information on partners' HIV status was not reported. Shotsky examined HIV seroprevalence data from New York state's HIV counseling and testing programs from 1993 to 1994.⁷³ HIV seroprevalence among the 27,370 women tested was highest among women who reported sex with men and women (4.8%), compared to that among women sexually active exclusively with women (3.0%) or with men (2.9%). Other studies have noted a high prevalence of risky or unprotected sexual behavior with female partners in HIV-infected lesbians who report IDU⁷⁴; however, because of the selection of the populations studied, the generalizability of these data cannot be assured.

■ VIRAL HEPATITIS

No systematically collected data have been reported on sexual transmission of hepatitis B between women, but anecdotal case reports have occurred (J. Hofmann, personal communication). Based on the observation that other blood-borne

viruses are transmitted between women, it is reasonable to presume that this occurs, but the frequency is unknown. Transmission of hepatitis A has also been reported among WSW.⁷⁵ Notably, in the Melbourne STD Clinic Study comparing lesbians with heterosexual women controls, lesbians' prevalence of hepatitis C was significantly higher (OR 7.7; $P < 0.001$), a finding that probably reflects more frequent report of IDU in this group (Table 14-3).³⁵

CHLAMYDIA TRACHOMATIS AND NEISSERIA GONORRHOEAE

Reports of clinically documented *C. trachomatis* and *N. gonorrhoeae* transmission between women are rare. The scant data available derive from clinic-based reports of prevalence among lesbian attendees and from survey respondents' self-report of having received these specific diagnoses. Clinic-based data reported primarily from STD (in the United States and Australia) and sexual health (in the UK) clinics indicate that the prevalence of both of these infections has been very low (typically 3% or less). For example, among 708 new patients attending a clinic for lesbians in London, prevalence of *C. trachomatis* was 0.6% and of gonorrhea was 0.3%.⁴⁷ Although a smaller proportion of women who reported sex exclusively with women underwent endocervical culture for *C. trachomatis* and *N. gonorrhoeae* relative to women who reported sex with men, chlamydial infection was diagnosed in two women reporting sex only with women. In the Melbourne STD Clinic Study, prevalence of *C. trachomatis* was 3%; interestingly, this did not differ from the prevalence among heterosexual control women, which was also quite low.³⁵ Finally, culture-based data from a Seattle STD clinic revealed *C. trachomatis* among only 2 (1.1%) of 187 women reporting sex only with women in the past 2 months and in 12 (1.9%) of 841 women reporting sex with both men and women during that time frame. Corresponding detection of gonorrhea was 0 of 192 women tested and 14 (2.1%) of 661 tested, respectively.³⁴ Limitations to generalization of these data include lack of truly universal testing in most settings, as well as relatively small numbers of patients in the U.S. studies. Survey data assessing lesbians' lifetime history of these STDs has been reported principally from the United States, where approximately 3–6% of respondents indicate that a health-care provider had diagnosed chlamydial infection.^{42,61}

■ SYPHILIS

Although *T. pallidum* is relatively uncommon compared to most other STDs, sexual transmission between female partners has been reported.⁷⁶ Because some lesbians who choose to have sex with men may be more likely to choose bisexual men for

partners,^{33,34} health-care providers should keep in mind that the incidence of early syphilis has markedly increased among men who have sex with men in the last several years.⁷⁷

■ VAGINITIS, INCLUDING BACTERIAL VAGINOSIS

Bacterial vaginosis (BV), a condition associated with depletion of hydrogen-peroxide-producing *Lactobacillus* species and the most common cause of vaginitis among women of reproductive age, is associated with pelvic inflammatory disease, increased risk of acquiring gonorrhea and HIV, and adverse outcomes of pregnancy.⁷⁸ Intriguingly, the prevalence of BV among lesbians is high and vaginal colonization with hydrogen-peroxide-producing lactobacilli is low relative to that of heterosexual women, even when subjects are matched for age and sexual risk behaviors.^{35,41,63,79–81} BV prevalence among lesbians in these studies has ranged from 24% to 51%, as compared to 21% for heterosexual STD clinic clients and 9–14% for pregnant women. Recently, BV prevalence was reported for women in the NHANES, which uses a complex, stratified, multistage probability sample design with unequal probabilities of selection to obtain a nationally representative sample of the U.S. civilian noninstitutionalized population.⁸² Of over 12,000 women in the 2001–2004 NHANES who supplied a self-collected swab of vaginal secretions for Gram stain analysis by Nugent score, BV prevalence was 45.2% (95% CI, 35.5–57.4) among women who reported having had a female sex partner, compared to overall prevalence of 29.2% (95% CI, 27.2–31.3) ($P = 0.003$). In the single study that has used culture to define the vaginal bacteria present in lesbians with BV, the microbiology of this condition appeared very similar to that in heterosexual women.⁴¹ Although BV is not a classic STD in that a specific microbial precipitant has not been identified, among heterosexual women it is frequently associated with report of a new male sex partner and with unprotected intercourse,⁷⁸ and the use of condoms by male partners of women who were successfully treated for BV significantly reduced rates of BV recurrence in these women.⁸³

The plausibility of BV being sexually transmitted between women is supported by three general findings. First, Criswell and Gardner successfully transmitted BV from one woman to another by the transfer of vaginal secretions in early studies of “*Hemophilus vaginalis vaginitis*.”⁸⁴ Second, limited evidence suggests that female sex partners share identical *Lactobacillus* strains as part of normal vaginal flora. Marrazzo and colleagues used repPCR to characterize vaginal *Lactobacillus* isolates among 30 monogamous (defined within the timeframe of the prior 3 months) female sex partners.⁸⁵ Identical strains were detected in 23 of these couples (77%). The likelihood of sharing *Lactobacillus* strains was directly related to report of fewer female sex partners in the

prior year and to increasing duration of the current partnership. Paired controls, designated as women not currently in monogamous partnerships and matched for mean age of couple and date closest to visit for each couple, had strains that were not shared. These findings suggest (but do not prove) that women sexually transmit vaginal *Lactobacillus* species. Third, BV is frequently found in both members of monogamous lesbian couples^{41,86} and BV concordance within couples has been associated with specific sexual behaviors.⁴¹ In a study of 326 women who reported sex with at least one other woman in the prior year, the prevalence of BV as determined by Nugent criteria was 27%. Factors associated with an increased risk of BV included sexual behaviors that are likely to result in the transfer of vaginal fluid, as well as oral–anal sex (Table 14-4).⁴¹ Moreover, among subjects with BV, 81% had partners with BV, whereas only 4% of those without BV had partners with BV ($P < 0.001$). Bailey reported on a cross-sectional survey of 708 lesbians attending two sexual health clinics in London, among whom BV prevalence as determined by Amsel criteria was 31.4%.⁸⁰ The odds of BV were significantly increased among women who reported higher number of female sex partners (OR 1.6 [95% CI, 1.05–2.44] for >11 compared to less than 6 partners) and with current cigarette smoking (OR 1.43 [95% CI, 1.01–2.03]).

These observations have prompted some authors to propose that sexual transmission of some etiologic factor, as yet undefined, is responsible for BV in lesbians.⁸⁶ Expanding the spectrum of bacteria specifically associated with BV may help clarify this issue. Several groups have found that *Atopobium vaginae* has relatively high specificity for BV among heterosexual women (in contrast to *G. vaginalis*, which is found in approximately 40% of women with normal vaginal flora).^{87,88} In addition to *A. vaginae* and other novel species, Fredricks and colleagues, using 16s rDNA methodology, reported the detection of three previously undefined bacteria in the *Clostridiales* group that were highly specific (95% or greater) for detection of BV in a study that included lesbians.⁸⁹ Interestingly, many of the newly identified bacteria associated with BV are anaerobes known to colonize the oral cavity, raising anew the hypothesis that lesbians’ relatively frequent practice of orogenital sex may also promote shifts in vaginal bacteria that could precipitate or support BV, a mechanism also postulated in small studies of heterosexual women.^{90,91} More research is needed in this area.

Finally, positing that transmission of vaginal fluid is likely during lesbian sex implies that vaginal infection with trichomoniasis should be relatively efficiently transmitted as well. Interestingly, only one detailed case report of this occurrence has been published and described a lesbian couple who had failed standard therapy with metronidazole. Both were

Table 14-4. Multivariate Analysis of the Risk of Bacterial Vaginosis Among 326 Lesbians Enrolled in a Cross-Sectional Study of Vaginal Flora^a

Characteristic	Multivariate OR (95% CI) ^b	P Value
Age	–	0.7
Nonwhite race	1.4 (0.7–3.0)	0.4
History of prior pregnancy	1.6 (0.8–3.1)	0.2
Lifetime number of female sex partners		
1–3	Reference	
4–6	2.0 (0.9–4.4)	0.08
≥7	2.2 (1.1–4.5)	0.03
Lifetime number of male sex partners		
0	Reference	
1–3	0.8 (0.3–1.9)	0.6
4–6	1.2 (0.5–2.9)	0.7
≥7	1.1 (0.5–2.5)	0.8
Receptive sexual behaviors (ever)		
Digital–anal	1.1 (0.6–2.0)	0.7
Oral–anal	2.4 (1.3–4.4)	0.004
Insertive sex toy cleaned between use on one partner and the other		
Always	Reference	
Never/sometimes	2.7 (1.2–6.1)	0.02
Question not answered	1.8 (1.0–3.6 (0.7)	0.07

^aEnrollment criteria required report of sex with another woman in the previous year. (Adapted from Marrazzo J, Koutsky LA, Eschenbach DA, Agnew K, Stine K, Hillier SL. Characterization of vaginal flora and bacterial vaginosis in women who have sex with women. *J Infect Dis* 2001.)

^bOR, odds ratio; CI, confidence interval.

infected with *Trichomonas vaginalis* that was resistant to metronidazole.⁹² Among 708 new patients attending a clinic for lesbians in London, trichomoniasis was detected in 1.3%, including lesbians who reported no prior sex with men.⁴⁷

SPECIAL CONSIDERATIONS IN STD/HIV PREVENTION AND CONTROL AMONG WSW

Questions about access to quality health care for lesbians persist.⁹³ One of the few population-based surveys performed with lesbians as a target audience used a random digit dialing approach to compare the physical and mental health status of

4135 respondents as a function of self-reported sexual orientation.⁹⁴ Both lesbians and bisexuals were more likely to report increased rates of poor physical and mental health, as other studies have also noted.²¹ Perhaps the most commonly assessed surrogate marker for whether lesbians receive appropriate STD-related preventive care is receipt of Pap smear screening. This is probably performed less frequently among many lesbians than national guidelines advise, even when lesbians accurately perceive themselves to be at risk for cervical cancer.^{95–97} In the Seattle Lesbian Health Study, 95% of respondents believed they should receive Pap smears annually or every 2 years after a normal smear, but 36% provided a

reason for not having done so.⁴⁵ Reasons most commonly cited were lack of insurance, adverse experience at prior Pap smear screening, and a belief they did not need it because they were not sexually active with men. Ten percent of subjects were told (by physicians in all but one case) that they did not need a Pap smear because they were not sexually active with men. Despite high levels of education and income, women with no prior sex with men were less likely to have ever received a pelvic examination, received their first Pap smear at an older age, and had less frequent Pap smears relative to women who reported prior sex with men. Among the few nationally representative surveys, the Boston Lesbian Health Project used snowball sampling to query a national sample of 1633 lesbians.⁹⁸ While overall screening rates approximated the general population, 39% of respondents younger than 20 years and 16% of those 20–29 years had never had a Pap smear and 29% of those 30–39 years had not had one in over 3 years. A multilingual population-based survey in New York City found that WSW were less likely to have had a Pap test in the past 3 years (66 vs. 80%, $P < 0.0001$) or a mammogram in the past 2 years (53 vs. 73%, $P = 0.0009$) than other women. After adjusting for health insurance coverage and other factors, WSW were ten times (adjusted OR 9.8, 95% CI 4.2, 22.9) more likely than non-WSW to have *not* received a timely Pap test. Of interest, subjects' likelihood of having received Pap tests was directly related to whether sexual behavior and self-reported sexual identity were concordant. WSW who identified as lesbians were more likely to have received timely Pap tests (97 vs. 48%, $P < 0.0001$) than those who identified as heterosexual.⁹⁹

What might constitute potential barriers to preventive care by lesbians and how can they explain reduced rates of Pap smear testing or STD-related risk assessment? The first area relates to providers' assessment of and patient's disclosure of sexual behavior and STD-related risk, which are intimately intertwined. Most providers do not routinely perform a sexual history, and thus fail to elicit report of risk behavior.¹⁰⁰ Even if a history is sought, many lesbians (53–72%) may not disclose their sexual behavior to physicians, because disclosures may elicit negative or inappropriate reactions.^{101,102} Of note, in a survey of 6935 self-identified lesbians, disclosure of sexual orientation was favorably associated with receipt of appropriate Pap smear screening.¹⁰³

Second, even if behavior is assessed and disclosure of same-sex behavior or lesbian sexual orientation occurs, many health-care providers lack specific knowledge about STD/HIV prevention and care as they pertain to lesbians. Professional health curricula, including medical schools and residencies, are not mandated to provide education about care of gay and lesbian patients, although some are increasingly doing so.^{104–107} Upon eliciting a history from a lesbian patient, providers may assume that STD risk is negligible and, in particular, may fail to obtain a complete sexual history or to do so in a sensitive,

nonjudgmental manner. Compounding lack of specific knowledge is the possibility of insensitivity, which may arise from lack of familiarity with gay patients or from frank discomfort dealing with gay people in general.^{108–111} For example, one-quarter of 249 Chinese medical students surveyed in 2004 viewed homosexuality as a psychiatric disorder that required therapy, and 25% of family medicine residency directors expressed hesitation in matching openly gay residents in a survey published in 1996.^{108,109} Qualitative research has raised serious concerns regarding a lack of sensitive health care that included knowledge specific to lesbian health concerns, and to sexual practices as they relate to risk of STD transmission between women.^{102,112} The general invisibility of lesbians in public policy statements and recommendations has compounded this problem; the 2006 CDC STD Treatment Guidelines were the first edition of this widely cited document to include a section on WSW.⁴⁸

Third, many lesbians may perceive themselves to be at low risk for STD acquisition from female partners and for cervical dysplasia. As described in depth in a large study of STD risk perception among lesbians, perceived vulnerability to STD is likely informed by a complex construct of social messages, perceptions of sex partners and their trustworthiness, and stigma.¹¹² Limited qualitative research has identified several specific misperceptions, notably the perception that the need for STD risk reduction behaviors is primarily a concern for heterosexual women. Participants in focus groups evidenced a very limited knowledge of BV and of the potential for common STDs, including genital herpes and HPV, to be transmitted between women.¹⁰² BV and vulvovaginal candidiasis, in particular, were frequently confused. In another large survey of 1086 lesbians, only 43% of women with the presence of a clear risk factor for HIV perceived themselves to be at risk.¹¹³ Similar assumptions about HPV acquisition from female partners may place lesbians at risk for delayed detection of cervical cancer by infrequent, or no, Pap smear screening, as evidenced by attitudes in several published studies.^{45,95–98}

Finally, while lesbians are an economically diverse group, the earnings of lesbian households as a whole are likely less than that of households inhabited by an employed male. Compounding this may be lack of insurance in the absence of domestic partner benefits or unwillingness to disclose sexual orientation to obtain such benefits when they are offered. Moreover, lesbians who do not also have sex with men may not access venues providing hormonal contraception, thus eliminating another "routine" opportunity for STD and Pap smear screening.

FUTURE DIRECTIONS TO IMPROVE STD/HIV PREVENTION AND CONTROL AMONG WSW

Available data—though limited—can help to inform recommendations for STD-related care of WSW. STD transmission risk likely depends on the STD under consideration and

sexual practices involved. Some practices, including oral–genital sex, vaginal or anal sex using hands, fingers, or penetrative sex toys, and oral–anal sex, are practiced commonly. Digital–vaginal or digital–anal contact, particularly with shared penetrative sex toys, could potentially transmit infected cervicovaginal secretions, a risk most directly supported by reports of metronidazole-resistant trichomoniasis and genotype-concordant HIV sexually transmitted between women who reported these behaviors, and by the high prevalence of BV, which frequently occurs in both members of mutually monogamous female partners. Transmission of common viral STDs, especially HPV and HSV, requires only skin to skin or mucosa contact, which frequently occur in this context. Studies have detected HPV DNA by PCR-based methods from the cervix, vagina, and vulva in 13–30% of WSW, including those who reported no prior sex with men. Both high- and low-grade SIL have occurred in WSW who reported no prior sex with men. Importantly, most self-identified lesbians (53–99%) have had sex with men, and many (21–30%) continue to do so. Given this, all WSW should undergo Pap smear screening using current national guidelines. While risk of *C. trachomatis* transmission between women is unknown, WSW who continue to have sex with men are clearly at risk; in the absence of data, WSW should undergo routine screening according to current national guidelines. HSV-2 genital transmission probably occurs with relative inefficiency, but the relatively frequent practice of orogenital sex may place WSW at higher risk of genital infection with HSV-1, a hypothesis supported by the association between HSV-1 seropositivity and lifetime number of female partners. Transmission of syphilis between female sex partners, likely through oral sex, has been reported. Finally, WSW who are also currently sexually active with men may, in some settings, demonstrate increased sexual risk-taking behavior. Among women attending STD clinics, reports of sex with women in addition to sex with men has been associated with markedly increased prevalence of HIV-related risk behaviors, including sex with gay or bisexual men, use of injection drugs and crack cocaine, and exchange of sex for drugs or money. No data on sexual transmission of viral hepatitis are available for WSW, but sexual contact involving menstrual fluid presents a potential exposure.

The relatively limited knowledge of risk-related behaviors among WSW has impeded the development of prevention strategies for this population, including effective behavioral interventions and counseling messages. Although “safe sex” messages pertaining to sex between women are available on the Internet and from some community organizations, none have been specifically tested for acceptability, potential for adherence, or efficacy in reducing STD/HIV transmission between women. An intervention among women with BV aimed at reducing the sexual transfer of vaginal fluid as a means of reducing BV recurrence is currently under study.¹⁰²

Such an intervention could conceivably employ one or more of several methods depending on the sexual practices involved. For example, transfer of vaginal fluid during digital–vaginal sex might be reduced by the use of disposable gloves, or by prophylactic use of a topical antimicrobial solution or gel, and a male condom could be used on vaginally inserted sex toys for the same purpose. Because lesbians generally believe that the risk of STD transmitted between women is low, any intervention must include an educational component explaining the evidence that exists to support such a possibility. If this is not adequately conveyed, women may have little motivation to adhere to such an intervention. Qualitative research indicates that lesbians may express a relatively high level of responsibility for not infecting sex partners with an STD or HIV, if they know themselves to be infected.^{102,112} Thus, any intervention should incorporate themes of personal responsibility and care for partners' well-being and health. Finally, an intervention would be most likely to succeed if the preventive practice is framed in terms of sexual enjoyment and healthy sexuality rather than in terms of disease, and if respect for one's body and one's sexual choices are emphasized.

A general lack of knowledge about the population of lesbians has been promulgated by omission in many natural history studies of health and disease in women. Research in WSW populations would clearly benefit from inclusion of some measure of same-sex behavior in surveys that have traditionally focused on reproductive health outcomes of women assumed to be exclusively heterosexual; such inclusion is unlikely to adversely affect overall response rates.⁷ Other research priorities should include the epidemiology of high-risk HPV types and SIL, conditions that could contribute to infrequent Pap smear screening, and better definition of risk of transmission of specific STDs. The most significant bacterial STD for which more precise data are needed is *C. trachomatis*. Moreover, health-care providers—particularly those in training—would benefit from education to enhance their skills in taking a thorough, sensitive sexual history from all patients, but especially sexual minorities, adolescents, and highly marginalized patient groups, such as HIV-infected lesbians of color.^{114–116} Beginning to describe the sexual networks in which lesbians participate—particularly as they involve men at potentially high risk for STDs, including HIV—should provide much-needed data on the sexual and social dynamics of a highly diverse population. The intriguing observation of BV concordance within female sexual partnerships should offer an opportunity to decipher the enigmatic etiology of this common condition. This information could not only contribute to advances in understanding the microbiology and sociology of STDs in general, but more immediately, would inform a cogent approach to counseling lesbians and educating health-care providers about STD-related risk and prevention.

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HIV and Other Sexually Transmitted Infections in Injection Drug Users and Crack Cocaine Smokers

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The burden of HIV and other sexually transmitted infections (STIs) in persons who use illicit, psychoactive drugs, including injection drug users (IDUs) and crack cocaine smokers, is certainly high enough to justify special consideration in a textbook on STIs. Fortunately, the scientific work on parenteral and sexual transmission of HIV infection in IDUs and crack cocaine smokers, has been extensive and includes systematic reviews and meta-analytic work.^{1–7} However, limited work exists on the burden of other STIs in IDUs and crack cocaine smokers. Given this imbalance—the extensive HIV literature and the limited literature on other STIs in IDUs and crack cocaine smokers—we present, in this chapter, a comprehensive review of the HIV situation and a more targeted review of three bacterial STIs: chlamydia, gonorrhea, and syphilis, and three viral infections: genital herpes, hepatitis B, and hepatitis C. HIV, hepatitis B, hepatitis C, and syphilis may be transmitted through both parenteral and sexual mechanisms and our review reflects the burden of these infections generated by these two transmission modes. Sexual transmission of hepatitis C is not responsible for the majority of infections. We discuss it in this chapter because the transmission of hepatitis C through injection equipment has been covered extensively elsewhere.^{8–12} *Trichomonas vaginalis*,^{13–15} bacterial vaginosis,¹³ and human papillomavirus^{16,17} are not addressed in this chapter because few studies have assessed rates of these STIs in IDUs and crack cocaine smokers. Because there is also an extensive literature on the association between smoking of crack cocaine and infection with syphilis^{18–22} and HIV,^{23–26} we focus our review on the recent literature on syphilis and other STIs in crack cocaine smokers, as well as in IDUs. The use of methamphetamine, unfortunately an emerging problem for drug users, is covered in other studies.²⁷ Sexual transmission is the main mechanism of transmission for the bacterial STIs: chlamydia, gonorrhea, and syphilis, and for the viral STI genital herpes; accordingly we cover these four STIs in this chapter.

In this chapter, we focus primarily on the literature published between 1995 and early 2005. We review a comprehensive list of the studies conducted in the United States and

an illustrative list of studies conducted in countries other than the United States. We refer to three groups of studies: (1) studies that were conducted exclusively with IDUs, (2) studies that were conducted exclusively with crack cocaine smokers, and (3) studies that included both IDUs and crack cocaine smokers and often presented the results for the combined sample of IDUs and crack users. The IDUs in these studies primarily injected heroin, cocaine, or speedball (heroin and cocaine in combination) and might also have smoked crack cocaine. We use the term IDUs and crack cocaine smokers (or drug users) to refer to samples or to studies of both IDUs and crack cocaine smokers.

In addition to assessing the burden of HIV and other STIs in drug users, we also summarize the public health efforts and successes that have been accomplished to date, as well as gaps in research and program activities. Our goal is to highlight the activities that still need to be addressed in the prevention and control of HIV and other STIs in this important and heterogeneous population.

INJECTION DRUG USE, HIV, AND OTHER STIs

The causal linkages between injection drug use, sexual behavior, and STIs are many and complex. The causal relationships may be mutual and nonlinear, and are often embedded in a variety of contextual and confounding variables. Potential relationships include (1) IDU leading to high rates of unsafe sex behaviors and to high rates of STIs through reducing inhibitions or increasing sexual desire, (2) IDU leading to exchange of sex for drugs or money to purchase drugs, with a possible increase in STIs, and (3) IDU leading to decreased libido or decreased ability to perform (for males) and thus to reduced sexual activity and reduced risk for STIs.

Contextual variables can include the local economic conditions, local prevalence of STIs, local norms regarding different sexual practices (including use of condoms), and social norms governing gender relationships. The majority of the studies reviewed in this chapter suggest that IDUs often

have higher rates of STIs than persons who do not inject illicit drugs. This higher association, however, should not be interpreted as evidence for direct causation. In particular, one should avoid assuming a dose-response relationship that more use of injection drugs will be associated with even higher rates of STIs.

Another aspect of the potential causal relationships between injection drug use (IDU) and STIs is worth noting. Randomized controlled trials (RCTs) are often considered the gold standard for determining causation in behavioral and biomedical research. It would clearly be unethical to randomly assign research subjects to IDU versus no IDU in order to observe changes in rates of STIs as an outcome variable. Indeed, it would be unethical to simply observe increases in IDU without making all reasonable attempts to reduce injection drug use. It is, of course, ethical and practical to randomly assign interventions to reduce IDU by users and then observe changes in rates of STIs. However, in such studies, current ethical standards require that some attempts also be made to reduce IDU and STIs of participants in the control condition. This may be “usual care” or some form of “minimal” or “basic” services for the control group. Just what is provided to the control group can vary greatly across studies. Such variation makes it demanding conceptually and analytically to synthesize results across different studies.^{28,29} Thus, while RCTs are usually considered the gold standard for assessing causal relationships in medicine and public health, they are not particularly useful designs for studying potential causal relationships among injection drug use, unsafe sexual behaviors, and STIs.

■ HIV INFECTION

A number of infectious agents, including HIV, hepatitis B, and syphilis, can be transmitted both through sexual and parenteral routes. HIV is certainly a special case among these pathogens. Both, the very high fatality rate of HIV-infected persons who do not receive antiretroviral treatment and the potential for HIV to reach very high prevalence levels in drug users make HIV by far the most important of the organisms that can be transmitted both sexually and parenterally.

The multiperson use (“sharing”) of needles and syringes is a relatively efficient method for transmitting HIV between IDUs. Extremely rapid spread of HIV has been observed in many populations of IDUs, with incidence rates of 10/100 person years up to 50/100 person years. Such rapid transmission has occurred in North America,³⁰ Western Europe,^{31,32} and, more recently, in many areas of Asia and Eastern Europe.³³

Several factors have been associated with rapid transmission of HIV between IDUs,³⁴ including lack of awareness about HIV and AIDS, limited availability of sterile needles and syringes, and situations that promote “rapid partner change” of IDUs. The term “rapid partner change” refers to

IDUs sharing needles and syringes with large numbers of other IDUs (sharing partners) within short time periods. Examples of injection situations and settings that create rapid partner change include injecting with a “dealer’s works” (injection equipment that a drug dealer lends to successive customers) and “shooting galleries” (locations where IDUs rent and use a needle and syringe, and then return them to the gallery operator to be rented to other IDUs). As people tend to be much more infectious in the few months just after they have become infected with HIV,³⁵ rapid partner change is an important factor in transmission of HIV between IDUs. If the conditions that facilitate rapid transmission of HIV in a population of IDUs are not ameliorated, very high levels of HIV infection can result. Around 80–90% of IDUs in certain areas in China and Myanmar have become infected with HIV,³³ essentially saturating the local IDU population.

At the other extreme, it is quite possible to prevent epidemics of HIV infection in IDUs. Three factors appear to be important in preventing HIV epidemics in IDUs: (1) beginning prevention efforts early, when the number of HIV-infected IDUs is still low; (2) developing trust and communication between health workers and IDUs; and (3) providing very good access to sterile needles and syringes. Community outreach,³⁶ peer outreach,³⁶ and syringe exchange programs^{37,38} have been the most commonly used programs to prevent epidemics. These prevention programs and strategies have kept HIV infection levels under 5% in many different cities³⁹ and in several countries, such as the UK⁴⁰ and Australia.^{41–43}

Prevention of HIV transmission is much more difficult after high HIV seroprevalence levels (20% or higher) have been reached. With both large numbers of infectious IDUs and large numbers of uninfected IDUs at risk for becoming infected, even modest levels of continuing risk behaviors can drive substantial rates of transmission. In such situations, HIV incidence rates of 4/100 person-years to 8/100 person-years have been observed.³¹ It does appear, however, that large scale implementation of HIV prevention programs for IDUs over long-time periods (a decade or longer) can lead to eventual declines in HIV incidence in IDU populations.^{39,44–49}

Although psychoactive drugs can reduce sexual drive and interfere with sexual performance, data on the number of sex partners and on the proportion of sexually active drug users indicate that drug users are a sexually active group.^{50–52} Once HIV prevalence has reached a high level in a population of IDUs (20% or more), sexual transmission between IDUs and from IDUs to sex partners who do not inject drugs becomes a potentially very important problem.^{53,54} The great concern is that sexual mixing and transmission in drug users would lead to widespread, self-sustaining, heterosexual transmission of HIV in the local area, where heterosexual transmission would continue

even if all further syringe sharing transmission of HIV were prevented.

The conditions under which high HIV prevalence rates in IDUs will lead to large-scale heterosexual transmission of HIV in persons who do not inject drugs have not been fully identified. Clearly, factors such as the number of HIV-infected IDUs, the scale of commercial sex work, the extent to which male IDUs purchase sex from sex workers, the background prevalence of STIs that facilitate HIV transmission, and the absence or presence of HIV prevention programs are all likely to be important. At present, IDUs are the leading edge of the HIV epidemic in many parts of Southeast Asia and Eastern Europe,⁵⁵ including China, Vietnam, Russia, and Estonia.^{33,56} The initial HIV epidemics in these areas seem to be developing into “generalized” heterosexual epidemics, with 1% or more of the adult population infected with HIV.

The HIV epidemic in IDUs in New York City has been the largest HIV epidemic of IDUs in the world. It offers useful lessons in both rapid transmission of HIV between IDUs and eventually successful prevention and in combinations of parenteral and sexual transmission of HIV. HIV was introduced into the IDU population during the mid-1970s and it spread very rapidly during the late 1970s and early 1980s. Substantial risk reduction efforts began with IDUs in New York City during the mid-1980s, and HIV prevalence stabilized at approximately 50%.^{30,57} The legalization and large-scale expansion of syringe exchange and other HIV prevention services for IDUs in the city, which began in 1992, was associated with drastic reductions in HIV prevalence and incidence in New York IDUs. These declines were seen in multiple studies, including IDUs recruited from drug detoxification programs, methadone maintenance programs, and through street outreach. HIV prevalence declined from approximately 50% in 1990 to the current level of 15–20%,⁴⁵ and HIV incidence declined from an estimated 4/100 person years to an estimated 1/100 person years.^{48,58} There has also been a decline in HIV incidence among IDUs in the United States as a whole.⁵⁹ Declining HIV prevalence among IDUs in cities with relatively good access to sterile syringes has also been observed in Northeastern cities in the United States,⁶⁰ and in Europe,⁶¹ particularly in northern Italy.⁶²

Sexual transmission of HIV from IDUs to sex partners who do not inject drugs has undoubtedly occurred in New York City since the beginning of the HIV epidemic in IDUs.⁵³ Initial sexual transmission was primarily from IDUs to the long-term sex partners. The crack cocaine epidemic that occurred in New York during the mid-to-late 1980s involved frequent exchange of drugs for sex and sexual transmission of HIV between persons who used crack.²⁶ Many IDUs also used crack cocaine⁶³ and IDUs were a major factor introducing HIV into the crack-for-sex exchange networks. The crack cocaine epidemic in New York and elsewhere has

diminished since the 1990s, although there continues to be substantial use of this drug.⁶⁴

Noninjection use of heroin increased greatly in New York City during the late 1980s and early 1990s and continues to the present. This is likely to be the result of both concern about contracting HIV and the reduced price and higher quality of heroin available in the city. Since the mid-1990s, approximately half of heroin users entering publicly funded drug abuse treatment in New York City have reported intranasal use (“sniffing”) as their primary route of heroin administration.⁶⁵ Noninjection users of heroin often associate with injection users, however, and there is undoubtedly sexual transmission of HIV between injection and non-IDUs.

HIV prevalence has been declining among IDUs in New York City, as mentioned earlier.⁴⁵ However, HIV prevalence among noninjection heroin and cocaine users has been increasing, with current prevalence between 10% and 15%.⁶⁶ Thus, while injection-related transmission was initially the dominant factor in HIV transmission in IDUs in the city, it now appears that sexual transmission is at least an equally important route of transmission, not only in New York City but also among IDUs in many other cities, including San Francisco and Baltimore.^{67,68} Even in areas where injection-related HIV transmission due to IDU is still the predominant mode of HIV transmission among IDUs, such as many parts of Eastern Europe,⁵⁵ Central and East Asia,³¹ it is important to address sexual transmission among IDUs and from IDUs to sex partners who do not inject drugs. Failure to do so may lead from an HIV epidemic that is concentrated among IDUs to a “generalized” heterosexual epidemic.

MEASUREMENT OF OTHER STIs IN DRUG USERS

STD clinics and the national STD surveillance system do not usually collect or report data by drug use behaviors because drug use behaviors do not represent a direct mode of transmission for most of the non-HIV STIs. Thus, research studies are the primary source of data on the rates of STIs in IDUs and crack cocaine smokers.⁶⁹

In the early part of the 1990s, data on rates of STIs, other than HIV, in IDUs and crack cocaine smokers relied primarily on self-reports of STI diagnoses. In these studies, IDUs and crack cocaine smokers responded to questions such as: “How many times have you been told by a doctor or nurse that you had (hepatitis B, chlamydia, syphilis, gonorrhea, genital warts, or genital herpes?)”⁷⁰ Data from these studies were either analyzed for each STI separately or, most often, the data were analyzed for several STIs combined together.^{70–73}

In the mid-1990s, investigators working with IDUs and crack cocaine smokers started using biologic markers

(e.g., assays performed in blood or urine samples) to measure STI rates. Data based on biologic markers provide more accurate assessment of the STI burden because these data are not subject to the limitations of self-reported data, which may include underreporting because of (1) a lack of awareness of previous infections, (2) an unwillingness to discuss sensitive subject matter, and (3) an inability to recall disease information provided by a health care provider. However, prevalence rates for self-reported STIs in IDUs and crack cocaine smokers are higher than the rates based on biologic data, probably because self-reported data have most often assessed lifetime experience. Although use of biologic markers is an important step in the assessment of STIs in IDUs and crack cocaine smokers, there are still few such studies. Increased willingness to work with drug users and increased funding for this research will help in assessing the burden of STIs in drug users and in developing relevant prevention and treatment activities. The data that follow on the prevalence and incidence of non-HIV STIs are summarized in [Tables 15-1 to 15-3](#).

CHLAMYDIA

Rates Based on Self-Reported Data: Two studies using self-reported data on lifetime history of chlamydia suggest that approximately one in six IDUs have been infected with chlamydia.^{70,74} A chlamydia prevalence of 17% was reported in one study of female IDUs and crack cocaine smokers whose average age was 35 years.⁷⁰ Another study reported a prevalence of 15%, (10% among males and 29% among females) in a jail-based sample of IDUs where most participants were older than 30 years.⁷⁴

Chlamydia Rates Based on Biologic Markers: Several studies tested for chlamydial infections in IDUs and crack cocaine smokers using nucleic acid amplification tests. Almost all these studies used the ligase chain reaction test. The overall prevalence ranged from 1% to 5%, with similar rates reported for IDUs and crack cocaine smokers recruited from drug treatment facilities^{14,15,75-78} and those who were not.^{13,79,80} Drug users recruited from out-of-drug-treatment facilities were younger (18-30 years)^{13,79,80} than those recruited from drug treatment facilities (median age of late 30s). The prevalence rates reported for women were higher than those reported for men and were slightly lower in white drug users compared to African Americans or Latinos. Analysis by type of drug-related behavior revealed rates as high as 14% in female crack users and as high as 13% in female IDUs.⁸⁰ Chlamydia prevalence was also substantial in those who engaged in the sex trade. For example, prevalence rates of 6% were found in those with a history of selling sex,⁷⁵ 8% in female IDUs and crack cocaine smokers who received money for sex,⁷⁹ 7% in female IDUs

and crack cocaine smokers who received drugs for sex,⁷⁹ 12% in male IDUs whose last sexual encounter was with a paying partner,⁷⁹ 9% among those with more than five partners in the past 4 weeks,⁷⁵ 10% in male IDUs who had ever been forced to have sex,⁷⁹ and 11% in male IDUs with more than 10 sex partners in the 6 months prior to data collection.⁷⁹

Chlamydia was common in those who reported that they had had chlamydia or other STIs in the past year. For example, chlamydia prevalence was as high as 33% in male and female IDUs who reported having had genital herpes in the past year, 20% in female IDUs who reported having had genital warts in the past year, and 14% in male IDUs who reported having had chlamydia in the past year.⁷⁹

One study reported incidence rates for chlamydia,⁷⁹ with 2% reported in male IDUs and 4% reported in female IDUs at the 6-month follow-up period. Another study examined correlates of prevalent chlamydial infection using regression analysis.⁷⁹ This study found that for male IDUs, younger age, younger age of penetrative sex, and African American race were significantly associated with chlamydia. For female IDUs, younger age of penetrative sex and having received money for sex were associated with chlamydia.

Selected International Studies: Studies conducted with drug users outside the United States showed similar rates to those reported in drug users in the United States, with a prevalence of 3% in Quebec city,⁸¹ 2% in Thailand,⁸² and 6% in Melbourne, Australia.⁸³

Overall Assessment of U.S. Rates: Review of the seroprevalence rates of chlamydia in drug users show that IDUs and crack cocaine smokers have relatively high rates of prevalent and incident infections. However, the 7-33% prevalence range observed among female IDUs and crack cocaine users is higher than the 3-20% (median 6.3%) chlamydia positivity rate seen among 15-24-year-old women screened in family planning clinics.⁸⁴ A similar range was observed for the 50 states where 3.1-14% (median 9.2%) state-specific prevalence rate was reported for 16-24-year-old economically disadvantaged women entering the National Job Training Program.⁸⁴ Variation in prevalence rates in IDUs and crack cocaine smokers by sociodemographic factors mirrors the variation in rates seen in other populations, with lower rates in older, white, and male drug users. Higher prevalence was seen in subgroups of drug users, especially in female crack cocaine users, female IDUs, and drug users of both genders who are simultaneously at risk for sexual transmission. Higher prevalence rates were found in those who reported having had other STDs including genital warts, genital herpes, and a previous infection with chlamydia.

Table 15-1. Summary of Selected Information on Rates of Bacterial STDs (Seropositivity Rates) in Drug Users in the United States^a

	Syphilis	Gonorrhea	Chlamydia
Incidence rate	6/1000 person years ⁸⁶ 26/1000 person years ⁸⁷	0% among male IDUs at 6 months follow-up ⁷⁹ 1% among female IDUs at 6 months follow-up ⁷⁹	2% among male IDUs at 6 months follow-up ⁷⁹ 4% among female IDUs at 6 months follow-up ⁷⁹
Prevalence rate	Seropositivity rate: 1–6% ^{14,76}	Prevalence rate: 1–3% ^{13,15,77–80}	Prevalence rate: 1–5% ^{79,86}
Prevalence rates for demographic variables ^b	Higher among African Americans (6–8%) ^{13,75,87} Mixed results with respect to age 12% among 18–25 IDUs ⁷⁷ 2% among 20–29 years and 7% among >40 years ⁷⁶	Higher (4%) among females ⁷⁵ Lower (1%) among whites ⁷⁵ Higher among younger drug users (4% among <20 years old) ⁷⁵	Lower among whites (4% among white males and 6% among white females) ⁷⁹ Lower among older drug users (2% among <25 years old) ¹³
Prevalence rates for drug-related variables ^b	Higher (9%) among crack users ⁸⁰ Higher (13%) among female IDUs ⁸⁰ Similar for those in- and out- of drug treatment	Higher (11%) among male crack users ⁸⁰ Higher (13%) among female IDUs ⁸⁰ Similar for those recruited from in- and from out- of drug treatment	Higher (14%) among female crack users ⁸⁰ Higher (13%) among female IDUs ⁸⁰ Similar for those recruited from in- and from out- of
Prevalence rates for sex-related variables ^b	Higher (14%) among those with >5 partners past 4 weeks ⁸⁷	Higher (5%) among those who exchange sex for money ⁷⁹	Higher (8%) among those who trade sex ⁷⁵ Higher (9%) among those with >5 partners past 4 weeks ¹³ 4 weeks ¹³
Prevalence rates for health-related variables ^b	Higher (33%) among females with previous syphilis infection ⁹⁰ Higher (42%) among HIV-positive drug users ⁸⁷	Higher (4%) among HIV-positive female IDUs ⁷⁹	Higher (33%) among those who had genital herpes past year ⁷⁹ Higher (14%) among male IDUs with previous chlamydial infection ⁷⁹
Multivariate correlates of prevalent infection ^c	History of an STD (O.R. = 11.7) ⁸⁸ Self-report of previous infection with syphilis (O.R. = 10.3) ⁸⁸	Among female IDUs: younger age of penetrative sexual debut (O.R. = 1.27) ⁷⁹ and having received money for sex past 6 months (O.R. = 5.17) ⁷⁹	Among male IDUs: younger age (O.R. = 0.89) ⁷⁹ , younger age of penetrative sexual debut (O.R. = 0.91) ⁷⁹ , and being African American (O.R. = 2.92) ⁷⁹ Among female IDUs: younger age of penetrative sexual debut (O.R. = 1.16) ⁷⁹ and having received money for sex past 6 months (O.R. = 1.96) ⁷⁹
Multivariate correlates of incident infection ^c	Recent initiation into drug use (H.R.) = 4.6) ⁸⁷	Not reported in the literature reviewed for this chapter	Not reported in the literature reviewed for this chapter

^aThe superscript numbers refer to the citation numbers in the reference list.

^bBased on bivariate results reported in the referenced studies.

^cBased on regression results reported in the referenced studies. The variables are statistically significant at $p = 0.05$. O.R. indicates odds ratio. H.R. indicates hazard ratio.

Table 15-2. Summary of Selected Information on Rates of Viral Infections in Drug Users in the United States^a

	HSV-2	Hepatitis B	Hepatitis C
Incidence rate	Not reported in the literature reviewed for this chapter	50–70% of IDUs become infected within 5 years of beginning to inject ¹⁰ Among HIV-positive drug users: incidence of acute HBV ¹¹¹ : - 3.5 cases per 100 person years for recent injectors - 1.9 cases per 100 person years for recent users of noninjection drugs	10–20% per year ^{12,121–124}
Prevalence rate	Range: 38–61% ^{75,76,88,89}	- among those in drug-treatment: 11%, ⁷⁸ 30%, ^{75,76} 57%, ¹⁰² 67% ^{103,104} - among those out-of-drug-treatment: 25%, ⁸ 30%, ^{106,135,181} 50% ⁸⁹ , 80% ^{106,108,109}	Among IDUs: reached 80% ^{8–12,121} and dropped to 50–60% ^{121,123} due to interventions among non-IDUs: 20–40% ¹³⁷ among noninjection sex partners of IDUs: 4% ¹³⁸
Prevalence rates by demographic variables ^b	Higher among females: 75–81% ^{75,89} Higher with age: ⁷⁵ <20 years: 15%; ≥40 years: 57% Lower among whites ^{75,88} Whites: 25%, 37% African Americans: 57%, 64% Latinos: 27% Others: 29% Higher among women with incarceration history vs. among those with no such history: 65% vs. 50% ⁸⁸	Not reviewed for this chapter	
Prevalence rates by drug-related variables ^b	Relatively higher among those who are out-of-drug-treatment: 38–61% ^{88,89} vs. those who are in-drug-treatment: 44% ^{75,76} Relatively similar rates among female sex workers who only smoked crack cocaine vs. those who smoked crack cocaine and also injected drugs: 73% vs. 65% ⁹⁸	IDUs vs. non-IDUs of cocaine crack, or heroin: 37% vs. 19% ¹⁰⁷	Not reviewed for this chapter
Prevalence rates by sex-related variables ^b	Higher among those with a history of selling sex vs. those without this history (74% vs. 41%) ⁷⁵ ; 81% ⁸⁸ High among male drug users who had sex with men: 50% ⁸⁸	Not reviewed for this chapter	
Prevalence rates by health-related variables ^b	HIV-positive vs. HIV-negative females: (93% vs. 56%) ⁸⁸ HIV-positive vs. HIV-negative males: (78% vs. 20%) ⁸⁸		

Table 15-2. (Continued)

	HSV-2	Hepatitis B	Hepatitis C
Multivariate correlates of prevalent infection ^c	Among both males and females ⁷⁵ : Age over 30 (O.R. = 4.8) Being female (O.R. = 4.5) Being African American (O.R. = 3.6) Among females ⁸⁸ : Being African American (O.R. = 6.0) Having traded sex past 6 months (O.R. = 3.2) Having used heroin daily past 6 months (O.R. = 3.6) Among males ⁸⁸ : Being African American (O.R. = 2.6) Having >30 lifetime sex partners (O.R. = 2.6) Being HIV-infected (O.R. = 11.1) Ever been incarcerated (O.R. = 2.7)	Not reviewed for this chapter	Receiving money for sex ⁹ Infection with hepatitis B ^{9,137}
Perceptions of being at-risk for infection	Not reported in the literature reviewed for this chapter	10–25% ^{112,113,182}	Not reviewed for this chapter
Vaccination rates	Not applicable; a vaccine does not exist	For all three doses: 10% at primary health care clinics 86% in drug treatment settings ^{114–116}	Not applicable; a vaccine does not exist

^aThe superscript numbers refer to the citation numbers in the reference list.

^bBased on bivariate results reported in the referenced studies.

^cBased on regression results reported in the referenced studies. The variables are statistically significant at $p = 0.05$. O.R. indicates odds ratio. H.R. indicates hazard ratio.

Table 15-3. Summary of Information on Prevalence Rates (mostly seropositivity rates) of STIs in Drug Users for the United States and for Selected Studies Conducted in Other Countries^a

Country	Chlamydia	Gonorrhea	Syphilis	Genital Herpes	Hepatitis B
United States	1–5%	1–3%	1–6%	38–61%	20–80%
Other Countries	Canada: 3% ⁸¹ Thailand: 2% ⁸² Australia: 6% ⁸³	Canada: 0.4% ⁸¹ Thailand: 0.4% ⁸² Australia: 1% ⁸³	Bangladesh: 10–23% Spain: 5% ⁹¹ Thailand: 2% ⁸² Jamaica: 6% ⁹² Russia: 12% ⁹³	Did not find studies	Argentina: 60% ¹¹⁹ Russia: 48% ⁹³ Australia: 33% ¹¹⁸

^aThe superscript numbers refer to the citation numbers in the reference list.

GONORRHEA

Gonorrhea Rates Based on Self-Reported Data: Few studies provided information on rates of lifetime infection with gonorrhea in IDUs and crack cocaine smokers. An overall rate of past infection of 18% was reported in a jail-based sample of IDUs, most of whom were older than 30 years,⁷⁴ with higher rates reported by incarcerated female IDUs than by incarcerated male IDUs (29% vs.15%).⁷⁴ History of gonorrhea was reported by 37% of IDUs and crack cocaine smokers recruited in Alaska (average age = 34 years)⁸⁵ and by 36% of participants in an 18 site-national sample⁸⁵ (average age = 37 years). That same study examined the multivariate correlates of past infection with gonorrhea using regression analysis. It found that in male IDUs and crack cocaine smokers, having ever used cocaine, being African American, younger age, having had illegal income in the past 30 days, and having ever used amphetamines were associated with higher frequency of history of gonorrhea.⁸⁵ These predictors were the same correlates found in the sample of male IDUs and crack cocaine smokers recruited in Alaska and in the national sample. For females, the significant predictors in the sample recruited from Alaska were having traded sex for money in the past 30 days, being native American, and having been homeless. The significant predictors in the 18-site national sample were having traded sex in the past 30 days, being native American, and having traded sex for drugs in the past 30 days.⁸⁵

Gonorrhea Rates Based on Biologic Markers: Several studies tested for gonorrhea in IDUs and crack cocaine smokers using nucleic acid amplification tests, mostly using the ligase chain reaction test. The overall prevalence rate, indicating current infection, ranged from 1% to 3% and was similar for those IDUs and crack cocaine smokers recruited from drug treatment facilities^{14,15,75,76,78} and those who were not.^{13,79,80}

While rates in female IDUs and crack cocaine smokers (ranging across studies from 1% to 13%) were higher than those in male IDUs and crack cocaine smokers, a few studies found little or no gonorrhea in male IDUs and crack cocaine smokers.^{13,77,78} A few studies reported gonorrhea rates by race^{13,75,79,80} and found that rates in white IDUs and crack cocaine smokers were lower than in IDUs and crack cocaine smokers of other racial or ethnic groups. In terms of drug-related behaviors, gonorrhea rates as high as 11% were found in male crack users and as high as 13% in female IDUs.⁸⁰ As with chlamydia, prevalence was substantial among drug users with sexual risk behaviors. Prevalence rates of 5% were found in those with more than five partners in the past 4 weeks versus 2.5% in those who had one to five partners in the past 4 weeks.⁷⁵ Prevalence rates of 5% were found in female IDUs who received money for sex versus 1% in those who did not receive money for sex.⁷⁹ Prevalence rates of

2% were found in female IDUs who were HIV-positive versus 0% in those who were HIV-negative.⁷⁹

One study examined the incidence rates of gonorrhea in IDUs with 0%–1% reported in males and females, respectively, at the 6-month follow-up period.⁷⁹ In that same study, younger age of penetrative sex and having received money for sex were significant correlates of higher prevalent gonorrhea rates in female IDUs.⁷⁹

Selected International Studies: Studies conducted with drug users outside the United States found low prevalence rates for gonorrhea: 0.4% (0% in males and 1% in females) in Quebec city,⁸¹ 0.4% in Thailand,⁸² and 1% in Melbourne, Australia.⁸³

Overall Assessment of U.S. Rates: The data on seroprevalence rates of gonorrhea in drug users show that IDUs and crack cocaine smokers have moderate rates of prevalence and incident infections, with lower incidence rates in males. However, the 4–13% prevalence range documented among female IDUs and crack cocaine users reporting ongoing sex risk behaviors is substantially higher than the 1% median positivity rate observed in 15–24 year old women screened in family planning clinics across the United States (range 0–3.8%) or the 2.4% median state-specific positivity rate among 16–24-year-old women entering the National Job Training Program (range 0–6.6%).⁸⁴ Variation in prevalence rates by sociodemographic factors again reflects the variation in rates seen in other populations, with lower rates in older, white, and male drug users. Higher prevalence rates were seen in subgroups of drug users, especially in male crack users, female IDUs, those who trade sex, and those with multiple partners. Higher rates of infection with gonorrhea were found in female IDUs infected with HIV.

SYPHILIS

Syphilis Rates Based on Self-Reported data: Self-reported lifetime history of syphilis among drug users was evaluated in the two studies of chlamydia described earlier.^{70,74} An overall rate of 6% (2% and 8% in male and female IDUs and crack cocaine smokers, respectively) was reported in one study.⁷⁰ The average age of the participants in that study was 39 years for men and 35 years for women. Lower rates were reported in white than in African American IDUs and crack cocaine smokers (in males: 2% vs. 6%; in females: 5% vs. 9%).⁷⁰ The second study of incarcerated IDUs, most of whom were older than 30 years,⁷⁴ reported a lifetime history of syphilis in 3% of participants, also with higher rates in female than in male IDUs (7% vs. 2%).

Syphilis Rates Based on Biologic Data: A number of studies screened participants for syphilis using a nontreponemal serological test, such as the rapid plasma reagin test.

Reactive results were then confirmed by a treponemal test, such as the microhemagglutination *Treponema pallidum* test. Similar rates of syphilis seropositivity were found in studies with IDUs and crack cocaine smokers recruited from drug-treatment facilities and those recruited from out-of-drug-treatment. Overall prevalence rates (seropositivity rates), ranging from 2 to 6%, were found for in-drug-treatment IDUs and crack cocaine smokers.^{14,75,76,86} In three of these studies, the median age of the participants was in the high thirties and age was not reported in the fourth study.⁸⁶ Similar overall prevalence rates, ranging from 1 to 6%, were found in recent studies with out-of-drug-treatment IDUs and crack cocaine smokers.^{80,87,88} The age range of these study participants was 18–30 years,⁸⁸ and 18–24 years,⁸⁰ in the first two studies, and a median age of 43 years was reported for the third study.⁸⁷ However, earlier studies conducted in the early-to-mid-1990s with out-of-drug-treatment IDUs and crack cocaine smokers found much higher rates ranging from 13% to 20%^{89,90} with a median age of 40 years reported for one study⁸⁹ and 38 years reported for the other study.⁹⁰ These differences may, in part, reflect the 90% decline in primary and secondary syphilis rates that was seen in the United States between 1990 and 2000.⁸⁴

Prevalence rates in female IDUs and crack cocaine smokers as high as 30% and 35% were reported in earlier studies.^{89,90} Echoing the epidemiology of syphilis in other U.S. nondrug using populations, rates in African Americans were higher than rates in IDUs and crack cocaine smokers of other racial or ethnic backgrounds.^{75,88,90} Rates as high as 12% were reported among 18–25-year-old IDUs in-drug-treatment,⁸⁶ but another study with in-drug-treatment IDUs and crack cocaine smokers showed higher rates in those who were older (20–29 years: 2% vs. ≥ 40 years: 7%).⁷⁵ Drug and sexual risk behaviors and STI/HIV history were again associated with higher prevalence rates. Rates as high as 9% were found in crack cocaine smokers⁷⁶ and as high as 13% in female IDUs.⁸⁰ In terms of sex-related behaviors, rates as high as 14% were found in IDUs and crack cocaine smokers who had more than five sex partners in 4 weeks prior to data collection.⁷⁵ Rates as high as 33% were found in female IDUs and crack cocaine smokers who reported having had a previous syphilis infection.⁸⁸ Syphilis rates in HIV-positive IDUs and crack cocaine smokers were as high as 42% and were 17% in HIV-negative IDUs and crack cocaine smokers.⁹⁰

Incidence rates were reported in a few studies with IDUs, with an overall incidence rate of 6/1000 person years reported in one study⁸⁶ and 26/1000 person years reported in another.⁸⁷ In the first study, incidence rates as high as 19/1000 person years were reported in those aged 18–25 years and as high as 16/1000 person-years in those who were

paid or paid for sex.⁸⁶ Rates as high as 187/1000 person years were found in the subgroup that included male IDUs who had sex with men, bisexuals, and female IDUs who had sex with women.⁸⁷

Studies that examined correlates of syphilis seropositivity rates found that being female,^{89,90} being HIV infected,⁹⁰ being African American,⁹⁰ having had a history of STDs,⁷⁵ and having reported a previous diagnosis of syphilis⁸⁸ were positively associated with higher rates. In one study,⁸⁶ significant correlates of syphilis seroconversion were HIV seroconversion and having multiple sex partners. In another study,⁸⁷ significant correlates of syphilis seroconversion were recent initiation into IDU and having multiple sex partners.

Selected International Studies: Studies conducted with drug users outside the United States have found prevalence rates of 2% in Thailand,⁸² 5% in Spain,⁹¹ 6% in Jamaica,⁹² 12% in St. Petersburg, Russia,⁹³ (and 7% in syringes obtained from drug users in St. Petersburg).⁹⁴ The rates in Bangladesh were 10% in clients of a detox clinic and 23% and 13% in clients of needle exchange programs in the central and northwestern parts of the country.⁹⁵

Overall Assessment of U.S. Rates: The studies of syphilis in drug users show that IDUs and crack cocaine smokers have relatively high seropositivity rates and high incidence rates. Overall seroprevalence rates of 1–6%, and seroprevalence rates of 14–42% in selected subgroups with simultaneous sexual risk behaviors or a history of prior infection with STI or HIV have been reported. Higher seropositivity rates were reported in studies conducted in the 1990s reflecting the syphilis epidemic seen in the United States during that period.^{96,97} In more recent studies, variation in seropositivity rates by sociodemographic factors mirrors the variation in rates seen in other populations, with lower rates found in older, white, and male drug users. Higher seropositivity rates were seen in subgroups of drug users, especially in crack cocaine users, those who trade sex, and those with multiple partners. Higher seropositivity rates were found in those who reported a previous episode of syphilis and in those infected with HIV. Higher incidence rates were reported in male IDUs who had sex with men.

GENITAL HERPES

Genital herpes Based on Self-Reported Data: Self-reports of having had genital herpes suggest, rather inaccurately, low rates of this genital ulcer disease among drug users. The rates ranged from 1%⁷⁰ reported in out-of-treatment IDUs and crack cocaine smokers (mean age of 35 years) to 5% in a jail-based sample of IDUs most of whom were older than 30 years.⁷⁴

Genital herpes (HSV-2) Based on Biologic Markers: In contrast, the prevalence of herpes simplex virus-type 2 (HSV-2) determined by serological testing was high in IDUs and crack users. Overall, prevalence rates of genital herpes ranged from 38% to 61%.^{75,76,88,89} In two studies, the majority of the participants were 25–44-years old,^{75,76} and a median age of 40 years was reported in the third study.⁸⁹ The fourth study had young participants in the 18–30 years age group.⁸⁸ The two studies with in-drug-treatment IDUs^{75,76} reported identical rates (44%). Similar (38%)⁸⁸ or higher (61%)⁸⁹ rates were reported in out-of-drug-treatment IDUs and crack cocaine smokers. Moderate rates (18%) were found in a household sample selected from a high-risk neighborhood.⁸⁰ Data on age were not reported for that sample.

Rates were two or three times higher in females than in males. They were as high as 75% for in-treatment female IDUs and crack cocaine smokers⁷⁵ and as high as 81% for out-of-treatment female IDUs and crack cocaine smokers.⁸⁹ Rates were higher in African American IDUs and crack cocaine smokers than in those of other racial or ethnic backgrounds. In one study with in-drug-treatment IDUs and crack cocaine smokers, the rates in whites, African Americans, Latinos, and others were 37%, 64%, 27%, and 29%, respectively.⁷⁵ In a study with out-of-treatment IDUs and crack cocaine smokers, the rates in whites and African Americans were 25% and 57% respectively.⁸⁸ Higher rates were reported by older age (20 years: 15% vs. ≥ 40 years: 57%).⁷⁵

A higher prevalence rate was associated with both sexual and drug-related risk behaviors. High seropositivity was found in those with a history of selling sex versus those without such a history (74% vs. 41%),⁷⁵ male drug users who had had sex with men (50%),⁸⁸ and women who traded sex (81%).⁸⁸ Female sex workers who only smoked crack cocaine had similar rates to female sex workers who smoked crack and also injected drugs (73% vs. 65%).⁹⁸ Female IDUs and crack cocaine smokers who had a history of incarceration had higher rates than those who did not report an incarceration history (65% vs. 50%).⁸⁸ Higher rates were found in HIV-positive IDUs and crack cocaine smokers than in those who were HIV-negative (females: 93% vs. 56%, males: 78% vs. 20%).⁸⁸

Independent correlates obtained in regression analysis included age over 30 years, female gender, and African American ethnicity.⁷⁵ In another study,⁸⁸ analysis was conducted by sex. In that study, significant correlates in female IDUs and crack cocaine smokers were being African American, having traded sex in the past 6 months, and having used heroin daily in the past 6 months. In males, the significant correlates were being African American, having had more than 30 lifetime sex partners, being HIV-infected, and ever been incarcerated.

International Studies: We did not find studies on HSV-2 conducted with drug users outside the United States.

Overall Assessment of U.S. Rates: Review of the data on biologic markers of genital herpes reported in four studies conducted with drug users shows that IDUs and crack cocaine smokers have high rates of HSV-2. The overall HSV-2 seroprevalence among IDUs and crack cocaine users of 38–61% contrasts with the 17% seroprevalence rate reported for the general U.S. population.⁹⁹ Variation in prevalence rates by sociodemographic factors among IDUs echoes the variation in rates reported for other populations, with lower rates in younger, white, and male drug users. Higher prevalence rates are reported in subgroups of drug users, especially in male drug users who have sex with men, in those who trade sex, in those who have multiple partners, in those who have a history of incarceration, and in those who are HIV-positive.

HEPATITIS B

Hepatitis B virus (HBV) is transmitted both parenterally and sexually. While HBV is transmitted in drug users primarily through the parenteral route,¹⁰⁰ sexual transmission of HBV in drug users is also common.¹⁰¹ Prevalence of hepatitis B virus (HBV) infection is determined by serologic testing.

Prevalence rates of HBV are high in both in-drug-treatment and out-of-drug-treatment drug users. For in-drug-treatment IDUs and crack cocaine smokers, rates ranged from 11%⁷⁸ and 30%^{75,76} to as high as 57%¹⁰² and 67%.^{103,104} Similar high rates were reported for out-of-drug-treatment IDUs starting from a higher level of around 25%,⁸ 30%,^{105–107} or 50%,⁸⁹ to as high as 80%.^{106,108,109} In one study with drug users in the 15–30 years age group, prevalence rates of HBV infection were much higher in IDUs than in non-IDUs (37% vs. 19%), with non-IDU defined as sniffing, smoking, or ingestion of cocaine, crack, or heroin.¹⁰⁷

Data from several studies show that 50–70% of IDUs become infected with HBV within 5 years of beginning to inject.¹¹⁰ In HIV-positive IDUs and crack cocaine smokers, incidence rates of acute HBV ranged from 3.5 cases per 100 person years for recent injectors to 1.9 cases per 100 person years for recent users of noninjection drugs.¹¹¹

A low proportion of IDUs (10–25%) perceive themselves to be at risk for HBV infection and, therefore, often do not get vaccinated.^{112,113} Studies reported IDU vaccination rates for all 3 doses of hepatitis B vaccine ranging from 10% in primary health care clinics to 86% in drug treatment settings.^{114–116} Low rates for hepatitis B vaccination indicate that IDUs and crack cocaine smokers, including recent injectors, and their sex and injection partners are at risk for infection with HBV. This situation of low vaccination rates continues, although an effective HBV vaccine has existed since 1982 and

recommendations for vaccinating IDUs and crack cocaine smokers were first made at that time.¹¹⁷ Given that IDUs get infected with HBV very early in their injection years, IDUs need to receive vaccination for HBV as soon as they start injecting drugs.

Selected International Studies: Rates of infection with HBV reported in studies conducted with IDUs outside the United States ranged from 33% in Melbourne, Australia,¹¹⁸ to 60% in Buenos Aires, Argentina,¹¹⁹ and 48% in St. Petersburg, Russia.⁹³ A prevalence of 16% was reported in syringes used by drug users in St. Petersburg.⁹⁴

Overall Assessment of U.S. Rates: Review of the data on Hepatitis B shows that IDUs get infected with hepatitis B primarily through injection of drugs, soon after initiation of drug injection. Despite the availability of an effective vaccine, a modest proportion of drug users are vaccinated for hepatitis B and a small proportion understand their risk for infection with HBV. IDUs with HBV infection have a high coinfection rate with HIV and HCV.⁸

■ IS HEPATITIS C VIRUS AN STI?

IDUs form the largest group of persons infected with hepatitis C virus (HCV), and most new infections occur in IDUs as a result of sharing syringes or injection equipment. Transmission of HCV is estimated to be 10 times more efficient than that of HIV.¹²⁰ The prevalence of HCV in IDUs is high and can reach 80%.^{8–12,121} Uninfected IDUs generally become infected at rates of 10–20% per year.^{12,122–124} Since the introduction of needle exchange and other HIV prevention interventions for IDUs, there is some evidence for decline in the prevalence rate of HCV in IDUs in general, including in recent users of injection drugs, but remains high, at around 50–60%.^{121,124}

Although direct use of injection drugs is the most important risk factor for infection with HCV, sexual infection with HCV also deserves attention. Although causality cannot be inferred, for 2003, it was reported that 14% of acute hepatitis C cases were associated with sexual contact with a hepatitis C patient during the 6 weeks to 6 months before illness onset and that 26% of acute hepatitis C cases had more than one sex partner during the same time period.¹²⁵ Because transmission of many viruses through blood transfusion has essentially stopped in industrialized countries, some have suggested that evolutionary pressure may select certain strains that are more easily transmitted sexually.¹²⁶

Review of studies that focused on HCV infection of monogamous heterosexual couples^{127–129} and of men who have sex with men^{130,131} showed that although sexual transmission of HCV is inefficient, it is possible. Recent case studies from Europe showed outbreaks of HCV infection in men who have sex with men.^{132–134}

For IDUs, studies have focused primarily on prevalence and incidence rates and on correlates of infection with HCV.^{9,106,135–139} Few studies among IDUs found significant correlates with risky sexual behaviors, however, hepatitis B infection was a significant correlate for infection with HCV in two studies,^{9,137} and receiving money for sex was a significant correlate in one study.⁹

A relatively high prevalence of HCV is found in non-IDUs ranging from 20% to 40%.¹³⁷ Another study found a prevalence of 24% in non-IDUs in an addiction treatment unit in Philadelphia, of whom 65% did not know how HCV is spread.¹⁰² A prevalence of 4% has been reported in noninjection sex partners of IDUs.¹³⁸ An additional concern is the high rate of unprotected sexual contact (29% for never injectors and 34% for former injectors) of HCV-infected current non-IDUs of heroin with partners who are either HIV-negative or who use noninjection drugs.¹³⁶

To assess whether HCV gets transmitted sexually in drug users, it is important first to rule out other modes of HCV infection in non-IDUs. Because current noninjectors might have been former injectors who changed route of drug administration to reduce the risk for infection with HIV and might have been infected with HCV during their earlier drug injection days, it is prudent to assess the rate of HCV infection in current non-IDUs by their injection history (i.e., former injectors vs. never-injectors). It is also important to assess how non-IDUs get infected with HCV because there have been reports that in persons who smoke cocaine, transmission of hepatitis C can occur through sharing of smoking equipment.¹⁴⁰

Review of the data on HCV rates in IDUs and in non-IDUs and of the reports of HCV outbreaks in men who have sex with men shows research gaps about the risk for HCV infection associated with specific sexual practices.¹⁴¹ In particular, we do not know whether the low HCV heterosexual risk is increased during prolonged vaginal sex under the influence of cocaine (owing to delays in male orgasm) or during sex under the influence of crack (owing to having multiple sex partners in a short time). Similarly, we do not know if traumatic sex (e.g., fisting) and concomitant STDs in male IDUs who have sex with men increase the sexual risk for HCV infection. Although one might assume that sexual activities causing micro tears and abrasions increase the sexual risk for infection with HCV, data about the role of these factors are currently limited. There is also a need to examine the role of HIV and coinfection with other STIs, especially ulcerative STIs, such as syphilis and genital herpes. Collecting data on the characteristics of the sex act (e.g., rough sex, visible or invisible blood-producing sex, fisting) and on the viral load of the HCV-infected partner is important for understanding the sexual risk for HCV infection in drug users. Given the large proportion of HCV-infected IDUs, it is also important to assess the sexual risk of their sex partners for HCV infection.

OVERALL ASSESSMENT OF RATES

The rates of HIV and other STIs in IDUs and crack cocaine smokers deserve public health attention. The evidence-based research and intervention literature on HIV in drug users is, in general, more extensive than the literature on other STIs in drug users. Few studies on bacterial STIs and genital herpes in drug users have been published. Almost all of these studies were conducted as part of HIV research projects.

To the extent that the rates reported in research studies are underestimated because a certain proportion of drug users have been lost to follow-up, the rates could be even higher. In general, the reported rates, when age-adjusted, could be comparable to or higher than those reported in surveys conducted with the general population.^{142–144}

The variation in the rates of the bacterial STIs—chlamydia, gonorrhea, and syphilis—in drug users by demographic characteristics, such as age, sex, and race, is similar to those reported in other populations.⁶⁹ Higher rates are usually reported in drug users who are younger, of a racial or ethnic background other than white, and in women. Rates of bacterial STIs also differ by drug use and sexual risk behaviors. Higher rates are reported in IDUs who are also crack cocaine users, in those who exchange sex for drugs or money, in those with multiple sex partners, and in those with a history of incarceration. Higher rates are also found in those who reported previous infection with the same STI or with other STIs and in those who were HIV infected.

The variation in bacterial STDs by sociodemographic characteristics is also noted for genital herpes, with the main difference being that higher HSV-2 rates are reported in older drug users because prevalence of this currently incurable STI increases with age. Because drug users are primarily infected with hepatitis B and C through injection drugs, variation in prevalence rates for these two infections is primarily dependent on injection-related history and variables. There is a high coinfection rate of HIV with HBV and HCV.

In general, the magnitude of the burden of STIs, other than HIV, reported in studies conducted with drug users in the United States is not different from the magnitude reported in international studies, although our review of international studies of IDUs and crack cocaine users has been limited. [Table 15-3](#) provides a comparison of the prevalence rates reported in the United States with those reported in selected studies conducted in other countries. Accordingly, it remains important for the public health system to work with drug users to reduce the burden of STIs in this population.

WORKING WITH INJECTION DRUG USERS AND CRACK COCAINE SMOKERS

The problem of drug addiction and the prejudices that drug users face may make IDUs and crack cocaine smokers look as

if they are a hard group with whom to work. The fact that HIV transmission has been greatly reduced among IDUs compared to other populations at risk for HIV infection^{58,59,145–147} speaks volumes about the intentions and behaviors of IDUs in taking steps to reduce their risk for getting infected and infecting others with HIV.

Addiction: Life pressures can lead people to become addicted to simple pleasures or activities, such as gambling, or to more dangerous activities such as smoking, drinking, or injecting illicit drugs. However, all drug users deserve humane and ethical treatment.¹⁴⁸ From a health and human rights perspective, people addicted to a heavy drug still have the same rights as people addicted to what may seem to be simple pleasures or safer addictions. In addition, societal factors that marginalize people in terms of life opportunities also contribute to the epidemic of drug addiction and STIs, including HIV infection.^{149,150}

Research conducted over the past 20 years have demonstrated how substance abuse treatment is associated with reduction in HIV transmission risk behaviors and in increased protection from HIV infection.^{151,152} However, for drug treatment to meet its potential, it is important to make drug treatment readily available and accessible to IDUs and crack cocaine smokers¹⁵³ and to reduce the use of incarceration to curb drug addiction.^{154,155}

Prejudice: IDUs and crack cocaine smokers often report feeling stigmatized and discriminated against by the health care system and by society in general. An awareness of how prejudices develop may help investigators, health care providers, and public health practitioners work with drug users in a humane way to reduce rates of addiction and rates of infection with HIV and other STIs.

A recent study explained how people develop prejudices toward others and identified the different feelings and reasons for these prejudices.¹⁵⁶ Results of this study indicate that different prejudices are associated with different feelings apparently aimed at reducing perceived threats. When IDUs and crack cocaine smokers are seen as posing a threat to physical safety, public health, or moral values, they evoke prejudices characterized by feelings of fear and disgust. However, recognition that societal conditions may lead some people to drug use and addiction may facilitate working with IDUs and crack cocaine smokers in an effective and humane way.

Partnering with IDUs and Crack Cocaine Smokers: Compassion and patience are required to work with IDUs and crack cocaine smokers. In working to control the HIV epidemic in IDUs in many cities in the United States and countries around the world, HIV investigators and their teams of interdisciplinary staff members showed IDUs the respect they deserve as human beings and demonstrated an understanding of how personal and structural determinants influence risk for addiction and for HIV infection.³⁶

Similar positive attitudes are needed in working with IDUs and crack cocaine smokers to reduce their risk for infection with other STIs.

A list of 13 principles has been advocated to manage health care relationships with IDUs.^{157,158} These principles are (1) developing a professional relationship that shows mutual respect and avoids blame or judgment; (2) educating IDUs and crack cocaine smokers about health care; (3) including IDUs and crack cocaine smokers in decision making; (4) establishing a multidisciplinary and case management team; (5) having a primary care provider who coordinates care needs; (6) developing an agreement on responsibilities; (7) providing a response to behaviors that violate mutual expectations or limits; (8) reducing barriers to accessing the health care system; (9) establishing realistic commitments to more healthful behaviors; (10) emphasizing the importance of risk-reduction measures; (11) acknowledging that success requires several attempts; (12) learning about local resources for IDUs and crack cocaine smokers; and (13) avoiding common pitfalls, such as unrealistic expectations, frustration, anger, moralizing, blame, and withholding therapy.

Despite real and potential difficulties, it is important that the public health system works with IDUs and crack cocaine smokers to reduce their rates of addiction and their rates of infection with HIV and other STIs.

INTERVENTIONS FOR HIV AND OTHER STIs

Efforts to control HIV and other STIs usually aim to interrupt transmission of infection and prevent the development of disease, complications, and sequelae. Primary prevention includes behavioral interventions that focus on information, education, and communication, use of barrier methods, vaccination, screening, testing, and case finding. Treatment strategies include promoting appropriate health-seeking behaviors, syndromic management, partner notification and management, and a supportive health care sector. Targeted interventions include working with those who trade sex for money or drugs, have high rates of sexual partnerships, or are HIV-infected. These subgroups of IDUs and crack cocaine smokers may be more likely to acquire and transmit HIV or STIs, forming a bridge with the general population.

Risk-Reduction Interventions: There is ample evidence in the literature that behavioral, social, and structural interventions have been effective in reducing the sexual risk behaviors of IDUs and crack cocaine smokers.^{2,150,159} Several reviews and meta-analyses articles were published recently on the effectiveness of behavioral interventions in reducing the sexual risk behaviors of IDUs and crack cocaine smokers.^{2,52,160} These reviews concluded that IDUs and crack cocaine smokers reduced their sexual risk behaviors to avoid becoming infected with HIV and to avoid transmitting HIV infection to others. The sexual risk reduction activities of IDUs

and crack cocaine smokers reflected their rational and altruistic response to HIV, which poses a major health threat. In three studies in which the comparison group did not receive an HIV intervention, the average protective odds ratio for risk reduction associated with the behavioral and social interventions provided, was 0.60 (95% CI = 0.43–0.85).² When the authors extrapolated this moderate average effect size (an OR of 0.60) to a population with a 72% prevalence of risk behavior, the proportion of IDUs and crack cocaine smokers who reduced their sexual risk behaviors was 12.6% greater in the intervention groups than in the comparison groups.² Given the importance of reducing sexual risk behaviors of IDUs and crack cocaine smokers and the likelihood that moderate effects are cost effective,¹⁶¹ the moderate magnitude of the odds ratio justifies providing intervention programs to IDUs and crack cocaine smokers at risk for the sexual transmission of HIV. In 30 studies in which an HIV intervention was also provided to the comparison group, the average protective odds ratio was 0.91 (95% CI = 0.81–1.03) and was not statistically significant, indicating that participants in both groups reduced their risk behaviors.² These results show that IDUs and crack cocaine smokers can reduce their sex-risk behaviors.

Providing evidence-based effective interventions is both superior and ethically responsible when compared to the alternative of providing nothing. Results of the evidence-based literature call for researchers, program providers, and policy makers to work together to make the interventions available to IDUs and crack cocaine smokers and to convert research interventions into materials for use in program settings. As interventions are implemented in different settings, it is important not to let stigmatization of drug use or infection with HIV or other STIs, and concerns about negative consequences of condom use limit effectiveness of interventions. It is equally important to develop and evaluate new interventions that would produce larger reductions in sexual risk behaviors including interventions that address the social roots driving drug addiction and the imbalance in gender relations.

Despite the vast number of behavioral intervention studies that aimed to reduce the sexual risk behaviors of IDUs and crack cocaine smokers, most of these studies focused on reducing the risk of getting infected with HIV.² Review articles on interventions that focused on risk reduction and treatment of STIs, other than HIV, do not specifically include IDUs and crack cocaine smokers.^{162–164} While information aimed at reducing sexual risk behaviors should work both for HIV and for other STIs, there is a need to assess this assumption by providing specific information for the different bacterial and viral STIs. In one study that randomized IDUs and crack cocaine smokers either to receive risk reduction counseling on HIV and other STIs or to only receive risk reduction counseling on HIV, participants in both groups reduced their sexual and drug risk behaviors.⁷²

Informing IDUs and Crack Cocaine Smokers About Safer Practices: Interventions with IDUs and crack cocaine smokers need to provide accurate information on how HIV and other STIs are transmitted sexually and how safer sex practices, including condom use, can reduce the risk for transmission. This information is necessary, though not sufficient, to change behavior. While abstinence prevents the transmission of HIV and other STIs, condoms provide a very effective alternative among sexually active persons in blocking the sexual transmission of HIV and many other STIs. Building on the message about the effectiveness of condoms for HIV prevention, IDUs and crack cocaine smokers need to learn that condoms also offer protection from the skin-to-skin and skin-to-sore transmission of STIs such as HPV, genital herpes, and syphilis if the site of infection is covered by the condom.¹⁶⁵ It is also important to inform IDUs and crack cocaine smokers that condoms offer good protection against discharge-related infections such as chlamydia and gonorrhea.^{166,167} Making condoms readily available either free or at low cost to IDUs and crack cocaine smokers is important to control the rates of HIV and other STIs. Making condoms publicly available to IDUs and crack cocaine smokers may also facilitate discussions of safer sex behaviors and may help develop peer norms supporting safer sex. IDUs and crack cocaine smokers also need to learn that reducing the number of sex partners and knowing the infectious status of partners is an important strategy in reducing risk of infection with HIV and other STIs.

It is also important to inform IDUs how to protect themselves when there is limited scientific knowledge related to a particular STI.¹⁶⁸ For example, use of condoms is important if other STIs are present or during sex acts that might traumatize the genital or rectal mucosa. HCV-positive individuals who are at risk for STIs and who have multiple sex partners may consider using condoms.¹²⁵

Social Norms: In addition to the provision of accurate information about key aspects of HIV and other STIs, including mechanisms of sexual transmission and symptom recognition, it is also important to influence norms supporting safer behaviors. It is useful for IDUs and crack cocaine smokers to develop peer norms supporting safer sexual behavior, a strategy that is also important for generating social support for reducing sexually risky behavior.¹⁶⁹ It may be helpful if peer leaders or other persons who are respected by IDUs and crack cocaine smokers serve as role models for reducing sexual risk behaviors. Social support, new social norms, and role modeling can reinforce sexual risk reduction in IDUs and crack cocaine smokers.^{150,170}

Informing IDUs and Crack Cocaine Smokers About the STIs: it is also important to inform IDUs and crack cocaine smokers about the different symptoms caused by different STIs, as well as the fact that most STIs are asymptomatic. Sharing this information with IDUs and crack cocaine smokers is

important so that they are aware that transmission of STIs can occur in the absence of symptoms. For example, IDUs and crack cocaine smokers should be aware that the asymptomatic presentation of gonococcal and chlamydial infections in women perpetuates the transmission of these infections and explains, in part, why exchange of sex for drugs is a contributory factor. Many may not know the basic information such as that most persons with genital herpes are asymptomatic, shedding occurs even in the absence of lesions, and rates of asymptomatic shedding is higher in HIV-infected and immuno-suppressed people. Education and counseling about recognition of symptoms and the importance of seeking medical care and follow-up, including treatment of sex partners, is important. The aim of an educational effort is to reduce the risk of having IDUs and crack cocaine smokers transmit or acquire HIV or other STIs.

Informing IDUs and Crack Cocaine Smokers About the Synergy Between HIV and Other STIs: It is also important for IDUs and crack cocaine smokers to be informed about the synergy between HIV and other STIs and about its implication for prevention and treatment.¹⁷¹ IDUs and crack cocaine smokers should learn that STI treatment decreases the risk for HIV transmission. They need to know that STIs, particularly those associated with genital ulcers, increase both the efficiency of HIV transmission and the susceptibility to HIV infection and, therefore, recognizing STI symptoms and seeking medical care are essential.

Vaccination for Hepatitis B: One of the healthy people 2010 objectives is to increase HBV vaccine coverage in IDUs and crack cocaine smokers and those with multiple sex partners to 90%.¹⁷² Health care providers need to inform IDUs and crack cocaine smokers about the risk for HBV infection and the seriousness of the disease, and offer them vaccination. A coordinated and well-funded approach at facilities frequented by drug users (e.g., STD clinics, HIV counseling and testing sites, needle exchange programs, drug treatment facilities, corrections facilities) is needed to improve vaccination rates. Cash incentives, outreach efforts, flexible immunization schedules, and coordination between public health practitioners and medical care providers have been useful in improving vaccination rates.^{107,173} Attention to issues surrounding reimbursement for vaccination would also help improve vaccination coverage. The use of a combined hepatitis A and B vaccine, with vaccination of drug users for hepatitis A recommended since 1995, would also be useful.¹⁷⁴

Partner Notification: Reinfection with STIs is common in IDUs and crack cocaine smokers, probably because of inefficient patient-partner notification and because of exposure to new partners. Partner notification should include counseling about behavior change and treatment of the patients and their partners.¹⁷⁵ It is important to teach drug users how to inform their partners about the need for testing and treatment for STIs and how to reduce the potential for violence

or any other unintended negative consequence of partner notification.¹⁷⁶

Provider-Based Interventions: Screening and testing for HIV and other STIs, including counseling, education, and provision of treatment, are central to acquiring knowledge of one's infectious status, reducing risky behaviors, and treating infected individuals and their sex partners. These services must be provided in a supportive climate that does not stigmatize IDUs and crack cocaine smokers and that keeps their information confidential. Counseling patients about following the medication regimen is important. Taking medications must be seen as a significant commitment on the patient's part, because inconsistent adherence to medications results in development of bacterial or viral resistance. Syndromic case management may be useful with IDUs and crack cocaine smokers especially if treatment is simplified by the use of clinical flow charts and standardized prescriptions and does not rely on IDUs and crack cocaine smokers returning for laboratory results to receive treatment. Investigators and health care providers committed to and experienced in working with drug users have been successful in establishing rapport and improving prevention and control outcomes. Recommended work-up for diagnosis of STDs in IDUs and crack cocaine smokers has been outlined recently.¹⁷⁵ Specific management recommendations for each STD appear in the CDC STD treatment guidelines.¹⁷⁷

Integration of Services: Integration of prevention and care services for STIs and HIV with drug treatment is an important mechanism to reach IDUs and crack cocaine smokers. Such strategies are possible and have been successful.^{15,78,178,179} However, such integration needs to be implemented on a wider scale, including assurance of appropriate funds and training of personnel.

Targeted Interventions: Targeted interventions are relevant because of the different physiologic effects of drugs and the differential effect on sexual behaviors among drug users. The stimulant properties of cocaine and methamphetamine, for example, are associated with increased levels of sexual risk taking. Although heroin has a depressive effect on engaging in sexual activities, recovering heroin addicts find themselves more sexually active and would benefit from safer sex messages, condoms, and other efforts for prevention and treatment of STIs. Those involved in commercial sex work and in informal exchange of sex for drugs or money are at increased risk for HIV and other STIs. HIV-positive IDUs is another subgroup that needs particular attention; for example, they are more likely to have active and severe genital ulcer disease caused by HSV-2.¹⁸⁰ Interventions that aim at identifying core groups will help target screening and management of STIs and may also help modify social, economic, and geographic characteristics that affect the behaviors of IDUs and crack cocaine smokers. Both generic interventions and targeted interventions can be effective with drug users, especially

when IDUs and crack cocaine smokers are treated in a humane manner without a judgmental or a stigmatizing attitude.

CONCLUSION

There is no doubt that drug addiction is associated with potentially severe personal and societal consequences, among which are the high rates of HIV and other STIs in drug users. Given that HIV and other STIs have potentially devastating short- and long-term sequelae, it is important to implement effective interventions aimed at prevention and treatment of STIs in this population.

HIV/AIDS is a particularly important infection in drug users. Globally, HIV is responsible for more deaths than all other STIs combined. While there are now drugs for managing HIV infection, there is no cure and no vaccine. HIV can spread very rapidly in IDUs with reported incidence rates of 10/100 person-years to 20/100 person years or higher.³¹ Conversely, if effective prevention programs are implemented on a large scale, it is possible to control HIV transmission in populations of IDUs.

Most IDUs are sexually active, so if HIV prevalence rates reach moderate to high levels in a population of IDUs, sexual transmission from IDUs to persons who do not inject drugs can become a substantial problem. This problem can be exacerbated by drugs such as crack cocaine, which is associated with both high rates of unsafe sexual activity and sexual mixing between IDUs and persons who use crack but do not inject drugs. Methamphetamine could potentially play a similar role in facilitating sexual transmission of HIV from injection to non-IDUs.

There are effective programs for reducing sexual risk behaviors in IDUs and crack cocaine users. These include basic education about HIV/AIDS, instructions on condom use, peer support, and voluntary HIV counseling and testing. These prevention efforts, however, have not been as effective as the efforts to reduce unsafe injection behaviors. Thus, to prevent sexual transmission of HIV from IDUs to persons who do not inject drugs, it is important to prevent drug injection-related-transmission in IDUs and initiation of injection drug use.

There are multiple complex relationships between IDU and STIs other than HIV, and between non-IDU and HIV and other STIs. Rates of STIs other than HIV are generally substantially higher in drug users than in an age matched "general household population." There have not, however, been any systematic efforts to control STIs in drug users as a targeted population.

Barriers and facilitators to prevention and control of HIV and other STIs in IDUs and crack cocaine smokers stem from the nature of the specific STI; the characteristics of the IDUs; the role of health care providers and public health

practitioners; and the nature of the health care system. It is critical, however, to work with IDUs and crack cocaine smokers as partners in addressing important public health problems. Collaboration among all those involved in the public health efforts to reduce rates of infection with HIV and other STIs in drug users has great potential. Such collaboration has already led to the success stories seen in the control of HIV in IDUs in many cities in the United States and in several countries throughout the world. Such collaboration has the same power to contribute to many more success stories in prevention of other STIs.

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INTRODUCTION

Throughout history, infectious diseases of humans have followed population movements. The great drivers of population mobility including migration, economic changes, social change, war, and travel have been associated with disease acquisition and spread at individual and population levels. There have been particularly strong associations of these key modes of population mobility and mixing for sexually transmitted diseases (STDs), including HIV/AIDS.¹ A prominent recent example was the wide array of population level changes that resulted from the dissolution of the former Soviet Union—a collapse with massive social implications and complex economic impacts. Key factors in the health impacts of this transition also included internal population migration, increases in illicit drug trafficking and availability, expansion of commercial sex work, and disintegration of a former functional, albeit punitive, public health system. As a result, there was an enormous epidemic of syphilis and other STDs.²

These social-epidemiological associations are more relevant today than ever before, as old forms and patterns of migration change, and as more people move further and more frequently than ever before. Modern wars increasingly target civilians and have forced population mobility and the creation of refugees as a primary conflict goal.³ Such conflicts have been all too common in our time, particularly across sub-Saharan Africa, the most AIDS affected region globally. And in an interconnected world, the outcomes of seemingly remote events can have far reaching effects. Indeed, the ongoing HIV/AIDS *pandemic* presents the starkest evidence we have of the truly globalized nature of our world, and of the ways in which sexual networks now swiftly span continents and impact even the most remote members of the human family. The interactions of either elective or forced mobility, and STDs, including HIV are complex and multifaceted. Successful interventions and programs for HIV/STD prevention must address emerging modes of mobility and face the challenges of providing both preventive and curative medical and public health services in enormously varied and sometimes challenging settings.

How does human mobility interact with STD and HIV risk? We will present four scenarios and propose intervention strategies for addressing the challenges of service provision and epidemic control. Migration and socioeconomic mobility are primary drivers and will be examined in the light of data on migratory and mobile risk groups including truckers, miners, and migrant sex workers, all of whom have been associated with increased rates of STD and or HIV spread in various settings. War and its multiple and widespread effects on population mobility, mixing, sexual behavior, and sexual violence against women will be discussed as a key factor in the ongoing vulnerability of much of the developing world. Trafficking of persons, predominately women, for the sex industry is a domain of considerable concern from human rights and legal perspectives, and one for which only sparse data on STD and HIV rates and risks exist. Nevertheless, this is an area of emerging concern globally and will be discussed in terms of potential health threats to trafficked women, and programs that might decrease both the frequency and the health risks associated with this grave wrong. Finally, travel medicine is increasingly faced with the challenges of sexual behavior and the STD and HIV exposures associated with global travel and population mixing, with implications for both developing and developed countries. We will address current thinking in management of travel-associated disease, and the need for prevention and counseling for travelers who may be at risk.

MIGRATION, MOBILITY, AND HIV AND STDs

There are currently around 175–200 million people documented as living outside their countries of birth.³ This number includes both voluntary migrants, people who have chosen to leave their country of origin, and forced migrants, including refugees, trafficked people, and internally displaced people.⁴ There are multiple modes of migration, including permanent migration, temporary migration such as “oscillating” migrants who travel for work and return home periodically, if circumstances allow, and seasonal migration, generally for work in agricultural sectors.⁵

Epidemiologists elucidated early in the HIV/AIDS epidemic that there was substantial geographic variability in incidence, as well as different risk factors for disease spread. As researchers better understood the characteristics of HIV transmission, its long incubation time, relatively low infectivity, and chronic disease course, it became clear that mobility of infected persons was a key determinant for further spread to new populations.⁶ Indeed, this had already occurred across Africa, Europe, and North and South America before HIV serological assays and diagnostic algorithms were developed in 1984.

In high-prevalence areas, migrants were consistently shown to have higher risk of HIV infection than stable populations. Early research done in Uganda and Senegal demonstrated that when stratifying for age and gender, there was higher HIV seroprevalence in migrant populations compared to their nonmigrant counterparts.^{7,8} This work provided early evidence that migration was an independent determinant for HIV infection. Recent work also suggests that migration and mobility are operating at community, national, and even regional levels (Southern Africa) in the dynamics of STI and HIV spread. We will review some of these data here; from

sub-Saharan Africa, South Asia, China, the former Soviet Union, and the United States.

■ SOUTHERN AFRICA

Migration was first identified as an independent determinant in HIV infection in African settings.^{7,9–11} Across the continent there were almost invariably higher rates of disease among migrants than their nonmigrant counterparts reported in early studies (Table 16-1). In many African contexts, the majority of migrants do not permanently move; rather, they migrate in an oscillating or “circular” pattern, returning home when circumstances permit.⁵ A model that demonstrates this pattern well is the labor migration associated with gold mines in South Africa. In 1997, the gold mines employed 350,000 male workers, of whom 95% were migrants from rural areas in South Africa and neighboring countries including Lesotho, Botswana, and Mozambique, making this a truly regional phenomenon. HIV risk determinants included living situations, high-risk sexual behaviors, and high HIV seroprevalence in the sex workers (SWs) used by miners.¹²

Table 16-1. Risk of HIV Infection Associated with Migration

Association with Migration	Gender	Country	Magnitude	Precision	Reference
Odds of HIV infection among migrants to gold mines	Male	South Africa	OR = 2.4	95% CI = 1.1–5.3	5
Odds of being infected outside of primary relationship compared to inside	Male	South Africa	OR = 26 (migrants)	$p < 0.0001$	17
			OR = 10 (nonmigrants)	$p < 0.01$	
Odds of being infected outside of primary relationship for female partners of migrating men compared to inside	Female	South Africa	OR = 2.0 (partner of migrants)	$p = 0.1685$	5
			OR = 0.8 (partner of nonmigrant)	$p = 0.6573$	
Odds of HIV acquisition associated with >14 occupational travel days per month	Male	Kenya	OR 2.8	95% CI 1.5–5.4	21
Odds of HIV infection for rural to urban migrants	Male	Guinea-Bissau	aOR 2.1	95% CI 1.06–3.99	22
Odds of HIV infection for rural women reporting casual sex in urban settings vs only rural settings.	Female	Guinea-Bissau	aOR 5.61	95% CI 1.56–20.15	22
Odds of HIV infection among Nepalese migrants to India compared to nonmigrants	Male	Nepal	OR = 4.1	95% CI = 0.51–33.5	29

Typically, miners reside adjacent to work areas, whereas their families remain in villages of origin. Miners stay in all male hostels during work periods promoting development of local commercial sex industries resulting in complex networks of sexual relationships extending to nearby urban and rural communities.¹³ The combinations of these factors contributed to a dramatic increase in HIV seroprevalence of HIV among these men from 1.3% in 1990 to between 20% and 30% in 1996.^{14,15} The end of apartheid era pass laws and restrictions on the free movement of these men doubtless also contributed to the rapid acceleration of this epidemic. This underscores a key point. Population movement and mobility increase disease spread and this may be an outcome of peace and increasing social freedom, as much as an outcome of war and dislocation. Further, established gender roles and high prevalence of gender-based violence in South Africa, also appear to have made the female partners of infected men less likely to refuse sexual intercourse or to negotiate condom use, resulting in increased risks of HIV infection at home.¹⁶

Studies of groups such as the gold miners have resulted in research on migration as a determinant of HIV infection in South Africa. A cross-sectional study of HIV seroprevalence was completed comparing 196 migrant men and 130 of their rural partners to 64 nonmigrant men and 98 rural women who are partners of nonmigrant men.⁵ The results demonstrated a 25.9% HIV seroprevalence in the migrant population compared with 12.7% in their nonmigrant counterparts (OR = 2.4, 95% CI = 1.1–5.3).⁵ In a careful assessment of migration as a risk for infection in the (nonmigrating) female partner, migrant couples were more likely to have at least one or both members seropositive for HIV than nonmigrant couples (OR 2.28, $p < 0.03$). In addition, migrant men were 26-fold ($p < 0.01$) more likely to have been infected outside of their primary relationship compared to inside in contrast to a 10-fold ($p < 0.0001$) increase in nonmigrating men. In HIV-serodiscordant couples, there was a trend for female partners of migrants to be more likely to have been infected outside of their primary relationship than female partners of nonmigrant men (RR 2.0 [$p = 0.1685$] versus RR 0.8 [$p = 0.6573$]). This reveals an additional risk in these South African couples; when men are migrating for work, their female partners are more likely to contract HIV from a relationship outside of their primary one.¹⁷ Further research in these regions have concluded that it is not the mix of high- and low-risk settings that resulted in the increased risk of HIV; rather, it is the increased prevalence of high-risk sexual behaviors during migration which explains the higher risk of HIV infection.¹⁸

In Tanzania, investigators studying the economic and cultural factors resulting in rural to urban migration found higher HIV seroprevalence in trading centers, hosts to predominantly mobile populations, compared to nearby rural villages.^{19,20} They propose that prevention strategies, especially in the context of limited resource regions, should focus

on these areas, as they may represent epicenters for the spread of disease. The determinants of disease identified among migrant populations in case-control studies have been verified by the few prospective studies that have been conducted. A prospective cohort study was started in 1993 studying seronegative truckers in Kenya to evaluate risk factors in HIV seroconversion. This study found that HIV acquisition during the study was associated with >14 days occupational travel per month (OR 2.8, 95% CI 1.5–5.4), history of sex with SW (OR 1.9, 95% CI 1.0–3.5, $p < 0.05$), and being positive for other STDs such as HSV-2 (OR 2.9, 95% CI 1.2–7.0).²¹

West Africa has an overall HIV seroprevalence rate that is lower than both Southern and Eastern Africa, although recent studies in these countries show that mobility remains very important. A project in rural Senegal and Guinea-Bissau demonstrated that short-term mobility to more urban areas was a risk factor for incidence among men in these communities (aOR 2.06, 95% CI 1.06–3.99). This study also showed that mobile women of rural origin who reported one or more sexual partners in the city during the preceding 12 months were more likely to be HIV seropositive than women who only reported casual sex in rural settings (aOR 5.61, 95% CI 1.56–20.15).²² These results further indicate that mobile populations are more likely to exhibit high-risk behaviors and that this population should be targeted for prevention strategies including education.

■ SOUTH ASIA

In some regions of the world, both permanent and seasonal migration have been an established feature of the social order. In the last quarter century, however, this phenomenon has spread and the absolute number of migrants has dramatically increased. The HIV epidemic in South and Southeast Asia began in earnest in the early 1990s, and because of the large population, it has the potential to become the region with the highest number of infected persons.²³ Migration in South Asia is common, and an estimated 22 million migrants originating in South and Southeast Asia are working throughout the world performing agricultural, construction, and service-sector jobs, especially in the Middle East, or, in many cases, escaping political persecution at home.^{24–26}

The landlocked South Asian State of Nepal, with a population of approximately 23 million, sharing long borders with Tibet to the North and India to the South, is a good example. In Nepal, international migration to India increased by 57% within a decade, coincident with an increase in HIV-1 seroprevalence.²⁷ In the Doti region in far western Nepal, male workers migrate to India in an oscillating annual pattern, functioning predominantly as truck drivers.²⁸ These individuals generally travel to Mumbai, Punjab, and Chennai, all of which are areas where the HIV prevalence among SWs is high. In 1997, Mumbai SWs were found

to have an HIV seroprevalence of 71%.²⁸ Regular brothel visits were common among the Nepalese migrants when in India, but condom use was infrequent. Not surprisingly, Doti district male migrants had an HIV seroprevalence of 10.3% (10/97), compared to 2.5% ($n = 1/37$) in their nonmigrant counterparts, although the results were not statistically significant due to the small sample size.²⁹

Upon returning home, migrants pose potential HIV/STD risk to their spouses. In Nepal, while few of these men reported extramarital sex before travel to India, extramarital sex was more common after return, and this appeared to be due to increased financial resources and higher social status of successful migrants.²⁹ These patterns suggest a pressing need for education, both for risk perception and developing technical skills for using condoms and other protective measures. Very low rates of condom use were reported with the women in villages of origin, as men perceived condoms to be unnecessary with low-risk women, increasing vulnerability to sexual pathogens among these nonmigrant female partners. While migrant men reported high levels of understanding that HIV is an STD, they also believe that it can be contracted by kissing or just socially interacting with an infected person. In addition, few understood the incurability or treatment regimens of HIV or AIDS.³⁰

While migration is a risk factor for the Nepali migrants, analyzing male migrant behaviors does little to explore the vulnerability to HIV/STI among rural women from these migrant communities in Nepal. In Kailali, another region of Western Nepal, women partners of migrants were much more vulnerable to HIV infection than women with nonmigrant partners.³¹ This was not only because of increased risk-taking behavior of their partners but also because of a variety of gender disparities that operate in Nepalese culture.³¹ While men gain increased social and financial standing from work done in India, women reported almost unanimously that their health status had declined compared to before their partners began migrating. This decreased perceived health status appears to be related to heavier workloads and less money to access adequate health care and nutritious food.³² As of 2001, the overall STI prevalence among women in Kailali district with migrant partners was 30%, suggesting that women's perceptions that health declines when male partners migrate were accurate.³¹

In contrast to Nepal, Myanmar, like South Africa, has huge gem mines that attract significant amount of migrant populations seeking employment, and consequent commercial sex work. This environment synergizes both with the lack of education, the lack of preventive services, and high prevalence of risk-taking behavior.³³ A study of 725 Burmese migrant workers found major gaps in the comprehension of HIV/AIDS and its transmission, high levels of risk-taking behavior, and low rates of condom use.³⁴ Studies of other occupation-based migrants such as fishermen and

other seafarers from South and South-East Asia had similar findings.^{35,36}

■ CHINA

During the Maoist era, STDs had been largely eliminated from China through a combination of enhanced screening and treatment and widespread and punitive public health measures, including the forced rehabilitation of several million former SWs.³⁷ These measures also included reeducation of persons diagnosed with STDs, and incarceration of persons who refused to identify sex partners.³⁸ Since the mid-1980s, China has been undergoing significant social change, including rapid urbanization and the movement of an estimated 110 million peasants, the “floating population,” off the land—perhaps the largest single migration in human history.³⁹ This social transformation has had a variety of consequences: economic, political, cultural, and may also be related to sharp increases in the number of drug users and increased level of sex work in a variety of regions of China which, in turn, increased incidence of STD/HIV.^{40,41}

Demographic features are poised to fuel migration in China. The Maoist “One Child per Family Policy,” combined with traditional preference for male heirs, resulted in a large number of selective female abortions.³⁹ It is thought that there are currently about 640,000 surplus men, with expected increases to about 8.5 million by 2020. The male-to-female ratio in the reproductive age group is anticipated to be as high as 1.18. This is unprecedented in human history and will result in large numbers of unattached and unmarried men. These men, in comparison to their married counterparts, are poor, unemployed, minimally educated, and are anticipated to constitute a significant portion of the urban lower classes.⁴² It is also anticipated that commercial SWs from neighboring, more impoverished countries, will migrate to China to provide sexual services to these unattached men. The female SWs, too, are generally a rural-to-urban migrant population of young, unmarried women with limited education.⁴³

STDs and HIV are high among rural-to-urban migrants in China.^{43,44} A recent study among such migrants in Beijing showed that higher prevalence of STD was associated with increased usage of SW, multiple sex partners in the previous month, and less regular usage of condoms.^{43,44} In addition, risk-taking behavior is common among female SWs in China with few using condoms due to lack of willingness of their customers and many SWs reporting substance use.^{45,46} Studies done in Beijing and Nanjing showed that only 28% of female SWs used condoms in their last three episodes of intercourse.⁴⁵ Behaviors such as these appear to be driving sexual spread in many regions of China, and national prevalence rates were estimated to be increasing annually by 30%

by 2002.⁴⁷ China presents a “dual-risk” example of the intersection of two migrant groups, surplus men and female SWs, both at risk for STDs, including HIV.

■ RUSSIA AND THE FORMER SOVIET UNION

Before 1990, Russia and the other states of the former Soviet Union were largely spared from the HIV/AIDS pandemic. Although some believed that this was due to concealment and underreporting, it was also likely due to the tight restrictions on population movement and contact with foreigners present in the former Soviet Union.⁴⁸ After the collapse of the Soviet Union, these social and structural impediments to transmission abruptly ended, resulting in sharply increased population mobility, mixing, migration, and consequent epidemics of infectious diseases such as syphilis and HIV-1.^{2,48} In 2006, the population prevalence of HIV was estimated at approximately 1% in reproductive age adults, with over 80% infections in persons under the age of 30.⁴⁹ Key determinants of spread include injection drug use (IDU), increase in commercial sex work, lack of STD control and education, and social transition and economic crisis.⁵⁰

There has been a sharp increase in both internal and external migration of SWs across the former Soviet Union, with increasing involvement of organized criminal syndicates.⁵¹ Sex workers are believed to play important roles in the emerging sexual risk component of the former Soviet Union epidemics, but the data are sparse and research in this area is fraught with logistical and human subjects protections challenges.⁵¹ In the former Soviet Union, because of the preexisting strong education system but dismal economy, migrant SWs often have at least a high school education, infrequently have drug abuse problems, and often anticipate remitting funds to their family of origin. They are, nonetheless, highly susceptible to being trafficked.^{52,53} Trafficked women are often unable to implement safer sex practices, even if they desire, because of fear or actual retaliation from the trafficker. A study of SWs in Vilnius, Lithuania, evaluated both STD prevalence and social characteristics among these women.⁵⁴ Most had been trafficked and their countries or area of origin included Poland, Russia, and more rural areas of Lithuania. Only one-third regularly used condoms and almost all (34/35 studied) were infected with at least one STD at the time of interview.⁵⁴ In Ukraine, the HIV seroprevalence rate of 1.4% is the highest in all of the former Soviet Union.⁵⁵ Initially, this outbreak was predominantly due to IDU risks, but it appears to have transitioned to sexual modes of spread, with migrant SWs playing a key role.⁵⁶ A St. Petersburg study found that female SWs regularly worked along transportation routes and targeted mobile populations by selling sex at train stations, along highways, and in hotels.^{57,58}

Clients of SWs in Russia may be either local residents, or migrants themselves, who pose additional risks for disease

transmission, underscoring the reach and complexity of these migrant networks.^{57,59} In the St. Petersburg study, male migrant clients included members of the military, *militia*, and migrant workers from Belarus and Ukraine. STD seroprevalence rates in the SWs are high. In Moscow, disenfranchised populations, such as homeless women and female SWs at a remand centre, were at higher risk of being seropositive for STDs and had a 30- to 120-fold increase in HIV seroprevalence compared with the general population.⁵⁰ These results from across the whole former Soviet bloc suggest that STD/HIV among migrant populations has become a regional challenge to prevention and control.

■ NORTH AMERICA

Migrant populations from all over the world congregate in the United States; some originating from countries with higher HIV seroprevalence rates and some from lower. One group of migrants that has been extensively studied is migrant and seasonal farm workers (MSFW) who are mostly of Hispanic origin, predominantly from Mexico.^{60,61} Determinants of increased risk in these migrants include poverty, limited education, constant mobility, feeling isolated, and living in a more open society.⁶² Migrants from Mexico to the United States tend to have more sexual partners, use condoms more regularly, and are more likely to inject drugs than otherwise similar nonmigrating populations in Mexico.^{62,63} Studies have also evaluated urban Latino migrant laborers as an at-risk population for STD. A study of 292 members of this population in San Francisco showed them to have a higher prevalence of syphilis and chlamydia compared to an equivalent population of non-migrant men living in San Francisco.⁶⁴ The determinants of increased risk included limited education, high-risk sexual behaviors, and low levels of condom usage.

WAR, CONFLICT, AND INCREASED VULNERABILITY

Political instability, social disruption, and the kinds of chaos seen during wars and their aftermaths have been long known to have adverse effects on population health.^{65–67} In conflict settings, there is often in-migration of military or paramilitary personnel and out-migration of local residents. Military and paramilitaries are often purchasers of commercial sex, and in undisciplined settings, may be perpetrators of sexual violence against vulnerable populations. Out-migration often results in disruption of local sexual and social networks, separations of family members, and economic dislocation that in turn may increase the attractiveness of sex work as a potential source of income. Recent examples of the interaction of infectious diseases and civil conflict include increases in visceral leishmaniasis in conflict areas of Sudan, and increases in HIV/AIDS associated with civil conflicts and/or their aftermaths in

Cambodia, Myanmar, El Salvador, Pakistan, Rwanda, and DR Congo.^{33,68–74} These associations make understanding more about infectious disease spread, and STDs in particular, in the contexts of conflict and instability, a global health priority.⁷⁵

The interaction of war, armies, and civilian populations with STDs is ancient but remains highly relevant in the current global context. Modern wars bring militaries into direct conflict with civilian populations, mixing young armed men and vulnerable women in an extreme, but common form of gender inequity that has been particularly important in the HIV/AIDS epidemic in Africa, where mass rape has accompanied conflicts in Rwanda, Burundi, northern Uganda, Sierra Leone, Sudan, Chad, and the DR Congo.⁷⁶ Indeed, Hankins et al. recently reviewed what is known about transmission and prevention of HIV and other STDs in war settings.⁷⁷ They reported on evidence implicating sexual risks, including sexual coercion and rape, in increasing HIV prevalence in the civil conflicts in Uganda, Rwanda, and Sierra Leone. Sexual risks, including increases in rates of partner change and changes in sexual network patterns have also been described among young adults in the conflict in Bosnia–Herzegovina.⁷⁸ An important caveat to these associations has been pointed out by Spiegel, who reported that not all conflicts lead to HIV/STD increases, since some may be associated with decreased population mobility and mixing.⁶⁷ Clearly, in several prominent cases, postconflict scenarios have posed greater social risks for disease spread.

An extreme, but still relevant example of conflict, sexual behavior, and HIV risks can be seen in the situation of women who survived the Rwandan genocide of 1994 and its aftermath. An estimated 800,000 persons were murdered by the Rwanda army and Hutu extremist militias in the 100-day genocide, and an estimated 250,000 women were raped.⁷⁹ This extreme example of gender-based violence led to tens of thousands of Rwanda women becoming HIV infected in a few short months.⁷⁹ While an array of NGOs and programs are attempting to provide services for these survivors, the unmet needs remain enormous.⁸⁰ Cohen et al. have suggested that provision of care to these survivors requires integrating medical care with psychosocial support and addressing barriers to care, including poverty and lack of empowerment.⁸⁰

An important element of modern civil conflicts has been the deployment of peacekeeping forces in conflict zones, and the increasing trend toward use of regional peacekeeping approaches.^{81,82} Tripodi and Patel have reviewed the HIV/STD associations for regional peacekeeping in African crisis settings and suggest several mechanisms by which disease spread may be exacerbated by peacekeepers.⁸² First, HIV rates in many African militaries are substantially higher than among civilians. Second, soldiers from high prevalence militaries may act as vectors of disease spread on deployment. And third, soldiers returning from deployment in high HIV/STD settings may act as vectors for their home communities upon

return. For example, of 1885 Dutch marines deployed to Cambodia in 1992–93, all received intensive STD education prior to deployment and condoms were available; 842 (45%) reported sexual contact during deployment, 301 (36%) had 1–3 contacts, and 541 (64%) had four or more contacts.⁸³ Sexual activity was associated with being younger and not having a steady sexual partner at home. Inconsistent condom use was higher in older men. The overall unadjusted attack rates (including nonsexually active soldiers in the denominator) was 3.5%; no cases were reported in consistent condom users. Recognizing these realities, the United Nations in 2001 implemented an HIV/STD policy for peacekeeping forces, which encourages all military personnel to undergo HIV voluntary counseling and testing, receive sexual health education, and be given 5–6 condoms per week while on deployment.⁸⁴ Nevertheless, concerns continue that peacekeeping forces may be vectors of sexual risk and disease spread in some settings.

TRAFFICKING IN PERSONS

Trafficking in persons has been called a modern form of slavery. Trafficking of women, girls, and children for sexual exploitation and work in sex industries is a small subset of the global illicit trade in labor and in persons, but is a particularly grievous form of the practice, and one with potentially important, though understudied, associations with STD and HIV risks, vulnerabilities, and global spread. In 2004, the United Nations estimated that 4 million persons per year were forced, sold, or coerced into trafficked work.⁸⁵ The proportion of these millions of persons in sex work is unknown. The U.S. State Department estimates that sex trafficked persons in the United States include 18–20,000 persons per year, mostly women—again, a small minority of overall trafficked persons in the United States.⁸⁶ Trafficking is a crime in virtually all UN member states. Trafficking in children for sex is a violation of the UN Convention on the Rights of the Child, the most widely ratified of all UN human rights conventions (all UN members except Somalia and the United States are signatories).⁸⁵ In addition to being a severe human rights violation, sex trafficking may have important health consequences in the AIDS era through mechanisms including the wide geographic movement of vulnerable persons, but it has proven to be a difficult domain for research, surveillance, and prevention.

Sex trafficking is usually an outgrowth of a poor economic environment. Countries involved in sex trafficking are generally divided into “Source” countries and “Destination” countries. The typical sex trafficking scheme involves women who are forced or enslaved into commercial sex work.⁵¹ Women are typically recruited in the source countries by recruiters associated with criminal syndicates. Although they are often recruited under false pretenses, for example, as

domestic help, in up to a third of cases, the women are aware of the prostitution-related potential.⁵¹ In qualitative studies, these latter women clearly indicate that this decision is driven by desperate economic circumstances.⁸⁷

Trafficked women are smuggled into destination countries, either through ports of entry under false travel documents or visas, or smuggled over dangerous remote border areas. Once inside the destination country, these women are often sold to brothel owners, and are expected to generate a specified income. Because of their migrant, oppressed, and illegal status, health service delivery, even in countries where health services are easily available, is poor or nonexistent.

Source countries where sex trafficking is known to be important include South East Asia, West Africa, Eastern Europe and the Balkans (Former Yugoslav Republics), Russia, and the Commonwealth of Independent States (including particularly Ukraine, Moldova, Belarus, and Uzbekistan). Destination countries include the Middle East (Lebanon, Israel, and the Gulf States), North Asia (Japan), and North America; making this little understood health threat a truly global phenomenon.⁵¹ Migration to the Middle East presents an example of the routes used and the ability of traffickers to circumvent tightly controlled borders. In 2000, trafficked women in Tel Aviv represented the majority of the estimated 2500 commercial SWs.⁸⁸ Most were from Eastern Europe, primarily from Ukraine and Moldova. After recruitment, they travel to Egypt, where entry occurs either at Cairo or Alexandria, and they are then transported across the Sinai desert by subcontracted Bedouin tribesmen. Crossing into Israel occurs at night, at remote locations along the border, where they are then handed over to collaborating traffickers, provided with false documentation, and auctioned to brothel owners. At each stage, the women are at risk for physical and sexual abuse.

Western European States are also destination countries for SWs. A recent study from Spain reports on HIV-1 subtypes among SWs in Madrid.⁸⁹ This group identified 1119 non-Spanish SWs in one city, of whom 70% were from Sub-Saharan Africa, 23% from South America, and 7% from Eastern Europe. Non-B clade HIV infections were common and included CRF02_a/G, A, and G. The highest rates of infection were found in women from Liberia (11.4%), Ecuador (7%), and Nigeria (5%). A very high HIV rate was also found among transgender SWs from Ecuador, 18%. This study did not report what proportion of SWs had been trafficked into Spain—a common occurrence in this emerging area of study.

What associations of STD and HIV are known with sex trafficking? Few studies have been done in this difficult area, and most have been hindered by small sample sizes and limited ability to directly assess biological outcomes and exposures from persons who often cannot provide consent or seek medical services. A recent large, multiyear effort of the

European Union to investigate sex trafficking into Western Europe was able to enroll and interview only 28 trafficked women.⁵¹ Nevertheless, for those women trafficked into sex work, the risks associated with prostitution are generally thought to apply and to be aggravated by the coerced nature of the work. These include high rates of exposure to STD/HIV where these infections are common in the male client pool. For example, a study of over 350 trafficked women in Tel Aviv found high rates of pharyngeal gonorrhea (8%), and these women had high rates of antimicrobial resistant gonococcal infection.⁸⁸ Sexual and physical trauma appear to be a nearly universal experience among trafficked women wherever they work, as are markedly limited access to health care and health information and mental health threats including depression, substance abuse, high rates of posttraumatic stress disorder (PTSD), and more complex psychological burdens associated with rape, slavery, exploitation, and fear.

Defining sex trafficking, as opposed to the wider category of sex work, or immigrant sex work, has been a challenge. The International Organization for Migration of the United Nations has developed a convention, *The Palermo Protocol against the Smuggling of Migrants by Land, Sea and Air*, which became UN enforceable policy in January, 2004. The Palermo Protocol is an important step in international efforts to deal with trafficking since it spells out a clear definition of trafficking in persons. “The recruitment, transportation, transfer, harboring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for purpose of exploitation,” which includes prostitution or other forms of sexual exploitation.

Palermo also asserts that “...the consent of a victim of trafficking shall be irrelevant.” This is an important element since previous attempts at defining trafficking, and specifically trafficking related to sex work, had often floundered on debates about whether sex work was voluntary or coerced, and whether the trafficked person had given knowing consent to enter sex work. For Palermo, this is irrelevant, and what matters in the law is the exploitative nature of the sex work.⁹⁰

Recognizing that persons trafficked into the United States should not be punished for illegal entry and were deserving of special protection and consideration, the United States passed into law in 2000 the “Victims of Trafficking Protection Act.” The law provides legal protection and limited health benefits, including STD services, for adults and children trafficked into the United States for sex services; however, it penalizes traffickers and owners/managers of sex venues. It provides 6 months of health insurance coverage to adult victims, and health benefits to age 18 for minors, as well as protection from incarceration and other punitive measures. Unfortunately, in

the first 3 years since its passage, the act appears to have reached far fewer trafficked SWs than expected and, hence, has generally been seen as well intentioned but less effective than its advocates had hoped.

Other components of the Victims Protection Act legislation include stratification of countries by their response to trafficking, with potential impact on foreign aid. This has been particularly effective in the Middle East, where the State Department, cooperating with local NGOs, has been able to prompt increased provision of medical services and increased prosecution of traffickers. Using the Israeli example cited above, by 2005, the number of trafficked SWs was reduced to approximately 1000, there were over 50 brothel closures in Tel Aviv, a large number of prosecutions, and the establishment of STD clinics specifically targeting vulnerable persons.

■ SEX TRAFFICKING IN SOUTHEAST ASIA

Southeast Asia has long been one of the world's prime regions for trafficking, due, in part, to its large commercial sex industries.²⁶ The region has both source and destination countries for women and girls, and several states that are involved in both aspects of the trade. As the most HIV/AIDS affected region after Africa, with an estimated 7.4 million persons living with HIV/AIDS at the end of 2004, this is also a key region for global spread of HIV.⁴⁹ Known source countries for trafficked women in the region include Myanmar, Thailand, Vietnam, Russia, Uzbekistan, Nepal, Laos, China, and the Philippines. Destination states for women from the region include Thailand, China, Cambodia, Malaysia, Japan, India, Russia, Sweden, Italy, the Netherlands, the UK, and the United States. Southeast Asian states with internal trafficking include Thailand, Myanmar, Cambodia, and China.⁹¹ It should be noted that trafficking in persons is illegal in all these states and that sex work, itself, is illegal in Myanmar, Thailand, and China.⁹¹ Nevertheless, the sex industries of these states continue to support extensive trafficking.

Some of the better data come from Thailand, where sex worker usage by Thai men was a clear driver of an explosive heterosexual HIV epidemic and where condom campaigns targeting the sex industry had important impacts on control of epidemic HIV.⁹²⁻⁹⁴ While prevention efforts through the early 1990s provide evidence for the success of this approach, the nature of the sex industry in Thailand changed over this period. Data from several studies suggest a shift in the demographic profile of SWs in Thailand.⁹⁵ Fewer Thai women were working in the industry by 1995, and since then, increasing numbers have been from Myanmar, China, and Laos, and from ethnic minority and tribal populations much more vulnerable to trafficking.⁹⁶ Few of these women can speak Thai, illiteracy rates have been high, and a number of trafficking related factors increase STD/HIV vulnerability. These factors include illegal status as SWs and as illegal

aliens; lack of documentation and identity documents; lack of access to care in host country settings, and in some home country settings, language and cultural barriers and exploitation by authorities, police, border guards, prison guards, and others.⁹⁷ Taken together, these factors suggest that trafficking has the potential to undermine Thailand's success in HIV prevention.

Trafficking and sexual slavery are severe rights abuses absent increased risks for HIV or STD. In considering global spread of STD and HIV, trafficking is arguably an important and understudied area. Available data suggest that risk factors relevant to sex work are compounded for trafficked persons, and that these women have a range of special medical and mental health needs.

STD, HIV, AND TRAVELERS

Each year about 700 million people travel internationally with an estimated 50 million originating in developed countries traveling to developing ones.⁹⁸ International travel can be temporary, permanent, or episodic, and for recreational or occupational reasons, with most travel being both temporary and recreational.⁹⁸ Throughout this chapter we have discussed populations migrating in search of financial and/or personal security and associated STD and HIV vulnerabilities; while these populations differ significantly from the recreational traveler, they may share some determinants of infection risk. A number of behavioral and epidemiologic studies have shown that travelers can be less socially constrained during travel and frequently engage in more sexual activities with local inhabitants or newly met fellow travelers.⁹⁹⁻¹⁰²

What are the behavioral and risk-taking associations with travel? The recent outbreaks of lymphogranuloma venereum among men who have sex with men (MSM) in Western Europe and the United States suggest that risk-taking patterns among some MSM subgroups may play important roles.¹⁰³ But travels risks are certainly not related to MSM alone: a study done in a genitourinary medicine clinic in Glasgow among heterosexual men and MSM reported an increase in sexual encounters from 0.1 to 0.25 per week ($p < 0.0001$).⁹⁹ In this study, only about 50% of people interviewed reporting condom usage. Low rates of condom usage among travelers have been reported in several other studies: a study of tourists traveling in Copenhagen showed that while 21% of males and 6% of females ($n = 1225$, mean age 22.5 years) had a condom while traveling, less than 50% of men and 0% of women who had engaged in sexual intercourse actually used one.¹⁰⁴ These and other studies suggest that travelers not only engage in more sexual activity while traveling abroad, they may be more likely to do so unsafely (Table 16-2). This may be true among groups well educated about the risks of unprotected sex. A study of Canadian HIV-1 positive people traveling internationally showed that 23.3% (31/133) had sexual activity but

Table 16-2. Prevalence of Condom Use Among Travelers

Population	Sample Size	Condom Usage if They Had Sexual Intercourse	Country of Origin	Reference
HIV-positive individuals	31	58%	Canada	105
Medical students	27	56%	UK	100
Peace Corp volunteers	432	30%	USA	101
Travelers (mean age = 22.5)	165	49% of men 0% of women	Denmark	104

only 58.1% (18/31) of these reported always using a condom.¹⁰⁵ In this study, among 119 HIV-positive persons on antiretroviral therapy, 29.4% (35/119) either discontinued treatment or were poorly compliant while traveling, underscoring the travel and disease risk associations.¹⁰⁵ A study of medical students done in England showed that 32% reported sexual activity with a new partner on their last trip abroad and only 56% reported always using a condom.¹⁰⁰ This increase in sexual activity is not limited to short-term travelers; rather, long-term travelers such as volunteers in underdeveloped and developing countries, military personnel, and other groups of expatriates generally have reported higher rates of sexual activity while abroad.¹⁰¹ A study done in 1080 American Peace Corps volunteers showed that 60% reported at least one new partner with 40% of those being local inhabitants and a total of 30% usage of condoms.¹⁰¹

These increased risk-taking behaviors would be expected to result in higher disease rates of STD among travelers. However, this has been notoriously difficult to demonstrate. One report from the UK showed that 5.7% of returning travelers acquired an STD while traveling.¹⁰⁶ However, this same group working at the Hospital for Tropical Diseases in London could only attribute 12% of the incidence of STD to sex while traveling.¹⁰⁷ There are certain biological markers that can be used to prove that certain STIs are imported. Strains of fluoroquinolone-resistant *Neisseria gonorrhoea* (QRNG) are increasing in prevalence in certain parts of the United States in the MSM population. This drug-resistant strain has arrived in the United States and other developed countries from travelers returning from Philippines and other regions of Asia.^{108–110} This example of the spread of drug-resistant strains of *N. gonorrhoea* illustrates not only the importance of prevention strategies on an individual level but also because these strains may become epidemic in developed countries, the potential to undermine our ability to treat this disease as a whole. QRNG is one example of many STDs, including HIV, that have been carried to other populations by travelers. This highlights the need to target STD control programs at these populations.

A significant amount of research has examined characteristics that predict high-risk sexual behavior while abroad. A study done in the UK showed that variables associated with reporting new sexual contacts abroad were being male ($p < 0.01$) and traveling with friends ($p < 0.01$); factors associated with reporting four or more sexual exposures were being female ($p < 0.05$), being a solitary traveler ($p < 0.01$), being from a higher Socio-economic Status (SES) ($p < 0.05$), and previous attendance at an STD clinic ($p < 0.05$).¹¹¹ Furthermore, people who practiced unsafe sex in their home country were more likely to practice unsafe sex when traveling ($p < 0.01$).¹¹¹ Another study done in Cuzco, Peru, a popular international destination in part due to its proximity to the Inca Trail, confirmed that factors associated with casual sex during travel included being male, unmarried, and between the ages of 15–35.^{112,113} Furthermore, MSM and bisexual travelers had multiple sexual partners more frequently than heterosexual travelers (OR = 6.17, 95% CI 1.16–33.5).¹¹³ A group that represents potentially the highest risk travel group is the sex-tourist. This is a population of people who not only have the expectation of having sexual activity during the course of the trip; it is the purpose the trip, itself. They tend to be an older group, single, and originating in a higher SES.⁹⁸ As this group generally interacts with the group with the highest seroprevalence of STD in their destination countries, SWs, they are at very high risk and also historically have not used condoms frequently.^{114,115}

As many travelers will seek medical advice before departing, there should be an emphasis in the travel clinic setting on sexual health education, education regarding endemic STDs, in region of travel, and the promotion of safer sex behaviors during these sessions.^{116,117} Travelers and those counseling travelers should emphasize that if there is even a remote possibility of sexual relations, the traveler should ensure that condoms are available and easily accessible. Counseling must be nonjudgmental and should identify “triggers” or “risk situations” for the traveler. The best example is the expatriate who does not anticipate being sexually active but does so because of an unforeseen opportunity, often associated with alcohol use. Counseling to anticipate and prepare for these settings is critical.

A study done of travel health brochures showed that only 11% contained any sexual health information at all with only 3% being in a prominent position.¹¹⁸ From the studies included, it is clear that a sexual history will help elucidate which subgroups of travelers are the most at-risk and where special care should be placed to vaccinate when possible, and promote low-risk behavior while abroad, particularly among young single men and MSM, the highest risk groups in most studies.¹¹⁷ In addition, travelers should be advised to seek medical care upon return for further testing and treatment, and clearly, travel histories should routinely include taking of travel sexual histories. These prevention strategies have the potential to simultaneously protect the individual and his/her steady partner from chronic sequelae of an acquired STI, and the host population from a new epidemic.

CONCLUSIONS

Mobility, forced and unforced, for work, survival, and leisure, is a reality of our time. The expansion of sexually-acquired HIV from presumed early foci in West and Central Africa to virtually the entire human community tells us that today's sexual networks are indeed globalized and interconnected. The drivers of population mobility and mixing, including labor migration, war, travel, and trafficking are unlikely to decrease in the future. Hence HIV and STD prevention and control programs will increasingly have to focus on these complex domains to achieve control, mitigate impacts, and address the needs of people on the move.

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PART 4

Host Immunity and Molecular Pathogenesis and STD

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Bacterial Infections 309

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Deborah J. Anderson

INTRODUCTION

Sexually transmitted pathogens face formidable challenges when attempting to infect cells and tissues of the genital tract. The host's first line of defense is the epithelial layer that delineates the boundary between body and environment. To cross the epidermal layer covering the external ("dry") surfaces of the genital organs, pathogens must penetrate a tough keratinized epithelial layer. To infect the interior mucosal ("wet") epithelial surfaces, they must navigate epithelial barriers that are covered by a thick mucus coat inhabited by commensal microflora and laden with a host of antimicrobial molecules. The second line of defense is the innate immune system, a rapid response system of which epithelial and other resident cells in both skin and mucosal epithelia are active participants. The third level of host defense is the adaptive immune system mediated by lymphocytes and antigen presenting cells, slower to initiate but highly specific, long-lived, and effective. The genital tract mucosal epithelium is a component of the mucosal immune system, an integrated network of specialized cells and tissues that employs specialized immune defense mechanisms at mucosal surfaces. Mediators of systemic immunity also penetrate into genital tract tissues and secretions to fortify the local mucosal immune response. Successful pathogens that cause sexually transmitted diseases (STDs) have devised strategies to overcome or circumvent many of these obstacles.

This chapter will review (1) genital tract epithelial barriers; (2) innate immune defenses at genital mucosal surfaces; and (3) adaptive (humoral and cellular) immunity at mucosal surfaces, with emphasis on specializations of the genital mucosal immune compartment. Since both male and female genital tracts comprise several distinct regions, immunological microenvironments at each of these sites will be delineated, with emphasis on the lower genital tract, where primary exposure to STD pathogens occurs. This information provides a foundation for the development of vaccines, adjuvants, and topical microbicides for the prevention of STDs.

Two other related topics that were covered in the earlier version of this chapter: STD vaccine development, and mechanisms of immune evasion by sexually transmitted bacteria and viruses are now covered in detail in other chapters in this book.

FIRST LINE OF DEFENSE: GENITAL TRACT EPITHELIAL BARRIERS

■ STRUCTURE OF GENITAL TRACT EPITHELIA

Epithelial surfaces vary in structure depending on their location and function. The skin covering the scrotum, foreskin, penis, and meatus in men, and labia, vulva, and introitus in women, is a keratinizing stratified squamous epithelium. This transitions to a mucosal nonkeratinizing stratified squamous epithelium lining the fossa navicularis in men and the vagina and ectocervix in women. Both keratinizing and nonkeratinizing stratified squamous epithelia are multilayered structures (up to 45 cells thick) consisting of a layer of basal germinative cells resting on a basal lamina (a 20–100 nm layer of extracellular material), which separates the epithelium from the underlying vascular connective tissue called the lamina propria (Fig. 17-1A). As the basal cells undergo mitosis and migrate toward the apical surface, they flatten and extrude their nuclei (a process termed cornification) and, in the keratinizing epithelium, further differentiate to form an interlocking layer of dead stratum corneum cells with an exterior lipid envelop that makes the surface tough and impermeable. Cadherins and other membrane adhesion molecules and numerous intercellular desmosomes tightly bind the epithelial cells within the cornified layer to one another. Gap junctions permit exchange of low molecular weight molecules (i.e., ions, cAMP, and cGMP) between cells enabling rapid intercellular communication and coordinated cellular functions.

As one ascends the interior genital tract, the stratified squamous epithelium transitions to a simple columnar epithelium, a single layer of polarized epithelial cells with apical tight junctions (Fig. 17-1B). In women, this transition

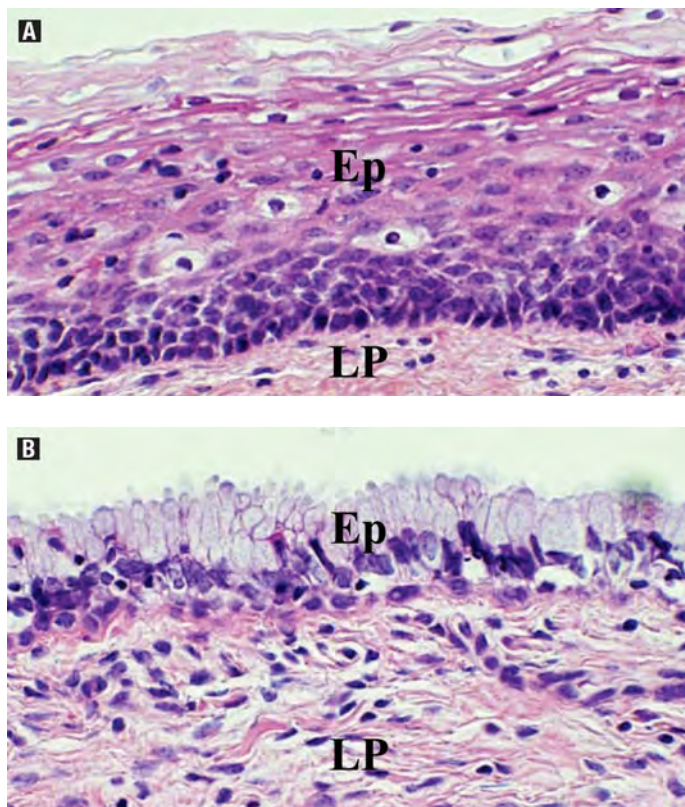


FIGURE 17-1. **A.** Stratified squamous epithelium lining the human ectocervix. **B.** Columnar epithelium lining the human endocervix.

normally occurs at the cervical os and in men at the inner boundary of the fossa navicularis. Thus, the epithelium lining the endocervical canal (women) and the penile urethra (men) is columnar; furthermore, these regions contain numerous mucin-secreting glands. The urinary tract is lined with a transitional epithelium, so called because it has features that are intermediate (transitional) between stratified cuboidal and stratified squamous epithelium. This epithelium is highly specialized to accommodate the high degree of stretching that occurs in the urinary tract. The uterine endometrium is a highly specialized glandular epithelium that undergoes dramatic structural changes during the menstrual cycle and pregnancy.

Physical and chemical trauma and ulcerating infections can cause epithelial disruptions that provide pathogens access to unprotected cells in the germinal layer and lamina propria. Epithelial disruptions and cervical ectopy (extension of endocervical columnar epithelium into the vagina through the cervical os) are major risk factors for the sexual transmission of HIV-1 and other STIs.

Mucosal epithelial layers are by no means inert structures. They shed surface cells at a high rate; the rate of epithelial cell turnover is unknown for the genital tract but is estimated to be $>10^{11}$ cells/day from the human small intestine. Furthermore, epithelial cells can propel the mucus layer in which they are bathed through peristaltic and ciliary action.

Shed cells and mucus carry with them a burden of microorganisms and their excretion is thought to constitute a major pathogen clearance mechanism. Furthermore, as described in a later section, epithelial cells actively participate in innate and acquired immune defense functions by secreting cytokines, chemokines, defensins, and other antimicrobial peptides, and performing antigen presentation functions via MHC Class II and CD1d pathways.

Mucus

Mucosal epithelial surfaces are coated with a mucus layer that lubricates and reinforces the epithelial barrier. Mucus obtains its structural characteristics from mucins, a family of large hydrophilic glycoproteins that contain tandem repeats of serine- and threonine-rich domains that are sites of extensive O-glycan attachment. Up to 80% of the mass of mucin molecules are comprised of complex oligosaccharides (for reviews on the molecular biology of mucins see^{1,2}). To date, at least 18 mucin genes have been cloned, and based on sequencing data, two classes of mucins have been identified: membrane-associated mucins (MUCs 1, 3A, 3B, 4, 11, 12, 13, 15, 16, 17, and 20), and secreted mucins, which include large gel-forming (MUCs 2, 5AC, 5B, 6, and 19) and small soluble mucins (MUC7 and 9).

Membrane-associated mucins are expressed at the apical surface of epithelial cells throughout the male and female genital tracts. These mucins have hydrophobic domains near the carboxy terminus of the protein that allow them to span the cell membrane. The extracellular domain of membrane-associated mucins may extend up to 500 nm from the epithelial cell surface and form a dense glycocalyx along the apical surface of the epithelia. Negatively charged carbohydrate residues on the mucin protein backbone confer disadhesive properties. The extracellular domain is shed from apical surfaces, and thus these mucins may contribute to protection/lubrication of the epithelia in both soluble and membrane-tethered forms. Several membrane-associated mucins (i.e., MUC 1, MUC 4) are multifunctional molecules, providing not only barrier and lubrication functions but also signal transduction through their juxtamembrane regions.

Secreted mucins are classified into two groups: large gel-forming mucins and smaller soluble mucins. The gel-forming mucins, formed by linking multiple mucin monomers, can be extremely long, with lengths up to several microns and molecular weights ranging from 0.5 to 200 Mda. Secreted mucins are produced in abundance by epithelial goblet cells and associated submucosal glands such as those found in the endocervix and penile urethra.

Numerous mucin genes are expressed in the reproductive tissues of men and women (Table 17-1). Mucins of the female reproductive tract have been extensively studied (for reviews, see³⁻⁵). Human endocervical cells express 5 mucin genes

Table 17-1. Mucin Gene Expression in Human Genital Tract Tissues^a

	Mucins	
	Transmembrane	Secreted
Female		
Vagina/Ectocervix	1, 4	
Endocervix	1, 4	5AC, 5B, 6
Uterus (endometrium)	1, 4, 6	8
Fallopian tube	1	
Male		
Urethra	1, 4, 20	5AC
Prostate	1, 3, 4, 20	5AC
Seminal vesicle	1, 20	6
Epididymis	1	
Testis	1, 20	
Foreskin	1, 17	

^aData summarized from Gipson et al. 1997; D'Cruz et al., 1996; Brayman et al., 2004; Hey et al. 2003; Bartman et al. 1998; Russo et al. 2006.

(MUC1, 4, 5AC, 5B, and 6); ectocervical and vaginal cells primarily express the membrane-associated mucins MUC 1 and 4. Expression of the large gel-forming mucin, MUC 5B, by the endocervix is under hormonal control, and dramatic changes in the amount and viscosity of cervical mucus can be demonstrated during the menstrual cycle. Midcycle cervical mucus is primarily comprised of MUC 5B. The uterine endometrium expresses MUC 1, and evidence from animal studies indicates that this mucin may play a critical regulatory role in embryonic implantation.

Mucin gene expression has also been described in tissues of the human male urogenital tract.⁶ Several membrane-associated mucins (i.e., MUC 1 and MUC 20) were found throughout the male reproductive tract, whereas secretory mucins were expressed primarily in seminal vesicles (MUC6), prostate and penile urethra (5AC). Semen was found to contain high concentrations of MUC1, MUC5B, and MUC6.

The composition of genital tract mucus is affected by a number of factors. As shown in Table 17-1, individual tissues in both the female and male genital tract express distinct combinations of mucin genes. Furthermore, mucin gene products are subject to tissue-specific posttranslational processing (i.e., glycosylation). Therefore, the composition and structure of mucins vary considerably along the length of the

genital tract. In addition, each mucin gene is polymorphic: their expressed proteins are polymorphic, and several membrane-associated mucins exhibit splice variants. This implies that there is significant variation in the structure of mucins between individuals. Furthermore, the composition of mucus can vary at different times within the same tissue due to several factors. The production and posttranslational modification of certain mucins is under hormonal control; for example, the expression of MUC5B in the endocervix and its glycosylation are both upregulated by estrogen, accounting for the large volume of watery mucus in the endocervical canal at the time of ovulation.^{7,8} In addition, the amount, molecular size, and morphology of mucin glycoproteins can be altered in disease states. Studies on mucin production in the lung and gastrointestinal tract have shown that proinflammatory cytokines (e.g., IL-4, IL-13, TNF- α), bacterial lipopolysaccharides (LPS), and certain host proteases can upregulate mucin gene expression, whereas other glycosidases, proteinases, and glycosulfatases produced by pathogenic organisms can degrade mucins (reviewed in^{9,10}). *Lactobacillus* organisms which colonize the normal human vagina can stimulate the expression of MUC2 and MUC3,¹¹ whereas microorganisms associated with bacterial vaginosis (BV) are capable of degrading cervicovaginal mucus.^{12,13} Therefore, mucin composition can vary considerably between anatomical sites within the genital tract and between individuals due to distinctive tissue-specific expression patterns, genetic polymorphism, and other variables such as endocrine status, infection, and inflammation.

The physical and biological properties of mucins are beginning to be elucidated (reviewed in¹⁴). It has long been known that certain bacteria bind to specific oligosaccharide ligands on mucins. In the case of commensal bacteria, attachment to mucins in the glycocalyx could slow the rate at which they are shed by the host.¹⁵ On the other hand, by providing competing receptors for cell-surface glycoconjugates, mucins may trap pathogenic bacteria and impede their attempts to colonize the epithelium.¹⁶ Thus, the array of oligosaccharides expressed on the mucins of an individual may play a key role in determining colonization by commensal bacteria and susceptibility to bacterial infection. In terms of viral infection, mucin fibers are densely packed in the glycocalyx and exclude 30 nm-sized particles (the size of the smallest viral particles). Mucin fibers are less dense in gel-forming secreted mucins. The space between midcycle cervical mucus fibers is large enough (20–200 nm) for proteins and small viruses to diffuse virtually unhindered. HPV (55 nm) and other capsid viruses diffuse freely through human cervical mucus; on the other hand, diffusion of HSV (180 nm) is impeded due to its large size and also through the formation of low-affinity bonds between the virus and mucin strands.¹⁷ Antibodies, especially polyvalent IgA and IgM, can agglutinate pathogens into clusters that are too large to diffuse through mucus. Secreted

antibodies also bind to mucin fibers through low-affinity molecular bonds with the Fc and SC components of the molecules¹⁷ and through interaction with a mucin-like IgG Fc binding protein that is found in most mucosal secretions.^{18,19} The interaction between antibodies and mucin fibers could promote trapping of pathogens within the mucus gel. Leukocytes migrate freely through midcycle human cervical mucus,²⁰ providing evidence that they can carry out immunosurveillance functions within this mucin layer. Soluble antimicrobial factors produced by the cells within the epithelium accumulate in the mucosal layer (see below). Commensal organisms that populate genital tract mucosal secretions also play an important role in preventing infections by maintaining an acidic environment and producing an array of antimicrobial factors. This topic is reviewed in detail in Chapter 18.

SECOND LINE OF DEFENSE: INNATE IMMUNITY

The innate immune system consists of cells that constitutively express antimicrobial factors and/or rapidly mount antimicrobial responses following recognition of conserved molecular features of microbes or substances produced during infections. The principal effector cells of innate immunity at mucosal surfaces are macrophages, neutrophils, natural killer (NK), epithelial and dendritic cells (DCs). Antimicrobial substances, an important feature of innate immunity, are abundant in mucosal secretions. These include small inorganic molecules (i.e., zinc, hydrogen peroxide, nitric oxide), small antimicrobial proteins (i.e., defensins and cathelicidins), and large proteins (i.e., lysozyme, azurocidin, cathepsin G, phospholipase A2, and lactoferrin). These antimicrobial factors limit the expansion of invading pathogens and provide time for more effective host innate and adaptive immunity to be generated. Activation of the innate immune defense system can also entail the secretion of type 1 interferons, which exert potent antiviral effects, and other chemokines and cytokines that attract and activate effector cells at the site of microbial invasion.

Innate immunity is triggered immediately after microbial invasion following recognition of highly conserved structures present on microorganisms. These include nucleic acids that are unique to microbes, such as double-stranded RNA found in replicating viruses or unmethylated CpG DNA sequences found in bacteria; features of proteins that are found in microbes, such as initiation by N-formylmethionine, which is typical of bacterial proteins; and complex lipids and carbohydrates that are synthesized by microbes but not by mammalian cells, such as LPS produced by gram-negative bacteria, teichoic acids in gram-positive bacteria, and mannose-rich oligosaccharides found in bacterial but not mammalian glycoproteins.

■ PATHOGEN-ASSOCIATED MOLECULAR PATTERNS AND PATTERN RECOGNITION RECEPTORS

The ability to discriminate self from nonself is a central feature of both acquired and innate immune defense. Innate immune recognition is principally mediated by cellular receptors known as pattern-recognition receptors (PRRs). These molecules detect virulent microorganisms through recognition of invariant pathogen-associated molecular patterns (PAMPs). The receptors of the innate immune system are encoded in the germ line and, therefore, have a much more limited repertoire than receptors involved in acquired immunity, which undergo somatic hypermutation recombination to attain their diversity. It is estimated that the innate immune system PRRs recognize about 10^3 molecular patterns whereas the acquired immune system can recognize 10^7 or more distinct antigens.²¹

PRRs are distributed throughout extracellular, cell membrane and cytoplasmic compartments to formulate a complete line of defense against extracellular and intracellular pathogens of viral, bacterial, fungal, and protozoan origin. Complement system components provide a front line of immune defense in extracellular spaces by opsonizing microbes for clearance by phagocytes. Microbes coated with opsonic fragments derived from C3 and C4 bind to complement receptors on the surface of phagocytic cells triggering phagocytosis; alternatively these microbes may be lysed by engagement of the membrane attack complex.^{22,23} Another class of cell-surface PRRs, the C-type lectins, enable phagocytes to bind and ingest microbes via recognition of pathogen-associated carbohydrate structures.²⁴ Many members of the C-type lectin family bind with high affinity to terminal mannose or fucose residues displayed as densely packed repetitive arrays on bacteria and fungi. Members of this receptor family include the type 1 transmembrane mannose receptor (MR), primarily found on macrophages, and type 2 receptors found on DCs, such as DC-SIGN and Langerin. The MR plays a major role in clearance of *Candida albicans*.²⁴ While data suggest that DC-SIGN also has a role in host immune defense, some pathogens can use DC-SIGN as part of an immune evasion strategy. For example, the capture of HIV-1 by DC through binding to DC-SIGN concentrates virions at the DC-T cell synapse from which they are efficiently transmitted to T cells.²⁵ On the other hand, Langerin, a C-type lectin expressed on epithelial Langerhans cells (LCs), prevents HIV-1 transmission by internalizing virions into Birbeck granules where they are degraded.²⁶

The most prominent members of the PRR class of molecules are the Toll-like receptors (TLRs), a family of membrane proteins that recognize a variety of microbe-derived molecules and activate both innate and acquired immune responses. TLRs and other key molecules involved in the innate immune response pathways are depicted in Fig. 17-2. TLRs are an evolutionarily ancient receptor family. Toll was

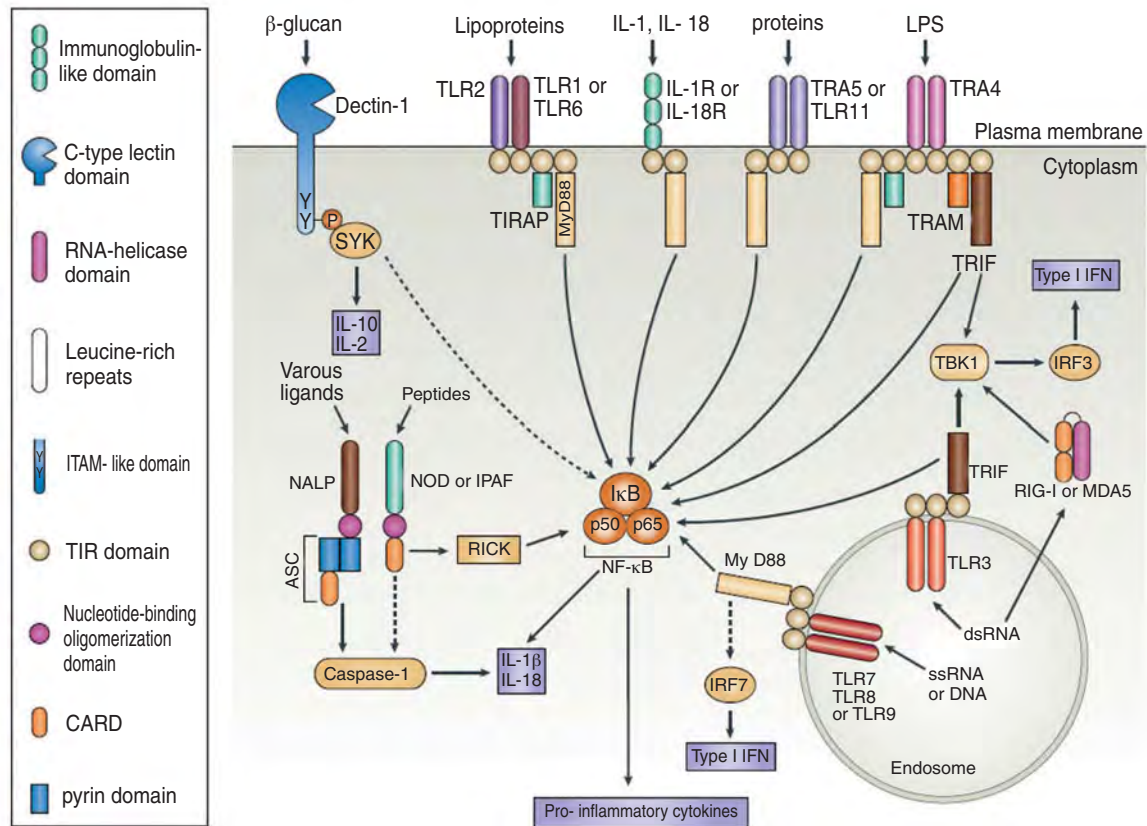


FIGURE 17-2. Schematic representation of structures and main signaling pathways of the major pathogen pattern-recognition receptor (PRR) families. Abbreviations: ASC, apoptosis-associated speck-like protein containing a CARD (caspase-recruitment domain); ds, double stranded; IFN, interferon; I κ B, inhibitor of NF- κ B; IL, interleukin; IPAF, ICE-protease-activating factor; IRF, IFN-regulating factor; LPS, lipopolysaccharide; MDA5, melanoma-differentiation-associated gene; MyD88, myeloid differentiation primary-response gene 88; NALP, NACHT-, LRR and pyrin-domain-containing protein; NOD, nucleotide-binding oligomerization domain; RICK, receptor-interacting serine/threonine kinase; RIG-I, retinoic-acid-inducible gene I; ss, single stranded; TBK1, TANK-binding kinase 1; TIRAP, Toll/IL-1R (TIR)-domain-containing adaptor protein; TRAM, TRIF-related adaptor molecule; TRIF, TIR-domain-containing adaptor protein inducing IFN β ; SYK, spleen tyrosine kinase. (From: Trinchieri G. and Sher A. *Nature Reviews Immunology* 2007; 7:179–190.)

originally identified in *Drosophila* as an essential embryonic patterning molecule that was also required for innate defense against fungal infection.²⁷ Since then, TLRs have been identified in various animal species ranging from sponges to mammals. To date 10 human TLRs have been identified and function as homodimers or heterodimers. Human TLRs fall into two broad categories: TLRs 1, 2, 4, 5, and 6 are expressed on the cell plasma membrane and recognize structures on a wide variety of microbes including bacteria, fungi, protozoa, and mycobacteria; TLRs 3, 7, 8, and 9 are found in endosomal membranes and detect viral and/or bacterial nucleic acids (see [Table 17-2](#)). A set of adaptor proteins, MyD88, TIRAP/Mal, Trif and Tram, are differentially recruited by TLRs and provide a degree of specificity to TLR-induced responses. Coreceptors are also involved in ligand recognition and intracellular signaling. For example, the primary LPS recognition pathway requires TLR 4 combined with MD-2, LPS binding protein (LBP), and CD14, a soluble protein present in serum and semen. MD-2 is directly involved in ligand binding, whereas LBP and CD14 control ligand presentation to the TLR4/MD-2 receptor complex.²⁸ The

genes that are expressed in response to TLR signaling encode proteins important in many different components of innate immune responses. Broadly speaking, there are two major signaling pathways activated by TLRs. The first of these, mediated by MyD88, culminates in the activation of the transcription factor NF- κ B which acts as a master switch for inflammation, regulating the transcription of many genes that encode proteins involved in immunity and inflammation. The second, mediated by TRIF, leads to the secretion of Type 1 interferons through the IRF signaling pathways.^{29,30}

Intracellular PRRs include the nucleotide-binding oligomerization domain (NOD)-like receptor gene family. These genes are related to ancient disease resistance (R) genes in the plant kingdom that provide immune defense against a host of infectious organisms.^{29,30} Cytoplasmic proteins expressed by NOD-like receptor genes, such as Nod1, Nod 2, and NALP3 detect intracellular bacterial invasion and regulate inflammatory and apoptotic responses. Both Nod1 and Nod2 sense bacterial peptidoglycans but each recognizes distinct molecular motifs.^{31,32} Nod1 expression is ubiquitous in human adult tissues whereas Nod2 expression

Table 17-2. Pattern Recognition Receptors (PRRs) and Pathogen Associated Molecular Patterns (PAMPs) Potentially Involved in STI Immune Defense

PRR	PAMP	Pathogen (Type/Specific)
<u>I. C-type lectins</u>		
Mannose receptor (MR)	Mannose, Fucose, <i>N</i> -acetyl glucosamine	<i>C. albicans</i>
DC-SIGN	Mannose, Fucose, <i>N</i> -acetyl glucosamine	HIV-1
Langerin	Mannose, Fucose, <i>N</i> -acetyl glucosamine	HIV-1
Dectin-1	β -glucans, zymosan	Fungi <i>C. albicans</i>
<u>II. Toll-like receptors</u>		
TLR 1	Bacterial lipoproteins	
TLR 2	Bacterial wall components (lipoteichoic acid (LTA), peptidoglycan, lipoproteins, zymosan)	Gram-positive bacteria <i>C. trachomatis</i> HSV-2, CMV, HCV <i>C. albicans</i>
TLR 3	Double-stranded RNA	HSV-2 Cytomegalovirus
TLR 4	Lipopolysaccharide (LPS) Viral envelop proteins	Gram-negative bacteria <i>N. gonorrhoeae</i> <i>C. albicans</i>
TLR 5	Flagellin	Flagellated bacteria
TLR 6	LTA, diacyl lipoproteins, zymosan	Gram-positive bacteria
TLR 7	ssRNA, imidazoquinolines	HIV-1
TLR 8	ssRNA, imidazoquinolines	HIV-1
TLR 9	Unmethylated CpG DNA	Bacterial DNA
<u>III. NOD-like receptors</u>		
NOD 1	Peptidoglycans	<i>C. trachomatis</i>
NOD 2	Peptidoglycans	
<u>IV. RNA helicases</u>		
RIG-I	Double-stranded RNA	RNA viruses
MDA 5		

is restricted mainly to leukocytes, DCs, and epithelial cells.^{33,34} Nod2 expression is increased by various inflammatory stimuli such as LPS, TNF- α , and IFN- γ ^{34,35} and by infection.³⁶ Nod1 and 2 activation results in their interaction with a downstream signaling molecule, the Rip2 kinase, which leads to activation of the NF- κ B inflammatory pathway.³⁷

Certain members of the NOD-like receptor family form inflammasomes to coordinate inflammatory responses upon ligand recognition.³⁸ Another newly discovered intracellular PRR family, the RNA helicases with members RIG-I and MDA-5, detect virus infection of DCs leading to cytokine induction.³⁹

Various TLRs have been detected in human female and male genital tract tissues,^{40–44} and are presumed to play a role in innate immune defense against sexually transmitted pathogens and other organisms that infect the genital tract. TLRs are expressed by DCs, macrophages, T cells, and other immune cells residing in genital tissues and can also be expressed by genital tract epithelial cells. Very few studies to date have explored the functional significance of TLR expression in the genital tract. It was recently shown that human LC, specialized DC that live within the stratified squamous epithelium of the vagina, ectocervix, and foreskin, have a selective impairment of cell surface expression of TLR2, TLR4, and TLR5, all involved in bacterial recognition.⁴⁵ The first report to document expression and function of TLRs on epithelial cells of the genital tract revealed that primary and immortalized epithelial cells derived from normal human vagina, ectocervix, and endocervix express mRNA for TLR1, 2, 3, 5, and 6 but interestingly expressed undetectable levels of TLR4 and MD2, two essential components of the receptor complex for LPS. The cells did not respond to LPS, but responsiveness was induced by the addition of soluble CD14, a high affinity receptor for LPS and other bacterial ligands present in high concentrations in semen and serum.⁴⁶ The lack of responsiveness of genital LCs and epithelial cells to LPS and other bacterial products may account for their tolerance to commensal bacterial flora. Another study detected protein and mRNA for the TLRs that play a role in antiviral immune defense, TLRs 3, 7, 8, and 9, in epithelial cells from the ectocervix and endocervix; these cells responded to TLR 3 and 9 ligands but were unresponsive to TLR7/8 ligands.⁴⁷ In a recent study, the Il-8 response to *Chlamydia trachomatis* infection was dependent upon TLR2 and MyD88 expression, and these molecules were detected in intracellular chlamydial inclusions, suggesting that TLR2 is actively engaged in signaling from this extracellular location.⁴⁸ A recent clinical study correlated the presence of single nucleotide polymorphisms (SNPs) in five PRRs with the prevalence of *C. trachomatis*-associated tubal pathology in subfertile women.⁴⁹ Although the study was underpowered to achieve statistical significance, subfertile women carrying two or more SNPs in *C. trachomatis* PRR genes were at increased risk of tubal pathology (73% vs. 33% risk). This area of research will no doubt provide vital information on the role of PRRs in immune defense against sexually transmitted human disease.

Research on the regulation of TLR expression at mucosal surfaces is in its infancy. TLR expression in the endometrium appears to be affected by hormonal changes that occur during the menstrual cycle,⁵⁰ and recent studies have begun to uncover molecular events underlying steroid hormone repression of TLR-activated intracellular signaling pathways (reviewed in^{51,52}). Evidence is also

mounting that infections per se alter TLR expression (reviewed in⁵³).

TLR agonists are excellent candidates for vaccine adjuvants because of their immunoregulatory and proinflammatory effects.⁵⁴ They are also being considered for inclusion in topical microbicide formulations because they can trigger antimicrobial innate immune responses. Imiquimod, a small imidazoquinolinen ligand for TLR7 and 8 is already marketed as a topical antiviral to treat pathology associated with persistent HPV infection.⁵⁵ Vaginal application of CpG oligodeoxynucleotides (TLR-9 agonists) and poly:IC (TLR-3 agonist) in mice induced upregulated expression of Type 1 interferons and protected the mice from herpes infection.⁵⁶ However, CpG and imiquimod (TLR-7 agonist) failed to protect rhesus monkeys from vaginal infection with simian immunodeficiency virus (SIV).⁵⁷ Manipulating the immune system with TLR agonists is often accompanied by unwanted side effects. The imiquimod-treated monkeys in the SIV-challenge study developed a severe vaginitis reaction that may have promoted SIV transmission. Other studies suggest that TLR activation may in some cases be associated with autoimmune syndromes and atherosclerosis.⁵⁸ This research area is clearly in its early days and holds much promise but should be pursued with due diligence.

■ ANTIMICROBIAL PROTEINS

Over 80 years ago, Alexander Fleming observed that respiratory mucosal secretions have microbicidal and microbistatic properties and went on to describe the activity of lysozyme, one of the principal antimicrobial factors in mucosal secretions.⁵⁹ At present, more than 700 animal and plant antimicrobial proteins are documented in the Antimicrobial Peptide Database (<http://aps.unmc.edu/AP/main.php>). A number of these antimicrobial host defense peptides are produced by genital tract mucosal epithelial cells and associated immune cells. Collectively, mucosal antimicrobial proteins have a wide range of antiviral, antibacterial, antifungal, and antiparasitic activities and modes of action and play an important role in innate immune defense at mucosal surfaces. Some of the prominent classes of antimicrobial proteins in genital tract secretions are the defensins, cathelicidins, lactoferrin, and lysozyme (Fig. 17-3).

Defensins are small (29–42aa), cationic, antimicrobial peptides with a broad spectrum of activity that includes bacteria, fungi, and enveloped viruses.⁶⁰ These peptides have six cysteine residues that form three disulfide bonds and depending on the spacing of the cysteines are classified as α -defensins or β -defensins.⁶⁰ The human defensin family includes at least 6 α -defensins and over 30 β -defensins.⁶¹ Among the α -defensins, the human neutrophil defensins (HNP) 1–4 are predominantly secreted by neutrophils, whereas HD-5 and HD-6 are expressed by mucosal epithelial cells and contribute

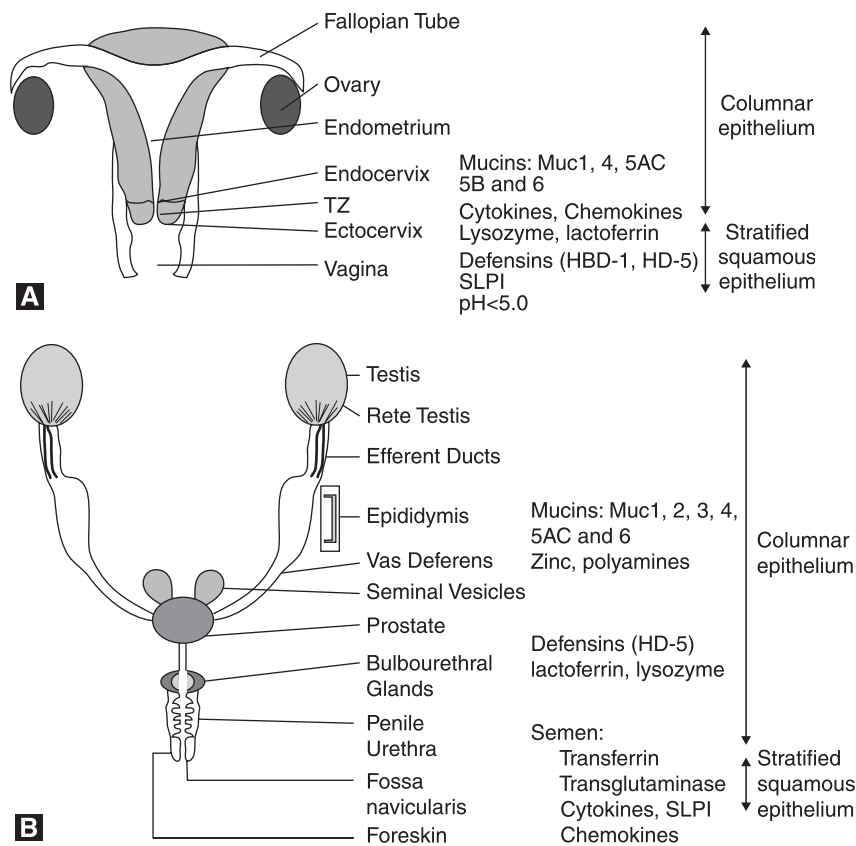


FIGURE 17-3. Soluble mediators of innate immunity in the human female, **A**, and male, **B**, genital tract. Abbreviations: TZ- transformation zone, HBD- human beta defensins 1–6, HD- human defensin, SLPI-serine leukocyte protease inhibitor.

to the innate defense of the mucosal surface. HD-5 is expressed by epithelial cells in the male and female genital tract. Constitutive expression of HD-5 was detected in human vaginal and ectocervical epithelial cells; expression was regulated by hormonal and proinflammatory factors in the endometrium and fallopian tube.⁶² In the penile urethra, HD-5 was secreted as a propeptide and its expression was upregulated by *C. trachomatis* and *Neisseria gonorrhoeae* infections. HD5 was activated when levels of HNP 1–3 were elevated, suggesting that neutrophils contribute key proteases to convert proHD-5 to its bioactive form in the urethra during infection.⁶³ Six human β - defensins (HBD 1–6) are expressed in epithelial cells.⁶⁴ HBD-1 is the major antimicrobial factor in airway surface fluid⁶⁵ and has also been described in epithelial cells in the human vagina, cervix, and endometrium.⁶⁶ Defensins target the negatively charged phospholipids in bacterial membranes, forming channels in the membrane that allow defensins and other host defense molecules to penetrate into the bacterium and cell contents to leak out, leading to cell death.⁶⁷ Members of the α - and β - defensin families also have antiviral activity against number of sexually transmitted viruses including HIV-1, HSV-2, CMV, and HPV. This activity is mediated directly via interactions with the viral membrane, or indirectly through recruitment and activation of other immune cells (reviewed in⁶⁸).

The cathelicidins comprise another important family of antimicrobial peptides. In humans, only one cathelicidin gene,

CRAMP, is expressed. Most cathelicidins are found in the peroxidase negative granules of neutrophils, but the CRAMP gene product, human cationic antimicrobial peptide-18 (hCAP-18), is also expressed by mast cells, subpopulations of monocytes and lymphocytes, and epithelial cells in the human vagina, cervix, urinary tract, and epididymis.^{69–73} hCAP-18 is synthesized as a propeptide and is proteolytically cleaved into two fragments, cathelin and the C-terminal peptide LL-37, both of which have a broad range of antimicrobial activity.⁷⁴ LL-37 has been attributed other important biological effects including neutralization of LPS, angiogenesis, and chemotaxis of neutrophils, monocytes, and T cells (reviewed in⁷⁵). Human seminal plasma contains high concentrations of hCAP-18, which is cleaved by a prostatic enzyme in the vagina following intercourse to produce a unique 38-amino acid antimicrobial peptide, ALL-38.⁷⁶ Studies in CRAMP-deficient mice demonstrated that hCAP plays an important role in protecting the urinary tract against invasive bacterial infections.⁷³

Both lysozyme and lactoferrin are produced in the genital tract (Fig.17-3) and are present in high concentrations in genital secretions (reviewed in⁷⁷). Human lysozyme consists of a single polypeptide of 129 residues and is mainly produced by neutrophils. Lysozyme hydrolyzes the β (1–4) glycosidic bond between N-acetylmuramic acid and N-acetylglucosamine in gram-positive bacteria cell wall peptidoglycans⁷⁸ and also has other modes of action independent of its enzymatic activity including blocking of bacterial adherence through

steric hindrance, bacterial aggregation, and activation of bacterial autolysins.⁷⁷ In cell cultures lysozyme had no inhibitory effect on chlamydiae and at some concentrations it actually stimulated the formation of intracytoplasmic chlamydial inclusions.⁷⁹ Lysozyme may act most effectively in concert with other antimicrobial defenses.^{78,79}

Lactoferrin is an iron-binding protein that may slow bacterial growth by competing for this essential element, or by direct microbicidal action.^{80–82} Furthermore, lactoferrin is a highly basic protein with a pI of about 9, making it an extremely sticky protein that binds readily to other macromolecules.⁸³ Some of the antimicrobial activities of lactoferrin could be a result of this property. Lactoferrin has been reported to prevent infection by a variety of viruses including cytomegalovirus, HIV-1, herpesviruses, and hepatitis B and C.⁸⁴ The lactoferrin concentration in vaginal secretions ranges between 3.8 and 218 g/mg of protein, and the concentration can increase during inflammation as neutrophils release their lactoferrin. Lactoferrin concentration is greatest just after menses and falls off sharply during the latter (secretory) phase of the menstrual cycle. Women receiving estrogen/progesterone oral contraceptive pills were found to have persistently low levels of lactoferrin, providing further evidence of the hormonal regulation of this compound.^{85–87}

Serine leukocyte protease inhibitor (SLPI) is also an important mediator of innate immunity in the genital tract. SLPI, a 10.7 Kda protein member of the trappin gene family, is produced and secreted primarily from epithelial cells, neutrophils, and activated macrophages. It is present in very high concentrations in mucosal secretions including breast milk, semen, and vaginal fluid.⁸⁸ SLPI participates in mucosal immune defense by reducing inflammation and inhibiting infection by bacteria, fungi, and viruses. Notably, SLPI protects human macrophages and CD4⁺ T cells from HIV-1 infection⁸⁹ and also inhibits HSV-2 infection in vitro.⁹⁰

■ CELLULAR MEDIATORS OF INNATE IMMUNITY

Epithelial cells

Epithelial cells express an array of PRRs including TLRs, NOD-like receptors, and complement and immunoglobulin receptors. When activated by pathogens or their products they release chemokines such as Il-8, RANTES, MIP-1 α and β , and SDF1, which recruit other immune cells to the site of infection, proinflammatory cytokines including Il-1 α and TNF- α , which activate leukocytes, and other cytokines such as Il-6, Il-15, TGF- β , and G-CSF that affect cell differentiation and regulate T and B lymphocyte responses. In addition, epithelial cells express adhesion molecules such as e-cadherin, ICAM-1, and LFA-3 that are

important for leukocyte adherence and persistence within the epithelial layer. Mucosal epithelial cells are also capable of expressing MHC Class II and CD1d molecules, suggesting that they can present peptide and glycolipid antigens to resident immune cells. Thus, the epithelial cell initiates and coordinates mucosal immune responses by regulating the “professional” immune cells.^{91,92}

The various types of epithelial cells in the male and female genital tracts express different sets of PRRs and produce distinctive arrays of chemokines and cytokines following activation. Epithelial cells are also rich sources of antimicrobial peptides including b-defensins, HD-5 and 6, hCAP-18, and SLPI. Therefore, genital tract epithelial cells can be considered the “gatekeepers” of both innate and acquired immunity in the genital tract.^{93–95}

Dendritic cells

Dendritic cells are a class of antigen-presenting cells derived from hemopoietic bone marrow progenitor cells that initiate and modulate immune function through stimulation of naïve T cells. These cells develop branched projections, called dendrites, which give them their name and provide a large surface area for enhanced sampling of the environment for antigens. Their state of maturity and activation, defined by the display of molecules that induce an immune response (i.e., PRRs, major histocompatibility antigens, costimulatory molecules, cytokines, adhesion, and homing receptors) determines the nature of the immune response. Dendritic cell biology is a rapidly advancing field and readers are advised to check the current literature for updated information concerning this important cell type.

Langerhans' cells (LCs), originally described by Paul Langerhans in the late nineteenth century, are immature DCs that reside in skin and mucosal stratified squamous epithelia. They have high endocytic activity and low T-cell activation potential and are characterized by Birbeck granules and upregulated expression of langerin, CD1a, MHC Class II molecules, e-cadherin, and CD11c. Most of these phenotypic characteristics depend on TGF- β 1 present in the epithelial microenvironment, as TGF-1 β induces the expression of these molecules in vitro and TGF-1 β knockout mice do not have LCs.⁹⁶ Recent evidence suggests that LCs do not express TLRs that convey the ability to recognize certain bacterial ligands (most notably LPS), and that gram-positive bacterial peptidoglycans trigger Il-10 but not Il-12 secretion in LCs, providing possible mechanisms for tolerance to endogenous microflora.^{45,97} LCs are present in genital skin and the stratified squamous epithelial surfaces of the human vagina and ectocervix in women,⁹⁸ and foreskin and fossa navicularis in men^{99–101} and may play an important role in antiviral immune defense in these locations.

Two other types of DCs have been characterized in mucosal tissues, the myeloid dendritic cell (mDC) and the plasmacytoid dendritic cell (pDC). MDCs reside in the lamina propria of most mucosal epithelia and express various TLRs and DC-SIGN, which enable them to interact with certain pathogenic bacteria and viruses. Once activated, these cells migrate to regional lymph nodes where they present antigen and activate naïve T cells. The capacity of mDCs to promote TH1 or TH2 CD4⁺ T-cell responses depends on different patterns of cytokine production and TLR activation. Secretion of interferon gamma by CD4⁺ TH1 cells triggers macrophage activation and a potent antimicrobial response whereas TH2 cells typically produce Il-4 and Il-5, which promote immunoglobulin production. PDCs express TLR 7 and 9 and specialize in microbial nucleic acid sensing. These cells produce large amounts of type 1 interferon and other proinflammatory cytokines in response to viral infection (for recent reviews on DCs.^{102,103}).

Macrophages

Mucosal epithelia comprise the largest reservoir of macrophages in the body. Long-lived tissue macrophages are derived from blood monocytes and recruited to the mucosal lamina propria by endogenous chemoattractants in the noninflamed mucosa. These resident lamina propria macrophages in normal tissues have downregulated expression of PRRs such as TLR4 and Fc receptors, and low expression of proinflammatory cytokines, but their phagocytic and bactericidal capabilities remain intact. A different population of macrophages is recruited to epithelial mucosae by inflammatory chemokines and bacterial products during infection and inflammation. These inflammatory macrophages express an abundance of PRRs including Fc receptors, MRs, and TLRs and upon activation secrete cytokines such as Il-1, Il-6, Il-8, and TNF- α , which activate neighboring cells and amplify the immune response.¹⁰⁴

Granulocytes

Granulocytes, short-lived, highly motile bone marrow derived white blood cells, rapidly migrate from the circulation to tissues upon activation. They migrate to sites of tissue damage and infection in response to selective chemokines (i.e., Il-8) and complement breakdown products (i.e., C5a). Human neutrophils express an array of PRRs that enable them to recognize pathogenic organisms including complement, Fc and lectin receptors, and TLRs 1–10 except for TLR3.¹⁰⁵ At sites of infection neutrophils (1) phagocytose pathogens, inactivating them in acidic endosomes, (2) release the contents of preformed granules which contain an array of antimicrobial substances such as defensins, lysozyme, lactoferrin, and reactive species of oxygen and nitrogen which inactivate extracellular pathogens, and (3) secrete cytokines and chemokines that activate and recruit additional immune cells.^{106–108}

NATURAL KILLER (NK) CELLS

NK cells constitute a major component of the innate immune system and play an important role in the host-rejection of both tumors and virally infected cells. NK cells are large granular lymphocytes that do not express T-cell or B-cell antigen receptors but usually express the surface markers CD16 (Fc γ RIII) and CD56. NK cells kill target cells through the release of lytic proteins such as perforin and proteases known as granzymes. Perforin forms pores in the plasma membrane of the target cell through which granzymes can enter and induce apoptosis, leading to the destruction of the infected cell and the virus inside.

As NK cells have potent cytolytic potential, their activity is tightly regulated. Many NK cells express MHC Class I receptors which when activated inhibit their response and thereby protect healthy autologous cells from NK-targeted lysis. A subset of NK cells does not express such receptors, but are normally hyporesponsive unless activated.¹⁰⁹ Type 1 interferons play a crucial role in NK-cell activation; as these are released by pDC and other cells upon viral infection, they serve to signal to the NK cell the presence of viral pathogens. Il-2 and IFN- γ , produced by activated T cells, and IL-12, produced by macrophages and mDCs also can activate NK cells. NK cells express most of the TLRs and NOD proteins.¹¹⁰ In addition, NK cells express Fc receptors which bind the Fc portion of antibodies and enable NK cells to target organisms against which a humoral response has been mobilized and lyse cells through antibody-dependent cellular cytotoxicity (ADCC).¹¹¹

NKT cells are a subset of T cells that express a highly restricted T-cell receptor specific for nonpeptide lipids and glycolipid antigens presented by CD1d molecules on the surface of specialized antigen-presenting cells.¹¹² Their function appears to be similar to that of NK cells. MR1 restricted mucosal invariant T (MAIT) cells are found in gut lamina propria in mice and represent another specialized killer cell that appears to play an important role in innate immune defense at mucosal sites.¹¹³ NK cells have been detected in the human cervix and penile urethra.^{98,101} Specialized NK cells (CD56^{bright}, CD16⁻) are numerous in the luteal-phase endometrium and decidua during the first trimester of pregnancy.¹¹⁴

Lymphocytes

Adaptive T-cell responses are generated when naïve T-cells receive signals through their T cell receptors, costimulatory molecules, and cytokine receptors. However, T- and B-lymphocytes express TLRs and other PRRs and participate in innate as well as adaptive immune responses. Circulating human T cells strongly express TLRs 1, 2, 3, 5, and 9. Regulatory T (Treg) cells, a specialized T-cell population that maintains immune tolerance and limits effector responses to

prevent excessive immune-mediated tissue damage, express TLRs 4, 5, and 8.¹¹⁵ Tregs are abundant in gut mucosae where they may downregulate immune responses to intestinal flora¹¹⁶ and are also present in large numbers at the fetal maternal interface where they may promote immunological tolerance to fetal tissues during pregnancy.¹¹⁷

■ SYNERGY BETWEEN INNATE AND ADAPTIVE IMMUNITY

The innate and adaptive arms of the immune system work together. Innate immunity provides signals for the adaptive immune system to mount a protective host immune response. The molecules produced during innate immune reactions that function as second signals for lymphocyte activation include costimulators, cytokines, and complement breakdown products.

DCs serve as a major link between innate and adaptive immunity. DCs recognize a wide range of pathogenic organisms through the expression of an array of *c*-type lectin receptors and TLRs, and their location within and below the mucosal epithelium places them in the front lines of immune defense. When DCs encounter a pathogen, they undergo a differentiation process associated with the upregulation of MHC Class II and costimulatory molecules (i.e., CD80 and CD86) enabling them to present antigens to lymphocytes. They also release signaling cytokines such as Il-12 and Type 1 interferons, which activate and expand lymphocyte populations and promote TH(1) type immunity.¹⁰²

Epithelial cells at sites of infection release chemokines such as Il-8, which recruits neutrophils, and RANTES and MIP-1beta, which recruit macrophages and T cells to the site. They also secrete cytokines such as Il-1, which activate lymphocyte mediators of adaptive immunity (reviewed in⁹⁴).

The best-defined innate immunity signal for B-cell activation is a breakdown product of the complement component C3, called C3d. Microbes, including HIV-1, can activate complement through interaction with immunoglobulins, or directly through the alternate pathway, giving rise to complement breakdown products including C3d. When B-lymphocytes recognize a microbial antigen through binding to their antigen receptors, and simultaneously recognize bound C3d via surface complement receptors, they become activated to produce antibodies against the antigen. In addition, some of the mediators of innate immunity, such as B-defensins, are chemotactic for T lymphocytes.

Adaptive immune responses also serve to enhance innate immunity. For example, in cell mediated adaptive immune responses, antigen-specific T lymphocytes produce cytokines that activate phagocytes—important effectors of innate immunity. B-lymphocytes produce antibodies that use two effector mechanisms of innate immunity, phagocytes and the

complement system, to eliminate microbes. This topic has recently been reviewed.^{118,119}

THIRD LINE OF DEFENSE: ADAPTIVE IMMUNE MECHANISMS AT THE MUCOSAL SITES

■ OVERVIEW OF THE MUCOSAL IMMUNE SYSTEM

Interest in mucosal immunology has increased due to the realization that mucosal responses may be key to preventing mucosal STD transmission and adverse effects of STDs on mucosal tissues. However, to date none of the STD vaccines has been designed to specifically induce mucosal immunity. The mucosal immune system has discrete immune induction sites, primarily in the Peyer's patches in the intestine, which give rise to mucosal humoral and cellular responses that are distinct from peripheral responses. It is also recognized that mucosal immunity employs some components of systemic immunity: serum antibodies are detected in mucosal secretions, although at much reduced concentrations, and recent studies indicate that most T cells in mucosal tissue have characteristics, such as distinct VB gene sequences, that are similar to those found in T cells in the periphery, indicating a common derivation. Furthermore, recent studies indicate that the mucosal immune system is regionally compartmentalized. Recent research on cellular homing indicates that lymphocyte homing receptors differ between populations of cells that end up in peripheral mucosal sites such as the genital tract versus central mucosal sites such as the intestine, suggesting that the mucosal immune system is not "common" but in fact displays regional specialization. Some vaccine research groups are exploring ways to target STD vaccines to the genital tract mucosal immune system, but most of the large commercial efforts are still using systemic immunization protocols.

■ MUCOSAL HUMORAL IMMUNITY

Humoral immunity is mediated by antibodies produced by terminally differentiated antibody-secreting cells (ASCs) called plasma cells. Following stimulation with antigen, B cells residing in lymph nodes or spleen, undergo clonal expansion and differentiate into memory B cells or ASCs. IgA ASCs mainly arise in mucosal lymphoid tissue and preferentially traffic back to mucosal effector sites whereas IgG ASCs mainly traffic to the bone marrow or inflammatory sites. ASC trafficking patterns depend on the upregulated expression of specific chemokine receptors and adhesion molecules. Expression of CC-chemokine receptor 9 (CCR9) promotes the migration of ASCs to the intestinal mucosa which secretes the CCR9 ligand CCL25 (TECK), whereas expression of CXCR3 by IgG ASCs promotes trafficking to sites of inflammation, and expression of CCR10 on IgA ASCs enables them to traffick to various mucosal effector sites that

secrete CCL28(MEC) such as the salivary glands, bronchi, mammary glands, and intestine.¹²⁰ Little is known about specific homing mechanisms for genital tract ASCs. Genital tract ASCs could use CCR10, which appears to be a ubiquitous homing receptor for mucosal tissues. The genital tract epithelium secretes SDF-1,¹²¹ which suggests that the CXCR4 chemokine receptor may also play a role in targeting ASCs to genital sites.

Antibodies produced in response to parenteral (systemic) immunization are detectable in mucosal secretions but usually in relatively low titer. Recent studies have shown that mucosal immunization generally achieves a superior antibody response in mucosal secretions. The mucosal immune response depends on inductive sites within mucosal tissues where antigens are sampled and host defenses committed. The best-studied inductive sites are the Peyer's patches in the small intestine (i.e., gut-associated lymphoreticular tissue), bronchus, and nasal tissue. It was once thought that such mucosal inductive sites activated cells that contributed to a common mucosal associated lymphoreticular tissue network,¹²² but recent evidence indicates that homing receptors differ between various mucosal sites, and that humoral immune responses in the female genital tract are best induced by local immunization.¹²³

IgA producing plasma cells are present in high numbers in the endocervix in women and the penile urethra in men.^{101,124} In most mucosal secretions, the concentration of IgA exceeds that of IgG or IgM. This is true in regions of the genital tract with high concentrations of IgA plasma cells, such as the endocervix and penile urethra, but in commonly sampled genital tract secretions (i.e., semen, vaginal fluid) IgG isotype antibodies predominate.^{122,124–128}

More than 40 mg/kg of mucosal IgA is generated each day.¹²² The IgA found in mucosal secretions (sIgA) is different from serum IgA. It is composed of a 10-S dimer (300,000 daltons) and a J chain. The J chain is made by plasma cells and joins 7-sIgA monomers (the IgA normally found in serum) into 10-S dimers and IgM monomers into pentameric structures. A polymeric Ig receptor (p-IgR), primarily expressed in the genital tract by columnar epithelial cells in the endocervix and penile urethra, binds polymeric IgA and IgM and transports it through the cell to the luminal mucosal surface; after their release, s-IgA and s-IgM retain a portion of the pIgR, called secretory component, that provides resistance to proteolytic substances found in genital secretions. Interferon gamma and tumor necrosis factor upregulate the expression of p-IgR,¹²⁹ and increased concentrations of s-IgA have been detected in mucosal secretions at sites of infection/inflammation.¹³⁰

Although sIgA antibodies are able to agglutinate bacteria, they do not have innate bactericidal activity.¹³¹ However, sIgA antibody may activate the alternative pathway of complement and thereby transform into a lytic complex.¹³²

Lysozyme, sIgA, and complement may synergize to enhance antibacterial defense.^{131,133} Complement is present in genital secretions but at reduced concentrations.^{134,135} Several bacterial species (including gonococci) have evolved mechanisms to evade the bactericidal activity of serum.^{136–138} The observation that many gonococci isolated from mucosal surfaces are sensitive to the complement-mediated action of serum raises serious doubt about the importance of the complement-mediated bactericidal mechanism as a mucosal defense.¹³⁹

A variety of microorganisms elaborate a protease that cleaves IgA at the hinge, thereby rendering sIgA subclass I inactive.^{140,141} Mulks and Plaut have reported that only pathogenic species of *Neisseria* produce IgA protease, implying that the protease is a major virulence factor in gonococcal infection.¹⁴² The relative importance, however, of sIgA in defense against gonococci remains poorly understood; the presence of sIgA in urethral secretion does not seem to prevent recurrent infection.^{143,144} On the other hand, sIgA may help to prevent symptomatic salpingitis in patients who develop local endocervical gonococcal infection.¹⁴⁵

Secretory antibodies are of undoubted importance in defense against a variety of viruses, as demonstrated by the ablation of the mucosal carriage of poliovirus after oral (Sabin) vaccine and the protection offered against certain rhinoviruses by nasal immunization capable of eliciting sIgA.^{146,147} The interaction between HIV and sIgA may be of particular importance in vaccine development. Serum IgA antibodies and sIgA induced by vaccination neutralize some strains of HIV in vitro¹⁴⁸ and block the transcytosis of HIV across epithelial layers.¹⁴⁹ In studies of women and men that have been highly exposed to HIV but remain uninfected, IgA antibodies directed against HIV were detected in cervicovaginal and seminal secretions.^{150,151} HIV infection is associated with reduced levels of IgA in genital tract secretions.¹⁵²

■ MUCOSAL CELLULAR IMMUNITY

Mucosal epithelia are covered by an epithelial cell layer sealed by tight junctions that exclude peptides and macromolecules. Some mucosal surfaces (e.g., bronchial and intestinal epithelia) have well-defined induction sites containing lymphoid follicles with an overlying follicle-associated epithelium (FAE) including unique M cells which provide functional openings to the epithelium. The biology and function of the M cell have been extensively reviewed.¹⁵³ Antigens presented to naive T cells in intestinal induction sites lead to their activation and migration through the lymphatics and blood stream to eventually “home” back to mucosal effector sites.¹⁵⁴ Well-differentiated organized induction sites such as those in the intestine and upper airway have not been identified in the lower male or female genital tract. However, numerous antigen presenting and effector cells are present in the male and female genital mucosa.¹⁵⁵ Langerhans' cells reside within the

stratified squamous epithelial layers and their dendrites sample genital secretions and extracellular spaces for pathogens. DCs perform a similar function in the lamina propria. After activation, these cells migrate to regional lymph nodes and are very effective at presenting antigens to naïve T cells to generate a cellular immune response.¹¹⁸ Macrophages are also numerous in the genital tract subepithelial lamina propria and can present antigens directly to CD8 and CD4⁺ T cells that reside within or below the epithelium. Gamma interferon induces the expression of MHC class II and upregulates the expression of MHC Class I molecules in cervical epithelial cells, suggesting that these cells may be capable of presenting antigens to T cells at sites of infection.¹⁵⁶

FEMALE GENITAL TRACT

The cellular components of the acquired immune defense of the female genital tract have been mapped and characterized (Fig. 17-4A).^{98,157,158} Plasma cells are concentrated in the subepithelial layers of the human endocervix but substantial numbers are also found in the ectocervix, vagina, and fallopian tubes. Plasma cells are rarely detected in the human ovary, endometrium, or myometrium. The T-cell population of the human and primate female reproductive tract varies considerably from tissue to tissue. In the normal human endometrium, T cells are rarely seen in the proliferative phase of the menstrual cycle but increase in number in the secretory phase, often forming small aggregates.¹⁵⁹ The majority of these endometrial T cells express the CD8 antigen,

particularly those found in the lymphoid aggregates and within the epithelium.^{159,160} A population of phenotypically unusual (CD2⁺, CD3⁻, CD4⁻, CD8⁻, CD56⁺) lymphocytes are seen in the endometrial stroma in the secretory phase of the menstrual cycle and early pregnancy.¹⁵⁹ CD8-positive T lymphocytes are numerous within the epithelium of the ectocervix, vagina, and transformation zone.¹⁶⁰⁻¹⁶² Substantial infiltrates of CD8 and CD4-positive cells are seen in the stroma of the transformation zone, but T cells are relatively sparse in the stroma of the ectocervix and vagina.¹⁶¹ The particularly high numbers of T lymphocytes in the transformation zone of the cervix have led some researchers to speculate that this is a particularly immunologically dynamic region.^{98,161} There are no apparent differences in the numbers of intraepithelial T cells in the lower genital tract at different stages of the menstrual cycle, although potential functional differences have not as yet been systematically addressed.

In the endometrium and endocervix, the predominant classical antigen presenting cells are macrophages and DCs; in the vagina and ectocervix, intraepithelial Langerhans' cells are also present.^{161,163,164} These are potent antigen presenting cells that are found throughout the epidermis and nonkeratinized squamous epithelia. After activation, these cells migrate from the epithelium to draining lymph nodes, where they present antigens to T lymphocytes, thereby initiating an immune response. Langerhans' cells in the epithelium express a phenotype that is characteristically CD1a, MHC class II, Fcγ, CD3, and CD4 positive; following activation

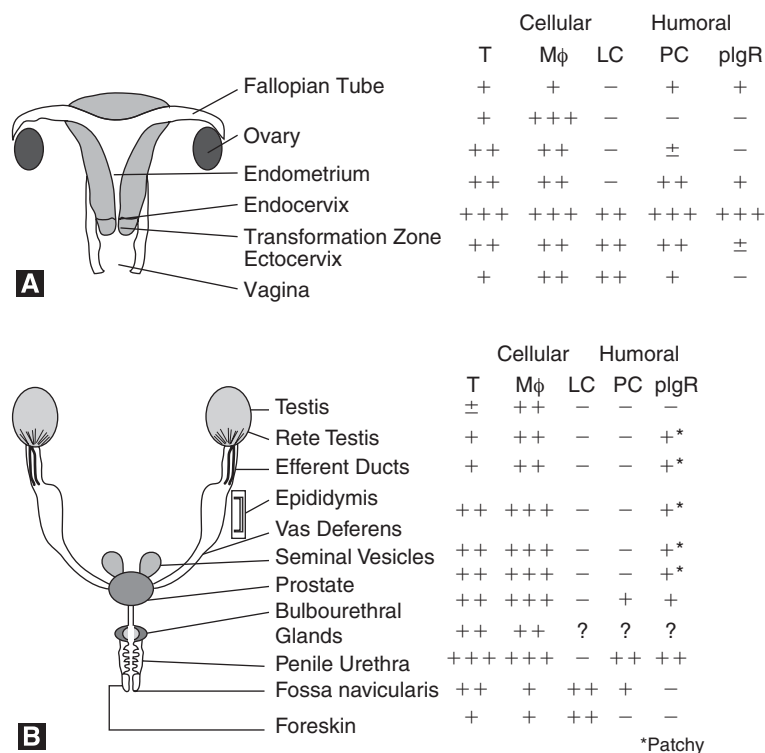


FIGURE 17-4. Mediators of adaptive immunity in the human female, **A**, and male, **B**, genital tract. Abbreviations: T-T lymphocyte, Mφ-macrophage, LC- Langerhans' cell, PC- plasma cell, pIgR-polymeric immunoglobulin receptor.

they also express a variety of adhesion molecules, including ICAM-1 (CD54) and LFA-3 (CD58).¹⁶⁵ Langerhans' cells show marked variation in their distribution within the lower genital tract, with the highest numbers found in the vulva and transformation zone, and the lowest numbers in the vagina.^{98,161} Macrophages and DCs express estrogen receptors, and antigen presentation capabilities within the female reproductive tract have been shown to vary with stages of the menstrual cycle.¹⁶⁶ This observation has implications for local vaccine delivery as well as for better understanding of the immunological events associated with reproductive processes.

Cervical and vaginal epithelial cells are a primary source of cytokines including IL-1 α , IL-1 β , growth factors including GM-CSF, M-CSF, TGF- β , and chemokines including IL-8, SDF-1, MIP1 α , MIP1 β , and RANTES.¹³⁴ Many of these cytokines can be detected in cervicovaginal secretions and provide important information on inflammatory and immune defense mechanisms in the lower female genital tract.¹⁶⁷ Cytokine concentrations differ between HIV+ and control subjects, and some cytokines may promote the replication of HIV.^{134,167–170} Other infections known to affect vaginal cytokine levels include BV, HPV, and Chlamydia.^{171–174}

Considerable effort is being spent on the development of improved methods to effect immune responses in the genital tract. There are essentially two schools of thought: The first contends that induction must occur in the gut or bronchus, with boosting and subsequent migration of sensitized cells to the genital tract mucosa; the second proposes that novel adjuvants or technologies can be developed to effectively stimulate and maintain local genital tract immunity.¹⁷⁵

MALE GENITAL TRACT

Cellular and humoral immune mediators of the male human genital tract have been described and are summarized in Fig. 17-4B. T lymphocytes are not usually detected in the healthy human testis but are seen in the rete testis, epididymis, vas deferens, and urethra, with CD8⁺ cells predominating within the epithelial cell layer.^{101,176,177} A majority of the intraepithelial lymphocytes (IEL) in the urethra are positive for the integrin $\alpha^E\beta 7$ (mucosal-associated antigen). T lymphocytes have been cloned out of human semen and urethral secretions and have been demonstrated to have cytolytic and helper cell functions.¹⁷⁸ Macrophages are abundant in the human and primate urogenital tract: in the testicular interstitium, the epididymis, the epithelium and connective tissue of the excurrent ducts and accessory glands, and in the penile urethra.^{101,176,177,179,180} Testicular macrophages actively secrete a variety of cytokines that have been implicated in Leydig cell endocrine function as well as spermiogenesis. Unlike the female lower urogenital tract, Langerhans' cells are rarely detected in the penile urethra but are abundant in the epithelium of the foreskin and the fossa navicularis.^{101,181}

CONCLUSIONS

Research over the past 20 years has garnered an astounding amount of information about the human immune system. Through the use of molecular tools, immunologists have identified and characterized the molecular signatures and functions of a wide array of immune cell types. Gene array technology has identified hundreds of molecules expressed by diverse immune cells undergoing various immunological functions. Improved tests of immune function, utilizing sophisticated techniques such as ELISPOT and flow cytometry, have enabled immunologists to monitor and understand immune responses at the level of the single cell. New molecular sequencing and synthesis methodologies have enabled scientists to construct precise antigenic epitope maps which have been used to study the fine specificity of immune responses; the most effective of the epitopes are being incorporated into molecularly-defined vaccines intended to elicit precise and maximally effective immune responses.

Yet the more we discover, the greater our appreciation and wonder for the complexities of biology and the immune response: the many ways infectious organisms subvert cellular mechanisms to infect and avoid detection in their host organisms; the intricate evolutionary dance between pathogens and the immune response; the fine line between protective immunity, immunopathology, and autoimmunity; the redundancy of molecular effectors of immune responses; the unexpected complexity provided by the genotypic, phenotypic, and functional polymorphism of many molecules involved in immune responses; and the elegance and importance of evolutionarily conserved genetic programs governing innate immune defenses.

Much has been learned about molecular immunology in a very short time. The STD vaccine effort, spearheaded by an intensive effort to develop an HIV-vaccine, is pushing forward through a combination of new-age molecular modeling technology and classical trial-and-error approaches. Consequently, a number of STD vaccine candidates are entering clinical trials. Knowledge about strategies used by STD pathogens to evade immune defense mechanisms may someday produce novel approaches to therapy and vaccination. Importantly, the immunological community is working together with unprecedented determination and urgency to address these problems. Microbes have experimented with the human immune system for millions of years; humans have only just begun.

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If we regard the vaginal microflora in its totality as a flexible population occupying a particular ecologic niche and acting as a barrier to the establishment of other organisms, then the degree of acute stress tolerated by this microflora must have defined limits. ... If the acute stress is either too large or too long, the flexibility of the microflora may not accommodate this degree of change. The microflora may then collapse as a functional entity, providing a less protective environment against pathogenic microorganisms that are capable of rapid proliferation.

Andrew Onderdonk, 1992¹

INTRODUCTION

Most women who become infected by sexually acquired microbes acquire them during heterosexual intercourse. For women, transmission of STDs occurs predominately within the vaginal ecosystem. However, our understanding of how the normal genital flora may confer resistance to STDs has been incompletely investigated. Several published studies provide support for a protective role for vaginal lactobacilli in decreasing a woman's susceptibility to heterosexually acquired HIV,²⁻⁴ and recent data also suggest women lacking a predominant vaginal microflora composed of lactobacilli have an increased risk for acquisition of herpes simplex virus 2 (HSV-2),^{5,6} human papilloma virus (HPV),⁷ and may have enhanced susceptibility to bacterial STDs.³ Disruption of the vaginal microflora is also associated with changes in the integrity of the mucin gel layer,⁸ the numbers and types of immune cells, and immune products such as cytokines and chemokines.⁹⁻¹⁴ This chapter on the human vaginal ecosystem is intended to summarize the microbial components of the vagina, the effects of contraceptive methods and sexual intercourse on this ecosystem, and how vaginal products can alter this flora. Further, the association between the vaginal flora and susceptibility to infections will be summarized.

HISTORICAL REVIEW OF THE STUDY OF VAGINAL MICROFLORA

The first definitive study of the vaginal flora was published by the German scientist Döderlein in 1894.¹⁵ This groundbreaking study provided the first evidence that the normal vaginal flora of healthy women is dominated by the acid-producing gram-positive bacteria now referred to as *Lactobacillus* species. Döderlein was also the first researcher to report the use of probiotic approaches to the treatment of a sexually transmitted disease, with *Lactobacillus* recovered from healthy women being used as a treatment for gonorrhea among sex workers.¹⁵

The role of anaerobic bacteria in the vaginal microflora was first established in 1928 by Harris and Brown, who reported that 26 of 30 women sampled in the postpartum period had anaerobes present in the vaginal flora.¹⁶ This work was extended by Weinstein a decade later when he reported that 93% of pregnant women and 90% of nonpregnant women had obligately anaerobic bacteria present as part of their vaginal flora.¹⁷ The important role of estrogen in stimulating the disposition of glycogen in the vaginal epithelial tissue and its subsequent effect on the vaginal microflora was also described by investigators in the 1930s.^{18,19}

In the 1970s, with the advent of newer methods for the culture and identification of anaerobes, several studies were published, which more carefully described the vaginal or cervical microflora.²⁰⁻²³ Genital mycoplasmas were first recognized to be part of the vaginal ecosystem over 50 years ago, and their possible association with vaginitis syndromes was first suggested in 1958.²⁴ A study published in the early 1980s supported the role of *Mycoplasma hominis* in bacterial vaginosis (BV).²⁵

Studies conducted over the past decade have relied on molecular techniques to identify previously noncultivable organisms in the vagina of women with "normal" and "abnormal" flora.²⁶⁻³⁵ These studies have confirmed that the microflora of some women is predominated by species belonging to the genus *Lactobacillus*, while women having BV have a broad

range of aerobic and anaerobic microorganisms. It has become increasingly clear that even with these more advanced tools to characterize the microbial ecology of the vagina the full range of microorganisms present has yet to be fully described.

NORMAL VAGINAL ECOSYSTEM OF WOMEN OF REPRODUCTIVE AGE

As shown in Table 18-1, the frequency and concentration of many facultative organisms depends upon whether the woman has BV or *Lactobacillus*-predominant microflora.³⁶ However, even if “normal” vaginal microflora is restricted to those women having a *Lactobacillus*-dominant flora as defined by Gram stain, 46% of women are colonized by *G. vaginalis*, 78% are colonized by *Ureaplasma urealyticum*, and 31% are colonized by *Candida albicans*.³⁶

The frequency and species of anaerobic members of the vaginal microflora based on culture techniques are summarized

in (Table 18-2). Nearly all women are vaginally colonized by obligately anaerobic gram-negative rods and cocci,³⁶ and several species of anaerobic bacteria, which are not yet named, are also present. While some species of anaerobes are present at higher frequencies or concentrations among women with BV, it is clear that the microbial flora is complex and cannot be defined simply by the presence or absence of lactobacilli, *Gardnerella*, mycoplasmas, and anaerobes. This observation has been confirmed with molecular characterization of the microflora.^{26–35}

VAGINAL MICROFLORA OF PREPUBERTAL GIRLS AND POSTMENOPAUSAL WOMEN

In premenarchal girls there is little glycogen or glucose present in the vaginal fluid and the vaginal epithelium is thin and fragile. At puberty, the vaginal epithelium undergoes profound changes under the influence of the female

Table 18-1. Frequency and Concentration of Facultative Microorganisms in the Vaginal Flora of 171 Pregnant Women, Stratified by Vaginal Flora Pattern (as Assessed by Gram Staining)³⁶

Organism (s)	Frequency ^a Among Women with Indicated Pattern (cfu/mL ^b)			<i>p</i> ^c
	Normal (n = 85)	Intermediate (n = 47)	BV (n = 39)	
<i>Lactobacillus</i> species				
Total	96 (10 ^{6.0})	85 (10 ^{6.6})	67 (10 ^{6.3})	<.001
H ₂ O ₂ positive	61 (10 ^{7.2})	40 (10 ^{6.5})	5 (...)	<.001
<i>Gardnerella vaginalis</i>	46 (10 ^{6.0})	79 (10 ^{6.8})	92 (10 ^{7.7})	<.001
Diphtheroids	72 (10 ^{3.8})	89 (10 ^{3.9})	76 (10 ^{4.4})	.15
<i>Bacillus</i> species	4 (...)	4 (...)	0 (...)	.28
<i>Staphylococcus aureus</i>	5 (...)	9 (...)	3 (...)	.64
Coagulase-negative staphylococci	89 (10 ^{4.0})	81 (10 ^{4.4})	67 (10 ^{4.0})	.02
Viridans streptococci	55 (10 ^{4.7})	66 (10 ^{4.0})	72 (10 ^{5.2})	.03
<i>Enterococcus</i> species	39 (10 ^{5.1})	30 (10 ^{5.4})	13 (10 ^{4.2})	.003
Group B streptococci	15 (10 ^{4.2})	17 (10 ^{4.1})	21 (10 ^{5.8})	.20
<i>Escherichia coli</i>	17 (10 ^{4.1})	15 (10 ^{3.0})	21 (10 ^{4.6})	.59
<i>Klebsiella</i> species	2 (...)	2 (...)	5 (...)	.40
<i>Haemophilus influenzae</i>	1 (...)	0 (...)	3 (...)	.52
<i>Mycoplasma hominis</i>	15 (10 ^{3.5})	38 (10 ^{4.8})	61 (10 ^{5.2})	<.001
<i>Ureaplasma urealyticum</i>	78 (10 ^{5.0})	91 (10 ^{5.0})	92 (10 ^{5.0})	.01
<i>Candida albicans</i>	31 (...)	17 (...)	21 (...)	.41

^aAs a percentage.

^bMean number of cfu/mL of vaginal fluid for women who were culture-positive for the organism. Mean concentrations were not calculated for *C. albicans* or for those organisms of which fewer than five isolates were obtained.

^cMantel–Haenszel linear association (for frequencies).

Table 18-2. Frequency and Concentration of Anaerobic Microorganisms in the Vaginal Flora of 171 Pregnant Women, Stratified by Vaginal Flora Pattern (as Assessed by Gram Staining)³⁶

Organism(s)	Frequency ^a Among Women with Indicated Pattern (cfu/mL ^b)			<i>p</i> ^c
	Normal (<i>n</i> = 85)	Intermediate (<i>n</i> = 47)	BV (<i>n</i> = 39)	
Anaerobic gram-negative rods				
Any number	91 (10 ^{4.3})	89 (10 ^{5.0})	100 (10 ^{6.0})	.11
>10 ⁵ cfu/mL	33 (...)	45 (...)	62 (...)	.002
<i>Prevotella bivia/disiensis</i> ^d				
Any number	61 (10 ^{4.1})	68 (10 ^{4.6})	77 (10 ^{5.5})	.11
>10 ⁵ cfu/mL	15 (...)	21 (...)	39 (...)	.005
<i>Prevotella intermedia</i>	7 (10 ^{4.0})	13 (10 ^{4.4})	10 (10 ^{4.4})	.55
<i>Prevotella corporis/Bacteroides levii</i> ^e	21 (10 ^{4.0})	28 (10 ^{2.5})	39 (10 ^{5.0})	.05
<i>Prevotella melaninogenica</i>	4 (10 ^{3.4})	6 (10 ^{3.5})	5 (10 ^{3.6})	.75
<i>Prevotella loeschii</i>	2 (...)	0 (...)	5 (...)	.29
<i>Prevotella species</i>	14 (10 ^{3.4})	13 (10 ^{4.2})	15 (10 ^{3.6})	.90
<i>Porphyromonas asaccharolytica</i>	31 (10 ^{3.0})	40 (10 ^{3.7})	36 (10 ^{3.7})	.44
<i>Bacteroides fragilis</i> group ^f	9 (10 ^{3.5})	19 (10 ^{3.6})	15 (10 ^{3.7})	.29
<i>Bacteroides ureolyticus</i>	36 (10 ^{3.0})	40 (10 ^{3.5})	59 (10 ^{4.0})	.01
<i>Fusobacterium nucleatum</i>	8 (10 ^{3.3})	19 (10 ^{2.9})	21 (10 ^{3.8})	.05
<i>Mobiluncus species</i>	5 (...)	13 (...)	28 (...)	.004
<i>Lactobacillus species</i>	17 (10 ^{5.2})	11 (10 ^{5.3})	21 (10 ^{6.0})	.58
<i>Clostridium species</i>	7 (...)	2 (...)	15 (...)	.11
<i>Actinomyces species</i>	6 (10 ^{2.1})	13 (10 ^{3.0})	15 (10 ^{4.0})	.09
<i>Propionibacterium acnes</i>	22 (10 ^{4.2})	13 (10 ^{4.0})	8 (10 ^{4.1})	.04
<i>Bifidobacterium species</i>	4 (...)	2 (...)		.48
<i>Peptostreptococcus</i> (any)				
Any number	92 (10 ^{4.2})	91 (10 ^{4.9})	90 (10 ^{5.3})	.73
>10 ⁵ cfu/mL	26 (...)	47 (...)	59 (...)	.002
<i>Peptostreptococcus prevotii</i>	32 (10 ^{3.0})	27 (10 ^{4.0})	49 (10 ^{5.0})	.02
<i>Peptostreptococcus tetradius</i>				
Any number	21 (10 ^{3.7})	36 (10 ^{4.3})	41 (10 ^{5.0})	.05
>10 ⁴ cfu/mL	6 (...)	19 (...)	28 (...)	.007
<i>Peptostreptococcus anaerobius</i>	1 (...)	2 (...)	8 (...)	.05
<i>Peptostreptococcus magnus</i>	53 (10 ^{4.2})	34 (10 ^{4.8})	49 (10 ^{4.1})	.67
<i>Peptostreptococcus asaccharolyticus</i>	88 (10 ^{4.0})	66 (10 ^{4.3})	72 (10 ^{4.5})	.14
<i>Peptococcus niger</i>	20 (10 ^{2.7})	30 (10 ^{3.2})	31 (10 ^{2.8})	.18
<i>Veillonella species</i>	14 (10 ^{3.5})	11 (10 ^{3.2})	13 (10 ^{3.6})	.83

^aAs a percentage.

^bMean number of cfu/mL of vaginal fluid for women who were culture-positive for the organisms. Mean concentrations were not calculated for *C. albicans* or for those organisms of which fewer than five isolates were obtained.

^cMantel-Haenszel linear association (for frequencies).

^dIncludes 106 isolates designated *P. bivia* and 24 designated *P. disiensis*.

^eIncludes 32 isolates designated *P. corporis* and 14 designated *B. levii*.

^fThe 32 isolates from 23 women included *B. fragilis* (6), *B. vulgatus* (5), *B. ovatus* (7), *B. distasonis* (4), *B. uniformis* (2), *B. caccae* (3), and *B. multiacidus* (5).

sex hormone estrogen. The epithelium thickens and becomes rich in glycogen.¹⁸ Glycogen is metabolized by vaginal epithelial cells to glucose and then to lactic acid, which serves to acidify the vaginal fluid from pH 7 in a prepubertal girl to pH 5 even when lactobacilli are absent (Table 18-3). In addition, serous fluid is transudated across the epithelium, the major source of glucose in the vaginal fluid. Both glycogen and glucose serve as substrates for *Lactobacillus* to produce lactic acid, which can further reduce the pH of the vagina from 5 to 3.8–4.2. Any woman with sufficient estrogen to have glycogen deposition on the vaginal epithelium has enough glucose to furnish adequate nutrients for the growth of *Lactobacillus* in the vagina.

Aside from lactobacilli, other components of the vaginal microflora are also directly related to levels of estrogen and its resultant impact on the vaginal environment. The vaginal microflora of a newborn female is thought to be derived from the mother's microflora at the time of delivery. Therefore, the vaginal microflora of newborn females is similar to that of the mother, although the data to support this is scant. As the maternally derived estrogen is depleted over the first 2 months of life and until girls enter their premenarchal period, the vaginal flora is comprised predominately of anaerobic rods and cocci.³⁷ In a study of 19 prepubertal girls who had not been sexually abused, 89% were reported to have anaerobic gram-negative rods in the vagina, and 89% were colonized by anaerobic gram-positive cocci.³⁷

Prepubertal girls³⁷ have low frequencies of lactobacilli, *G. vaginalis*, *Prevotella bivia*, genital mycoplasmas, and yeast (Table 18-4). In contrast, women of reproductive age without vaginal infections are usually colonized by lactobacilli (92%) and over half of women will be vaginally colonized by *G. vaginalis*.³⁶ In postmenopausal women who have not received estrogen replacement therapy, only about half remain colonized by lactobacilli and the frequencies of *G. vaginalis*, *P. bivia*, and the genital mycoplasmas are also decreased.³⁸ Other members of the vaginal microflora do not

appear to be under estrogenic control. As shown in (Table 18-4), the frequency of *E. coli*, *Enterococcus*, viridans streptococci, and staphylococci are relatively constant among women regardless of estrogen status. *E. coli* may be somewhat less frequent among women having adequate levels of estrogen.

The complex interactions between vaginal pH and *Lactobacillus* is suggested by studies evaluating the effect of estrogen replacement therapy on the vaginal microflora of postmenopausal women. In two studies,^{39,40} the frequency of vaginal lactobacilli increased among women receiving estrogen replacement therapy. In a study following a group of women before and after estrogen replacement therapy, it was found that the mean vaginal pH after estrogen therapy in lactobacilli-positive subjects was 4.4 ± 0.4 compared to 5.2 ± 0.3 in lactobacilli-negative subjects ($P = 0.02$).⁴⁰ Prior to estrogen therapy, there was no difference in vaginal pH for women with or without lactobacilli, suggesting that both the presence of estrogen and lactobacilli are needed to achieve an optimal vaginal pH. Heinemann and Reid⁴¹ further supported the critical role played by reproductive hormones in maintenance of the vaginal flora in a study of 40 postmenopausal women using Premarin (conjugated equine estrogen in combination with progesterone) and 20 women not using hormone replacement therapy (HRT). They demonstrated that *Lactobacillus* species were dominant members of the microflora only among women receiving HRT based on denaturing gradient gel electrophoresis analysis of swabs taken at baseline and monthly for 3 months thereafter.

ROLE AND SPECIES OF *LACTOBACILLUS* IN THE VAGINA

■ ROLE OF H₂O₂

In addition to producing acid, some species of lactobacilli produce hydrogen peroxide (H₂O₂).⁴² H₂O₂ is toxic to a wide variety of microorganisms, and H₂O₂ of microbial origin interacts with peroxidases produced by the host along with halide (chloride) ion to generate a potent oxidant which is toxic to many bacteria. Over the past several years a number of studies have been published on the prevalence of H₂O₂-producing *Lactobacillus* in the vaginal flora of women. H₂O₂ production is detected by an agar plate method as shown in Fig. 18-1. H₂O₂-producing stains of lactobacilli reduce tetramethylbenzidine, causing colonies to turn blue. In studies of women between the ages of 16 and 45, the prevalence of H₂O₂-producing *Lactobacillus* has varied from 42% to 74%.^{36,42–49} Comparatively, premenarchal girls are unlikely to be colonized with H₂O₂-producing lactobacilli,³⁷ while postmenopausal women have an intermediate prevalence of H₂O₂-producing lactobacilli.³⁸

The capacity of H₂O₂-positive, but not H₂O₂-negative, strains of lactobacilli to kill HIV in vitro was first documented

Table 18-3. Vaginal pH Over the Lifespan

Premenarchal girls	pH 7
Reproductive aged women with estrogen:	
<i>Lactobacillus</i> predominant	pH 4.0–4.5
<i>Lactobacillus</i> reduced or had intercourse in past 24 hours	pH 5–4.7
BV	pH 4.7–5.5
Menses	pH 6.0
Reproductive aged women breastfeeding	pH 6.5–7.0
Postmenopausal and no HRT	pH 6.5–7.0

Table 18-4. Comparison of the Vaginal Microflora of Prepubertal Girls, Women of Child-Bearing Age, and Postmenopausal Women³⁸

Isolate	Percentage of Women with Indicated Isolate (Mean Concentration) ^a		
	Prepubertal (n = 19)	Pregnant (n = 132)	Postmenopausal (n = 73)
Facultative lactobacilli	11 (ND)	92 (10 ^{6.8})	49 (10 ^{5.7})
<i>Gardnerella vaginalis</i>	0	58 (10 ^{6.4})	27 (10 ^{5.3})
Coryneforms	42 (10 ^{5.2})	78 (10 ^{3.8})	58 (10 ^{4.0})
Yeasts	0	26 (ND)	1 (ND)
Coliforms	32 (10 ^{5.3})	16 (10 ^{3.7})	41 (10 ^{4.8})
Anaerobic gram-negative rods	89 (10 ^{6.9})	90 (10 ^{4.5})	89 (10 ^{4.1})
<i>Prevotella bivia</i>	11 (ND)	61 (10 ^{4.3})	33 (10 ^{3.8})
<i>Fusobacterium</i> species	26 (10 ^{5.7})	12 (10 ^{3.1})	7 (ND)
<i>Peptostreptococcus</i>	89 (10 ^{6.9})	92 (10 ^{4.5})	88 (10 ^{4.5})
Staphylococci	68 (10 ^{5.3})	86 (10 ^{4.1})	59 (10 ^{3.1})
Viridans streptococci	42 (10 ^{6.1})	59 (10 ^{4.4})	74 (10 ^{4.2})
Group B <i>Streptococcus</i>	0	16 (10 ^{4.2})	23 (10 ^{5.6})
<i>Enterococcus</i>	32 (ND)	33 (10 ^{5.2})	38 (10 ^{4.4})
<i>Mycoplasma hominis</i>	0	23 (10 ^{4.3})	0
<i>Ureaplasma urealyticum</i>	20 (ND)	82 (10 ^{5.0})	13 (10 ^{4.6})
Actinomyces	32 (10 ^{6.8})	8 (10 ^{2.5})	15 (10 ^{5.1})

^aData in parentheses are cfu/g; mean concentration calculated for those categories in which five or more subjects were positive.

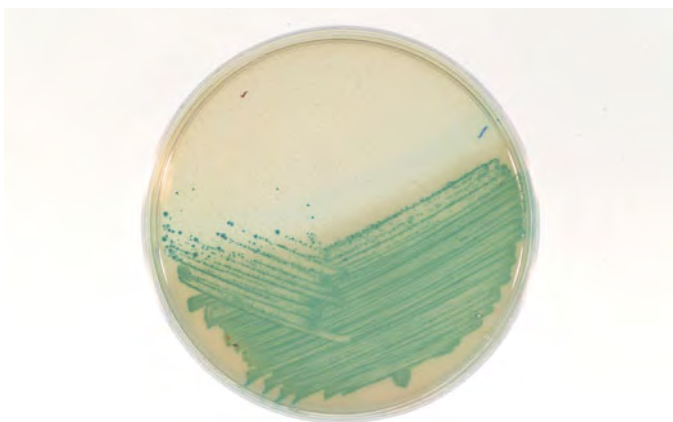


FIGURE 18-1. Tetramethylbenzidine agar plate showing typical blue pigmentation of colonies indicating production of hydrogen peroxide. This is a human vaginal isolate of *Lactobacillus crispatus*.

in 1991.⁵⁰ The in vitro activity of H₂O₂-positive strains of lactobacilli against the BV-associated microorganism, *G. vaginalis*, and *P. bivia* was established by the same laboratory.⁴⁴ The specific importance of H₂O₂ as the toxic molecule produced by lactobacilli was shown by demonstrating that the microbicidal activity of lactobacilli was destroyed when catalase, an enzyme which degrades H₂O₂, was added. These data suggested that the H₂O₂ produced by lactobacilli may play an

important role in acting as an endogenous microbicide within the vaginal ecosystem.

Several clinical studies conducted in populations of pregnant and nonpregnant women in the United States and Japan have shown that the prevalence of BV is low (4%) among women colonized with H₂O₂-producing strains of lactobacilli. By comparison, approximately one third of women who are vaginally colonized by *Lactobacillus* that do not produce H₂O₂ have BV.⁴⁵⁻⁴⁷ As noted below, rectal colonization by H₂O₂-producing *Lactobacillus* is strongly linked to vaginal cocolonization and appears to confer a very low risk of BV.⁴⁹ Surprisingly, not all women lacking *Lactobacillus* have BV. These data suggest that the absence of *Lactobacillus* is not synonymous with the presence of BV. Further, the consistency of the findings among pregnant and nonpregnant women, and the similarity of the findings among women enrolled in the United States and Japan, suggests that the production of the H₂O₂ by lactobacilli may play a crucial role in protecting against the overgrowth of pathogens in the reproductive tract.

The identity of the species of *Lactobacillus* of importance in the vagina has been the subject of several studies.^{42,43,48,49,51,52} Older studies using conventional identification methods such

as sugar fermentation and other biochemical assays have identified *Lactobacillus acidophilus* and *Lactobacillus fermentum* as the primary species of importance in the vagina. However, several investigators have since questioned the reliability and reproducibility of these methods for the species identification of *Lactobacillus*. One recent study demonstrated that commercially available methods which are used to identify *Lactobacillus* to the species level using phenotypic characteristics are usually incorrect.⁵³ In one study, investigators used phenotypic tests to identify 90 strains of lactobacilli recovered from the vagina of women as well as seven reference strains purchased from the American Type Culture Collection (ATCC). The commercial system correctly identified the species of lactobacilli, on the basis of DNA homology with ATCC type strains, for only 4 of 90 isolates. The inherent phenotypic variability of lactobacilli, combined with the limited database available in commercial identification systems for lactobacilli can lead to misidentification of *Lactobacillus* species derived from human studies of the microflora. The commercial system incorrectly identified *L. vaginalis* as *L. fermentum*, and *Lactobacillus crispatus* was always identified as *L. acidophilus*.⁵³ The lack of reliable phenotypic methods for identification of lactobacilli have led to a broad misunderstanding of the species of lactobacilli present in the vagina, and the common misperception that dairy and food derived lactobacilli are similar to those found in the vagina. The taxonomy of *Lactobacillus* has undergone extensive revision based on DNA homology.⁵⁴ When DNA homology methods were employed in evaluating the lactobacilli recovered from 27 healthy women, Giorgi et al. identified *crispatus* and *Lactobacillus jensenii* as the predominant vaginal *Lactobacillus* species which colonize asymptomatic women.⁵² This has been confirmed in additional studies using based on nucleic acid methodologies.^{40,49,55,56} Similar trends are seen among pregnant⁵⁶ and nonpregnant women.^{49,55} Amplified ribosomal DNA restriction analysis, ribotyping, and PCR with specific oligonucleotide primers were used to identify lactobacilli recovered from 22 Bulgarian women. They reported that the species present included *L. crispatus*, *L. fermentum*, *L. gasseri*, *L. helveticus*, and *L. plantarum*.⁵⁷ Overall, hundreds of isolates obtained from women on different continents have been identified using molecular techniques, and *L. crispatus* has been identified as the most common species of vaginal lactobacilli, followed by *L. gasseri*, *L. jensenii*, *L. vaginalis*, and *L. iners*.

There are relatively few studies of lactic acid bacteria colonizing the vagina from women in Africa. One such study evaluated the lactobacilli recovered by culture methods from women in Uganda, and the isolates were then identified based on 16S rRNA and BLAST analysis.⁵⁸ The authors reported that *L. crispatus* was common in both African and Asian women, and that *L. reuteri*, *L. gasseri*, and *L. vaginalis* were the most frequent isolates recovered from Ugandan

women. Because their initial detection of lactobacilli relied on culture detection using Rogoas agar, and *L. iners* do not grow well on this media, it is likely that *L. iners* was not recovered due to the failure to cultivate this organism during the primary culture.⁵⁸ By contrast, a study of 241 Nigerian women in which lactobacilli were identified using DNA sequencing and a BLAST algorithm²⁹ reported that *L. iners* was the predominant species (64%), followed by *L. gasseri* (7%) and other species. Additional studies will be needed to confirm whether the species distribution of lactobacilli actually differs from that observed among American women, or whether the reported differences reflect differences in methodology. *L. iners* do not produce H₂O₂,⁴⁹ so it is possible that the relative predominance of this species among African women could account for the high prevalence of BV observed in some studies of African women.² This may have implications for the future use of probiotic approaches for the restoration of normal flora among African women, which have been proposed as one approach to decrease the susceptibility of women to HIV.^{59,60,61,62}

■ OTHER ANTIMICROBIAL PRODUCTS PRODUCED BY LACTOBACILLI

Lactic acid is the principle component responsible for vaginal acidity. Both vaginal and cervical epithelial cells have the capacity to convert glycogen to glucose, which is further metabolized to lactic acid through cellular glycolysis. The residual glucose can be converted to lactic acid by lactic acid bacteria which may be present in the vaginal microflora as well. Therefore, vaginal acidity is dependent on having adequate levels of estrogen as well as the presence of lactic acid producing bacteria such as lactobacilli.

Some authors have suggested that vaginal pH by itself is an important marker for bacterial pathogens and menopausal status. In 55 premenopausal patients who were evaluated and assessed for the presence of pathogens, Caillouette et al. described that women with normal flora or yeast colonization had statistically significantly lower vaginal pH levels as compared with women colonized by β -hemolytic streptococci, *G. vaginalis*, or mixed organisms.⁶³ Among postmenopausal women who had not received HRT, they reported that 55 of 64 women had vaginal pH levels above 4.5. By contrast, 80 of 88 postmenopausal women who had received HRT had a vaginal pH of ≤ 4.5 . Further, these investigators noted that vaginal pH was a marker for the serum estradiol level. Although the study was small, the authors suggested that the use of vaginal pH assessment could be a powerful screening tool to assess estradiol levels and, in effect, to establish proper estrogen dosing.⁶³

Some investigators have suggested that there is racial variation in vaginal pH among sexually active young women.⁶⁴

In one study of 273 sexually active adolescents in Denver, CO, vaginal pH was measured through the use of pH paper. Women with lower genital tract infections including BV, were excluded. These authors reported that the mean vaginal pH among African American women was 5.3 ± 0.7 , whereas women of other races had a mean pH of 4.7 ± 0.6 . Some recent studies have also documented that African American women are less likely to be vaginally colonized by lactobacilli compared to Caucasian women.^{65,66} This finding may explain the increased vaginal pH in African American women, but requires confirmation in additional studies.

Valore et al. characterized the antimicrobial components of vaginal fluid collected on preweighed tampons.⁶⁷ The extracted vaginal fluid was tested for total lactic acid and antimicrobial polypeptides. They performed individual assays for calprotectin, lysozyme, lactoferrin, secretory leukocyte protease inhibitor, and human beta defensins for activity against target microorganisms. They reported that lactic acid, rather than host-derived defense molecules, is the major antimicrobial product in the vaginal fluid. They further documented that concentration of lactic acid in the vaginal fluid exceeded 5 mmole/L among women with a vaginal pH of 4.2 or less (Fig. 18-2). These data confirm the critical role of lactic acid as an antimicrobial agent in the vaginal fluid of women of reproductive age.

The antibacterial activities of human lactobacilli strains have been evaluated in a number of ways. Coconnier et al. evaluated the antibacterial properties of *acidophilus* using spent cultures supernatants.⁶⁸ They demonstrated that culture supernatants of human strains of *L. acidophilus* had in vitro activity against gram-negative and gram-positive pathogens as well as enteroinvasive pathogens. They also tested the activity of these supernatants in a *Salmonella typhimurium* mouse model and demonstrated the in vivo protective effect of this *Lactobacillus* metabolite. These authors speculated that the antimicrobial activity produced by *acidophilus* could be due to an unusual acidic amino acid present in a novel peptide agent.⁶⁸

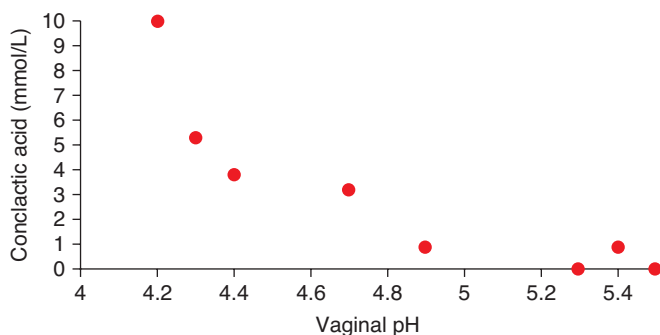


FIGURE 18-2. Lactic acid concentration vs. vaginal pH. (Data derived from Valore EV, Park CH, Igteti SL, et al. Antimicrobial components of vaginal fluid. *Am J Obstet Gynecol* 2002; 187: 561–568.)

Other investigators have reported that *Lactobacillus* does not inhibit common genital pathogens such as *vaginalis* and anaerobic gram-negative rods.⁶⁹ However, the testing was performed at pH of 6.0–6.5, a vaginal pH not frequently found in estrogenized women. These investigators speculated that antagonistic properties between lactobacilli and other species in the ecosystem were probably due to bacteriocins. Lactacin B is a bacteriocin produced by *acidophilus*. Barefoot and Klaenhammer described bacteriocins produced by 52 vaginal strains of *acidophilus*.⁷⁰ There was no broad spectrum inhibitory activity of *acidophilus* against other organisms when the effects of H_2O_2 and other organic acids were eliminated. Lactacin B activity was limited to other lactobacilli. These investigators did not confirm earlier reports that a second bacteriocin called lactocidin was produced by lactobacilli.⁷¹ Thus, Barefoot and Klaenhammer confirmed that production of bacteriocins occurs, but suggested that antagonism of lactobacilli against other pathogens may be due to other products.

Kaewsrichan et al. evaluated strains of lactobacilli recovered from Thai women, and identified a bacteriocin-like compound produced by *L. jensenii*, which has activity against *G. vaginalis*, *C. albicans*, and *E. coli*.⁷² They noted that the production of hydrogen peroxide by itself was insufficient to inhibit growth of *C. albicans*. Other investigators have continued to identify antagonistic activity of lactobacilli.^{73,74} But, the roles of these components in stabilizing the vaginal flora and preventing acquisition of infection is not known.

FLUCTUATIONS IN THE NORMAL VAGINAL FLORA

The normal vaginal flora is complex and dynamic. One method to assess daily fluctuations in vaginal microflora is through the use of Gram-stained vaginal smears.^{75,76} In one such study, Schwebke et al. used self-obtained vaginal smears from 18 women to assess vaginal flora patterns over a 30-day period.⁷⁶ They reported that among women with a *Lactobacillus*-predominant vaginal flora, two patterns were observed. The first pattern was one in which *Lactobacillus* persisted at high levels throughout the 30-day period. A second pattern consisted of intermittent predominant lactobacilli interspersed with days in which *Gardnerella* and anaerobic gram-negative morphotypes appeared along with normal or reduced numbers of *Lactobacillus* morphotypes. Three of seven women who initially had *Lactobacillus*-predominant flora achieved vaginal scores as high as seven or eight, indicative of BV, but these alterations persisted for only 1–2 days. They noted that the increase in *Gardnerella* and anaerobic rod morphotypes was most concentrated around the time of menses, but that there were sporadic variations that also occurred throughout the cycle for some women. These authors suggested that alterations in vaginal microflora around the time of menses may represent a “critical period”

during which exogenous factors could tip the ecology balance in favor of BV.⁷⁶

Fluctuations in normal vaginal flora was studied by Priestley et al.⁷⁷ Twenty-six subjects were followed over an 8-week period. Sampling was conducted two to seven times weekly and women completed diary cards reporting sexual and other behaviors. In addition, vaginal swabs were obtained for culture of *Candida*, *vaginalis*, anaerobes, *hominis*, and *U. urealyticum*. Only 4 of the 26 subjects had normal vaginal microbiology throughout the study period. One woman who was not sexually active had BV throughout the 8-week period of follow-up and 9 (35%) developed intermittent BV. While some women developed symptoms during the study period, symptoms correlated very poorly with microbiologic findings. These authors concluded that BV and candidiasis can occur intermittently at high frequencies and that acquisition of BV occurred more commonly among women having unprotected sex.⁷⁷ A third study using vaginal smears to assess vaginal microflora over menstrual cycle was conducted in 22 volunteers.⁷⁸ These authors reported that one half of the women had normal flora throughout the cycle and an additional third had basically normal flora which transitioned to intermediate flora or BV. Like the other studies, most of the changes in the microflora occurred during menses.

A fourth study of 101 women enrolled and followed at 4-month intervals for 8 months, reported that both a higher frequency of sexual intercourse and use of antibiotics was associated with loss of vaginal lactobacilli.⁷⁹ This study also showed that 23 (40%) of 57 women initially colonized by *L. crispatus* or *L. jensenii* remained colonized by these species over 8 months, while 1 (5%) of 21 women colonized by other species remained colonized by lactobacilli during follow-up. All these studies suggest that alterations in the vaginal microflora most frequently occur with menses, intercourse, and/or antibiotic usage, but that the species of *Lactobacillus* present may also influence the stability of the vaginal flora.

Two longitudinal cohort studies have been published assessing the vaginal microflora in pregnant women. One study was conducted in 163 women with paired cultures 4 months apart, in the second and third trimester of pregnancy.⁴⁵ Lactobacillus cultures and assessment of H₂O₂ production was assessed at each of the two visits. Seventy-nine percent of 107 women initially colonized by H₂O₂-producing *Lactobacillus* were persistently colonized by H₂O₂-producing strains 4 months later. By contrast, fewer than one half of women initially colonized by H₂O₂-negative strains of lactobacilli remained persistently colonized by those strains 4 months later. Finally, 40% of 20 women initially lacking lactobacilli remained negative for lactobacilli, whereas only 25% of women spontaneously acquired vaginal colonization by an H₂O₂-producing strain. These data are supportive of observation derived from studies of nonpregnant women, suggesting that H₂O₂-producing lactobacilli are more persistent over time than lactobacilli that do not produce H₂O₂.^{46,79}

ROLE OF THE RECTAL RESERVOIR IN MAINTENANCE OF THE VAGINAL MICROFLORA

The gut has a complex microflora which is known to play a role in health. However, it is increasingly recognized that the rectum is an important reservoir for organisms that colonize the vagina. This also appears to be true for lactobacilli. In a study of 531 women, 80% were found to be colonized either vaginally and/or rectally by lactobacilli,⁴⁹ and 67% harbored H₂O₂-producing strains. While colonization of both the vagina and rectum with lactobacilli was common, lactobacilli were more commonly isolated from the vagina than the rectum (61% vs. 43%, $P < 0.001$). Among these 531 women, vaginal and rectal patterns of colonization were correlated with rates of BV. As shown in (Table 18-5) cocolonization of the rectum and vagina with H₂O₂-producing lactobacilli was associated with the lowest prevalence of BV, suggesting that

Table 18-5. Prevalence of Bacterial Vaginosis Among Women with Vaginal vs. Rectal Colonization by Facultative H₂O₂-Producing Lactobacilli

H ₂ O ₂ -Producing Lactobacilli Present		Total Women ($n = 531$)	BV (%)	RR (95% CI)
Vagina	Rectum			
+	+	198 (37%)	9 (5)	Referent
+	–	126 (24%)	25 (20)	4.4 (2.1–9.0)
–	+	32 (6%)	15 (47)	10.3 (4.9–21.6)
–	–	175 (33%)	123 (70)	15.5 (8.1–29.5)

Data from Antonio, MA, Rabe LK, Hillier SL. Colonization of the rectum by *Lactobacillus* species and decreased risk of bacterial vaginosis. *J Infect Dis* 2005; 192: 394–398.

colonization of both the vaginal and rectum may be protective against BV.

Song and colleagues⁴⁸ reported that *L. gasseri*, *L. fermentum*, and *L. paracasei* were the most common species of *Lactobacillus* isolated from the stool samples of Japanese women, while Antonio reported that *L. crispatus*, *L. jensenni*, and *L. gasseri* were the most frequent rectal species.⁴⁹ The difference in species identified by these investigators may reflect the different specimen types evaluated (stool vs. rectal swab) or true differences in the two populations related to diet or behavior. Many commercially available preparations containing lactobacilli are sold as dietary supplements which are recommended for ingestion. One theory is that strains of lactobacilli delivered to the gut will migrate to the vagina and may thereby stabilize the vaginal microflora. None of the published studies has identified the species of lactobacilli, which are frequently used as probiotics such as *L. acidophilus* or *Lactobacillus delbrueckii bulgaricus* in the vagina, suggesting that these organisms rarely migrate to colonize the vagina.

EFFECT OF MENSES AND INTERCOURSE ON THE VAGINAL MICROFLORA

Longitudinal studies in which vaginal flora has been assessed using Gram-stained vaginal smears, suggest that *Lactobacillus* may decrease during menses and after intercourse, two times when vaginal pH is elevated due to the presence of menstrual fluid or semen. A study of 74 women characterized the flora of women who used no hormonal contraception or condoms over the menstrual cycle. Women were evaluated during menses (days 1–5 of the cycle), during the preovulatory phase (days 7–12 of the cycle), and in the postovulatory phase (days 19–24). The data from 50 women without BV were analyzed separately from that of the 25 women having BV. Among the women without BV, the changes in the *Lactobacillus* populations was modest, with a decreased in

prevalence to 82% during menses and increasing to 98% after menses.⁸⁰ Other non-*Lactobacillus* components of the vaginal microflora decreased from a prevalence of 72% during menses to 40% following menses. Among women with BV, the only statistically significant change in the microflora was an increase in lactobacilli from 33% during menses to 54% following menses. These data suggest that there is a slight decrease in numbers of lactobacilli, with a concomitant increase among other organisms during menstrual bleeding.

Morison et al.⁸¹ evaluated the impact of menses and sexual activity on the microflora of 30 women in Ghana. Women with BV collected a total of 1724 swabs from themselves on alternate days over a 4-month period, and the swabs were used to prepare vaginal smears that were evaluated by the Nugent criteria.⁷⁵ Days of menstruation and sexual intercourse were recorded by the women. Four groups of flora patterns were identified (Table 18-6). Eleven of the 30 women had stable normal flora, five had unstable normal flora, six were categorized as having unstable abnormal flora, and eight women had persistently abnormal flora. Women in each of the four groups were more likely to have BV flora patterns during menses (Table 18-6). In this same study, sexual intercourse had no significant input on acquisition of BV (data not shown).

The shifts in vaginal flora observed during menses have been widely attributed to the increased pH of the vagina in the presence of menstrual fluid. However, there is no evidence that adherence of lactobacilli to vaginal epithelial cells is altered at increased pH. There was no significant difference in the adherence of *Lactobacillus* species, *vaginalis*, or *E. coli* to exfoliated vaginal epithelial cells over the menstrual cycle.⁸² This suggests the alterations in the vaginal microflora observed over the menstrual cycle probably do not relate to hormonally related changes in binding of organisms to epithelial cells. Lactobacilli can bind to erythrocytes⁸³ and

Table 18-6. Variation in BV by Stage of Menstrual Cycle and Shifts in Vaginal Flora Associated with Sexual Intercourse⁸¹

Group	Women	Smears	Percentage of BV by Menstrual Cycle Day		
			< 7 Days	7–13 Days	14+ Days
Stable normal flora	11	638	9.1 ^a	4.1 ^a	0.3
Unstable normal flora	5	278	37.7 ^a	24.1 ^a	10.5
Unstable abnormal flora	6	327	60.6 ^a	72.9 ^a	57.1
Stable abnormal flora	8	453	80.6 ^a	93.3 ^a	84.1

^aStatistically different from 14+ days.

Data from Morison L, Ekpo G, West B, et al. Bacterial vaginosis in relation to menstrual cycle, menstrual protection method, and sexual intercourse in rural Gambian women. *Sex Transm Infect* 2005; 81: 242.

competitive binding of lactobacilli to erythrocytes could account for some of the observed decrease in lactobacilli during menses.

A large number of studies have evaluated the effects of various catamenial products on the vaginal microflora during menses. In one such study, the effect of tampon usage on the vaginal microflora of 35 healthy women was determined following the random assignments of these women to either tampon or sanitary napkins usage for three consecutive menstrual cycles.⁸⁴ Colonization by coagulase negative staphylococci increase significantly among tampon users compared to napkin users, but the shifts in microflora occurred only during menstruation and no difference in the microflora was noted at other sampling times, suggesting the changes observed during menses were transient.

A large study evaluated 101 women over two menstrual cycles using two different tampon types.⁸⁵ There were modest changes noted in the vaginal flora when comparing the premenstrual samples from those obtained from women during tampon use. Although anaerobic gram-negative rods and *vaginalis* were more prevalent during menses, the decrease in vaginal lactobacilli was subtle. It is unknown whether the use of tampons, which might absorb red blood cells during menses, may minimize the impact of menses on colonization by lactobacilli. However, some observational data suggests that women who routinely use tampons for catamenial protection are more likely to maintain colonization by lactobacilli compared to women who use pads for catamenial protection (Hillier, unpublished data).

Vaginal intercourse appears to have little effect on the presence of vaginal lactobacilli. However, in one study there was a significant increase in vaginal colonization by both *Enterococcus* and *E. coli*, and a trend toward increased colonization by group B *Streptococcus* following intercourse.⁸⁶ These three groups of organisms are all carried in the rectum and colonize the perineum. A second study evaluated 22 women randomly assigned to use no condoms or lubricated antispermicidal condoms. As with the larger study, vaginal intercourse was associated with increased colonization by *E. coli*, among both condom users and noncondom users.⁸⁷ It is likely that the act of heterosexual intercourse introduces fecal bacteria into the ecosystem, and that the increased vaginal pH occurring during intercourse may increase survival of these organisms.

EFFECT OF VAGINAL PRODUCTS AND BARRIER DEVICES BIRTH ON THE VAGINAL FLORA

Many young women use vaginal products including lubricants, contraceptives, antifungals, and douches. Each of these products can alter the vaginal ecosystem by changing vaginal pH, altering the vaginal fluid by direct dilution, or by altering the capacity of organisms to bind to the vaginal epithelium.

Nonoxynol-9 (N-9) is the most commonly used over-the-counter contraceptive, and it is available in the form of gels, foams, suppositories, or creams for use with or without barriers. Some studies have demonstrated a significant decrease in lactobacilli among spermicide and diaphragm users^{86,88} or with N-9 alone^{89,90} while other studies have found no association between N-9 use and decreased populations of lactobacilli.⁹¹ In vitro, N-9 was reported to have inhibitory activity against lactobacilli^{92,93} but other more recent studies suggest that N-9 is not cidal to most strains of *Lactobacillus* recovered from the vagina.⁹⁴

Clinical studies of N-9 have yielded conflicting results. Gupta published a prospective evaluation of 331 university students who were initiating use of a new birth control method. Women were evaluated at baseline and weekly thereafter.⁸⁸ Multivariate modeling of the data showed that use of an N-9 contraceptive in the previous week was associated with having an abnormal Nugent Gram stain score, and with increased colonization by *E. coli*, anaerobic gram-negative rods, and *Enterococcus*.⁸⁸

However, in another study conducted among commercial sex workers, use of N-9 containing gel was actually associated with increased colonization by H₂O₂-producing lactobacilli compared to women using placebo gel.⁹¹ In a study of 48 women evaluating the impact of N-9 on vaginal microflora, there was only a transient impact on vaginal lactobacilli but *E. coli* colonization was increased in women using these different formulations of N-9.⁹⁴ The lack of consistency among various studies evaluating different formulations of N-9 for different durations in different population has led to confusion regarding the impact of N-9 on the microflora.

A subsequent large prospective study of 235 women followed for 6 months randomly assigned to use of five different commercially available formulations of N-9, found no significant alterations in the vaginal microflora of most women. Only women having exposure to more than 280 mg of N-9 per week developed sustained changes in the vaginal microflora.⁹⁵ Different formulations of microbicide did not have differential effects on the flora. However, this study demonstrated that N-9 did have a dose-dependent impact on the prevalence of anaerobic gram-negative rods, and was associated with a twofold increase in BV (OR 2.3, 95% CI 1.1–4.7). It is likely that the inconsistencies observed in previous studies were attributable to small sample size, short study duration, and failure to account for total weekly exposure to N-9.

On the basis of the above data, it was not surprising that prophylactic use of a 3% nonoxynol gel during vaginal intercourse during a 6-month study did not reduce the incidence of BV, trichomoniasis or yeast vaginitis.⁹⁶

Like the effects on the microflora, the effects of N-9 contraceptives on the vaginal epithelium probably relate to exposure frequency and dosage. Use of sponges containing 1000 mg of N-9 was associated with an increased frequency of genital

ulcers,⁹⁷ but daily application of a gel containing 52.5 mg of N-9 did not result in epithelial disruption among commercial sex workers.⁹⁸ However, in another study evaluating suppositories containing 150 mg of N-9, disruption of the vaginal and/or cervical epithelium occurred two to four times as frequently when women used N-9 one to four times daily as compared to women who used N-9 suppositories every other day.⁹⁹

Several studies evaluated the effects of oral contraceptives (OCs) use on the vaginal ecosystem. In one study, 30 women (mean age 21.9 years; 87% nulliparous) were evaluated before and 2 months after the start of OC use. At both visits, genital symptoms were assessed by a questionnaire; vaginal signs were assessed by speculum examination and colposcopy; vaginal microflora was evaluated by quantitative culture; and a vaginal biopsy was obtained for histopathologic evaluation. The results showed that no change was observed in discharge amount, consistency, viscosity, cervical ectopy, or amount of cervical mucus. There also was no change in the prevalence of hydrogen peroxide-producing lactobacilli, yeast colonization, vaginal pH, or in thickness of the vaginal epithelium. Other studies reported that OC users are less likely to have BV, with one study noting the risk of BV is 50% less among OC users overall.^{100,101} Depot medroxyprogesterone acetate (DMPA) produces a systemic hypoerogenic state associated with decreased hydrogen peroxide-positive *Lactobacillus* colonization and a slight thinning of the glycogen vaginal epithelial layer. Such changes possibly comprise the vaginal barrier to infection.

Women who desired DMPA for contraception were evaluated before and at 3 and 6 months after initiation of 150-mg DMPA injections every 3 months.¹⁰² At each visit, genital symptoms, vaginal microflora, and histopathology were assessed via vaginal biopsies. The most notable changes were in the epithelium in which the number of cell layers, thickness of glycogen, and mean number of microorganism-inducing polymorphonuclear neutrophilic leukocytes (PMNs) decreased over time. There was also a statistically significant reduction in hydrogen peroxide-positive lactobacilli from baseline to 6 months (53% vs. 32%; $P = 0.005$). Such changes possibly compromise the vaginal barrier to infection and BV.

Theoretically, intrauterine devices (IUDs) should be neutral to the vaginal ecosystem, since they are placed in the upper genital tract. None of the existing studies has evaluated the impact of progestin-releasing IUDs on the vaginal microflora. Cross-sectional longitudinal studies link nonhormonal IUD use with BV. In a 24-month study that compared IUD users to women who used OCs, BV occurred 2.8 times more frequently in IUD users than in OC users.¹⁰³ During the 2-year follow-up period, 50% of women using an IUD had at least one episode of BV, compared with 20% of the OC users ($P = 0.001$). Bacterial infections associated with IUD use may depend on the type of IUD used. A chronic inflamma-

tory response in the upper genital tract might disrupt the vaginal flora. Since condom usage decreases following initiation of IUD use,¹⁰² the decline in condom use by IUD users also may contribute to the increased BV.

Data are lacking with respect to the degree by which transdermal contraception affects BV, but since it delivers the same hormones as OCs, users of the patch may not be at increased risk for BV.

The connection between condom use and the incidence of BV has not been widely studied. During 7908 person-months of observation of 917 Peruvian female sex workers, the prevalence of BV, gonorrhea, chlamydial infection, and trichomoniasis declined significantly, and condom use increased significantly.¹⁰⁴ BV also was positively associated with the use of an IUD and negatively with douching. Because condoms are a barrier method of contraception, they are likely protective of the vaginal flora and have no known effects on the vaginal epithelium or immune cells.

The vaginal ring releases hormonal contraceptives, typically over a 3-week period. In a crossover study of 64 women of child-bearing age, patients were randomized to receive either a daily OC or the vaginal ring for three consecutive 28-day cycles, directly followed by three cycles of the other study drug.¹⁰⁵ The results showed vaginal white blood cell count and pH were not significantly affected by either method. However, women who wore the vaginal ring had two- to three-fold higher levels of hydrogen peroxide-producing *Lactobacillus*, suggested a possible benefit.

In summary, contraceptive methods have varied effects on the vaginal ecosystem. N-9 usage promotes *E. coli* colonization. DMPA may cause a decline in the density of hydrogen peroxide-positive lactobacilli, a thinning of the epithelium, and a loss of glycogen. IUDs have been linked with increased rates of BV, although newer progestin-releasing IUDs have not been evaluated for their effects on the vaginal microflora. Hormonal contraceptives appear to enhance a *Lactobacillus*-dominated flora. The impact of contraceptives on the vaginal ecosystem, including their impact on susceptibility to infection, has not been adequately investigated to date.

EFFECT OF DOUCHE PRODUCTS AND "DRY-SEX" ON THE VAGINAL ECOSYSTEM

Douching is a common practice in women throughout the world. Douching may alter a woman's susceptibility to infection by altering the vaginal microflora, removing protective components from the vagina or cervix or by promoting ascension of microorganisms from the lower to the upper reproductive tract. Douching is more frequent among low-income women and ethnic minorities in the United States.¹⁰⁶ Routine douching for hygiene has been shown to double the risk of acquiring BV.⁴⁶ A cross-sectional observational study

of African women showed an increased prevalence of vaginal yeast among women who used douche products containing antiseptics.¹⁰⁷ Women who douched using noncommercial preparations were 70% more likely to have HIV, while women douched with commercial antiseptics had a 40% decreased frequency of HIV.¹⁰⁷

Onderdonk evaluated the effects of a single use of a douche product on the vaginal microflora. Nonmedicated douches had a more transient effect on the vaginal microflora compared to those containing antimicrobial agents such as iodine.¹ However, even nonantiseptic douches had an effect on the vaginal microbial ecosystem and persistent use apparently altered the microflora. A better understanding of how different douche products affect young women's susceptibility to infection are urgently needed so that women can be counseled appropriately regarding douching.

The thick, glycogen rich vaginal epithelium is one of the primary structural defenses mechanisms of the female reproductive tract. In premenarchal girls and postmenopausal women, the lack of estrogen results in a thinning of the vaginal epithelium. There is a decreased cell division on the basal and parabasal levels of the vaginal epithelium.¹⁰⁸ In postmenopausal women elastic fibers of the lamina propria are replaced with nonelastic collagen. The decreased thickness of the epithelium, combined with loss of elastic structure renders the vagina more susceptible to damage during sexual activity. In some cultures, the use of drying or astringent agents is common in order to heighten a sense of "tightness" during sex.¹⁰⁹ The practice of "dry sex" acts to remove the lubricating vaginal fluid and may increase the susceptibility of the genital tract to infection. Dryness during sex has been associated with pain during intercourse, which is linked to postcoital bleeding.¹¹⁰ Postcoital bleeding increases the risk of male-to-female transmission of HIV three- to five-fold.^{111,112} Whether the use of traditional vaginal agents for "dry sex" is linked to postcoital bleeding has not been studied extensively, but the use of these agents has been linked to the HIV in some populations.¹¹³

EFFECT OF ANTIBIOTICS USED TO TREAT GENITAL INFECTIONS ON THE VAGINAL MICROFLORA

Antimicrobial agents used to treat nongenital and genital infections can adversely affect the vaginal microbial ecosystem. Lactobacilli are susceptible to beta-lactam antibiotics such as amoxicillin as well as cephalosporins, which are frequently used to treat genital tract infections.^{114,115} The impact of beta-lactam antibiotics on the normal vaginal microflora was evaluated by Sullivan et al.¹¹⁶ who followed women at baseline, on the day of ovulation, and at 3 and 7 days after ovulation. During the second ovulatory cycle, women were treated with pivmecillinam (a penicillin which

binds to penicillin binding protein 2) administered orally 200 mg three times daily for 7 days. They documented that antibiotic was detectable in the vaginal fluid at a concentration of approximately 2 μ L per mL. Surprisingly, they found that antibiotic usage had only a modest impact on the vaginal microflora, with little impact on lactobacilli, anaerobic bacteria, staphylococci, or *Gardnerella*.¹¹⁶

The activity of systemic or local antibiotics on the vaginal ecosystem is hard to predict because they have effects on many organisms present within the ecosystem. For example, ampicillin has activity against lactobacilli and its use initially leads to a decrease in vaginal colonization by lactobacilli among women with BV. However, because ampicillin presumably has activity against some of the other organisms present in the vagina which compete in that same ecosystem, ampicillin usage was found to have a net beneficial impact on vaginal colonization by lactobacilli 1 month after therapy.¹¹⁷ Metronidazole, applied either topically or orally was associated with a net increase in vaginal colonization by lactobacilli.¹¹⁷ Clindamycin cream used for the treatment of BV and applied locally lead to an initial decrease in colonization by lactobacilli but, like ampicillin, lead to an increase in *Lactobacillus* colonization 1 month posttherapy. Two recent studies comparing *Lactobacillus* colonization rates following metronidazole or clindamycin therapy for BV showed no long-term negative impact of clindamycin treatment on colonization by lactobacilli.^{117,118} By contrast, one study, which followed a group of women over time to assess factors associated with loss of lactobacilli from the vaginal ecosystem, found that exposure to antibiotics was associated with loss of lactobacilli.⁷⁹ Like other factors, antibiotic usage may likely have a transient impact on the microflora of most women, but may play a more persuasive role among women with unstable flora.

Topical microbicides (Chapter 94) differ substantially from traditional antimicrobics in that they optimally target specific pathogens and should not impact other beneficial components of the vaginal microflora such as lactobacilli. Although it may be desirable to have microbicides with activity against all common bacterial STDs including *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, herpes, and HIV, it is unlikely that any single microbicide agent will be effective against the full range of sexually transmitted organisms.

Assessment of the impact of any vaginal product being developed is now a standard part of the initial safety evaluation for new barrier and microbicide products. BufferGel is a product being developed as both a topical microbicide and as a contraceptive. It was evaluated in a study in which women used the product once or twice daily for 14 days.¹²¹ Assessment of the flora was conducted prior to use of the product and after 14 days of gel exposure. There was no impact of this product on the frequency of lactobacilli, but there was a marked reduction in the prevalence of several

acid-sensitive organisms including *G. vaginalis* and the anaerobic gram-positive cocci and gram-negative rods associated with BV. However, there was a statistically significant increase in colonization by *E. coli* and other facultative gram-negative rods, which was also observed among women using N-9.⁹⁴ Because this agent is an acidifier rather than a surfactant like N-9, it is likely that the perturbation of flora and increase in *E. coli* is related to the insertion of the gel or disruption of innate immunity.

ASSOCIATION BETWEEN THE VAGINAL MICROFLORA AND STDs

In addition to playing a role in determining whether microbial flora are conducive to the development of BV, H₂O₂-producing lactobacilli may also confer protection upon exposure to sexually transmitted disease. The concept that the vaginal microflora plays a role in resistance to gonorrhea was investigated widely in the 1970s.^{122–124} Kraus and Ellison speculated that the urethral flora of the male might protect against acquisition of gonorrhea.¹²² In vitro studies showed that *gonorrhoeae* could be inhibited by some components of the normal microflora including staphylococci and diphtheroids.¹²³ Studies of female sex contacts of infected males suggested protection might be afforded by vaginal colonization by lactobacilli.¹²⁴ Presence of H₂O₂-producing lactobacilli was associated with decreased prevalence of *trachomatis*, *vaginalis*, and symptomatic *Candida*.⁴⁵ A larger study from the Vaginal Infections and Prematurity cohort of pregnant women found that the prevalence of *gonorrhoeae*, *trachomatis*, and *vaginalis* was significantly lower in women with predominant vaginal lactobacilli compared to women with reduced or no lactobacilli.¹²⁵ In a large cross-sectional study of rural Ugandan women, similar trends were found.²

Little is understood about how lactobacilli prevent these infections. However, H₂O₂-producing lactobacilli directly

inhibit the growth and catalase activity of *gonorrhoeae* by producing a combination of acid, peroxide, and protein inhibitor of catalase activity.⁴⁵ A longitudinal study of sex workers in Kenya demonstrated a twofold-decreased incidence of gonorrhea acquisition among women vaginally colonized by lactobacilli.

RELATIONSHIP BETWEEN THE VAGINAL ECOSYSTEM AND VIRAL STIs

The relationship between the vaginal microbial flora and susceptibility to viral STIs is summarized in [Table 18-7](#). Alterations in vaginal flora have been linked to an increased risk of HSV-2 in two studies.^{5,6} Chernes et al. screened 1207 women aged 18–30 years for HSV-2 antibody, and after excluding HSV-2 seropositive women, followed the remaining women quarterly for a year. There were 32 acquisitions of HSV-2 over 628 women-years of follow-up, for an incidence rate of 5 per 100 women-years. Women with BV by Gram stain had a twofold-increased risk of HSV-2 (HR 2.1, 95% CI 1.0–4.5, *P* = 0.05) after adjustment for education and having a new sexual partner.⁵ BV was confirmed as a risk factor for acquisition of HSV-2 in a study by Gottlieb et al. which included 946 women attending STD clinics. These investigators estimated that the population attributable risk of BV for HSV-2 acquisition was 21%.⁵ Chernes et al. also documented an increase in HSV-2 shedding among women lacking a *Lactobacillus*-predominant flora.⁵

Only a single study evaluated the impact of vaginal microflora on the acquisition and persistence of HPV.⁷ A total of 1763 HIV+ and 493 HIV– women were evaluated for genital infections, including testing for 43 types of HPV in cervicovaginal lavage semiannually. Women with a Nugent intermediate (OR 1.2, 95% CI 1.1–1.4) or BV score (OR 1.4, 95% CI 1.3–1.6) were at increased risk of incident HPV infection. However, vaginal microflora was not associated with persistence of HPV.⁷

Table 18-7. Longitudinal Studies of Altered Vaginal Flora and Risk of Viral Sexually Transmitted Infections

Pathogen	Author, Year	Number of Women	Reference	OR or HR (95% CI)
HSV	Chernes, 2003 ⁵	670	5	2.1 (1.0–4.5)
	Gottlieb, 2004 ⁶	946	6	1.9 (1.1–3.5)
HIV	Taha, 1998 ²	1196	2	3.0 (1.2–7.6)
	Martin, 1999 ³	657	3	2.0 (1.2–3.5)
	Myer, 2005 ⁴	5110	4	2.0 (1.1–3.6)
HPV	Watts, 2005 ⁷	2256	7	1.4 (1.3–1.6)

Longitudinal studies have linked vaginal ecology to HIV acquisition. Taha et al. followed a group of 1196 pregnant women in Blantyre, Malawi, through delivery.² Alterations in vaginal ecology were assessed by measurement of vaginal pH, discharge, and amine odor. There was a dose-related increase in HIV risk associated with alterations of the vaginal flora. Martin et al. followed a group of sex workers enrolled in Mombasa, Kenya, and conducted monthly evaluations for HIV and vaginal lactobacilli.³ He demonstrated that the absence of vaginal lactobacilli was associated with a twofold-increased risk of HIV acquisition. A third study from Cape Town, South Africa, assessed risk factors for acquisition of HIV in 5110 women enrolled in a cervical cancer trial. Eighty-six women who acquired HIV infection were matched in a nested case-control design to 324 women who did not acquire HIV during follow-up.⁴ Compared to women having a Nugent score of 0–3, women having intermediate flora had a modestly increased risk of HIV (OR 1.5, 95% CI 0.6–4.3), while women having a Nugent score of seven or greater had a twofold-increased risk of HIV (OR 2.0, 95% CI 1.1–3.6).⁴

These studies suggest that there is a strong interaction between the health of the vaginal ecosystem and susceptibility to viral STIs. Some possible biologic explanations for these associations include the impact of lower pH on viral transmission, the effect of vaginal microbes on the mucin gel, which coats and protects the epithelium, and the proinflammatory environment of the cervix when BV is present. Some probiotic approaches using lactobacilli that bind to HIV have been proposed as one approach to address the increased risk of HIV observed in women lacking lactobacilli.^{59–62}

These longitudinal studies showed a consistent link between increased incidence of HIV, HSV-2 and HPV and altered vaginal microflora. Additional studies will be needed to confirm the relationship between an altered vaginal microflora and acquisition of viral STIs. In addition, studies are urgently needed to better identify the biologic basis explaining why women with an altered vaginal system are at increased risk of HIV. Because the vaginal microflora is also impacted by sexual behavior and contraceptive use, it is critical that vaginal microflora be evaluated in ongoing studies of HIV risk associated with microbicides use, contraceptives, and behavior.

NORMAL VAGINAL ECOLOGY OF PREGNANCY

The vaginal ecology of pregnant women does not differ substantially from that of nonpregnant women. Studies have established that some organisms considered to be part of the normal vaginal microflora are associated with an increased risk of preterm and/or low birth weight delivery when they are present at high-density concentrations in the vaginal fluid. Both group B *Streptococcus*¹²⁸ and *E. coli*^{129,130} have been linked with preterm and/or low birth weight delivery,

and are known to directly invade the chorioamnion and cause chorioamnionitis.¹³¹ Other vaginal microorganisms which are part of the normal flora, including those associated with BV, have been linked to an increased risk of preterm birth, amniotic fluid infection, and chorioamnionitis, as discussed. In contrast, high-density vaginal colonization by *Lactobacillus* species has been linked with a decreased risk of most adverse outcomes of pregnancy.^{132–136} Thus, the constituents of the normal vaginal ecosystem play a role in establishing the risks of preterm and/or low birth weight delivery, amnionitis, chorioamnionitis, and postpartum infections during pregnancy. Data derived from a cohort of pregnant women evaluated at three time points (23–26, 30–33, and 34–36 weeks' gestation) has shown that the frequency of lactobacilli remains relatively constant over the second and third trimesters of pregnancy.¹²⁵

Ethnicity has been reported to have an impact on the vaginal microflora of pregnant women. In a large study of pregnant women, it was found that black women were more likely to be colonized by group B *Streptococcus*, anaerobic gram-negative rods, *hominis*, and *urealyticum* as compared with white or Hispanic women.¹³⁷ Black women were also significantly more likely to have BV, *vaginalis*, *trachomatis*, and *gonorrhoeae* compared to white women. In contrast, Hispanic women were more likely than white women to be colonized by group B *Streptococcus*, but were otherwise very similar to white women with respect to the frequency of genital microorganisms. Asian women had comparatively lower frequency of all genital pathogens, and had significantly less *urealyticum* compared to white women.¹³⁷

In a smaller study from Great Britain, African and Caribbean women were found to have higher levels of abnormal vaginal flora and BV compared to white women, while Asian women were found to have lower frequencies of BV and abnormal vaginal flora than white women.¹³⁴ It has been noted that when black women and white women of similar incomes are compared, there is still a twofold or greater discrepancy in the rate of preterm delivery among black women.¹³⁷ Hispanic women, on the other hand, have one of the lowest rates of low birth weight in the United States, even though the Hispanic women included in studies have usually had modest income levels. Some authors have postulated that the disparity of preterm low birth weight among black women versus white women may relate to the substantial ethnic differences in the rates of genital tract infections, which may lead to preterm birth.¹³⁷

As noted above, sexual activity is thought to have an impact on the vaginal ecosystem. Frequency of sexual intercourse during pregnancy was evaluated in the Vaginal Infections and Prematurity Study.¹³⁸ Women were interviewed at 23–26 weeks' gestation, at two time periods in the third trimester and again at delivery. Not surprisingly, 61% of the pregnant women reported having vaginal intercourse one or more times weekly

in the second trimester of pregnancy while only 28% of women reported this frequency of intercourse in the last month of pregnancy. Women positive for *vaginalis* or *hominis* who engaged in frequent sexual intercourse during pregnancy were at higher risk of preterm delivery, compared to women colonized by these organisms who did not have frequent intercourse. The authors speculated that frequent sexual intercourse may introduce organisms from the vagina into the cervix, which could begin the process of upper tract infection leading to preterm birth. What emerged from this study was that intercourse itself was not a risk factor for preterm birth, but rather frequent intercourse among women with certain lower genital tract infections.

While many constituents of the normal flora have been linked with adverse outcomes of pregnancy, this is a substantial body of data, which suggests that vaginal colonization by lactobacilli may protect against adverse outcomes of pregnancy.^{136,139,140}

In one study conducted in Great Britain, it was reported that women having *Lactobacillus*-predominant vaginal flora had a rate of pregnancy loss between 16 and 24 weeks' gestation of only 1%, compared to a 5% incidence amongst those with reduced lactobacilli, and an incidence of pregnancy loss of 7% in those women lacking vaginal lactobacilli.¹³⁴ A follow-up cross-sectional study compared the history of second trimester pregnancy loss among women with *Lactobacillus*-predominant flora, women with reduced lactobacilli, and BV. Women with *Lactobacillus*-predominant vaginal flora were significantly less likely to have a history of a second trimester pregnancy loss compared to women with reduced or no lactobacilli detected by direct Gram stain.¹⁴¹ In the Vaginal Infections and Prematurity Study, women with *Lactobacillus* detected by culture or by vaginal Gram stain were significantly less likely to deliver preterm and low birth weight.¹³²

The mechanism by which lactobacilli could protect against adverse outcomes of pregnancy probably relate to their effect against other genital pathogens including those associated with BV. Many women treated for BV do not become recolonized with *Lactobacillus*, which produce hydrogen peroxide.¹¹⁷⁻¹¹⁹ Thus, additional strategies for reconstituting the vaginal microflora of women following treatment of BV are needed in order to prevent these adverse outcomes of pregnancy.

MICROBIAL INTERACTIONS IN THE VAGINAL ECOSYSTEM

The complex nature of the microbial interactions in the vaginal ecosystem have often been studied but little understood. Perhaps the most frequently discussed example of this misunderstanding relates to the perception that vaginal lactobacilli decrease yeast vaginitis. While some suggest in vitro studies that *albicans* is inhibited by culture supernatants of *acidophilus*,¹⁴² others have reported no inhibition of yeast by

lactobacilli.⁷² Further, H₂O₂-produced by lactobacilli in combination with myeloperoxidase also have antifungal effects.¹⁴³ *Acidophilus* in various forms have been used to treat yeast vaginitis.¹⁴⁴ Some investigators have gone so far as to suggest that ingestion of yogurt containing *acidophilus* prevents recurrent *Candida* vaginitis.¹⁴⁵ Nevertheless, clinical studies of women with acute recurrent vulvovaginitis have demonstrated that women who have recurrent yeast vaginitis have the same frequency and concentration of *Lactobacillus* as women without recurrent infections.¹⁴⁶ Hawes et al. in their longitudinal study of vaginal infections showed that women who were vaginally colonized by lactobacilli had a somewhat increased risk of acquisition of yeast vaginitis compared to women without lactobacilli.¹⁴⁶ Nevertheless, many women who seek medical care for chronic vaginal symptoms report using *Lactobacillus*-containing products orally or vaginally to restore the vaginal microflora in the mistaken belief that this will prevent recurrent vaginitis.¹⁴⁷ Well-controlled trials have failed to document any decrease in vaginal candidiasis whether orally or vaginally applied preparations of lactobacilli are used by women.¹⁴⁸

Microbial interactions in the vagina probably are much more complex than have been appreciated in the past. For example, Pybus and Onderdonk recently published data establishing that there is a commensal, symbiotic relationship between *vaginalis* and *P. bivia* involving ammonia.¹⁴⁹ *Vaginalis* produces amino acids, which are in turn utilized by *bivia*. *Bivia* produces ammonia, which stimulates the growth of *vaginalis*. The symbiosis between *bivia* and *vaginalis* may explain the increased frequency of these organisms in BV and the fact that they appear to increase in concert among women with abnormal vaginal flora.

Another example of microbial interactions in the vagina comes from Sturm, who described the inhibition of the chemotactic response by granulocytes by obligate anaerobes.¹⁴⁷ Coincubation of *G. vaginalis* with *Mobiluncus mulieris* or *Bacteroides ureolyticus* significantly reduced the chemotactic response of granulocytes compared to *G. vaginalis* alone. Culture filtrates of *Prophyromonas asaccharolytica* similarly decreased the chemotactic response of granulocytes to both *G. vaginalis* and *E. coli*.¹⁵⁰ These data were interpreted as showing that the presence of succinate-producing anaerobes in the vagina could inhibit chemotaxis of white blood cells, which may play a role in inhibiting the immune response to these pathogens.

Vaginalis produces a number of cysteine proteases, which are thought to play an important role in the virulence of this protozoan.¹⁵¹ The cysteine proteases must be activated by disulphide-reducing reagents in order to be functional. Alderete evaluated the vaginal washes from 48 patients and found vaginal fluid has a reducing environment adequate for activation for trichomonad proteases. Importantly, H₂O₂ reversibly neutralizes these trichomonad proteases.

This suggests that *vaginalis* may be carried as a commensal among women with H₂O₂-producing *Lactobacillus* because of its inability to express its primary virulence determinant. This is possible only if sufficient amount of H₂O₂ is produced, but this observation does raise other questions. For example, could the increased prevalence of trichomoniasis in African American women be related to a greater reducing level (higher pH) in the vaginal fluid, perhaps due to lower levels of lactobacilli?

Another manner in which vaginal microorganisms may interact is through their adherence to vaginal epithelial cells or their competition with other organism for attachment sites. Vaginal strains of *Lactobacillus* from healthy premenopausal women were shown to self-aggregate and adhere to vaginal epithelial cells, displacing other vaginal pathogens such as *vaginalis*.¹⁵² The surface components of lactobacilli involved in self-aggregation appear to be proteins for *gasseri* and lipoproteins for *acidophilus* and *L. jensenii*. The vaginal epithelial cell receptors for lactobacilli apparently are glycolipids, which act as the targets for the competition between lactobacilli and other pathogenic microbes.¹⁵² It is possible that lactobacilli in the vagina may protect the vaginal epithelium by self-aggregating and adhering to vaginal epithelial cells, or by interfering with colonization through binding of common receptors to those of potential pathogens. Binding of *L. crispatus* to vaginal epithelial cells was increased in women with a history of urinary tract infection ($P = 0.04$) and a nonsecretor phenotype ($P < 0.001$).¹⁵³ These data suggest there may be a complex interaction between the normal vaginal flora, pathogen, and host genotype. Efforts are underway to develop probiotic products containing lactobacilli for use in colonization of the vagina for prevention of disease.^{154, 155} As summarized in Chapter 42, use of probiotic products for treatment of BV has met with limited success. The development of a successful probiotic for use in “normalizing” the vaginal microflora will require careful strain selection and a better understanding of the factors, which permit colonization of the vaginal ecosystem by various lactobacilli.

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Pathogenesis of Sexually Transmitted Viral and Bacterial Infections

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INTRODUCTION

Viruses and bacteria represent fundamentally different life forms. Although, like viruses, many bacterial species are obligate intracellular parasites, bacterial cells generally contain most if not all of the elements of an energy-generating system required for life (chlamydia are an exception). Viruses, on the other hand, derive their energy sources exclusively from those available within the host cell. Thus, viruses are typically much smaller and biochemically much simpler pathogens. Unlike bacteria, viruses generally contain only a single species of nucleic acid, either RNA or DNA, and follow biochemical processes of transcription and translation that are based on eucaryotic biology. Thus, viruses and bacteria differ fundamentally in their strategies for multiplication. Viruses dissociate into their constituent biochemical components following entry into host cells, then reassemble after replication of their genomes and expression of their protein components. Bacteria maintain their integrity throughout the multiplication cycle, even if they are obligate intracellular parasites.

Despite these basic differences in their biology, pathogenic viruses and bacteria have evolved remarkably similar strategies for invasion of and persistence within their human hosts. These common strategies include general mechanisms by which pathogens attach to and enter specific host cell types, cause disease, and attempt to evade host immune responses.

The production of disease by invading bacteria or viruses results ultimately from the tendency of these infectious agents to evolve toward species with enhanced capacity for survival within human populations. However, whether disease occurs or not is irrelevant to the infectious agent as long as its capacity to spread and persist among humans is maximized. This overriding Darwinian principle applies to all infectious agents and has resulted in many different microbial survival strategies. Some infectious agents have evolved strategies that maximize their replication within the infected host, such that large quantities of virus or bacteria may be shed and result in new human infections. Good examples of such pathogens are influenza virus and HIV, as well as the

bacterium *Neisseria gonorrhoea*, although in the case of HIV much of the released virus may remain cell-associated. However, many infectious agents have evolved strategies that result in long-term colonization or persistence of infection, usually with lesser quantities of virus or bacteria present within secretions or shed into the environment. Long-term persistence results in repetitive opportunities for transmission of the agent between individuals, ensuring its survival within human populations. Examples include HIV, herpes simplex virus (HSV) and human papilloma virus infections, and *Treponema pallidum*, the bacterial cause of syphilis. Such persistence is typically dependent upon the ability of the pathogen to evade innate and adaptive immune responses either by stealth, deception, or active disruption of host responses. Thus, the ability to establish persistent infection is a common and important determinant of the pathogenicity of many bacteria and viruses. This is particularly true for sexually transmitted pathogens.

CELLULAR ATTACHMENT AND ENTRY

Cellular attachment and penetration represent the first two steps in the replication cycle of any virus. Similarly, virtually all bacteria must attach to cells to cause infection. Attachment is generally achieved through a highly specific interaction between surface features of the infectious virion or bacterium and one or more molecules expressed on the cell surface that represent the cellular receptor or accessory coreceptor molecules. In the case of viruses, binding to the cellular receptor molecule brings the virion into close proximity with the cell surface, while secondary interactions with coreceptors are often required to facilitate penetration of the cell by the virus. In the absence of either receptor or coreceptor, there is no infection. These interactions are important determinants of the pathogenicity of individual viruses and bacteria, as they often play an important role in determining cellular tropisms and host range.

The human immunodeficiency virus type 1 (HIV-1) represents a good example of such specific interactions among

sexually transmitted viruses. HIV-1 usually initiates infection of certain lymphocyte subsets, monocytes, and macrophages via binding of its surface envelope glycoprotein (env) with the cellular CD4 molecule. Although this interaction is generally necessary for infection of a cell by HIV-1, it is not sufficient, as further interactions between the virus and additional surface molecules (coreceptors) are essential for viral entry.^{1,2} T-cell adapted laboratory strains of HIV-1 require a seven-transmembrane, G protein-coupled receptor, fusin or CXCR4, to mediate penetration. Fusin enables the env protein of HIV-1 to mediate cell fusion, and in CD4-negative cells it can also serve as a primary receptor for these strains of HIV-1. In the case of nonsyncytium-inducing virus strains that have a predilection to infect monocyte/macrophages, the viral coreceptor is the cellular beta chemokine receptor, CCR5. These molecular interactions have important clinical consequences. Caucasian individuals who are homozygous for a 32-basepair deletion that abrogates expression of functional CCR5 appear to be resistant to infection with macrophage-tropic or dual-tropic strains of HIV-1.³ This mutant allele is present with a high frequency in Caucasian populations but absent in the black populations of Western and Central Africa. Population-based studies have also shown that the frequency of heterozygotes is 35% lower among HIV-1 infected persons than in the general population, suggesting that persons with a single mutant allele have quantitatively lower expression of CCR5 leading to relative resistance against the infection. In recent years, knowledge of the specific intramolecular interactions involved in virus entry has been exploited in the development of effective small molecule inhibitors that have proven to be useful for antiviral therapy in HIV-infected persons.⁴

There are numerous other examples where specific interactions of viruses with their receptors and accessory coreceptor molecules play an important role in defining the host range and thus pathogenicity of viruses. For many viruses, however, the identity of cellular receptor is not known. In other cases, the cellular receptor may be expressed in a ubiquitous fashion, and therefore plays little or no role in determining the types of cells that can be infected with the virus. This may be the case with human cytomegalovirus, as its surface glycoprotein B is capable of interacting with surface heparin sulfate proteoglycans from a wide variety of cell types.⁵ Similarly, HSV is able to infect a wide variety of different cell types. The envelope glycoprotein D of HSV (gD) binds to no less than three different receptor molecules: the herpes virus entry-mediator molecule (HVEM) which is a member of the tumor necrosis factor receptor family, nectin-1 which is a cell adhesion molecule in the immunoglobulin superfamily, and a modified heparan sulfate.⁶ The expression of HVEM-1 in Chinese hamster ovary cells (one of few cell types resistant to HSV penetration and infection) renders these cells permissive for infection.⁷ The interaction of gD

with these receptor molecules leads to conformational alterations of multiple viral envelope glycoproteins, activating the fusogenic properties of the virus and causing the fusion of viral and cellular membranes.⁸

In the case of sexually transmitted bacteria, tissue and species tropisms are also determined, at least in part, by the specificity of interactions between attachment ligands and host receptors, and use of multiple binding ligands and specific receptors also is a common strategy. For example, gonococcal pili initiate attachment but the appropriate receptor is found only on human cells.⁹ The receptor for binding pili has been thought to be CD46,¹⁰ but this is now unclear. Gonococci also use opacity (Opa) proteins and probably Lipooligosaccharide (LOS) to bind tightly to host cells (see Chapter 34). Indeed there are multiple forms of the Opa proteins and individual Opa bind to quite different receptors, either in the glycosaminoglycan family or CEACAM family.¹¹ Binding by other ligand-receptor systems may convert initial loose binding mediated by pili to tightly adherent binding, and promote cellular invasion. Other gonococcal adhesins include the porin protein, which binds the CR3 receptor on cells from the female genital tract,¹² and LOS, which binds the asialoglycoprotein receptor on epithelial cells.¹³ High-frequency phase and antigenic variation of attachment ligands may prepare the bacterium for attachment to different cells (which may have different receptor specificities), both on different organs in the same person, and on the same tissues in different persons. At least, this is the inferred basis for the very rapid (1–2 days) *in vivo* selection of different pili and opacity proteins that has been noted during experimental gonococcal infection of male volunteers.^{14,15} These variants emerge too quickly for *de novo* immune responses to select such variants.

Many bacteria also invade host epithelial cells. Such bacteria include supposedly extracellular pathogens such as the gonococcus.^{16,17} Others apparently do not invade cells but slip between cells during systemic infection. *T. pallidum* is an example of the latter. Mechanisms are unclear in both pathogens, especially *T. pallidum*. There are several coordinated steps involved in invasion of epithelial cells by gonococci, including expression of a particular Opa variant; a switch from the piliated to a nonpiliated state and a switch from a sialylated LOS to nonsialylated LOS.^{16,18} With the apparent assistance of porin protein, the epithelial cell membrane is functionally penetrated, and at least a measure of intracellular growth ensues before gonococci egress from the basal surface, gaining access to the subepithelial space and to the bloodstream.¹⁷

OTHER DETERMINANTS OF TISSUE TROPISM

In addition to specific receptor interactions, other features of cellular physiology may define the host range and tropisms of

viruses as well as bacteria. Although they are known to exist, in many cases, the specific nature of these cellular “host factors” remain poorly defined. In the case of DNA viruses, it is likely that in many cases such host factors are differentiation-specific cellular transcription factors. This is where the general dependence of viruses on eucaryotic regulatory mechanisms becomes very important, as viruses utilize tissue-specific promoter-enhancer elements and may also express proteins capable of modulating the activity of cellular transcription factors.^{19,20} For example, human papillomaviruses (HPVs) replicate only within suprabasal cells of the epithelium. These viruses cannot be propagated in conventional cell cultures, reflecting the absence of differentiated cellular function(s) required for their replication. In vivo, the expression of RNA transcripts from the DNA genomes of HPV type 16 and 18 (HPV16 and HPV18) is generally restricted to differentiated suprabasal cells, and there is little evidence that these DNAs are transcriptionally active within undifferentiated basal cells. This distribution matches the tissue distribution of the differentiation-specific transcriptional activator Epc-1/Skn-1a. This transactivator specifically stimulates the E6/E7 promoters of multiple HPVs.^{19,21} This positive interplay between differentiation-dependent, epidermis-specific transactivators and viral enhancer elements is likely to play an important role in restricting the replication of HPVs to differentiated epithelial cells. In turn, through interactions of the HPV E6 and E7 proteins with p53 and retinoblastoma protein (pRb), respectively, papillomavirus infection disrupts normal cell cycle controls, driving cellular proliferation and promoting a cellular environment favorable for replication of the virus.²²

Similarly, the liver-specific tropism of human hepatitis B virus (HBV) may be related at least in part to a requirement for liver-specific transcriptional transactivators. Candidate transcriptional factors include hepatic nuclear factor 3 (hnf-3) and the CCAAT/enhancer binding protein (C/EBP). These have been shown to bind to, and in the case of C/EBP transactivate, the HBV enhancer element.^{23,24} In the case of HBV, however, it is likely that other factors, including possibly cellular receptor interactions, also play roles in restricting the replication of the virus, since the HBV enhancer element is very active in rat hepatoma cells that do not otherwise support replication of the virus.²⁵ Liver cells do not maintain their differentiated functions for long periods in tissue culture systems; this likely explains why HBV cannot be grown in any type of continuous cell culture in vitro. However, HBV proteins are also capable of modulating the intracellular environment by manipulating the activity of cellular transcriptional factors and transcriptional coactivators. Recent work suggests, for example, that the HBx protein functionally interacts with the coactivators CPB/300 to modulate the activity of the transcription factor CREB.²⁶ Hepatitis C virus (HCV) is also highly hepatotropic. Unlike HBV and HPV,

however, HCV is a positive-strand RNA virus that does not replicate its genome via a DNA intermediate (see Chapter 29). Nonetheless, HCV infection stimulates the activity of cellular E2F promoters by downregulating the abundance of the retinoblastoma protein, using a strategy with numerous parallels to that adopted by HPVs to promote the proliferation of epithelial cells.²⁷ The upregulation of E2F transcription factors activity by HCV promotes hepatocellular proliferation, both favoring replication of the virus and possibly promoting hepatocellular carcinogenesis. A number of other interactions of HCV proteins with host cell factors have been shown to be required for HCV entry or RNA replication, but the specific factors restricting replication of the virus to the liver remain unknown.

Some bacterial cell tropisms may have similar underlying mechanisms. *Haemophilus ducreyi* were found to grow preferentially in the deepest cell layers of the subepithelial dermis. In addition, chlamydia are requisite intracellular pathogens because they cannot synthesize their own ATP. As a consequence, they have evolved to scavenge intracellular mitochondrial supplies of ATP. Although there is no evidence that chlamydial tissue tropisms are driven by cellular differences in availability of energy, it is possible that this may contribute to the apparent preference of chlamydia for mucosal epithelium.

MECHANISMS OF DISEASE PRODUCTION

■ DIRECT VERSUS IMMUNOPATHOLOGIC EFFECTS ON THE INTEGRITY OF TISSUES

At the simplest level, infection of a cell by a virus or bacterium may lead to cell death. In the case of viruses, specific disease syndromes may be caused by destruction of certain subsets of cells that express essential differentiated functions. A classic example of this is the development of the AIDS following HIV-1 mediated depletion of the CD4 lymphocyte population. Virus-induced cell death may result from one or more specific mechanisms. Many viruses express specific proteins that have as their major function the induction of a blockade in normal host cell metabolism (cellular translation and transcription) such that the metabolic machinery of the cell is subverted preferentially to viral replication. For obvious reasons, the expression of such proteins is usually highly toxic to the cell. Cellular destruction or “direct cytopathic effect” is considered responsible for the disease manifestations of many lytic viruses, including, for example, HSV and poliovirus. On the other hand, many cells may respond to the presence of an invading virus by the induction of apoptosis and the initiation of programmed cell death. Some viruses appear to have evolved mechanisms to prevent or delay apoptosis, thus potentially prolonging productive infection and maximizing replication. For example, HSV-1 infection

induces apoptosis at multiple metabolic checkpoints but has also evolved mechanisms to block apoptosis at each point.²⁸ Importantly, the inhibition of apoptosis by HSV-1 also prevents apoptosis induced by virus-specific cytotoxic T lymphocytes, thereby conferring on the infected cell a certain measure of resistance to the host's cell-mediated immune responses.²⁹

However, many viruses are not intrinsically cytopathic. HBV is a prime example, as many infected HBsAg carriers are asymptomatic and without overt evidence of active liver disease. Despite this, such carriers may be very infectious, with a high titer of virus in their blood, semen, saliva, and genital secretions (see Chapter 29). The presence or absence of liver disease is largely determined by the T-cell response to the virus.³⁰ Thus, chronic hepatitis B results from a relatively vigorous but unsuccessful attempt on the part of the host to eliminate the infection. Human leukocyte antigen (HLA)-restricted, CD8-positive T lymphocyte responses play a critical role in this process, initiating an inflammatory cascade that involves the elaboration of soluble cytokines, including interferon- γ , and the recruitment of other types of inflammatory cells to the liver. In some instances, this immunologic response ultimately results in elimination of the infection, perhaps largely as the result of soluble factors secreted by immune cells rather than T cell-killing of infected cells.³¹ However, in many HBsAg carriers, these responses result in the immune destruction of hepatocytes and the activation of stellate cells that produce an abnormal matrix, the hallmark of cirrhosis. Oxidative stress accompanies this process and may lead to mutations in cellular DNA resulting in the malignant transformation of hepatocytes.³² Thus, chronic liver inflammation and the occurrence of hepatocellular carcinoma reflect the immune response to the virus, rather than specific virus effects. Similar indirect mechanisms may contribute to the progressive immune destruction of infected CD4-positive lymphocytes in patients with HIV-1 infection.

Some bacterial disease processes may also be caused largely to immunopathologic responses. For instance, there is substantial evidence that complications of genital chlamydia infections (salpingitis, Reiter's syndrome) are correlated with and may be owing to stimulation of antibodies against a heat-shock protein (hsp60).^{33,34} In principle, such antibodies can cross-react with human homologs, which are antigenically similar to chlamydia hsp60. Further evidence for an immune mechanism underlying tissue damage in chlamydia infections is the association of salpingitis with particular HLA haplotypes in primates and women.^{35,36} Pathology associated with *T. pallidum* infections may also be owing to immune mechanisms. The paucity of organisms in spinal cord samples from patients with tabes dorsalis suggests a possible immunopathogenic process. In experimental inoculations of humans, gummas occurred only in those subjects who had a history of earlier syphilis, strongly suggesting that

hypersensitivity contributed to the development of the granulomatous lesions.³⁷

In contrast, gonococcal tissue damage appears to be caused by the direct toxic effects of lipid A and peptidoglycan fragments, although each of these endotoxins triggers a complex cascade of inflammatory mediators, including cytokines, which are integral to normal host immune defenses such as interleukin-1, tumor necrosis factor (TNF), and others.^{38,39} Recent evidence shows that gonococci activate the inflammatory complex in macrophages, inducing cell necrosis and death, which may contribute to tissue damage in complicated gonococcal infection (personal communication JA Duncan and J Ting, 2007). Cytokines and chemokines may also play important roles in viral infections. For example, the HSV-1 envelope glycoprotein gD inhibits the interaction of LIGHT, a member of the TNF family and an important regulator of dendritic cell function, with its receptor, HVEM.^{7,40} While LIGHT may interfere with the ability of HVEM to act as a cellular receptor for HSV-1, thus inhibiting HSV replication, the binding of gD to HVEM may alter normal downstream signaling processes leading to dendritic cell maturation and possibly promote immune evasion.⁴¹ The replication of HIV is also significantly influenced by a complex network of inhibitory and stimulatory cytokines and chemokines, at least in part by modulating the availability of the HIV coreceptors, CCR5 and CXCR4.⁴² Macrophage-tropic strains of HIV-1 induce a signal when the HIV env glycoprotein binds to the CCR5 chemokine receptor.⁴³ This signal may promote the replication of the virus by activating the infected cell, increasing the number of infected cells by inducing chemotaxis of activated CD4-positive cells to the site of virus replication. At the same time, recent evidence suggests that NS5A protein expressed by GBV-C virus induces release of the chemokine SDF-1, downregulating surface expression of CXCR4, and potently inhibiting HIV-1 replication.⁴⁴

■ PRODUCTION OF TOXINS BY BACTERIA AND VIRUSES

Despite similarities in mechanisms of disease production by viruses and bacteria, there are important differences. The elaboration of extracellular toxins plays an important role in the pathogenesis of many bacterial infections, both purulent and nonpurulent. *H. ducreyi* is a prime example, since it produces two cytotoxins, which probably are crucial to the tissue-destructive, ulcer-generating pathology that characterizes chancroid.^{45,46} In contrast, virus infections generally have not been associated with production of specific toxins. Recently, however, the nonstructural glycoprotein 4 (NSP4) of rotavirus has been shown to induce diarrhea in mice in an age- and dose-dependent fashion.⁴⁷ Rotavirus NSP4 enhances chloride secretion through a calcium-dependent signal transduction pathway, and thus it acts as a true

enterotoxin. In addition, the envelope protein of Ebola virus, a filovirus, has been suggested to be a major determinant of the enhanced vascular permeability that characterizes Ebola fever.⁴⁸

■ ALTERED CELLULAR GROWTH AND DIFFERENTIATION

Some viruses are capable of altering differentiated cellular functions, resulting in the production of disease by mechanisms that do not exist among bacteria. A prime example is the altered cellular growth that follows infections by molluscum contagiosum virus (MCV), leading to the distinctive cutaneous lesions of molluscum. A more extreme example is the proliferation of epithelial cells that is induced by infection with HPVs. HPV-related epithelial malignancies and cellular transformation are related to the expression of two specific HPV proteins, the E6 and E7 oncoproteins, by high-risk HPV subtypes.²² These proteins interact with p53 and pRb, both promoting cellular proliferation and cell survival. Oncogenic transformation is usually associated with high-level expression of E7 from integrated HPV DNA. The Kaposi's sarcoma-associated herpes virus (KSHV) also expresses a number of proteins that mimic important host regulators of cellular proliferation and survival, including virally encoded bcl-2, interleukin 6, cyclin D, and G-protein-coupled receptor.^{49,50} Expression of these proteins may result in deregulation of cell growth, with changes in the cellular morphology and/or acquisition of the ability of the cells to form colonies in soft agar, changes that are indicative of transformation.

On the other hand, hepatocellular cancers occurring in the context of chronic viral hepatitis are likely to have an alternative explanation. Although it is possible that integration of HBV DNA may be responsible for altered cellular growth control in some hepatitis B-associated cases, liver cancer in this setting may be primarily immunopathogenic.^{30,32} Chronic inflammation accompanied by oxidative stress and cellular DNA damage are likely to play important roles. This may also be the case with hepatitis C-associated liver cancer although, as mentioned above, HCV appears to have evolved mechanisms similar to those of the HPVs that downregulate pRb abundance and promote cellular proliferation.²⁷ Because it is an RNA virus without the capacity for reverse transcription of its genome to DNA, HCV is incapable of integrating any of its genomic sequences into host chromosomes. Nonetheless, infection with this virus is increasingly associated with the occurrence of hepatocellular carcinoma, which is typically fatal. Evidence suggests that HCV may modulate the activity of several tumor suppressor proteins, p53, DDX3, and DDX5, as well as pRb, in order to promote cellular proliferation and enhance its replication. Altered p53 and pRb activities in HPV-infected cells may cause malfunctioning of critically important cell cycle checkpoints.⁵¹ It is possible that similar effects on p53 and pRb associated with HCV

infection may allow hepatocytes with damaged chromosomal DNA to survive and even proliferate. Such a model readily explains the synergy noted clinically between HCV infection and alcohol ingestion in promoting hepatocellular carcinogenesis.

MECHANISMS OF IMMUNE EVASION

Persistence of an infecting agent almost always involves a mechanism to evade or otherwise foil both innate and adaptive host immune responses. In the case of viruses, this involves four general strategies: latency, stealth, active disruption of immune responses, and antigenic variation. Bacteria use fundamentally similar strategies, with the exception of latency that, strictly defined, is specific to viruses.

■ VIRAL LATENCY

The induction of latent infection by herpes viruses such as HSV represents a uniquely effective mechanism of evading the host immune response. During latent infection only a very small number of viral proteins are actively expressed, providing few targets for the immune system.⁵² Major structural antigens of the virus are not synthesized, and there is no production of infectious virus. There is no cytopathic effect, and the viral genome is maintained through cell divisions largely by the cellular metabolic machinery. However, latency is periodically reversed, with reactivation of the infection leading to the production of infectious virions. Thus, latent infections clearly contribute to the overall survival of herpes viruses within human populations. This general strategy is not available to bacteria (and most other types of viruses) because of fundamental differences in replication strategies.

However, certain bacteria can persist for prolonged periods with little evident replication: mycobacteria are one example and *T. pallidum* may be another. *T. pallidum* can be reactivated by corticosteroid therapy after a long period of dormancy in rabbits, and a similar phenomenon may underlie the long periods in which there is no disease activity (clinical "latency") before the onset of late syphilis. While not meeting the strict definition of latency as applied to the herpes viruses, there is some evidence that chlamydia can persist in eukaryotic cells without overt replication and release of infectious particles. Unlike latent viral infection, however, there is little evidence that such latency of chlamydia is clinically important.

■ EVASION AND DISRUPTION OF INNATE IMMUNE RESPONSES

The earliest immune responses to an invading pathogen are triggered by recognition of the products of viral and bacterial replication which act as ligands for "pathogen-associated

molecular pattern” (PAMP) receptors such as Toll-like receptors (TLRs), caspase recruitment domain-containing RNA helicases such as retinoic acid-inducible gene I (RIG-I), and other groups of cytosolic proteins called the NOD and NALP proteins.^{53,54} These are specialized receptors, each of which recognizes a ligand expressed during invasion by a specific class of pathogen. For example, TLR3 recognizes double-stranded RNA produced during the replication of RNA viruses, while peptidoglycans produced by bacteria are recognized by a NOD protein. The engagement of these receptors leads through complex signaling cascades to the activation of a variety of cellular transcription factors, including interferon regulatory factors and NF- κ B. This leads to the subsequent induction of dozens or even hundreds of genes encoding pro-inflammatory cytokines, chemokines, interferons, other cellular proteins with direct antiviral activities, as well as regulators of programmed cell death. These responses serve to limit the replication of viruses and regulate inflammation occurring in response to infection. They may also modulate cellular innate immune responses and contribute to the effective priming of cytotoxic T cells, thus potentially shaping the development of antigen-specific adaptive immunity. Because these responses are encoded in the germ line of the host, they are immediate, and may play important roles in limiting the degree of initial replication and/or spread of a virus. They can be viewed as important stopgap responses, buying the host time while antigen-specific adaptive immunity develops.

The activation of interferon regulatory factor 3 (IRF-3) through these pathways is central to the induction of interferons in response to virus infection, and in recent years many RNA and DNA viruses have been recognized to possess mechanisms that actively disrupt its activation. For example, HCV expresses a serine protease, NS3/4A, that targets cellular adaptor proteins that play essential roles in signaling pathways leading from TLR3 and RIG-I to the induction of interferon synthesis.^{55,56} The proteolytic destruction of these adaptor molecules, TRIF and MAVS, enables the virus to evade type 1 interferon responses and escape cellular control of the infection, possibly contributing to viral persistence in chronic hepatitis C. HSV targets the same cellular signaling pathways to block the expression of type 1 interferons, in part through expression of its immediate-early protein ICP0, which prevents the nuclear accumulation of activated IRF-3.⁵⁷ Similar strategies have been evolved by bacteria. For example, invasive enteropathogenic strains of *Shigella* inject a set of potent enzymes into epithelial cells through their type III secretory system that target cellular pathways controlling inflammation and cell death.⁵⁸ A unique approach to evading activation of innate immune responses appears to be taken by HBV, which replicates its genome within nascent core particles and maintains the cccDNA form of its genome cloaked within host cell histones. This stealth approach prevents the recognition of

viral components by cellular PAMP receptors and leads to a paucity of innate cellular antiviral responses in hepatitis B.⁵⁹ In addition to the mechanisms that viruses and bacteria have evolved to prevent or blunt the induction of innate immune responses, there are many examples, too numerous to mention here, of these pathogens blocking or disrupting the effector actions of cellular proteins induced through these pathways.

■ DISRUPTION OF ADAPTIVE IMMUNITY

Similar to the mechanisms by which viruses and bacteria may evade innate immune responses are mechanisms that directly disrupt the subsequent development of antigen-specific, adaptive immunity. Herpes viruses such as HSV and cytomegalovirus (CMV) express proteins (ICP47 in the case of HSV and US6 in the case of cytomegalovirus) that block the normal peptide transporter (TAP) function required for presentation of viral peptide fragments to major histocompatibility complex (MHC) Class I restricted T cells.^{60,61} ICP47 binds to TAP within the cytosol, preventing the transport of peptide fragments into the endoplasmic reticulum, whereas the CMV US6 is a secreted glycoprotein that interacts with TAP within the lumen of the endoplasmic reticulum. Disruption of transporter protein function by CMV and HSV may lessen the extent to which the infection is recognized by the host immune system.

Bacterial strategies for disruption of adaptive immunity are an active area of investigation. They include production of enzymes that cleave immunoglobulins such as the gonococcal IgA1 protease. This cleaves IgA1 at the hinge region, thereby largely inactivating it, which may help to evade specific immune responses on mucosal surfaces. The importance of IgA1 protease is uncertain, however, since human responses at genital surfaces appear to be made up of 50% sIgA1 and 50% sIgA2. The latter lacks the hinge structures required for cleavage by the gonococcal IgA1 protease, and thus is protease resistant. Moreover, there are considerable quantities of IgG at the site of mucosal infections that is also not susceptible to IgA1 protease.

Many bacteria have the ability to downregulate the adaptive immune response. Gonococci appear to be able to suppress the B and T cell responses by engaging lymphocytes with particular members of the Opa family.^{62,63} Induction of the innate immune responses that activate the cell death response “as distinct from apoptosis” may contribute to downregulation of B and T cell responses after gonococcal infection, contributing to the weak adaptive immune responses that characterize gonococcal infection.⁶⁴

Another mechanism to escape the adaptive immune response is to interfere with the ability of complement to carry out its biological functions, thus impeding the effectiveness of antibodies that depend on complement for

their effect. Gonococci have evolved strategies for binding serum inhibitors of complement to the major outer membrane protein porin, which prevent the bactericidal activity of antibodies directed to porin or neighboring molecules. Two different inhibitors may be involved, binding to different domains of porin: C4bp binds to one epitope, whereas factor H binds to another loop epitope.^{65,66} The net effect is to protect the gonococcus from an otherwise effective bactericidal attack by immune serum antibodies.

■ ANTIGENIC VARIATION

Antigenic variation is a very common strategy by which infectious agents foster persistence. Mechanisms exist among all classes of infectious agents, viruses, prokaryotes, and eukaryotes, for altering the sequence of key epitopes of the pathogen that are recognized by both cellular and humoral arms of the host adaptive immune system.

The simplest mechanism for antigenic variation is that which is found among the RNA viruses and lentiviruses including HIV-1. The polymerases expressed by these viruses, whether RNA-dependent RNA polymerase or reverse transcriptase, lack the 3′–5′ exonuclease activity associated with the proof-reading function of DNA polymerases. This results in a high error rate during transcription of the viral genome, leading to impressive mutational rates among these viruses (Fig. 19-1). The extent to which antigenic variation actually occurs is dependent on the ability of the viral protein to sustain mutations without loss of critical function (which limits viral fitness) and the strength and type of selective forces applied by the host immune response.

Prime examples of this phenomenon include antigenic variation within hypervariable regions of the envelope glycoproteins of HIV-1 and HCV. Antigenic variation in the V3 loop of HIV reduces the ability of preexisting antibodies to bind to the newly mutated peptide sequences in the loop. Thus, these mutations cause a reduction in the ability of these antibodies to neutralize virus infectivity.⁶⁷ Variation in the envelope glycoproteins is likely to contribute to B cell escape and viral persistence. Similar mechanisms have been posited to play an important role in the long-term persistence of HCV in chronic hepatitis C. Cytotoxic T-cell escape may also follow a mutational event within short sequential peptide sequences that serve as T-cell epitopes. These mutational and selection mechanisms account for the extensive “quasispecies” variation seen with many persistent RNA viruses such as HCV, and also result in the rapid emergence of resistance of HIV-1 as well as HCV to small molecule inhibitors of viral replication. The best defense against the latter phenomenon is to severely limit viral replication with a cocktail of antiviral drugs, as replication of the virus and transcription of its genome are essential to the generation of new quasispecies variants.

Antigenic variation is also common in many pathogenic bacteria. Among the sexually transmitted bacteria, the gonococcus is most completely studied. The dominant theme that emerges from these studies is the complexity and elegance of the strategies for rapid alteration in expression of cell surface antigens (on-off), and for variation in the primary sequence (and thus antigenicity) of many of these antigens. Pili and opacity proteins each undergo phase variation (expression alternating with nonexpression) and antigenic variation (variations in antigenic structure of the expressed protein) at rates approximating 1×10^3 – 1×10^4 per cell per generation (Figs. 19-2 and 19-3). Interestingly, these rates closely approximate the frequency of base misincorporation by the RNA polymerases of RNA viruses. In the case of *pili*, the fundamental mechanism is crudely analogous to those used in antibody variations. Recombination between one of many variant incomplete *pil* loci (*pilS*, for silent) and a pilin expression locus, *pilE* results either in a different pilin protein (antigenic variation) or a faulty one that cannot be secreted and assembled into a pilus (phase variation).^{68–70} *Opa*



FIGURE 19-1. Mechanism accounting for antigenic variation among viruses such as hepatitis C virus and HIV-1 which replicate through an RNA intermediate. RDRP represents “RNA-dependent RNA polymerase” (or reverse transcriptase, in the case of HIV-1).

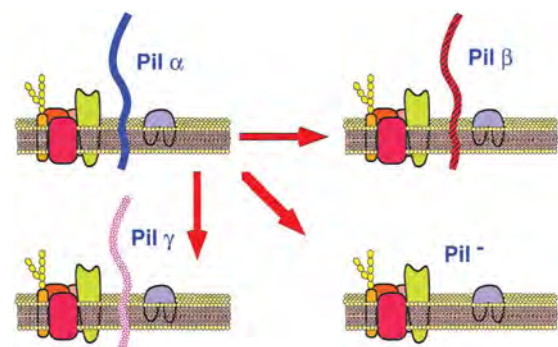


FIGURE 19-2. Phase and antigenic variation in gonococcal pili. Recombination between variant incomplete *pilS* genes and *pilE* (the pilin expression locus) result in either antigenic variations ($Pil\alpha \rightarrow Pil\beta$ or $Pil\gamma$), or phase variation ($Pil\alpha \rightarrow Pil^-$). The Pil^- phenotype sometimes reverts to Pil^+ when recombination with another for *pilS* gene restores the ability of *pilE* to produce functional pili.

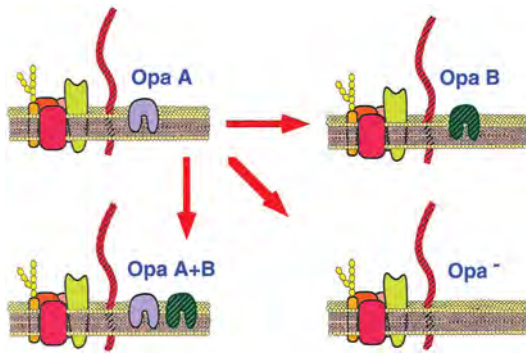


FIGURE 19-3. Phase and antigenic variation in the gonococcal opacity protein family. Gonococci possess multiple (up to 12) complete *opa* genes, each of which is transcribed but only some of which are translated. Successful translation depends on the number of [CTCTT] repeats in the *opa* genes; when $N = 3, 6, 9, 12, 15$ etc., Opa is expressed, but all other variations in the number [CTCTT] repeats throws the gene out of translational frame and no Opa is expressed. Slipped-strand errors during DNA replication frequently alters the number of the [CTCTT] repeats, resulting in spontaneous on-off switching in each *opa* gene. Since the product of each *opa* gene is somewhat different, this also results in antigenic variation.

proteins vary by a totally different mechanism involving slipped-strand mispairing of a pentameric CTCTT repeat element in the *opa* gene, leading to translational frame shifts. An *opa* gene is “off” when out of translational frame and “on” when in frame. Since there are about 12 complete *opa* genes, each of which is slightly different, the random high frequency shifting in each *opa* gene results in a constantly shifting mosaic of expressed Opa proteins.^{71,72} Similar mechanisms underlie the high frequency variations in expressed length of the gonococcal core LOS polysaccharide chain (Fig. 19-3)^{73,74} and also the on-off phase variation in expression of the *pilC1*, *pilC2* genes, and the *hpuAB* genes for utilization of hemoglobin and haptoglobin.⁷⁵ The result is that any population of $>10^6$ gonococci is quite heterogeneous, with multiple variants expressing a bewildering mixture of pili, Opa, and LOS antigens. This prepares the organism for specific immune evasion from antibodies aimed at epitopes on one of these antigens and for binding to different receptors on different cells on different tissues and/or people. Truly, gonococci always “have their bags packed ready to travel.”

T. pallidum also apparently undergoes phase variation in expression of certain rare outer membrane proteins designated the *T. pallidum* repeat family, or *Tpr*. One of the *TprD* evolves in vivo and may contribute to immune escape from humoral immune responses to infection, perhaps helping to explain the remarkable persistence of *T. pallidum* in human infection.^{76,77}

Other bacterial antigens undergo slower evolution by relatively rare missense mutations that slowly alter antigenic structure (e.g., gonococcal porin, chlamydia major outer membrane protein, or MOMP). Recently, however, it has been recognized that gonococci can exchange blocks of chromosomal DNA between different strains in nature, resulting

in mosaic genes that have altered structure, function, and antigenicity.^{78–81} Indeed, horizontal DNA exchange of this sort appears crucial to evolution of gonococcal IgA1 protease, altered penicillin binding protein 1, and probably porin protein (M. Hobbs et al., personal communication),^{78,79} and plays a key role in the general problem of emergence of bacterial species.⁸²

■ MASKING OF ANTIGENS

By “masking,” we mean “covering up,” as for instance one raises an umbrella to ward off rain. In a sense, all intracellular pathogens are “masked” because antibody and complement cannot follow them inside the cell. However, in this usage we refer particularly to production of specific structures that physically block access of host defenses to the cell surface of the pathogen. Bacterial capsules may play such a role but none is important for any of the bacterial STD pathogens. Although gonococci do not make a true capsule, they clearly display masking when they add neuraminic acid (sialic acid) to their LOS polysaccharide chain.^{83,84} (This is done by the use of a gonococcal sialyltransferase and host-derived CMP-N-acetyl neuraminic acid.) Sialylation creates a sort of molecular umbrella, effectively covering up both LOS and neighboring porin protein from attack by complement fixing antibodies, rendering the organism resistant to bactericidal antibodies.^{85,86} The extensive glycosylation of the HIV env protein and the HCV E1 and E2 envelope proteins (which results in an approximate doubling of molecular mass of each of the proteins) may also serve to mask the exterior surface of the viral envelope from antibody recognition.

■ EXPRESSION OF BLOCKING ANTIGENS

Production of so-called “blocking antigens” is yet another mechanism that bacteria have evolved to evade otherwise effective antibody defenses. In the case of the gonococcus, a constant (invariant) antigen designated reduction modifiable protein (Rmp) strongly elicits host production of noncomplement fixing IgG antibodies. On binding to Rmp, these antibodies prevent the proper conformational deposition of complement-fixing antiporin antibodies onto the closely juxtaposed porin molecule, thus blocking the antiporin bactericidal attack.^{87,88} The presence of blocking antibodies helps to render gonococci resistant to killing by normal human serum and promotes infection between sexual partners.⁸⁹ Thus, gonococci have evolved two separate mechanisms for evading complement dependent attack; blocking antigen, and binding by porin of serum factors that inhibit complement, as described above. A somewhat similar masking strategy may also exist among viruses. Crystallographic studies suggest that the V3 loop of the HIV-1 envelope protein may act to mask the cellular receptor interaction site on the assembled HIV

envelope from antibody attack. This would be a clever trick, because the CD4 interaction site must be relatively conserved in structure if it is to function effectively. The CD4 receptor-binding site is unmasked by a conformational rearrangement of the env protein that flips the V3 away and precedes docking of the envelope protein to the CD4 molecule.

■ OTHER MECHANISMS OF IMMUNE EVASION

Although no term has been coined yet to aptly describe the phenomenon, *T. pallidum* is thought to evade host defenses in part by presenting very few antigenic proteins on its phospholipid rich outer envelope.⁹⁰ This strategy is not dissimilar to the mechanism adopted by HBV to evade detection by PAMP receptors, and by analogy to the relative radar invisibility of airplanes with certain shapes and compositions, this microbial strategy might also be termed “stealth.”⁹¹

MOLECULAR MIMICRY

Another mechanism of pathogenesis involves the expression of proteins that are able to mimic specific host cell molecules in either structure or function. This strategy is particularly evident among viruses with larger genomes that are capable of expressing a wider variety of proteins. KSHV is an excellent example, as its genome encodes a number of proteins with sequences or motifs similar to those encoded by the human genome as mentioned above receptor.^{49,92} Bacterial mimicry also occurs, as for example, the identity between host glycolipids and the terminal epitope on gonococcal LOS, and meningococcal group B sialic acid capsule and brain sialic acids of identical structure.⁹³

CONCLUSION

Clearly, many STD pathogens are masters of immune evasion. This explains, at least in part, why herpes viruses, papillomaviruses, HIV, and *T. pallidum* persist so long in human hosts, and why gonococci are so adept at causing repeat infections. These concepts also help to understand how gonococci, chlamydia, HCV, and others persist in the host in the face of an apparently vigorous immune response. Details of the strategies are discussed further in the respective chapters that follow. We can readily appreciate how difficult is the task of designing vaccines for these infectious agents. Most have evolved over a very long time in humans, and it is no surprise that these pathogens are survivors.

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PART 5

Sexually Transmitted Viral Pathogens

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Patrick R. Harrington and Ronald Swanstrom

INTRODUCTION TO RETROVIRUSES

■ TAXONOMY AND CLASSIFICATION

The human immunodeficiency viruses (HIV-1 and HIV-2) and the simian immunodeficiency viruses (SIV) (with a subscript indicating the species of origin) are members of the lentivirus genus of the *Retroviridae* family, commonly called retroviruses. Retro (Latin for backward) refers to an unusual step in the virus life cycle. Typically, the flow of genetic information in a cell is from DNA to mRNA to protein. However, retroviruses have a single-stranded RNA genome that serves as the template for the synthesis of viral DNA, reversing the normal flow of genetic information and giving retroviruses their name. This reverse flow of genetic information is not unique to retroviruses but rather identifies a widely dispersed set of viruses and endogenous genetic elements. Most share the feature of encoding the enzyme responsible for DNA synthesis utilizing an RNA template—reverse transcriptase (RT), first discovered in retrovirus particles in 1970^{1,2} and now a key therapeutic target.

Many organisms carry mobile DNA elements that duplicate themselves at new positions in the host genome by reverse transcribing an RNA copy of the element into DNA and inserting the DNA copy at a new location in the host chromosome. With the availability of the human genome DNA sequence, it has become apparent that upward of 45% of our own is composed of various types of mobile genetic elements, although most of the copies are defective. A major component is the L1 family, representing 17% of our DNA. L1, and a parasitic element of L1 called Alu, are present in thousands of copies throughout our genomes. Both of these elements duplicate themselves using an RT activity encoded within L1. These elements are still active, giving rise to new human mutations.^{3,4} There are three distinct families of viruses that utilize a reverse transcription strategy: the plant virus family of caulimoviruses (with cauliflower mosaic virus as the best known example), the hepadnavirus family (found in birds and mammals, with human hepatitis B virus as the best known example), and retroviruses.

Retroviruses are divided into two subfamilies: *Orthoretrovirinae* and *Spumaretrovirinae* (International Committee on Taxonomy of Viruses, <http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdb/index.htm>). The spumaretroviruses have distinctive features of their replication cycle that require this more distant classification. They have been isolated from primates, but not humans, and are not associated with any known disease. The orthoretroviruses are divided into six genera and represent viruses that infect snakes, fish, birds, and mammals. The phylogenetic relationships among the orthoretrovirus genera, with selected examples of viruses within each genus, are shown in [Fig. 20-1A](#).

Human infections occur with viruses from two of these genera. The Deltaretrovirus genus includes human T-cell leukemia virus type I (HTLV-I), the causative agent of adult T-cell leukemia,⁵⁻⁷ and human T-cell leukemia virus type II (HTLV-II), which is not known to be associated with any disease syndrome. HTLV-I is also associated with another syndrome called HTLV-associated myelopathy (HAM). HTLV-I and HTLV-II are related to viruses found in primates and more distantly related to bovine leukemia virus. The lentivirus genus includes HIV-1⁸ and HIV-2⁹ as well as viruses found in a variety of mammals ranging from primates to sheep. Viruses within these different genera vary widely in the diseases they cause and the mechanisms of disease induction, in contrast to the many common features of their replication cycle.

In its DNA form the viral genome is inserted into the host genome (integration, see below). This step in the virus life cycle has important implications for several features of virus-host interactions. For example, viral DNA that integrates into the genome of a cell but is not expressed becomes silently carried in the descendants of that cell. When this happens in a germline cell, or in the cell of an early embryo that becomes a germline cell, this copy of viral DNA becomes a linked physical part of the host genome, is present in every cell in the body, and is passed on to subsequent generations. Such a genetic element is called an endogenous retrovirus. Most of the elements that become fixed are defective, as there is probably a strong selective pressure against elements that can activate to produce

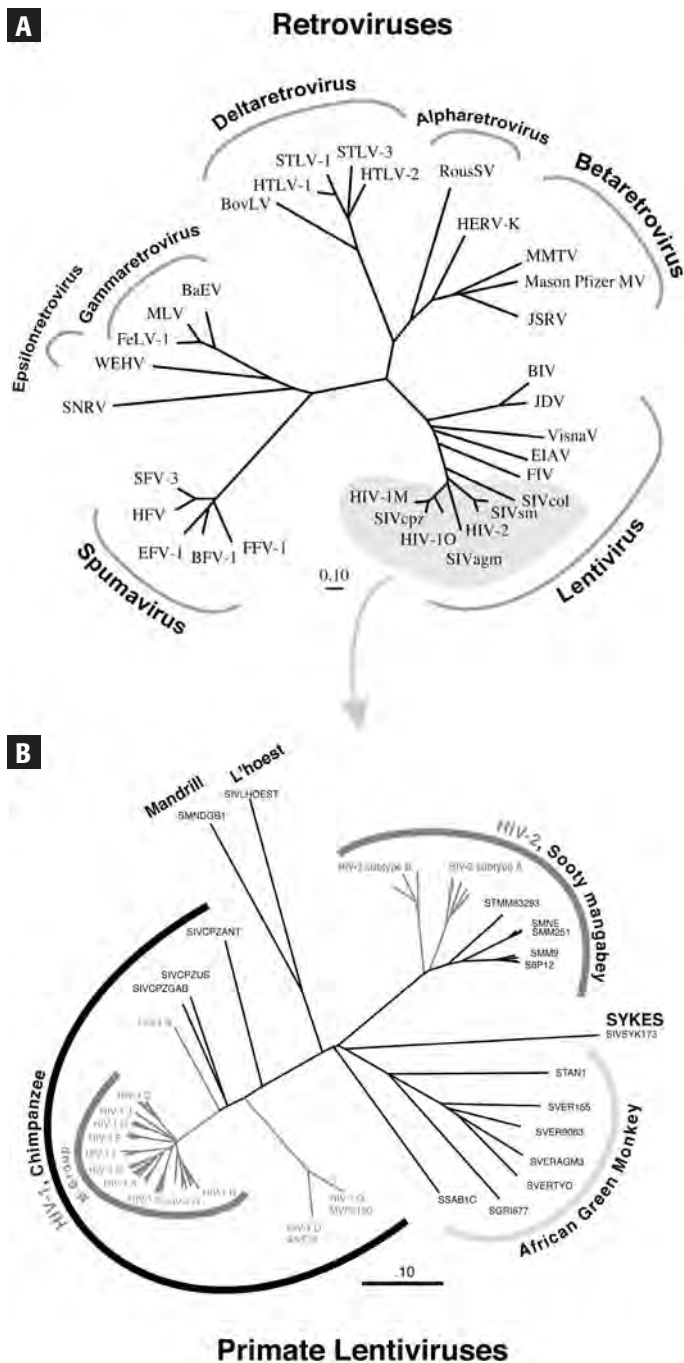


FIGURE 20-1. Phylogenetic relationships between, **A**, representative vertebrate retroviruses and, **B**, primate lentiviruses based on Pol protein sequences. Figure courtesy of Brian Foley, Los Alamos National Laboratory.

infectious virus. Thus, they represent an archive within the host genome of previous waves of retroviral infections. In fact, the human genome carries a record of retroviral infections over the last 40 million years of primate evolution. These are viruses that we do not recognize as active in the human population at present but are represented by 110,000 genomic inserts of gammaretroviruses, 10,000 inserts of betaretroviruses, and 80,000 inserts of a genus that may be distantly related to spumaretroviruses or may represent an uncharacterized

lineage.¹⁰ Most of these elements contain large deletions; however, if these deletions had been retained, our genomes would be 40% endogenous retroviruses by mass and outnumber our normal genes 7 to 1. A recent sequence analysis of one of these endogenous virus families has suggested that at least one of the elements may still be active within the human population, capable of infection and the creation of new endogenous virus loci in our genome.¹¹

DISCOVERY OF RETROVIRUSES AS CANCER-CAUSING AGENTS

Most histories of retroviruses start with the dramatic discovery by Peyton Rous in 1911 that a virus, Rous sarcoma virus (RSV), could cause cancer.¹² Rous showed that a cell-free extract of a chicken sarcoma could be passed through a filter and the filtrate used to induce sarcomas in new chickens. The work of Rous was preceded by that of Ellermann and Bang, who described the transmission of chicken leukemia using cell-free extracts (avian leukosis virus, ALV).¹³ However, the neoplastic nature of leukemia was not appreciated at the time and their observations received much less attention.

The isolation of other tumor-causing retroviruses followed and in time it became apparent that there were two broad classes of agents: one class of viruses caused cancer after a long latency period (e.g., ALV, mouse mammary tumor virus [MMTV], and murine leukemia virus [MLV]), while the other class caused tumors that appeared rapidly (e.g., RSV). We now know that the acutely transforming retroviruses carry a cell-derived oncogene that is responsible for the transforming activity,¹⁴ while the slowly transforming retroviruses act by the chance integration of viral DNA near these cellular oncogenes in the host genome to induce their expression and promote tumor formation.^{15,16} Importantly, many of these same genes can be mutated or overexpressed in human cancers, and the proteins they encode are now the targets of new generations of specific antitumor therapies (for example see review by Pegram et al.¹⁷). One can confidently surmise that the remnants of the beta- and gammaretroviruses littered in our genomes had such oncogenic effects when they were active. Ironically, for the active human retroviruses, HTLV-I causes tumors by a different but still poorly understood mechanism, and HIV is involved in tumor formation only indirectly through immune suppression.

DISCOVERY AND PHYLOGENETIC RELATIONSHIPS OF LENTIVIRUSES

The first description of a retrovirus was in retrospect that of an animal lentivirus (equine infectious anemia virus, EIAV), through the demonstration of transmission of anemia by a cell-free extract of blood from an infected horse.¹⁸ However, the conceptual framework that has led to our understanding

of the lentivirus family came from later work with a lentivirus of sheep.

There are two fundamental differences between lentiviruses and most other retroviruses: Lentiviruses do not cause cancer and they establish chronic infections that result in a long incubation period followed by a chronic symptomatic disease. The “slow” (lenti is Latin for slow), chronic nature of these viral infections was first appreciated for a disease of sheep called maedi-visna (maedi = labored breathing, visna = paralysis and wasting). The recognition of this disease in Icelandic sheep flocks was likely the result of their previous prolonged isolation and the subsequent introduction of visna virus with the importation of European sheep.¹⁹ Other animal lentiviruses were identified in goats (caprine arthritis and encephalitis virus, CAEV) and cows (bovine immunodeficiency virus, BIV) prior to the appearance of HIV-1, with feline immunodeficiency virus (FIV) identified later.

■ DISCOVERY OF HIV-1 AND OTHER PRIMATE LENTIVIRUSES

An infectious agent that would come to be recognized as HIV-1 was first suspected based on the appearance of opportunistic infections due to an acquired immunodeficiency syndrome (AIDS) among otherwise healthy, sexually active gay men in the United States in 1981.^{20–22} A virus was isolated from one such case,⁸ and a serological test based on this isolate and further isolations showed linkage between the presence of this virus and AIDS.^{23–26} With the availability of a serological test it became clear that HIV-1 was spreading around the world and that the high infection rates in central Africa made this area the likely source of the virus. A second, related virus, HIV-2, was also identified among AIDS patients in western Africa.⁹ Finally, it also became clear that there was a long clinical latency between infection and disease during which virus spread among the population was inapparent, a major public health challenge that persists.

At the time HIV-1 was discovered it seemed as if it had come out of nowhere. However, in 25 years since its discovery, we have learned of a complex history between this virus and the human host. Three observations initially suggested a longer history of this virus with humans. First, a clinical sample obtained in 1959 from a man with an AIDS-like illness and who had been in central Africa was shown to contain HIV-1 sequences.²⁷ This indicated that the virus had been in the human population prior to its inferred existence in 1981. Second, the level of genetic diversity of HIV-1 in central Africa was more consistent with established infections in isolated populations,^{28–30} not an introduction of the virus into the population around 1980. Finally, the detection of related viruses among diverse primate species indicated that viruses like HIV-1 had been in the larger biological environment for a long time, as discussed below.

The larger history of primate lentiviruses (SIV) can be seen in the phylogenetic relationships shown in Fig. 20-1B. These viruses have not been detected in new world monkeys, suggesting that they entered the old world monkey population some time after the split of the continents ~40 million years ago. However, they are widely dispersed among old world monkeys, present in over half of the 70 primate species present in sub-Saharan Africa.³¹ For some species it appears that the virus has been stably associated and coevolving with the host for an extended period of time, while other species may have been infected by a cross-species transmission event more recently. Finally, some of the viral genomes appear to be recombinants between different SIVs suggesting past dual infections.³²

The relationship of the two human viruses, HIV-1 and HIV-2, is apparent from these phylogenetic relationships. HIV-2 is closely related to the SIV from sooty mangabeys,³³ and the interspersions of multiple HIV-2 isolates among different SIVsm isolates is most easily explained by multiple introductions of HIV-2 into humans from sooty mangabeys.³⁴ The geographical concentration of HIV-2 infections in western Africa overlaps the range of sooty mangabeys.

The relationship between HIV-1 and SIV has been more complex to unravel. A likely linkage to the SIV of chimpanzees was inferred from SIVcpz sequences, although the interpretation was complicated by surprising diversity among the SIVcpz sequences and the low prevalence of seropositive animals.^{35,36} It is now clear that HIV-1 is derived specifically from SIVcpz of the chimpanzee subspecies *P. t. troglodytes*.³⁷ In a way that is analogous with HIV-2 and SIVsm, different isolates of SIVcpz from *P. t. troglodytes* are phylogenetically interspersed with HIV-1 group M, N, and O isolates, and this is most easily explained as three distinct introductions of HIV-1 into the human population. Chimpanzees appear to be recently infected as not all subspecies carry SIVcpz, a split in the chimpanzee population that occurred about 1.5 million years ago. Furthermore, SIVcpz itself appears to be a recombinant of several other SIV lineages.³²

Although there have been three recognized transmissions of SIVcpz into the human population, giving rise to the M, N, and O groups of HIV-1, it is the M or “main” group of HIV-1 that has given rise to the global epidemic. Extant isolates of HIV-1 carry a phylogenetic fingerprint of what was likely an early isolation of distinct epidemics of the M group virus within central Africa. These lineages are called clades or subtypes and they continue to tell the story of the spread of HIV-1 among populations: subtype B in the United States and western Europe, subtype C in southern Africa and spread to India and then China, etc. It is not clear if the subtypes have any biological meaning as recombinants between subtypes are increasingly found, especially

in areas where two subtypes are cocirculating. Using the current sequence diversity in the HIV-1 population, the 1959 sequence, and estimates of the rate of sequence change per year, it has been possible to suggest that the cross-species transmission event that gave rise to the M group of HIV-1 occurred early in the twentieth century.³⁸ If we accept that SIVcpz has entered the human population three times in the last century (the three groups N, O, and M), then it follows that this virus likely has been transmitted to humans any number of times over the last 10,000 years. Only in the last century the human institutions of large cities and efficient transportation corridors have given these transmission events access to a human environment that could support an epidemic.

RETROVIRUS STRUCTURE AND GENOME ORGANIZATION

■ MORPHOLOGY OF THE RETROVIRUS PARTICLE

Retroviruses are enveloped viruses with two identical copies of viral genomic RNA condensed in a nucleocapsid core (Fig. 20-2). The viral envelope is derived from a cellular membrane of the host cell during virus budding. Inserted in the envelope are the Env glycoprotein spikes encoded by the viral *env* gene. The Env proteins are associated as trimeric complexes of gp120-gp41 heterodimers. Underlying the envelope is the viral matrix protein (MA), which is derived from the Gag (group-specific antigen) polyprotein precursor, the product of the *gag* gene. The nucleocapsid core consists of two other proteins derived from the Gag precursor, the capsid protein (CA) and the nucleocapsid protein (NC). The NC protein binds viral RNA in the core, which is surrounded by CA. The core can have a variety of forms depending on the

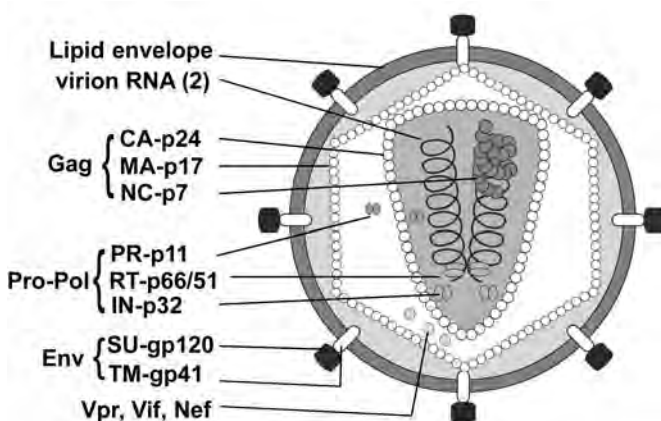


FIGURE 20-2. Virion structure. This diagram shows a model of the major components of the HIV-1 particle. Viral proteins are identified by size (e.g., p24 is a 24-kDa protein), by a two-letter identifier (e.g., CA for capsid), and as part of the gene product from which they are derived (e.g., CA from the Gag precursor).

retrovirus, ranging from essentially spherical to cylindrical. In the case of HIV-1 and other lentiviruses, the core is cone-shaped. The viral enzymes protease, encoded by the *pro* gene, as well as reverse transcriptase (RT) and integrase (IN), both encoded by the *pol* gene, are also associated with a retrovirus particle. In the case of HIV-1, the accessory protein Vpr and small amounts of two other accessory proteins, Vif and Nef, are also incorporated into virions.

■ RETROVIRUS GENOME ORGANIZATION

The viral genome as found in virus particles consists of two identical single-stranded RNA molecules noncovalently associated in a dimer structure. Each RNA molecule has features of a eukaryotic mRNA in that it has a 5' cap, a 3' poly-A tail, and is of the coding or positive sense. The length of the monomeric RNA for retroviruses ranges from approximately 7000 nucleotides for simple retroviruses to 10,000 nucleotides for complex retroviruses like HIV-1.

All retrovirus genomes encode four primary replicative genes: *gag*, *pro*, *pol*, and *env* (Fig. 20-3). The *gag* gene encodes the structural proteins of the capsid, *pro* encodes the viral protease responsible for cleaving precursor proteins, *pol* encodes RT and IN, and *env* encodes the Env glycoprotein. These genes always appear in this order in the retroviral genome starting near the 5' end. More complex retroviruses, like lentiviruses, encode genes in addition to the four primary replicative genes, referred to as accessory genes. Contrary to their name, lentivirus accessory genes serve several indispensable functions in the viral replication cycle. The HIV-1 genome encodes six accessory genes, all within its 3' half: *vif*, *vpr*, *vpu*, *tat*, *rev*, and *nef*.

Cis-acting replication sequences are those that function as part of the genome either to identify it as the viral genome or to participate directly in its expression or replication. The retrovirus genome exists in an RNA and a DNA state at different times during the virus life cycle, and as a result several *cis*-acting sequences are present in the genome that function within the context of either RNA or DNA (Fig. 20-3). A *cis*-acting sequence near the 5' end of the viral RNA, termed the dimerization initiation signal (DIS), plays an important role in the dimerization of the RNA genome. The DIS is a stem-loop RNA structure that contains a 6-nucleotide palindromic sequence at the crown of the loop, such that the DIS loops of two monomeric RNAs can form Watson-Crick base pairs to initiate their dimerization (known as the “kissing loop” model). It is believed that this complex subsequently forms a more stable dimer, or “extended complex,” by expanding the base pairing between sequences that represent the DIS stem structures, a process that is facilitated by the NC protein.^{39,40} Also at the 5' end, a packaging signal (ψ) tags the viral genomic RNA for encapsidation into the virus particle. The RNA has short direct repeats (R) at the 5' end and at the

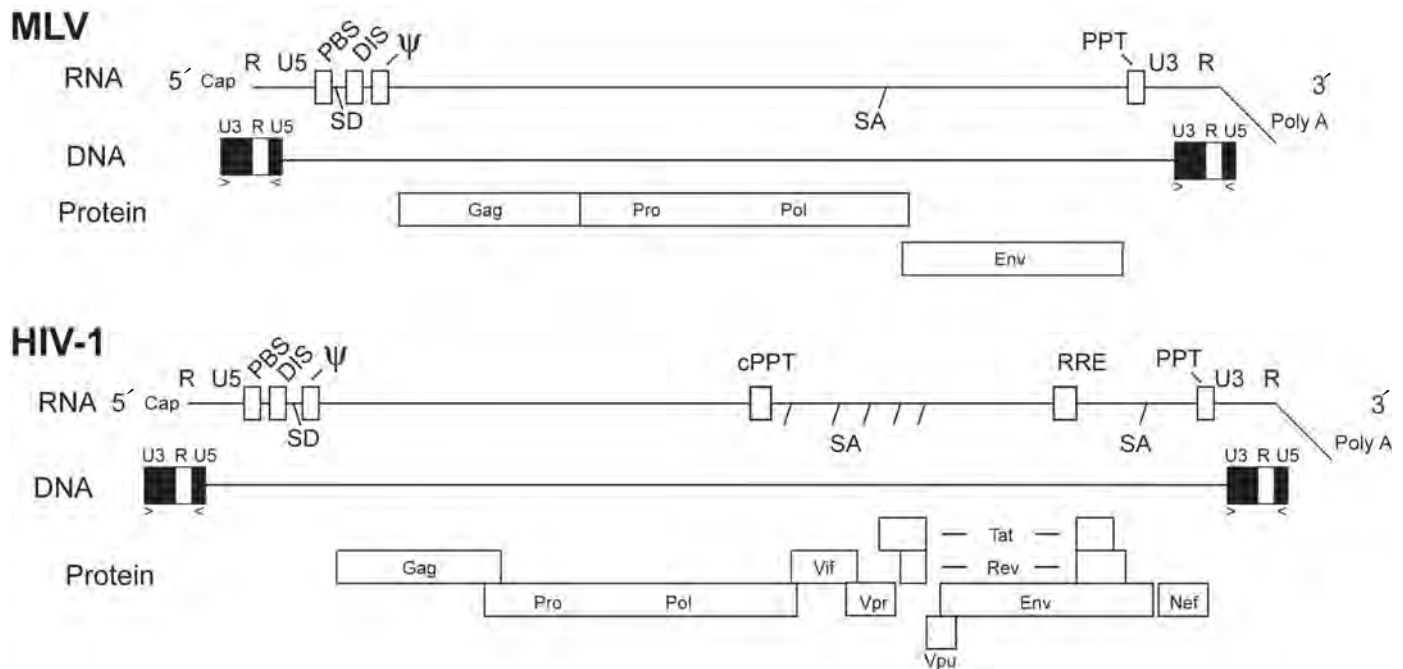


FIGURE 20-3. Retrovirus genome organization. The structure of viral genomic RNA, linear viral DNA, and the encoded protein reading frames are shown for both MLV (a simple retrovirus) and HIV-1 (a complex retrovirus). The RNAs are capped at the 5' end and have a poly-A tail at the 3' end. *Cis*-acting elements in the viral RNA and DNA include: the PBS, major splice donor (SD), splice acceptor (SA), dimerization initiation signal (DIS), the RNA packaging sequence (Ψ), polypurine tract (PPT), long terminal repeats (LTRs), short inverted repeats (\gg and \ll), and for HIV-1 the Rev response element (RRE). For MLV, *gag* and *pro-pol* are in the same reading frame and their encoded proteins are joined at a low frequency by readthrough suppression during protein synthesis in which the termination codon is read as a coding triplet and translation proceeds from *gag* into *pro-pol*, forming the Gag-Pro-Pol precursor. For HIV-1, Gag and Pro-Pol are expressed from different reading frames and are joined at a low frequency by translational frame-shifting.

3' end just inside the poly-A tail, which function during viral DNA synthesis.

Located near the 5' and 3' ends are positions for primers of the first and second strand of viral DNA synthesis. Near the 5' end is the primer-binding site (PBS), a sequence that is complementary to the 3'-terminal 20 nucleotides of a cellular tRNA. A tRNA bound to the PBS primes the first, or minus, strand of viral DNA synthesis. A stretch of purines near the 3' end, called the poly-purine tract (PPT), serves as a primer for the plus strand of viral DNA synthesis. An additional PPT present in the middle of the lentivirus genome allows the second strand of DNA to be synthesized in two segments, presumably to increase the rate of synthesis. The RNA also encodes signals for splicing and polyadenylation, functions that are carried out by the host machinery. Finally, two additional regions of HIV-1 RNA interact with two viral gene products: the TAR region interacts with Tat to upregulate the synthesis of full-length viral RNA during transcription, and the Rev response element (RRE) interacts with Rev to enhance nuclear export of singly spliced and unspliced viral RNAs.

A different set of *cis*-acting sequences functions at the DNA level. During viral DNA synthesis, the U5 and U3 sequences of the viral RNA are duplicated to make a DNA product that is longer than its RNA template. This generates direct repeats at both ends of the DNA that were not present in the RNA, known as the long terminal repeats (LTRs). Within the LTRs

are sequences that function as promoters and enhancers for the expression of viral RNA, but these sequences are selectively active only in the 5' LTR. Also, the LTRs are themselves flanked by short inverted repeats that function at the ends of the DNA during the integration reaction.

RETROVIRUS LIFE CYCLE

Some of the basic biological properties of retroviruses were characterized prior to the identification of HIV-1 in the 1980s, including the size and components of a retrovirus particle, its genome organization, the reverse transcription process that converts viral RNA to DNA, and even the realization that certain aspects of the retrovirus life cycle are inhibited by heritable host factors. However, the identification of HIV-1 as the infectious cause of AIDS and the subsequent recognition of its enormous impact throughout the world has resulted in a large amount of research focused particularly on HIV-1. Although most of the precise molecular details about the life cycle that are described below are specific for HIV-1, the general replication steps and their order of succession are applicable to all retroviruses: attachment, entry, reverse transcription, nuclear import and integration of viral DNA, transcription of proviral DNA, RNA nuclear export and processing, expression of viral proteins, assembly, budding, release, proteolytic processing, and virion maturation.⁴¹

■ ATTACHMENT AND ENTRY

The process of infection initiates when a retrovirus binds to its receptor molecule on the surface of a target host cell, a process mediated by the Env protein spikes. Each spike on an HIV particle consists of a complex of three Env gp120-gp41 heterodimers. The receptor for HIV-1, HIV-2, and SIV is the CD4 molecule,⁴² a surface protein that marks the T-helper subset of T lymphocytes, and is also expressed on macrophages and certain other cells of the monocyte lineage. Binding to CD4 is not sufficient for infection, as entry requires Env attachment to a second molecule, or coreceptor, which for HIV-1 is usually either CCR5 or CXCR4.⁴³ In general, viruses able to utilize CCR5 (R5-tropic HIV-1) can infect both macrophages and CD4⁺ T cells, while viruses that can only utilize CXCR4 (X4-tropic HIV-1) usually only infect CD4⁺ T cells. Coreceptor use by HIV-1 is often associated with disease stage, as R5-tropic HIV-1 is most often transmitted and predominates throughout infection, while X4-tropic HIV-1 can emerge later in infection and is associated with more rapid disease progression.

Attachment, fusion, and entry of HIV-1 and other lentiviruses is a complex, multistep process that requires multiple conformational changes in the viral Env protein before the viral core can enter the cytoplasm of the target cell (Fig. 20-4).^{44,45} The gp120 subunit of Env in the virus spike first binds to CD4 on the target cell. Once bound, a conformational change occurs in gp120, exposing a binding site for subsequent attachment to a coreceptor. After binding to the coreceptor, a second conformational change occurs in the Env complex, this time in gp41 that exposes an amino terminal fusion peptide that inserts into the plasma membrane of the target cell. At this point the Env complex is in a “prehairpin intermediate” form, resulting in the exposure of an N-terminal heptad repeat domain of gp41 (HR1). Next, gp41 folds to

bring together HR1 with a C-terminal heptad repeat (HR2), resulting in the formation of three sets of antiparallel HR1-HR2 helical complexes in the trimeric Env complex, termed the “six-helix bundle.” The formation of the six-helix bundle brings the virus in close proximity with the target cell, driving fusion of the viral envelope with the plasma membrane. Finally, the viral core is released through a fusion pore and into the cytoplasm of the target cell. The first clinically available HIV-1 entry inhibitor, T20, is a peptide mimetic of HR2 and, therefore, binds to HR1 in the prehairpin intermediate, blocking the association of HR1 and HR2 that is required for fusion to progress.⁴⁵

In some instances HIV-1 can utilize other mechanisms for attachment to target cells. In rare cases, especially *in vivo*, HIV-1 may infect cells in a CD4-independent manner or may utilize alternative coreceptors.⁴³ The HIV-1 gp120 subunit of Env can also attach to dendritic cells (DCs). Although DCs themselves are probably not infected, the attachment of HIV-1 to DCs can augment infection of target cells. The HIV-bound DCs can efficiently pass the virus directly to target CD4⁺ T cells, known as trans-infection.^{46,47} Alternatively, HIV-1 virions can be internalized into DCs, trafficked through cellular endosomes, and released via the exosome pathway at sites of contact with susceptible target cells. Some studies have suggested that viral interactions with DCs may play an important role in HIV-1 transmission, especially at mucosal sites of infection.^{48,49}

Multiple host genetic factors that likely affect viral attachment *in vivo* have been shown to influence one’s susceptibility to HIV-1 infection. Individuals that are homozygous for a deletion in their CCR5 gene, known as the CCR5-Δ32 allele, are highly resistant to infection by CCR5-tropic HIV-1, while having few recognizable adverse effects due to the lack of functional CCR5 expression on cellular surfaces.⁵⁰ It was also recently demonstrated in a large population-based study that humans have a wide copy number range of the CCL3L1 gene, which encodes a ligand for CCR5 that acts as a potent inhibitor of

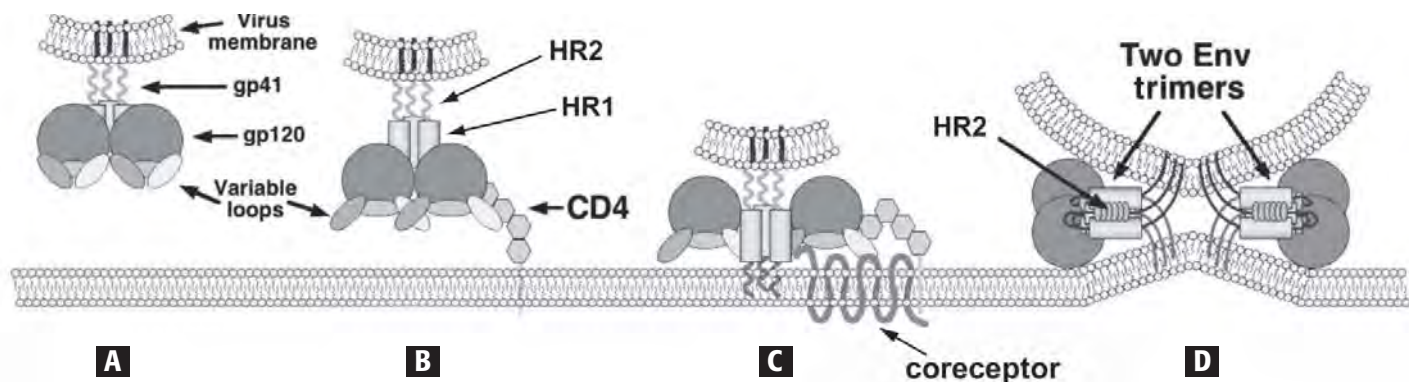


FIGURE 20-4. Steps of HIV-1 attachment and entry. **A.** Attachment and entry of HIV-1 is a multistep process mediated by the Env protein, which is present in the virion as a trimeric complex of gp120-gp41 heterodimers. **B.** Attachment to target cells is initiated by the binding of one gp120 subunit of Env to CD4. **C.** Following a conformational change in gp120, the virus attaches to a coreceptor (either CCR5 or CXCR4), and gp41 undergoes structural changes to insert a hydrophobic fusion peptide into the target cell plasma membrane. **D.** The association of the HR1 and HR2 helices of gp41 into a six-helix bundle structure brings the viral and cellular membranes in close proximity. Contact between the viral and cellular membranes results in membrane fusion and the formation of a fusion pore through which the viral core passes into the target cell cytoplasm. (Figure modified from a version kindly provided by Robert W. Doms, University of Pennsylvania, and John P. Moore, Weill Medical College of Cornell University, with permission.⁴⁵)

HIV-1 infection *in vitro*, the MIP-1 α chemokine.⁵¹ A higher copy number of the CCL3L1 gene results in greater expression levels of the CCR5-interacting chemokine, which can reduce one's susceptibility to HIV-1 infection presumably by the competitive inhibition of HIV-1 attachment to CCR5. These and other observations suggest that drugs targeting the coreceptor binding step may be effective in treating HIV-1 infection. In fact, multiple steps of the HIV-1 attachment and entry processes are targets for several novel antiretroviral therapies that are currently in clinical development.^{44,52}

■ VIRAL DNA SYNTHESIS

The synthesis of viral DNA follows an elegant and complex pathway.⁵³ There are two aspects of this process that make it especially distinctive. First, during the course of DNA synthesis three breaks in the template must be negotiated. The second distinctive feature of DNA synthesis is that the DNA product is longer than the RNA template.^{54,55} RT that was packaged during virion formation mediates the synthesis of viral DNA in the cytoplasm of a newly infected cell. The template for DNA synthesis is the single-stranded viral RNA genome. The essential elements of viral DNA synthesis are (1) RT, (2) its associated RNase H activity that degrades the RNA template after it is converted into an RNA-DNA hybrid, (3) a cell-derived tRNA annealed to the PBS at the 5' end of the viral RNA, which serves as the primer for the minus strand of DNA synthesis, and (4) one or more PPTs in the RNA template that are left by RNase H to prime synthesis of the plus strand of DNA.

Viral DNA synthesis initiates from the tRNA primer annealed to the PBS near the 5' end of the viral RNA. The growing minus strand DNA chain quickly reaches the 5' end of the template (first template break in DNA synthesis), generating a DNA complement to the U5 and short direct repeat (R) RNA sequences. The 5' end of the RNA template is then degraded by the RT-associated RNase H activity. Reverse transcription continues when the newly synthesized DNA subsequently base pairs with the R sequence at the 3' end of the viral RNA, priming minus strand DNA synthesis to continue along the length of the remaining template until it terminates at the PBS at the 5' end of the RNA (second break). During minus strand DNA synthesis the RNase H activity of RT continues to digest the RNA template that has been reverse transcribed, but the RNA is incompletely digested, leaving one or more PPT RNAs of approximately 11 bases annealed to the newly synthesized minus strand DNA. The PPT RNA(s) primes plus strand DNA synthesis, which continues copying the minus strand DNA until the RT complex reaches a modified base in the tRNA primer, which is still attached to the 5' end of the minus strand DNA template. Plus strand DNA synthesis stops at this point because RT cannot copy the modified base (third break). The RNase activity of RT then removes the tRNA primer, leaving a plus strand DNA overhang sequence

at the 3' end. At this point the 3' end of the plus strand DNA represents the PBS sequence, while the 3' end of the minus strand DNA is its complement, allowing the sequences at the 3' end of each DNA strand to base pair to generate a circularized molecule. DNA synthesis continues as each strand uses the other as a template and concludes with a strand displacement event to decircularize the molecule, creating a complete, linear, double-stranded DNA product. A more detailed description of this process is reviewed elsewhere.⁴¹

Although there are no new sequences in the newly synthesized DNA, some of the sequences in the RNA are duplicated and rearranged during DNA synthesis so that the DNA product is longer and has several features that were not present in the RNA template. Where the RNA template had a short terminal repeat R, the newly synthesized DNA has an LTR. The LTR sequences flanking the linear DNA are generated by synthesis through the template breaks, bringing together U3, R, and U5 sequences (Fig. 20-3). This complex process of viral DNA synthesis is necessary for the critical translocation of transcription and integration signals in the viral DNA and also ensures the authentic viral RNA genome is reproduced during transcription.

■ NUCLEAR IMPORT AND INTEGRATION OF VIRAL DNA

Prior to integration into the host genome, newly synthesized lentiviral DNA remains associated with multiple cellular and viral proteins, collectively termed the preintegration complex (PIC). Unlike other retroviruses, lentiviruses do not require cells to undergo mitosis and breakdown their nuclear envelope for the viral DNA to access the host genome for integration. Instead, the PIC can be actively transported into the nucleus, a process that involves multiple host and viral factors.⁵⁶ This property of lentiviruses enables them to infect nondividing cells, such as macrophages, and, therefore, plays a key role in pathogenic processes of lentivirus infection. The role of monocytes and macrophages in lentivirus infection *in vivo* is discussed later in this chapter.

The integration of viral DNA is mediated by the viral IN protein, which like RT is also brought into the cell as part of the infecting nucleoprotein complex. At least one host factor, lens epithelium-derived growth factor (LEDGF/p75),⁵⁷ is required for efficient integration of viral DNA into the host cell DNA. The integration reaction actually starts in the cytoplasm as each 3' end of the linear, double-stranded viral DNA is shortened by the removal of the two terminal nucleotides that are adjacent to a conserved CA dinucleotide.⁵⁸ A short inverted repeat that is a feature of the LTR boundaries plays an important role in the efficiency and specificity of IN-mediated processing of the viral DNA 3' ends. The CA-3'-hydroxyl DNA ends serve as the intermediate for the second step of integration mediated by IN, known as strand transfer, which occurs once the PIC is imported into the nucleus.⁵⁹ Here, IN makes a

cleavage in the host DNA that is staggered by five nucleotides and joins the 3' ends of the shortened strands of linear viral DNA to the cleaved host DNA. At this intermediate stage, the 5'-phosphate ends of viral DNA are not yet linked to the host DNA. Finally, cellular repair enzymes fill in the five-base, single-stranded gap at each integration junction, generating a short direct repeat of the host DNA flanking the integrated viral DNA, and also trim the two-base flap at each of the 5' ends of the viral DNA to complete the integration reaction. In the integrated state, the viral DNA is referred to as the provirus or proviral DNA. The IN enzyme is unique to retroviruses and required for their replication, and, therefore, represents a promising therapeutic target. Consequently, HIV-1 IN-inhibitors are currently in clinical development.⁵⁹

■ TRANSCRIPTION OF INTEGRATED DNA AND PROCESSING OF VIRAL RNA

Integrated DNA is transcribed into RNA by the host RNA polymerase II, and the RNA transcript has the features of a cellular mRNA, including a 5' cap and a 3' poly-A tail. Transcription starts within the 5' LTR and ends just downstream of the corresponding position in the 3' LTR, creating the "R" repeat in the RNA. Viral DNA sequences upstream of the RNA start site, referred to as the U3 region, function both as promoter and enhancer for transcription, utilizing primarily host machinery for these functions. Many retroviruses also encode *trans*-acting transcription activators that enhance viral RNA synthesis. In the case of HIV-1, short, prematurely terminated RNAs are often generated in the absence of any supplementary host or viral transcription factors. To enhance transcription of HIV-1 DNA, newly synthesized Tat protein interacts with a host protein, termed cyclin T, to bind the trans-activation response element (TAR) RNA stem-loop, which forms near the 5' end of newly synthesized viral RNA. The Tat-TAR-cyclin T complex recruits a cyclin-dependent kinase, CDK9, that hyperphosphorylates the C-terminus of RNA Pol II, resulting in enhanced transcription elongation and increased synthesis of full-length viral RNA.^{60,61}

Newly synthesized HIV-1 RNA has one of four fates, all of which are essential for completing the viral replication cycle. (1) It can be multiply spliced, which removes several introns to generate small transcripts that encode *tat*, *rev*, or *nef*. (2) It can be singly spliced, which removes a single intron spanning *gag*, *pro* and *pol* to express *env* and *vpu*, *vpr*, or *vif*. (3) It can remain unspliced and used as mRNA for *gag*, *pro*, and *pol*. (4) Finally, it can remain unspliced and serve as genomic RNA in the assembly of new virions. In general, cellular pre-mRNAs remain in the nucleus until splicing is complete, which poses a problem for export of singly spliced and unspliced viral RNAs since they retain *cis*-acting splicing signals. To overcome this nuclear export problem, the singly spliced and unspliced RNAs of HIV-1 and other lentiviruses

interact with the Rev accessory protein.^{62–64} After being translated in the cytoplasm from a multiply spliced viral RNA, Rev is imported back into the nucleus with the assistance of cellular nuclear import machinery. Once in the nucleus, Rev binds to a region of secondary structure in the viral RNA called the RRE, which is located within the *env* gene and in the *tat/rev* intron. The Rev-RNA complex interacts with a nucleocytoplasmic transport factor, Crm1, to exit the nucleus using a pathway that is normally not used by cellular mRNAs.^{65,66} Finally, uncoupling of Rev-RNA complexes occurs in the cytoplasm prior to translation or packaging of the viral RNA.

■ SYNTHESIS OF VIRAL PROTEINS

Most of the viral proteins are synthesized in the cytoplasm of the host cell. The exceptions are the integral membrane proteins Env and Vpu, which are synthesized by endoplasmic reticulum (ER)-bound ribosomes and transported into the lumen of the ER. Most of the RNAs encode a single protein. Viral mRNAs for *vif*, *vpr*, *tat*, *rev*, and *nef* are expressed from separate spliced RNAs. However, HIV-1 uses two different strategies to translate two different multicistronic mRNAs. First, the full-length RNA transcript is translated using the 5' most open reading frame to synthesize the Gag protein. Approximately 5% of the time a frame-shifting event occurs near the 3' end of the *gag* reading frame that leaves the translation machinery in the -1 reading frame, which encodes the *pro* and *pol* genes. Translation continues, generating a Gag-Pro-Pol fusion protein that is present at 5% the concentration of the Gag precursor. In contrast, a small open reading frame for *Vpu* is present upstream of the *env* reading frame. Both the *vpu* and Env proteins are synthesized from a single bicistronic mRNA.⁶⁷

■ ASSEMBLY AND BUDDING

The Gag p55 precursor plays a primary role in the assembly process and can even assemble and bud from infected cells in the absence of any other viral proteins.^{68,69} During the virus life cycle, Gag is involved in (1) recruiting viral proteins essential for the next round of infection to sites of assembly, (2) binding to cellular factors involved in the budding process, and (3) binding and encapsidation of the viral genomic RNA. Distinct functional domains in Gag drive the assembly and release processes. The N-terminal MA domain of Gag is myristylated, which targets the protein to cellular membranes, and also contains several basic residues that interact with negatively charged lipid head groups to further stabilize Gag-membrane associations. The preferential targeting of Gag to lipid raft microdomains enhances the association of assembly complexes with the plasma membrane.⁷⁰ The CA domain is involved in multimeric Gag-Gag interactions during particle assembly. The NC domain binds and packages the viral RNA and also promotes Gag-Gag interactions. The late (L)

domains, which are near the C terminus of HIV-1 Gag, interact with cellular proteins during budding and release.

The Gag and Gag-Pro-Pol precursors multimerize at sites of assembly, incorporate other viral and cellular proteins, and encapsidate the viral RNA genome to complete the assembly process. Like other membrane glycoproteins, newly synthesized retroviral Env proteins use the cellular secretory machinery to traffic to cellular membranes. The Env precursor, gp160, is translocated into the ER as a transmembrane protein during its synthesis where it is glycosylated and forms a homotrimer. The Env protein is then transported into the Golgi where it is cleaved by a cellular furin-like protease to generate the gp120 and gp41 mature products that stay non-covalently associated. The mature Env proteins, now in a trimeric complex of gp120-gp41 heterodimers, are then transported to the cell surface membrane. A specific interaction between the cytoplasmic tail of gp41 and the MA domain of Gag brings oligomeric gp41/gp120 complexes into the virus particle as it buds through a cellular membrane. During the assembly process the viral accessory protein Vpr is packaged into virions through an interaction with Gag,^{71,72} as are small amounts of Vif and Nef.

Recent advances in cell biology and virology have revealed that retroviruses, and probably many other enveloped viruses, utilize the protein sorting machinery of their host cells to bud at sites of viral assembly. This general mechanism of retrovirus budding first became evident when it was observed that an interaction between the C-terminal p6 region of Gag and a key component of the cellular endosomal sorting complex, Tsg101, is essential for HIV-1 release.^{73,74} The L domains of retrovirus Gag p6 proteins associate with cellular proteins involved in the formation of vesicles that bud into multivesicular bodies (MVBs), which are late endosomal compartments that normally sort and transport cellular proteins to the lysosome. Ubiquitin tags direct many cellular proteins to the MVB machinery, and the Gag proteins of multiple retroviruses, including HIV-1, are also ubiquitylated, although the precise role of ubiquitin transfer in retrovirus budding remains to be determined. Remarkably, it appears that retroviruses have preferentially exploited the cellular MVB machinery to assist in the budding process due to the unusual ability of MVB vesicles to bud away from the cytoplasm, much like an enveloped virus buds from an infected cell.⁶⁸

Retroviruses redirect this host cell MVB machinery to sites of assembly at the plasma membrane to bud from infected cells (Fig. 20-5). Retroviruses can also bud intracellularly, presumably into MVBs, followed by release into the extracellular space via the cellular exosome pathway. This has been suggested to be a preferred exit strategy for HIV-1 in macrophages.^{75,76} Similarly, HIV-1 virions that have been captured and internalized by (DCs) are subsequently released through exosomes.⁷⁷ Regardless of the site of budding, retroviruses are often

released at sites of cell-to-cell contact, termed “virological synapses,” which may have important implications for virus spread *in vivo*.^{78,79} The ability to release at virological synapses may increase the chance that a newly produced virus reaches a target cell for its next round of infection, and may also protect viruses from immune recognition.

■ PROTEOLYTIC PROCESSING

An integral part of the assembly and maturation process is the proteolytic processing of the Gag and Gag-Pro-Pol precursors by the *pro*-encoded viral protease (PR). The protease is activated during the assembly process and mediates the cleavage of these precursors to their mature components (for HIV-1 Gag: MA, CA, NC, and p6; for Pro: PR; and for Pol: RT and IN). The enzymes gain full activity only after being released from the precursor, and with the processing of the Gag precursor the virion undergoes a dramatic morphological change from an open immature state to a condensed nucleocapsid core. The proteolytic processing of Gag is a required step for virion maturation and subsequent infectivity, and for this reason the viral protease is an important therapeutic target.

■ ROLE OF ACCESSORY PROTEINS

Some retrovirus genomes encode only Gag, Pro, Pol, and Env and their entire replication scheme can be understood with only the function of these proteins. However, primate lentiviruses encode additional gene products, termed accessory proteins, which perform a number of functions that are essential in the virus life cycle. The HIV-1 genome encodes six accessory proteins: Tat, Rev, Vpr, Vpu, Vif, and Nef. As described above in more detail, Tat functions primarily as a transactivator of transcription, and the primary role of Rev is to direct nuclear export of singly spliced and unspliced viral RNAs. The Vpr protein is packaged into virions and serves multiple functions, including participating in nuclear translocation of the PIC, enhancing Tat-induced transcription, and facilitating virus production by arresting infected cells in G2 of the cell cycle.^{80,81} The Vpu protein assists Env translocation to cellular membranes by degrading intracellular CD4 and may enhance virus particle release by disrupting an uncharacterized host cell restriction.^{82–85} Vif is packaged into virions and has been known for many years to play an important role in the reverse transcription process during the next round of replication, with its activity being dependent on the virus-producing cell. It was recently revealed that Vif functions to ensure the fidelity of HIV-1 replication by blocking a robust intracellular antiviral defense (described in detail below).⁸⁶

The Nef protein is produced by all primate lentiviruses and has several known and postulated functions.^{87,88} The most extensively characterized activity of Nef is its ability to down-modulate CD4 from the cell surface and target it for

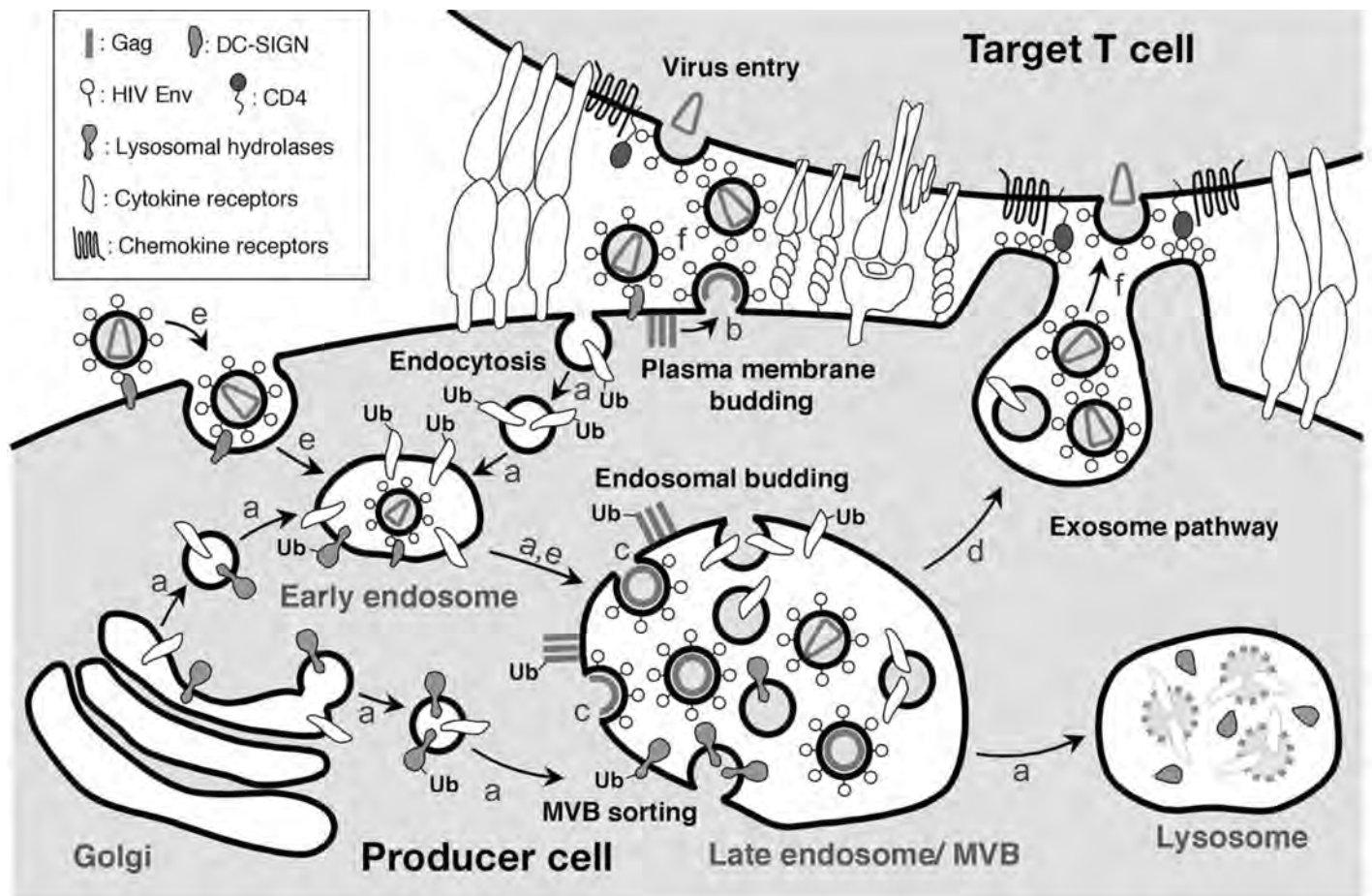


FIGURE 20-5. Mechanisms of HIV-1 Release. This model illustrates, (a) the normal cellular trafficking of molecules from the Golgi and plasma membrane to the lysosome; (b) HIV-1 budding at the plasma membrane; (c) HIV-1 budding at the multi-vesicular body; (d) release of cellular molecules and HIV-1 via the exosome pathway; (e) Internalization and endosomal trafficking of infectious HIV-1 particles in dendritic cells; and (f) release of HIV-1 at sites of close contact with target T cells. Figure modified from a version kindly provided by Eiji Morita and Wesley Sundquist, University of Utah.⁶⁸ (Reprinted with permission from the Annual Review of Cell and Developmental Biology, Volume 20 ©2004 by Annual Reviews www.annualreviews.org.)

lysosomal degradation.^{89,90} By reducing levels of cell surface CD4, the processes of assembly, budding, and release are less inhibited by the localized presence of receptor molecules on the virus-producing cell. In addition, Nef disrupts the immune response to virus-infected cells by modulating cell surface expression of major histocompatibility class I and II (MHC I/II), T-cell receptor, and other immune effector molecules,^{91–95} and also interacts with host p21-activated kinases (PAKs) to enhance viral replication.^{96,97} One or more of the functions of Nef greatly enhance the infectivity and pathogenesis of SIV and HIV infections in vivo, as evidenced by a much slower disease course in macaques and humans infected with *nef*-defective viruses.^{98–101}

■ INTRACELLULAR RESTRICTIONS ON RETROVIRUS REPLICATION

Based on studies of MLV infection of mice, it has been apparent for decades that certain heritable host traits can govern susceptibility to retrovirus infection.^{102–104} However, several

recent studies of virus-host interactions have dramatically enhanced our understanding of some of the mechanisms of innate intracellular restriction on virus replication, and it also appears that retroviruses have evolved efficient mechanisms to evade such restrictions. A major class of intracellular antiviral defenses was first uncovered by the observation that the HIV-1 accessory protein Vif interacts with a host protein termed APOBEC3G (apolipoprotein B mRNA-editing enzyme, catalytic polypeptide-like 3G).¹⁰⁵ The APOBEC3 host-cell proteins are cytidine deaminases, which mutate single-stranded DNA by converting cytosine residues to uracil. Cellular APOBEC3G (or APOBEC3F¹⁰⁶) packaged into virions during the assembly process targets viral minus strand DNA that is synthesized during reverse transcription in the next round of infection.⁸⁶ The cytidine deaminase activity of APOBEC3G/F can be detrimental to retrovirus replication in two ways: First, the presence of uracil residues in newly synthesized DNA tags it for degradation by a host enzyme termed uracil-DNA glycosylase (UDG). If any viral DNA survives UDG-mediated degradation, the conversion of

a C nucleotide to U in the DNA minus-strand will result in a G-to-A mutation when the positive-strand is synthesized. The presence of G-to-A hypermutation in the proviral DNA would likely alter coding sequences or even introduce premature stop codons throughout the genome, thus rendering any number of essential viral genes nonfunctional. To counter this antiviral defense, Vif prevents incorporation of APOBEC3G/F into virions by binding to the host protein and targeting it for degradation.¹⁰³ Subsequent studies have revealed that an active, low-molecular-weight form of APOBEC3G is present in resting CD4⁺ T cells and targets incoming virions to restrict HIV-1 infection in a manner that is independent of cytidine deamination,¹⁰⁷ which may partly explain the relative resistance of these cells to HIV-1 infection.

A second major class of intracellular restriction that targets incoming lentivirus capsids has also recently been elucidated. Previously referred to as Ref1 and Lv1 (for “restriction factor 1” and “lentivirus susceptibility factor 1”), the TRIM5 α (tripartite interaction motif 5 alpha variant) proteins of humans and nonhuman primates strongly inhibit retroviral infection in a somewhat species-specific manner.^{108–112} For example, rhesus macaque TRIM5 α potently restricts infection by HIV-1, but not SIV, whereas human TRIM5 α normally has little effect on HIV-1 replication. Replacing the SIV capsid gene with that of HIV-1 in a chimeric SIV-HIV virus construct (SHIV) renders the virus susceptible to rhesus macaque TRIM5 α , indicating that the HIV-1 capsid is the target for restriction. Interestingly, different human and non-human primate TRIM5 α variants exhibit different potencies and ranges of retrovirus restriction. The mechanisms by which different TRIM5 α proteins interact with incoming retroviral capsids, and how these interactions restrict retrovirus infection are active areas of research.

In the case of HIV-1, another host protein termed cyclophilin A (CypA) participates in viral restriction processes,¹¹³ although its precise role is unclear. A specific site on the HIV-1 capsid binds CypA, and inhibition of capsid-CypA binding impairs HIV-1 replication during the next round of infection in human cells. Conversely, inhibition of capsid-CypA binding enhances HIV-1 replication in owl monkey cells, which are otherwise poorly infected by HIV-1. The observation that owl monkey cells express an unusual TRIM5 α -CypA fusion protein has provided additional clues regarding the relationship of TRIM5 α and CypA and their role in HIV-1 restriction.¹¹² Remarkably, of all retroviruses, only the HIV-1 capsid is known to bind CypA, and the owl monkey TRIM5 α -CypA has been shown thus far to specifically restrict only HIV-1. Taken together, these findings suggest a preliminary, though not fully resolved,¹¹⁴ model in which CypA bound to the HIV-1 capsid protects the virus from human TRIM5 α -mediated restriction, while binding of the HIV-1 capsid to the CypA component of the TRIM5 α -CypA fusion protein brings it in

close association with the TRIM5 α component, resulting in potent TRIM5 α -mediated restriction in owl monkey cells.^{103,104}

The study of innate intracellular restriction of retrovirus infection is still in an early stage, and the precise molecular interplay between the virus and host that results in either retrovirus restriction or escape has only begun to take shape. It is also likely that additional restriction factors exist and target various other stages of the viral replication cycle. As mechanisms of innate antiviral restriction are resolved, and aspects of retrovirus replication that are indispensable for countering such host defenses are revealed, research in this emerging field of retrovirus biology will almost certainly result in novel strategies to treat HIV-1 infection.

MECHANISMS OF VIRAL GENETIC DIVERSITY

■ VIRAL REPLICATION RATES

HIV-1 grows efficiently only in cells expressing CD4 and CCR5 (for R5 viruses) or CXCR4 (for X4 viruses). Robust replication occurs in cell culture in activated CD4 positive T cells. Resting T cells can also be infected but viral DNA synthesis is much less efficient and slower, requiring 2–3 days.^{115–118} Reduced levels of nucleotide precursors¹¹⁹ and an active form of APOBEC3G¹⁰⁷ restrict the efficiency of viral DNA synthesis in resting T cells. Viral replication is similarly slow in macrophages. While viral DNA is synthesized within a 4–6 hour period in activated T cells, this process takes 36–48 hours in differentiated macrophages.¹²⁰ Viral replication (HIV or SIV) in vivo can be detected in activated T cells but also in resting memory T cells.¹²¹ Replication in these cells has been proposed as a major mechanism of pathogenesis leading to the early depletion of the large fraction of resting CD4⁺ T cells found in the gut lamina propria and other lymphoid tissues.^{122–124}

■ SOURCES OF POINT MUTATIONS

Viral DNA synthesis is usually characterized as an error-prone process. The appearance of sequence diversity in the viral genome is the result of several factors: an error prone DNA polymerase (RT), a large replicating population, many generations, and ultimately selective pressures that lead to the fixation of mutations. The most accurate measurements of the error rate during replication show that about one nucleotide substitution occurs per every three HIV-1 genomes synthesized.^{125,126} Deletions and insertions can also occur but in general these will be deleterious and only occasionally give rise to a beneficial change.¹²⁷ RT does not have a proof-reading function for misincorporated nucleotides, so it is assumed that the viral enzyme is the source of the high error rate; the inability to remove misincorporated

nucleotides makes viral DNA especially sensitive to the chain terminating nucleoside analogs that are an important part of current therapies. It is unlikely that the host cell DNA replication machinery contributes to the error rate, but the contribution of RNA polymerase II during the synthesis of viral RNA is plausible.¹²⁸ Another source of sequence diversity is cytosine deamination of minus strand DNA associated with APOBEC3G.^{105,129–131} Although the virus uses the Vif protein to block APOBEC3G activity, any leakiness will lead to G to A changes in the coding strand. When this happens as hypermutations it is likely always deleterious. However, the potential for low-level activity leading to additional sequence diversity has not been ruled out and may be contributing to the A-rich nature of the HIV-1 genome.

■ RECOMBINATION

Whereas the effects of point mutations are evident in HIV-1 sequence diversity and in the appearance of drug resistance mutations, a major factor in the utilization of sequence diversity in the virus population is recombination. The virus particle contains two copies of the RNA genome. During viral DNA synthesis, RT moves back and forth between the two templates to make a DNA product that is a mosaic of the two RNA strands. If the sequence of the two strands is identical then this process is inapparent. However, if the virus particle is produced from a cell that has two genetically different proviruses, the particles can contain one copy of each RNA (forming a heterodimer). The resulting DNA copy can link the sequence markers that differed between the two RNAs. HIV-1 recombination rates are very high, even among retroviruses, resulting in up to 10 strand switches per round of viral DNA synthesis.^{132,133} However, a prerequisite for recombination to be biologically relevant is the need for dually infected cells that would allow genetically different viruses to be brought together for heterodimer formation. The detection of an average of 3–4 proviruses per cell in infected cells found in the spleen¹³⁴ reveals the potential of recombination *in vivo* to be a major determinant of HIV-1 sequence evolution. It has recently been argued that successful therapy is in part the result of the reduction in the number of dually infected cells, closing off this pathway of sequence evolution and making the virus a more static target for therapy and the immune system.¹³⁵

EVOLUTION OF HIV-1 INFECTION

■ CORECEPTOR SWITCH

HIV-1 requires two cell surface proteins to enter the cell: CD4 and a chemokine receptor that serves as a viral coreceptor. Most variants of HIV-1 use CCR5 (the receptor for the chemokines MIP1 α , MIP1 β , and RANTES) as the coreceptor,

and this is the specificity of most transmitted viruses (called R5 variants). However, in a subset of infected people, HIV-1 will evolve to use CXCR4 as the coreceptor as the CD4 cell count decreases (reviewed by Moore et al.¹³⁶). The appearance of these X4 variants is associated with an immunodeficient state and a more rapid decrease in CD4 cell counts, although it is still not known which is cause and which is effect. R5 variants replicate predominately in memory T cells, while X4 variants, when they appear, are found in naïve T cells, perhaps suggesting some of the selective pressures at work in the evolution of X4 variants.^{137,138} In one model of Env protein function the V3 loop interacts with the extracellular domains of the coreceptor.¹³⁹ In support of this model, the major changes in *env* sequence in X4 variants are in the V3 loop, typically involving the addition of basic amino acid residues at specific positions in V3.¹⁴⁰

■ IMMUNE EVASION

There are three arms of the immune system and HIV presents examples of evasion of all three. APOBEC3G/F represent a novel feature of innate immunity with the ability to be packaged into virions and modify the newly synthesized viral DNA during the subsequent round of infection; the viral Vif protein blocks uptake into the virion thus protecting the next round of viral DNA synthesis (as described above). The evasion of innate immunity typically involves specific strategies, such as the evolution of a protein that can modulate or inactivate a cell-based protective activity. However, viral evasion from the two arms of host adaptive immunity requires a more dynamic strategy.

Cell-mediated immunity is based on the presentation of peptide epitopes by MHC class I molecules, with the specificity of the epitopes presented determined by the alleles at the MHC locus. Evasion of cell-mediated immunity occurs by two mechanisms. As noted above, the viral Nef protein is able to reduce the level of MHC class I molecules on the surface of the cell by directing the newly synthesized molecules to a lysosomal compartment.^{91–93} This results in a reduced capacity of the cell to present viral peptide epitopes to cytolytic CD8⁺ T cells (CTLs).¹⁴¹ The second mechanism of immune evasion is through viral sequence evolution within the epitope. Sequence changes within CTL epitopes are clearly associated with the initial viral escape to establish the viral set point^{142–144} and also with delayed immune escape.^{145–147}

The virus particle displays copies of a single viral protein on the surface of the membrane envelope, the viral Env protein. Although the host makes antibodies to all of the viral proteins, only the Env protein on the surface of the particle is the target of virus-neutralizing antibodies. The Env protein is also a target of CTL selection, but being the target of neutralizing antibodies likely dominates the biology of this

protein. The *env* gene is the most variable gene in the viral genome. Much of the variability is concentrated in linear sequences that represent surface loops on the protein structure.¹⁴⁸ The variability in these loops likely represents decoy targets for antibody binding that can tolerate rapid sequence evolution. Another mechanism for avoidance of antibodies is the placement on nonimmunogenic carbohydrate side chains on much of the surface of the Env protein. The HIV-1 Env protein typically encodes signals for 25 carbohydrate addition sites capable of occluding much of the Env protein surface. Furthermore, small adjustments of the placement of the carbohydrate side chains can further impact the binding of neutralizing antibodies.¹⁴⁹ One of the features of the viral Env protein is that it undergoes at least a limited number of sequential rounds of evolution giving rise to neutralization escape variants.^{150,151} An important question is how long the host can maintain this response during the course of infection, and whether immunogens can be designed to induce responses that have potent and broad neutralizing activity.

■ KINETICS OF VIRAL REPLICATION IN VIVO

Infection with HIV-1 typically involves a very small inoculum, as indicated by the low transmission rates. The presence of one or a few genotypic variants after transmission supports the notion that infection is started by a single virus particle or at most a small number of particles.^{152–154} There is an initial period of logarithmic expansion of the virus with the virus doubling every 10–20 hours, and each infected cell results in the infection of approximately 20 new cells.¹⁵⁵ Peak viremia is reached in approximately 3 weeks, concurrent with a large depletion of memory CD4⁺ T cells in mucosal tissues and peripheral lymphoid organs.¹⁵⁶ A decrease in the amount of virus in the blood is correlated with the appearance of a CD8⁺ T cells response.^{144,157,158} By 4–6 weeks the level of virus has reached a steady state, or set point, that is predictive of the rate of disease progression.¹⁵⁹ During this steady state the half-life of an infected CD4⁺ T cell is only 1–2 days.^{160–162}

■ ROLE OF MONOCYTES IN VIRAL PERSISTENCE

One of the paradoxical features of a long term HIV-1 infection is the inverse relationship between the levels of virus found in the blood and the number of target CD4⁺ T cells. Not only is the amount of virus present in the blood plasma predictive of the rate of CD4⁺ T cell loss,¹⁵⁹ but the level of virus in the blood increases with the decline of CD4⁺ T cells. There are two models to account for the increase in virus as the target cells are decreasing. First, reduced immune surveillance could result in increased virus production per infected cell. Evidence in support of this explanation comes

from studies in which SIV-infected macaques were given an anti-CD8 antibody, which transiently reduced the number of cytotoxic CD8⁺ T cells. In these animals there was a transient increase in the amount of virus detected in the blood.^{163,164} Second, tissue macrophages are known to be infected and may produce substantial amounts of virus even with the decline of CD4⁺ T cells.^{165,166} Macrophages are an attractive target cell to be the source of persistent viral infection as they have a longer half-life than a productively infected CD4⁺ T cell, at least in vitro. *env* gene markers for viruses that are able to infect macrophages have been identified in the context of virus isolated from the CNS.^{167,168} It will be important to identify the extent to which, and under what circumstances, viruses with these properties can be found in the peripheral blood as an indication of the source of the virus and as a function of disease progression.

■ VIRAL RESERVOIRS DURING HAART

Perhaps the most confounding aspect of HIV-1 infection has been the inability of an infected patient to clear the virus, even with the use of multidrug therapy. Regardless of the length of time on suppressive therapy virus invariably reappears with therapy discontinuation. There are two models to explain the persistence of virus on therapy.

In one model, viral replication persists at a low level despite the presence of active antiretroviral drugs. The stable persistence of low levels of detectable virus while on therapy supports the idea that residual virus replication is occurring.^{169–171} However, the absence of sequence evolution in some patients on suppressive therapy and the inability to suppress viremia below a stable set point with intensified therapy argue against active replication, but leave unexplained the source of residual virus or the virus that rebounds when therapy is discontinued.^{172–174} The alternative model is that although virus replication is halted by antiretroviral therapy, there is sufficient integrated viral DNA in resting CD4⁺ T cells to be the source of virus to rekindle active replication when the drugs are removed. Virus can be cultured from such cells taken from people on suppressive therapy,^{175–177} and the activation of these cells may well induce expression of a quiescent provirus to produce infectious virus. The viral DNA reservoir that persists during suppressive therapy includes not only DNA encoding infectious virus but also various forms of defective DNA that may not be useful for producing virus but is able to maintain the genetic complexity of much of the history of the infection in that host. More recently a novel model of HIV-1 persistence during therapy was proposed, where in infected stem cells of the monocyte-macrophage lineage undergo clonal expansion and produce low levels of virus, which may explain the detection of residual, clonal HIV-1 populations in some patients on antiretroviral therapy when such viruses cannot be detected in resting CD4⁺ T cells.¹⁷⁸ It remains debatable whether a single reservoir is

responsible for HIV-1 persistence during suppressive antiretroviral therapy,^{179–181} but it is widely assumed that it will be necessary to clear all possible HIV-1 reservoirs to permit the long-term cessation of treatment. Strategies are being explored,¹⁸² although this remains a very challenging problem.

LESSONS FROM OTHER LENTIVIRUSES

The lentivirus genus is distinctive among the genera of retroviruses. The entire lineage of lentiviruses fails to induce tumors (except indirectly through immunodeficiency). Also, lentiviruses are characterized by a persistent infection that frequently involves neurologic involvement. A unifying hypothesis is that the ability of lentiviruses to establish a persistent infection is linked to their ability to infect macrophages. This is a common feature of a number of lentiviruses where it has been examined. The ability of these viruses to persist would then be linked to the long-lived nature of macrophages. Similarly, the ability of macrophages to migrate into the CNS, and/or the ability to infect microglia as cells of the monocyte/macrophage lineage, would account for the frequently observed neuropathogenesis. Finally, infection of other cell types that shares the receptors used to infect macrophages could account for differences in pathogenesis associated with different lentiviruses. Ultimately it is difficult to study macrophages *in vivo* given their dispersion in the body. However, the study of pathogenic mechanisms of other lentiviruses will continue to inform the study of HIV-1 and to define common features of this entire group of distinctive viruses.

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Immunology and Pathogenesis of Human Immunodeficiency Virus Infection

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INTRODUCTION

HIV/AIDS is best described as an infectious disease of the immune system. First described in 1981 by puzzling accounts of opportunistic infections and lymphadenopathy in otherwise healthy gay men, HIV/AIDS has evolved over the years to become one of the most devastating diseases to afflict humankind in history. The effect of HIV on the host is one of profound immunodeficiency in the setting of aberrant immune activation.¹ Whereas immune activation is desirable in most infections, helping the body rid itself of the pathogen, the relentless hyperactivity observed in HIV infection leads not only to an increase in the number of cell targets available to the virus for productive replication but also to aberrancies in lymphocyte turnover, differentiation, and function that ultimately lead to exhaustion of the immune system.

In the early years of the pandemic, when effective antiretroviral therapy (ART) and sensitive means of measuring HIV were not available, immunopathogenic mechanisms associated with the virus were difficult to delineate in infected individuals, and the majority of *in vitro* models developed were later found to be poor surrogates of *in vivo* events.² Since the availability of triple drug regimens in the mid-1990s, the benefits of effective ART have extended beyond the obvious declines in morbidity and mortality to include new opportunities toward understanding the immunopathogenic mechanisms associated with HIV infection. Through cross-sectional and longitudinal studies, it is now possible to establish clear correlates of disease progression and to distinguish in some cases between those effects related predominantly to declining CD4⁺ T cell counts and those effects induced directly or indirectly by ongoing HIV replication. The advent of effective ART, combined with improved techniques for detecting and measuring HIV,³ has also led to a better understanding of HIV reservoirs. These include actively turning over cell populations such as activated CD4⁺ T cells and macrophages, extracellular reservoirs consisting primarily of follicular dendritic cells (FDC) in lymphoid tissues where

over 90% of the viral burden resides,⁴ and persistent intracellular reservoirs such as the resting subset of CD4⁺ T cells. The presence of reservoirs for HIV is thought to be one of the major impediments to the eradication of HIV.⁵

Over the past decade, more thorough analyses of the distinct stages of HIV infection have led to a better understanding of the virologic and immunologic parameters associated with disease progression (Fig. 21-1). Such advances have also given rise to debates on when to initiate ART and when/whether to interrupt ART.⁶ There is growing evidence that the acute phase of HIV infection, defined as the first several months following primary infection, differs markedly from the chronic phase of infection in terms of immune competency and dynamics of HIV replication.⁷ The initial burst of HIV viremia is followed by a reduction in the viral burden that some would argue is mediated by an immune response against HIV and others would argue is driven by exhaustion of the existing pool of target cells for HIV.⁸ The ensuing chronic and usually clinically asymptomatic phase of the disease is thought to be modulated by set-point parameters of infection, including levels of plasma HIV RNA and CD4⁺ T cell count.⁹ There are also indications that the integrity of the immune system, especially CD4⁺ T cell function, can be preserved if ART is initiated during the acute phase of infection.^{10,11} Recent findings suggesting the rapid and possibly irreversible decimation of the CD4⁺ memory T cell pool during the early phase of HIV infection^{12,13} may explain why early intervention with ART preserves immune function.

At the molecular level, impressive advances have been made in a number of areas, ranging from identifying components of the innate immune system involved in transmission of HIV, to delineating why only certain variants of HIV are transmitted, to the discovery of certain host factors thought to be involved in restricting HIV replication and disease progression. The identification of host factors involved in restricting HIV has relied heavily on a select group of HIV-infected patients who remain healthy for many years after infection without having received ART. These individuals called long-term nonprogressors have provided a wealth of

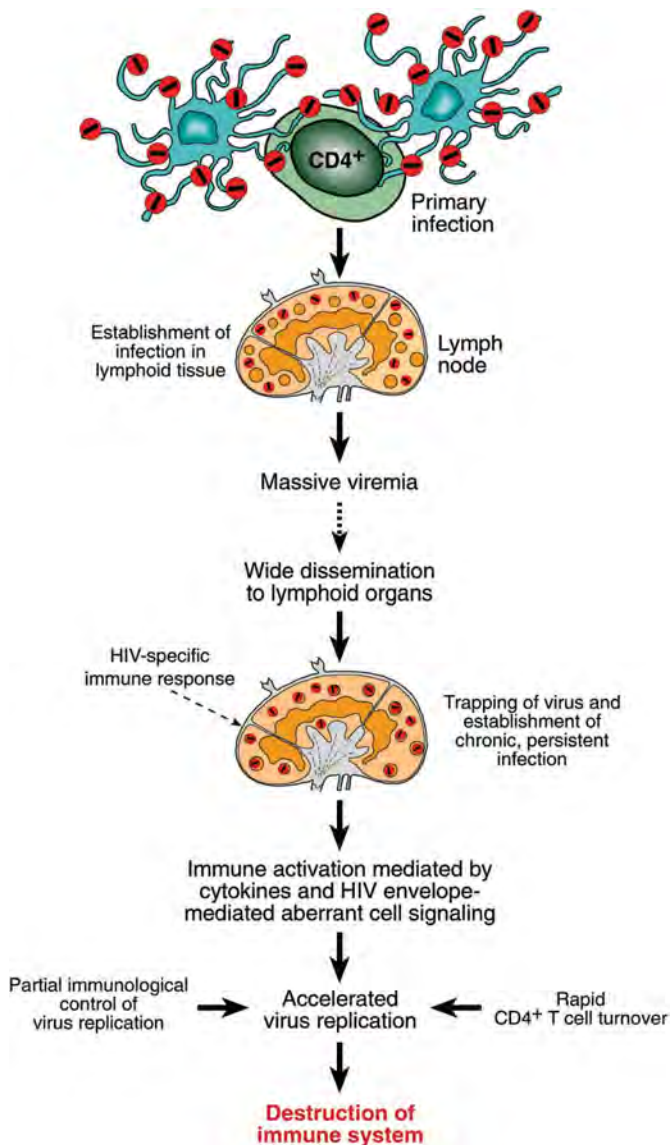


FIGURE 21-1. Events associated with HIV immunopathogenesis, beginning with the initial burst of viremia during primary infection, followed by the induction of an HIV-specific immune response that ultimately fails, leading to exacerbation of HIV-induced immune activation and finally, destruction of the immune system. (From Fauci AS. HIV and AIDS: 20 years of science. *Nat Med* 2003; 9: 839.)

information on the correlates of disease progression and how genetic factors may dictate some of these traits.

The objective of this chapter is to provide an overview of the immunopathogenic mechanisms of HIV disease, to highlight the complex process of immune cell depletion and dysfunction that leads to the collapse of the immune system, and to discuss the host immune response to HIV.

TROPISM AND TRANSMISSION

Several studies carried out in 1983¹⁴ and 1984^{15–17} definitively established HIV as the causative agent of AIDS. In 1984, CD4-expressing helper T lymphocytes were identified as selective targets for HIV replication,¹⁸ another seminal

finding that would begin to explain why CD4⁺ T cells are depleted in HIV-infected patients. However, it would take almost another decade before the full scope of the insult exacted by HIV on the immune system would be appreciated. In 1993, with the use of in situ hybridization, studies on clinically asymptomatic patients revealed that HIV replication was unabated in the germinal centers of lymphoid tissues.^{19,20} It is now well accepted that from a very early stage of infection, HIV establishes itself in lymphoid tissues, where it replicates in CD4⁺ T cells and macrophages, and becomes trapped on the surface of FDC. Whereas lymph nodes and spleen have been extensively studied as sites of active HIV replication, more recent studies indicate that other lymphoid tissues, namely, gut-associated lymphoid tissue (GALT), are also sites of intense viral replication.^{12,13}

Despite the fact that it was well established in 1984 that CD4 was the primary receptor for HIV, mounting evidence over the years indicated that CD4 alone was essential but not sufficient for entry of HIV into its target cell. It became clear that entry of HIV into susceptible cells required a second receptor. The discoveries of chemokine receptors CXCR4²¹ and CCR5^{22–25} as coreceptors for HIV heralded a new era of research on pathogenesis, transmission, epidemiology, and treatment (Fig. 21-2). Prior to these discoveries, variants of HIV were characterized as either T-tropic or M-tropic for their capacity to replicate in vitro in CD4⁺ T cell lines and macrophages, respectively. Pursuant to the discoveries of the chemokine coreceptors, T-tropic variants became known as X4 variants for their ability to infect CXCR4-expressing cells such as CD4⁺ T cell lines which express CXCR4 but not CCR5. Conversely, M-tropic variants became known as R5 virus for their ability to infect CCR5-expressing cells including macrophages.

The discoveries of CXCR4 and CCR5 as coreceptors for HIV have also led to a better understanding of the events that take place during the establishment of infection. Irrespective of the route of transmission and the tropism of transmitted virus, it is increasingly clear that there is strong selection in favor of R5 variants of HIV during transmission and into the early phases of infection.²⁶ Compelling evidence that X4 variants of HIV do not transmit efficiently comes from two sources: (1) individuals who are homozygous for a 32-base-pair deletion in the CCR5 gene that prevents cell surface expression of the receptor are extremely resistant to HIV infection,²⁷ and (2) rapid reversion to R5 variants has been observed in individuals who have been accidentally infected with pure X4 laboratory variants.²⁸ It has been intensely debated whether the selective forces favoring R5 variants are related to available target cells at the site of transmission as discussed below, or replication fitness, or host-mediated responses. However, the fact that all routes of primary infection lead to R5 variants would argue for selection against X4 variants. A related debate that has yet to be resolved

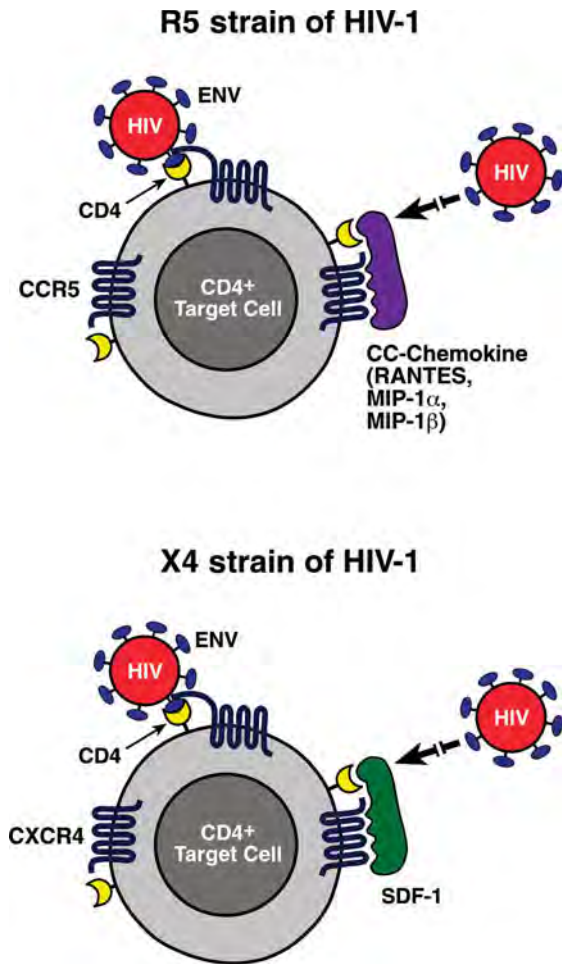


FIGURE 21-2. Elements associated with the tropism and restriction of HIV. Early events of transmission restrict HIV replication to R5 strains of HIV that use CCR5 for entry into CD4-expressing target cells. These strains can be blocked by CC-chemokines. Later during disease progression, X4 strains of HIV may arise. These strains use CXCR4 as coreceptor and can be blocked with SDF-1, the sole natural ligand for CXCR4.

involves the observation that disease progression is associated with the appearance of X4 variants in some but not all patients. Whether the switch relates to the exhaustion of targets for R5 variants or a decline in host responses that keep X4 variants in check remains an open question that has implications not only for pathogenesis but also for the development of antiretroviral therapies aimed at blocking the availability of the CCR5 or CXCR4 receptors to the virus.

Several new areas of HIV research have begun to provide answers to some of the controversies surrounding the earliest events of transmission. Dendritic cells (DC) have long been proposed to play a key role in the transmission of HIV across mucosal barriers and in the migration of HIV to draining lymph nodes where high levels of viral replication take place.⁴ Although DCs are not considered major sources of productive HIV replication, they have the ability to capture virus and form stable conjugates with CD4⁺ T cells, creating favorable conditions for efficient passage of HIV through cell-to-cell

contact.^{29,30} More recently, with advances in imaging technology, the passage of replication-competent HIV from DCs to CD4⁺ T cells has been demonstrated at the cellular membrane level, establishing the term of “infectious synapse” to describe the formation of pores where transfer of HIV from a cell that binds HIV but does not allow replication to a virus-replicating cell is shown to occur.³¹ The binding or “capture” of virus and transfer of HIV virions is thought to be facilitated by C-type lectin receptors (CLR) such as DC-SIGN which was first described in 2000 for its capacity to capture HIV particles and transfer them to target cells for productive viral replication.³² CLR, enriched on DCs,³³ recognize complex carbohydrate structures expressed on pathogens such as the envelope of HIV. These receptors are participants in the innate immune response where pattern recognition, such as recognition of complex carbohydrates by DC-SIGN and the growing number of related CLRs, is being proposed as an important early step in the process of mounting an immune response against an invading pathogen.³⁴ The harnessing of CLRs by HIV is yet another example of how well HIV hijacks various elements of the immune system to facilitate its transmission and propagation.

Finally, there are some indications that macrophages and various DC subsets present in the epithelium and submucosa selectively express CCR5, and as such, may contribute to the selection of R5 viruses during transmission.^{33,35} The selective forces favoring R5 variants of HIV during early infection may also relate to recent evidence indicating that CCR5-expressing memory CD4⁺ T cells, enriched in the GALT, are the primary targets of HIV. Several well-controlled studies in the SIV model have shown that the GALT is decimated during the early phase of infection, with the majority of the depletion being observed in the memory CD4⁺ T cell compartment.^{36–38} Recent findings on intestinal tissues obtained from HIV-infected patients at various stages of disease also suggest that massive depletion of CCR5-expressing memory CD4⁺ T cells occurs during early infections.^{12,13}

IMMUNE ACTIVATION

Immunodeficiency in the face of aberrant immune activation remains one of the most paradoxical hallmarks of HIV disease.¹ In the vast majority of HIV-infected patients who do not receive ART, progression to AIDS is an inevitable outcome that results from a gradual and relentless destruction of the immune system (Fig. 21-3). As will be discussed in greater detail below, the assaults on the immune system are not only restricted to direct and indirect effects on CD4⁺ T cells but also include detrimental effects on B cell, NK cells, and CD8⁺ T cells. Of note, the increased expression of activation markers on CD8⁺ T cells resulting from HIV-induced chronic activation has been shown to be a better indicator of disease progression than either plasma HIV viremia or declining CD4⁺ T cell counts.³⁹

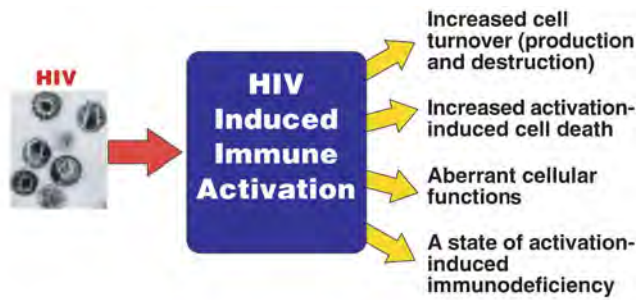


FIGURE 21-3. HIV replication is associated with immune activation that has profound and extensive effects on all cellular compartments of the immune system.

Recent studies on the course of SIV infection in natural and experimental settings in nonhuman primates are providing potentially important insights into HIV-mediated immunopathogenesis in humans. Whereas naturally occurring SIV infection in sooty mangabeys and African green monkeys proceeds without disease progression, the artificial infection of rhesus macaques with the same strain of SIV leads to rapid disease progression in association with heightened immune activation.⁴⁰ A detailed analysis of the differences between these dichotomous outcomes has revealed that sooty mangabeys infected with SIV remain healthy with relatively constant CD4⁺ T cell counts and little evidence of immune activation, despite high levels of viral replication.⁴¹ The current thinking suggests that similar to artificially SIV-infected rhesus macaques, disease progression in HIV-infected humans occurs as a result of aberrant immune activation; however, this association of disease progression with aberrant immune activation needs further delineation.

Why hyperactivation of the immune system would be induced in a pathogenic but not in a nonpathogenic host-virus relationship is a matter of intense research, and has regenerated interest in dissecting virus-host factors involved in the direct and indirect effects of ongoing viral replication on disease progression.¹ As will be elaborated in the following sections on defects of various cell populations of the immune system, there is considerable evidence for indirect effects of ongoing viral replication on cells that are not themselves direct targets of HIV replication. There is also considerable evidence that even cells that can be direct targets of HIV replication, such as CD4⁺ T cells, die through indirect effects of ongoing viral replication, including bystander apoptosis and increased turnover, both proposed to be consequences of persistent immune activation.⁴²

The dysregulation of cells of the immune system that occurs during the course of HIV disease has in part been attributed to HIV proteins released from infected cells and imbalances in cytokine production (Fig. 21-1). The literature is replete with evidence from *in vitro* models demonstrating that HIV-mediated dysregulation occurs through a variety of direct virus or indirect host factors. However, very few of

these observations have been validated *in vivo* where a myriad of interdependent factors contribute to pathogenesis. The studies that have addressed dysregulation patterns *in vivo* have provided conflicting views, some indicating a skewing of the immune system toward a cytokine pattern that would impede cellular immune responses while others have been unable to confirm such shifting patterns.⁴³ Whether cytokine dysregulation plays a role in HIV disease progression remains an open question. Nonetheless, with recent advances in genomic and proteomic technologies, there is good reason to believe that in future the multifactorial nature of HIV immunopathogenesis will be more clearly delineated and correlates of disease progression and immunologic control will be better understood.

ABNORMALITIES IN CELLS OF THE IMMUNE SYSTEM

■ CD4⁺ T CELLS

Mechanisms of CD4⁺ T cell depletion

The depletion of CD4⁺ T cells constitutes one of the major hallmarks of HIV infection and is a primary indicator of disease progression. The underlying mechanisms that lead to progressive CD4⁺ T cell depletion remain a topic of intense debate. This area of research can be broken down into three broad categories: (1) the direct effects of HIV replication on CD4⁺ T cell depletion, (2) the indirect effects of HIV replication on CD4⁺ T cell depletion, and (3) the more elusive systemic effects of the virus on the dynamics of cell turnover, trafficking, and replenishment. Each of these categories will be addressed in this section.

HIV infects and replicates in host cells that not only express CD4 but also express genes that will enable the virus to complete its life cycle.^{44,45} Activated CD4⁺ T cells fulfill both these requirements and as such, represent the main target for HIV. Once a cell is infected, it is likely to die through HIV-induced cytopathic effects or cytotoxic T cell (CTL) activity, thus contributing to CD4⁺ T cell depletion as a result of direct HIV infection. In recent years, investigation of the mechanisms of CD4⁺ T cell depletion by HIV has focused on the subsets of CD4⁺ T cells that were depleted and on their anatomical location. Because HIV also requires a chemokine receptor to enter a cell and because the chemokine receptor CCR5 is the main coreceptor used by HIV, especially in the early stage of infection, it was not surprising to find that memory CD4⁺ T cells, enriched for CCR5 expression, harbored more virus than their naïve counterparts in infected individuals.⁴⁶ More recently, it was also demonstrated that HIV preferentially infects HIV-specific CD4⁺ T cells, suggesting that the virus not only kills CD4⁺ T cells in general, but it has a

preference for those cells whose function is to recognize HIV and mobilize an immune response against it.⁴⁷ These HIV-specific CD4⁺ T cells are preferred targets in large part because they are activated. The concept of activated memory CCR5-expressing CD4⁺ T cells being the preferred targets for HIV has been at the forefront of provocative recent findings suggesting that a preponderance of these cells in mucosal tissues, which are in close proximity to the major routes of HIV transmission, leads to a massive depletion of such cells shortly after infection with either HIV or SIV.^{12,13,37,38} It remains to be determined how these findings impact the slow progressive depletion of CD4⁺ T cells over the subsequent course of HIV infection, and whether such a massive loss of memory CD4⁺ T cells accounts for some of the defects in immune response against HIV. It should also be noted that while mucosal tissues may represent an underappreciated site of HIV replication, peripheral lymphoid tissues throughout the body sustain the bulk of the viral burden, both by virtue of the close proximity of target CD4⁺ T cells and the high density of virions trapped on FDC, and the high levels of activation as evidenced by extensive HIV-induced cellular hyperplasia.^{19,20}

Early in the course of the HIV pandemic it quickly became apparent that the relatively low frequency of infected CD4⁺ T cells during the chronic stages of infection could not account for the progressive depletion of CD4⁺ T cells. Even with the development of sensitive tools to measure HIV and with the ability to probe various tissues, this discrepancy remained true.⁴⁸ Part of the explanation is likely to come from indirect effects of HIV replication on CD4⁺ T cell depletion, often referred to as bystander effects. These effects can be further divided into those bystander effects that are directly induced by HIV proteins and those that are related to a more systemic consequence of viral replication. Apoptosis appears to be the main mechanism by which CD4⁺ T cells die as a result of bystander effects of HIV replication.^{49,50} The aberrant levels of activation induced by HIV lead to the upregulation of ligands and receptors associated with apoptosis, of which Fas (CD95) and FasL (CD195) are participants of the main proapoptotic program that is activated in HIV infection.⁵¹ For example, activated Fas-expressing bystander CD4⁺ T cells undergo apoptosis after interaction with infected CD4⁺ T cells that express FasL as a result of induction by the HIV protein Nef.⁵² Other viral proteins such as Vpr,⁵³ Tat,⁵⁴ and Env⁵⁵ have also been associated with the induction of bystander apoptosis. Taken together, there is a large body of evidence to suggest that bystander killing of uninfected CD4⁺ T cells represents an important mechanism of CD4⁺ T cell depletion.

Finally, CD4⁺ T cell depletion must also be considered in the context of cell turnover, cell trafficking, and the very challenging concept of lymphocyte homeostasis, which reflects how the body strives to maintain a constant number of cells. All three of these elements are controversial and have been actively debated.^{42,56} With regard to T cell turnover, there is

an abundance of evidence to suggest that HIV infection results in increased T cell turnover that reflects an increase in both cell proliferation and cell death. In the 1990s, a series of seminal studies were conducted in HIV-infected individuals before and shortly after receiving effective ART, providing new insight into viral dynamics and lymphocyte turnover.^{57,58} The findings indicated that HIV itself undergoes a high rate of turnover and that HIV-infected CD4⁺ T cells have a very short lifespan, and that the result is a faster rate of CD4⁺ T cell destruction compared to proliferation. In more recent years, notions of increased T cell proliferation and death resulting from HIV-induced immune activation have been added to the paradigm,^{42,56} based primarily on studies that applied DNA labeling techniques to investigate cell turnover in HIV-infected and uninfected individuals.^{59,60} It is now more widely accepted that progressive immune cell depletion occurs over time because cell death occurs at a faster pace than cellular proliferation. However, other factors including cell trafficking, cellular regenerative capacity, and homeostatic compensation, while beyond the scope of this review likely contribute to a greater or lesser degree to the phenomenon of immune cell depletion. HIV infection leads to changes in the expression of receptors involved in migration of cells between tissues, collectively known as homing receptors. Changes in the expression of homing receptors are especially seen in HIV-infected individuals who manifest poorly controlled viral replication.⁶¹ It has been argued that when these individuals begin ART, part of the changes observed in CD4⁺ T cell numbers has to do with tissue redistribution and not simply replenishment.⁶² Furthermore, one of the markers (TREC) used to study the replenishment of CD4⁺ T cells in ART-treated individuals,^{63–65} which measures thymic emigrants such as naïve CD4⁺ T cells, is also modulated by other factors such as immune activation and rate of cell division.⁶⁶ Finally, it is also clear that HIV disease progression is associated with poorly-understood homeostatic compensations, including a tendency to replace loss of CD4⁺ T cells with CD8⁺ T cells as well as CD4⁺ T cells, and increased levels of cytokines such as IL-7.⁶⁷

Functional abnormalities of CD4⁺ T cells

In addition to causing the depletion of CD4⁺ T cells, HIV leads to perturbations in the function of CD4⁺ T cells, limiting their capacity to provide help to the adaptive arms of the immune system. One of the earliest abnormalities to arise in HIV-infected patients is the loss of responsiveness to recall antigens such as tetanus and influenza,⁶⁸ a function that is dependent on the memory response of CD4⁺ T cells. In most patients who do not initiate ART, the degree and spectrum of CD4⁺ T cell defects increase over time to include loss of responsiveness to soluble antigens, mitogens, and finally alloantigens.⁶⁹ Many of these dysfunctions have more recently been attributed to phenotypic changes of CD4⁺ T cell subsets

that occur over the course of HIV infection.⁷⁰ Loss of expression of CD28, a costimulatory molecule for CD4⁺ T cell effector function, occurs during HIV disease progression,⁷¹ possibly as a result of loss of central memory CD4⁺ T cells.⁷² Production of IL-2 by antigen-specific CD4⁺ T cells also declines over the course of HIV infection.⁶⁸ This decline is more pronounced against HIV than other antigens,^{73,74} and recently it has been linked to alterations in CD4 T cell subsets.^{75,76} Finally, CD4⁺ T cells demonstrate poor proliferative response against specific antigens,⁷⁷ a defect that has also recently been linked to the central memory compartment.⁷²

Studies have shown that ART can reverse many of the CD4⁺ T cell defects described in untreated HIV-infected individuals,^{77,78} although recoveries are often incomplete.^{77,79,80} There are indications that individuals who initiate ART during the acute phase of infection, reconstitute their CD4⁺ T cell functions more completely than do those who initiate treatment later during the chronic phase of infection.⁸¹ This reconstitution appears to be more dramatic for HIV-specific CD4⁺ T cell responses.^{10,11} The myriad of functional defects that arise early after infection may be related to the selective and extensive depletion of memory CD4⁺ T cells that has been described in the mucosal tissues.^{37,38} It remains to be thoroughly investigated whether these changes explain the differences in functional reconstitution between rapid and delayed initiation of ART.

■ B CELLS

Very early into the pandemic, even before HIV was identified, numerous abnormalities in B cell of HIV-infected individuals were reported. The initial observations indicated that HIV-infected individuals manifested increased levels of polyclonal B cell activation as evidenced by hypergammaglobulinemia, spontaneous immunoglobulin secretion of cultured cells, and decreased B cell proliferation in response to B cell mitogens resulting from excessive hyperactivity *in vivo*.⁸² Other signs of aberrant cellular activation include the presence of circulating immune complexes and autoantibodies,^{83–85} increased numbers of circulating B cell expressing markers of activation,^{86–88} and increased risk of developing B cell malignancies.⁸⁹ Although the precise mechanisms associated with increased B cell activation have not been fully delineated, ongoing viral replication is a major contributing factor to the B cell aberrancies observed in the setting of HIV infection. Both cross-sectional and longitudinal studies have demonstrated that B cell abnormalities observed in HIV-viremic patients are absent or greatly diminished in HIV-aviremic patients.^{90–93} Furthermore, although some of the effects of HIV on B cell function may in part be related to direct interactions between virions and B cell,⁹⁴ it is widely accepted that most of the detrimental effects of HIV on B cell are due to indirect mechanisms associated with

systemic manifestations, such as imbalances in cytokine and chemokine profiles,^{87,95} and the effects of HIV proteins such as the viral envelope on B cells that are altered by HIV infection.⁹⁶ More recent evidence suggests that interferon-induced genes play an important role in HIV-mediated immune activation through the induction of genes associated with B cell apoptosis and modulators of B cell terminal differentiation.⁹¹ As described below for other cellular immune defects, interferon-induced genes affect all cells of the immune system and may represent a major determinant in dictating disease progression in SIV-infected nonhuman primates.

One of the most paradoxical observations regarding HIV pathogenesis is the notion of profound immune deficiencies in the face of massive cellular immune activation. A very telling example is the notion that B cells demonstrate numerous signs of activation *in vivo*, yet patients respond very poorly to immunization. Antibody responses to both T-dependent and T-independent antigens have been shown to be defective in HIV-infected patients, especially late stage patients.^{97–100} There are indications that ART can partially restore certain responses, especially those to T-independent antigens.¹⁰¹ Antibody responses to HIV itself will be dealt with in a later section.

There is little evidence that HIV productively infects B cell *in vivo*. However, as alluded to above, direct interactions between HIV virions and B cell have been demonstrated both *in vivo* and *in vitro*.^{94,102} The major mode of interaction described *in vivo* involves interaction between components of complement protein C3 breakdown products, which along with anti-HIV antibodies shroud HIV particles circulating *in vivo*, and the receptor for C3, the complement receptor CD21, expressed on B cell and FDC. This interaction enables B cell and FDC to serve as extracellular reservoirs for HIV, with B cell having the unique capacity to migrate in and out of the circulation and into lymphoid tissues where they contribute to the dissemination of HIV infection throughout the body through direct interactions with CD4⁺ T cells.¹⁰³ There has also been some evidence to suggest that the HIV gp120 envelope binds to B cell through a superantigenic type of interaction with members of the VH3 gene family of immunoglobulins.¹⁰⁴ There has also been evidence that this interaction leads to preferential deletion of B cell that express surface immunoglobulins of the VH3 family,¹⁰⁵ although these observations remain controversial.

The role of CD21 in HIV pathogenesis is not only restricted to participation in the dissemination of virus; CD21 also serves as a powerful marker for identifying a subset of B cell that appear to account for a large portion of the functional defects ascribed to B cell in viremic HIV-infected patients.⁹⁰ The expression of CD21 is tightly regulated during B cell differentiation, first appearing when immature B cell start to form functional B cell receptors, modulated to various

degrees in the secondary lymphoid tissues, and downregulated in the final stages of differentiation when B cell become antibody-secreting cells, otherwise known as plasma cells.¹⁰⁶ In HIV-infected viremic patients, a substantial proportion of B cell no longer express CD21, an observation that is consistent with changes that occur during terminal differentiation, including increased immunoglobulin secretion, decreased proliferation in response to mitogenic stimulation, and distinctive morphologic changes.⁹⁰ This subset of B cell, which gradually disappears in aviremic HIV-infected patients, may thus account for several of the B cell abnormalities first described over 20 years ago,⁸² and recent findings demonstrate that it accounts for several of the abnormalities described by DNA microarray technology.⁹¹

In addition to loss of CD21 expression, HIV-infected patients manifest deficiencies in frequencies of memory B cell, as measured by phenotypic and functional markers.^{107,108} In contrast to the loss of CD21, decreased levels of CD27, the major marker used to identify memory B cells, are observed in all chronically HIV-infected patients, irrespective of viral burden.¹⁰⁸ Whether this defect can be modulated depending on the stage of HIV infection at which patients initiate ART, in essence asking whether there is an immunologic benefit to be gained from starting ART during acute infection, remains to be determined. Finally, if the relative percentage of total B cell represented by memory B cells is depleted in HIV-infected patients then the question arises as to what subpopulation replaces these memory B cell. Increases in the frequency of B cell expressing activation markers have been described in both the naïve¹⁰⁹ and more differentiated^{88,91} B cell compartments, in addition to increases in more immature B cell,⁸⁶ and B cell expressing CD5, a marker often associated with autoimmunity.⁸⁵ A few of these findings are conflicting, likely a reflection of the wide variability in the expression levels of certain markers such as CD27, and differences in disease status of patients. A clarification of these observations will require analysis of large number of patients representing a wide spectrum of HIV disease.

■ CD8⁺ T CELLS

One of the most prominent features of HIV infection is the chronically elevated levels of CD8⁺ T cell numbers that are contrasted with a gradual loss of viral suppression by CD8⁺ T cells, especially observed in individuals experiencing high plasma viremia. Among the many immunologic surface markers expressed on CD8⁺ T cells, the presence of CD38 has consistently been shown to be associated with HIV disease progression. CD38 expression is thought to be directly associated with HIV-mediated aberrant immune activation, a process that disables CD8⁺ T cells from effectively controlling viral replication and preventing disease progression.^{110,111}

Although control of viral replication by CTLs is thought to occur in the initial stage of HIV infection,^{112,113} the emergence of HIV escape mutants that evade virus-specific CD8⁺ T cells is almost inevitable and ultimately leads to loss of control of viral replication.^{114–116} However, not all viral CTL epitopes bear signs of escape from immune selection,¹¹⁷ suggesting that functional impairment of CD8⁺ T cells may also contribute to the failure to control viral replication. In this regard, it has been suggested that the bulk of HIV-specific CD8⁺ T cells resides within the CD38⁺CD8⁺ T cell compartment of infected individuals, and that these cells are prone to deletion by apoptosis.¹¹⁸ These findings suggest that increased levels of CD38 expression and increased susceptibility to spontaneous and CD95/Fas-mediated apoptosis in CD8⁺ T cells of infected individuals with active viral replication may seriously compromise the effectiveness of HIV-specific CD8⁺ T cells in eliminating productively infected target cells.¹¹⁸ It has also been suggested that the loss of help from HIV-specific CD4⁺ T cells to HIV-specific CD8⁺ T cells due to impaired proliferation and expansion of the former may contribute to poor CTL function.¹⁰

Several additional mechanisms of immunologic dysfunction of CD8⁺ T cells have been described over the past few years as basic understanding of factors associated with an effective CTL response have been elucidated and new tools for analyzing them have been developed. The delineation of functionally distinct subsets of CD8⁺ T cells, based on the expression of the homing chemokine receptor CCR7,¹¹⁹ led to the observation that one of these subsets, namely preterminally differentiated CD8⁺ T cells lacking expression of CCR7, was overrepresented in HIV-infected individuals and was likely to contribute to the skewing of the HIV-specific memory CD8⁺ T cell response observed in these individuals.¹²⁰ It was speculated that high levels of antigenic stimulation due to ongoing HIV replication, combined with a lack of adequate CD4⁺ T cell helper function, were responsible for the skewing of the HIV-specific memory CD8⁺ T cell response. Chronic antigenic stimulation was also proposed as an explanation for the appearance of a dysfunctional subset of HIV-specific CD8⁺ T cells, defined by the expression of CD57, that produced cytokines but failed to proliferate, and were more susceptible to activation-induced apoptosis than were their CD57⁻ counterparts.¹²¹ In a similar type of study, HIV-specific CD8⁺ T cells from HIV-infected individuals who had not progressed after over 10 years of infection were found to be qualitatively superior to those of patients who progressed at a faster pace.¹²² In this case, it was the effector phase of the CTL response, as measured by the release of perforins which are involved in lysing target cells, that was maintained in HIV-infected individuals who were not experiencing disease progression and lost in individuals who were. Finally, recent studies on both CD4⁺ and CD8⁺ T cell compartments have demonstrated that the pattern of cytokine expression is important for function. It is thought that the expression of

both IL-2 and IFN- γ is necessary for an effective cell-mediated response against HIV and that in the setting of HIV infection, the less effective IFN-secreting T cells often predominate over the more effective IL-2- and IFN- γ -secreting T cells.^{73,123} While this concept needs to be more thoroughly investigated, the notion that the qualitative nature of a CD8⁺ T cell response is more important than its quantitative nature may explain in part the immune cell dysfunction in HIV infection. In essence, these findings are beginning to explain how the paradoxically high levels of CTLs in HIV-infected can nonetheless be ineffective at controlling the virus.

■ NK CELLS

Natural killer (NK) cells are a subset of lymphoid cells that participate in immunosurveillance against tumors and virally infected cells.¹²⁴ They are characterized by the lack of expression of conventional receptors for antigen, but are able to distinguish between cells expressing normal levels of MHC class I molecules and cells that have lost expression of such molecules as a consequence of HIV infection.¹²⁵ A delicate balance between opposite signals delivered by the MHC-I-specific inhibitory NK receptors (iNKR) and by the activating receptors, such as natural cytotoxicity receptors (NCR) and NKG2D, regulates NK cell cytotoxicity.^{126,127} NK cells are capable of eliminating HIV-infected target cells by direct lysis and by mediating antibody-dependent cellular cytotoxicity (ADCC) during the effector phase of immune responses.¹²⁸ It has been demonstrated that HIV downregulates MHC class I molecules on the surface of infected cells, most likely in order to escape from lysis by CD8⁺ T cells;^{129,130} however, there are a number of subgroups of HLA class I molecules that are relevant to the ability of NK cells to exert their cytotoxic effects on HIV-infected targets.^{131,132} HIV appears to selectively downregulate HLA-A and -B molecules while preserving the expression of HLA-C and -E molecules on the cell surface.¹³³ The above findings suggest that the NK-mediated cytotoxicity is probably limited to infected cells that lack HLA-C and -E as certain NK cell inhibitory receptors can bind to those molecules to abrogate lysis.

Several phenotypic and functional abnormalities of NK cells have been described in HIV infection, although it is unclear how HIV induces such changes. Phenotypic analysis of NK cells has shown an expansion of the CD56^{neg}/CD16^{high} subset in HIV viremic individuals.¹³⁴ This subset of NK cells expresses higher levels of iNKR, significantly lower levels of NCR, and is defective in lysing cell targets, suggesting that the expansion of a highly dysfunctional CD56^{neg}/CD16^{high} NK population in HIV viremic individuals is likely to be at least in part responsible for the defective NK cell functions.¹³⁴

It has been demonstrated that the suppression of HIV replication by NK cell-secreted soluble factors is almost entirely mediated by CC-chemokines.¹³⁵ The ability of NK cells to secrete CC-chemokines and thereby to inhibit entry

of HIV into CD4⁺ T cells is significantly depressed among infected individuals with active viral replication.¹³⁶ Finally, NK cells of chronically infected individuals have been shown to be impaired at mediating FC γ RIII (CD16) receptor-dependent ADCC in vitro against target cells expressing HIV envelope proteins.¹³⁷

IMMUNE RESPONSES TO HIV

■ CD8⁺ T CELL RESPONSES

CD8⁺ T cell-mediated immune responses play an important role in host defenses against viral infections. The importance of CD8⁺ T cells in suppression of HIV infection was initially demonstrated in vitro.¹³⁸ Subsequently, it was shown that HIV-specific CD8⁺ CTLs play a central role in controlling viral replication, as evidenced by the emergence of CTL activity coinciding with a decline in plasma viremia during primary infection^{112,113} and a diminution of CTL responses preceding disease progression in infected individuals.^{139,140} CTLs have been found in large quantities in various tissue compartments in infected individuals. They exert their antiviral activities against virally infected cells via several mechanisms. CTLs can directly lyse HIV-infected cells from infected individuals.¹⁴¹ They can also produce CC-chemokines, such as MIP1- α , MIP1- β , and RANTES, which block entry of virus into susceptible target cells¹⁴² and secrete granzymes and perforin after being triggered by antigen presenting cells.¹⁴³ Perhaps the most compelling evidence for the importance of CTLs came from several studies in which CD8⁺ T cells were depleted using monoclonal antibodies to CD8 in SIV-infected monkeys, resulting in an increase in plasma viremia and rapid disease progression.^{144,145}

The qualitative nature of the CTL response is also thought to predicate the ultimate clinical course of HIV infection. T cell subsets (both CD4⁺ and CD8⁺ T cells) can be divided into families based on the variable (V) region of the β chain of the T cell receptor. There are 24 V β families within the T cell receptor repertoire. In examining the diversity of the CTL response during primary infection, it was observed that some individuals had a marked expansion of an individual V β family, while others had more marginal expansions of multiple V β families.¹⁴⁶ Those individuals with restricted CD8⁺ T cell expansions appeared to be at greater risk for disease progression.¹⁴⁷ The basis of such a clinical outcome is unclear but may involve the rapid deletion of the expanded, high-affinity, HIV-specific CTL clones as well as the selection of viral variants that escape killing by CTLs because of the restricted nature of the CTL response.^{115,116} In contrast, patients who generate a broad CTL response, with respect to both epitope and protein targets and the diversity of the T cell repertoire, may be best able to handle the mixture of viral variants or quasi-species that evolve during the course of their infection. The

initial observation that CTL responses may be involved in immune selection of viral variants originated from the observation that particular viral epitopes underwent progressive changes in sequence over time in infected individuals, resulting in subsequent changes in the CTL response of that individual.¹⁴⁸ It was then observed that adoptive transfer of *in vitro* expanded autologous CTL clones that were directed against the HIV Nef protein resulted in the selection of viral variants possessing escape mutations within that viral protein.¹⁴⁹ Moreover, CTL-driven selection of new viral variants was observed in primary HIV infections¹¹⁴ and later during the chronic phase of infection.¹¹⁶ The MHC class I haplotypes of HIV-infected individuals also play a major role in predicting clinical outcome. Given that infected cells display fragments of HIV proteins in association of MHC class I molecules to initiate CTL-mediated immune responses, the magnitude of virus-specific CTL-responses is largely determined by the MHC class I molecules. Indeed, the expression of the MHC class I molecules HLA-B27 and HLA-B57 is associated with favorable clinical outcomes in HIV-infected individuals.¹⁵⁰ The inadequacy of the CTL response to eliminate viral persistence could be attributed to several mechanisms. The best documented evidence comes from the fact that HIV escapes immunologic control by generating mutations in targeted viral epitopes.¹¹⁴ It has been demonstrated that when CTLs exert selection pressure against a particular viral epitope, the error-prone HIV reverse transcriptase and the generation of an enormous number of virions allow replacement of preexisting wild-type virus with ones carrying resistant mutations against CTLs. In addition, there is a marked shift in the composition of the CD8⁺ T cell population following acute infection, with expansion of total CD8⁺ T cells and CD8⁺CD28⁻ cells in particular.¹⁵¹ Induction and expansion of CTLs in the latter subpopulation may be less efficient due to the absence of a vital CD28-CD80 costimulatory pathway.¹⁵² The persistence of these activated CTLs, especially those coexpressing CD38, could be subject to signals that induce apoptosis.¹¹⁸ In addition, there is some experimental evidence that viral variants can actually inhibit CTL effector function against wild-type viruses.¹⁵³ Infected cells may be less susceptible to lysis as a consequence of Nef-dependent downregulation of MHC class I expression, required for the presentation of processed antigen.^{129,130} Finally, the expansion of certain CD8⁺CD57⁺ cells has been associated with the production of factors that inhibit cytotoxic function.^{121,154}

■ CD4⁺ T CELL RESPONSES

CD4⁺ T cells play a pivotal role in adaptive immune responses by providing help to both B cell and CD8⁺ T cells as they mount and maintain antibody and CTL responses, respectively. As described above, the depletion of CD4⁺ T cells

that occurs over the course of HIV infection is an important factor contributing to the inadequacy of the HIV-specific immune response to control viral replication. However, even from the earliest studies there was considerable evidence to suggest that in addition to the quantitative loss of CD4⁺ T cells, there are also qualitative defects that arise in these cells during disease progression and that contribute to the lack of immunologic control of HIV.^{68,155} Similar to the CTL response, most untreated HIV-infected individuals develop HIV-specific CD4⁺ T cell responses,¹⁵⁶ yet these responses are thought to be ineffective due to imbalances in cytokine profiles,⁷³ skewing of CD4⁺ T cell subsets,⁷⁴⁻⁷⁶ apoptosis,⁵¹ and inadequate proliferation.¹⁵⁷ It should be noted, however, that several of these observations remain controversial because there have been conflicting data regarding the association between CD4⁺ T cell responses and HIV viral load. Nonetheless, there is a general consensus to suggest that functional abnormalities in HIV-specific CD4⁺ T cells contribute to loss of immunologic control of HIV in infected individuals.

Evidence that HIV-specific CD4⁺ T cells contribute to the control of HIV infection comes from two sources: HIV-infected individuals who are long-term nonprogressors and those treated early after infection. Strong HIV-specific CD4⁺ T cell lymphoproliferative responses have been documented in individuals who are considered long-term nonprogressors.^{11,158} Similarly, high levels of HIV-specific CD4⁺ T cell responses have been documented in HIV-infected individuals treated during primary infection.^{10,11} It has been suggested that early intervention with ART is associated with a strong HIV-specific CD4⁺ T cell response that leads to a better immunologic control of HIV, as evidenced by slow rebound of HIV viral load when such individuals interrupt therapy.¹⁰ Although these observations are of considerable interest, the number of individuals who were carefully studied remains low and there are indications that the immunologic control is not sustained. In this regard, the effect and clinical relevance of early ART intervention on the HIV-specific immune responses warrant further investigation.

ANTIBODY RESPONSES

Antibody responses play a central role in clearing established viral infections and in providing protection from infection following vaccination. HIV infection is relatively unique in that antibodies appear to be ineffective at clearing the virus in infected individuals or at providing protection against infection. It is not that antibodies are not elicited; to the contrary, the high levels of HIV replication that often occur in the absence of antiretroviral drugs are accompanied by high serum titers of anti-HIV antibodies that decrease substantially as viral load is decreased with antiretroviral therapy.⁹² The reason why HIV is so difficult to neutralize remains a matter of much debate and is the subject of intense research. The high genetic

diversity and high rates of mutations associated with HIV are well accepted as reasons for the lack of effectiveness of the anti-HIV antibody response; however, structural properties of the HIV envelope and its difficulty in eliciting a broadly reactive neutralizing antibody response, the mode of interaction with CD4 and chemokine receptors, as well as immunologic sanctuaries and the timing of the antibody response have also been added to the growing list of reasons why HIV is so difficult to control by antibody.

The initial HIV-specific antibody response that appears 2–4 weeks following infection is non-neutralizing and is thought to have little impact on the dynamics of early viral replication.^{159,160} Recent studies indicate that the appearance of neutralizing antibodies places a strong selective pressure on HIV, and that from that point onward,^{161,162} the presence of antibodies capable of neutralizing the replicating virus is always one step behind virus diversification, essentially enabling HIV to escape its antibody response. This is not to say that HIV-specific antibodies cannot alter the course of infection. There are indications from simian models that the infusion of larger quantities of isolate-specific neutralizing antibodies, a process known as passive immunization, can prevent the establishment of infection.^{163,164}

HIV-1 has evolved a number of strategies to successfully evade control by antibody. At the top of the list is the structure of the HIV envelope, the primary target of HIV-specific antibodies. The external receptor-binding component of the HIV envelope, gp120, assembles as a trimer and associates with the membrane cell-fusion component of the HIV envelope, gp41, through noncovalent interactions. The trimeric nature of the HIV envelope, while regarded as an essential component for a successful vaccine strategy, is also considered a hindrance to antibody binding because of steric occlusion.¹⁶⁵ Another strategy that HIV uses to resist an effective antibody response is to shroud its envelope with carbohydrates, which are highly variable and far less immunogenic than protein. This masking of the HIV envelope, recently termed a glycan shield, is thought to represent an important mechanism of persistence for the virus.¹⁶² Furthermore, the most exposed epitopes of the envelope, namely, the variable loops V1-V5, are as their name implies, highly variable and strain-specific, which make them poor candidates for vaccines and prime candidates for escape. The positioning of the five variable loops also provides a physical barrier to the neutralization-sensitive and more conserved regions of the envelope,¹⁶⁵ adding a further layer of protection for the virus. Recent studies also indicate that the face of the envelope involved in receptor binding is highly malleable and not very accommodating for antibody binding, a concept termed conformational masking.¹⁶⁶ Combined with previous observations indicating that the CD4 binding site is largely inaccessible to the immune system by its positioning at the bottom of a deep cleft,¹⁶⁷ these recent findings underscore the

difficulties the host faces in mounting an effective antibody response against the HIV envelope. Thus, HIV uses a variety of mechanisms to shield its most vulnerable components, namely, the CD4 and chemokine receptor binding sites, from the immune system.

Over the past few years, a major emphasis has been placed on characterizing the few naturally occurring anti-HIV monoclonal antibodies that have been shown to possess broadly cross-reactive neutralizing activities against HIV. It is hoped that by understanding the nature of these unique antibodies it will be possible to find ways of eliciting similar ones either during the course of HIV infection or following vaccination. Four classes of antibodies specific for various constant regions of the HIV envelope have been considered as targets for vaccine development: (1) antibodies to the CD4 binding site of gp120, (2) antibodies to sites in gp120 induced by the binding of envelope to CD4, (3) antibodies to carbohydrate entities on the side chains of gp120, and (4) antibodies to epitopes in gp41. The CD4 binding site of gp120 is highly conserved, restricted in its conformational flexibility, and not very accessible in primary isolates. However, one human monoclonal antibody directed against the CD4 binding site of gp120, b12, has been extensively studied and found to have an unusual protrusion that enables it to fit into the pocket that forms the CD4 binding site and to neutralize a broad range of HIV isolates.¹⁶⁸ Efforts are underway to design an immunogen that would elicit similar antibodies. Similar approaches have been applied to better define and expand those antibodies that bind the HIV envelope more effectively once CD4 is bound. These antibodies, termed CD4-induced antibodies, are found in HIV-infected individuals¹⁶⁹ and have been shown to recognize epitopes of gp120 involved in binding chemokine receptors.²¹ Two of these antibodies, 17b and 48D, have been shown to neutralize most HIV isolates,¹⁷⁰ and it is hoped that the extensive information gleaned from crystallographic studies of this class of antibodies will lead to new vaccine candidates. The conformationally unique and broadly neutralizing antibody 2G12, directed against a carbohydrate moiety in gp120,^{171,172} has also received considerable attention in terms of vaccine potential. However, it remains to be determined whether a carbohydrate entity, which is not usually very immunogenic, could be used as a target for an effective HIV-specific antibody response. Finally, several regions of gp41, the fusogenic component of the HIV envelope, have been shown to be effective targets for neutralizing activity. The most widely discussed anti-gp41 antibody, 2F5, directed against a conserved epitope in the membrane-proximal region of gp41,¹⁷³ is broadly neutralizing¹⁷⁴ and thought to represent an attractive target for vaccine development.

One of the most immunogenic and structurally important regions of the HIV envelope is the V3 loop. Neutralizing antibodies against the V3 loop are the first to arise in HIV-infected individuals,¹⁷⁵ yet have poor immunogen potential for vaccine

development because they are strain-specific and easily mutate under selective pressure. The pressures of the immune system on the V3 loop and other variable regions of gp120 have recently been extensively documented as a means of understanding how the virus mutates in the presence and absence of neutralizing antibodies. Several years ago, when it became evident that most HIV envelope-specific antibodies with potent neutralizing activity against strains of HIV grown in the laboratory, known as laboratory adapted strains, were ineffective at neutralizing isolates obtained directly from infected individuals, the reasons for this conundrum remained unknown. It is now accepted that strains of HIV that are grown in vitro, in the absence of immune pressure, alter their variable regions to expose receptor binding sites and as such, increase their replicative fitness.¹⁷⁶ Conversely, it would be expected that as a neutralizing antibody response is mounted following infection, the virus would alter its variable regions in order to protect its vulnerable regions from exposure. Evidence now exists for immune pressure-driven changes in the HIV envelope;¹⁷⁷ early after infection, when neutralizing antibodies are absent, the HIV isolates present are highly susceptible to neutralization. As neutralizing antibodies begin to appear, modifications in the glycosylation and variable loops of the HIV envelope begin to arise so as to restrict the exposure of conserved vulnerable regions such as the CD4-binding site,¹⁷⁷ in essence, preventing the existing antibodies from accessing neutralization-sensitive regions of the envelope and preventing new antibodies from arising. This extraordinary flexibility thus enables HIV to stay one step ahead of an effective immune response.

■ HOST ANTI-HIV FACTORS

CC-Chemokines

In 1995, shortly before chemokine receptors were shown to be coreceptors for HIV entry into target cells, CC-chemokines MIP-1 α , MIP-1 β , and RANTES were identified as potent inhibitors of replication of certain strains of HIV.¹⁴² This seminal discovery revealed the nature of a major class of soluble HIV-suppressive factors produced by activated CD8⁺ T cells. The general phenomenon of CD8⁺ T cell-derived factors that suppress HIV replication was first described in 1986.¹³⁸ Several months later, CCR5, a chemokine receptor that binds CC-chemokines, was discovered to be a major coreceptor for HIV, thus elucidating the mechanism by which this family of chemokines blocks HIV replication.^{22,23} CC-chemokines are secreted by a variety of cells, including CD8⁺ T cells, NK cells, monocytes, and dendritic cells.¹⁷⁸ They exert potent anti-HIV activity by binding CCR5 on CD4-expressing cells and blocking R5 strains of HIV from accessing their coreceptor (Fig. 21-2). The intrinsic capacity of CC-chemokines to modulate HIV infection and disease pro-

gression has been proposed based on genetic studies,^{179,180} in vitro studies,^{181,182} and association with lack of disease progression.^{183,184} There are also indications that susceptibility to HIV infection is influenced by levels of CC-chemokines that vary according to patterns of gene duplication in the CC-chemokine family.¹⁸⁵ These latest findings suggest that intrinsically high levels of MIP-1 α can outcompete HIV by blocking enough CCR5 receptors to prevent a host from becoming infected. Finally, there is also hope that natural host factors such as CC-chemokines can be developed as therapeutic and prophylactic anti-HIV agents.¹⁸⁶

CD8⁺ T cell-mediated noncytolytic, nonchemokine, anti-HIV factors

The main role of CD8⁺ T cells is to destroy infected cells through MHC-restricted pathogen-specific CTL activity; however, activated CD8⁺ T cells have also been shown to potentially inhibit HIV replication through a mechanism that is not related to CC-chemokines.¹⁸⁷ When activated CD8⁺ T cells are added to cultures of infected peripheral blood mononuclear cells (PBMCs) from HIV-infected patients they can profoundly inhibit HIV replication.^{138,187} The soluble factors that mediate this CD8-derived inhibitory effect other than CC-chemokines have not been fully delineated. The CD8-mediated inhibition occurs independently of the haplotype of the donor used as source of the CD8⁺ T cells, indicating that the effect is not MHC-restricted.¹⁸⁷⁻¹⁸⁹ When HIV-infected CD4⁺ T cells, obtained either directly from HIV-infected individuals or following HIV infection in vitro of CD4⁺ T cells isolated from HIV-negative donors, are cocultured with activated CD8⁺ T cells derived either from HIV-infected or uninfected individuals, potent suppression of HIV occurs although the magnitude of the effect can vary greatly.^{138,183}

The inhibitory effect of CD8⁺ T cells does not require direct contact with CD4⁺ T cells, as activated CD8⁺ T cells separated by a membrane filter still inhibit HIV replication; however, the magnitude of the effect is greater if the cells are in direct contact with each other.^{183,186,187,189} The anti-HIV activity exhibited by CD8⁺ T cells requires that they be activated with stimulating agents such as mitogens and antigens. With the latter, inhibition can be observed with either mixed populations or specific clones, including HIV-specific and non-HIV-specific CTLs.¹⁹⁰ Whereas CD8⁺ T cells produce a number of well-characterized cytokines that inhibit HIV in vitro, addition of antibodies that neutralize these cytokines do not fully abrogate the anti-HIV activity exerted by activated CD8⁺ T cells.¹⁸⁶ The fact that the inhibitory activity cannot be fully neutralized may be related to the nature of the cytokines being secreted by the CD8⁺ T cells, where some may have HIV-inhibitory properties while others have HIV-stimulator properties. Finally, whereas CC-chemokines exert their antiviral activity at the entry of HIV into CD4⁺ T cells and

macrophages, the unknown soluble factor(s) has been shown to suppress viral replication at a postentry step, as evidenced by decreased HIV transcription in infected cells.^{187,191}

OTHER HOST-DERIVED ANTI-HIV FACTORS

Recently, a number of studies have described new cellular factors that inhibit HIV replication, some of which may eventually lead to new therapeutic opportunities.^{192,193} One of the most interesting discoveries involves members of a family of enzymes with cytidine deamination activity, called APOBEC, that are involved in various facets of DNA and RNA editing.¹⁹⁴ The best known member of this family, called AID for activation-induced deaminase, is a key player in the immunoglobulin gene diversification process that takes place as B cell mature in their ability to mount an antibody response. With regard to HIV, another member of the APOBEC family, APOBEC3G, was discovered a few years ago to have potent anti-HIV activity but only when the accessory protein, Vif, was deleted from the viral genome.¹⁹² Shortly thereafter, the mechanism of action was determined, revealing that under wild-type conditions, Vif inactivates the very potent retroviral cDNA-editing activity of APOBEC3G.^{195,196} In the absence of Vif, APOBEC3G induces extensive and debilitating mutations in the HIV genome, essentially rendering newly formed virions incapable of undergoing subsequent rounds of infection. Whether the tightly regulated cellular enzymatic activity of APOBEC3G and its relatives can be harnessed to inactivate HIV without causing extensive damage to the host cell itself remains a daunting task, albeit one that could lead to one of the most potent natural suppressors of HIV.

■ VIRAL RESERVOIRS

CD4⁺ T cells

Any cell type that expresses the CD4 molecule, along with a chemokine coreceptor, can be infected with and harbor HIV in vivo. However, it has been firmly established that CD4⁺ T cells and CD4⁺ cells of the monocyte/macrophage lineage constitute the major reservoirs of HIV in infected individuals.^{197–200} Cellular activation plays a key role in viral replication as well as in the pathogenesis of HIV disease.²⁰¹ In terms of HIV replication, the level of cellular activation in CD4⁺ T cells dictates the extent of the completion of the viral replication cycle in infected cells.⁴⁴ At any given time, only approximately 5–15% of CD4⁺ T cells in the peripheral blood are in an activated state, explaining the relatively low frequency of infected cells found in this compartment.^{202,203} In contrast, a much higher level of cellular activation is observed in the lymphoid tissue compartment where the vast majority of HIV replication and productive infection of CD4⁺ T cells take place.^{19,20} In addition, it has been recently demonstrated that nearly every memory CD4⁺

T cell in mucosal tissue of SIV-infected rhesus macaques becomes infected during the primary phase of infection.³⁷ During the chronic phase of infection, a relatively constant state of heightened cellular activation allows maintenance of stable levels of productively infected CD4⁺ T cells.^{201,204}

The introduction of effective ART has enabled patients to achieve a substantial degree of viral suppression and consequently achieve a dramatic reduction of the frequency of HIV-infected CD4⁺ T cells.²⁰⁵ These observations generated considerable optimism and hope that HIV could be eradicated in infected individuals receiving effective therapy.^{206,207} However, over several years this optimism has largely subsided with the realization that certain HIV reservoirs persist and may be impossible to eliminate, even after several years of effective antiretroviral therapy.^{208–210} One of the most sobering realities regarding efforts to completely eradicate HIV in infected individuals relates to the persistence of latently infected, resting CD4⁺ T cells carrying replication-competent HIV.^{203,209,210} Latently infected, resting CD4⁺ T cells were first identified in chronically infected individuals by demonstrating the presence of integrated HIV DNA and replication-competent virus in these quiescent cells.^{203,211} Numerous studies have since demonstrated that this pool of cells carrying infectious virus persists in essentially all infected individuals tested, who have received effective ART for considerable time, and in whom plasma viremia has been suppressed to below levels of detection, as measured by the most sensitive assays.^{212–215} The mechanism by which latently infected, resting CD4⁺ T cells persist in vivo is unclear. The long lifespan (a half-life of up to 44 months) of infected resting CD4⁺ T cells has been proposed as a possible mechanism for the persistence of virus-infected cells, although low levels of ongoing viral replication may serve to continually replenish the latent viral reservoir in infected individuals receiving effective antiviral therapy.^{212,213,215}

CD8⁺ T cells

Several anecdotal studies have shown that CD8⁺ T cells can sustain HIV replication when patients experience disease progression and their activated CD8⁺ T cells coexpress CD4.^{216,217} However, recent data have indicated that the frequency of highly enriched CD8⁺ T cells carrying HIV is extremely low in infected individuals.²¹⁸ Therefore, it is unlikely that the various immunologic abnormalities observed in the CD8⁺ T cell compartment of HIV-infected individuals are the consequence of direct viral infection. It is also unlikely that CD8⁺ T cells contribute significantly to the viral burden of the infected individual. Finally, it is unlikely that CD8⁺ T cells serve as a significant reservoir for HIV.

Natural killer T cells

NK T cells are a subset of lymphocytes that have been shown to be susceptible to HIV infection.²¹⁹ These cells expressed

CD4 and coreceptors CXCR4 and CCR5. It is unlikely that infected NK T cells are of any clinical significance.

Dendritic cells

Dendritic cells play an important role in modulating the initiation of HIV infection. The primary role of dendritic cells is to capture antigen in peripheral tissues for transport to the lymphoid tissue compartments where proteins are processed and presented to T cells.²²⁰ As discussed in a previous section, HIV can be captured by DC-SIGN expressed on dendritic cells, yet the question of whether these cells can be productively infected *in vivo* remains controversial.^{31,221,222} However, a growing body of evidence suggests that dendritic cells fuel HIV replication by concentrating infectious viral particles on their surface and transmitting them to CD4⁺ T cells.

Monocyte/macrophages

Monocyte/macrophages express low levels of CD4 and several chemokine coreceptors, therefore making them targets for productive HIV replication *in vivo*.^{199,200} They also express high levels of heparan sulfate proteoglycans that facilitate adsorption of virus on to their surface by binding to gp120.²²³ The degree of cytopathicity of virus for monocyte/macrophages is relatively low; hence, their longevity predicts that they may play an important role in the dissemination of HIV and serve as a viral reservoir that is relatively resistant to effective antiviral therapy.²²⁴

Follicular dendritic cells

FDC do not constitute a source for productive HIV replication; however, in the absence of ART, they represent a formidable extracellular reservoir for HIV by trapping an estimated 5–50 billion virions during the acute and subsequent stages of infection.^{19,20,225} Virions bind to FDC in the form of immune complexes that include complement breakdown products and antibodies. Passage of FDC-bound virions to CD4⁺ T cells is very effective and has been shown to occur even in the presence of neutralizing anti-HIV antibodies.²²⁶ Furthermore, this extracellular reservoir is impervious to antiretroviral drugs and has been shown to persist for long periods of time, thus representing a long-lived reservoir that can contribute to the maintenance of low levels of viral replication even in the presence of effective ART.²²⁷

SUMMARY

This chapter has attempted to give an overview of HIV infection as it relates to the impairment and ultimate destruction of the immune system. While it is clear that the information that has been presented will be refined and even altered over the next several years, a few key elements of the disease deserve emphasis. First, among HIV-infected individuals

who do not receive ART, the vast majority will progress to AIDS within an average of 10 years. Second, HIV infection, when left untreated, leads to a quantitative and qualitative destruction of CD4⁺ T cells. Third, other cells of the immune system, including CD8⁺ T cells, NK cells, B cell, and cells of the myeloid lineages, also become dysfunctional over the course of HIV disease. Fourth, a substantial proportion of the deleterious effects of HIV on the components of the immune system can be attributed to HIV-induced immune activation. Fifth, there is clearly a distinction to be made between the events that take place during the acute phase of the infection and the chronic, protracted phase of the infection. It remains to be determined whether therapeutic intervention during the acute phase of disease can reverse the level of immune dysfunction observed during the chronic phase of disease. Sixth, it is clear that the virus uses sanctuaries that enable it to persist, perhaps for the lifetime of the infected individual. Finally, effective correlates of immune protection have yet to be delineated, making the development of an effective vaccine problematic at this time.

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William A. Blattner and Manhattan E. Charurat

The field of human retrovirology was inaugurated with the discovery of human T-cell lymphotropic-virus type 1 (HTLV-1), first isolated in 1979 from an African American patient with what is now recognized as adult T-cell leukemia lymphoma (ATL), but then classified as a variant form of cutaneous T-cell leukemia.¹ This discovery is the culmination of a long search for human retroviruses dating to the first decade of the twentieth century, and proof of such viruses in humans—along with the techniques developed—accelerated the discovery of the HIV family of viruses that cause acquired immune deficiency syndrome (AIDS). There are now a total of three known members of the HTLV family of viruses. HTLV-2 was discovered in 1982² and HTLV-3 discovered in 2005.^{3,4} A single isolate, termed HTLV-4, has also been sequenced but has yet to be confirmed.³ Beyond HTLV-1, the other members of this class of viruses do not have clear relationships with disease. All four HTLV viruses have related nonhuman primate homologues in old world primate species; the recent discovery of HTLV-3 and the putative HTLV-4 resulted from molecular epidemiologic field studies targeting persons from remote areas of Cameroon, where human–primate contact through hunting and processing of primate meat is common. The HTLV viruses entered man thousands of years ago and spread exogenously with HTLV-1 and -2 having a well-defined, worldwide distribution characterized by endemic foci and defined modes of transmission, while patterns for the newly discovered types beyond suspected enzootic spread are not yet determined. An estimated 15–25 million people worldwide harbor HTLV-1 infection with approximately 4% developing ATL and an equal number nonmalignant, HTLV-associated diseases.^{5,6}

CLASSIFICATION AND MORPHOLOGY

■ CLASSIFICATION

Within the taxa of RNA reverse transcribing viruses, the HTLV viruses, along with bovine leukemia virus (BLV), are classified in the subfamily *Retroviridae* within the genus

Deltaretrovirus (formerly termed oncovirus).⁷ The oncogenic properties of these viruses and their molecular structure distinguish them from retroviruses HIV-1 and HIV-2, which are the member of the genus *Lentivirus*. Both *Deltaretroviruses* and *Lentiviruses* are capable of prolonged asymptomatic infection. In vitro, however, HIV-1 and HIV-2 have cytopathic effects on human T cells, whereas HTLV-1 and HTLV-2 are capable of transforming T cells, resulting in immortalized cell lines.

■ MORPHOLOGY

HTLV-1 and HTLV-2 are diploid single-stranded RNA viruses that replicate through cDNA, a proviral intermediate, via reverse transcriptase, a viral enzyme.⁸ This strategy seems to be central to the ability of retroviruses to induce lifelong infection and diseases of long latency. Both viruses are approximately 100 nm in diameter, with a thin, electron-dense outer envelope and an electron-dense, roughly spherical core (Fig. 22-1).

■ REPLICATION CYCLE

The life cycle of the HTLV viruses involves attachment, membrane fusion, and reverse transcription from an RNA template to a circular DNA provirus that is transported to the cell nucleus and integrated into the host genome. There are, as detailed below, certain viral genes that process structural, genomic, and regulatory processes to create new virions. Both cell-free and cell-to-cell transmission of HTLV-1 are documented, but once infected, viral expansion is primarily through proliferation of proviral DNA-harboring cells rather than through repeated cycles of cell-to-cell infection.⁹ Cell-free transmission engages a cell receptor that has eluded identification for almost 25 years; while cell-to-cell transmission engages additional structures. The discovery of the receptor for HTLV-1, Glut-1, the major vertebrate glucose transporter, derived from careful molecular analysis of the first 160 residues of the HTLV-1 and -2 envelopes. This envelope receptor binding

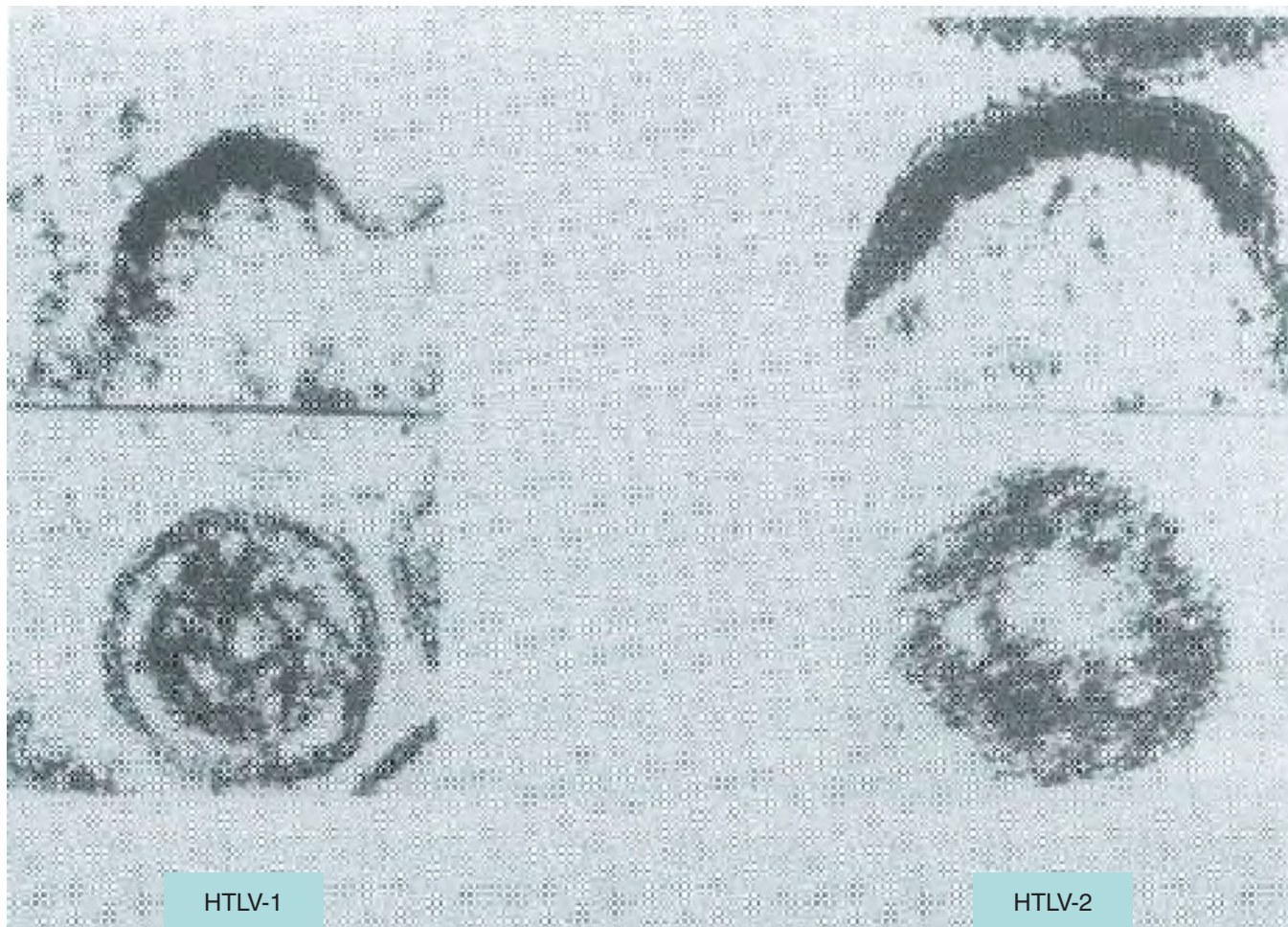


FIGURE 22-1. HTLV-I and HTLV-II have a diameter of approximately 100 nm. The budding particles are shown in the upper panel for each virus and the mature virion in the lower panel. The HTLV-I and HTLV-II viruses have a roughly spherical electron-dense core.

motif shares homology with similar structures of other *Gammaretrovirus* envelopes which also use multimembrane-spanning nutrient transporters as receptors.^{10–12} Given the ubiquity of this receptor, the cellular tropism of HTLV-1 for CD4 cells and HTLV-2 for CD8 cells appears to involve postinfection transcriptional mechanisms, in contrast to HIV which targets CD4 cells through direct binding with a cell-specific receptor.¹³ However, recent studies employing chimeric HTLV-1 and -2 viruses where envelope sequences were swapped demonstrate that cellular tropism is determined by type-specific envelope indicating that *env* is a major viral determinant for HTLV T-cell transformation tropism in vitro.¹⁴ HTLV is preferentially transmitted via direct contact between infected and target cells, through a structure referred to as the virological synapse. The homologue of the *Drosophila* Dlg tumor suppressor (hDlg), a widely expressed scaffold protein implicated in the organization of multiprotein complexes, serves as a cellular binding partner of the envelope glycoprotein of HTLV-1 by stabilizing these glycoproteins at the virological synapse formed between infected and target cells,

hence assisting the cell-to-cell transmission of the virus.¹⁵ HTLV-1 employs a novel strategy to trigger synapse formation by employing the Tax protein in conjunction with ICAM-1 engagement to cause microtubule polarization. In this process, Tax provides an intracellular signal that synergizes with ICAM-1 engagement to cause the T-cell microtubule polarization observed at the virological synapse.¹⁶

MOLECULAR VIROLOGY AND PATHOGENESIS

GENOMIC STRUCTURE AND GENE EXPRESSION

The HTLV provirus genome consists of roughly 9000 nucleotides with two *long terminal repeats* (LTRs) at the 5′ and 3′ ends of the genome (Fig. 22-2A). LTRs mediate proviral integration and *cis*-acting regulatory elements important for viral transcription, viral mRNA processing, and reverse transcription. Retroviral genes generally code for large overlapping polyproteins that are processed by a virally encoded protease and cellular proteases into functional peptide products. The HTLV viruses share with other replication-competent

retroviruses the three main genomic regions of *gag* (group-specific antigen), *pol* (protease/polymerase/integrase), and *env* (envelope) (Table 22-1). However, unlike other vertebrate leukemia viruses, these *Deltaretroviruses* have an additional region called pX that contains four small open reading frames (ORFs): pX-I, pX-II, pX-III, and pX-IV, which employ alternative splicing for protein expression¹⁷ (Fig. 22-2B). The pX ORFs III and IV encode two transcriptional regulatory proteins, the Tax and Rex proteins, which are involved in regulation of virus expression. As shown in Fig. 22-2A and B, two overlapping reading frames are involved in the expression of both of these gene products translated from a doubly spliced mRNA involving the initiation codon from *env* and the remaining sequences from the pX region. The pX ORFs I and II employ alternate splicing to code for other accessory and regulatory genes whose protein products involve cell cycle regulation.¹⁸

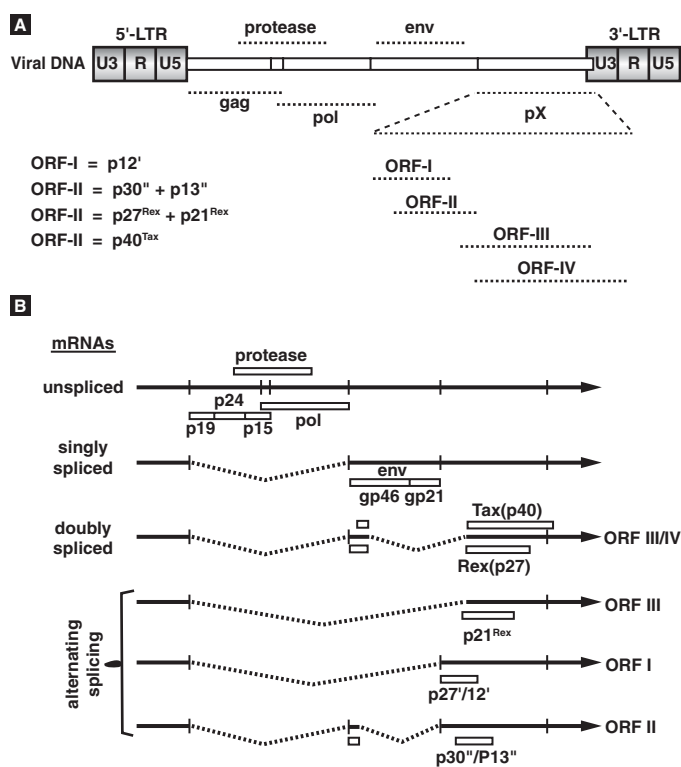


FIGURE 22-2. A. Genomic structure of HTLV-1. The long terminal repeat is organized into three regions: (1) U3, R, and U5, which house the polyadenylation site; the (2) *rev* (response element); and (3) 21-bp enhancer transactivating response elements which are involved in controlling virus expression. *Gag*, group specific antigen, whose products form the skeleton of the virion (matrix, capsid, nucleocapsid, nucleic acid binding protein); *pol/pro*, gene for reverse transcriptase, integrase, and protease; *env*, envelope gene; *tax*, transactivator gene; *rex*, viral regulatory gene involved in promoting genomic RNA production. **B.** HTLV-1 employs several splicing strategies for producing various gene products including unspliced, singly spliced, doubly spliced, and alternatively spliced message. Table 22-1 summarizes the function of various gene products. (With permission from Azran I, Schavinsky-Khrapunsky Y, Aboud M. Role of Tax protein in human T-cell leukemia virus type-I leukemogenesis. *Retrovirology* 2004; 1: 20.)

LONG TERMINAL REPEAT

The LTR is organized into three regions: (1) U5, R, U3; (2) *rev* (response element); and (3) 21-bp response element (Fig. 22-2A). The U3 region contains sequences that control transcription of the provirus. The 21-bp repeats are necessary for *trans*-activating transcriptional activation involving Tax protein. The U3 region also contains sequences responsible for termination and polyadenylation of mRNAs.

GAG AND POL

The Gag proteins form the nucleocapsid, capsid, and matrix structures with a size of p15, p24, and p19, respectively. The *pol* gene encodes for several enzymes: protease that cleaves Gag and Gag-Pol polypeptides into proteins of the mature virion; reverse transcriptase that generates a double-stranded DNA from the RNA genome; and integrase that integrates viral DNA into the host-cell chromosomes. Production of the Gag proteins derives from the translation of the full-length mRNA, which yields a large precursor polypeptide that is subsequently cleaved by the virally coded protease. For the Pol proteins, production depends on translation made possible when the stop codon of the *gag* gene is bypassed, leading to a large polypeptide including *gag*- and *pol*-related proteins, which are subsequently cleaved into functional proteins by the viral protease.

ENV

The *env* gene encodes the major components of the viral coat: the surface glycoprotein of 46,000 MW (gp46) and the 21,000-MW transmembrane glycoprotein (gp21). The envelope is involved in defining cell tropism of HTLV-1 and -2.¹⁴ Production of the Env surface and transmembrane proteins involves translation of a spliced message (Fig. 22-2A) that results in an envelope precursor, cleaved into the subunits.

TAX

From the point of view of viral pathogenesis of HTLV-associated diseases, particularly ATL, the gene products of the pX region—especially HTLV-1 Tax—are among the most intriguing viral proteins in human virology. HTLV-1 Tax is a 40-kilodalton (kDa) protein (p40), while HTLV-2 Tax is a 37-kDa protein (p37).^{19,20} These proteins localize primarily to the nucleus of infected cells, although small amounts of Tax have been found in the cytoplasm and at the viral synapse at the cell surface. The Tax proteins are responsible for enhanced transcription of viral and cellular gene products and are essential for transformation of human T-lymphocytes.²¹ The Tax viral regulatory protein for HTLV-1, like its counterpart, Tat of HIV-1, plays an important role in promoting viral growth and disease pathogenesis. Both promote transacting, transcriptional

Table 22-1. Major Structural and Regulatory Proteins of HTLV-1

Viral Gene	Gene Product (Protein Size in Kilodalton)	Function
<i>LTR</i>		Regulation of viral gene expression, integration of provirus into host genetic material, and regulation of virion production
<i>gag</i>	p15	Nucleocapsid is a small basic protein found in the virion in association with the genome RNA characterized with zinc finger motifs associated with nucleic acid binding
<i>gag</i>	p19	Matrix protein forms close linkage to internal surface of viral envelop via myristic acid
<i>gag</i>	p24	Capsid protein forms the major internal structural feature of the core shell of the virion
<i>gag</i>	p53	Precursor protein for other gag
<i>pol</i>	Integrase	Integrates viral DNA into the host-cell chromosomes
<i>pol</i>	Reverse transcriptase (95 kDa)	Reverse transcriptase generates a double-stranded DNA from the RNA genome
<i>pro</i>	Protease (p14)	Cleaves Gag and Gag-Pol polypeptides into proteins of the mature virion
<i>env</i>	gp46	Envelop surface glycoprotein attached to surface lipid bilayer involved in virion binding to target cell
<i>env</i>	p21e	Envelop transmembrane protein
<i>pX</i>	Tax (p40)	Transactivator for enhanced transcription of viral and cellular gene products
<i>pX</i>	Rex (p27/p21)	Regulator of expression of virion proteins for HTLV stabilizes viral mRNAs and modulates the splicing and transport from the nucleus of viral RNA
<i>pX</i>	ORF I (p12 ^l)	Activation of STAT5 and interference with MHC I trafficking; elevation of cytoplasmic calcium which is antecedent to T-cell activation
<i>pX</i>	ORF II (p30 ^{ll} , p13 ^{ll})	Inhibition of acetyltransferase activity of P/CAF on histones and stabilization of p53. Functions as "latency" protein

activation of the LTR, but the effect of Tax appears to be mediated via expression of cellular growth factors that are abundantly activated by Tax through its transactivation properties. This transactivation of cellular genes by Tax not only facilitates viral replication but has also emerged as a cofactor in disease pathogenesis. The *tax* gene is responsible for the transactivation of virus transcription via *tax*-responsive elements of a number of regulatory enhancers such as the 21-bp enhancer, the nuclear factor- κ B (NF- κ B) binding site, and serum-responsive element. Such promoter interactions lead to activation of a number of cellular genes such as those encoding interleukin-2 (IL-2) and the IL-2 receptor (IL-2R), which promote cell proliferation. Additionally, *tax* activates the proto-oncogenes *c-fos* and *c-erg*, as well as the gene for granulocyte-macrophage colony stimulating factor, an array of early response genes,

the human lymphotoxin gene, and parathyroid hormone-related protein gene, while it transrepresses the β -polymerase gene. Overproduction of IFN- γ via this pathway has been implicated in promoting chronic inflammation that characterizes diseases such as HAM/TSP.²² The mechanism by which Tax interacts with a variety of cell regulatory elements involves nuclear regulatory elements (the NF- κ B pathway); Tax also operates cytoplasmically through the induction of nuclear translocation of active transcriptional factors, but not via pathways typical of other oncoviral proteins that target tumor suppressor genes.²³ The potential role of Tax in leukemogenesis is detailed below.

■ REX

The *rex* gene of HTLV-1 and HTLV-2 encodes two protein species in each virus. In HTLV-1, a 27-kDa protein (p27) and

a 21-kDa protein (p21) appear to result from the use of alternative initiator methionine codons. In HTLV-2, however, a 26-kDa protein appears to be formed by phosphorylation of a serine residue in a 24-kDa protein.²⁴ Unlike the products of *tax* gene, Rex does not directly regulate RNA transcription but, instead, appears to act chiefly at a posttranscriptional level to regulate viral gene expression. The Rex (regulator of expression of virion proteins for HTLV) stabilizes viral mRNA and is essential for export of full-length *gag/pol* and single-spliced *env* mRNA from the nucleus to cytoplasm.²⁵ This function is analogous to that of Rev in HIV-1 and HIV-2.^{26–28} Rex localizes to the nucleus and specifically to the nucleoli of infected cells.^{29,30} Phosphorylated Rex binds with high affinity to *cis*-acting RNA sequences, called Rex-responsive elements, in the viral mRNA.^{31–33} This interaction facilitates the export of mRNA. Rex binding also inhibits mRNA splicing by preventing early steps in spliceosome assembly.³⁴ As a consequence of the accumulation of Rex in the cell, there is an accumulation of unspliced and single-spliced mRNA, favoring the production of structural proteins (Gag and Env). This is accompanied by a decrease in the levels of double-spliced mRNA encoding Tax and Rex. Rex accumulation may also inhibit *tax*, thus slowing viral transcription.³⁵ A fine balance between *tax* and *rex* expression and function may dictate the rate of viral replication within infected cells.

■ OTHER PROTEINS ENCODED BY THE pX REGION

pX ORF I, produced by a similar double-splicing mechanism to the gene products of pX ORF III and IV, codes for a hydrophobic 12-kDa protein, p12^I, and pX ORF II result in the production of two nuclear proteins, p13^{II} and p 30^{II}.¹⁸ In addition to activating nuclear factor of activated T-cells³⁶ (NFAT), p12^I localizes in the endoplasmic reticulum and *cis*-Golgi apparatus and elevates cytoplasmic calcium which is antecedent to T-cell activation and essential for establishing persistent infection.³⁷ Other major structural and regulatory proteins of HTLV-1 are summarized in Table 22-1. The gene products of pX ORF I and II also appear to impact cell proliferation and modulate host-immune responses to HTLV-1 infection.³⁸ Tax and the ORF I and II gene products may play an integral role in pathogenesis of HTLV-associated diseases through their effects on cyclins that regulate cell growth.

■ MOLECULAR COMPARISON OF HTLV-1 AND -2

There is 65% overall nucleotide homology between HTLV-1 and HTLV-2 isolates. For the regions of HTLV-3 that have been sequenced, the distances between HTLV-3 and HTLV-1 and -2 are comparable to the distances between HTLV-1 and HTLV-2. Homology is lowest within the LTRs (30%) and highest within the 3' Tax and Rex regulatory genes (75–80%).^{39–41} The

polymerase region contains the largest ORF in the HTLV genome, potentially able to encode an 896-amino acid product for HTLV-1 and a 982-amino acid product for HTLV-2, which share only 56% homology between types.

■ DETECTION

Several commercially available enzyme-linked immunosorbent assays (ELISA) are the mainstay of HTLV diagnosis, but are not able to distinguish between HTLV-1 and HTLV-2 infection.⁴² The Western immunoblot is the standard confirmatory test,⁴³ and current versions use recombinant synthetic peptides both to confirm positivity and distinguish virus type based on reactivity to both *gag* and *env* gene products. The interpretation of WB results such as reactivities to *gag*-encoded proteins (p19, p24, or p53) without reactivity to *env*-encoded glycoproteins (gp21, gp46) is still a question that needs to be solved in order to avoid overestimating the rate of HTLV-1/2 seroprevalence.^{44–46} The polymerase chain reaction technique (PCR) has proven useful in epidemiologic studies for precisely confirming virus type and more recently for quantifying viral load.⁹ PCR has also been useful for confirming that infection in the absence of antibody is extremely rare.⁴⁷

WORLDWIDE EPIDEMIOLOGY OF HTLV-1

Geographically, HTLV-1 is widely disseminated and estimated to infect 15–25 million persons worldwide.⁶ As shown in Fig. 22-3, distribution is not uniform, with endemic clustering of virus in selected populations in Japan, the Caribbean, central and west Africa, and pockets in Iran and south India. Molecular epidemiology suggests that the three major subtypes identified in man arose from separate interspecies transmissions from simians to humans.⁴⁸ The three major lineages are Melanesian (Papua New Guinea, Melanesia, and Australian aborigines), Central African, and Cosmopolitan groups. Within the Cosmopolitan group are four subtypes: (A) Transcontinental, (B) Japanese, (C) West African, and (D) North African. Within these subtypes, there is a high degree of sequence stability of the viral genome despite hundreds of thousands of years of evolution since human adaptations of these viruses of simian T-lymphotropic retrovirus origin entered man. The stability of HTLV-1 arises because HTLV-1, compared to HIV-1, favors viral expansion through proliferation of proviral DNA-harboring cells rather than infection of new cells by cell-free virions.⁴⁹ As such, the replicative machinery of the cell, rather than the error-prone viral reverse transcriptase, is responsible for maintaining viral genomic stability. HTLV-1 is distributed at low endemicity worldwide but has unique macro- and microepidemiologic features. Virus prevalence varies significantly by geographic region, racial and/or ethnic group, and risk-group subpopulation.⁵⁰ Geographic clustering is

Worldwide distribution of HTLV-I

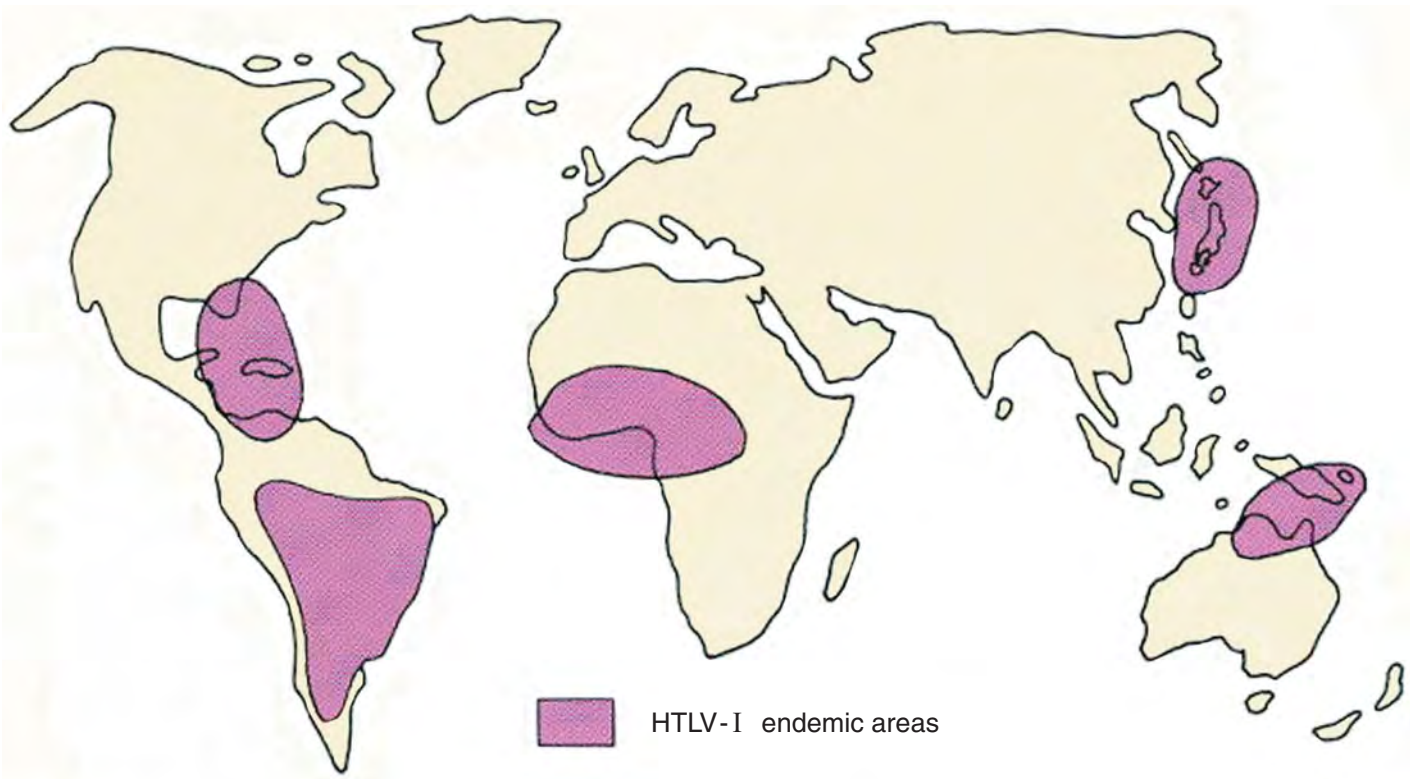


FIGURE 22-3. Geographic distribution of five molecular subtypes of HTLV-I. HTLV-I is endemic to some regions of the world, especially southwest Japan, the Caribbean islands, Southern India, Central Iran, the countries surrounding the Caribbean basin, parts of South America, and parts of Central Africa.

evident in that adjacent national populations are characterized by markedly different prevalence rates. Microgeographic clustering is also observed within endemic regions, with adjacent regions, villages, houses, and families having disparate prevalence rates.

■ ASIA

Geographic clustering of HTLV-1 was first documented in southern Japan (Kyushu, Shikoku, and Okinawa),⁵¹ where population prevalence levels of up to 30% have been recorded, but infection was also seen in villages in Honshu and in Hokkaido in the north among the aboriginal Ainu^{52,53} and among migrants from these endemic areas. Based on *gag* and *env* sequencing, the virus prototype from Japan is termed Cosmopolitan because it is found in other parts of the world, including Africa and the Caribbean, but very rarely in the rest of Asia. HTLV-1 seems to be largely absent in mainland China, Taiwan, Korea, and Vietnam.⁵⁰ Isolates from southern India map with subgroup A (Transcontinental subgroup) of the Cosmopolitan group with diversity representing examples of South African/Caribbean, Middle Eastern, and East Asian subtypes.^{54,55} The Seychelles in the Indian Ocean also appear to be endemic for HTLV-1, probably again reflecting

migration of peoples of African descent.⁵⁶ Melanesia has an unexpectedly high seroprevalence rate, particularly in Papua New Guinea,⁵⁷ where a rate of 14% has been recorded in certain population groups. High rates are also noted in Australian aborigines and in some areas of the Solomon Islands but not in Polynesia.⁵⁷ These Melanesian and Micronesian isolates display the greatest sequence diversity of all HTLV subtypes, implying that they entered when these populations were cut off from outside populations many thousands of years earlier.

■ CARIBBEAN BASIN

This is a well-studied endemic focus of HTLV-1 infection. Soon after the description of ATL in Japan, it was observed that cases of ATL occurred among Caribbean migrants to the United States⁵⁸ and the United Kingdom, and that the virus and disease were prevalent in the region.⁵⁹ Serosurveys have since documented significant rates of positivity in Jamaica, Trinidad and Tobago, the French Antilles, Barbados, St. Lucia, Haiti, and the Dominican Republic.^{60–63} Adjacent areas of South America, including Venezuela, Guyana, and Surinam, and some areas of Central America, including Panama and Honduras, harbor significant foci of seropositivity.⁶⁴ Infection seems to correlate with African-derived New World

populations, fueling the speculation that HTLV-1 was brought to the New World via the slave trade. In Trinidad, where the population is equally divided between Afro-Caribbeans and persons of Indo-Asian descent, and despite these two groups sharing a common environment for over 100 years, HTLV-1 positivity is confined almost exclusively to persons of African descent.^{61,65} These data support the concept of an African origin of the virus in the region. In Jamaica, a population survey provided no evidence of microgeographic clustering such as that reported in Japan.⁶⁶ Socioeconomic group appears to be a strong determinant of seropositivity, and may reflect host factors that serve to maintain low endemicity. Level of sexual exposure is also important, and men and women attending sexually transmitted disease (STD) clinics have markedly elevated rates of seropositivity in both Jamaica and Trinidad.^{67,68} Among blood donors, usually healthy young adults, rates are generally lower than in other population groups.⁶⁹

■ SOUTH AND CENTRAL AMERICA

Endemic foci of HTLV-1 have been observed in South and Central America, but the distribution of HTLV-1 infection is markedly varied and detection is confounded by the coincidence of HTLV-2 infection in many of the same regions. Along the Pacific Coast of Colombia, in an area with an unusually high rate of HTLV-1-associated neurologic disease, very high rates of HTLV-1 seropositivity have been reported among persons largely of African descent.⁷⁰ Altitude is also a significant correlate of HTLV-1 seropositivity in Colombia. Controlling for race, HTLV-1 rates are higher in persons residing at low altitude; controlling for altitude, rates are higher in persons of African compared with Mestizo background. Other areas in South America with documented foci of HTLV-1 include Brazil, Peru, and Chile.⁷¹ The majority of seropositives are persons of African descent, except in Brazil, but some isolated Amerindian groups usually linked to endemic HTLV-2 infection have been found to harbor HTLV-1. One survey in Chile identified pockets of HTLV-1 in persons of non-African descent, which raises the possibility of a transpacific viral passage.⁷² Study of DNA from pre-Columbian mummies have confirmed that the molecular characteristics of this Chilean virus are closely related to the virus from Japan.⁷³

■ NORTH AMERICA

HTLV-1 infection has been documented in African Americans, in certain Alaskan population groups, and in migrants from endemic areas. Blood donors in the United States have rates of HTLV-1/2 infection of 0.43 per 1000, with approximately half the positives carrying HTLV-2.⁷⁴ Among HTLV-1-positive cases, the demographic profile of the positive donor includes direct or indirect links to known viral endemic areas.⁷⁵ HTLV prevalence is higher among tissue donors than among blood donors, with a prevalence rate of 0.068% and incidence of

5.586 per 100,000 person-years (py).⁷⁶ Various population surveys including military populations show a similar pattern, with persons with ancestry in a viral endemic region having elevated rates of seropositivity.⁷⁷ Infection acquired early in life in a viral-endemic area can be carried to a nonendemic area and even transmitted to the next generation. Examples of such migrant groups include persons born in Okinawa who migrated to Hawaii and individuals from the Caribbean who came to the United States.⁷⁸ Another source of seropositivity of persons residing in the United States are persons who have experienced sexual exposure as part of travel in viral-endemic areas or through marriage to a seropositive person from a viral-endemic area.⁷⁹

■ AFRICA

Numerous countries, including Ivory Coast, Cameroon, Ghana, Nigeria, Democratic Republic of Congo (DRC), Kenya, Tanzania, and South Africa, have elevated rates of HTLV-1 seropositivity, but significant artifacts resulting from false-positive results on screening and confirmatory assays have made it difficult to precisely quantify rates.^{46,80–82} In some instances, this “false positivity” has been shown to be due to new variant viruses, HTLV-3 and -4.^{3,4,83} Population-based surveys in Africa have not been specifically designed to fully characterize the patterns of HTLV-1 occurrence, and therefore detailed epidemiologic profiles have not been developed. In the DRC (formerly Zaire), an area of microgeographic clustering of HTLV-1 was detected in the northern equatorial region by surveying HTLV-1 among female prostitutes from different provinces residing in the capitol, Kinshasa.⁸⁴ Reports suggest that HTLV-1-associated neurologic disease is common in this area,⁸⁵ which is now also the epicenter for the DRC HIV-1 epidemic. A cluster of this neurologic disease has also been detected in Senegal.⁸⁶

■ EUROPE AND THE MIDDLE EAST

In Europe, most infected individuals are migrants from viral-endemic areas.⁵⁰ In the Middle East, a focus of HTLV-1 has been detected among Iranian Jews from northeastern Iran but residing now in Israel and New York.⁸⁷ Studies in Iran demonstrate a focus of viral endemicity among persons residing in the Mashad region.⁸⁸ The high frequency of intermarriage among the Mashad people could have amplified and sustained HTLV-1 in this isolated population, and the proximity to ancient transcontinental trade routes could have contributed to viral introduction.

DEMOGRAPHIC FEATURES AND EPIDEMIC BEHAVIOR OF HTLV-1

There is a consistent age-dependent increase in HTLV-1 seroprevalence in practically all geographic areas studied. For example, the age-related HTLV-1 prevalence patterns in

Jamaica and Okinawa share similar features, although the overall prevalence of infection in Okinawa is higher than in Jamaica (Fig. 22-4). Characteristically, the rise in both male and female rates begins in adolescence, but prevalence levels off in males around age 40, while it continues to rise in females.^{52,60} This may be explained by continued exposure throughout life, primarily via sexual exposure but with more efficient male-to-female transmission, and a cohort effect where declining rates of infection in younger birth cohorts give the appearance of rising rates in older birth cohorts.⁸⁹

There is considerable evidence to document that new infections are taking place, in particular among sexually active populations such as attendees of STD clinics.⁹⁰ For example, the rates of seroconversion in STD clinics in Jamaica and Trinidad could potentially account for the age-dependent pattern and the female-to-male rate differential. Among discordant couples identified in the context of transfusion transmission of the index case, the male-to-female rate is estimated at 1.2 transmissions/100 py (95% CI, 0.1–4.3) and 0.4 transmissions/100 py (95% CI, 0.05–1.6), consistent with more efficient male-to-female rather than female-to-male transmission.⁹¹ In Japan, there is evidence to support a cohort effect due to a decline in infection rates in younger birth cohorts contributing to the apparent age-dependent rise.⁹² Possible explanations for this declining rate include changes in standard of living leading to improved nutrition, changes in breast-feeding patterns, elimination of environmental cofactors that facilitate transmission, and declines in other STDs that amplify transmission. Among migrants from Japan to

Hawaii, HTLV-1 rates were highest in those born in Okinawa, lower in first-generation Hawaiian born, and lowest in the grandchildren of migrants.⁹³ The likely factors explaining this pattern of declining prevalence include changes in environmental cofactors for transmission and improvement in socioeconomic status. Nevertheless, there is evidence in Japan of both more common male-to-female and less common female-to-male transmission in older HTLV-1-discordant couples, which may explain the continued rise in female prevalence after that in males plateaus.⁹⁴

EPIDEMIOLOGY OF HTLV-2

HTLV-2 shares some features with HTLV-1 in that endemic clusters have been identified in aboriginal people including selected native American populations and in some isolated populations of pigmys in central Africa.^{95,96} Amerindians residing in North, Central, and South America have varying rates of positivity for HTLV-2. Pockets of relatively high prevalence are encountered among the Seminoles in south Florida and the Pueblo and Navajo in New Mexico but not among various tribal groups in Alaska, a pattern also observed in South America: some indigenous populations in Brazil in the Amazon River basin and Argentina and Paraguay have high rates of HTLV-2.⁹⁷ In Central America, the Guaymi Indians, residing in northeastern Panama near the Costa Rican border, have high seroprevalence rates, but this is not the case for the Guaymi living in southwest Panama. Worldwide spread of the virus has occurred via injection drug use, and very high rates are reported among

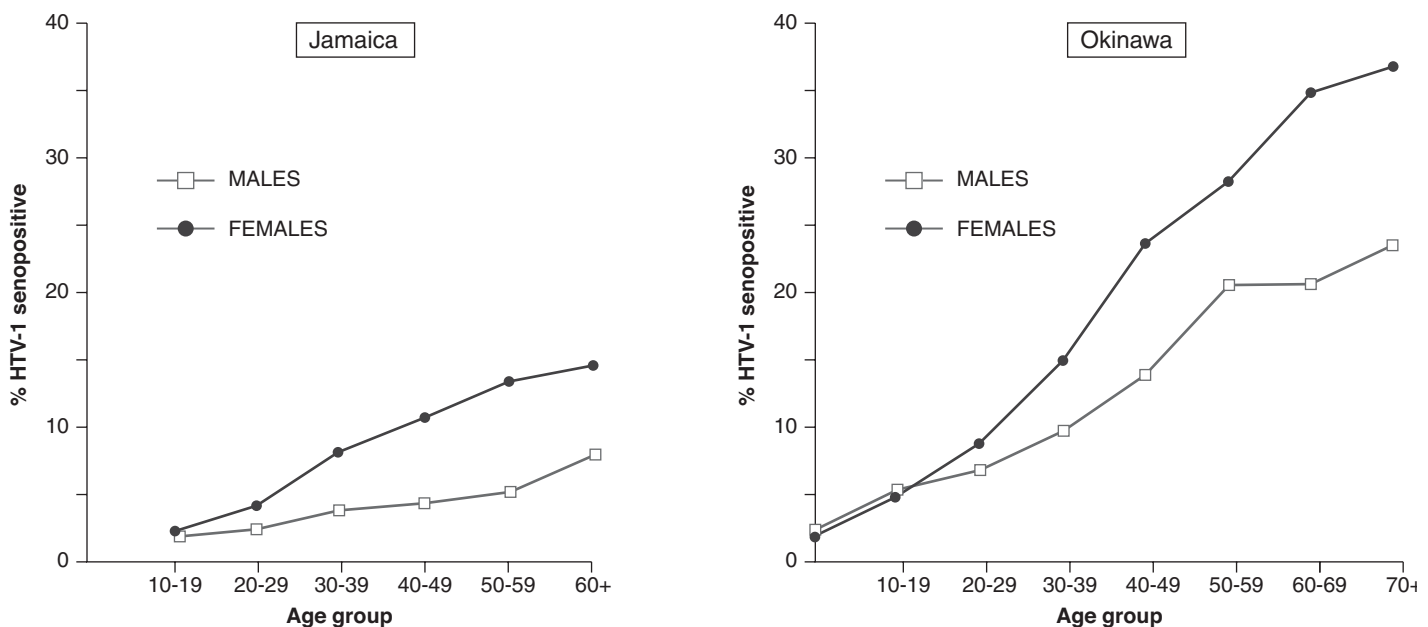


FIGURE 22-4. Age-specific seroprevalence of HTLV-1 in Jamaica and Okinawa. There is a characteristic pattern of higher rates in females than in males, with an age-dependent increase in seroprevalence and a plateauing in males at age 50 but an increase in females. (With permission from Kajiyama W, Kashiwagi S, Nomura H, Ikematsu H, Hayashi J, Ikematsu W. Seroepidemiologic study of antibody to adult T-cell leukemia virus in Okinawa, Japan. *Am J Epidemiol* 1986; 123: 41–47; Murphy EL, Figueroa JP, Gibbs WN, et al. Human T-lymphotropic virus type I (HTLV-1) seroprevalence in Jamaica: I. Demographic determinants. *Am J Epidemiol* 1991; 133: 1114–1124.)

injection drug users in the United States and Europe. Samples from injection drug users dating back to the 1960s document evidence of HTLV-2 infection with prevalence rates of 10–15% and higher. From a molecular epidemiology perspective, HTLV-2 includes four subtypes which appear to originate from a common human ancestor virus that emerged from only one simian-to-human transmission, and the evolutionary pattern in human and primates is separate without the repeated interspecies jumps that characterize HTLV-1.⁴⁹ However, the epidemic spread of HTLV-2 through intravenous drug users to many geographical regions is associated with a 150–350-fold higher mutation rate than observed in endemic strains among aboriginal peoples. The implications of this shift on viral virulence is unknown.⁴⁹ HTLV-2, like HTLV-1, has a characteristic age-dependent increase in the seroprevalence of HTLV-2 antibodies, but without gender differences at any age. Unusually high rates of seropositivity in older groups of injecting drug users in the United States have been linked to the sharing of injection equipment, increasing the possibility of a “cohort effect” resulting from the use of injection techniques that increase risk of blood exposure (e.g., using an eyedropper in place of a syringe).

MODES OF HTLV TRANSMISSION

Table 22-2 shows the list of the routes, modes, and cofactors associated with HTLV-1 and HTLV-2 transmission. The available evidence suggests that routes of transmission of HTLV-2 are similar to those of HTLV-1.

■ SEXUAL TRANSMISSION

Sexual transmission of HTLV-1 occurs among married couples and within sexually active population groups such as commercial sex workers and homosexual/bisexual men. Male-to-female, female-to-male, and male-to-male transmission has been documented. In a well-conducted study of secondary transmission to sexual partners following transfusion-acquired infection, the rate found was 0.6 transmissions/100 py (95% CI, 0.2–1.6).⁹¹ Cross-sectional surveys of heterosexual couples show an excess of couples concordant for HTLV-1 infection; among discordant couples, the female partner is more likely than the male to be positive, except among younger couples, where the low prevalence in husbands approaches that in wives.⁹⁸ The difference in HTLV-1 prevalence between men and women probably reflects the low efficiency of female-to-male transmission as noted above,⁹¹ which requires longstanding sexual exposure, except in the presence of cofactors that interrupt normal mucosal barriers.

Even in the absence of obvious cofactors, female-to-male transmission does occur, as seen in a group of Marine Corps veterans married to seropositive Okinawan women⁹⁹ and in a

Table 22-2. Transmission of HTLV-1/2

	HTLV-1	HTLV-2
Mode of transmission		
Mother to infant		
Transplacental	Low efficiency	Not known
Breast milk	High efficiency	Probable but not quantified
Sexual		
Male to female	Most efficient	Yes but not quantified
Female to male	Efficient	Yes but not quantified
Male to male	Efficient	Not known
Parenteral		
Blood transfusion	Very efficient	Very efficient
Intravenous drug use	Efficient	More efficient
Cofactors of transmission		
Elevated virus load		
Mother to infant	Yes	Not known
Heterosexual	Yes	Not known
Ulcerative genital lesions	Yes	Not known
Cellular transfusion products	Yes	Yes
Sharing of needles and paraphernalia	Yes	Yes

community-based cohort study conducted in the prefecture of Miyazaki, southwestern Japan, in which over 100 discordant married couples have been followed.¹⁰⁰ Seroconversions have been documented in both husbands and wives, with transmission taking place up to the seventh decade. Of 33 seronegative wives married to carrier husbands, 9 (27.3%) converted to antibody-positive status, whereas 4 (6.7%) of 60 initially seronegative husbands of carrier wives seroconverted. Based on these data, the incidence rate of male-to-female transmission (4.9 per 100 py) is 4.2 times higher than that of female-to-male transmission (1.2 per 100 py), with the 95% CI around this estimate of relative risk being 1.3–13.5. While this rate is higher, the relative efficiency (3 or 4:1) of male-to-female versus female-to-male is similar to that reported among sexual partners of seroconverting transfusion recipients

(male-to-female 1.2 transmissions/100 py [95% CI, 0.1–4.3]) and compared to 0.4 transmissions/100 py (95% CI, 0.05–1.6) for female-to-male transmission.⁹¹ In contrast, among 359 concordantly negative couples from the Japanese cohort, the seroincidence was 0.048 per 100 py for females and zero for males over the same period.⁹⁴ The late seroconversion of a discordant partner with a longstanding sexual relationship may be explained in part by increases in virus titer, a marker of virus load that may occur as the couple ages. This relationship has been more directly documented using quantitative PCR; the presence of anti-*tax* antibody is also associated with heightened transmission in this setting.¹⁰¹

Markers of enhanced sexual activity are linked to HTLV-1 transmission. A cross-sectional study conducted in 1989 in Fukuoka Prefecture, Japan, documented a significantly higher HTLV-1 prevalence of 5.1% in female prostitutes, 5.7% in female STD patients, and 2.8% in male STD patients when compared with age- and sex-matched blood donor controls.⁹⁰ Among those with STDs, female patients with syphilis and gonorrhea and male patients with nongonococcal urethritis had a significantly higher HTLV-1 prevalence than controls. Among attendees of an STD clinic in Jamaica, seropositivity in females but not males was associated with a large number of sexual partners.⁶⁷ In a group of homosexual men in Trinidad, a higher number of lifetime partners and longer duration of sexual activity were associated with HTLV-1 seropositivity.¹⁰² The coincidence of other STDs involving an ulcerative genital lesion appears to amplify the risk of horizontal HTLV-1 transmission. In the Jamaican study, current diagnosis of syphilis, among other factors, was associated with HTLV-1 positivity in the STD clinic population.¹⁰³ A study of Haitian women infected with HTLV-1 ($n = 45$) and HIV-1 ($n = 95$) found a significantly higher coincidence of antibodies to herpes simplex virus type 2 (HSV-2) in both the groups, consistent with the notion that recurrent disruptions of the mucous membranes caused by HSV-2 infections facilitate transmission of both the viruses.¹⁰⁴

Studies in Latin America have documented the role of sexual transmission of HTLV-1 in commercial sex workers. In Peru, 467 prostitutes from the capital, Lima, had an overall prevalence of 21.8% compared with 3.1% overall among 510 antenatal clinic patients.¹⁰⁵ The estimate of annual HTLV-1 incidence in this prostitute population over a 3-year period was 1.6%.¹⁰⁶ Further study of 400 sex workers in Lima showed that the prevalence of HTLV-1 increased almost linearly with the duration of prostitution, reaching 16% in those with over 6 years' experience. In a multivariate analysis, duration of prostitution, lack of consistent condom use, and past infection with *Chlamydia trachomatis* were independent risk factors for HTLV-1 infection.¹⁰⁷ In Paraguay, HTLV-1 prevalence was 2.2% in 178 city prostitutes and 3.4% among 117 gay/bisexual men.¹⁰⁸ However, in Chile, where the population prevalence appears to be much lower, serologic testing of 502 prostitutes from Santiago revealed a 0.8% prevalence, similar to other

population-based groups. Additional evidence is available from other parts of the world to support enhanced HTLV-1 transmission in population groups with greater sexual exposure.^{109,110}

■ PARENTERAL TRANSMISSION

Transfusion involving the cellular components of blood is associated with transmission of HTLV-1; approximately 50% of recipients of 1 unit of HTLV-1-positive blood seroconvert.¹¹¹ Transfusion of plasma or cryoprecipitate is not associated with transmission, and whole blood or packed cells are less likely to be infectious if stored for prolonged periods (greater than 1 week), presumably because of the loss of white blood cell viability.¹¹² Elevated antibody titer (a surrogate for virus load) is not associated with increased risk for transmission.⁷⁴ Recipients on immunosuppressive drugs such as corticosteroids are more susceptible to infection, possibly due to a blunting of the immune response to HTLV-1 in the recipient. Blood bank screening was implemented in the United States following reports of HTLV-associated myelopathy in transfusion recipients. U.S. donors with a positive Western blot have a 50% HTLV-1 and a 50% HTLV-2 distribution; risk factors for seropositivity include intravenous drug abuse, birthplace in a viral-endemic area, and sexual contact with a person with this profile.^{75,113} Japanese studies clearly demonstrate that blood donor screening effectively prevents transfusion transmission.¹¹⁴ Intravenous drug use is also a significant vector for the spread of HTLV-1, but most transmission associated with intravenous drug use involves HTLV-2.¹¹⁵

■ MOTHER–INFANT TRANSMISSION

Mother-to-child transmission may account for up to 15% of all cumulative infections,¹¹⁶ and this early-life infection may disproportionately contribute to the subsequent risk for adult T-cell leukemia.¹¹⁷ HTLV-1 has been detected in breast milk and transmitted via breast milk in nonhuman primate and rabbit animal models.¹¹⁸ Intervention trials done in Japan, where bottle feeding is widespread, showed that breast-feeding accounts for most perinatal transmission.¹¹⁹ Bottle-fed infants experienced a 1–2% seroconversion rate, whereas breast-fed infants experienced a 20% seroconversion rate. In a prospective study conducted in Jamaica,¹²⁰ among children born from HTLV-1 positive mothers in follow-up for more than 2 years, 32% of children breast-fed for 12 months or longer were HTLV-1 seropositive, compared with 9% of those breast-fed for less than 12 months. These data strongly suggest that limiting the duration of breast-feeding to less than 12 months might significantly reduce mother-to-child transmission of HTLV-1. Serial Western blots of seroconverting infants of HTLV-1-positive mothers show a pattern in which maternal antibodies are present in

the first few months, but all bands usually disappear at about 6 months of age and new bands subsequently appear in association with native infection. For some infants, breast-feeding had ceased several months prior to seroconversion, but latent HTLV-1 viral infection was not detected by PCR of peripheral blood. Viral load measured by maternal antibody titer and viral antigen level on short-term culture is a significant predictor of transmission; presence of antibody to the *tax* antigen is also associated with transmission. Directly measured provirus load in breast milk is the strongest predictor of risk of transmission to children, with the risk of transmission increasing from 4.7/1000 person-months when the provirus load in breast milk was <0.18% to 28.7/1000 person-months when it was >1.5%.¹²¹ Elevated HTLV-1 transmission was reported in association with high-titer antibodies to certain envelope epitopes; this suggests that enhancing antibodies might contribute to transmission.¹²² Additionally, while particular HLA types were not associated, high levels of concordance between maternal and child HLA types are strongly associated with mother-to-child transmission, suggesting a role for cell-mediated immune responses in preventing transmission.¹²³

■ MODES OF HTLV-2 TRANSMISSION

Sexual transmission of HTLV-2 has been difficult to study in the United States because of the high frequency of injection drug use among the study populations. In virtually every study of female prostitutes, injection drug use was the major risk factor for seropositivity. Studies in aboriginal populations do document evidence for sexual transmission. For example, a case-control study conducted among the Guaymi Indians of Panama showed among females that early sexual intercourse and number of lifetime sex partners were associated with increased risk. Among males, intercourse with prostitutes was associated with HTLV-2 seropositivity.¹²⁴ Among blood donors in the United States, high viral load and duration of relationship in concordant couples support a role for sexual transmission as well.¹²⁵

HTLV-1 AND HTLV-2 DISEASE ASSOCIATIONS

Since the first description of the link between ATL and HTLV-1, the list of possible associations has expanded greatly (Table 22-2). ATL is a clinicopathologic entity first described in 1977 in Japan¹²⁶ and subsequently shown to be caused by HTLV-1, representing the only disease where a virus is directly involved in leukemogenesis. Other HTLV-1-associated diseases include a chronic neurologic disease called *HTLV-1-associated myelopathy/tropical spastic paraparesis* (HAM/TSP),¹²⁷ a chronic skin condition of children called *infective dermatitis*,¹²⁸ and a variety of inflammatory/autoimmune syndromes thought to result from immune perturbation.

■ ADULT T-CELL LEUKEMIA/LYMPHOMA

ATL was first reported in Japan as a mature T-cell leukemia/lymphoma with a spectrum of clinical signs and symptoms including peripheral blood involvement, characteristic polylobated mononuclear cells called “flower” cells, hypercalcemia, lytic bone lesions, and cutaneous, nodal, and extranodal lymphoma exhibiting considerable pleomorphism.^{129,130} HTLV-1 was originally isolated in the United States from an African American male patient presenting with features of classic ATL but originally diagnosed as having an aggressive variant of mycosis fungoides.¹

HTLV-1 and ATL

Studies in Japan and the Caribbean and among migrants from these areas unequivocally linked HTLV-1 to ATL^{59,58} and through molecular analysis documented monoclonal integration of HTLV-1 in the genome of the cell. ATL cases have been reported in Africa, North and South America, the Caribbean region, the Middle East, Taiwan, Japan, and in Australian aborigines.¹³¹ ATL occurs with equal frequency in men and women, despite the disproportionate occurrence of HTLV-1 infection in women—a finding consistent with the hypothesis that most ATL is associated with early-life infection with HTLV-1 when the sex ratio is equal.^{132–135} For unexplained reasons, the peak incidence of ATL is in the fifties in Japan and a decade younger in the West Indies.⁵⁸ In persons under the age of 50, HTLV-1 is the chief cause of lymphoma in viral-endemic areas.¹³⁶

Risk of ATL among HTLV-1 carriers

The attributable risk of HTLV-1 as a cause of leukemia/lymphoma is highest in the forties to fifties and thereafter declines. In Jamaica and Trinidad, over 70% of all lymphoid malignancies are attributable to HTLV-1 exposure.^{117,135} In some instances, ATL occurs in the pediatric age group, with patients as young as 5 and 6 years of age reported, but these instances are extremely rare.¹³⁷ The lifetime risk of developing ATL among healthy carriers is approximately 1–5%, but this figure might underestimate the attack rate for those infected early in life. In comprehensive studies conducted over an 8-year period in Jamaica and Trinidad, all cases of non-Hodgkin’s lymphoma (NHL) in the population were ascertained and blood collected for HTLV-1 determination. The world age-standardized NHL incidence rate in Jamaica was 1.9 ± 0.2 per 100,000 py and in Trinidad was 2.9 ± 0.4 per 100,000 py. Overall, the incidence of NHL increased with age and was higher in males than in females. In the HTLV-1-infected population, NHL incidence was inversely related to age, and age-specific rates were higher in males than in females. However, NHL incidence in those estimated to have acquired HTLV-1 infection in childhood showed no sex difference, and 1 in 1300 such carriers (95% CI, 1 in 1100

to 1 in 1600) per annum were estimated to be at such risk (Fig. 22-5). For T-cell NHL, as proxy for ATL, incidence was highest in those who were infected with HTLV-1 early in life (perinatally or via breast milk), with a high sustained risk from early adulthood in both sexes. Thus, while overall NHL incidence rates reveal that HTLV-1 endemicity does not impose an exaggerated lymphoma burden on these populations, the risk for lymphoma among carriers who acquire infection early in life is dramatic and consistent with the hypothesis that virus exposure early in life is critical for lymphomagenesis.¹¹⁷

ATL subtypes

Four major categories of ATL have been characterized: acute or prototypical type, lymphoma type, chronic type, and smoldering type¹²⁹ (Fig. 22-5). A feature of the natural history of this disease is for the more benign types, smoldering and

chronic types to evolve into the more aggressive types. Acute ATL is an aggressive mature T-cell lymphoma with frequent leukemic involvement (80% of cases) with characteristic pleomorphic polylobulated cells, hypercalcemia (50% of cases), and cutaneous involvement (40% of cases ranging from maculopapular rashes to tumorous lesions). Organ and extranodal involvement is common. Lymphoma-type ATL shares many features with acute ATL, but it is distinguishable by the absence of peripheral leukemic involvement. Both acute and lymphoma types have the most aggressive clinical course and poor prognosis. Chronic ATL presents as T-cell chronic lymphocytic leukemia, and a substantial proportion of patients have cutaneous involvement; nodal or extranodal involvement is rare, and hypercalcemia is absent. Smoldering ATL resembles mycosis fungoides/Sézary syndrome, with cutaneous involvement presenting as erythema or as infiltrative plaques or tumors, and Pautrier's microabscesses may be

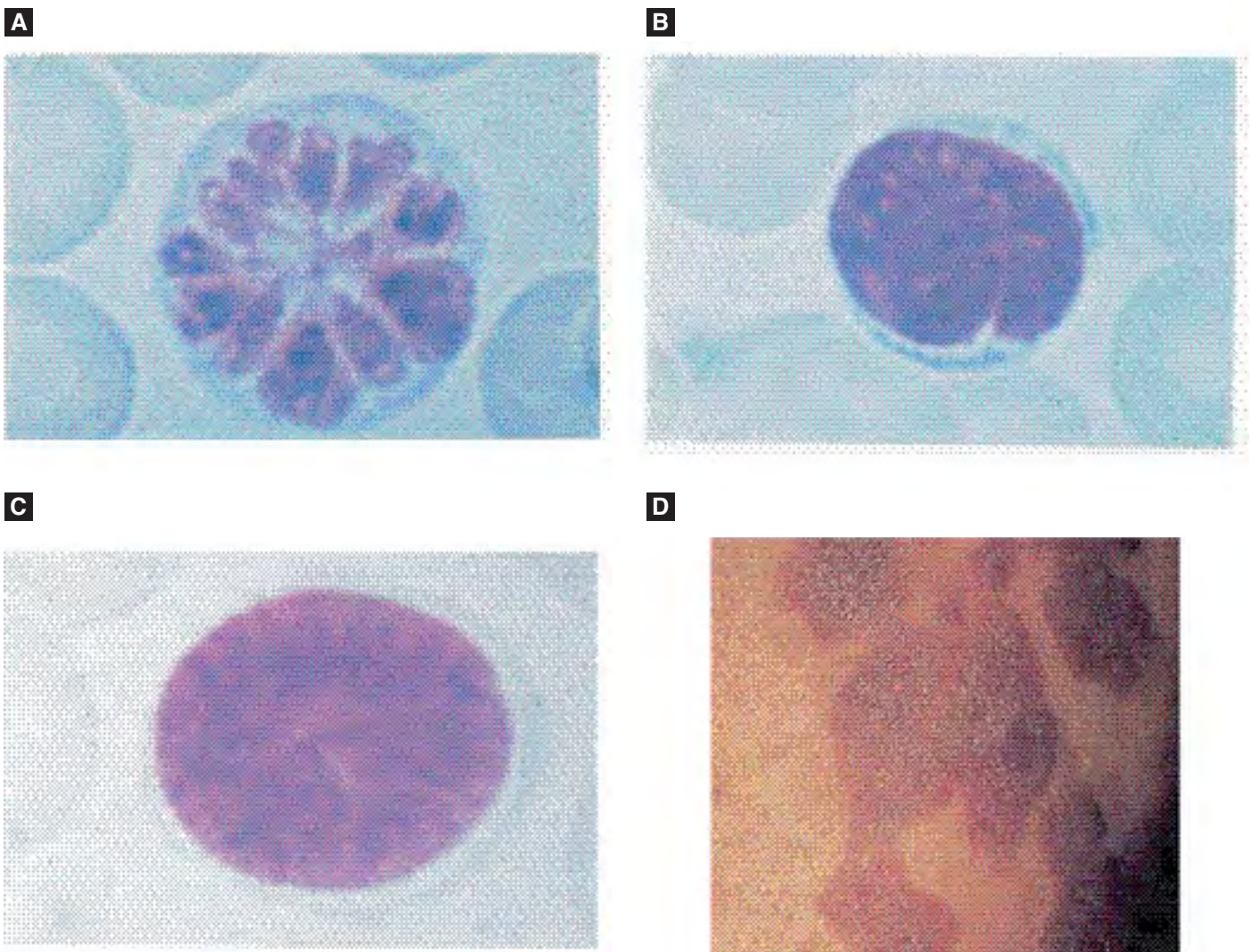


FIGURE 22-5. Features of adult T-cell leukemia: **A.** “flower cell” from acute ATL; **B.** buttock cell from chronic ATL; **C.** typical cell from smoldering ATL; **D.** cutaneous involvement details of the features are discussed in text. (With permission from Yamaguchi K, Kiyokawa T, Futami G, et al. Pathogenesis of adult T-cell leukemia from clinical pathologic features. In: Blattner WA, ed. *Human Retrovirology: HTLV*. Philadelphia, PA: Lippincott-Raven, 1990, p. 163.)

observed. Chronic and smoldering forms have a better prognosis than acute and lymphoma type. The distribution of clinical subtypes appears to vary by geography with acute forms more prominent in Japan than in Jamaica where the lymphoma type is more frequent.¹³⁶

Pathogenesis

The etiology of ATL is well established by the virtually universal association of HTLV-1, either in the context of positive HTLV-1 antibodies in the vast majority of cases and the finding of monoclonally integrated HTLV-1 or, in some cases, defective virus that always includes viral genes critical for transformation, notably the HTLV *tax* gene whose integration sites vary markedly between individuals.^{138,139} As summarized above, HTLV Tax has pleiotropic effects that along with some accessory genes have powerful impacts on fundamental cellular gene control mechanisms that contribute to malignant transformation.¹⁴⁰ However, by the time the multistage process involved in malignant transformation is complete, the *tax* genes of HTLV-1 are fully silenced as mutagenic mutations of the cell promoted by Tax become constitutively expressed and host-immune responses to Tax are made irrelevant to host-tumor responses.¹⁴¹ Over the course of HTLV-1 infection leading to malignancy, Tax interacts with numerous cellular proteins to reprogram cellular processes to alter transcription, cell-cycle regulation, DNA repair, and apoptosis, resulting in proliferation of cells that increasingly accumulate carcinogenic mutations.¹⁴² Among its targets, Tat upregulates CREB, NF- κ B, and SRF signaling pathways, transactivates

by *cis*-acting mechanisms cellular promoters including those of cytokines (IL-13, IL-15), cytokine receptors (IL-2R- α), and costimulatory surface receptors (OX40/OX40 L) leading to upregulated protein expression and activated signaling cascades (e.g., Jak/STAT, PI3Kinase, JNK), and stimulates cell growth by direct binding to cyclin-dependent kinase holoenzymes and/or inactivating tumor suppressors such as p53 and DLG.^{143–146} Tax also silences cellular checkpoints such as checkpoint kinase 2 (Chk2) that coordinate cell-cycle progression with DNA repair and cell survival or death which in turn guard against DNA structural damage and chromosomal missegregation. By inactivating these processes, cells with potential carcinogenic mutations survive, they do not undergo cell death, and they allow leukemia to emerge in a portion of HTLV-1 carriers.¹⁴⁷ Additionally, host genetic factors are implicated in the findings that show that HLA-A*26, -B*4002, -B*4006, and -B*4801 alleles predispose to ATL because of the limited recognition of HTLV-1 Tax peptide anchor motifs and epitopes capable of generating anti-HTLV-1 Tax CD8⁺ cytotoxic T-lymphocytes (CTLs), thus predisposing such individuals to persistent and poorly regulated HTLV infection.¹⁴⁸ Thus as summarized in Fig. 22-6, Tax exerts pleiotropic effects on cell growth by promoting uncontrolled cell growth, abrogating DNA repair mechanisms, and preventing cell-cycle arrest and apoptosis in promoting the development of the malignant T-cell phenotype.¹⁴⁰ Additionally, the gene products of the ORF I and II impact other cellular functions that promote cell growth and may also promote the carcinogenic process.

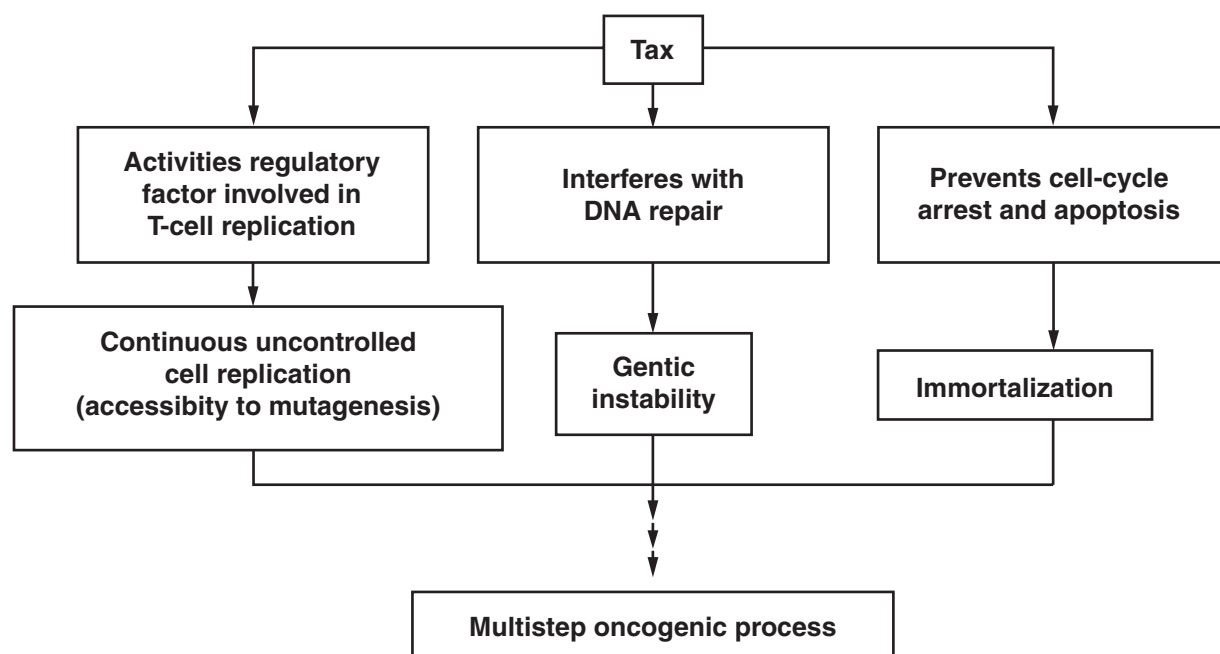


FIGURE 22-6. The role of Tax in ATL pathogenesis involves multiple pathways of cellular dysregulation and oncogenic mutation as detailed in the text. (With permission from Azran I, Schavinsky-Khrapunsky Y, Aboud M. Role of Tax protein in human T-cell leukemia virus type-1 leukemogenicity. *Retrovirology* 2004; 1: 20.)

Prognosis

The prognosis of patients with acute and lymphoma-type ATL is poor.¹⁴⁹ Most patients with the acute and lymphoma types die within 6 months of diagnosis (Fig. 22-7¹⁵⁰). Significant prognostic factors include poor performance status at diagnosis, age over 40, extensive disease, hypercalcemia, and high serum LDH level.⁵⁸ Death usually results from rapid growth of tumor cells, hypercalcemia, bacterial sepsis, opportunistic infections such as *Pneumocystis carinii* pneumonia, and other infectious complications seen in patients with lymphoma-associated immunodeficiency. In Jamaica and Trinidad, a major cause of death is bacterial sepsis.¹³⁴ Smoldering ATL has a relatively good prognosis with a 70% 5-year survival. The chronic subtype has a 20% 5-year survival that while dismal is better than the 5% 5-year survival observed in acute and lymphoma types.

Treatment

ATL carries a very poor prognosis because of the resistance of leukemic cells to conventional chemotherapy. With a 70% 5-year survival, many hematologists recommend watchful waiting in the case of smoldering and chronic ATL, although treatment with prednisone with or without cyclophosphamide is sometimes used. Treatment with aggressive therapy for these forms is associated with high rates of complicating infections resulting from the damaging effects of therapy on the bone marrow. The acute and lymphoma types of ATL are aggressive high-grade lymphomas with a generally poor prognosis, although some cases do respond with prolonged remission to multidrug regimens.^{61,151,152} In Japan, large trials of vincristine, cyclophosphamide, prednisolone, and doxorubicin (VEPA) or VEPA-M (adding methotrexate) as well as more complex 9- and 10-drug regimens have shown some success but poor long-term survival.^{152,153} While initial

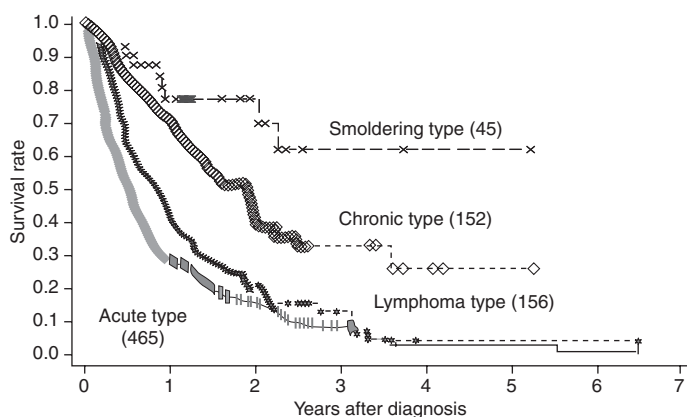


FIGURE 22-7. Survival patterns of different ATL subtypes after polychemotherapy. Acute and lymphoma-type ATL have the poorest prognosis after chemotherapy (see text). (With permission from Tsukasaki K, Ikeda S, Murata K, et al. Characteristics of chemotherapy-induced clinical remission in long survivors with aggressive adult T-cell leukemia/lymphoma. *Leuk Res* 1993; 17: 157–166.)

response rates, even for the poorest risk categories, are over 50% and complete remissions are achieved in 20%, these responses can be short-lived, with relapses occurring in weeks to months often involving the central nervous system.¹⁵² Recent reports suggest a therapeutic role for allogeneic hematopoietic stem cell transplantation (allo-HSCT) for patients with ATL. An analysis of 40 patients receiving allo-HSCT for aggressive ATL cases in Japan reported that all evaluable cases entered complete remission with median survival time at 9.6 months for all patients. The estimated 3-year overall survival was 45.3%, relapse-free survival 33.8%, and disease relapse 39.3%. While not statistically significant among 10 who relapsed, 5 cases achieved a second complete remission including 3 by reduction or cessation of immunosuppression, suggesting a graft-versus-ATL effect.¹⁵⁴ Another approach that requires systematic evaluation builds on the observation that some patients respond to a combination of zidovudine and IFN- α , which induces a high rate of complete remission and lengthens survival when used in combination with conventional cytoreductive therapy.¹⁵⁵ A recent study of arsenic trioxide demonstrated responses in patients failing prior chemotherapy but involved high levels of toxicity.¹⁵⁶ Newer agents such as proteasome inhibitors, retinoids, and angiogenesis inhibitors, as well as cellular immunotherapy, are also being evaluated.¹⁵⁷

NEUROLOGIC DISEASE

A neurologic syndrome called HAM/TSP is etiologically linked to HTLV-1.¹²⁷ The syndrome results from demyelination of the long motor neurons of the spinal cord causing a variety of symptoms, sometimes acutely, including stiff gait, spasticity, lower extremity weakness, back pain, urinary incontinence and impotence, and rarely ataxia. Lesions of the central nervous system are detected in some cases. Transfusion transmission of HTLV-1 has been associated with dramatic examples of acutely progressive neurologic symptoms; in Japan, blood transfusion is a significant risk factor for HAM/TSP.¹⁵⁸ It is estimated that disease incidence among carriers is approximately half that of ATL.¹⁵⁹ Females are approximately two times more likely to develop HAM/TSP; in Jamaican cases, sexual transmission is a documented risk factor.¹⁶⁰ The majority of adult cases occur in the 30–50-year age group, but pediatric cases as young as 3 years of age do occur. These patterns suggest that the latency period for HAM/TSP is shorter than that for ATL and both early-life and adult exposures cause disease.

Pathogenesis

The pathogenesis of HAM/TSP results from a complex interaction of defective host-immune responses that fail to control viral overproduction despite very high levels of cytotoxic

T cells, an imbalance in the T-helper response, immunogenetic factors that signal increased susceptibility to disease, and recently identified molecular mimics of viral proteins to neurocellular structures. Following HTLV infection, CTLs that target viral antigens play an essential role in the regulation of viral expression and control¹⁶¹ as seen by the fact that up to 1% of all CD8⁺ CTL among carriers recognize at least one epitope of HTLV.^{162–167} In the case of the healthy carrier, there appears to be a dynamic equilibrium between viral replication and immune CTL responses that target Tax expressed by infected CD4 target cells.^{165–168} As a consequence of ongoing Tax proliferation, there is a cell-associated expansion of HTLV-1 genome-containing CD4⁺ cells and a compensatory expansion of CD8⁺ CTL. As the number of CD4⁺ cells containing the HTLV-1 genome expands, HTLV-1 antigens are expressed on the cell surface and become targets for CD8-mediated cytotoxic killing, maintaining this equilibrium. In the case of HAM/TSP, there is an imbalance in immune response manifested by an overexpression of Tax, high numbers of Tax-specific CTL, and excessive elevations in viral load, reflecting an aberrant immune response. Recent studies have started to unravel the pathogenic basis of this response. For example, CXCL10/IP-10, a T-cell type 1 (Th1)-associated chemokine, is significantly elevated in the CSF of HAM/TSP patients compared with controls, and exceeding levels noted in multiple sclerosis where this chemokine has been shown to be elevated, in which CXCL10/IP-10 upregulation was previously reported.¹⁶⁹ Similarly, cytokine signaling molecules, including transcription factors T-bet and GATA-3, IL-12R- β 2 and suppressors of cytokine signaling (SOCS), such as SOCS1, all markers of Th1 signaling, are significantly increased in HAM/TSP patients in comparison with HTLV-I-uninfected individuals; while SOCS3, a marker for Th2 cells, decreased in HTLV-I-infected individuals, pointing to an imbalance in Th1 immunity in HAM/TSP.¹⁷⁰ Immunogenetic factors play an important role as noted by the finding that the class I allele HLA-A*02 halves the odds of HAM/TSP and is associated with proviral load one-third that of HLA-A*02(-) HTLV-I carriers. Additionally, HLA-DRB1*0101 doubled the odds of HAM/TSP in the absence of the protective effect of HLA-A*02.¹⁷¹ These data are consistent with the hypothesis that deficient immune recognition of Tax epitopes blunts a robust cell-mediated immune response, resulting in elevated HTLV viral load associated with HAM/TSP.^{166,172–174} Additionally, CD4⁺ lymphocytes from HAM/TSP patients express HTLV-I protein significantly more readily than lymphocytes from asymptomatic carriers of similar HTLV-1 proviral load high rate, a finding that—when coupled with prior observations of overexpression of Tax and low efficiency of CD8-mediated cytotoxic T-cell responses—supports a mechanisms of immune-mediated pathogenesis.¹⁷⁵ Employing a novel antibody that specifically recognizes Tax11–19 peptide-HLA-A*201 complexes, the level of Tax11–19-HLA-A*201 expression on

CD4⁺ CD25⁺ T cells, the major reservoir of HTLV-I provirus, was demonstrated to be increased in HAM/TSP and correlated with HTLV-I proviral DNA load, HTLV-I tax mRNA load, and HTLV-I Tax-specific CD8⁺ T-cell frequencies. Such CD4⁺ CD25⁺ T-cell subsets stimulate and expand HTLV-I Tax-specific CD8⁺ T cells, which may play an important role in the pathogenesis of HTLV-I-associated neurological disease.¹⁷⁶ A viral component to this effect is suggested by recent phylogenetic data showing a higher incidence of 1 *tax* subgroup (*taxA*) in HAM/TSP than *taxB* subgroup.¹⁷⁷ Additional data point to an indirect mechanism of pathogenesis whereby HTLV-1 induces an autoimmune process through molecular mimicry between a viral and cellular antigen and/or through indirect cytopathic effects of infiltrating virus-negative CD8 cells in the central nervous system milieu.¹⁷⁸ This hypothesis is supported by the finding that HAM/TSP patients make antibodies to heterogeneous nuclear ribonuclear protein A1 (hnRNP A1), a neuron-specific autoantigen.¹⁷⁹ Monoclonal antibodies to Tax cross-reacted with hnRNP A1, indicating molecular mimicry between the two proteins and providing a pathogenic basis for autoimmune neurologic disease.¹⁸⁰ Additionally, the finding that there are oligoclonal immunoglobulin bands in the CSF of HAM/TSP patients that react to HTLV-1 antigens supports this hypothesis.¹⁶⁶

Treatment

The mainstay of HAM/TSP treatment has been corticosteroids, which are reported in open-label trials to reduce symptoms in approximately 40% of cases, especially in the context of early disease or those with rapid progression.^{181,182} Cyclophosphamide¹⁸² has also shown benefit in some patients. More recently, a number of therapies have emerged that target some of the pathogenic pathways of HTLV infection that are known to be imbalanced in the context of HAM/TSP. One example is Pentoxifylline (PTX), a phosphodiesterase inhibitor that has been shown to decrease TNF- α levels and to downregulate neutrophil activation, likely because of increases in intracellular cyclic AMP. In 13 of the 15 patients studied, motor disability, especially spasticity, improved substantially. PTX suppressed spontaneous proliferation of peripheral blood mononuclear cells in 14 of the 15 patients at 4 weeks.¹⁸³ In another study, the mechanism of PTX upregulation of IL-4 and IL-10 in both sera and CSF were associated with clinical improvement in six patients. IFN- γ levels in the sera were decreased but not correlated with clinical improvement. These data suggest that correction of the overrepresentation of the Th1 cytokine response may impact clinical symptoms.¹⁸⁴ In a small open-label study, long-term, high-dose IFN- α therapy administered at a dose of 6×10^6 international units daily for 2 weeks and thereafter three times a week for 22 weeks showed that five of seven patients experienced sustained improvement in motor

performance during and up to 6 months after the completion of IFN- α . Another responder developed depression and another deteriorated and thereafter dropped out. Viral load declined in the responders, and autoprolieration of CD4⁺ T cells even after the cessation of IFN- α was noted. CD8⁺ DR⁺ T cells in the peripheral blood and soluble IL-2 receptor levels in the sera increased significantly during the therapy in all patients, suggesting that both the reduction of HTLV-I proviral DNA load and immunomodulation by long-term IFN- α therapy contributed to its sustained clinical benefits.^{185–187} Other experimental approaches such as antiretroviral therapy with lamivudine, which shows reduction in viral load,¹⁸⁸ and treatment with humanized anti-Tac associated with downregulation of activated T cells and a decrease in the HTLV-I viral load¹⁸⁹ have not been advanced to formal trials to assess impacts on clinical symptoms. Treatment with danazol, an androgenic steroid, has resulted in improvement in urinary and fecal incontinence but not in the underlying neurologic deficit.¹⁹⁰

■ OTHER DISEASES ASSOCIATED WITH HTLV-1

Most of the other conditions listed in Table 22-2 associated with HTLV-1 also appear to involve an autoimmune/inflammatory pathogenesis; most include elevated viral-load levels as seen for HAM/TSP, and often these conditions are coincident with the neurologic syndrome. These include polymyositis of skeletal muscle,¹⁹¹ sporadic inclusion body myositis,¹⁹² large joint polyarthropathy among elderly patients,^{193,194} infiltrative pneumonitis,¹⁹⁵ and uveitis.¹⁹⁶ In viral-endemic areas, 30–40% of idiopathic uveitis may be caused by the virus.¹⁹⁷ Other evidence for an immunologic abnormality includes parasitic infestations such as *Strongyloides stercoralis* that are refractory to treatment¹⁹⁸ and skin test anergy.¹⁹⁹ Depressed hemoglobin and lymphopenia have been reported in healthy HTLV-1 carriers.²⁰⁰ Infective dermatitis is an HTLV-1-associated syndrome in children; it also appears to involve HTLV-1-associated immunodeficiency that is manifested by refractory generalized eczema and saprophytic staphylococcal and streptococcal bacterial infections. In most cases, onset occurs in early life with persistence into adulthood¹²⁸ or even develop in adulthood²⁰¹; some cases go on to develop ATL and HAM/TSP.²⁰² The finding of spontaneous neutrophil activation in HTLV-1 infected patients may provide a pathogenic basis for infective dermatitis, since a defect in granulocyte function may explain the impaired capacity of the immune system to clear saprophytic bacterial infections.²⁰³

■ IMPACT OF HTLV-1 INFECTION ON OTHER INFECTIOUS DISEASES

HTLV-1 infection may cause subclinical and clinical immunosuppressive effects that mediate increased susceptibility to

certain bacterial and parasitic diseases, including *S. stercoralis*¹⁹⁸ and *Mycobacterium tuberculosis*.^{204,205} In Japan, AIDS-like illnesses have been reported in some HTLV-1 carriers.²⁰⁶ Coinfection with HTLV-1 and HIV-1 has been thought to result in acceleration of clinical immunosuppression and shortened survival in cross-sectional studies.²⁰⁷ However, published data are all cross-sectional and therefore subject to problems of interpretation. Thus HTLV-1 infection in these patients may have been a marker of greater sexual exposure through common modes of transmission, or HTLV-1 may have facilitated HIV-1 transmission in some way.²⁰⁸

■ DISEASE ASSOCIATIONS OF HTLV-2

The disease associations of HTLV-2 also remain to be defined (Table 22-3), but there are suggestive case reports of degenerative neurologic conditions, suggesting an emerging link to HAM/TSP. Rare hematologic manifestations such as

Table 22-3. HTLV-Associated Diseases

Disease	HTLV-1	HTLV-2
Childhood		
Infective dermatitis	++++	No
Persistent lymphadenopathy	++	No
Adult		
Adult T-cell leukemia/lymphoma	++++	No
HTLV-associated myelopathy	++++	+++
Infective dermatitis	+++	No
Polymyositis	++	No
Inclusion body myositis	+	Unknown
Uveitis	+++	No
HTLV-associated arthritis	++	No
Sjogren syndrome	++	No
Strongyloidiasis	++	No
Pulmonary infiltrative pneumonitis	++	No
Invasive cervical cancer	+	Unknown
Small cell carcinoma of lung	+	Unknown

++++, very strong evidence; +++, strong evidence; ++, possible association; +, weak association; No, evidence does not support association. Unknown—no data to support association or lack of association.

atypical hairy-cell leukemia and large lymphocytic leukemia have also been reported, but consistent associations have not been found. One prospective study of HTLV-2 positive drug users showed an excess of asthma-related deaths and an increased frequency of skin and soft-tissue infections.^{209,210} These are currently under investigation in a number of cohorts. The finding that HTLV-2 provirus load is lower than that in HTLV-1 carriers as well as the tropism for CD8 cells may explain differences in viral pathogenesis.²¹¹ A recent cohort analysis from Italy suggests that HTLV-2 protects against progression to AIDS, a finding that might be confounded by survivor bias in the cohort.²¹²

CONTROL OF HTLV INFECTIONS

■ PREVENTION

Guidelines for prevention and counseling have been developed for HTLV-1 and -2 by a Centers for Disease Control and Prevention Working Group.²¹³ Standard prevention approaches address each of the major avenues of transmission and are similar for both viruses: screen blood, eliminate breast-feeding by known infected mothers or where not feasible, limit breast-feeding to the first 6 months of life, and advise use of condoms by discordant couples.

The value of blood donor screening has been well documented in Japan, where up to 15% of HTLV-I infections have been eliminated. In nonendemic areas such as the United States, the cost-effectiveness of screening has been questioned, but because of the risk for HAM/TSP in the transfusion setting, all blood bank units in the United States are screened. However, because HTLV-I is transmitted only in blood units containing cells and not in plasma, plasma donations are not screened for HTLV-I.

Pregnant women who are HTLV-I positive should not breast-feed their infants, and this is official policy in the United States. However, in developing countries where safe alternatives to breast-feeding may not be available, limiting breast-feeding to the first 6 months may afford some protection via maternal antibodies.

The use of condoms is recommended for couples who are discordant for HTLV infection. Given the relatively low frequency of sexual transmission for each sexual encounter, couples who desire a pregnancy could plan to have unprotected sex during periods of maximal fertility. Such decisions require careful discussion between physician and patient, and there are no absolute guidelines in this particular area.

Counseling seropositive patients involves a clear discussion of the distinction of HTLV from HIV. In addition, HTLV virus type should be defined by serologic methods, and the distinctions in disease associations of the two virus types should be emphasized.

On a population level, prevention measures that have been developed for HIV infection also are applicable against HTLV. Since the populations at risk for HIV are also at risk for HTLV-I in viral endemic areas (e.g., persons at risk for STDs, persons with high rates of partner exchange, commercial sex workers, etc.), HIV prevention guidelines will also benefit those at risk for HTLV-I. Thus prevention measures that promote condom use, treatment of sexually transmitted infections, and decrease of high-risk exposures will also prevent HTLV-I infection. Nosocomial infection has only been reported in one instance involving a “micro-transfusion” and thus HTLV-I is unlikely to be transmitted in this setting. There is no therapy for HTLV-I infection and thus no chemoprophylaxis. Passive immunoprophylaxis is hypothetically effective as noted in animal studies, but has no practical clinical application given the low risk for transmission except through sexual, breast-feeding, and transfusion exposure where other prevention methods are more applicable.

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INTRODUCTION

Over 100 herpesviruses have been identified, with at least eight infecting humans. All human herpesviruses are well adapted to their natural host, being endemic in all human populations studied and carried by a significant fraction of persons in each population. The human herpesviruses include herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), and human herpesvirus 8 (HHV-8) or Kaposi's sarcoma (KS)-associated herpesvirus. Disease caused by human herpesviruses tends to be relatively mild and self-limited in immunocompetent persons, although severe and quite unusual disease can be seen with immunosuppression.

A few key characteristics differentiate the herpesviruses from other viruses. These include (1) a double-stranded linear DNA genome ranging in size from 125,000 to 250,000 base pairs, (2) an icosahedral capsid approximately 125 nm in diameter consisting of 162 capsomers, (3) an amorphous layer of viral proteins located between the capsid surface and outer envelope and called the *tegument*, and (4) a lipid bilayer envelope containing viral glycoproteins. In addition to these structural elements that define members of the Herpesviridae family, all herpesviruses share biologic traits. These include expression of a large number of viral enzymes, assembly of the nucleocapsid in the cell nucleus, cytopathic effects on the cell during productive infection, and ability to establish latent infections in an infected host.

The pathology and epidemiology of herpesvirus infections depend not only on viral replication and associated cytotoxicity but also on the capacity of herpesviruses to establish latent infections. The term *productive infection* will be used here to describe, at the cell level, an infection in which the invading virus replicates to yield progeny virus. *Latent infection* or *latency* means that the genome of the invading virus is stably maintained by the cell with only limited expression of viral genes, no production of progeny virus, and no evident

virus-induced cytotoxicity. Latent infections can be converted to productive infections by factors and stimuli that have not yet been fully defined. This conversion results in activation of virus replication, possibly at levels sufficient to cause clinical symptoms. Recurrence of disease due to periodic or sporadic activation of viral replication is an important feature of the pathology caused by HSV. In addition, asymptomatic shedding of herpesviruses may play a significant role in transmission from person to person.

This chapter will focus on the sexually transmitted herpesviruses, HSV, CMV, EBV, and HHV-8, all of which can also be transmitted in other ways. HSV is a major cause of genital ulcers and also causes similar mucocutaneous lesions in and around the mouth and on any other part of the body surface where inoculated. Other disease manifestations include keratitis, encephalitis, and meningitis. CMV infections are mostly asymptomatic, but can be severe and disseminated to multiple organ systems in the immunodeficient. CMV can cause AIDS-associated retinitis. CMV is probably the only herpesvirus capable of infecting the fetus transplacentally, which can result in various developmental abnormalities including hearing loss and mental retardation. EBV causes infectious mononucleosis and is associated with a variety of benign and malignant lymphoproliferative diseases and carcinoma, particularly under conditions of immunodeficiency. HHV-8 is the cause of KS and AIDS-associated primary effusion lymphoma (PEL).

TAXONOMY AND GENOMIC ORGANIZATION

Members of the family Herpesviridae are diverse and have been isolated from mammals, birds, reptiles, bony fish, amphibians, and oysters. The herpesviruses from mammals, birds, and reptiles have been classified into three subfamilies based on biologic differences. The α -herpesviruses are neurotropic viruses that replicate relatively rapidly and infect a wide range of cells in cell culture. Examples include HSV-1, HSV-2, and VZV. The β -herpesviruses replicate slowly and are restricted in the types of cells productively infected in cell

culture. Cells infected by β -herpesviruses often become enlarged. Examples include CMV, HHV-6, and HHV-7. The γ -herpesviruses are lymphotropic viruses that also replicate relatively slowly and are restricted in the types of cells productively infected. Examples include EBV and HHV-8. Except for the close relationship between HSV-1 and HSV-2, each of the human herpesviruses appears to be more closely related to biologically similar animal herpesviruses than to each other. This classification scheme based on biologic differences is for the most part concordant with evolutionary inferences that can be drawn from nucleotide sequence analysis.¹ In this chapter, HSV, CMV, and EBV will be discussed as the prototypes of their respective subfamilies, with some attention also given to HHV-8.

The genomes of the various herpesviruses are clearly evolutionarily related but differ in size, in organization of unique and repeated sequences, and in gene content and order.¹ Although each virus encodes unique genes, a large fraction of the genes of herpesviruses is conserved among members of the family. These homologous genes are arranged in several colinear blocks (Fig. 23-1). The blocks are themselves arranged in the same order and orientation for members of any one subfamily of herpesviruses and in different orders and orientations for viruses from different subfamilies. Genes specific for a virus or subfamily tend to be at the genomic termini or in clusters between the blocks of homologous genes. Certain key regulatory proteins and genes expressed in latency tend to be different for members of the different subfamilies.

MOLECULAR BIOLOGY OF VIRAL REPLICATION

Herpesvirus genomes encode approximately 100 or more proteins. Although a relatively large percentage of viral genes may not be essential for viral propagation in cell culture, all are most likely required for efficient viral function during naturally occurring infections. Many of these genes encode proteins that modulate or prevent certain host immune responses or that permit each herpesvirus to establish and maintain long-term infections in their natural hosts in ways that are biologically distinct for each virus.

Despite the fact that HSV infections outside the laboratory are, for the most part, limited to humans, the virus has an extremely broad host range. Many animal species can be experimentally infected with HSV and many types and species of cultured cells will support HSV replication. On the other hand, the other human herpesviruses have a much more limited host range, are fastidious about the cell types in which they will replicate, and are often much more difficult to propagate in cell culture. Consequently, the molecular details of viral replication are much better understood for HSV than for the other human herpesviruses.

Herpesvirus infection is initiated by attachment of the virus to a susceptible cell. Viral glycoproteins in the virion envelope bind to components of the cell surface in a cascade of interactions that culminates in fusion between the viral envelope and a cell membrane, thereby delivering the nucleocapsid into the

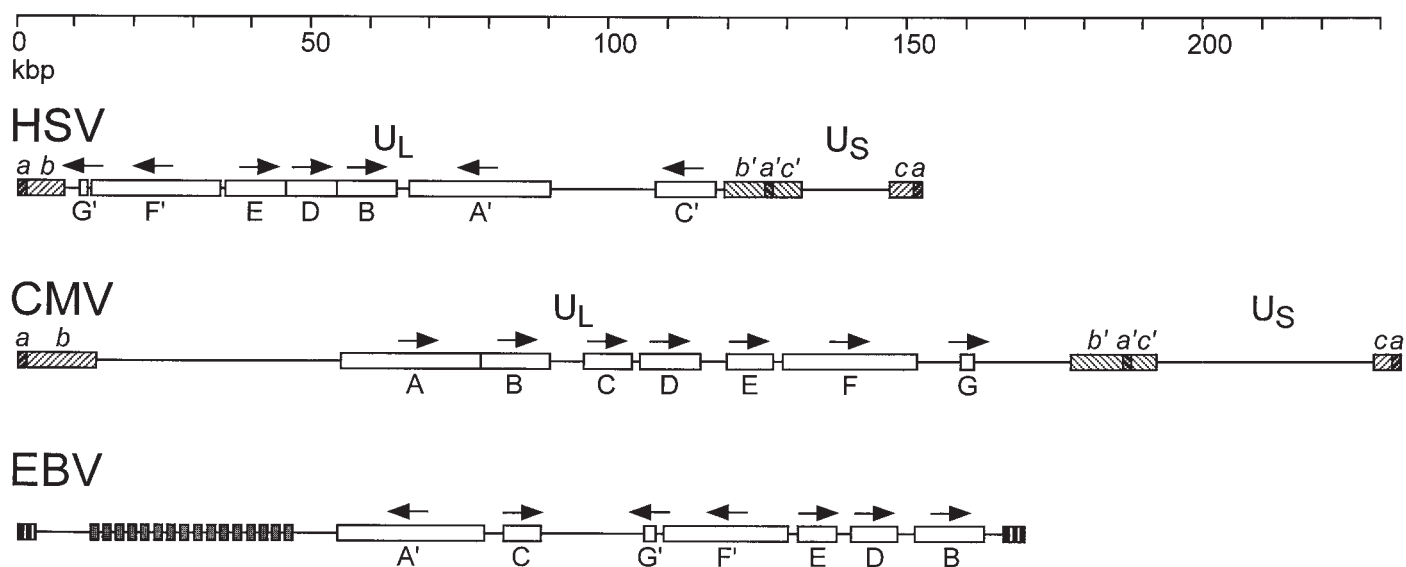


FIGURE 23-1. The genomes of three representative α , β , and γ herpesviruses (HSV, CMV, and EBV) showing the positions of repeated sequences and of conserved gene blocks. The scale of these maps is in thousands of base pairs (kbp). The hatched boxes on the CMV and HSV maps represent repeated sequences present in two copies with inverted orientations. These repeated sequences divide the CMV and HSV genomes into unique long (U_L) and unique short (U_S) segments. The small shaded boxes on the EBV genome represent multiple repeated sequences all in the same orientation. The open boxes and letter designations represent conserved blocks of genes. The arrows denote the orientation of the blocks relative to CMV. These maps were adapted from Mocarski² and are based largely on the nucleotide sequence analyses of Kouzarides et al.,³ McGeoch et al.,⁴ and Baer et al.⁵

cell cytoplasm. After penetration, the nucleocapsid is transported to the cell nucleus. In productively infected cells, herpesvirus gene expression proceeds in a well-coordinated cascade.⁶ Expression of the immediate-early (α) regulatory genes is necessary for the subsequent transcriptional activation and expression of the delayed-early (β) and late (γ) genes of the lytic cascade required for viral replication. In latently infected cells, the immediate-early (and delayed-early and late genes) ordinarily will not be expressed. The factors that determine whether immediate-early genes will not be expressed, permitting the establishment of latency, or will be expressed, initiating the cascade of viral gene expression required for viral replication, have not been adequately defined for any herpesvirus.

Viral DNA replication and nucleocapsid assembly are in the cell nucleus. Subsequent steps in viral morphogenesis include envelopment of the nucleocapsid by budding through the inner nuclear membrane, de-envelopment of the virus particle by fusion of the primary envelope with the outer nuclear envelope, and secondary envelopment of the nucleocapsid by budding into the trans-Golgi network or an endosome. The virion is then transported out of the cell by exocytosis.

■ VIRION PROTEINS

Highly conserved among herpesviruses are the capsid proteins that comprise the icosahedral shell surrounding the viral genome and the scaffold and DNA packaging proteins that permit capsid assembly followed by insertion of the viral genome. Less well conserved are the proteins that lie between the capsid shell and the inner aspect of the lipid-containing outer envelope. These proteins, collectively called the tegument, serve a number of regulatory functions, including enhancement of transcription of immediate-early viral genes, shut-off of host protein synthesis, phosphorylation of host and viral proteins, etc. At least a dozen viral-encoded proteins and glycoproteins are integral components of the virion envelope and serve several functions. A subset of these membrane proteins mediates entry of virus into the host cell by inducing fusion between the virion envelope and a cell membrane. Another subset includes IgG Fc-binding proteins and complement-binding proteins that can modulate host immune effector functions. Others have the role of traffic control inside the infected cell, ensuring that the envelope proteins are targeted to the appropriate cytoplasmic membrane where envelopment takes place and that vesicles containing virions are targeted to the appropriate cell surface for exocytosis.

■ VIRAL ENTRY INTO CELLS

Depending on the host cell type, herpesvirus entry can occur by fusion of the virion envelope with the cell plasma membrane or with the membrane of an endocytic vesicle. The first

step in entry is binding of the virus to the cell surface. For most herpesviruses studied to date, with the exception of EBV, the initial binding is to heparan sulfate chains on cell-surface proteoglycans.⁷ The viral glycoproteins that mediate this binding to heparan sulfate include a highly conserved herpesvirus glycoprotein designated gB and less highly conserved or unique glycoproteins that have different names in different viruses. In general, the binding of virus to heparan sulfate is reversible. Virions retaining infectivity can often be released from cells by use of a soluble competitive inhibitor such as heparin, which is closely related to heparan sulfate.

Following initial virus binding to the cell, entry requires the activation of a viral-membrane-fusing complex of glycoproteins. For most or all herpesviruses, this complex is thought to include the conserved glycoproteins designated gB, gH, and gL.⁸ For individual herpesviruses, membrane-fusing activity may require other glycoproteins in addition, glycoproteins that are generally not conserved among all herpesviruses. The entry of HSV, CMV, EBV, and HHV-8 will be discussed separately to illustrate how different cellular requirements for entry influence cellular tropism and pathogenesis.

HSV entry

HSV can infect a variety of cultured cell types, including epithelial cells, fibroblasts, neurons, and leukocytes. The binding of HSV to heparan sulfate on cells can be mediated either by gB or by gC, the latter of which is also able to bind to and inactivate the C3 component of complement and is conserved among α -herpesviruses but not other herpesviruses. The glycoproteins required for entry are the conserved glycoproteins, gB, gH, and gL, as well as gD, which is conserved among most α -herpesviruses (with the exception of VZV), but not among other herpesviruses.⁹ The membrane fusion required for entry is triggered by the binding of gD to one of its cell-surface receptors. This binding somehow activates the fusogenic activity of gB, gH, and gL. The latter two glycoproteins form a stable heterodimer (gH/L), the functional unit, whereas gB forms a homooligomer, probably a trimer.

The gD-binding entry receptors include three classes of cell-surface molecules: herpesvirus entry mediator (HVEM), a member of the tumor necrosis factor receptor family; nectin-1 and nectin-2, cell-adhesion molecules belonging to the immunoglobulin superfamily; and specific sites in heparan sulfate generated by the action of particular 3-O-sulfotransferases.¹⁰ All of the HSV entry receptors are expressed on a variety of differentiated cell types, although nectins are likely to be the receptors for entry of virus into neurons.^{11,12} It remains to be determined which of these receptors is chiefly responsible for the entry of HSV into various cell types that are targets in disease, such as epithelial cells, neurons, cells of the immune system, etc.

Electron microscopy of HSV virions labeled with gold-tagged antibodies (Fig. 23-2) has permitted the demonstration that three of the glycoproteins involved in viral entry (gB, gC, and gD) constitute three morphologically distinct spikes projecting from the virion envelope.¹³ X-ray structures of gD crystallized alone and in complex with HVEM have been determined.¹⁴ These structures and mutagenic analyses of gD have shown that gD presents different interfaces for binding to its various cell surface receptors and can assume different conformations depending on the receptor.^{11,15-17}

CMV entry

As with HSV, the initial attachment of CMV to cells is mediated by binding of viral glycoproteins to cell-surface heparan

sulfate.¹⁸ Glycoprotein complex II (gC-II), now known to be a disulfide-linked heterodimer of gM and gN, is the predominant component of the viral envelope that mediates virus binding to heparan sulfate.¹⁹ By use of a cell fusion assay, it was shown that gH and gL are sufficient for the fusion of certain cell types but not others.²⁰ This indicates that gH and gL are probably also required for the membrane fusion leading to viral entry. It seems likely that gB is also required for viral entry although this has not been established. However, it has been shown that gB binds to cell surface heparan sulfate and other receptors²¹⁻²³ and has a role in signal transduction, including the induction of interferon-responsive genes.²⁴⁻²⁶

A variety of cell-surface molecules have been implicated in CMV entry into cells. The leading candidates as of this writing are the epidermal growth factor receptor (EGFR) and

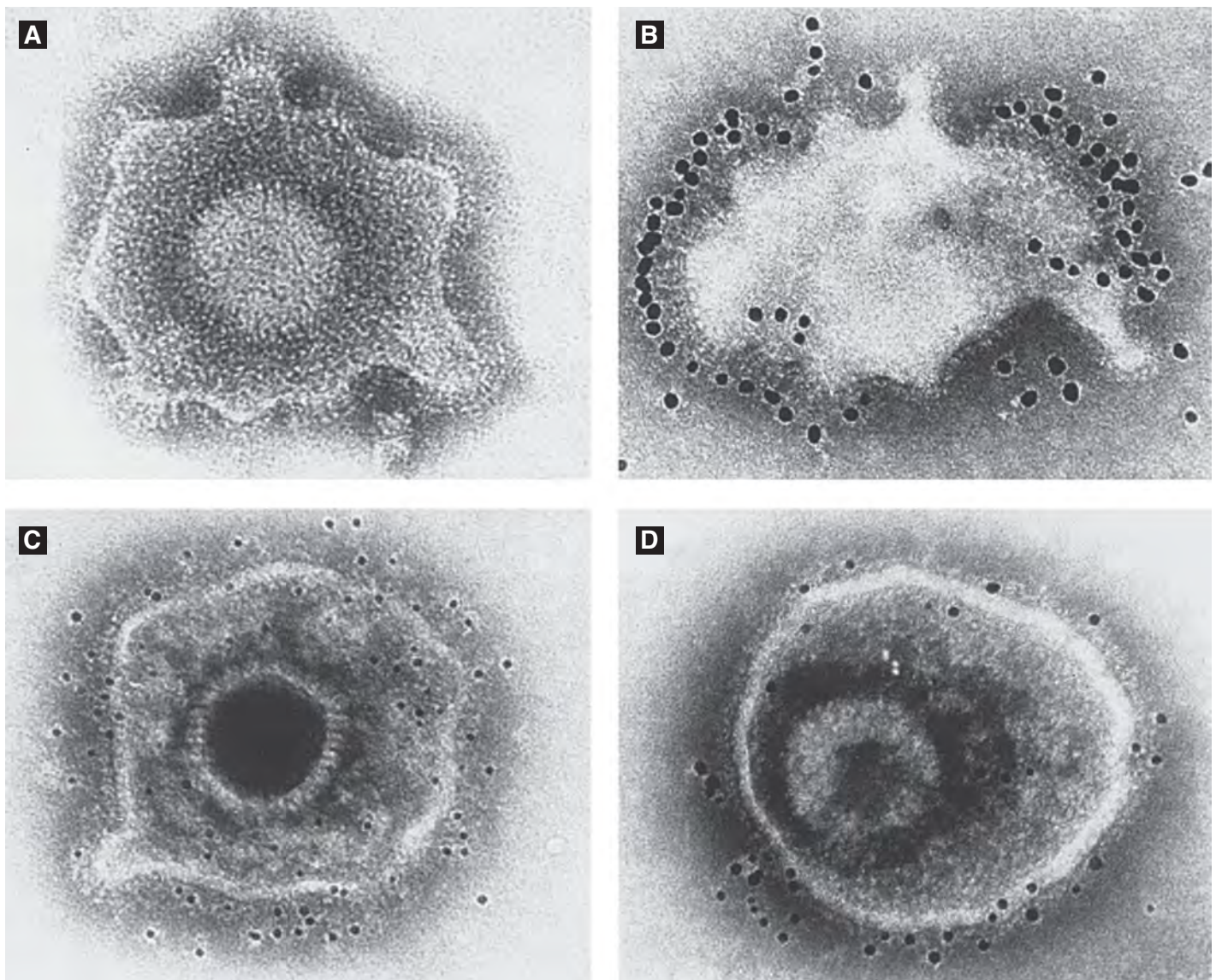


FIGURE 23-2. Electron micrographs of negatively stained HSV showing different kinds of spikes projecting from the virion envelope. The most prominent spikes are composed of gB, as shown by the decoration of these spikes with gold-labeled anti-gB, **B**. Similarly, long, slender structures, difficult to resolve, are gC, **C**, and some of the short, fuzzlike structures are gD, **D**. No antibody was added in panel, **A**. Similar figures were published by Stannard et al.¹³ (Courtesy of L. M. Stannard.)

integrins.^{22,23} CMV gB is thought to bind to several different integrins via a disintegrin domain.²²

EBV entry

EBV can infect both B lymphocytes and epithelial cells. The viral and cell requirements for entry into each cell type are different, however. The attachment of EBV to B cells is mediated by the binding of gp350/220 to CD21,²⁷ a receptor for the complement component C3d. Entry into B cells requires at least gH/L and gp42, which forms a tripartite complex with gH/L.²⁸ Entry is triggered by the binding of gp42 to major histocompatibility complex (MHC) class II molecules.^{29,30} An x-ray structure of gp42 in complex with MHC class II has been determined.³¹ The structure revealed a hydrophobic surface on gp42, which includes amino acid residues critical for entry and which probably interacts with gH/L or other viral or cell proteins required for entry.³² The receptors required for entry into B cells are usually not expressed on epithelial cells, and EBV entry into epithelial cells does not require gp42.²⁸ The identities of epithelial cell receptors for EBV entry and the viral ligands for these receptors remain to be determined. It is thought that interaction of gH/L with an epithelial cell receptor may be critical. On the basis of cell fusion studies, it seems likely that EBV gB, in addition to the glycoproteins mentioned above, is required for viral entry into both B lymphocytes and epithelial cells.^{33,34}

HHV-8 entry

As for HSV and CMV, the initial interaction of HHV-8 with cells can be the binding of virus to heparan sulfate.³⁵ For HHV-8, this binding is mediated by the virion glycoproteins gpK8.1A or gB.^{36,37} HHV-8 gB can also bind to certain integrins on the cell surface and this interaction has a role in induction of signaling pathways that may be necessary to prepare the cell for viral entry.^{38–40} Glycoproteins gB, gH, and gL are necessary and sufficient for HHV-8-induced cell fusion of two human cell lines.⁴¹ However, the addition of glycoprotein K8.1A enhances cell fusion and the range of cell types that are permissive for HHV-8-induced cell fusion and entry.^{41a} A cystine transporter has been identified as a fusion-entry receptor.^{41b} HHV-8 is capable of infecting a variety of cultured cell type, but most of these infections lead to latent infection rather than to viral replication.

■ INTRACELLULAR SYNTHESIS OF VIRAL COMPONENTS

Once a herpesvirus nucleocapsid enters the cytoplasm of the cell, it is transported to the vicinity of a nuclear pore. Transport of the nucleocapsid to the nucleus is mediated by specific interactions of the nucleocapsid with components of the cellular cytoskeleton, especially microtubules. The nucleocapsid docks to a nuclear pore and the viral genome is delivered into the nucleus. There the viral genes are transcribed by cellular RNA

polymerase II under control of viral regulatory components, some of which are tegument components. In productive infection, the immediate-early or α genes, which encode mostly regulatory proteins, are transcribed first. For HSV, optimal transcription of the α genes requires the activity of a viral regulatory protein called α trans-inducing factor (α TIF) or VP16. This viral regulatory protein is a component of the tegument and is delivered to the cell along with the viral genome. Homologous genes have been identified in EBV (BPLF-1) and in CMV (pp71).

Once the α genes have been transcribed and the α proteins translated, one or more of these proteins enables the transcription of the delayed-early or β genes. The β genes encode enzymes and other proteins required for viral DNA replication. Most herpesviruses encode enzymes that can phosphorylate nucleosides and therefore also can activate nucleoside analogue inhibitors of viral DNA replication. In addition, all herpesviruses encode a DNA polymerase, which is responsible for genomic replication during lytic infection and is the target of nucleoside analogue inhibitors. Following α and β gene expression and DNA replication, the late or γ genes are expressed. The γ genes encode most of the virion structural proteins and glycoproteins.

Herpesviruses and certain other DNA viruses have provided excellent experimental systems for the study of eukaryotic gene expression and its regulation, in part because these viruses use cellular machinery for transcription of viral DNA to RNA and subsequent transcript processing to yield functional mRNAs. The virus superimposes on this cell machinery its own regulatory factors that aid in targeting cell transcription factors to virus-specific nucleotide sequences. Interestingly, herpesviruses differ from other DNA viruses and from eukaryotic cells in that most viral genes expressed during productive infection are free of introns (intervening sequences that are removed from RNA transcripts by splicing to yield the functional mRNAs). In productively infected cells, RNA splicing can be inhibited by viral proteins; for example, by the HSV protein ICP27.⁴² One can speculate that expression of ICP27 homologs and evolution toward intron-free genes facilitate the expression of viral genes in preference to cell genes during a productive infection. In contrast, herpesvirus genes expressed in latently infected cells are usually spliced.

After synthesis of herpesvirus proteins in the cytoplasm, most of the proteins are transported to the nucleus, where they serve as regulatory factors, enzymes involved in DNA replication, or structural components of the nucleocapsid. Viral glycoproteins and other integral membrane proteins are made on membrane-bound ribosomes and become distributed to most membranes of the cell.

■ ASSEMBLY AND EGRESS OF VIRIONS

Assembly and egress of herpesvirus virions begins in the cell nucleus and ends with exocytosis of virions from the cell.⁴³

Herpesvirus nucleocapsids are assembled in the cell nucleus. The nucleocapsids then acquire an envelope by budding through patches of the inner nuclear membrane that have been modified to contain viral proteins. These enveloped virus particles can be observed in the perinuclear space. Subsequent events in virion assembly include de-envelopment of these particles by fusion with the outer nuclear membrane, followed by reenvelopment of the cytoplasmic nucleocapsids at membranes of the trans-Golgi network or endosomes. These mature virions, enclosed within cytoplasmic vesicles, are then transported to the cell surface and released from the cell by exocytosis.

■ FATE OF THE CELL THAT PRODUCES VIRUS

Herpesviruses kill the cells in which they replicate, at least in cell culture. For HSV, a viral gene product, virion host shutoff protein, a tegument component introduced into the cell during viral entry, causes degradation of preexisting cytoplasmic mRNAs such that cell protein synthesis is immediately inhibited. Other viral factors produced after infection inhibit or alter various host functions, including DNA replication and RNA processing. In contrast, CMV initially stimulates host cell DNA, RNA, and protein synthesis, and effective CMV replication is dependent on this stimulation. Later in the replicative cycle, host macromolecule synthesis is inhibited.

A hallmark of α -herpesvirus infections *in vivo* is the presence of polykaryocytes, at least in infected epithelia. Herpesvirus-induced cell–cell fusion may function as an alternative method for spreading virus from cell to cell and could facilitate evasion of host immune responses.

LATENCY

The ability of herpesviruses to persist for the life of their natural hosts depends in large part on their ability to establish latent infections. Latency occurs when the viral genome is stably maintained in the cell nucleus with expression of only a limited subset of viral genes. The latently infected cell is not killed by the virus, and viral gene products expressed may actually stimulate cell division or other cell activities. Virions or infectious virus cannot be recovered from latently infected tissue immediately after its removal from an experimental animal or human cadaver. However, activation of latent virus to the replicating state, yielding infectious virus, often can be achieved by *in vitro* cultivation of the explanted latently infected tissue.

EBV and HHV-8 can induce the proliferation of latently infected cells, causing cell division even in the absence of antigenic or other mitogenic stimuli. HSV is not known to induce the proliferation of latently infected cells. This apparent difference may be related to properties of the cells that

harbor latent viral genomes. EBV and HHV-8 genomes are latent in premitotic cells whereas HSV genomes are latent in postmitotic neurons. Thus, the observed differences in viral gene expression during latency, as described below, may in part reflect the need for EBV and HHV-8 to regulate cell proliferation and to partition their genomes to daughter cells when cell division does occur.

■ HSV LATENCY

A major site of latency for HSV is sensory ganglia of nerves innervating the site of initial infection.⁴⁴ Infection of the sensory neurons occurs during initial HSV infection when the nerve endings are exposed to the virus. Virus is subsequently transported up the axons to the cell bodies. The HSV genomes present in ganglia of latently infected animals and humans are probably episomal and circular, in contrast to virion-associated genomes, which are linear.

Although gene expression by HSV is apparently not required during a latent infection, analyses of latently infected animal and human cells reveal the presence of transcripts (Fig. 23-3) from one specific region of the viral genome.⁴⁷ These latency-associated transcripts (LATs) are transcribed from the DNA strand opposite that encoding one of the immediate-early proteins ICP0 or IE110. A relatively large transcript gives rise to a stable intron, from which two different spliced forms are derived. Expression of HSV proteins from LAT transcripts has not been reproducibly demonstrated.

The expression of LATs is not absolutely essential for the establishment of latency or for the reactivation of latent virus in animal models, and LATs can be detected during productive infections. However, the significance of LATs in latency is suggested by observations that LAT expression is a good marker for the latent state induced by wild-type virus and that LAT-negative mutants may be somewhat impaired in their ability to reactivate from latency.

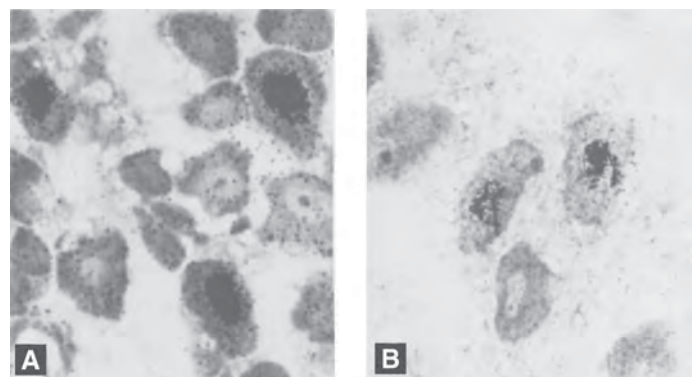


FIGURE 23-3. Detection of HSV-1 LAT in neurons of peripheral ganglia by *in situ* hybridization and autoradiography. The black autoradiographic grains are localized over nuclei of some of the neurons in mouse tissue, **A**, and human tissue, **B**, taken from latently infected subjects. Experimental details are given in publications by Stevens et al.^{45,46} (Courtesy of J. G. Stevens.)

Reactivation of latent HSV can result after exposure to a variety of stimuli, including stress, fever, colds, sunlight, menstruation, etc. The mechanism by which virus is reactivated is unknown. Virus is subsequently transported down the axon to the site of initial infection or nearby. The frequency and clinical severity of reactivation depends on several factors, including immunocompetence of the infected host and severity of the initial infection. Presumably, a larger number of peripheral cells infected during a severe initial outbreak will result in a larger number of infected sensory neurons. Interestingly, HSV-1 reactivates more readily from trigeminal and cervical sensory ganglia, whereas HSV-2 reactivates more readily from sacral ganglia.^{48,49} This correlates with the tendency for HSV-1 to cause recurrent orolabial disease and for HSV-2 to cause recurrent genital disease. The reasons for this are not known but may be secondary to differences in the cell or viral proteins needed for reactivation and lytic growth in each cell type.

■ CMV LATENCY

Epidemiologic studies first implicated leukocytes as a possible site of CMV latency. CMV can be transmitted by blood transfusions, and the risk of infection can be decreased substantially by using leukocyte-depleted blood.^{50,51} Tissue-resident macrophages or dendritic cells have also been implicated as sites of latency because any organ or tissue can transmit CMV from a seropositive to a seronegative individual. CMV DNA-positive cells are rarely detected in peripheral blood monocytes from healthy seropositive individuals. However, bone-marrow-derived myelomonocytic progenitors of monocytes, macrophages, dendritic cells, and neutrophils are routinely viral DNA positive at a frequency of 1/100,000 cells.⁵² CMV gene expression in myeloid precursors is restricted. Transcripts derived from both strands of the CMV genome at the region encoding the immediate-early proteins IE1 and IE2 can be detected but these differ from the transcripts produced during productive infection. One unspliced and two spliced transcripts have been characterized, and their expression appears to correlate with latent infections.⁵³ These transcripts may function to downregulate expression of IE1 and IE2. Differentiation of monocytes into macrophages⁵⁴ or dendritic cells⁵⁵ can result in reactivation of natural latent infection. Mature cells support productive infection.

In immunocompromised individuals, CMV infection is associated with production of immediate-early antigens in many cell types, including endothelial and epithelial cells, sometimes without evidence of productive viral infection. These infected cell types may be important in viral dissemination and transmission. Cell-to-cell spread of CMV from endothelial cells to monocytes and macrophages⁵⁶ can contribute to viral dissemination within a host. CMV replication

in epithelial cells lining the ducts of the salivary glands and kidneys can contribute to viral transmission to new hosts.

■ EBV LATENCY

EBV establishes latent infections in B lymphocytes. In latently infected B cells, the viral genomes usually persist as closed circular episomes that are not integrated into the cellular DNA. At least 11 viral proteins that can be expressed during latency have been identified in cultures of lymphoblastoid cells immortalized by EBV.⁵⁷ These include EBV nuclear antigens (EBNAs) and viral latent membrane proteins (LMPs). Maintenance and controlled replication of the EBV episome require EBNA-1.⁵⁸ This protein interacts with the origin of DNA replication for latent EBV (*ori-p*) and also interacts with chromosomal proteins for the partitioning of EBV episomes to the progeny of dividing cells. The protein LMP-2 inhibits the switch from latent to lytic EBV infection by influencing transmembrane signal transduction, including blocking of signaling through the B-cell receptor.⁵⁹

The proteins EBNA-2, EBNA-3A, EBNA-3C, EBNA-LP, and LMP-1 all appear to have roles in growth transformation of B lymphocytes.⁶⁰ These proteins function by interacting with cell signaling pathways. For example, LMP-1 interacts with human proteins (TRAFs) that are involved in tumor necrosis factor receptor family signaling, whereas EBNA-2 transactivates several cell and viral genes. Expression of all these viral latency proteins *in vivo*, however, will usually induce cytotoxic responses by natural killer (NK) cells and T cells.

Two additional EBV products that may have a role in latency include small nonpolyadenylated virus-encoded RNAs (EBERs), which are expressed in both lytic and latent infections, and the protein BHRF-1, which is an EBV homolog of the human oncogene *Bcl-2* and can protect B cells from apoptosis. EBERs are not absolutely required for EBV immortalization of B cells but significantly contribute to efficient growth transformation.⁶¹

It has been proposed that EBV infects naïve B cells *in vivo* and directs their antigen-independent differentiation to memory B cells, with different sets of EBV gene products expressed at the various stages of this differentiation.⁵⁷ In naïve B cells, the full set of EBV latency-associated genes, as described above, can be expressed, resulting in cell proliferation (and the induction of potent anti-EBV T cell responses). EBV-driven differentiation of the naïve B cells to cells with properties of germinal-center cells is thought to be accompanied by expression of EBNA-1, LMP-1, and LMP-2A. As the germinal-center cells differentiate to memory B cells, expression of most or all EBV genes is extinguished. If these resting memory cells are induced to divide, they may express EBNA-1, which is required for the partitioning of EBV genomes to daughter cells. Terminal differentiation of the B cells into plasma cells can initiate viral replication.⁶²

■ HHV-8 LATENCY

Most of the cells in lesions of KS and in primary effusion (B cell) lymphoma are latently infected. Many of the cultured cell types that are susceptible to HHV-8 entry also become latently infected. Similar to EBV, HHV-8 can express several (at least seven) genes in latently infected cells.⁶³ The best studied of the gene products is LANA-1, a multifunctional protein that is a reliable marker of HHV-8 infection. This protein both activates and represses transcription, blocks apoptosis, and has roles in cell transformation. In addition, LANA-1 is able to tether the viral genome to cell chromosomes, as does EBNA-1 of EBV, to ensure partitioning of viral genomes to daughter cells. Other HHV-8 proteins expressed in latency have a variety of activities, including enhancement of cell proliferation, blockage of apoptosis, transformation of cells to a tumorigenic phenotype, and immunomodulation. These viral proteins expressed in latency can explain many aspects of the pathology characteristic of KS and PEL.

VIRAL AND HOST DETERMINANTS OF DISEASE

Herpesviruses are well adapted to their natural hosts. Many more people become infected than ever show overt signs of disease. This is particularly true for EBV and CMV. The specific manifestations of disease for each virus are determined by the types of cells targeted for entry, the ability of these cells to support viral replication or latent infections, effects of viral gene products on latently infected cells, the tendency for reactivations to occur, the nature of immune responses, ability of each virus to subvert particular immune responses, and, undoubtedly, genetic variations of virus and host that influence susceptibility or resistance to disease. The manifestations of disease described below can be explained, at least in part, by information presented in the preceding sections on the properties of each virus.

■ HSV DISEASE

HSV can cause gingivostomatitis, herpes labialis, keratoconjunctivitis, cutaneous herpes, genital herpes (see Figs. 23-4 to 23-7), encephalitis, meningitis, and neonatal herpes (see Fig. 23-8). Infection with HSV is initiated by contact of virus with mucosa or abraded skin. Replication of HSV in cells of the epidermis follows, resulting in cellular destruction and inflammation. Clinically, vesicles on an inflammatory base are noted. Microscopically, multinucleated giant cells (see Fig. 23-9), focal cellular necrosis, and ballooning of infected cells are noted. During an initial infection, virus gains access to sensory neurons, allowing establishment of latent infection. Further spread of virus is limited primarily by innate responses of the host. In animal models, HSV can be detected in sensory nerve ganglia

within 2 days of infection. Limited viral replication follows in neural tissue, allowing virus to migrate back down axons to sites near the inoculation site. This phenomenon, called zosteriform spread, along with contiguous spread of virus in the cells of the epidermis, may explain the large surface area affected during a primary HSV infection. Ultimately, the host immune response in immunocompetent persons will control viral replication and allow healing of lesions.

Reactivation of latent HSV and recurrent lesions can be induced by multiple stimuli, including ultraviolet light, immunosuppression, fever, pneumococcal pneumonia, and trauma to the latently infected neuron. The severity of symptoms associated with reactivation can vary substantially and may be related to the amount of replicating virus, the virulence of the HSV strain, and the integrity of the host immune system. Virus reactivation and replication occur periodically in asymptomatic persons, allowing apparently healthy people to spread infection to others.⁶⁴

The location of recurrent HSV lesions depends on the anatomical structure of the nervous system, providing an explanation for apparently anomalous recurrent lesions.⁶⁵ For example, recurrent HSV lesions following a primary genital herpes infection can involve other lower body sites, such as the



FIGURE 23-4. Severe primary HSV infection with extensive vesicles, ulcerations, and penile edema.



FIGURE 23-5. Less severe primary genital HSV infection showing intact vesicles and pustules with surrounding erythema together with an earlier lesion, which is crusted and healing.



FIGURE 23-7. Primary genital herpes of the vulva.



FIGURE 23-6. Recurrent HSV infection, showing grouped vesicles of the glans penis.



FIGURE 23-8. Neonatal HSV infection. Ulcers and crusted lesions on the buttocks.

buttocks and perianal region, because sensory nerves that arise from the lumbosacral ganglia innervate diverse areas.

HSV-1 can cause sporadic cases of encephalitis. It has been proposed that virus spreads via neurons from peripheral ganglia to the brain. This can occur either after primary infection or recurrent disease in adults with no known immunological or developmental abnormalities. It remains unclear what determines the ability of HSV to spread from peripheral ganglia to the brain, which occurs more rarely in humans than in animal models of disease. In severe primary HSV-2 genital infection, meningitis may occur.

Despite the ability of HSV to infect many cell types, HSV disease is usually localized to the body surface at the site of inoculation and to the sensory and autonomic ganglia of

nerves communicating with this site. Undoubtedly, an effective immune response is responsible in part for limiting the spread of infection. The possibility exists, however, that there are nonimmunologic barriers to the spread of infection in the normal adult. For example, certain cell types in fully differentiated tissues may not be able to support HSV replication, due either to inaccessibility or lack of required cell-surface receptors or to lack of other factors needed for biosynthesis of viral components. In addition, the basement membrane underlying epithelial surfaces contains high concentrations of heparan sulfate proteoglycans, which could trap virus and impede its spread to the dermis.⁶⁶

Infections of many cell types can be seen, however, in cases of HSV disease in infants. Perinatal infections with HSV can

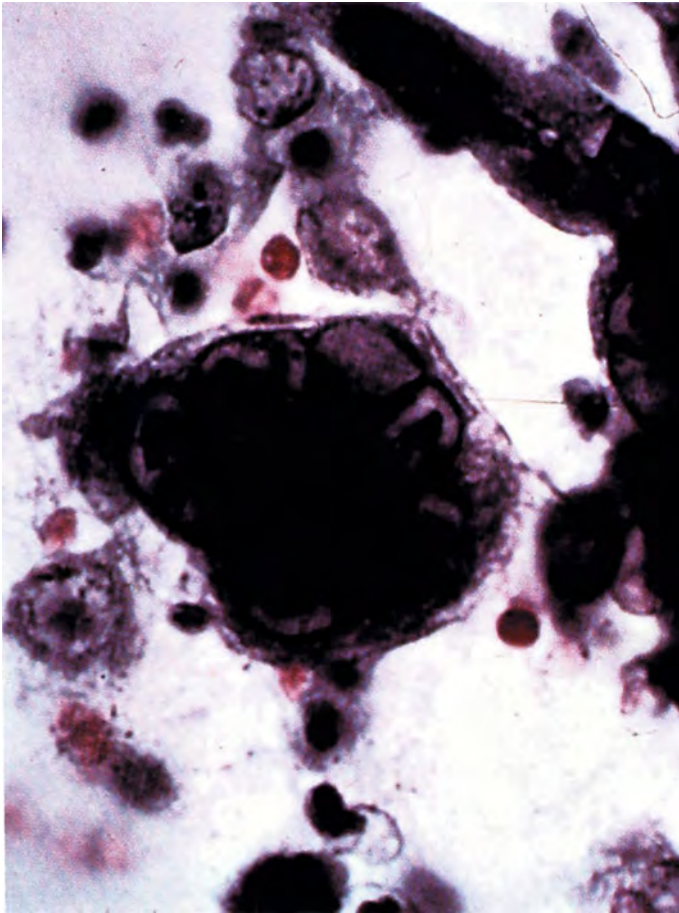


FIGURE 23-9. Wright Giemsa stain of scrapings from a herpetic lesion (Tzanck smear) showing multinuclear giant cell and ground-glass appearance of nuclei with nuclear inclusions.

occur by delivery of the infant through an infected birth canal or by postnatal exposure. HSV disease in newborn infants can be disseminated, involving many organ systems, including the central nervous system.⁶⁷ Treatment can reduce lethality but neurological sequelae might not be avoided. These manifestations of disease in newborns are clearly distinct from the more localized disease seen in children and adults. It is unclear whether the susceptibility of infants to disseminated disease is due to an immature immune system and/or to enhanced susceptibilities of newborn cells and tissues to HSV infection and spread.

HSV rarely causes severe or disseminated disease in adults, except when cell-mediated immunity is compromised. It seems likely that both innate and adaptive cell-mediated mechanisms are critical for limiting the spread of HSV infection and controlling viral replication.^{68–70} Cell-mediated immunity directed against HSV-infected cells involves NK cells, activated T cells, and macrophages. Both MHC class I and class II restricted T cells have direct cytotoxic effects against HSV-infected cells. Cytokines released by lymphocytes may have direct antiviral activity or may act to regulate other components of the host immune response.

Humoral immune mechanisms also appear to play important roles in controlling infection.⁷¹ HSV glycoproteins expressed on the surface of the viral envelope or infected cells are targets for neutralizing antibodies and antibody-dependent cell-mediated cytotoxicity, respectively. In addition, monoclonal antibodies against viral glycoproteins have been shown to protect against neurologic disease and to prevent the establishment of latency in animal models.^{72,73} The role of these antibodies in human infections is not clear, but the quantity of maternally derived neutralizing and antibody-dependent cell-mediated cytotoxic antibodies does correlate inversely with disseminated disease in newborns.^{74–76} Interestingly, high titers of antibodies correlate with high frequency and severity of recurrent disease in adults.^{49,77} The reason is not clear, but the high titers of antibodies appear to reflect a more severe primary infection. More severe primary infections correlate with an increase in frequency and severity of recurrent disease and, therefore, with repeated antigenic stimuli.

■ CMV DISEASE

CMV can cause mononucleosis, hepatitis, chorioretinitis (see Fig. 23–10), pneumonitis, colitis, and congenital cytomegalic inclusion disease. Infection with CMV usually is initiated by contact of virus with cells of the oropharynx or the genital tract or by transfusion of contaminated blood. CMV infections are typically subclinical. The most common clinical manifestation is a self-limited mononucleosis, although disease can be quite severe and life-threatening in immunosuppressed persons. Clinical disease most likely results from viral cytolysis and the host's inflammatory response. However, additional pathology may result from abortively infected cells. The hallmark of CMV disease on histology is the cytomegalic inclusion-bearing cell.

Neutralizing antibodies directed against CMV can decrease the efficiency of viral transmission and can attenuate clinical

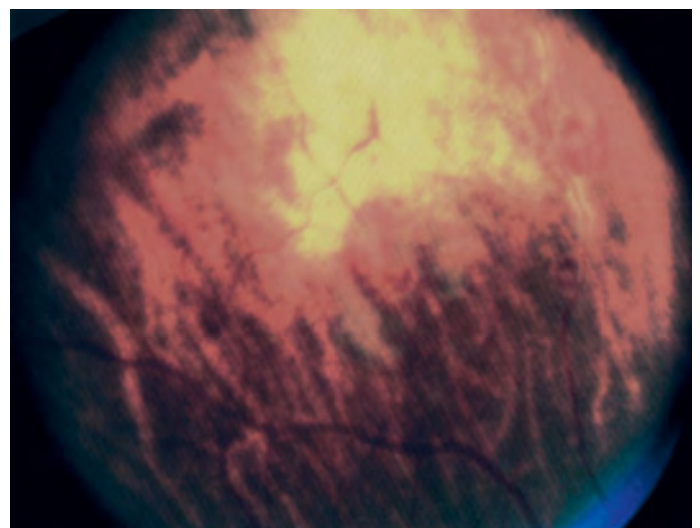


FIGURE 23-10. CMV chorioretinitis in a patient with AIDS.

disease. However, cell-mediated immunity appears to be much more important in controlling CMV replication. The incidence of severe CMV disease is markedly increased in persons with suppressed cell-mediated immunity, and the risk of CMV disease correlates with the degree of immunosuppression.^{78–80} Cell-mediated immunity against CMV involves activated T cells, NK cells, and macrophages. The cytotoxic T-cell response can be both MHC class I and class II restricted. Transfer of CD8⁺ cytotoxic T-cell clones to immunodeficient bone marrow transplant recipients may be able to restore protective immunity.⁸¹ The immunosuppressive agents used to prevent graft rejection by transplant recipients can have profound and specific effects on CMV reactivation and replication.⁸² Allogeneic transplantation itself can provide stimuli that reactivate CMV replication in leukocytes resident in the organ, and immunosuppression can facilitate replication and spread of virus. CMV is a significant cause of morbidity and organ failure in transplant patients.

CMV infection itself is immunosuppressive, consistent with the fact that leukocytes are targeted by the virus. Normal monocyte, T-cell, and NK cell function can all be inhibited.^{83–85} CMV infection of monocytes or lymphocytes reduces interleukin-1 and interleukin-2 production and responsiveness. Thus, there are global effects of CMV infection on immune responses due to viral infection of cells of the immune system. More specific effects of particular CMV proteins are outlined in a later section.

■ EBV DISEASE

Diseases caused by EBV include mononucleosis, hepatitis, encephalitis, and lymphoproliferative syndromes. EBV initially infects epithelial cells and/or B cells in lymphoid tissues in the oropharynx. The virus disseminates throughout the lymphoreticular system. Clinical symptoms typically are not seen in young children but are seen in adolescents and adults. Symptoms and signs of infection in large part result from the inflammatory and immune responses directed against EBV.

The humoral immune response to an EBV infection consists of specific antibodies directed against viral antigens and heterophile antibodies.⁸⁶ Heterophile antibodies probably result from polyclonal stimulation of immunoglobulin synthesis in EBV-infected B cells and consist mostly of immunoglobulin M (IgM) molecules, some of which can bind to animal red blood cell antigens. Heterophile antibodies are detected in approximately 90% of persons with infectious mononucleosis due to EBV, and their presence can be used to confirm the diagnosis. Antibodies directed against platelets, neutrophils, nuclear antigens, and ampicillin have all been reported. These antibodies may have a role in mediating some of the complications of infectious mononucleosis, such as the rash that develops in over 70% of infectious mononucleosis patients treated with ampicillin.

Early in an EBV infection a mononuclear lymphocytosis consisting mostly of NK and T cells specific for EBV is noted. Cytotoxic T cells can destroy EBV-infected B cells that express viral antigens.⁸⁷ The importance of cytotoxic T cells in controlling EBV replication *in vivo* is indicated by the abnormally high levels of EBV-infected B cells in persons with diseases associated with suppressed cell-mediated immunity, such as persons with AIDS and those receiving immunosuppressive medications. The cytotoxic T cells are directed against epitopes on LMP-1, LMP-2, and several EBNAs, but not EBNA-1. This is consistent with the expression of EBV proteins known to be required for B-cell immortalization and proliferation, which in the appropriate environment results in differentiation to memory B cells. Early in infectious mononucleosis most of the circulating latently infected B cells have properties of resting B cells.⁸⁸

Ultimately, the immune response generated in immunocompetent persons controls viral replication and B-cell proliferation, and the number of infected B cells circulating in the body drops about 100- to 10,000-fold. This drop correlates with the development of EBV-specific cytotoxic T cells. These cytotoxic T cells persist for the lifetime of the infected host, probably because of the continued presence of latently infected B cells that periodically reactivate or express additional proteins that can be recognized by the immune system. In addition, EBV can be isolated from the oropharynx for 12–18 months after the resolution of clinical disease and then intermittently in both immunocompetent and immunosuppressed persons.⁸⁹

Many of the symptoms and signs of infectious mononucleosis, including pharyngitis, fever, lymphadenopathy, and splenomegaly, may in part be a direct consequence of the host immune response. The systemic symptoms, including fever, malaise, and headaches, may result from the immune response directed against the infected B cells. Treatment of infectious mononucleosis with high doses of acyclovir stops viral replication in infected cells but does little to attenuate clinical symptoms.⁹⁰

In persons with congenital or acquired immunodeficiencies, virus-induced B-cell proliferation may occur relatively unchecked and can result in polyclonal or monoclonal lymphomas. Monoclonality probably results from mutations during EBV-induced cell proliferation that confer a selective advantage to the mutated cell. EBV also has been implicated as a causal factor in Burkitt's lymphoma, Hodgkin's lymphoma, lymphoproliferative syndromes, and nasopharyngeal carcinoma, along with the hyperproliferative disorder oral hairy leukoplakia in persons with AIDS.

■ HHV-8 DISEASE

Primary HHV-8 infection in immunocompetent persons can be associated with mild nonspecific symptoms and signs, including fever, fatigue, rash, diarrhea, and lymphadenopathy.⁹¹

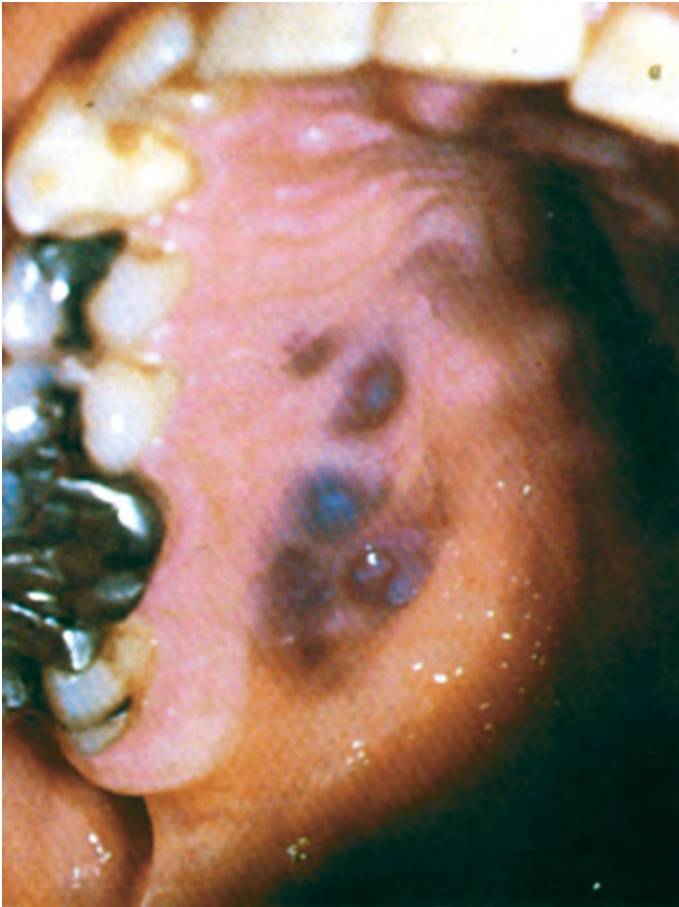


FIGURE 23-11. Kaposi's sarcoma in the palate as a manifestation of AIDS.

Proliferative forms of disease are usually, but not always, associated with immunodeficiency. It is now clear that HHV-8 infection is causally associated with all four epidemiologic forms of KS: classic KS occurring in elderly Mediterranean men; endemic KS in young men and children in Africa; iatrogenic KS in organ and tissue transplant recipients; and AIDS-associated KS (see Figs. 23-11 and 23-12). HHV-8 DNA is invariably detected in diseased but not healthy tissues of KS patients. HHV-8 infection is also associated with AIDS-associated PEL and multicentric Castlemann disease.

It is unclear whether KS is a true malignancy or a reactive proliferation.⁶³ Nevertheless, the HHV-8 proteins expressed in latently infected cells can explain the cellular proliferations characteristic of KS lesions, which are composed of various cell types including endothelial cells, extravasated inflammatory cells and erythrocytes, and the characteristic “spindle” cells. Whereas most of the cells in KS lesions and cells of PEL are latently infected, a small fraction undergo lytic replication with the production of virus.

VIRAL IMMUNOMODULATORY PROTEINS

As mentioned above, most infections by the herpesviruses described here are asymptomatic or subclinical. With the

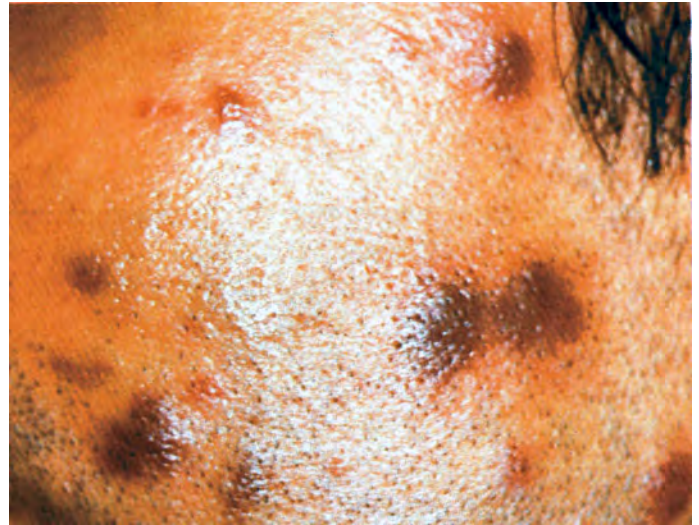


FIGURE 23-12. Kaposi's sarcoma on the face of a homosexually active man with AIDS.

exception of primary and recurrent HSV lesions, HSV encephalitis, CMV congenital disease, and infectious mononucleosis, most diseases caused by these viruses occur in the context of immunodeficiency. Virus–host interactions have evolved to a point of fine balance, wherein the virus can maintain itself for the life of the host, with periodic shedding to enable transmission, but very little morbidity or mortality. This balance has apparently required that these viruses block or modulate certain kinds of immune responses. To this end, all herpesviruses, particularly those in the β - and γ -herpesvirus subfamilies, express proteins that modulate both innate and adaptive immune responses. Most, but not all, of these immunomodulatory proteins are expressed during productive infections, which provoke the most brisk innate and adaptive responses. In many cases, the genes encoding these immunomodulatory proteins appear to have been acquired from the host genome, with each subfamily of herpesviruses acquiring different sets of genes that are interspersed among the blocks of genes encoding core viral functions.

Type I interferons are key mediators of innate resistance to viruses. Herpesviruses, as well as most other viruses, express products capable of blocking the production of interferon itself or the protective cell products made in response to interferon or preventing the action of these cell products. HSV, CMV, EBV, and HHV-8 all encode several proteins and small RNAs that have these activities. Those targeting just one of the interferon-induced proteins will be described. This protein is the dsRNA-dependent protein kinase PKR, a key factor in rendering cells incapable of replicating viruses. When PKR is activated by the binding of dsRNA, it phosphorylates eIF2 α , a translation factor, thereby shutting down protein synthesis. Several herpesvirus proteins can inhibit the activation of PKR or phosphorylation of eIF2 α , including HSV US11,⁹² CMV TRS1 and IRS1,⁹³ EBV SM,⁹⁴ and HHV-8

vIRF2.⁹⁵ A small RNA encoded by the EBV genome (an EBER) can also inhibit activation of PKR.⁹⁶ Finally, HSV ICP34.5 directs a cellular phosphatase to dephosphorylate eIF2 α .⁹⁷

NK cells also play important roles in the innate responses to viruses. The ability of herpesviruses to control interferon induction serves to reduce interferon-induced activation of NK cells. There are more specific strategies to evade NK cells, however. The binding of NK cells to receptors on other cells can result in inhibition or stimulation of NK cytotoxic activities, dependent on whether the potential target cell is recognized as unaltered by virus infection or other assaults or as altered, respectively. When HLA-E on potential target cells presents a leader peptide from other MHC class I proteins, it can bind to the inhibitory receptor, CD94/NKG2A, on NK cells. CMV-infected cells can sustain this inhibition of NK activity by presentation of a leader peptide derived from the viral protein gpUL40.⁹⁸

There are a variety of ways in which herpesviruses subvert adaptive cell-mediated responses, including downregulation of MHC antigen expression and presentation on cell surfaces, blockade of antigen processing and peptide transport to sites for loading onto MHC antigens, and direct inhibition of T-cell function. Recent examples of the latter have been reported for HSV and CMV. HSV-infected cells in direct contact with primed cytolytic T cells can inhibit their cytolytic activity by an unknown mechanism.⁹⁹ HVEM, one of the entry receptors for HSV, is a ligand for the B and T lymphocyte attenuator (BTLA)^{100–102} and also for LIGHT,¹⁰³ a member of the TNF family. By binding to BTLA, HVEM can inhibit T-cell activation whereas its binding to LIGHT can provide a second signal for T-cell activation. It is not yet known whether the interaction of HSV itself or HSV gD with HVEM can influence either the inhibitory or stimulatory activities of HVEM. CMV encodes a homolog of HVEM that is able to bind to BTLA and to inhibit T-cell activation.¹⁰²

Although humoral immunity may not be as important for protection against herpesviruses as cell-mediated immunity, both HSV and CMV encode Fc-binding proteins that can block the effector functions of antibodies.^{104,105} Also, HSV gC is a complement control protein that can protect virus from complement-mediated neutralization.¹⁰⁴ The HSV Fc-binding glycoprotein complex gE/I and complement-binding glycoprotein gC have been shown to have relevance to pathogenesis in a mouse model of disease. HSV mutants defective for these activities have reduced virulence.¹⁰⁶

ANTIVIRAL AGENTS

Most of the drugs now in use for therapy of herpesvirus infections are nucleoside analogs or other agents that interfere with viral DNA replication. One of these medications is acyclovir.¹⁰⁷ Acyclovir is highly selective against cells infected

with HSV or other herpesviruses that encode thymidine kinases. This selectivity is based on properties of two of the viral enzymes involved in DNA replication. First, acyclovir is initially phosphorylated to the monophosphate form by a viral-encoded thymidine kinase (TK) but not by cellular kinases. Subsequent phosphorylation to the active triphosphate form is by cellular kinases. Second, viral DNA polymerase is more sensitive to inhibition by phosphorylated acyclovir than are cell DNA polymerases. Unfortunately, mutations in either of these viral enzymes can render virus resistant to acyclovir. For the most part, clinically significant disease caused by resistant viral mutants is limited to immunosuppressed patients. Most acyclovir-resistant isolates are deficient in TK production, although missense mutations in the viral TK or in the viral DNA polymerase gene also can confer resistance.¹⁰⁸ Although resistant HSV isolates can be selected for after prolonged therapy with acyclovir, reactivated virus causing subsequent recurrences often retains susceptibility to the medication.¹⁰⁹ Valaciclovir is a prodrug of acyclovir that has increased oral bioavailability and is rapidly metabolized to acyclovir.¹¹⁰

Acyclovir is less effective against CMV, apparently because CMV does not encode a TK. Ganciclovir is more effective against CMV than is acyclovir. Although generation of ganciclovir monophosphate requires HSV TK in HSV-infected cells,¹¹¹ initial phosphorylation in CMV-infected cells is by a CMV protein kinase (UL97).^{112,113} Resistance to ganciclovir can result from mutations in this protein kinase.

Newer nucleoside analogs include penciclovir and famciclovir. Penciclovir, like acyclovir, also requires initial phosphorylation by viral TK. Although penciclovir inhibits viral DNA polymerase less effectively than does acyclovir, high intracellular levels of the phosphorylated drug and its longer intracellular half-life result in viral inhibition similar to that achieved with acyclovir.¹¹⁴ Famciclovir is itself inactive, but it is converted to penciclovir following absorption through the intestinal wall.¹¹⁵ Ganciclovir, penciclovir, or famciclovir cannot be used to treat TK-deficient strains of HSV. In contrast, strains resistant to acyclovir because of mutations in the HSV DNA polymerase may still be sensitive to one or more of these medications. However, most resistant strains are deficient in TK production. For these strains, foscarnet therapy can be an alternative. Foscarnet is a pyrophosphate analog that noncompetitively inhibits the viral DNA polymerase.¹¹⁶ Isolates of HSV, CMV, and VZV that are resistant to foscarnet because of mutations in the viral DNA polymerase have been described. Because foscarnet requires intravenous administration, topical application of trifluridine may be considered in select patients.¹¹⁷ Both cellular and viral-encoded TK can initiate phosphorylation of trifluridine.¹¹⁸ As a result, trifluridine is too toxic to be used systemically but can be used topically to treat TK-deficient strains of herpesviruses.

Vidarabine is an analog of adenosine that is highly effective at inhibiting HSV and VZV replication.¹¹⁹ The mechanism by this inhibition is not known. Although vidarabine inhibits viral DNA synthesis, it is not an absolute chain terminator. Vidarabine can be used to treat TK-deficient viral strains, but foscarnet is more efficacious and is currently recommended.¹²⁰

Cidofovir is an acyclic phosphonate analog of cytosine that is phosphorylated to the active form by cellular enzymes.¹²¹ Because initial phosphorylation by viral enzymes is not required, cidofovir can be active against resistant herpesvirus strains. The antiviral activity of cidofovir is prolonged, allowing for infrequent dosing of drug.

Other drugs, mostly still under development, target other processes in herpesvirus replication. Fomivirsen is a 21-base antisense oligonucleotide complementary to CMV immediate-early 2 mRNA.¹²² Fomivirsen is available for the treatment of CMV retinitis. Inhibitors of a serine protease that is essential for viral capsid maturation and is unique to herpesviruses (encoded by UL26 in HSV) may prove effective for the treatment of a wide range of herpesvirus infections.¹²³ Additional agents include those that inhibit HSV helicase and HSV ribonucleotide reductase.^{124,125}

As more is learned about the molecular interactions essential for herpesvirus replication and for the establishment of latency, attention is likely to be focused on developing new drugs or agents that can block interactions specifically required by the virus. Known inhibitory agents, even if not therapeutically useful, can provide structural information needed to design clinically acceptable drugs with antiviral activity. For example, analogs of heparin might bind to HSV, CMV, or HHV-8 and block their adsorption to cells without possessing all the other pharmacologic activities of heparin. In fact, several sulfated or sulfonated polymers, or unrelated compounds that can also block the binding of HSV and HIV to cells, are being advanced to clinical trials for testing as intravaginal topical microbicides.¹²⁶ Similarly, finding compounds that can block the interaction between a herpesvirus and its entry receptor(s) may lead to the development of medications that can prevent viral entry into cells.

VACCINES

Many viral vaccines in current use prevent or attenuate clinical disease but do not necessarily prevent infection. The goal in vaccination has been to induce immunity that is equivalent to that induced during recovery from natural disease and which often confers long-lasting protection against another episode of the disease. However, even vaccines with limited efficacy may have a substantial impact on the prevalence of infection in a population by reducing the risk of acquiring the virus. Vaccine development poses great challenges in the case of herpesviruses because recovery from natural disease is

not associated with elimination of virus and does not always protect against another episode of disease.

Live-attenuated, killed, and recombinant subunit herpesvirus vaccines have all been studied. Whole-virus vaccines have the advantage of exposing the immune system to all viral antigens. Live-attenuated vaccines have tended to produce longer-lasting immunity than killed preparations. However, live-attenuated herpesvirus vaccines may be capable of establishing latent infections. The risks are not clear and there is concern that vaccine recipients who subsequently become immunosuppressed may develop disease caused by reactivated virus. Two avirulent HSV strains have been shown to generate lethal recombinants in mice.¹²⁷ Thus, recombination between an attenuated vaccine strain and a superinfecting wild-type strain could occur. Because several herpesviruses have been associated with malignancies in humans, the long-term safety of any live-attenuated vaccine needs careful study. The establishment of a latent infection is not a concern with subunit vaccines. However, effective subunit vaccines require knowledge as to which viral proteins are the best immunogens for protective immunity.

Although there are no licensed vaccines currently available for HSV, CMV, EBV, or HHV-8, research in this area is ongoing. For HSV, several different recombinant subunit vaccines have been tested successfully in animal models.¹²⁸ In persons seronegative for HSV-2, immunization with a subunit vaccine containing both HSV-2 gB and gD has resulted in humoral and cellular immune responses equivalent to or greater than those typically seen with natural infections.¹²⁹ However, vaccination with both gB and gD in two large randomized and controlled trials failed to protect seronegative persons from the acquisition of HSV-2, despite high levels of HSV-2-specific neutralizing antibodies.¹³⁰ In two other large randomized and controlled trials, vaccination with gD reduced the acquisition of genital herpes among seronegative women but not among women seropositive for HSV-1 and seronegative for HSV-2 and not among men.¹³¹

In addition to preventing initial disease, another goal of vaccination may be to bolster the natural immunity of persons already infected and therefore prevent recurrent disease. In a study of persons with recurrent genital herpes, recipients of a HSV-2 gD subunit vaccine had fewer and less severe recurrences than placebo recipients.¹³² The vaccine recipients in this study had higher titers of neutralizing antibodies.

A variety of vaccines against CMV (subunit, DNA-based, peptides, CMV antigens in viral vectors, and live-attenuated viruses) are also in various stages of testing and investigational use.¹³³

SUMMARY

Despite the remarkable diversity of the human herpesviruses with respect to the diseases they cause, latent infection and subsequent reactivation of viral replication are key aspects of

their biology and pathology. The prevalence and epidemiology of herpesvirus-induced diseases are determined in large part by the fact that latently infected persons experience periodic reactivation and production of transmissible virus, whether or not clinical symptoms accompany the virus production. The management of immunocompromised patients is complicated by the facts that most of us carry one or more latent herpesviruses and that reactivation of these viruses can be devastating in the absence of normal immune responses. In immunocompetent persons, however, it is principally HSV that causes recurrent disease through reactivation of latent virus. This kind of disease poses difficult but interesting challenges for prevention and treatment.

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Lawrence Corey and Anna Wald

Genital herpes simplex virus (HSV) infection is a disease of major public health importance, with markedly increased prevalence throughout the world during the last four decades. The morbidity of the illness, its high recurrence rates, its complications such as aseptic meningitis and neonatal transmission, have made this disease of great concern to patients and health-care providers. Multiple interactions between HSV and HIV, both on epidemiologic and clinical levels, further highlight the importance of this infection.

HISTORY

The word herpes (from the Greek, “to creep”) has been used in medicine for at least 25 centuries. Cold sores (herpes febrilis, fever blisters) were described by the Roman physician Herodotus in 100 AD.¹ Genital herpes was first described by the French physician John Astruc in 1736, and the first English translation appeared in his treatise on venereal disease in 1754.² The disease also appeared to be well recognized by the venereologists of nineteenth century. In 1893 Unna diagnosed genital herpes in 9.1% of 846 prostitutes visiting his infirmary.³ In 1886 Diday and Doyon published the monograph *Les Herpes genitaux* in which they observed that genital herpes often appeared after a venereal infection such as syphilis, chancroid, or gonorrhoea. They also described cases of recurrent genital herpes.⁴

Fluid from oral–labial infection was shown to be infectious to other humans in the late nineteenth century. The disease was successfully transferred to rabbits in the early twentieth century, and HSV was grown in vitro in 1925.^{5–7} In 1921, Lipshultz inoculated material from genital herpetic lesions into the skin of humans, eliciting clinical infection within 48–72 hours in six persons and within 24 days in one case. In other experiments, he observed that rabbits developed corneal infection more readily with strains originating from genital sites than oral–labial sites. While he surmised that there were epidemiologic and clinical differences between oral and genital herpes,⁸ most workers felt that the viruses of genital and labial herpes were identical. In the early 1960s,

Schneeweiss in Germany and Dowdle and Nahmias in the United States reported that HSV could be divided by neutralization tests into two antigenic types and that there was an association between the antigenic type and the site of viral recovery.^{9–12}

EPIDEMIOLOGY

■ SEROEPIDEMIOLOGY OF HSV INFECTION

The development of accurate serologic assays for HSV-1 and HSV-2 has markedly enhanced our understanding of HSV-1 and HSV-2 epidemiology. In both infections, most people have subclinical disease and can be identified only by antibody status. The type-specific serologic assays allow the detection of HSV-2 in the presence of HSV-1 antibodies and vice versa.^{13,14} Most of these assays utilize purified type-specific proteins such as glycoprotein gG1, and glycoprotein gG2, which are antigenically distinct between the two subtypes. The gG1 and gG2 assays accurately evaluate persons with long-standing HSV infections, regardless of clinical symptoms.¹⁵ In the last 5 years, several of these assays, either in an ELISA or immunoblot format, have become commercially available, allowing for large-scale seroepidemiologic studies in various populations. Another approach for defining type-specific antibodies to HSV-1 and HSV-2 has been the use of Western blot assays to prototype antigens that has undergone extensive evaluation in defining subtype-specific antibody patterns.¹⁴ The Western blot remains the most accurate test for serologic diagnosis of HSV-1 and HSV-2 infection, with a sensitivity of >98% and a specificity of >98% for distinguishing HSV-1 specific and HSV-2 specific antibodies. Commercially available HSV antibody assays have specificity and sensitivity (>95%) that are sufficient for clinical use,^{16–19} although many of them have lower sensitivity for detection of incident and prevalent HSV-1 infection. ELISA and IFA assays which utilize prototype viral antigens are inaccurate and should not be utilized for clinical diagnosis or seroepidemiologic studies.^{20,21}

Prevalence of antibody to HSV increases with age and correlates inversely with socioeconomic status.^{12,22–26} Serosurveys of western populations in the post-World War II era found that 80–100% of middle-aged adults of lower socioeconomic status had antibodies to HSV, as compared with 30–50% of adults of higher socioeconomic groups.^{27–29} In the United States in the 1970s, HSV-1 antibodies were detected in about 50% of high and 80% of lower socioeconomic class persons by age 30.²⁹ In the most recent data from NHANES, the prevalence of HSV-1 appears to have fallen slightly from 62% in the years 1988–1994 to 57.7% in the years 1999–2004 in the general population.³⁰ In Western Europe, the prevalence of HSV-1 infection in young adults remains 10–20% higher than that in the United States.³¹ In STD clinics in the United States, about 60% of attendees have HSV-1 antibodies. In Asia and Africa, HSV-1 infection remains almost universal with the infection acquired in early childhood, although the HSV-1 prevalence in Japan is considerably lower.³²

Antibodies to HSV-2 are not routinely detected in sera until puberty, and antibody prevalence with rates correlate with indices of sexual activity. The wider availability of serologic tests for HSV-2 has allowed for extensive characterization of HSV-2 infection worldwide (Fig. 24-1). Consistently, HSV-2 seroprevalence is higher among women than men. In the United States, the rates of HSV-2 have been assessed in consecutive nationwide surveys of adults. These studies showed that the HSV-2 seroprevalence has increased from 16.4% to 21.7% of adults in the United States between 1979 and 1991.³³ However, the most recent data that spans the 1999–2004 years suggest that the overall prevalence has decreased somewhat to 17%, reflecting a lower rate of infection among teenagers and young adults.³⁰ The cumulative lifetime incidence of HSV-2 reaches 25% in white women, 20% in white men, 80% in African American women and 60% in African American men (Fig. 24-2). Higher rates of HSV-2 among African American have been observed, which reflect higher rates of infection in the African American community as well as patterns of sexual networking rather than higher individual sexual behavior.

Worldwide, the HSV-2 seroprevalence appears lower in Europe, including Great Britain (9.7%) and Eastern Europe (6–25%),^{34–36} and Australia (16% in women, 8% in men).^{37,38} In Africa, population-based studies indicate very high level of infection, with teenagers becoming infected at the onset of sexual activity. For example, in South Africa, HSV-2 infection rates reach 80% in women and 40% in men by age 24.³⁹ In Latin America, HSV-2 infection rates range from 20% in women in Peru to 43% in female blood donors in Brazil to over 60% among men in STD clinic.^{35,40} Fewer population-based studies have been conducted in Asian countries; among pregnant women the prevalence was 27% in Saudi Arabia, 8% in India, and 30% in the South Pacific Island Nation of Vanuatu.^{35,41,42}

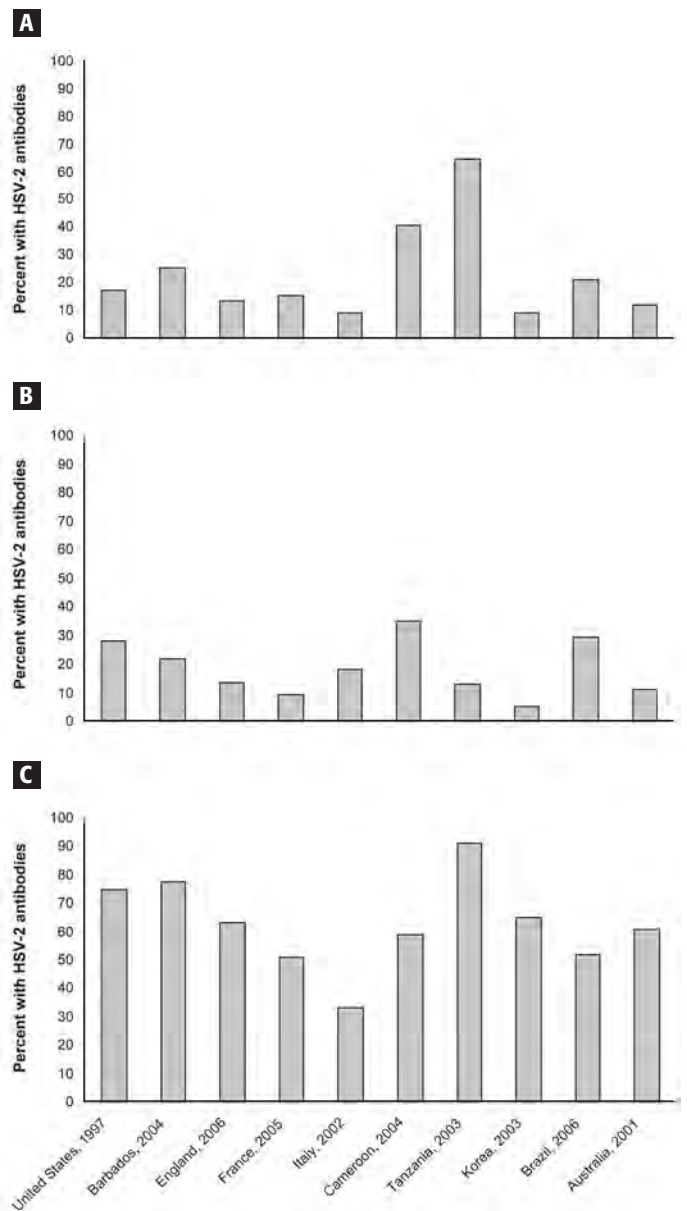


FIGURE 24-1. Seroprevalence of HSV-2 in population-based studies, and among pregnant women, and HIV-1 seropositive persons.

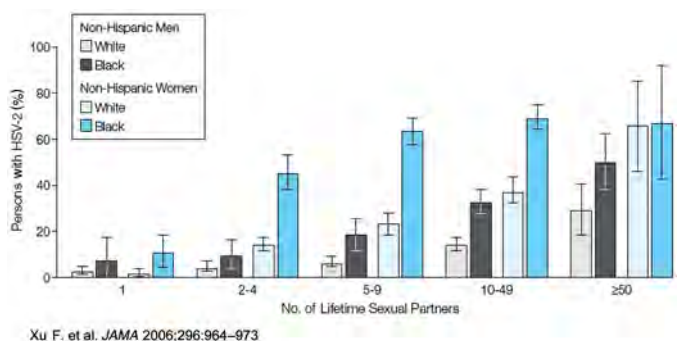


FIGURE 24-2. Age-adjusted herpes simplex virus type-2 seroprevalence according to the lifetime number of sex partners, by race/ethnicity and sex on NHANES in 1999–2004.

Not surprisingly, the frequency of HSV-2 antibody is higher among persons recruited from STD clinics and among men who have sex with men (MSM).^{43,44} In both general population and high-risk groups, HSV-2 antibody is closely related to the lifetime number of sexual partners, age of sexual debut, and a history of other STDs. As such, it can serve as a serologic marker for sexual behavior in different populations.⁴⁵ HSV-2 infection rates are also higher among people with HIV infection; the complex interactions between HSV-2 and HIV are summarized below.

Incidence rates for HSV infections are difficult to estimate as most infections are acquired subclinically. A 15-year study of 839 adolescent women in Sweden showed that 50% of the cohort has acquired HSV-1 and 22% acquired HSV-2 by the end of the study.⁴⁶ Studies of candidate vaccines have shown that the risk of HSV-2 varies with gender, sexual orientation, and risk behavior.⁴⁷ Among HSV-2 seronegative women with partners who have documented genital HSV-2 infection, the rates of infection were 8.6% per 100 patient years.⁴⁸ Conversely, the rate of HSV-2 acquisition among men partnered with HSV-2 infected women was 1.5%. However, the rates of HSV-2 acquisition were higher among men recruited from STD clinics.⁴⁹ In Project RESPECT, a behavioral intervention study of high-risk urban youth, the incidence of HSV-2 was 9.9 per 100 person years for men and 14.8 for women.⁵⁰ In prospective studies of HIV seronegative MSM, the rates of acquisition of HSV-2 were 1.9 per 100 patient years and 1.0 per 100 patient years in two studies of HIV prevention.^{51,52} HSV-2 acquisition is also common among persons with HIV. In a study from Zimbabwe, the risk of HSV-2 acquisition was 4.7-fold higher among HIV-positive versus HIV-negative persons; in a Ugandan study, the risk was 2.7-fold higher.^{53,54} In a study of Ethiopian women with HSV-2 seropositive spouses, the rate of HSV-2 acquisition was 25% per 100 person years and in Tanzanian bar workers, 14.2 cases per 100 person years.^{55,56} This high rate of HSV-2 acquisition in HIV seropositive person may reflect high-risk behavior, increased susceptibility, and/or exposure of HIV/HSV-2 infected person who are likely to be more infectious for HSV-2 than those without HIV (see below).

■ PREVALENCE OF GENITAL HSV INFECTIONS

The reported prevalence of genital herpes depends upon the demographic and clinical characteristics of the patient population studied and whether clinical and/or laboratory techniques are used for diagnoses. Seroepidemiologic studies have shown a wide disparity between antibody prevalence and clinical infections, indicating that many persons acquire subclinical infection.^{12,57} Reasons for lack of recognition of the infection include mild disease in most persons, attenuation of symptoms in those with prior HSV-1 infection, location of lesions in difficult-to-examine areas, e.g., perianal

region, and differential access to health care and availability of diagnostics in various populations. As such, there are great differences in the prevalence of HSV-1 and HSV-2 infection versus the frequency of symptomatic genital and oral-labial herpes seen by medical practitioners. HSV has been isolated from 0.3% to 5.4% of men and 1.6% to 10% of women attending STD clinics.^{58–60} In non-STD clinic patient populations, HSV has been isolated from the genital tract in from 0.25% to 5.0% of patients. Most of these patients are asymptomatic.^{61–64} HSV-2 has been shown to be the dominant cause of genital ulcer disease both in developing and developed countries. In Africa, the Far East and the United States, genital herpes is from 2 to 10 times more common than other infections in genital ulcers. The shift from syphilis and chancroid to genital herpes as the etiologic cause of genital ulcer disease can primarily be attributed to the use of HSV DNA PCR for detection of viral genome, in combination with the relative decrease in syphilis and chancroid caused by improved control methods and wider use of antibiotics. Etiologies of genital ulcer disease as defined by molecular diagnostics from diverse locations are shown in [Table 24-1](#).

In the United States, HSV predominates as the most common cause of genital ulcers at all locations, and remains stable, unlike the rates of detection of *T. pallidum* and chancroid that have marked temporal and geographic variations.⁶⁵ The lack of detection of HSV in studies historically from developing countries based on clinical diagnosis or viral culture reflects the insensitivity of both methods. Overwhelmingly, the predominant cause of genital ulcers worldwide is HSV-2, accounting for 40–80% of diagnosed etiologies of genital ulcers. Of note, ~25% of genital ulcers continue to be undiagnosed.^{67,68,73} This may partly reflect imperfect sensitivity of the multiplex assay often used. Detailed studies that employ both sensitive molecular techniques and serologic assays that characterize the natural history of such ulcers have rarely been performed. Additionally, the long duration of ulcers prior to seeking health care in developing countries skews the presentations observed in STD clinics toward more chronic etiologies. Consistent with this, HIV epidemic has resulted in greater proportion of persons presenting with genital herpes as the ulcers persist and are more extensive.^{69,76}

The prevalence of genital herpes has increased markedly between the early 1960s and 1990s. In Britain, reports of patients with genital herpes in STD clinics increased sixfold between 1972 and 1994.⁷⁷ Initial visits to physicians in the United States for first-episode genital HSV increased 15-fold, from 16,986 in 1970 to over 240,000 in 2004,^{78,79} and continue to increase, in marked contrast to the leveling off of HSV-2 seroprevalence results.

In the last decade, an increase in genital HSV-1 infections has been reported from Europe, North America, and Australia.^{80,81,82,83} Several laboratory-based studies reported a shift in the relative proportion of HSV-1 and HSV-2 isolated

Table 24-1. Etiology of Genital Ulcers Worldwide Using Molecular Methods

Location	HSV (%)	Syphilis (%)	Chancroid (%)	Unknown/Other (%)
10 US cities ⁶⁵	65	13	3	22
Brooklyn, NY ⁶⁶	30	41	33	21
Amsterdam ⁶⁷	56	3	1	37
Durbin, South Africa ⁶⁸	48	14	10	35
Carletonville, South Africa ⁶⁹				
1993–1994	17	10	69	11
1998	35	12	51	21
Dakar, Senegal ⁷⁰	13	15	57	26
Dar es Salaam, Tanzania ⁷¹	73	2	23	21
Mbeya, Tanzania ⁷¹	42	0	18	56
Maseru, Lesotho ⁷²	26	23	56	9
Pune, India ⁷³	31	14	28	34
Bombay, India ⁷⁴	29	15	52	4
Northern Thailand ⁷⁵	84	2	0	16

Percent may not add to 100%, as more than a single pathogen were found in some lesions.

from genital lesions, often with predominance of HSV-1 isolates from young people, women, and MSM.^{84,85} The relative proportion of HSV-1 approximates 50% in some studies of college students.⁸⁶ While laboratory-based reporting is perhaps not a good indicator of overall incidence of genital herpes, the shift in the type of HSV found has been consistent. The reasons are not clear: both decrease in oral acquisition of HSV-1 during childhood and frequent oral–genital contact, especially among teenagers, have been postulated as a cause. Confirming this observation has been a change in the proportion of neonatal HSV-1 versus HSV-2 infection, with HSV-1 causing most infections in some series.⁸⁷

■ SEXUAL TRANSMISSION OF HSV

The frequency of transmission of HSV-2 is influenced by gender, past HSV-1 infection, and frequency of sexual activity with a person with known infection. Transmission of HSV between sexual partners has been addressed most often in prospective studies of serologically discordant couples, i.e., in couples in whom one partner has and the other does not have HSV-2. Longitudinal studies of such couples have shown that

the transmission rate varies from 3% to 12% per year.^{47,88–90} Several studies have described couples in which HSV-2 has not been transmitted despite frequent sexual activity. Whether this is due to genetic or acquired resistance is unclear. Unlike other STDs, persons usually acquire genital HSV-1 and genital HSV-2 in the context of a steady rather than casual relationship.⁹¹ Women have higher rates of acquisition than men; in one study the attack rate among seronegative women approached 30% per year.⁸⁸ This increased risk for acquisition among women compared with men is evident in the 5–20% higher seroprevalence of HSV-2 antibodies among women than men.³⁰ The reasons probably include anatomic differences which lead to greater mucosal surface area exposed in the genital area of women compared with men and possibly a lower perception of discomfort in men with active lesions than in women.^{92,93} This latter feature may lead to increased sexual activity when lesions are present and hence higher transmission rates. Patterns of sexual behavior probably also play a role, with older men serving as a source of infections for younger women.

Sexual contact with persons with undiagnosed genital herpes may lead to higher acquisition rates. In a study of

66 source partners who were interviewed and examined, a third had a history of recurrent genital herpes, a third had a clinical history of recurrent genital lesions consistent with herpes, and a third denied a history of such lesions.⁹⁴ Median time of the relationship before transmission occurred was 3 months and the median number of sexual encounters was 24, suggesting that HSV is transmitted rather easily. These data have recently been confirmed in a study that showed the potential source partners' awareness of having genital herpes and disclosing it to the sexual partner is associated with a 50% decrease in the risk of HSV-2 transmission.⁹¹ Thus, the diagnosis of genital herpes in the potential source partner and awareness of both partners as to the existence of a transmissible sexually transmitted infection (STI) may help reduce the risk of transmission. Most transmission events occur during episodes of subclinical shedding (discussed below). In prospective studies of HSV acquisition, only 40% of newly acquired cases of genital HSV-2 develop genitourinary complaints around the time of acquisition; prior HSV-1 infection protects against symptomatic acquisition of HSV-2. The disease pattern in the person who acquired the disease does not reflect the disease pattern of the source partner, suggesting that host factors rather than viral factors determine the severity of disease. Fifty-eight percent of patients with newly acquired genital herpes presented within 5 days of last sexual contact and 95% within 14 days of sexual intercourse, confirming the short incubation period noted in experimental human and animal studies.^{8,95} There is conflicting data on whether past HSV-1 infection protects against HSV-2 acquisition, with the protection being marginal in most studies.⁹⁶

PATHOGENESIS OF INFECTION

Transmission of HSV infections most frequently occurs through close contact with a person who is shedding (excreting) virus at a peripheral site, mucosal surface, and in genital or oral secretions. Since HSV is readily inactivated at room temperature and by drying, aerosol and fomite spread are unusual means of transmission.^{97–100} Infection occurs via inoculation of virus onto susceptible mucosal surfaces (e.g., the oropharynx, cervix, conjunctivae) or through abrasions on the skin. HSV infection is associated with focal necrosis and ballooning degeneration of cells, production of mononucleated giant cells, and eosinophilic intranuclear inclusions (Cowdry type-A bodies).¹⁰¹ The initial cellular response is predominantly polymorphonuclear, followed by lymphocytic response. When viral replication is restricted, lesions reepithelialize.

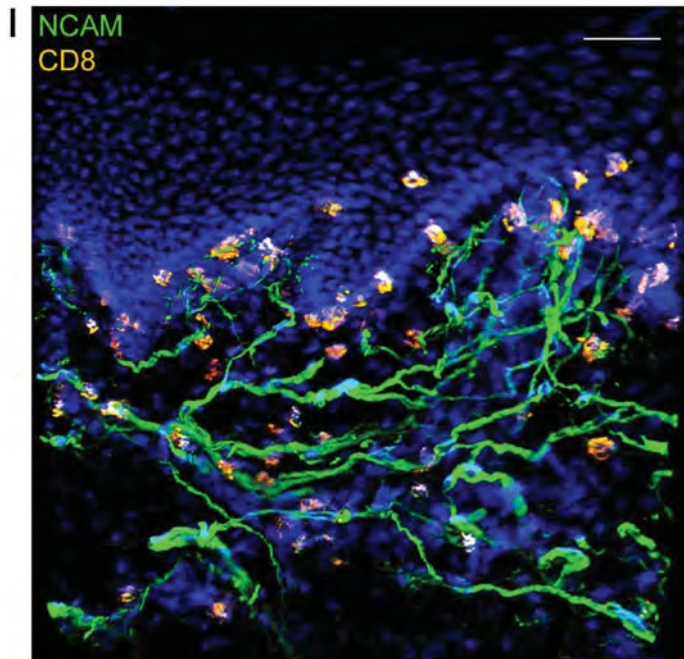
Concomitant with initial infection, HSV ascends peripheral sensory nerves and enters sensory or autonomic nerve root ganglia where latency is established.^{102–105} Using cocultivation techniques HSV-2, and rarely, HSV-1 have been isolated from sacral nerve root ganglia.¹⁰⁴ The biological

mechanism by which latency is established and the nature of the virus–cell interaction that results in latency is incompletely understood. Latency can be established after both symptomatic and asymptomatic initial infection. Available evidence suggests that all HSV seropositive persons have latent virus in nerve ganglia and possibly all HSV-2 seropositive persons intermittently reactivate infection with HSV shedding occurring at least briefly on mucosal surfaces. Reactivation of disease may be clinically symptomatic or asymptomatic. Reinfection with different strains of virus has also been demonstrated; however, this appears to be an infrequent event and recurrences are usually due to reactivation of the initial strain of virus from latently infected ganglia.^{106,107}

The molecular mechanisms by which HSV establishes latency and intermittently reactivates are unknown. Moreover, little is known about the molecular mechanisms of reactivation; largely because there are few accurate experimental systems to study these issues *in vitro*. In animal models, many HSV genes influence neuroinvasion and spread. When the region containing the latency-associated transcripts of HSV-2 is inserted into an HSV-1 virus, increasing reactivation in sacral nerve root ganglia has occurred, indicating that viral factors influence reactivation.¹⁰⁸

Host factors also appear operative in influencing reactivation. Immunocompromised patients have both more frequent and more severe reactivations. Both HSV-1 and HSV-2 encode for proteins that are directed at subverting host T cell responses. The HSV protein, ICP-47 (infected cell protein no. 47), interacts with the transporter activity protein to prevent the interaction between HSV-specific peptides to HLA class I molecules. This downregulates certain HSV-1 peptides with HLA class I antigen on the cell surface and subverts the host CD8⁺ CTL response to HSV.^{109–111} Similarly, HSV infection can “stun” cytotoxic T lymphocytes and impair both their signaling and cytokine secretion.^{112,113} This CTL inactivation appears unique to HSV-1 and HSV-2 and is associated with viral-cell entry.

Biopsies of herpetic lesions have shown that initially the predominant infiltrating cell is the CD4⁺ lymphocyte.¹¹⁴ Staining of such lesions shows the presence of activation markers on these CD4-bearing cells. These include IL-2 receptor, DR+, and ICAM-1+ within 2–4 days. These early CD4⁺ infiltrating T cells produce γ IFN and other cytokines in response to HSV antigen. γ -IFN in particular upregulates cellular HLA class I expression, which can then overcome the virus's ability to downregulate this response.¹¹¹ Infiltration of CD8⁺ T cells into the lesion then occurs and helps clear virus. Clearance of HSV-2 from genital lesions is associated with detection of cytolytic killing of HSV-2 in lesional T cells.¹¹⁵ Most of this CTL activity appears to be in the CD8⁺ T lymphocytes. HSV-2 specific CD8⁺ T cells appear to persist after healing resolution in the dermal epidermal junction and are



Zhu J. et al. *J Exper Med* 2007;204:495–503

FIGURE 24-3. HSV-specific CD8⁺ T cells at dermal epidermal junction juxtaposed to neuronal bodies from cutaneous neurons in biopsy of patient 3 weeks posthealing of lesions. (Reproduced from *J Exp Med* 2007, 204: 595–603. Copyright 2003 The Rockefeller University Press.)

juxtaposed to the neural endings that innervate the region (Fig. 24-3).¹¹⁶ These data imply that such cells participate in immune surveillance.

There is evidence that CD8⁺ T cells can be found in dorsal nerve root ganglia and such T cells appear to secrete γ -IFN, and removal of such cells is associated with viral reactivation.^{117–120} These host responses may be important in controlling HSV at a ganglion level.

CLINICAL MANIFESTATIONS OF GENITAL HERPES

The severity of clinical manifestations and recurrence rate of genital herpes are influenced by viral and host factors such as viral type, prior immunity to autologous or heterologous virus, gender, and immune status of the host. The influence of other host factors such as age, race, and site of inoculation on the acquisition of infection or expression of disease are poorly understood. Host genetic background is likely to influence the natural history of HSV infections, but with exception of few well-characterized genetic mutations that are associated with severe outcomes,^{121–125} the genetic determinants of severity of mucosal HSV infections are unknown. Many HSV infections (both HSV-1 and HSV-2) are subclinical and the differences in persons with symptomatic versus clinically silent disease have not been defined. Moreover, identical strain of virus may have markedly different patterns of reactivation between persons.

■ FIRST EPISODE OF GENITAL HERPES

The clinical manifestations of genital herpes differ greatly between first versus recurrent episode of HSV. First episodes of genital herpes often are associated with systemic symptoms, a prolonged duration of lesions, and viral shedding, and involve multiple genital and extragenital sites.¹²⁶ Patients who are experiencing true primary infection (i.e., the first infection with either HSV-1 or HSV-2) have more severe illness than patients who have clinical or serological evidence of prior HSV-1 infection.^{127–129} In most surveys, about 50% of persons who present with their first episode of symptomatic genital herpes have primary infection with either HSV-1 or HSV-2.⁶¹ Most persons with nonprimary first episodes of genital HSV infection have serological evidence of past HSV-1 infection;¹³⁰ acquisition of HSV-1 infection in persons with prior HSV-2 infection is rare. About 25% of persons with their first clinical episode of symptomatic genital herpes already have antibody to HSV-2 at presentation, indicative of past asymptomatic acquisition of HSV-2.¹³¹ Thus, their initial clinical episode is their first recognized episode of past infection and does not indicate recent acquisition. Isolates recovered from sequential recurrences almost invariably have identical restriction enzyme patterns. Most genital HSV-1 infections are primary infections, as genital HSV-1 acquisition is rare after HSV-2 infection.^{93,126,132,133}

Prior oral–labial HSV-1 infection appears to protect against the acquisition of genital HSV-1 disease,¹³⁰ although this has not been rigorously studied and the degree of this protection is not quantified. Genital HSV-1 disease does not protect completely against acquisition of genital HSV-2 infection, as sequential genital infections have been described.^{134,135} Persons with first-episode nonprimary genital HSV-2 infection (i.e., prior HSV-1 infection) are less likely to have systemic symptoms and have a shorter duration of symptoms and signs than persons with primary genital herpes due to either HSV-1 or HSV-2.^{61,126} However, prior HSV-1 infection does not appear to alter the subsequent rate of recurrences of genital HSV-2 disease.⁹³

Primary genital herpes

Primary genital HSV-2 and primary genital HSV-1 infections are characterized by frequent and prolonged systemic and local symptoms (Fig. 24-4). Fever, headache, malaise, and myalgias are reported in nearly 40% of men and 70% of women with primary HSV-2 disease ($p < 0.05$). Systemic symptoms appear early in the course of the disease, usually reach a peak within the first 3–4 days after onset of lesions, and gradually recede over the subsequent 3–4 days.

Pain, itching, dysuria, vaginal or urethral discharge, and tender inguinal adenopathy are the predominant local symptoms of disease. The severity of local symptoms, duration of

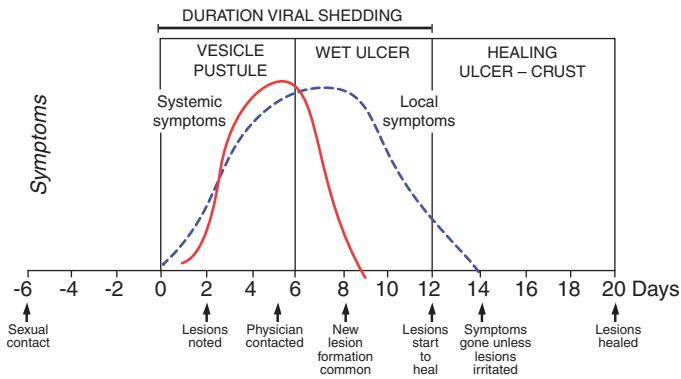


FIGURE 24-4. Clinical course of primary genital herpes.

lesions, and viral shedding appear similar in patients with primary HSV-1 and primary HSV-2 disease. Painful lesions are reported in 95% of men (mean duration 10.9 days) and 99% of women (mean duration 12.2 days) with primary HSV infection. Dysuria, both external and internal, appears more frequently in women (83%) than in men (44%). The isolation of HSV from the urethra and urine of both men and women with primary genital herpes suggests that, in addition to external dysuria resulting from urine touching active genital HSV lesion, HSV urethritis and/or cystitis may account for the higher frequency and longer duration of dysuria in women.

Urethral discharge and dysuria are noted in about one-third of men with primary HSV-2 infection. HSV can be isolated from a urethral swab or from first-voided urine of these men. The urethral discharge is usually clear and mucoid, and the severity of dysuria is often out of proportion to the amount of urethral discharge elicited on genital exams. Gram stain of the urethral discharge reveals between 5 and 15 polymorphonuclear leukocytes per oil-immersion field. Occasionally, a mononuclear cell response is seen.

The clinical symptoms of pain and discomfort from lesions gradually increase over the first 6–7 days of illness, reach their maximum intensity between days 7 and 11 of disease, and gradually recede over the second week of illness. Tender inguinal adenopathy usually appears during the second and third week of disease and often is the last symptom to resolve. Inguinal and femoral lymph nodes are generally firm, nonfluctuant, and extremely tender to palpation. Suppurative lymphadenopathy is a very uncommon manifestation of genital herpes.

Clinical signs and duration of viral shedding in primary genital herpes.

In both men and women with primary genital HSV infection, widely spaced bilateral vesicopustular or ulcerative lesions on the external genitalia are the most frequent presenting sign (Figs. 24-5 and 24-6). Lesions are characteristically described as starting as papules or vesicles which rapidly spread over the genital area. At the time of the first clinic visit, multiple small vesicular lesions that coalesce into large areas of ulcerations are usually present, especially in women. The number, size, and shape of the ulcerative lesions vary greatly



FIGURE 24-5. Primary HSV in a man.



FIGURE 24-6. Primary Vulvar HSV.

between patients. Edema of the labia or penis is common. These ulcerative lesions persist from between 4 and 15 days until crusting and/or reepithelialization occurs. In general, lesions in the penile and mons areas crust over before complete reepithelialization ensues. Crusting does not occur on mucosal surfaces. Residual scarring from lesions is uncommon. New

lesion formation (the development of new areas of vesiculation or ulceration during the course of infection) occurs in over 75% of patients with primary genital herpes. New lesions usually form between days 4 to 10 of disease and one of the most obvious clinical effects of early systemic antiviral therapy of primary genital herpes is the reduction in new lesion formation. The median duration of viral shedding, as defined from onset of lesions to the last positive culture, is 12 days. The mean time from the onset of lesions to complete reepithelialization of all lesions appears slightly longer in women (19.5 days) than in men (16.5 days).

HSV cervicitis in first episodes of genital herpes. From 70% to 90% of women with first-episode HSV-2 infection have HSV cervicitis.^{126,136} This compares to a 15–20% isolation rate of HSV-2 from the cervix among women who present with recurrent external genital lesions.^{126,137} Primary genital HSV cervicitis may be symptomatic (purulent or bloody vaginal discharge) or asymptomatic.^{61,138} Areas of diffuse or focal friability and redness, extensive ulcerative lesions of the exocervix, or severe necrotic cervicitis (Fig. 24-7) may be seen, occasionally in the absence of external herpetic lesions. HSV infection of the cervix usually involves the squamous epithelium of the exocervix in contrast to the mucopurulent cervicitis of *C. trachomatis* and *N. gonorrhoeae* infection. Clinical differentiation may be difficult, although cervical ulceration and necrosis is highly correlated with HSV cervicitis.

Pharyngeal infection. HSV of the pharynx is commonly seen in association with primary genital herpes and may be the presenting complaint in about 20% of patients with either primary HSV-1 or primary HSV-2 infections. Both HSV-1 and HSV-2 may cause pharyngitis and may be associated with oral–genital exposure to the source contact.^{139,140} In children, autoinoculation of the genital area during the course of primary

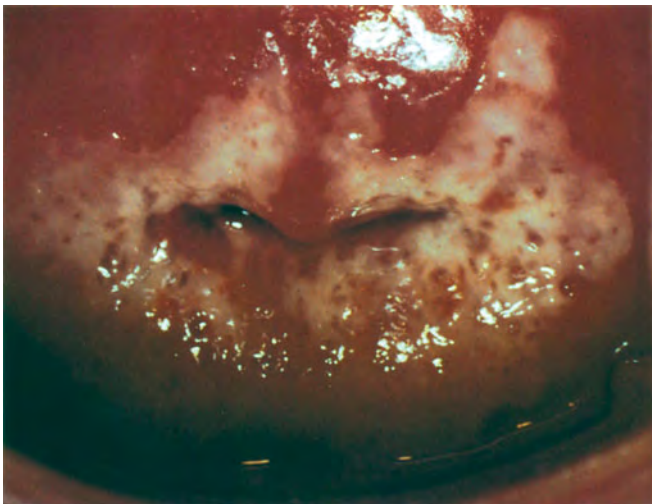


FIGURE 24-7. Cervicitis. (Reprinted from Doorbar J. The papillomavirus life cycle. *J Clin Virol* 2005; 32S: S7–S15, with permission from Elsevier.)

HSV-1 gingivostomatitis may be seen occasionally. HSV pharyngitis is seen much less frequently in patients with non-primary first-episode genital herpes or patients with recurrent genital herpes (1%). Among persons with primary genital herpes who complained of sore throat during the acute episode of the disease, HSV was isolated from the pharynx in 70%. Viral cultures of the pharynx from 20 patients with primary HSV-2 who did not complain of sore throat did not yield HSV, indicating that HSV pharyngitis is usually symptomatic. Clinical signs of HSV pharyngitis may vary from mild erythema to a diffuse ulcerative pharyngitis.^{139–142} The inflammatory response to these large areas of ulceration may produce a whitish exudate; when wiped away the extensive ulceration may be visualized. In rare cases severe swelling of the posterior pharynx resulting in obstruction of the airway may occur.¹⁴³ Extension of the ulcerative posterior pharyngeal lesions into the anterior gingival area may occur. Most patients with HSV pharyngitis have tender cervical nodes, and constitutional symptoms, such as fever, malaise, myalgia, and headache, are common. Many are misdiagnosed as having streptococcal pharyngitis, or infectious mononucleosis, and tonsillectomies in such patients have been reported.

HSV-1 pharyngitis is common in teenagers and college students and is often due to primary oral HSV-1 infection. The mode of transmission often is kissing during subclinical oral shedding. Reactivation of HSV in the pharynx rarely leads to symptomatic pharyngitis. Instead, recurrent oral–labial lesions or asymptomatic oral shedding are seen. Reactivation of HSV-2 in the trigeminal ganglia occurs less frequently than reactivation of trigeminal nerve root latent HSV-1 infection.^{140,144}

■ COMPLICATIONS OF GENITAL HERPES

The complications of genital herpes are related both to local extension and to spread of virus to extragenital sites. Central nervous system involvement and fungal superinfection are also frequently encountered. Complications of primary genital herpes occur more frequently in women than in men.

Central nervous system complications

Aseptic meningitis. Central nervous system involvement may occur in several forms, including aseptic meningitis, transverse myelitis, or sacral radiculopathy.^{145–147} In one series of patients with primary genital HSV-2 infection, stiff neck, headache, and photophobia on two consecutive examinations was reported in 36% of women and 13% of men ($p < 0.001$). Hospitalization was required for clinically overt aseptic meningitis in 6.4% of women and 1.6% of men with primary HSV-2 infections.¹²⁶ A study of primary genital herpes in the early 1900s reported a high frequency of CSF pleocytosis in patients without overt clinical evidence of meningeal irritation, suggesting that meningeal involvement may be frequent during primary genital herpes.¹⁴⁸

Both HSV-1 and HSV-2 have been isolated from CSF, although nuchal rigidity and isolation of HSV-2 are much more common.^{149,150} HSV aseptic meningitis is more frequently associated with genital HSV-2 infection, while HSV encephalitis in older children or adults is usually associated with oral HSV-1 infection.^{93,151–153} Fever, headache, vomiting, photophobia, and nuchal rigidity are the predominant symptoms of HSV aseptic meningitis. Meningeal symptoms usually start from 3 to 12 days after onset of genital lesions. Symptoms generally reach a maximum 2–4 days into the illness and gradually recede over 2–3 days. The CSF in HSV aseptic meningitis is usually clear and the opening pressures may be elevated. White blood cell counts in CSF may range from 10 to over 1000 cells per cubic millimeter (mean 550). The pleocytosis is predominantly lymphocytic in adults, although early in the course of disease and in neonates, a predominantly polymorphonuclear response may be seen. The CSF glucose is usually more than 50% of the blood glucose, although hypoglycorrhachia has been reported, and the CSF protein is slightly elevated.¹⁵⁴ HSV is rarely isolated from the CSF, but HSV DNA detection with PCR assay is a sensitive diagnostic test (see section on diagnosis). The differential diagnosis of HSV aseptic meningitis includes diseases that result in neurological involvement and genital ulcerations: sacral herpes zoster, Behcet's syndrome (Fig. 24-8), collagen vascular disease, inflammatory bowel disease, and porphyria. Occasionally, patients will present with aseptic meningitis as the sole presenting sign of new HSV-2 acquisition; HSV detection in the spinal fluid in a patient lacking antibodies to autologous type virus is diagnostic.

Aseptic meningitis associated with genital herpes appears to be a benign, albeit uncomfortable, disease in immunocompetent persons. Signs and symptoms of encephalitis are unusual and persistent neurological sequelae are rare. Use of

systemic antiviral chemotherapy of primary genital herpes decreases the subsequent development of aseptic meningitis.¹⁵⁵ Controlled trials of IV acyclovir (ACV) for established HSV meningitis have not been conducted. However, we recommend that IV ACV 5 mg/kg q 8 hours be given for hospitalized symptomatic patients. Once symptoms are resolved, oral antiviral therapy, preferably with valacyclovir, can be resumed. Oral antiviral agents should not, however, be utilized for patients with HSV-1 encephalitis.

Other neurological complications. Both autonomic nervous system dysfunction and transverse myelitis have been described in association with genital HSV infection.^{146–148} Symptoms of autonomic nervous system dysfunction include hyperesthesia or anesthesia of the perineal, lower back, and sacral regions and urinary retention and constipation. This complication occurs more frequently among women and men with HSV proctitis.^{156,157} Physical examination reveals a large bladder, decreased sacral sensation, and poor rectal and perineal sphincter tone. In men, impotence and absent bulbocavernosus reflexes may occur. CSF pleocytosis may be present in some patients. Electromyography usually reveals slowed nerve conduction velocities and fibrillation potentials in the affected area, and urinary cystometric examination shows a large atonic bladder. Most cases gradually resolve over 4–8 weeks.^{158–161}

Transverse myelitis occasionally occurs in association with primary genital HSV infection.^{158,162,163} Decreased deep-tendon reflexes and muscle strength in the lower extremities, as well as the above-described autonomic nervous system signs and symptoms, are present. In one reported case, significant residual dysfunction was present years later.¹⁶² Whether autonomic nervous system dysfunction results from viral invasion of the central nervous system or an unusual immunologic response to infection is unknown.

■ EXTRAGENITAL LESIONS

The development of extragenital lesions during the course of infection is a common complication of first-episode primary genital herpes and is seen more commonly in women than in men. Extragenital lesions are most frequently located in the buttock, groin, or thigh area, although finger and eye can also be involved. Among patients with primary HSV-2, 9% develop extragenital lesions, most commonly on the buttocks.¹⁶⁴ Among patients with primary genital HSV-1, 25% develop extragenital lesions, usually in or around the mouth. Characteristically, the extragenital lesions develop after the onset of genital lesions, often during the second week of disease. The distribution of lesions on the extremities and/or areas near the genital lesions and their occurrence later in the course of disease suggests that the majority of extragenital lesions develop by viral reactivation in another



FIGURE 24-8. Behcet's syndrome.

part of the affected dermatome rather than viremic spread.¹⁶⁵ However, the recent demonstration of HSV DNA in plasma of patients with primary HSV suggests that viremic spread may also be a factor in these lesions. Prior to universal use of gloves in health-care settings, HSV-1 was commonly isolated from herpetic infections of the hand.⁹⁷ Currently, herpetic infections of the hand are more likely to be caused by HSV-2 than HSV-1.¹⁶⁶

■ DISSEMINATED INFECTION

Blood-borne dissemination evidenced by the appearance of multiple vesicles over widespread areas of the thorax and extremities occurs rarely in persons with primary mucocutaneous herpes.^{167,168} Cutaneous dissemination usually occurs early in the disease and is often associated with aseptic meningitis, hepatitis, pneumonitis, or arthritis.^{169,170} Other complications of primary genital HSV-2 infection include monoarticular arthritis,^{171,172} hepatitis,^{173,174} thrombocytopenia,¹⁷⁵ and myoglobinuria.¹⁷⁶ Pregnancy predisposes to severe visceral dissemination in primary genital HSV disease.^{177–179} Diagnosis of disseminated HSV or HSV hepatitis is often delayed as skin lesions may be subtle or absent. Mortality is high, even in patients treated with IV ACV; liver transplant following HSV hepatitis has been reported. Severe mucocutaneous and occasionally visceral dissemination of disease may occur in patients with atopic eczema.^{180–182} In immunosuppressed patients, especially those with impaired cellular immune responses, reactivation of genital HSV infection can be associated with viremic spread to multiple organs.^{183–187} Such patients may develop interstitial pneumonia, hepatitis, and pneumonitis, similar to the manifestations of disseminated infection of the neonate. Disseminated visceral infections in the immunosuppressed and pregnant patient have high mortality and should be treated presumptively with systemic antiviral chemotherapy.

■ LOCAL EXTENSION OF DISEASE

Both HSV-1 and HSV-2 have been shown to be rare causes of pelvic inflammatory disease.¹⁸⁸ Some patients with primary cervical HSV infection may manifest lower abdominal pain and adnexal uterine tenderness, and extension of HSV infection into the uterine cavity has been reported, as well as laparoscopic evidence of vesicular lesions on the fallopian tube from which HSV has been isolated.¹⁸⁸

Superinfection

Bacterial superinfection of genital herpes in immunocompetent patients is uncommon. In rare cases, pelvic cellulitis presenting as an advancing erythema and swelling of the perineal area is encountered. In such patients, systemic antimicrobial therapy should be administered.

In contrast, fungal vaginitis is frequently encountered during the course of initial genital herpes. In one series, yeast vaginitis was reported in 14% of women with first episodes of genital disease.¹²⁶ In another study of women attending an STD clinic, concurrent yeast infection was reported significantly more frequently in women with genital herpes than those without.⁶¹ Characteristically, vaginal fungal infection develops during the second week of disease and is associated with a change in character of the vaginal discharge, and reemergence of local symptoms such as vulvar itching and irritation. Typical hyphal yeast forms can be demonstrated on potassium hydroxide examination of vaginal secretions. If symptomatic, appropriate treatment is recommended.

■ SUMMARY OF THE CLINICAL COURSE OF INITIAL GENITAL HERPES

First-episode genital HSV infection is a disease with both systemic and local manifestations. Over one-half of the patients with primary genital herpes suffer from constitutional complaints and one-third complain of headache, stiff neck, and mild photophobia during the first week of disease.

Patients with serological evidence of prior HSV-1 infection are less apt to have systemic symptoms and have a lower rate of complications and a shorter duration of disease than persons with true primary genital herpes. Neutralizing antibody to herpes simplex virus has been shown to inactivate extracellular virus and interrupt the spread of HSV infection.¹⁸⁹ In addition, a cellular immune response to HSV antigens appears earlier in persons with nonprimary genital HSV than in persons with true primary infection.¹³⁷ It is likely that both of these immune mechanisms account for the clinical differences between primary and nonprimary first episodes of genital infection.

Untreated primary genital herpes is a disease of significant morbidity warranting prompt diagnosis and treatment. We recommend initiation of oral antiviral therapy of all persons with a presumptive clinical diagnosis of first-episode genital herpes. Confirmation of the diagnosis with laboratory tests should be sought in all cases, but therapy should not be delayed. Early use of therapy will abrogate the frequency of systemic manifestations of disease and prevent local extension of lesions into the upper genital tract. Moreover, early use of oral antivirals prevents the frequent development of new lesions that occur during the latter part of episode. In general, patients tend to note the resolution of headache, fever, and fatigue within 48 hours of initiating therapy with ACV, famciclovir, or valacyclovir. Lesions will continue to extend for the initial 48 hours, but the frequency of new lesions will decrease. Healing may take 7–10 days. We prefer to use at least 10 days of therapy with first-episode infection, as reactivation of virus with a new crop of vesicles is quite common in the initial 30 days posthealing of primary genital HSV-2. In our experience, early discontinuation of therapy tends to exacerbate this phenomenon. Besides

initiation of therapy, laboratory diagnosis and subsequent counseling about the nearly universal likelihood of reactivation and the potential for transmission of infection are the most important messages the treating clinician must convey to the patient with first-episode genital herpes. These latter issues are best discussed after symptoms and signs of disease abate at a later visit and are discussed more fully later in the chapter.

■ RECURRENT GENITAL HERPES: CLINICAL SIGNS AND SYMPTOMS

In contrast to first episodes of genital infection, the symptoms, signs, and anatomic sites of infection of recurrent genital herpes are localized to the genital region.^{126,137,190} Local symptoms such as pain and itching are mild to moderate compared to initial genital infection, and the duration of the episode usually ranges from 6 to 12 days (Table 24-2). About 90% of persons with recurrent genital herpes develop prodromal symptoms in some episodes; the development of symptoms prior to appearance of lesions occurs in about 60% of the episodes.¹⁹¹ Prodromal symptoms vary from a mild tingling sensation, occurring 0.5–48 hour prior to the eruption, to shooting pains in the buttocks, legs, or hips 1–5 days prior to the episode. In many patients, the symptoms of sacral neuralgia are the most bothersome part of the episode. In about 20% of episodes, patients experience prodromal symptoms without subsequent lesions. The risk of viral shedding is high during prodromal symptoms, even in the absence of lesions.

As with initial genital disease, symptoms of recurrent genital herpes tend to be more severe in women (Table 24-2). In several studies, painful genital lesions are reported more frequently (60–90%) in women (mean duration 5.9 days), compared with men (30–70%, 3.9 days, respectively). In addition, pain is more frequent and more severe in women compared with men.⁹² Dysuria occurs in only 17% of women with recurrent disease. Most report only external dysuria, and isolation of HSV from the urethra is uncommon in both sexes (3–9%).

Lesions of recurrent genital HSV are usually confined to one side, with an area of involvement approximately one-tenth that of primary genital infection (Fig. 24-5). Untreated, the average duration of viral shedding from the onset of lesions is about 4 days; and the mean time from the onset of lesions to crusting of lesions averages between 4 and 5 days for both men and women (Table 24-2). The mean time from the onset of vesicles to complete reepithelialization of lesions is about 6–10 days. Considerable variability exists in the severity and duration of disease both among patients and in a patient between episodes. Some recurrences have only 1–2 lesions lasting 2–3 days, while others may be associated with 15–20 lesions lasting 12–16 days. Although symptoms of recurrent genital disease are more severe in women, objective signs of disease are relatively similar in the two sexes. Only

Table 24-2. Selected Clinical Signs of Recurrent Genital Herpes in Patients Followed at the University of Washington Genital HSV Clinic

	Men N = 218	Women N = 144
Percent experiencing prodromal symptoms	53	43
Percent with pain	67 ^a	88
Mean duration pain, days (range)	3.9 (1–14) ^b	5.9 (1–13)
Mean duration itching, days (range)	4.6 (1–16)	5.2 (1–15)
Percent with dysuria	9	27
Percent with tender lymph nodes	23	31
Mean duration tender nodes, days (range)	9.2 (1–25) ^b	5.9 (1–15)
Percent with bilateral lesion	15 ^c	4
Percent forming new lesions during episode	43 ^c	28
Mean number of lesions at onset of episode, days (range)	7.5 (1–25)	4.8 (1–15)
Mean time to crusting, days (range)	4.1 (1–15)	4.7 (2–13)
Mean time to healing, days (range)	10.6 (5–25)	9.3 (4–29)
Mean duration viral shedding from lesions, days (range)	4.4 (1–20)	4.1 (2–14)

^a*p* < 0.01 by chi square.

^b*p* < 0.01 by student's *t* test.

^c*p* < 0.05 by chi square.

about 15–30% of women who present with recurrent genital lesions experience concomitant cervical infection. When present, the duration of cervical viral shedding is short, occurs early in the episode, and is often without visible cervical lesions, unless routine colposcopy is performed (see “HSV cervicitis” section below).

■ “ATYPICAL” HSV REACTIVATION

Whereas the classical clinical findings of genital HSV are described above, recent studies have illustrated the diverse clinical spectrum of genital HSV infection. For example, among randomly selected women in an STD clinic, HSV was isolated from 33% of the women with genital lesions which lacked the characteristic appearance of vulvar ulcers; many of these lesions were small linear ulcerations, thought to be due to trauma or yeast vaginitis.⁶¹ HSV was also isolated from cervical ulcerations, some of which could be seen only with colposcopy. HSV can often be identified from nonconcentric genital ulcers without an erythematous base (Figs. 24-9 and 24-10). Perhaps these findings illustrate that when an infection is as prevalent as HSV-2, varied clinical signs and symptoms are to be “expected.” These observations, in concert with the epidemiological data indicating HSV as the most common cause



FIGURE 24-9. Immunofluorescence assay showing HSV-2 antigen specific cells. (From Hunter Handsfield's Color Atlas of STDs.)

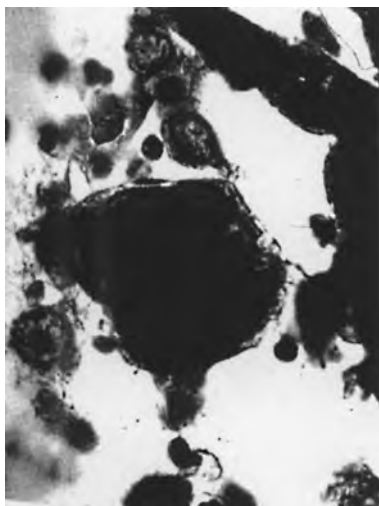


FIGURE 24-10. Wright Giemsa stain showing multinucleated giant cell. (From Hunter Handsfield's Color Atlas of STDs.)

of GUD, indicate that all genital lesions, regardless of appearance, should be evaluated for herpes. Laboratory diagnostic tests to detect HSV in the lesional area using either HSV PCR or the use of viral type-specific serologic assays can be employed by the clinicians to aid in the diagnosis. The detection of HSV-2 antibodies increases the likelihood of the ulcer in HSV, but coinfection with *T. pallidum* and *H. ducreyi* should be considered, depending on local epidemiology.

■ RECURRENCE RATE OF GENITAL HSV INFECTION

The major morbidity of recurrent genital herpes is its frequent reactivation rate. Most likely, all HSV-2 seropositive persons reactivate HSV-2 in the genital region. Moreover, because of the extensive area enervated by the sacral nerve root ganglia, reactivation of HSV-2 is widespread over a large anatomic area.

A prospective study of 457 patients with documented first-episode genital herpes infection has shown that 90% of patients with genital HSV-2 developed recurrences in the first 12 months of infection.⁹³ The median recurrence rate was 0.33 recurrences/month. Most patients experienced multiple clinical reactivations. After primary HSV-2 infection, 38% of patients had at least 6 recurrences and 20% had more than 10 recurrences in the first year of infection. Men had slightly more frequent recurrences than women, median 5 per year compared with 4 recurrences per year (Fig. 24-11). Also, patients whose primary infection lasted more than 34 days had more frequent recurrences than those who healed faster, median 8 compared with 4.3 recurrences per year, respectively. This echoes the finding in the guinea pig model in which the number of ganglia which express the HSV latency transcripts correlates with subsequent recurrences.¹⁹² Patients

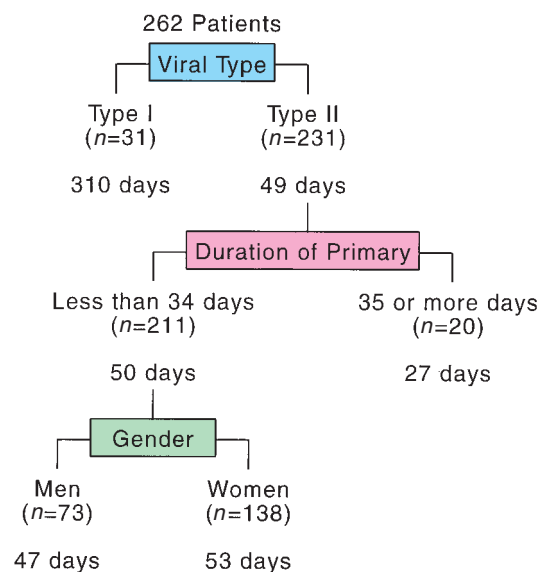


FIGURE 24-11. Determinants of median time to first recurrence after documented initial HSV infection.

with primary genital HSV-2 infection who have a more prolonged initial episode develop high titers of HSV-2 complement-independent neutralizing antibody in convalescent sera and are more likely to develop recurrences than those who do not develop anti-HSV neutralizing antibody.^{130,193} Development of high titers of complement-independent neutralizing antibody in convalescent-phase sera after primary infection may reflect a high degree of antigenic exposure and/or a large number of latently infected cells in sacral nerve root ganglia. In the mouse model of mucocutaneous HSV infection, high levels of neutralizing antibody in convalescent sera have been associated with increased numbers of latently infected ganglionic cells.¹⁹⁴

Recently, long-term cohort studies indicate that the frequency of symptomatic recurrences gradually decreases over time. In the initial years of infection, reported recurrence rate decreases by a median of 1 recurrence per year. As discussed below, almost all patients studied with recurrent symptomatic genital HSV also experience episodes of subclinical shedding. In general, these subclinical shedding episodes account for one-third to one-half of the total episodes of HSV reactivation as measured by viral isolation and for 50–75% of reactivations as measured by PCR.

Reactivation, both symptomatic and subclinical, is less frequent with genital HSV-1 versus genital HSV-2 infection. Overall, 57% of patients with genital HSV-1 will recur clinically in the first year of follow-up, and only 34% in the second year. In addition, the rate of recurrences is 1.3 recurrences per year in the first year and only <5% will have 4 or more recurrences.¹⁹⁵ In fact, frequent recurrences of genital herpes in persons with past genital HSV-1 suggest recent acquisition of genital HSV-2.¹⁹⁶

■ OTHER CLINICAL SYNDROMES ASSOCIATED WITH GENITAL HSV INFECTION

HSV cervicitis

HSV may involve the cervix alone, without involvement of the external genitalia. Cervical HSV infection may be asymptomatic or may present as a mucopurulent cervicitis (Fig. 24-7). In a recent survey of women attending an STD clinic, HSV was isolated from the cervix of 4% of randomly selected women attendees.⁶¹ Of these women with HSV cervicitis, half had concomitant first-episode genital lesions, 15% had evidence of recurrent genital lesions as well as HSV cervicitis infection, and 35% had only HSV cervicitis. Evidence of cervical lesions on routine speculum examination was present in 50% of these women, and an additional 15% of women had HSV lesions present on colposcopy. Overall, colposcopy detected 65% of women with HSV cervicitis. Papanicolaou smear revealed evidence of HSV cervicitis in 60% of women from whom HSV was isolated. Thus, even the most detailed clinical examination and cytologic testing will pick up only

65–70% of cervical HSV infection. Cervical HSV shedding is an occult site of reactivation of importance in transmission of HSV to infants and sexual partners.

Herpes simplex proctitis

HSV has been isolated from rectal mucosal and rectal biopsies in men and women with symptoms of rectal pain and discharge.^{157,197–200} In the early 1980s, among 100 consecutive homosexual men who presented to an STD clinic with symptoms of rectal discharge and pain, HSV was isolated from rectal swabs and/or biopsies in 23%.²⁰⁰ In men with nongonococcal proctitis, HSV was the most frequent pathogen isolated.

Unlike gonococcal proctitis, HSV proctitis is commonly associated with fever, systemic symptoms, severe rectal pain, discharge, tenesmus, and evidence of sacral autonomic nervous system dysfunction.^{157,163,197–199,201–204} Patients usually present with acute onset of rectal pain, discharge, tenesmus, constipation, and bloody and/or mucoid rectal discharge. Fever, malaise, and myalgia are common and urinary retention, dysesthesia of the perineal region, and impotence may be reported. External perianal lesions are seen in about one-half of the cases. Anoscopy and/or sigmoidoscopy generally reveal a diffuse, friable rectal mucosa, although occasionally discrete ulcerations of the rectal mucosa may be present (Figs. 24-12 and 24-13). In most cases, the pathology is limited to the lower 10 cm of the rectum. Rectal biopsies of involved mucosa generally reveal diffuse ulcerations and lymphocytic infiltration. If multiple histological sections are performed, intranuclear inclusions may be demonstrated in rectal biopsies in about 40% of cases.¹⁵⁷ Both HSV-1 and HSV-2 have been isolated from patients with HSV proctitis.^{157,199} Systemic ACV ameliorates the signs and symptoms of herpetic proctitis.²⁰⁴ Most episodes of HSV proctitis are associated with the initial acquisition of HSV-1 or HSV-2, as overt proctitis is



FIGURE 24-12. Primary anorectal–sigmoidoscopic view (early).

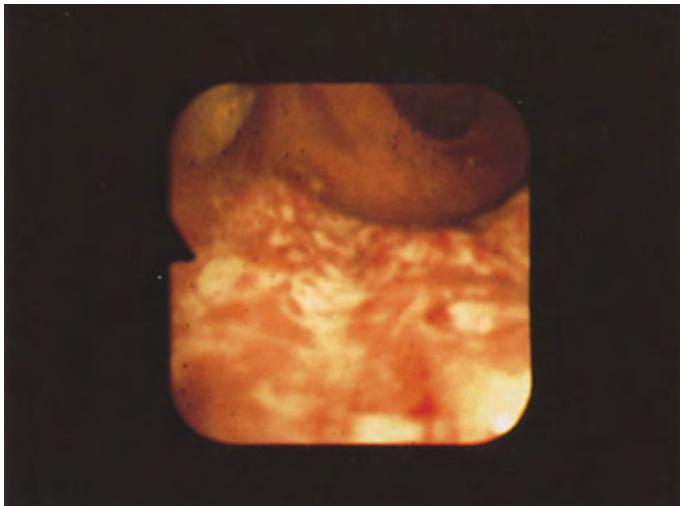


FIGURE 24-13. Primary anorectal–sigmoidoscopic view (late).

uncommon with HSV-1 or HSV-2 reactivations. Symptomatic anorectal HSV infection may also be seen in women with primary genital herpes.

HSV proctitis should be distinguished from subclinical reactivation of HSV in the perianal/perirectal region. Perianal reactivation of HSV as measured by the detection of HSV DNA in a perianal swab or by viral isolation is common in MSM as well as heterosexual men and women. Natural history studies suggest that perianal reactivation in men is especially common in MSM, reflecting perhaps the site of initial infection.²⁰⁵ This subclinical perianal shedding is likely due to reactivation in latent sacral ganglionic reservoirs and occurs without any recent or past anal intercourse.

Recurrent aseptic meningitis

Benign recurrent lymphocytic meningitis, or Mollaret's meningitis, is a syndrome characterized by recurrent episodes of aseptic meningitis lasting 3–7 days and resolving without neurologic sequelae.²⁰⁶ The CSF shows protein elevation and predominantly mononuclear pleocytosis. Recent studies have demonstrated HSV (usually HSV-2) DNA and the intrathecal persistence of HSV antibodies in the spinal fluid of patients with benign recurrent lymphocytic meningitis, indicating that HSV-2 is the etiologic agent for many, if not most, cases of this disease.^{207–210}

Recurrent episodes of aseptic meningitis following initial episodes of genital HSV-2 infection complicated by aseptic meningitis have been described.²¹¹ In one series of 27 patients with HSV-2 meningitis associated with first-episode genital HSV-2, recurrent meningitis was noted in 5 patients, headache in association with genital recurrences in 4, and possible recurrent meningitis in 7. Thus, 16 (27%) patients appeared to have recurrent HSV reactivation in the CNS. The advent of PCR assay and methods to detect HSV-specific intrathecal antibodies helped define the spectrum of HSV

infections in the CNS. In a series of 13 patients who met strict diagnostic criteria for benign recurrent lymphocytic meningitis, 11 had HSV DNA and HSV-specific antibodies recovered from the CSF and the remaining 2 patients had intrathecal HSV-2 antibodies.²⁰⁹ HSV-2 appears to be more frequently involved than HSV-1 and only a fraction of patients have a history of genital herpes.^{209,210,212} Anecdotal reports and the our experience support the use of antiviral therapy to shorten or prevent the episodes.²¹²

Subclinical Reactivation of HSV

Subclinical or asymptomatic viral shedding is an important aspect of the clinical and epidemiologic understanding of genital herpes, as most episodes of sexual and vertical transmission appear to occur during such shedding.^{88,213,214} HSV has been cultured from the lower genitourinary tract of women and men in the absence of genital ulcerations or other lesions. Transmission of genital herpes usually occurs by sexual contact with a person who is shedding HSV subclinically.^{94,214–216}

Longitudinal studies of persons with HSV-2 antibodies suggest that >90% of persons reactivate HSV intermittently in the genital tract.²¹⁷ The frequency of detection of reactivation varies with frequency of swabbing of the genital mucosa, the anatomic sites sampled, and the technique used to detect HSV. Women reactivate HSV in the cervicovaginal and vulvar as well as perianal area; men reactivate HSV on the penile skin and the perianal area.²¹⁸ The increasing recognition of perianal reactivation of HSV, which relates to the overlapping dermatomal innervation of this area with the vulvar area in women and the penile/scrotal area of men, has increased the rate of HSV detection on genital mucosa. Development of PCR assays for HSV DNA has markedly broadened our understanding of the pathogenesis of subclinical HSV-2 infection and many laboratories have developed very sensitive and specific PCR assays. The use of PCR assays to detect HSV on mucosal surfaces has increased the rate of HSV detection up to fourfold.²¹⁹ Subclinical episodes of HSV reactivation share several characteristics with clinical episodes: (1) 25% episodes last more than 1 day, (2) 17% of subclinical versus 22% of clinical episodes involve more than one anatomic site, (3) subclinical shedding is most likely to occur in temporal proximity to recurrences, and (4) women with frequent recurrences have frequent subclinical shedding.

Figure 24-14 depicts the pattern and frequency of subclinical shedding in a man and a woman with genital HSV-2 infection. As shown in the diagram, shedding occurs in “clusters” of time, and subclinical shedding often occurs prior to episodes of genital lesions or culture positivity. The frequency of subclinical HSV-2 shedding in both the oral and genital area is high, even in persons with no reported clinical lesions (Fig. 24-15). Quantitative HSV DNA PCR assays show that the number of viral copies in subclinical reactivation often is as high as that found during clinically recurrent HSV

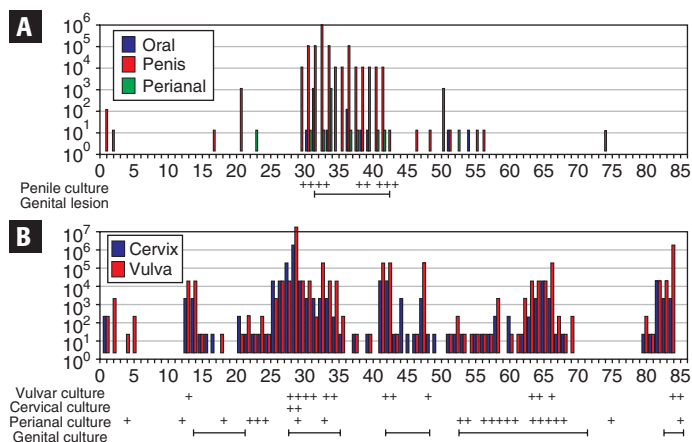


FIGURE 24-14. Clinical and virologic shedding pattern as detected by viral culture and HSV DNA polymerase chain reaction in, **A.**, a man and, **B.**, a woman. The man began obtaining daily viral cultures around day 30 after acquisition of genital HSV-2 infection. The woman was within 6 months of genital HSV-2 acquisition when she was enrolled into the study.

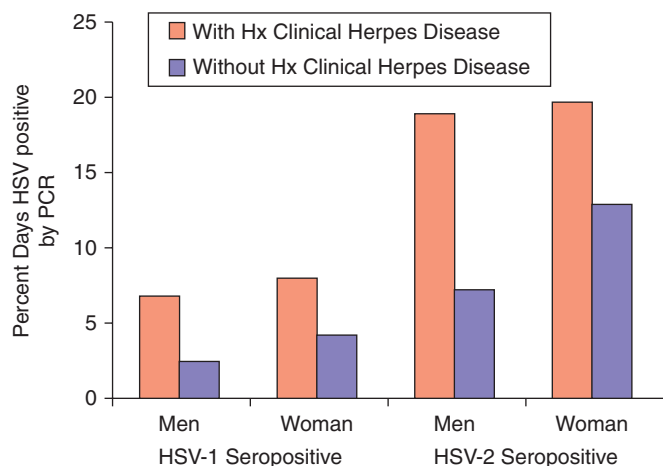


FIGURE 24-15. The frequency of subclinical shedding in both the oral and genital area; HSV-2 reactivation is frequent even in persons with no reported clinical lesions.

episodes. Thus, the risk of HSV transmission is likely similar regardless of the presence of lesions, supporting the epidemiologic observation that most HSV is acquired from asymptomatic partners. Of note, the amount of HSV required for sexual or perinatal HSV transmission is not known.

Subclinical HSV reactivation is highest in the first year after acquisition of infection. During this time period, HSV can be detected from genital sites by PCR on a mean of 25–30% of days (Fig. 24-16). This is about 1.5 times higher than patients sampled later in their disease course. While longitudinal studies of sampling by PCR are limited, it appears that rates of shedding are relatively stable within individuals over a 1- to 2-year period (Fig. 24-17). These estimates represent averages, as individual variability is great.

Among men, the most common site of shedding is penile skin, followed by the perianal area, although among MSM the opposite pattern is observed.²²⁰ Shedding can also occur from

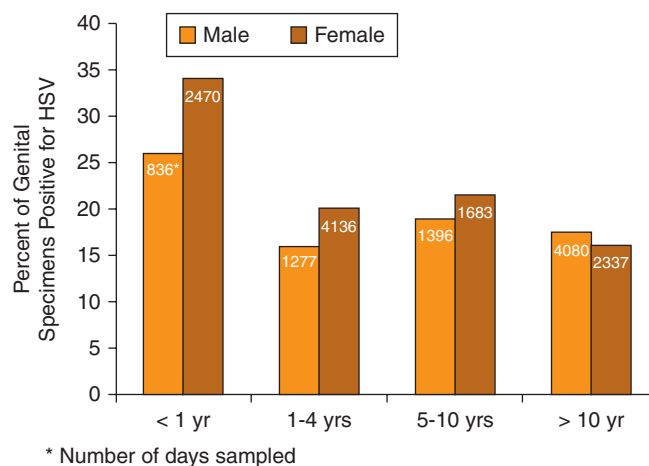


FIGURE 24-16. Frequency of HSV-2 reactivation by time since acquisition of HSV-2.

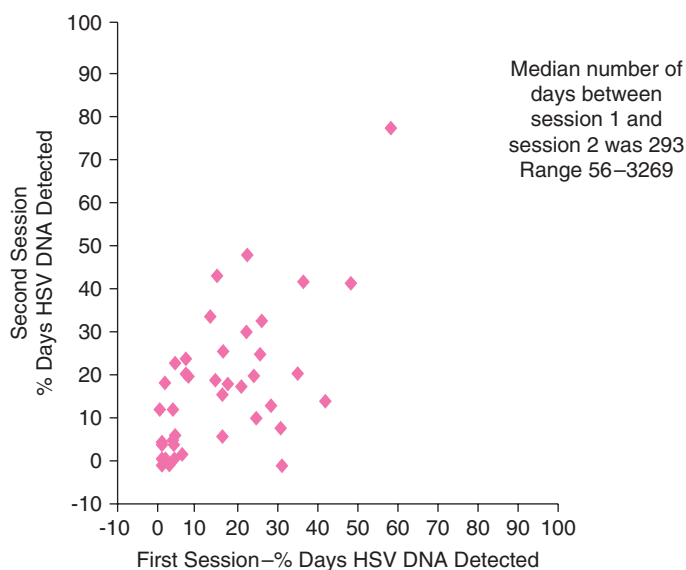


FIGURE 24-17. Percent days PCR positive during session: Comparison of shedding rates over time among 43 patients with HSV-2 infection.

the urethra and from the semen, especially close to the time of acquisition, and transmission of HSV via infected semen has been documented.²²¹ However, semen viral cultures or PCR assays rarely yield virus²²² despite an early report of high rate of HSV isolation from seminal secretions in men undergoing vasectomy.²²³ It is likely that penile skin shedding is the most important source of transmission from men to women, and perianal shedding is important in transmission of HSV among MSM.

The existence of frequent subclinical shedding implies that the control of genital herpes will not be achieved by the prevention of sexual encounters during recurrences of lesions, as transmission can occur at times when no lesions are noted. Counseling of patients with genital herpes needs to emphasize this potential for infectivity and provide appropriate strategies to decrease risk to patients' sexual partners.

■ THE PROBLEM OF UNRECOGNIZED RECURRENT GENITAL HERPES

Several recent studies have suggested that the vast majority of HSV-2 seropositive persons who deny having genital lesions are not truly asymptomatic, but have genital lesions that they do not recognize as herpetic. This observation has been demonstrated in several studies in different clinical settings. The initial study was conducted by Langenberg et al. in a gynecology clinic in a public hospital.²²⁴ In this study, HSV-2 seropositive women unaware of genital herpes were instructed on the clinical signs and symptoms of genital disease. Pictures of genital HSV lesions were shown to them and the nature of HSV transmission and reactivation explained. The women were then asked to attend the clinic for any subsequent genitourinary complaints. Of 62 such women, 48% presented with recognizable genital lesions of HSV. Symptomatic genital herpes was the most common genitourinary complaint in this group of women during follow-up. Similar findings were reported by Frenkel et al. in a group of pregnant women.²²⁵ Most recently, in a cohort recruited in a family practice clinic, we have followed 53 persons identified as HSV-2 seropositive without a history of genital herpes. During a median of 3-month follow-up, 62% of patients developed a typical recurrent HSV lesion, another 25% developed other localized genital complaints, and 83% had HSV detected in swabs of genital secretions. Only 1 person lacked either clinical and virologic evidence of genital herpes.²¹⁷ In comparison with a previously observed cohort of men and women with a clinical history of genital HSV-2 infection, the rate of subclinical viral shedding was similar (3.0 vs. 2.7) but the frequency of clinical recurrences and their duration was shorter in those who previously denied genital lesions. These findings help explain the unrecognized nature of lesions that tend to be mild and infrequent, and have shown that many people can be identified as having typical recurrences but they are not aware of having a lesion until they receive education about genital herpes (Table 24-3).

The studies showing the high rate of genital reactivation provide a framework for defining clinical and virologic manifestations of genital HSV infection. Rather than regarding HSV-2 as a predominantly silent infection with occasional clinical outbreaks with marked viral shedding, HSV is a dynamic infection, with very frequent reactivation, mostly subclinical, and active effort on the part of the immune system of the host is required to control mucosal viral replication. Thus, accurate serologic testing with an appropriate counseling session can effectively identify persons with unrecognized but virologically active genital HSV-2. As sexual contact with such persons is an important factor in HSV transmission, such an approach may be useful in containing the epidemic spread of this infection.

Table 24-3. Correlation Between the Recognition of Genital Herpes Lesions and Viral Shedding in 53 HSV-2 Seropositive Subjects with No Reported History of Genital Herpes

Variable	Herpes Simplex Virus Recovered ^a		Total Number of Subjects
	Yes	No	
Genital ulcers, blisters, or crusts	28 (85%)	5	33
Localized genital itching or soreness	10 (77%)	3	13
No clinical evidence of genital herpes	6 (86%)	1	7
Total	44 (83%)	9	53

^aHerpes simplex virus was isolated from culture or identified with use of a polymerase-chain-reaction assay for viral DNA. (With permission from Wald A, Zeh J, Selke S, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 2000; 342(12): 844–850.)

GENITAL HERPES VIRUS INFECTION IN THE IMMUNOCOMPROMISED PATIENT

Although initial literature on HSV infections in the immunosuppressed patient has concentrated on oral–labial disease, the increasing prevalence of genital herpes has resulted in an improved awareness of the consequences of genital herpes in this population. Immunocompromised patients have frequent and prolonged mucocutaneous HSV infections.^{226–228} Over 70% of renal and bone marrow transplant recipients who have serologic evidence of HSV infection reactivate HSV infection clinically within the first month after transplantation.^{229,230} Patients receiving chemotherapy often reactivate HSV at the time of neutropenia. While low neutrophil count by itself is unlikely to account for HSV reactivation, the epithelial destruction results in clinical and subclinical reactivation, further worsening the mucositis. In some trials, prophylactic-ACV-reduced bacteremia with oral pathogens in patients after chemotherapy.^{231,232} Mucocutaneous HSV infections in the immunocompromised host may be associated with systemic complaints, prolonged local symptoms, and durations of viral shedding for greater than 30 days.

Recurrent genital herpes in immunosuppressed patients often results in the development of large numbers of vesicles which coalesce into extensive deep, often necrotic, ulcerative lesions.²²⁸ Dissemination of virus may occur, although visceral involvement is relatively uncommon.²³³ The routine administration of prophylactic ACV prior to

bone marrow transplantation has decreased the reactivation of HSV.^{234,235} Several studies have demonstrated the benefit of ACV in shortening the clinical and virologic course of mucocutaneous HSV infection in the immunocompromised patients.²³⁶ Residual host immunity is important, as the severity of infection is greater and response to antivirals is less in HSV seropositive persons who received stem cell transplant from HSV seronegative donor. Clinically, the optimal approach to serologically identified HSV infection in the immunosuppressed patient is suppressive antiviral medication initiated at the time immunosuppressive agents are administered and continued for the duration of immunosuppression. While breakthrough infection with ACV-resistant HSV has been reported,²³⁷ our experience is that institution of acyclovir prophylaxis for the duration of immunosuppression in bone marrow transplant patients leads to lower incidence of ACV-resistant episodes.²³⁸ Recurrent episodes of mucocutaneous lesions should be treated, usually with oral or IV ACV until resolution, and suppressive therapy is advised until host immunity recovers.

■ HSV IN PATIENTS WITH HIV INFECTION

Chronic, persistent genital herpes was noted as a sentinel feature of acquired immunodeficiency syndrome in 1981. Since that time, our understanding of the interactions between HIV and HSV-2 has increased, and trials of potential interventions are in progress. The interactions between these two viruses are examples of “epidemiologic synergy”: both on a population level, and clinically, the two infections influence each other.²³⁹

■ IMPACT OF HSV-2 ON HIV INFECTION

HSV-2 is among the most common infection in HIV seropositive persons, as about 70% of HIV-infected persons in the developed world and 95% in the developing world have HSV-2 antibody. In the early 1980s, reports describing the increased risk of HIV infection, both prevalent and incident, among HSV-2 seropositive MSM were described.²⁴⁰ Several recent reviews and metaanalyses of these studies have documented that HSV-2 infection preceded HIV acquisition and also showed that HSV-2 increases the risk of HIV infection among women (threefold), men (twofold), and MSM (1.7-fold).²⁴¹ Another study of couples in Africa showed that HSV-2 infection in one or both partners was the strongest risk factor for HIV concordance.²⁴² In Rakai, HSV-2 antibody in susceptible partner in HIV-discordant couples was associated with a fourfold increased risk of HIV acquisition; the magnitude of the increased risk was comparable with the increased risk conferred by higher systemic HIV RNA in the source partner (Table 24-4).

The role of HSV-2 in HIV transmission has been more difficult to define for methodological reasons. However, a study of 121 HIV-discordant heterosexual couples found a fivefold

Table 24-4. Per-Contact Probability of HIV-1 Acquisition, Stratified by Plasma HIV-1 RNA in HIV-1 Seropositive Partner and HSV Serostatus in the Susceptible Partner^a

HIV-1 plasma RNA in source partner (copies/mL)	Per-Contact Probability in the HIV-1 Susceptible Partner	
	HSV-2	HSV-2
<1700	0.0001	0.00004
1700–12,499	0.0023	0.0005
12,500–38,499	0.0018	0.0002
≥38,500	0.0036	0.0007

^aNone of the source partners were treated with antiretroviral therapy.

elevated risk for HIV transmission in the presence of an ulcerative STD in the source partner and the presence of newly acquired GUD was associated with new HIV infection.^{243,244} This observation is biologically supported by potential of epithelial breaks to allow entry to HIV and the recruitment of CD4⁺ lymphocytes to HSV lesions that allow for HIV initial attachment. Trials to define the ability of antiviral therapy for HSV-2 to decrease the risk of HIV acquisition among HSV-2 seropositive persons are currently in progress. Unlike HSV-2, HSV-1 infection does not appear to increase the risk of HIV acquisition. However, most persons who acquire HIV have prior HSV-1 infection, making it difficult to observe HIV acquisition in HSV seronegative persons. As noted above, HSV-1 reactivation in the genital tract is infrequent, perhaps also accounting for its lack for association with HIV acquisition.

The epidemiologic interactions between HIV and HSV-2 have led to calculation of potential population-level impact of these intersecting epidemics. If the risk of HIV infection is doubled in HSV-2 seropositive people, 50% of HIV infections among these persons are attributable to HSV-2 infection. The population attributable risk will depend on the prevalence of HSV-2 in the population at risk; at 50% HSV-2 prevalence, common among MSM, or African Americans in the United States, or general population in sub-Saharan Africa, 35% of HIV infections will be attributable to HSV-2. More complex modeling demonstrates the potential for “telescoping” of HIV epidemics in the presence of HSV-2—a much more rapid spread of HIV in HSV-2 seropositive populations.²⁴⁵

Several studies have shown that HIV-infected persons are at increased risk for HSV-2 acquisition. Potential reasons include increased susceptibility to infection or increased risk of contact with partners who are shedding HSV-2 in the context of HIV infection.

The frequent genital HSV-2 reactivation in HIV seropositive persons results in chronic antigenic stimulation. Schacker et al. showed that HIV strains initially in herpes ulcers subsequently appear in plasma.²⁴⁶ A transient increase in plasma HIV RNA has been noted during recurrent genital herpes.²⁴⁷ This increase of $-\frac{1}{2}$ log in HIV RNA has been noted in acute, chronic, and advanced HIV disease.²⁴⁸ In studies among HIV-infected women, the risk of HIV detection in genital secretions is higher if HSV is also present.²⁴⁹

Antiviral therapy for HSV has been used as a probe to define the effect of HSV reactivation on systemic and mucosal HIV replication. In a study among HIV-infected women in Burkina-Faso, treatment with daily valacyclovir decreased plasma HIV $\frac{1}{2}$ log and genital secretions HIV $\frac{1}{4}$ log.²⁵⁰ Preliminary analysis of study among MSM in Peru showed a similar decrease in plasma HIV of about $\frac{1}{2}$ of a log with a stronger effect among men with higher CD4 count. Both studies were done among persons not treated with antiretroviral therapy. The reductions in HIV plasma RNA take 6–12 weeks to demonstrate and are not seen with episodic use of the anti-HSV antivirals. These findings suggest that more attention to the treatment of HSV-2 infection in the HIV-infected persons is needed. For patient management, suppressive antiviral therapy could reduce viral load and potentially delay the time to initiation of antiretrovirals, or delay the time to emergence of HIV resistance in patients who responded to antiretroviral medication. Whether the smaller reductions in mucosal HIV observed during ACV therapy decrease the risk of sexual and perhaps perinatal HIV transmission is unclear. Studies to define these potential benefits are needed.

Laboratory studies have provided supportive evidence that HSV may be an important cofactor for HIV expression. The HSV regulatory proteins ICPO and ICP4 can upregulate the rate of HIV replication in vitro.²⁵¹ Both replicating and heat-inactivated HSV induces TNF- α activity and HIV expression in macrophages.^{252,253} Herpetic lesions are associated with an influx of activated CD4-bearing lymphocytes,²⁵⁴ which may result in increased expression of HIV on mucosal surfaces. In vivo, HSV-1 and HIV coinfection of epithelial cells results in higher copy number of HSV virions.²⁵⁵

■ HSV-1 AND HSV-2 IN HIV-INFECTED PERSONS

HSV infections are one of the most common clinical presentations and manifestations of HIV infection. However, the most significant impact of HIV on HSV disease is in the marked increase in the rate of viral reactivation, most of which is subclinical. Recent studies demonstrate that this subclinical reactivation persists even with effective HAART therapy.²⁵⁶

Chronic persistent genital ulcers caused by HSV were among opportunistic infections included in the definition of AIDS, and a small fraction of HIV- and HSV-infected patients present with persistent chronic mucocutaneous

ulcerations often involving large areas of perianal, vulvar, or penile areas.²⁵⁷ While most HIV-infected MSM have HSV-1 and 70% have HSV-2 infection, usually reactivation of HSV-2 causes severe clinical disease. Pain and lesions may present for months and can be disabling. Systematic evaluation of clinical genital herpes among HIV-positive MSM showed that rate of recurrences is increased and the episode is prolonged compared with HIV-negative MSM.²⁵⁸ Interestingly, HSV-2 does not appear to disseminate even in persons with advanced HIV disease, and visceral disease is rare. HSV-2 meningoencephalitis has been reported occasionally in HIV-infected persons.

Recent studies of genital HSV-2 reactivation have shown that the risk of viral shedding is increased among HIV-infected persons, especially the risk of subclinical shedding. Table 24-5 compares HSV reactivation rates among a cohort of HIV-positive persons versus HIV-negative MSM and within HIV-positive and HIV-negative women. An inverse correlation between CD4⁺ count and rate of genital HSV-2 shedding and a direct correlation between plasma HIV RNA and HSV-2 shedding exist. However, as with the HIV-negative persons, great individual variability in HSV-2 reactivation rates is observed, and even those with high CD4 count may shed HSV-2 frequently in the genital tract. Effective antiretroviral therapy (HAART) has led to an improvement in the clinical manifestations of HSV-2 infection; however, the impact on HSV genital shedding has been minimal. Thus, HSV-2 seropositive persons on HAART with low plasma RNA continue to shed HSV in the genital area frequently, and often at high copy number.

Most HSV infections in persons with HIV infection will respond to antiviral therapy, and ACV, valacyclovir, and famciclovir have all been shown to be useful in reducing clinical and subclinical reactivation of HSV in HIV-positive persons.^{259–261} Suppressive therapy with ACV increases the daily pill burden, but prevents most clinical episodes, reduces the

Table 24-5. Frequency of HSV-2 Reactivation by HIV Status and Gender

	HIV Negative	HIV Positive
<i>Women</i>	<i>N</i> = 329	<i>N</i> = 83
No. days sampled	<i>N</i> = 14,328	<i>N</i> = 1,218
No. women	253	21
% days positive for HSV	20.0	25.8
<i>Men</i>		
No days sampled	<i>N</i> = 12,549	<i>N</i> = 9,527
No. men sampled	216	162
% days positive for HSV	14.1	23.4

risk of HSV-2 shedding, and may have indirect effects on HIV, as noted above. Some patients who initially respond to ACV may develop thymidine kinase deficient mutants for which standard antiviral therapy is ineffective (see below).

An additional complication of HSV in HIV seropositive pregnant women is the potential impact of HSV-2 on the risk of maternal–fetal HIV transmission, as studies have observed an increased risk of HIV transmission to infants among women who are HSV-2 seropositive compared with HSV-2 negative or those who have genital ulcers in late pregnancy.^{262,263} Whether the mechanism is mediated by a breach in epithelial barrier or higher systemic or local HIV RNA is unknown. Further studies are warranted to delineate the potential of HSV-2 to directly, or indirectly (though increase in HIV in the genital tract), affect vertical HIV transmission, both among women treated with potent complex antiretroviral regimens as well as those receiving single-dose nevirapine to reduce maternal to child HIV transmission.

GENITAL HSV INFECTIONS IN PREGNANCY

One of the major concerns to patients with genital herpes is the effect of disease on pregnancy and the neonate. Both congenital and intrapartum transmission of HSV infection have been described.^{264,265} Neonatal herpes is a disease of high mortality and morbidity.^{266–268} Transmitting this STD to a newborn also has devastating effects on the parents.

■ EPIDEMIOLOGY OF HERPES IN PREGNANCY

The prevalence of genital HSV infection during pregnancy as well as the relative incidence of neonatal HSV infection is influenced by the socioeconomic status, age, and past sexual activity of the patient population studied. In the United States, serologic evidence of HSV-2 infection is present in about 30% of middle class women attending prenatal clinics; the percentage is 50–70% in nonwhite lower socioeconomic obstetrical populations. Despite this high serologic prevalence, clinical evidence of HSV is much less. In Seattle, where an obstetric population has a 30% prevalence of HSV-2, a past or current history of genital HSV is present in 8% of women.

Neonatal HSV infection is a reportable disease in only few states in the United States. Estimates of the incidence of neonatal herpes have varied from 1 in 3000 to 1 in 20,000 live births.²⁶⁷ The overall estimated frequency of neonatal HSV infection in the United States has been estimated to be approximately 1 in 7500 live births or about 400–1200 cases yearly nationally.²⁶⁹ A recent survey in Canada reported an incidence of 5.9 per 100,000 live births.⁸⁷

The highest risk for transmitting HSV in the perinatal period occurs during the acquisition of HSV in the woman at or near the time of labor.²⁷⁰ This helps explain the wide

variability in frequency of neonatal herpes worldwide. Obstetrical populations with high HSV-2 prevalence have low incidence of neonatal HSV infection. Populations with high risk of acquiring HSV in pregnancy have the highest neonatal HSV infection rates. Thus, contraceptive and behavioral practices markedly influence the epidemiology of neonatal HSV infection. Scandinavia and the west coast of the United States appear to have the highest neonatal HSV rates (about 1 in 3000 live births). As with genital HSV infections, recent data have shown a shift toward neonatal HSV-1 infection.

Among 7046 women followed with serologic evaluation during pregnancy, 94 seroconverted to HSV (64 to HSV-2 and 30 to HSV-1) during pregnancy, for an overall rate of 2.1%.²⁷¹ Of those with known time of seroconversion, 30% seroconverted in the first trimester, 35% in the second, and 40% during the third trimester. Overall, only 34 (36%) women presented with clinical signs of infection. None of the women who acquired antibody to HSV during pregnancy transmitted HSV to the neonate. However, 9 women in the cohort were found to acquire HSV in late third trimester and 4 of these 9 women transmitted HSV to the neonate. In this cohort, the risk of neonatal transmission was confined to the women who acquired HSV close to the time of labor. A subset of women were evaluated together with their sexual partners.²⁷² Among women who were seronegative for HSV-1 whose partners had HSV-1 antibody, the rate of HSV-1 acquisition during pregnancy was 3.5% (adjusted for the length of gestation). The rate of HSV-2 acquisition among susceptible women who had HSV-2 infected partners was 20%. Thus, the rate of HSV-2 acquisition among pregnant women appears very high, perhaps modified by high progesterone milieu that has been shown to shift susceptibility to HSV by 100-fold in a mouse model.²⁷³ Despite the studies showing that the risk of HSV is highest among women who acquire HSV in late pregnancy, 30–50% of infants with neonatal HSV are born to women who have established, although often unrecognized, genital herpes.

■ CLINICAL COURSE OF GENITAL HERPES IN PREGNANCY

Most of the clinical manifestations of recurrent genital herpes, including the frequency of subclinical versus clinical infection and the duration of lesions, pain and constitutional symptoms are similar in pregnant and nonpregnant women.^{274,275} The frequency and severity of recurrences appears to increase over the course of pregnancy.²⁷⁵ Visceral dissemination of HSV in pregnant women acquiring primary genital disease has been described, especially if infection is acquired in the third trimester.^{177–179} Routine antiviral therapy for first-episode HSV is not required in pregnancy but may be given for severe disease. IV ACV should be initiated in pregnant women who have evidence of disseminated infection, especially hepatitis, pneumonitis, or coagulopathy.

■ EFFECTS OF HSV ON PREGNANCY OUTCOME

Studies in the 1960s suggested that genital HSV infection was associated with an increased frequency of spontaneous abortion and premature delivery.^{276,277} These studies also suggested that primary HSV cervicitis had a higher risk of complications than other aspects of disease. Brown et al. accumulated 28 cases of women who acquired first-episode genital HSV in pregnancy.²⁷⁸ Pregnancy morbidity was only seen in the 15 women with clinical primary infection; that is, those with fever, constitutional symptoms, and severe lesions. Serologic and clinical evidence of nonprimary infection was not associated with pregnancy morbidity. Neonatal HSV and prematurity was most frequently seen in women who acquired primary genital infection during the third trimester.²⁷⁸

Several potential explanations may account for these differences in neonatal morbidity among women with primary versus recurrent genital HSV infection. With primary disease, both hematogenous spread of HSV as well as ascending chorioamnionitis may result in neonatal infection and disease.²⁷⁹ Recurrent vulvar genital herpes is usually not associated with cervicitis or viremia. Several clinical series and a recent population-based study of women with recurrent genital HSV in pregnancy suggested no effect of clinical recurrent infection on neonatal outcome, including birth weight and gestational age.^{274,275,280}

■ TRANSMISSION OF HSV TO THE NEONATE

Almost all cases of neonatal herpes are perinatally acquired: The infant acquires infection at the time of delivery through contact with HSV-infected genital secretions.^{266,267,270,280–284} Over 70% of infants with neonatal HSV infection are born to mothers who lack symptoms or signs of HSV lesions at delivery. [Table 24-6](#)

describes the frequency of viral shedding and serologic status at the time of labor and its relationship to neonatal HSV from studies conducted at the University of Washington. As shown in [Table 24-6](#), neonatal HSV can occur in women regardless of serologic status. However, the risk varies according to the serostatus: 1/1900 in HSV seronegative, 1/3900 in HSV-1 seropositive, and 1/4600 in HSV-2 seropositive women. An alternative calculation that may provide more relevant clinical risk is that the risk of transmitting HSV to the neonate is 30–50% in women with newly acquired HSV versus <1% in women with established infection. The low risk among HSV-2 seropositive women reflects low efficiency of transmission from women with reactivation HSV-2. This low risk may be mediated by the passage of maternal antibodies, or by limited viral replication in the genital tract during shedding in established disease, or both. HSV isolation is the strongest risk factor for intrapartum HSV transmission to the neonate with a relative risk of 346 compared with women in whom virus was not isolated.²⁷⁰ However, HSV transmission from women who are culture negative can also occur; we have detected HSV DNA in swabs of 2 women who transmitted the infection to their neonates, indicating limited sensitivity of viral culture. Among women who have HSV isolated in the genital tract, new acquisition of HSV versus reactivation (OR = 49), isolation of HSV-1 versus HSV-2 (OR = 35), isolation of cervical versus vulvar HSV (OR = 15), and young maternal age are risk factors for neonatal herpes. In addition, cesarean delivery was protective against HSV transmission (OR = 0.14) and obstetrical manipulations such as scalp electrodes were associated with increased risk of HSV (OR = 3.5). This was the first study to demonstrate a protective effect of abdominal deliveries, although the practice has been endorsed for many decades, based on the goal of

Table 24-6. Frequency of HSV Isolation from Cervix and Vulva of Women in Labor in Relation to the Type of HSV Infection and to Transmission of Infection to the Neonate

	Culture (+)	Culture (–)	Note Done	Total Delivered
<i>Mothers & cultures</i>	202	39,821	18,339	58,362
<i>Mothers with serology</i>	177	22,630	11,928	34,735
<i>Maternal disease</i>	<i>Cases of neonatal herpes</i>			
Primary HSV-1	3	0	1	4
Primary HSV-2	1	1	0	2
Non-Primary FE	4	1	0	5
Recurrent HSV-1	2	1	1	4
Recurrent HSV-2	0	3	0	3
Total neonatal HSV	10	6 ^a	1	18 cases

^aHSV DNA by PCR positive in 2 of 5 specimens recovered. (With permission from Brown ZA, Wald A, Morrow RA, Selke S, Zeh J, Corey L. Effect of serologic status and cesarean delivery on transmission rates of herpes simplex virus from mother to infant. *JAMA* 2003; 289(2): 203–209.)

avoiding contact of the neonate with infected genital secretions. The benefits of C-section after rupture of membranes are uncertain.

These studies have also illustrated that the risk of viral shedding is assessed inaccurately by clinical examination that uses the presence of genital lesions as a proxy for viral reactivation. Among women who received abdominal deliveries for genital herpes, HSV DNA was detected from genital secretions among 46% of women.²⁸⁵ Thus, the use of virologic rather than clinical approach to assess the presence of the virus at the time of delivery may potentially target surgical intervention at women who are at greatest risk for HSV transmission to the neonate.

■ MANAGEMENT OF PREGNANT WOMEN WITH GENITAL HERPES

The management of the pregnant women with genital HSV must be individualized and based on the clinical course of disease in the mother as well as the availability of virological and serologic methods of diagnosis. The acquisition of primary disease in pregnancy carries the risk of potential transplacental transmission of virus to the neonate. In some women, primary infection will result in spontaneous abortion; albeit this appears to be relatively uncommon. One common question raised by patients with first episodes of genital herpes during pregnancy who do not abort is the use of amniocentesis to determine if intrauterine infection, and hence a congenitally infected child, is present. The vast majority of pregnant women with recurrent genital herpes deliver normal infants, and routine amniocentesis is not recommended in these women.

Criteria for laboratory testing and surveillance, as well as delivery procedures for women with recurrent genital HSV infection, are the most frequently encountered questions of obstetricians handling pregnant women with HSV-2. The high prevalence rate of HSV-2 infection in pregnancy (antibody prevalence 30–60% depending on the population studied) and the low incidence of neonatal disease (1:6000 to 1:20,000 live births) indicates that only a few infants are at risk of acquiring disease. Cesarean section is therefore not routinely warranted for all women with recurrent genital disease. As intrapartum transmission of infection accounts for the vast majority of cases, only those women who shed HSV at the time of delivery need be considered for abdominal delivery. The presence of viral shedding at term is not predicted by shedding in weeks prior, and as such, weekly cytologic and virologic monitoring is not advocated.^{274,275,280} Unfortunately, a rapid, reliable diagnostic method to detect asymptomatic cervical viral shedding of HSV is not currently available. This diagnostic gap is likely to be filled by a sensitive, rapid PCR that can be done at the time of labor to guide the delivery approach. Such an assay may be most useful in identifying women who acquired HSV

in late pregnancy and are still seronegative but are shedding large amounts of HSV in the genital tract and are at high risk for HSV transmission to the neonate. In such women, the ~30–50% risk of HSV transmission justifies an operative delivery.

The risk of transmitting neonatal HSV among women who are HSV-2 seropositive is low, <1%. Patients with recurrent genital herpes should be encouraged to come to the delivery room early at the time of delivery. At this time, careful examination of the external genitalia and the cervix should be performed. Women who have no clinical evidence of lesions should be delivered vaginally; a swab for detection of HSV by viral isolation or HSV DNA PCR helps with subsequent infant management. The presence of active lesions of the cervix or external genitalia, or prodrome, i.e., clinical evidence of herpes virus infection of the lower genital tract, are indications for abdominal delivery.²⁸⁶ This policy will result in the exposure of some infants to episodes of cervical and/or vulvar shedding. Only a few infants exposed to maternal excretions containing HSV-2 develop neonatal herpes.²⁸⁴ Identification of such infants to communicate the HSV exposure to the attending pediatrician is necessary.^{287,288} Currently, experts advise obtaining samples for HSV detection from the throat, nasopharynx, eyes, and rectum of these infants immediately and then at 5–10 day intervals. Any clinical evidence of lethargy, skin lesions, or other symptoms of neonatal HSV should be evaluated promptly. All infants from whom HSV is isolated after 24 hours of delivery should be treated with systemic antiviral chemotherapy.

Definitive studies on the relationship between the duration of ruptured membranes in the women with clinically apparent lesions and transmission of HSV to the infant are lacking but prolonged contact with infected secretions may increase the risk of acquisition. Delivery of infants by cesarean section, even from women with intact membranes, will occasionally result in neonatal herpes.²⁸⁷ Many authorities recommend that if membranes have been ruptured for over 4–6 hours, cesarean section should no longer be considered for protection against HSV transmission. However, studies of neonatal HSV infection in Seattle have shown that transmission can occur from exposure to only external genital lesions, i.e., from women who are culture positive only on vulvar and not cervicovaginal swabs.

Infants born by cesarean section to women prior to the rupture of membranes or by vaginal delivery to women with no evidence of recent HSV infection are at minimal risk of developing HSV infection. Infants born of women at risk of transmitting disease to the neonate (i.e., women with active lesions)²⁸⁹ should be observed closely for the first month of life and some experts recommend virologic evaluation throughout that time (see above). Any symptoms of neonatal disease (e.g., poor feeding, fever, hypothermia, skin lesions, or central nervous system signs such as seizures) should be

investigated expeditiously for evidence of neonatal HSV infection.^{288,290} Management of contact between infant and mother should also be handled on an individual basis. In women who acquire primary genital herpes late in pregnancy, the high incidence of developing extragenital lesions and the potential of viremia suggest that a brief separation between mother and infant is warranted until therapy has produced a clinical and virological response. As recurrent genital herpes is rarely associated with disseminated disease or the development of extragenital lesions in exposed extremities, protection of the infant from exposure to infected genital secretion is adequate. When handling the infant in the hospital, education of the mother about handwashing techniques is appropriate, but rooming in should be allowed. Oral–labial herpes is a greater risk of postnatal acquisition of HSV infections to the newborn than genital herpes.²⁹¹ Thus, nursery personnel and other adults with external labial lesions caused by HSV should also be excluded for intimate contact with the newborn infant.²⁹²

Recent increase in genital HSV-1 has resulted in increase in neonatal HSV-1 infection. While HSV-1 reactivates in the genital tract less frequently than genital HSV-2, the risk of transmission to the neonate is much higher when HSV-1 rather than HSV-2 is isolated from genital secretions. This poses a question about management of women with HSV-1 during pregnancy. Women with known genital HSV-1 can be managed in the same way as women with genital HSV-2. All HSV-1 infected women should be carefully examined to rule out genital lesion at the time of labor. If such women are known to be shedding HSV-1 at the time of delivery, cesarean section prior to rupture of membranes should be considered.

Antivirals in pregnancy

Controversy exists regarding the use of antiviral therapy during pregnancy. The incidence of neonatal HSV-2 is low among women with recurrent genital herpes so that the efficacy of this approach for prevention of neonatal disease is very difficult. However, the incidence of cesarean delivery among women with genital HSV-2 is much higher and several studies have evaluated routine antiviral suppression in reducing HSV shedding at delivery and the frequency of abdominal delivery. In general, the studies have used daily therapy with ACV 400 mg tid or valacyclovir 500 mg bid starting at 36-week gestation for women with recurrent genital herpes. A systematic review of five of these studies has shown that this approach reduces the risk of recurrences, the risk of viral shedding, and the risk of abdominal delivery.²⁹³ As such, this approach is listed as a management option in both the ACOG and the CDC guidelines and is widely used in the community. While this approach may decrease the risk of HSV-related cesarean sections, it is unlikely to have an impact on neonatal HSV, as most women who transmit HSV to their neonate have subclinical (new or recurrent)

disease. The safety of ACV in late pregnancy has not undergone an extensive evaluation and concerns about the potential for neutropenia or renal impairment in the newborn remain. These potential issues are greater with the use of prodrugs (valacyclovir) as they achieve higher drug levels in the neonate. Thus, while a useful patient management approach, widespread use of antivirals to prevent neonatal HSV among women who are HSV-2 seropositive is of unproven benefit.

Prevention of HSV acquisition in pregnancy

The key to prevention of neonatal HSV is the prevention of acquisition of genital HSV-1 or HSV-2 infection late in pregnancy. As 30% of pregnant women are HSV-2 seropositive, identification of women at risk requires the use of type-specific serologic assays and testing for antibody during pregnancy. Women who are HSV-2 seronegative should be counseled about abstinence or at least avoiding unprotected coital activity in the last trimester. Some have advocated testing of the sexual partner to identify “discordant couples.” Testing of the partner may present logistic difficulties, but allows for more precise definition of the risk of HSV acquisition in the pregnant women, as only about 20% of women have discordant strategies, with women being at risk for HSV acquisition.^{272,294}

DIAGNOSIS OF GENITAL HERPES

CLINICAL DIFAGNOSIS

The differentiation between genital HSV infection and other infectious or noninfectious etiologies of genital ulceration is difficult and laboratory confirmation of the infection should always be sought. Epidemiologically, HSV is the most common cause of genital ulcerations both in the developed and in the developing world, especially with the decline of *T. pallidum* and *H. ducreyi* infections. While the characteristics described below can lead the clinician on a diagnostic pathway, the overlap in the clinical presentation is substantial, and the etiologic diagnosis based on clinical appearance is often inaccurate. This is especially true in HIV-infected persons, who may be at increased risk for several different STDs. In a prospective study where persons at risk for HSV-2 infection returned to clinic for evaluation of genitourinary symptoms, only 39% of those with newly acquired HSV-2 were diagnosed on clinical grounds.²⁹⁵ Thus, the sensitivity for diagnosis of HSV-2 is low, even in a carefully monitored population. In addition, 20% of those who were given a clinical diagnosis of genital herpes were not infected, suggesting that false positive diagnosis of clinical grounds occur frequently. Given the gravity of diagnosing a lifelong viral STI, we feel that appropriate management of the patient should include laboratory confirmation.

In a patient with multiple grouped vesicles or a history of lesions of similar size, duration, and character, HSV infection is the most likely etiology of the ulceration. Lesions of genital herpes are often painful when touched and this clinical sign may be useful in differentiating coalesced genital herpetic ulcers from other etiologies such as *T. pallidum*. It should, however, be remembered that occasionally both organisms may coexist in the same lesion.²⁹⁶ A persistent, tender, large ulcerative lesion in a patient at risk of *T. pallidum* infection, especially one in whom nontender, rubbery bilateral inguinal adenopathy is present, should raise the suspicion that both pathogens may be present.

Both primary and recurrent HSV infection can be accompanied by tender lymphadenopathy. The inguinal nodes upon palpation are usually nonfixed, and only slightly firm. Suppuration, commonly seen with *H. ducreyi* and/or lymphogranuloma venereum, is only rarely seen in genital HSV infection. Nontender, rubbery, firm lymph nodes are more commonly seen with *T. pallidum* infection. Because of the diversity of the signs and symptoms of HSV infections, laboratory confirmation of the etiology of genital ulcers should be sought in nearly all cases.¹⁵⁶

Noninfectious causes of genital ulcerations, such as inflammatory bowel disease (Crohn's disease), mucosal ulcerations associated with Behcet's syndrome, or fixed drug eruption, may also be confused with genital herpes. These noninfectious causes are usually associated with ulcers that persist for much longer periods of time than those associated with recurrent genital herpes. In addition, the lesions themselves appear larger and deeper than those typically seen in genital HSV infection. The history of persistent lesions waxing and waning with the symptoms of bowel disease is usually elicited in those who have genital ulcerations as mucocutaneous manifestation of Crohn's disease. Persistent oral lesions, conjunctivitis, and/or central nervous system disease may help differentiate Behcet's syndrome from recurrent genital herpes. The overlap between primary genital HSV infection with conjunctivitis and aseptic meningitis and Behcet's syndrome may, however, cause diagnostic confusion (Fig. 24-8). In patients with a fixed drug eruption, a history of recent medication (e.g., trimethoprim-sulfamethoxazole) can be elicited. Excoriations resulting from scratching due to scabies infestation of the penile shaft can also mimic genital herpes, although these lesions lack the evolution seen in HSV. Persistent lack of laboratory evidence of HSV infection is often useful in establishing the clinical diagnosis of these noninfectious entities.

■ LABORATORY DIAGNOSIS

Laboratory confirmation of genital herpes should be performed on all persons. Knowledge of the diagnosis is useful in (1) explaining the potential infectivity during episodes of lesions, (2) identifying persons at risk for transmitting infection

subclinically, (3) selecting women at future risk for transmitting the infection to the neonate, and (4) confirming the diagnosis in those in whom antiviral therapy is prescribed. Viral isolation, HSV DNA detection by PCR, HSV antigen detection by EIA or FA are all useful assays. In the last 5 years, HSV DNA PCR has emerged as the best test to be utilized on patients who present with genital herpes ulcers. The PCR assay is up to 4 times more sensitive than viral culture, can be done in high throughput system, within a short timeframe and with type-specific primers. HSV DNA is stable and thus the yield is not sensitive to transport time or condition. Historically, viral isolation has been considered a gold standard, followed by subtyping of the isolate.

Serodiagnosis is useful for documenting newly acquired infections and for diagnosis in persons who present without lesions or with atypical lesions. The commercial development of type-specific serologic methods provides the opportunity to identify person with undiagnosed HSV-2 infection. As most HSV appears to be transmitted from persons who have undiagnosed disease or asymptomatic infection, more active serologic testing for HSV-2 infection should be initiated in high-prevalence populations. The presence of HSV-2 antibodies in serum identifies HSV-2 infection that is nearly always genital, and is likely to reactivate intermittently, potentially resulting in transmission. Thus, the counseling provided for persons who are HSV-2 seropositive should parallel that of persons with clinical diagnosis of genital herpes.

COUNSELING/PREVENTION

Because of its chronicity, for many persons the diagnosis of genital herpes brings with it significant long-term complications. Many patients diagnosed with genital herpes report feelings of depression and isolation and fear of rejection and discovery.^{297,298} These feelings tend to subside, although not completely, with time. A survey of members of the American Social Health Association support groups showed that 50% of respondents experienced depression and feelings of rejection,²⁹⁸ even after many years of living with the disease. The distress associated with the diagnosis of HSV is exacerbated by the frequent difficulties in obtaining an accurate diagnosis and the difficulties of health-care providers in dealing with the emotional and sexual issues that surround the diagnosis. During the acute illness, the patient is often too concerned with the physical illness and with having the diagnosis of an STD to comprehend the chronic nature of the infection. Thus, the best strategy for counseling is to ask the patients to return after the primary illness resolves to deal with the long-term issues posed by having an incurable STD. At the first visit, palliation of symptoms is the most important

objective. In addition to antiviral therapy, local measures such as sitz baths or drying the genital area with a hair dryer can decrease the discomfort of lesions.

Clinicians should emphasize the recurrent and highly variable natural history of herpes infection and explain the potential for transmission during subclinical shedding. However, it is also important to reassure the patients that they will be able to continue to have intimate relationships, despite the infection. Women are often concerned regarding the potential for having healthy children and need reassurance that the risk of transmission during delivery is minimal for women with recurrent genital herpes. Patients need to be encouraged to tell the potential sexual partners of their infection, to abstain during recurrences, and to use condoms consistently at other times. It is useful to reinforce these issues over several visits and to see patients at their first recurrence to confirm their ability to recognize recurrences. Many patients are dismayed at their first recurrence because they realize that this infection will recur, while others are relieved that the symptoms are much milder than those during the primary episode. Most patients resent the lack of predictability of the disease as much as the discomfort. Attempts at controlling the recurrences include avoidance of certain foods, vitamin supplements, and stress reduction. Scientific evaluation of the benefit of these methods is lacking and fraught with difficulties. Despite the common perception that stress causes recurrences, a prospective study suggested that stress follows recurrences.²⁹⁹

In many settings, including pregnant women, STD clinic attendees, and persons seen in primary care, the interest in HSV-2 serologic testing among patients is high and both acceptability and acceptance exceed 50%.^{300–303} Since most persons with HSV-2 infection do not have a history of genital herpes, serologic testing to identify those who are infected is also an important part of control of genital herpes. The settings in which serologic screening is useful for patient management are prenatal clinics, STD clinics, and settings that care for HIV-infected patients. Type-specific serologic tests should be available as part of general evaluation for STDs.

The frequent psychosocial distress that accompanies the diagnosis of symptomatic first-episode genital herpes has been used to obstruct wider use of serologic tests to identify persons with undiagnosed HSV-2.³⁰⁴ However, several studies have shown that the distress that accompanies a serologic diagnosis of genital herpes is mild and transient.^{305–307} In addition, such diagnosis often provides an explanation for previously undiagnosed genital symptoms. Knowledge of HSV-2 status and disclosure to partners is associated with lower risk of HSV-2 transmission. Thus, the potential individual and the public health benefit of serologic testing likely outweigh the understandable upset that follows being told of an HSV-2 infection.

Strategies for the control of genital herpes have not been well defined, although the tools to test such strategies are now

available. A combination of methods is likely to be needed to contain the current epidemic of genital herpes. For persons with diagnosed HSV infection, disclosure of infection to partners results in ~50% decrease in the risk of HSV-2 transmission.⁹¹ Avoiding sex during a recurrence or prodrome is also important, as viral shedding is most likely to occur at those times. Condoms decrease the risk of HSV-2 transmission from men to women and from women to men.^{49,50} The protection offered by a condom is incomplete (~50%), given the wide distribution of HSV reactivation. Antiviral therapy has been shown to effectively suppress subclinical shedding.³⁰⁸ An international, randomized, clinical trial demonstrated that daily valacyclovir given to source partners in HSV-2 discordant partnerships results in a 50% decrease in HSV-2 transmission to susceptible sexual partners.³⁰⁹ Thus, chronic suppression of viral reactivation may become one of the strategies for HSV control in selected settings. Given that most people with HSV-2 infection have mild symptoms and unrecognized disease, the public health impact of suppressive therapy in discordant couples is likely to be limited. The interaction of the three control modalities—disclosure to partners, condom use, and suppressive therapy—has not been studied. Behavioral disinhibition may potentially offset the benefit of suppressive therapy if it leads to lower condom use, as has been observed in some patients with HIV receiving antiretroviral therapy. While nonoxynol-9 and other microbicides have been shown protective in animal models of HSV infection, human data are lacking,³¹⁰ and at this time microbicides are not recommended. Other microbicides with antiviral activity are understudy.

THErapy OF GENITAL HERPES

The therapy of genital herpes includes the following goals: (1) preventing infection; (2) shortening the clinical course of disease, including the frequency of complications of primary infection such as aseptic meningitis and urinary retention; (3) preventing the development of latency and subsequent clinical recurrences after initial genital infection; (4) preventing subsequent recurrences of disease in those with established latency; (5) decreasing the transmission of disease; and (6) eradicating established latent infection. Despite major inroads in the therapy of genital herpes in the last 25 years, only some of the goals described above have been achieved by the available therapeutic interventions.

■ NUCLEOSIDE ANALOGS

Acyclovir

The mainstay of the therapy of genital HSV infection are formulations of nucleoside analogs, most often used in an oral form. ACV is the first antiviral developed and used for the

therapy of genital herpes. ACV is an acyclic nucleoside analog that is a substrate for HSV-specified thymidine kinase (TK).^{311,312} ACV is selectively phosphorylated by HSV-infected cells to ACV-monophosphate (ACV-MP). Cellular enzymes then phosphorylate ACV-MP to ACV-triphosphate, a competitive inhibitor of viral DNA polymerase.^{313–315} ACV-TP is incorporated into the growing DNA chain of the virus and causes chain termination.

ACV has potent *in vitro* activity against both HSV-1 and HSV-2.³¹⁶ In animal models, topical or systemic ACV markedly reduces the severity of mucocutaneous HSV infections and, if administered within 96 hours after inoculation of virus, prevents ganglionic latency.³¹⁵ Numerous trials of ACV in primary and recurrent genital herpes have been conducted. In primary genital HSV infection, IV ACV (5 mg/kg q 8 h for 5 days), oral ACV 200 mg (5 times/day for 10–14 days) and topical ACV (5% in polyethylene glycol ointment) all reduce the duration of symptoms, viral shedding, and speed lesion healing.^{132,155,317,318} Systemic therapy prevents new lesion formation and abrogates systemic symptoms. As such, oral ACV is preferable to topical which has limited efficacy and its use is not recommended. The clinical effect of ACV on first-episode infection is considerable, reducing fever and constitutional symptoms within 48 hours of initiating therapy and rapidly relieving symptoms. As such, therapy should be initiated in all patients with presumptive first-episode genital HSV who present with active lesions. Our personal recommendation is to initiate therapy with 400 mg tid per day (Table 24-7). Higher dose of ACV (800 mg 5×/day) does not offer additional benefit nor does the addition of topical to oral medication.³¹⁹ We initiate therapy with a presumptive clinical diagnosis. If an alternative diagnosis is made, then therapy can be discontinued. Because the natural history of disease is for symptoms to progressively increase over the first week, early initiation of therapy is recommended even in patients who present with few lesions. Oral ACV is also effective for treatment of first episode of HSV proctitis in homosexual men²⁰⁴ and of HSV stomatitis. While treatment of first-episode infection markedly shortens the course of first episode, it has no discernible effect on the long-term natural history of recurrences.^{318,320} As such, all patients need to be counseled about the natural history, high rate of recurrences, especially among those with HSV-2 infection, potential complications (including neonatal herpes), and risk of transmission to sexual partners. As shown in Table 24-7, ACV has also been studied for therapy of recurrent episodes of genital herpes and daily suppressive therapy in those with clinical recurrences. Daily ACV markedly decreases the rate of HSV detection on genital mucosa by viral culture and HSV DNA PCR.

Valacyclovir

A major limitation of ACV has been poor oral availability, as only small fraction—10–20% of the dose—is absorbed.³²¹ As

such, an effort has been made to manufacture a compound which would result in higher blood level of ACV. Valacyclovir, an ester of ACV, is rapidly and almost completely converted to ACV by intestinal and hepatic enzymes³²² and increases the bioavailability of ACV to 54%. Therefore, an oral dose of valacyclovir 1000 mg results in a similar area under the curve to IV ACV.³²³ In general, studies comparing valacyclovir to ACV in genital HSV infection have shown the drugs to be comparable in the immunocompetent host. Valacyclovir offers potential convenience through reduced dosing frequency. Valacyclovir has been evaluated for the treatment of genital herpes in several studies^{324,325} and is recommended by the FDA and CDC STD guidelines for treatment of first-episode genital herpes, suppressive daily therapy, and recurrent outbreaks.

Valacyclovir has been evaluated for suppression of herpes recurrences.³²⁶ Valacyclovir 500 mg once daily was compared to placebo in 382 patients with a history of at least 8 recurrences per year. The study continued until first recurrence or for 16 weeks. At that time, 69% of valacyclovir recipients were recurrence free, compared to 9.5% of placebo recipients. Studies comparing valacyclovir 500 mg once daily to other doses and to ACV for 1 year of suppression of recurrent genital herpes indicate that valacyclovir 500 mg PO once daily is effective for patients with 9 or fewer recurrences per year. However, in patients with 10 or more recurrences per year, valacyclovir 250 mg PO bid or 1000 mg once daily is more effective.³²⁷

Valacyclovir 1000 mg bid has been compared to ACV 200 mg five times a day for 10 days for therapy of first-episode genital herpes.³²⁸ No significant differences were noted between ACV and valacyclovir and both were well tolerated. Another study of 739 patients with recurrent genital herpes which compared valacyclovir 500 mg bid with ACV 200 mg five times a day for 5 days did not find any significant differences between the two regimens. A comparative trial showed that the efficacy of ACV 400 mg bid and valacyclovir 500 mg bid for suppression of clinical recurrences and viral reactivation is very similar.^{325,218} Both drugs decrease the rate of viral isolation by 95% and the rate of HSV DNA detection by ~75%. The remaining shedding episodes are short and with low copy numbers; however, the amount of HSV required for transmission is unknown. Valacyclovir is the only anti-HSV drug that has been evaluated for reducing transmission of HSV-2 between sexual partners; 500 mg once daily reduced transmission of HSV-2 by 48%.³⁰⁹

Adverse effects during therapy with valacyclovir are rare and do not occur at a different rate in placebo or valacyclovir recipients. As expected from clinical experience with ACV, headache and nausea are the most frequent complaints. Dose adjustment is needed in persons with severe renal impairment disease.

Valacyclovir 8 g/day has been evaluated in clinical trials for the prevention of cytomegalovirus disease in immunocompromised patients. A syndrome of thrombotic microangiopathy has been described in about 3% of patients with HIV

Table 24-7. Recommended Regimens of Antiviral Chemotherapy of Mucocutaneous HSV Infections

Indication	Drug	Dose	Duration	Comments
First-episode genital herpes	Acyclovir	400mg p.o. 3×/day	10–14 days	Therapy has substantial benefit on all clinical and virologic aspects of the infection. Patients who have not healed after 2 weeks of therapy should be treated for additional 7 days.
	Acyclovir	200 mg p.o. 5×/day		
	Valacyclovir	500 mg–1000 mg p.o. 2×/day		
First episode of herpes proctitis	Famciclovir	250 mg p.o. 3×/day	10–14 days	
	Acyclovir	400 mg p.o. 5×/day		
Suppressive therapy	Acyclovir	400 mg p.o. 2×/day		Benefits of suppressive therapy are usually evident after 3–6 months of daily antiviral treatment. However, unless contraindications develop, it is preferable to continue therapy for at least 1 year.
	Valacyclovir ^a	500 mg p.o. 1×/day		
Recurrent genital herpes	Famciclovir	250 mg p.o. 2×/day	5 days	Therapy shortens episode by 1–2 days. May be useful in patients with prolonged recurrences or significant distress during recurrences. Short course therapy is more convenient and economical
	Short duration			
	Acyclovir	800 mg tid for 2 days		
	Valacyclovir	500 mg bid for 3 days or 1000 mg bid for 1 day		
	Famciclovir	1000 mg bid for 1 day		
	Standard duration			
	Acyclovir	400 mg p.o. 3×/day		
Acyclovir	200 mg p.o. 5×/day			
Valacyclovir	500 mg p.o. 2×/day or 1000 mg p.o. once daily			
Famciclovir	125 mg p.o. 2×/day			
Aseptic meningitis	Acyclovir, intravenous	5 mg/kg q 8 h		After clinical improvement, oral administration of valacyclovir is recommended for a total of 10–145 days of treatment.

^aPatient with very frequent recurrences (≥ 10 per year) benefit from valacyclovir 250 mg p.o. bid or 1000 mg qid.

infection, bone marrow and renal transplant recipients who received this high dose of valacyclovir for a median of 53 days (range 8–100 days). The relationship between valacyclovir and the syndrome is uncertain at this time; thrombotic microangiopathy has not been described in immunocompetent persons receiving up to 3 g of valacyclovir per day.³²⁹

Famciclovir

Famciclovir is a prodrug of penciclovir, a nucleoside analog that effectively inhibits HSV-1 and HSV-2. Similar to ACV, penciclovir requires viral TK for phosphorylation to monophosphate³³⁰ and cross resistance with ACV is common. Penciclovir triphosphate inhibits viral DNA synthesis with a similar in-vitro activity to ACV.³³¹ The intracellular half-life of penciclovir appears longer than ACV (>10 hours). Oral famciclovir is 77% bioavailable.³³² The safety of famciclovir has been evaluated in several clinical trials, and the drug appears to be well-tolerated.³³³ The most common reported adverse effects were nausea, headache, and diarrhea, occurring in similar proportion of famciclovir and placebo recipients. Although laboratory evaluation of famciclovir recipients did not indicate any deleterious effects, a lower dose is advised for patients with impaired creatinine clearance.

The efficacy of oral famciclovir for the treatment of recurrent genital herpes has been evaluated in several trials. In one trial involving 467 subjects with recurrent genital herpes, famciclovir recipients compared to placebo recipients had significantly reduced healing time (median 3.8 days for famciclovir recipients vs. 4.8 days for placebo recipients), viral shedding (1.7 days vs. 3.3 days), and duration of all symptoms (3.2 days vs. 3.7 days).³³⁴ Famciclovir 125 mg twice daily was effective; higher doses did not confer additional benefit for immunocompetent patients with recurrent genital herpes.

In clinical trials comparing famciclovir with ACV 200 mg 5 times daily for the treatment of first-episode genital herpes, the two drugs appeared comparable in their ability to effect viral shedding, lesion healing, and resolution of symptoms.³³⁵ Famciclovir is also effective for suppression of genital herpes when compared with placebo. It is not clear why a lower dose of famciclovir is effective for episodic treatment (125 mg bid) compared with suppressive treatment (250 mg bid). In comparative studies of daily suppressive famciclovir versus valacyclovir, the time to first recurrence was shorter among famciclovir recipients, and HSV was detected on 3.2% of days among famciclovir recipients vs. 1.3% of days among valacyclovir recipients ($p = 0.014$).³³⁶ These data suggest that famciclovir may not be as effective as ACV or valacyclovir for HSV suppression and might be less effective if used to reduce the risk of sexual HSV-2 transmission.

Oral ACV, famciclovir, and valacyclovir have all been shown to be of benefit in reducing the duration of recurrent genital herpes.^{337,338} A series of studies have demonstrated that both physician and patient initiated therapy reduces the duration of

lesions and shortens the time in which virus can be isolated from lesions. Patient-initiated therapy tends to offer greater benefit due to earlier initiation of drug than physician-initiated therapy.³³⁷ Recent studies of episodic therapy of genital herpes show that the clinical benefit of treatment of recurrences is substantial and that prompt administration of antiviral drugs is associated with increased rate of aborted lesions (recurrences that do not progress beyond prodrome). Regardless of the agent chosen, therapy should be initiated by the patient at the first sign or symptom of a recurrence. Such management requires education of patients regarding the manifestations of genital herpes and provision of appropriate supply of the antiviral drug for use at home. The currently recommended doses are shown in [Table 24-7](#). Short courses of therapy (1–2 or 3 days) offer similar efficacy, more convenience, and reduced expense over the more standard 5-day treatment regimens. The success of very short courses of antiviral therapy reflects the importance of viral replication at the initiation of the recurrence, after which the immune system contains the infection. Not all episodes or patients with recurrent HSV require antiviral therapy, as the episodes will self-heal in immunocompetent patients with supportive care. In persons with severe symptomatic episodes, episodic antiviral therapy may be useful but suppressive therapy is more effective. Most immunosuppressed patients require therapy, in such patients short courses of therapy should not be used.

Topical antiviral therapy also has minimal benefit in recurrent genital HSV. Both the antiviral and the delivery base affect the outcome. In the United States, a 5% topical preparation in polyethylene glycol produced an antiviral effect but little clinical benefit.¹³² In Europe where the preparation is a 5% ACV preparation in an aqueous cream, more consistent therapeutic benefit has been achieved.³³⁹ We do not recommend topical therapy for genital HSV alone, or in addition to oral therapy.³⁴⁰

■ SUPPRESSIVE ANTIVIRAL THERAPY

Recurrence rates of genital herpes vary in individuals over time. Most patients who seek medical attention for symptomatic genital HSV report from 5 to 8 recurrences per year. Several studies have shown that daily oral ACV therapy among patients with frequently recurring genital HSV (4–12 episodes per year) is effective in preventing clinical recurrences of genital herpes.^{341–345} ACV in doses of 200 mg two to five times daily for up to 6 years will prevent recurrences in 65–85% of patients as long as therapy is continued. In a 5-year study of suppressive ACV, the mean number of breakthrough recurrences declined from 1.7 during the first year to 0.8 during the fifth year.³⁴⁶ Suppressive therapy in persons with frequently recurring disease produces considerable relief of symptoms and can provide major medical and psychosocial benefit.²⁹⁷ Isolates recovered from patients who have received

long-term ACV therapy do not differ in their susceptibility to pretreatment isolates.³⁴⁷

For long-term therapy, simple and convenient dosage regimens are required to achieve maximum compliance. ACV 400 mg bid or valacyclovir 500 mg qid are the best initial starting dosage in the immunocompetent patients.³⁴⁴ More than 90% of persons with frequently recurring genital herpes who are immunocompetent have a significant reduction in the number of clinical recurrences on suppressive therapy. Even among those on suppressive therapy, breakthrough recurrence will, however, still occur. About 25% of persons on suppressive therapy will develop a breakthrough recurrence each 3-month period.³⁴⁴ Thus, it is likely that most patients on chronic suppressive therapy will, at some time, develop a breakthrough. Compared with untreated recurrences, breakthrough recurrences are associated with milder symptoms, shorter duration of viral shedding, and shorter duration of lesions.^{341,348} Most patients prefer suppressive therapy to episodic therapy and rate their quality of life on herpes-related scales higher while on suppressive therapy.^{349,350}

Because frequently recurring genital herpes may plague a patient for years, many patients desire to take oral ACV for prolonged periods. Preclinical animal studies of ACV showed no drug-related carcinogenicity, effect on fertility, or abnormal fetal development.³⁵¹ Chronic suppressive therapy taken at doses of 200 mg 5 times a day or 200 mg 2 times a day have had no effect on spermatid function in men.²²² Side effects of daily suppressive oral ACV are uncommon. Data from a multicenter trial and trials of smaller number of patients treated for up to 10 years do not show any clinical or laboratory toxicity.^{346,347} Allergic reactions to ACV are rare and successful desensitization has been reported.^{352,353}

One of the major issues facing the clinician with a patient with genital herpes is the use of intermittent versus chronic suppressive ACV therapy. We believe all patients should be informed about the option of episodic and suppressive antiviral therapy. Patients with frequently recurring genital herpes who have considerable physical discomfort, emotional upset, and potential for transmission of infection to sexual partners are all candidates for chronic suppressive therapy.³⁵⁴ In addition, natural history of HSV-2 shows that the risk of viral shedding is highest within the first year of acquisition and such persons may be excellent candidates for suppressive therapy.³⁵⁵ Early suppressive therapy may prevent further transmission at a time of potentially greatest risk, assist in adjustment to having genital herpes, and improve quality of life. Studies indicate that it takes from 5 to 7 days of therapy before clinical effect can be seen.³⁴¹ The decision to initiate suppressive therapy should be made with regard to patient preferences, objective severity of disease, psychological distress at having recurrences, and the potential for infection in susceptible partners. The cost of chronic therapy is concerning for many persons, although

the price of generic ACV in the United States is relatively low (~\$60 per year for ACV 400 mg bid).

■ HSV THERAPY IN PERSONS WITH HIV INFECTION

Relatively few clinical trials have been performed in this population, despite wide clinical use of these medications. The lack of clinical trials reflects underestimating of the importance of HSV in HIV infection as well as the perception that the market for antivirals in that setting is small. Recent studies, detailed above, showing an effect of drugs for HSV on plasma HIV are likely to lead to wider use of nucleoside analogs in this population. ACV, valacyclovir, and famciclovir have been studied as therapy for HSV in HIV-infected persons and appear effective.³⁵⁶ Suppressive therapy is preferred for HIV-infected persons rather than episodic, and the dosing should be twice a day, even for valacyclovir.

■ TREATMENT OF RECURRENT GENITAL HERPES

ACV in pregnancy

Although ACV is not teratogenic in animals, until studies defining its role and safety in pregnancy are available, the routine use of oral ACV in pregnancy cannot be advocated. A pharmacokinetic evaluation of ACV in third trimester of pregnancy showed that the disposition of ACV appears similar in pregnant women to other adults.²³⁵ A potential concern is the development of obstructive uropathy in the newborns secondary to ACV crystals. However, no such abnormalities have been observed in this study, or in a much larger number of infants with neonatal herpes treated with prolonged, and often high-dose, IV ACV.^{357,358} However, neutropenia does occur in infants treated with prolonged ACV therapy and such infants need to be monitored.³⁵⁹ While a recent study showing no laboratory abnormalities in infants of mothers treated with daily valacyclovir at the end of pregnancy is somewhat reassuring, the numbers are small and rare events have not been ruled out.³⁶⁰

Glaxo-Wellcome, in collaboration with the Centers for Disease Control, maintained a voluntary registry of women who received ACV (and few that received valacyclovir) during pregnancy. As of 1999, 756 women who received ACV in the first trimester were reported. A total of 3.2% of the children had birth defects compared to a background rate of 3%.³⁶¹ No consistent pattern of abnormalities has been noted. Although the number of women evaluated is insufficient to exclude a small increase in the rate of congenital abnormalities, lack of statistically significant increase in the incidence of defects and lack of pattern of abnormalities is reassuring. The safety of valacyclovir and famciclovir in early pregnancy has not been established. The use of ACV and valacyclovir in late pregnancy to prevent abdominal deliveries is discussed above; no data on famciclovir have been published in pregnancy.

■ EMERGENCE OF RESISTANCE

In vitro resistance to ACV can result from TK-deficient, TK-altered, or DNA-polymerase-resistant strains of HSV. TK deficiency is the most common mechanism of resistance of HSV to ACV.^{362–365} Animal studies have suggested that TK-deficient mutants are less virulent and less able to establish neural latency.³⁶⁶ However, some ACV-resistant strains appear to make enough TK to establish ganglionic latency and reactivate especially in immunocompromised patients.³⁶⁷ Disease caused by strains with DNA polymerase mutation has also been reported.³⁶⁸ ACV-resistant strains of HSV have been recovered from patients who have never been treated with ACV.^{363,365} About 3% of isolates obtained from immunocompetent patients demonstrate in vitro resistance to ACV. The frequency of in vitro resistance has not changed from the time prior to availability of ACV and does not appear increased among patients who received several years of daily suppressive ACV.³⁴⁷ Among women followed longitudinally with daily viral cultures, about 3% of isolates were ACV resistant in vitro.³⁶⁹ The resistant strains were isolated on same day as sensitive strains from other genital sites and were followed on subsequent days with ACV-sensitive strains. As such, the demonstration of ACV resistance in vitro in immunocompetent population has not been associated with clinical failure of ACV therapy and routine testing for sensitivity is not recommended. Rare isolation of ACV-resistant strain likely represents a random mutation that is rapidly cleared by the immune system in a healthy host. An exception is a report of genital herpes with an HSV-2 strain characterized by an altered TK.^{367,370} In this person, all isolates recovered from multiple recurrences had an altered TK and ACV did not offer clinical benefit. Additional cases of ACV-resistant HSV infection have been reported from immunocompetent patients, often with nongenital HSV infection.

The vast majority of ACV-resistant isolates have been from immunocompromised patients undergoing multiple courses of ACV for established infection.³¹³ However, the frequency of ACV resistance in HIV-infected patients appears low and the risk factors for the development of resistance have not been well-defined. In a surveillance study for ACV-resistant herpes, 5% of isolates were ACV resistant.³⁷¹ The risk for ACV resistance included low CD4 count and topical ACV therapy. Thus, continued surveillance of HSV strains associated with breakthrough recurrences and/or persistent mucocutaneous HSV is needed. At present, routine in vitro testing of HSV isolates for ACV sensitivity is not recommended. However, isolates from patients with persistent HSV infections unresponsive to ACV, especially those with advanced HIV disease, should have testing for ACV resistance. In this setting, in vitro resistance correlates well with ACV failure.³⁷² Most ACV-resistant HSV infections require therapy with alternative agents. As famciclovir has a similar mechanism of

action, most ACV-resistant strains are also famciclovir resistant. Treatment with high-dose continuous infusion of ACV has also been reported as successful.³⁷³ Recent observation that suppressive therapy with ACV compared with episodic therapy is associated with lower incidence of ACV-resistant HSV among bone marrow recipients implies that withholding of suppressive antiviral therapy in HIV-infected patients because of concerns for ACV resistance may result in increased rate of ACV resistance.²³⁸

The introduction of antiretroviral therapy has decreased the rate of ACV-resistant HSV among HIV-infected persons. However, severe and prolonged episodes of genital herpes recalcitrant to antiviral therapy have been noted as part of immune reconstitution syndrome in patients initiating retroviral therapy.^{374,375} In some cases, in vitro studies show ACV susceptibility of the isolates and suggest that brisk immune response is responsible for the clinically severe lesions.

■ THERAPY OF ACV-RESISTANT HSV

Foscarnet

Foscarnet is a viral DNA polymerase inhibitor similar in structure to phosphonoacetic acid. In vitro, it has potent antiviral activity and has been effective in speeding the healing of lesions in animal models.³⁷⁶ It is an insoluble compound and can be effectively administered only intravenously or topically. One study demonstrated in men a reduction in healing with 0.3% foscarnet cream as compared with placebo.³⁷⁷ However, a collaborative Canadian trial of foscarnet cream 0.3% in men and 1% in women demonstrated little overall effect on reducing symptoms or lesions.³⁷⁸

Systemic toxicity during IV administration limits the use of foscarnet to patients who fail ACV therapy because of development of resistance. In this population, however, foscarnet has become the preferred agent. Foscarnet infusion healed 81% of 26 patients with ACV-resistant HSV infection.³⁷⁹ A comparative study of foscarnet 40 mg/kg IV q 8 hours and vidarabine 15 mg/kg q day showed that foscarnet therapy led to healing of all 8 patients while all patients assigned to vidarabine failed therapy.³⁸⁰ Adverse reactions are frequent but only rarely require discontinuation of therapy. The most common toxicities are renal insufficiency and metabolic disturbances, especially hypophosphatemia. Recurrences of HSV after foscarnet therapy can be either ACV-sensitive or ACV-resistant. HSV resistance to foscarnet has also been reported, usually in the setting of prolonged foscarnet therapy.³⁸¹ In that setting, the addition of ACV can be beneficial.

Cidofovir

Another nucleotide analog with good activity against herpes viruses is cidofovir, an acyclic nucleoside phosphonate.

Unlike ACV, which requires phosphorylation by HSV-specified enzymes, cidofovir is phosphorylated only by cellular enzymes. Therefore, cidofovir is active against HSV strains with a deficient or altered TK and, in fact, its appears more active against these isolates than against wild-type strains.³⁸² Topical and IV cidofovir has been used successfully to heal ACV-resistant lesions in some patients with AIDS and after marrow transplant,^{383,384} although cidofovir resistance associated with polymerase mutations in immunocompromised patients has also been reported. A randomized, double-blind, placebo-controlled trial of topical cidofovir gel 0.3% or 1.0% in 30 patients with AIDS who did not respond to ACV therapy showed that 10 of 20 cidofovir recipients healed by at least 50% compared with none of the placebo recipients.³⁸⁵ Most patients treated with topical cidofovir ceased viral shedding. No systemic reactions were noted; however, 23% of cidofovir recipients had mild or moderate local cutaneous adverse effects. However, as long-term toxicity studies of cidofovir showed tumors in animals, further development of the drug for immunocompetent persons has been slowed. Because of the potential for renal toxicity with IV administration, use of topical cidofovir is preferred for treatment of genital herpes. Availability of safer agents for therapy of herpes in healthy persons suggests that cidofovir will be an important therapeutic alternative only in the immunocompromised population.

Trifluridine

Trifluridine is a potent antiviral agent; toxicity precludes systemic administration. However, trifluridine is frequently used for treatment of ophthalmic herpes infections. A series of 26 patients with AIDS and herpes unresponsive to ACV demonstrated complete healing in 7 patients and partial healing in 14 patients.³⁸⁶ Anecdotal reports also suggest that the use of IFN- α may potentiate the antiviral effects of trifluridine.³⁸⁷ Topical imiquimod, a TLR-7 and 8 agonist used for treatment of warts, has also been effective in some patients

Resiquimod and Imiquimod

Resiquimod and imiquimod have been evaluated in clinical trials for genital herpes; both work in the animal model, although resiquimod has greater anti-HSV activity. These agents are applied topically during a recurrence to stimulate local immune response while the antigen is present, and delay time to subsequent recurrence. However, imiquimod was not effective in delaying time to next genital HSV recurrence in a clinical trial.³⁸⁸ Resiquimod has been tested more thoroughly but the results have been inconsistent. A pilot efficacy trial showed a substantial delay to the time of next recurrence compared to vehicle administration, 169 versus 57 days ($p = 0.006$).³⁸⁹ However, three-phase studies yielded negative results and patients who received resiquimod had a prolonged time healing of their initial recurrence. In contrast, a study to

evaluate viral shedding after resiquimod application showed that participants receiving resiquimod had a lower subclinical shedding rate, lower rate of days with lesions, as well as a longer time to first recurrence.³⁹⁰ Further commercial development of this compound has ceased, in our view, prematurely.

OTHER ANTIVIRALS

Several other therapies for genital HSV have been attempted with a variety of topical medications. Medication in which no therapeutic benefit can be demonstrated are listed in [Table 24-8](#) below. Helicase inhibitors have been shown to have potent in vitro antiviral activity but their clinical development is still in early phases.

The following agents have been tested for genital herpes and the results demonstrate lack of efficacy: vidarabine, idoxuridine, edoxuridine, isoprinosine, ether, 2-deoxy-D-glucose, BCG vaccine, chloroform, povodine iodine, topical surfactants, photodynamic dyes, topical IFN- α transfer factor, and lysine.

IMMUNOTHERAPY

The use of HSV antigens to boost host immune responses has been a longstanding area of HSV research. In animal models, administration of HSV vaccines with varying adjuvants has been associated with reduction in the frequency of reactivation. In people, a double-blind, placebo-controlled trial of a recombinant gD2 vaccine in alum was shown to reduce the recurrence rate of genital HSV by 25%.³⁴² In a follow-up study, a recombinant gD2 gB2 vaccine (10 μ g) in MF-59 reduced the severity of the HSV recurrence after immunization but did not reduce recurrence rates.³⁹¹ These effects are clinically modest but demonstrate the principle that immunotherapy offers promise as therapy for genital herpes. Several new approaches to immunotherapy are under investigation. Several immune modulators, especially those involving enhancing the toll-like receptor 7 and 8 pathways have shown in vivo activity in both small animals and humans.

Table 24-8. Ineffective Therapies for Genital Herpes

Vidarabine	Povodine iodine	Isoprinosine
Idoxuridine	Topical surfactants	2-deoxy-D-glucose
Edoxuridine	Photodynamic dyes	BCG vaccine
Ether	Topical interferon α	Lysine
Chloroform	Transfer factor	Nonoxynol 9

The ability to reduce disease severity for a prolonged time period is an attractive therapeutic alternative for many patients, but an effective product has proven elusive.

PREVENTION OF INFECTION

Several partly effective modalities have been established for HSV-2 prevention; disclosure to partners, suppressive antivirals, and condoms are discussed above. However, transmission of disease may still occur despite the use of condoms when viral shedding occurs in areas of genital tract not covered by a condom. Spermicides contain the topical surfactant nonoxynol 9, which inactivates HSV in vitro. Nonoxynol 9 has been shown to be ineffective in the treatment of established genital HSV infection.¹²⁹ Other microbicides that are currently in development include Carraguard and PRO2000. Human efficacy data for prevention of transmission or acquisition of HSV-2 with these products are not available.

The high prevalence of asymptomatic and atypical HSV infection implies that development of an effective HSV vaccine is the best approach to the prevention of HSV. Prophylactic subunit protein vaccines have been tested and shown effective in a variety of animal models.³⁹² The effort has concentrated on glycoprotein D and B, as the immune response to these glycoproteins appears to induce high levels of neutralizing antibodies. A trial of HSV vaccine composed of glycoprotein mixture elicited low levels of antibody titers and did not protect against infection.³⁹³ A recombinant HSV-2 gD and gB vaccine in a novel MF-59 adjuvant emulsion induced humoral and cellular immunity comparable to that observed in natural infection.³⁹⁴ However, in an efficacy trial of partners discordant for HSV-2 infection and persons attending STD clinics, the vaccine did not afford clinically useful protection from infection.⁴⁷ A similar subunit vaccine consisting of HSV-2 gD has shown partial efficacy against HSV-2 infection in women seronegative for HSV-1 and HSV-2.⁹⁰ The vaccine decreased the risk of developing clinical genital herpes by 75% and the risk of acquiring HSV-2 infection by 40%. The vaccine did not protect men or HSV-1 seropositive women. Another trial is evaluating this vaccine in a large cohort of HSV seronegative women. Protection against clinical disease but not against infection may not be of benefit from a public health standpoint, if the infected persons continue to shed virus subclinically and can transmit the virus to sexual partners.³⁹⁵ Other vaccines under development include attenuated live vaccines, replication-defective viral mutants, live virus vectors expressing subunit protein, recombinant-vector-based vaccines and DNA vaccines.^{192,392,394,396–400} These products are currently in preclinical or early clinical stages of development.

SUMMARY

Genital HSV infection is a disease of major public health importance. In the last 4 decades, genital herpes infection has

increased in prevalence in many population groups, is widespread in the general population in the developing countries, and has emerged as the predominant cause of genital ulcer disease worldwide. First-episode genital HSV infection is a disease of multiple anatomic sites, lasts 3–4 weeks, and has a high rate of complications. In contrast, episodes of recurrent genital disease are of much milder intensity and duration. The major morbidity of recurrent genital herpes is its frequency of recurrences, its chronicity, and its effects on the patient's personal relationships and sexuality. The transmission of disease to the neonate is a major concern to women. Studies have shown effectiveness and safety of ACV and related compounds in reducing many of the clinical manifestations of genital herpes. Greater attention to the diagnosis of the unrecognized HSV-2 infection is needed as such persons are the major source of new infections. The cellular, mucosal, clinical, and epidemiological interactions between HSV-2 and HIV have become clearer in the last decade and the role of HSV-2 in fueling the HIV epidemic has been elucidated. Further investigations on the mechanism of HSV reactivation will hopefully provide additional tools to attempt to control this disease. In the meantime, knowledge of the natural history of the disease will aid the physician in providing the patient with the information necessary to understand this complex entity, decrease the transmission to sexual partners and neonates through education, and explain the long-term complication of the illness. In this way, the physician may do much toward allowing the patient to cope with the psychological and physical components of this illness.

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Morgan Hakki and Adam P. Geballe

INTRODUCTION

Human cytomegalovirus (CMV) infections were first described at the beginning of the twentieth century based on the distinct histologic appearance of enlarged cells with viral inclusions associated with fatal infections in newborns.¹ Successful cultivation of the virus, initially in the mid-1950s, enabled a steady accumulation of knowledge about the epidemiology, molecular biology, immunology, and pathogenesis of CMV. While the introduction of effective antiviral drugs in the early 1990s led to significant improvements in the treatment of CMV, numerous questions about the biology and pathogenesis of CMV have not yet been answered and there remains an urgent need for improved therapeutic and preventative measures.

CMV shares many characteristics with other herpesviruses.² Its general structure, genetic organization, and ability to persist in a latent state for the lifetime of the infected individual are common to herpesviruses. Based on biological properties including slow growth, salivary gland tropism, and species specificity, CMV has been classified as a member of the beta subfamily of the herpesviridae. The beta subfamily also includes human herpesvirus (HHV)-6, HHV-7, as well as CMVs that infect many other mammalian species such as mice, rats, guinea pigs, and nonhuman primates. During the past few years, the grouping of these viruses into the beta-herpesvirus subfamily has been well supported by phylogenetic analyses of nucleotide sequence data.³⁻⁵

More than 50% of individuals in most populations throughout the world demonstrate serological evidence of prior CMV infection.⁶ The coevolution with and adaptation to its human host over millions of years may account for the observation that in most cases, CMV infection causes few if any symptoms.⁵ However, in immunocompromised individuals, primary infection or reactivation of latent virus can be life-threatening. As well, congenital infections are common and can result in serious lifelong sequelae. The possibility that subclinical CMV infection contributes to chronic diseases

such as atherosclerosis remains a hypothesis under active investigation.⁷⁻⁹ Although CMV does not typically come to medical attention as a result of genital tract lesions or disease, it can be transmitted sexually and has important consequences for the sexually active, child-bearing population.

VIRUS STRUCTURE

■ VIRION ORGANIZATION

The CMV virion, like those of other herpesviruses, is approximately 200 nm in size and contains a large double-stranded DNA genome encased in an icosahedral capsid (Fig. 25-1). Surrounding the capsid is an unstructured region known as the tegument (or matrix) and an outermost lipid membrane containing viral glycoproteins. In addition to infectious virions, CMV infections produce at least two other types of particles, dense bodies, and noninfectious enveloped particles.¹⁰ Although these particles cannot establish productive infections, they can bind and fuse to cell membranes and therefore have the potential to alter cellular activities.

CMV virions contain over 70 viral proteins as well as many cellular proteins and even some viral and cellular RNAs.^{11,12} Viral glycoproteins on the virion surface are key determinants in mediating binding to and entry of the virus into the cell.^{13,14} These proteins are also the major targets of anti-CMV neutralizing antibodies. Several internal proteins form structural elements of the virion and others serve regulatory roles in activating transcription of the first (immediate early, or α) kinetic class of viral genes to be expressed after infection.^{15,16} Despite these functions, preformed virion proteins are not essential for viral replication following entry since the experimental introduction of naked viral DNA into permissive cells can yield infectious virus. The roles of many of the other virion proteins and RNAs in the infectious process are unknown, and some of these may be only incidentally acquired during virion assembly.

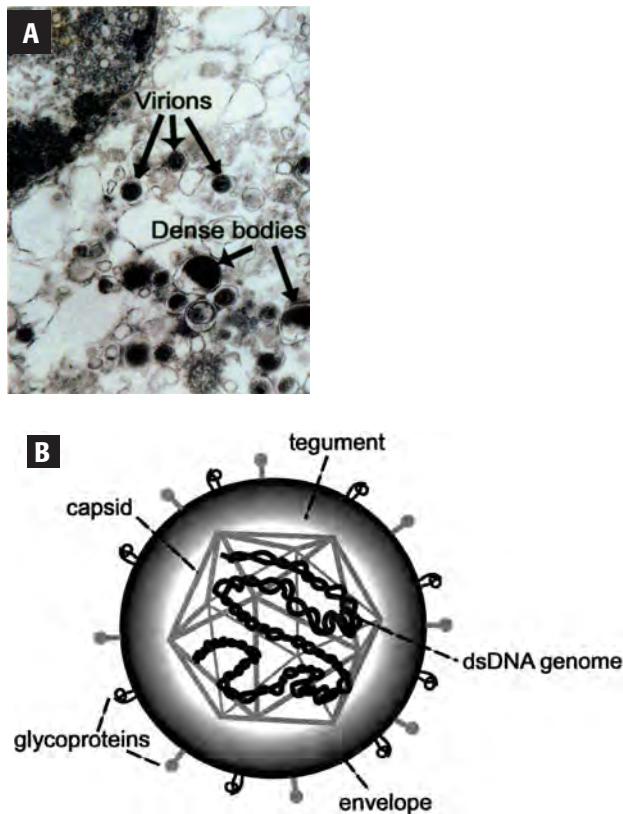


FIGURE 25-1. A. CMV infected cells as viewed by transmission electron microscopy. Cytoplasmic virions and dense bodies are indicated (55,000 \times , provided by Julie Randolph-Habecker, Fred Hutchinson Cancer Research Center). **B.** Diagram of a CMV virion. The lipid envelope contains glycoproteins and surrounds the unstructured tegument. The dsDNA genome is packaged within an icosahedral capsid.

■ GENOME

The CMV genome contains approximately 230 thousand base pairs of duplex DNA organized into long and short unique segments (Fig. 25-2). The short segment is flanked by inverted repeats. Although the long unique region is also flanked by inverted repeats in laboratory-adapted strains, these repeats are minimal or absent in clinical isolates that have not been passaged many times in cell culture.^{3,17,18} For example, in place a portion of these repeats, the low-passaged clinical isolate CMV (Toledo) contains 15 kilobase base pairs of unique DNA encoding 19 genes that are missing from the laboratory-adapted strain CMV (AD169).¹⁹

Computer analyses of the sequences of several CMV isolates suggest the presence of approximately 200 protein-coding open reading frames (ORFs).⁴ In addition, several genes that produce noncoding RNAs, including microRNAs, have been identified.^{20,21} By convention, CMV genes are named based on their position within each segment of the genome, although some genes have additional common names based on historical usage or homologies to genes of other herpesviruses. For example, UL55 is the 55th ORF in the unique long segment of the genome and is also known as the

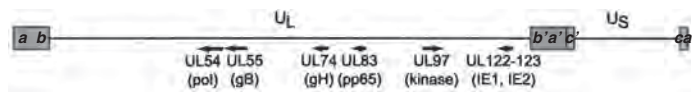


FIGURE 25-2. The CMV genome. Long unique (U_L) and short unique (U_S) segments are flanked by repeats of varying sizes ($[ab]$, $[b'a'c']$, $[ca]$). The example shown here represents the laboratory adapted strain CMV (AD169). Arrows show the positions and orientations of several of the approximately 200 ORFs encoded by the genome.

glycoprotein B (gB) gene. While many genes are highly conserved among strains, others are surprisingly variable; the DNA polymerase varies at only 4% of amino acids, while UL144, which encodes a tumor necrosis factor-like protein, varies at as many as 21% of positions.^{22,23}

CMV genes can be grouped into three phylogenetic classes.²⁴ One set of approximately 40 genes, including UL54 (DNA polymerase), UL55 (gB), and UL57 (ssDNA-binding protein), are located primarily in the central portion of the U_L region of the genome and have homologues in most other herpesviruses. Flanking this region are an additional approximately 40 genes that have homologues in other betaherpesvirus subfamily members. Finally, much of the U_S region and the ends of the U_L region contain genes specific to human or primate CMVs.

The functions of many CMV genes have not been evaluated in detail, but recent advances in engineering of the genome have provided some insights. As with other well-studied herpesviruses, only approximately half of all CMV genes are essential for the virus to replicate in cell culture.^{25,26} These include genes involved in regulating the expression of other viral genes, those needed to replicate the viral DNA, and those which play an integral role in the formation of new virions. Genes nonessential for growth in cell culture are likely important for viral replication and spread in nature. These include genes involved in evading the host cellular immune response, determining cell tropism, and participating in the establishment and maintenance of latency.

DNA sequence polymorphisms between the genomes of distinct CMV isolates have been useful in tracking transmission. Many more differences are found when comparing isolates from epidemiologically unrelated cases than from isolates obtained from related cases such as mother–infant pairs, sexual partners, and transplant recipients following transplantation of organs from a common infected donor.^{6,27,28} Studies attempting to correlate genetic sequence polymorphisms, most commonly in the gB gene, with different disease manifestations have been inconclusive.²⁹ Nonetheless, genetic variation among strains may account for some of the differing pathogenic manifestations of CMV infections. Interestingly, polymorphisms in one gene have generally been found to be unlinked to those in other genes, suggesting that genetic recombination between isolates occurs frequently in nature.

REPLICATION

■ LYTIC CYCLE

A common property of betaherpesviruses is their species specificity.² CMV causes disease only in humans, and the virus replicates only in cells of human origin. With a few exceptions, other mammalian CMVs display similarly limited species tropism. In cell culture, the virus grows well in diploid human fibroblasts and some, but not all, strains will grow in other cell types including endothelial cells and macrophages. In infected patients, evidence of CMV has been found in a wide range of cells, including fibroblasts, endothelial cells, epithelial cells, blood cells, smooth muscle cells, and macrophages.³⁰ However, it is not certain in which of these cell types the virus can complete its replication cycle and produce new virus.

CMV receptors are expressed on many cell types and, in fact, CMV can enter most human cells.² The virus initially binds to target cells through low-affinity interactions with cell surface heparan sulfate proteoglycans. More specific interactions between viral envelope proteins and cellular receptors then mediate the entry process resulting in fusion of the viral and cellular envelope. Studies aimed at identifying cellular receptors have implicated the integral membrane protein heterodimers $\alpha 2\beta 1$, $\alpha 6\beta 1$, and $\alpha V\beta 3$, and the epidermal growth factor receptor.^{14,31} The ubiquity of these receptors may explain the ability of CMV to enter many cell types.

Binding of the virus to the cell surface activates signaling pathways, resulting in a large number of changes in the target cells.^{32,33} Part of this cellular response appears to be mediated by sensing of the incoming virus by Toll-like receptor 2.³⁴ Thus, in addition to activating pathways that the virus uses for its replicative cycle, CMV binding to and entry into the cell may also initiate host innate immune responses.

After envelope fusion, the viral capsid and associated tegument translocate to the cell nucleus where transcription of immediate early genes commences, stimulated in part by preformed tegument proteins.^{15,16} Potent transcriptional control elements that direct the expression of the major immediate early gene (UL122/UL123) have led to its widespread application for expression of foreign genes in many other experimental systems. The protein products of immediate early genes generally function to activate expression of early and late classes of proteins as well as to thwart apoptotic and other antiviral cellular responses.^{2,35–37}

Early (or β ,) genes are, by definition, those genes whose transcription requires prior immediate-early viral gene expression but not viral DNA replication, while late (or γ) gene transcription is dependent on viral DNA replication. In fact, many CMV genes are expressed at low levels at early times and at much higher levels at late times, after viral DNA replication has begun. DNA replication is thought to occur by a rolling circle mechanism.³⁸ Newly replicated genome

length segments are cleaved from the rolling circle and packaged into viral particles. Egress of the virus from the cell is not well understood but, by analogy to other herpesviruses, is likely a complex process involving budding through the nuclear membrane followed by deenvelopment, reenvelopment, and eventual budding through the plasma membrane.

■ LATENCY

The ability to persist in a latent state in which no infectious virus is present but from which reactivation of viral production can occur is a hallmark of herpesviruses. In the case of CMV, little is known about the sites or mechanisms of latency. After recovery from acute CMV infection, individuals may continue to produce infectious virus for months, indicating that symptomatic resolution is not a reliable indicator of the transition from productive infection to latency.

Viral transmission from healthy seropositive blood donors suggests that a blood component is one site of latency. The fact that reducing the number of leukocytes in blood greatly reduces the risk of transmission suggests that these cells represent a latently infected population. A variety of laboratory studies support the hypothesis that cells of the granulocyte–monocyte lineage harbor latent CMV.³⁹

CMV may persist in a latent state at sites other than blood leukocytes. Transplantation of solid organs clearly can transmit the virus and murine CMV resides latently in organs including the lung and spleen.⁴⁰ However, whether the latently infected cell type in these organs is transitory blood cells, temporary residents such as monocytes or macrophages, or permanent cells in these organs is not yet certain.

HOST IMMUNE RESPONSES

As with many viruses that cause chronic infection, CMV seems to have coevolved with humans to a balanced state in which the virus persists but generally causes little clinical illness. The host's innate and adaptive immune responses are usually successful at limiting CMV infection as is evident by the clear association of immune system dysfunction with CMV disease. In the absence of prophylactic antiviral treatment, CMV often reactivates in seropositive individuals who undergo hematopoietic stem cell transplantation (HSCT).⁴¹ Immunosuppression resulting from drugs used to treat cancer and autoimmune disorders, and from impaired T-cell function that occurs with advanced AIDS, is also associated with reactivation of CMV.

A key component of the host immune response is the HLA class I-restricted CD8⁺ T cell. Among the viral antigens recognized by these cells is the virion tegument protein pp65, the product of the UL83 gene. Using tetramer and intracellular cytokine staining techniques, many groups have reported that 5% or more of circulating CD8⁺ T cells in normal

individuals can be specific for this one protein.⁴² CD8 responses to IE1, gB, and other largely uncharacterized proteins are also detectable.⁴³ It is possible that the remarkably high number of CMV-specific CD8⁺ cells is linked to frequent subclinical reactivations or to the endothelial cell tropism of the virus, causing repeated stimulation of CD8⁺ T cells.

CD4 helper T cells also play an important role in controlling CMV. In a recent study of AIDS patients, loss of CMV-specific CD4⁺ cells preceded the development of CMV disease even though CMV-specific CD8⁺ cells were present.⁴⁴ In HSCT recipients, undetectable CMV-specific CD4⁺ cells were significantly associated with late CMV disease and death.⁴⁵ CMV-specific CD4⁺ cells likely function in part by helping to maintain robust CMV-specific CD8⁺ cell responses.⁴⁶

Infected individuals develop antibodies to multiple different CMV proteins. Many of the antigenic targets are present internally within the cell or virion and are unlikely to have roles in immune protection. However, antibodies to gB and gH, two envelope glycoproteins, can neutralize the virus in cell culture assays.¹³ Although high titer CMV immune globulin may have some antiviral utility in conjunction with antivirals, passive immunity by itself has not been convincingly shown to be effective in preventing or treating established infection.⁴⁷

VIRAL EVASIVE MECHANISMS

CMV has evolved a variety of mechanisms to avoid elimination by host's multifaceted antiviral responses (Fig. 25-3). Several CMV genes have been found to block intracellular response pathways as well as antiviral responses mediated by cells of the innate and adaptive immune systems.^{24,48}

Autonomous cellular responses to viruses include ones that shut down basic processes necessary for viral replication, even at the risk to the health and viability of the cell. For example, viral infections often trigger apoptotic pathways, and CMV has several genes that block steps in this response.⁴⁸ CMV contains at least two genes, *IRS1* and *TRS1*, that bind double-stranded RNA (dsRNA) and can prevent activation of interferon-induced, dsRNA-activated enzymes that inhibit overall protein synthesis.^{37,49} CMV counters the interferon system in part by preventing translocation of interferon regulatory factor 3 from the cytoplasm to the nucleus, one of the key steps in Toll-like receptor signaling and activation of the interferon response.⁵⁰

Several viral genes including *US2*, *US3*, *US6*, *US8*, and *US11* act at different stages in the HLA class I and class II pathways to prevent presentation of viral peptides to T cells.²⁴ Cells lacking surface HLA class I are frequent targets for NK cells, but CMV has other genes that help it avoid these cells as well.

CMV also encodes several chemokines and chemokine receptors that mediate interactions with the host immune system. Chemokine receptors have been hypothesized to bind and

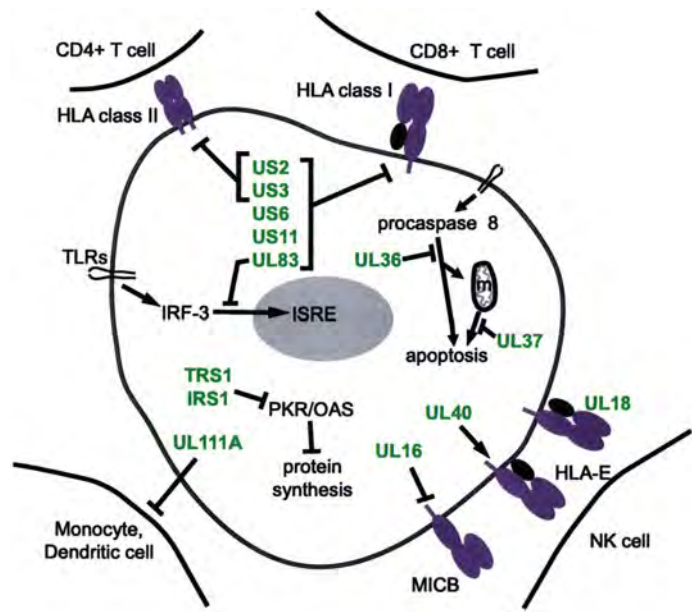


FIGURE 25-3. Immune evasion strategies. CMV encodes multiple genes (green) that interfere with cellular anti-viral responses. Among the targets of these CMV genes are cell autonomous responses (e.g., induction of apoptosis, stimulation of interferon gene expression, and shut off of protein synthesis) as well as responses mediated by various cells of the innate and adaptive immune system. (Abbreviations: IRF-3, interferon regulatory factor 3; ISRE, interferon-stimulated response element; m, mitochondrion; MICB, major histocompatibility complex class I chain-related B; OAS, oligoadenylate synthetase; PKR, protein kinase R; TLRs, toll-like receptors.)

sequester host cell chemokines, thereby inhibiting the influx of inflammatory cells. Conversely, viral chemokines may promote viral dissemination by attracting inflammatory cells, which then serve as vehicles for viral spread to distant sites.⁴⁸

EPIDEMIOLOGY

CMV is a ubiquitous virus, as evidence of infection has been found in persons of all ages, socioeconomic groups, and geographic locales. In the United States and Western Europe, 5–30% of children will be CMV seropositive by 5 or 6 years of age; this number reaches 40% by adolescence and increases by roughly 1% per year thereafter.^{1,51} CMV infection is usually acquired earlier in life among persons living in developing countries and among those in lower socioeconomic strata in developed nations. As discussed below, the mode of acquisition and precise seroprevalence rate in the United States vary significantly among different populations.

■ CMV IN HETEROSEXUALS

CMV has long been thought of as a sexually transmissible infection based on several lines of evidence. CMV seroprevalence was found to be significantly higher among male partners of CMV seropositive women than of CMV seronegative women (74% vs. 31%).²⁸ The prevalence of CMV

seropositivity in sexually active women between the ages of 15 and 30 years was greater than that in celibate women of the same age.^{52–55} Among women, predictors of CMV seropositivity included young age at the time of first sexual intercourse, greater number of lifetime sexual partners, and the presence of other STDs.^{56–58} Seroconversion, presumably a marker for primary infection, occurred at a rate of 37% per year in women attending STD clinics compared to 2–7% in the general population, and correlated with having multiple sex partners in the preceding month and a prior history of any STD.⁵⁶ Additionally, an outbreak of CMV-associated mononucleosis was documented among sex partners but did not affect nonsexually active persons living in the same quarters.⁵⁹

Consistent with these clinical observations, in adults CMV was isolated most frequently and in greater titers from cervical secretions and semen than from other sources.^{54,60–62} Using molecular strain-typing techniques, it has been demonstrated that in the majority of cases, seroconcordant couples shared a similar CMV isolate, indicating spread from one partner to another.²⁸ In sum, evidence from clinical and molecular studies supports the role of sexual transmission as a major mechanism of CMV spread among heterosexuals.

■ CMV IN HOMOSEXUAL MEN

In the era before highly active antiretroviral therapy (HAART), CMV was a significant cause of morbidity and mortality in the HIV/AIDS population. The first documentation of the high prevalence of CMV in homosexual men originated from studies performed in San Francisco in the late 1970s and early 1980s.⁶³ The rate of CMV seropositivity in homosexual men attending an STD clinic was 93.5% compared to 54.3% in heterosexual men attending the same clinic and 42.7% in heterosexual men randomly selected from a pool of blood donors. Urinary excretion of CMV was found to be significantly more common in homosexual men compared to heterosexual men (7.4% vs. 0%). A similarly high rate of CMV seropositivity (86.9%) was found in homosexual men enrolled in a hepatitis vaccine trial.⁶⁴ Of the CMV seronegative participants enrolled in this study, 71% experienced primary infection during the 9 months of follow-up. Passive anal–genital contact was the only identifiable sexual practice associated with CMV seropositivity. Excretion of CMV was found more commonly in semen (34.6%) than in urine (7.7%) and semen-harbored virus for longer periods of time than urine (22 months vs. 9 months). Thus, it appears that the main route of transmission of CMV among homosexual men involves exposure of anal mucosa to semen that contains CMV. Finally, it should be noted that infection with multiple strains of CMV has been documented in homosexual men, with and without HIV/AIDS.⁶⁵ Therefore, the presence of CMV IgG does not seem to confer immunity to reinfection in an individual engaging in high-risk sexual practices.

■ CONGENITAL AND NEONATAL INFECTION

Transmission of CMV from the mother to her fetus or newborn represents an important mechanism by which CMV is spread within a population. Infants who acquire CMV from a maternal source will typically shed CMV for months to years, thereby serving as a source of viral transmission to others. Contact with body fluids from infected children in day-care centers is a common means of transmission of CMV from child to child and from child to day-care workers as well as to the parents of children of other attendees.^{66–71} One pattern of transmission is for a first child to acquire CMV at day care and transmit the infection to his or her pregnant seronegative mother, resulting in a congenitally infected second child. Therefore, preventing infection of the newborn and infection in day-care centers could have a major impact on interrupting transmission of CMV in the general population.

CMV is transmitted from mother to child by three different routes: transplacental, intrapartum, and breast milk. Transplacental transmission can occur after primary maternal CMV infection during pregnancy, by reactivation of endogenous virus, or, less commonly by reinfection with a new strain of CMV.⁷² While the rate of primary maternal infection during pregnancy is only 0.7–4.1%, the risk of transmission to the fetus in this setting is considerably higher (20–40%) than when the mother is seropositive prior to conception (2.2%).^{73–75}

Intrapartum CMV transmission is directly related to local viral shedding during delivery. Close to 50% of infants born to the 2–28% of women who shed CMV from the vagina or cervix at the time of delivery will become infected.^{60,75}

Finally, transmission via breast milk depends on the presence of CMV in the breast milk and on the duration of nursing. CMV can be recovered from breast milk in 30–70% of seropositive women, depending on the method of detection and the frequency of sampling.^{76–79} Infants who nurse for less than 1 month are at low risk of becoming infected compared to those who nurse for a longer time.⁷⁶

■ TRANSMISSION VIA BLOOD PRODUCTS AND TRANSPLANTED ORGANS

First described among patients receiving transfusions during cardiopulmonary bypass for open heart surgery,^{80,81} CMV transmission can occur with transfusion of whole blood, red blood cells, and platelets. Transmission of CMV from seronegative donors occurs rarely and is likely due to inaccuracies with the CMV serology result or to the donor having been infected so recently that detectable antibodies have not yet been generated. Infection of an immunocompetent, seronegative recipient of blood products from a seropositive donor typically does not lead to clinical disease.⁸² The incidence of CMV transmission from seropositive donors to seronegative recipients is estimated to be about 1%, this risk

being directly proportional to the number of blood units transfused.^{83,84} Transfusion-transmitted CMV poses the greatest risk for morbidity and mortality among low-birth weight infants born to seronegative mothers and to seronegative HSCT or solid organ transplant (SOT) recipients.⁸² For example, between 28% and 57% of CMV seronegative HSCT recipients of unselected, unmanipulated blood products will seroconvert and a significant proportion of these individuals will develop CMV disease in the absence of prophylactic or preemptive therapy.⁸⁵

The leukocyte is believed to be the primary vehicle of CMV transmission.^{86,87} Two methods for reducing the risk of CMV transmission include the use of blood products from CMV seronegative donors and leukocyte reduction of blood products by filtering. The use of CMV-seronegative screened blood products dramatically reduces the incidence of infection in high-risk populations, such as transplant recipients and infants born to CMV seronegative mothers.^{88–92} Leukocyte reduction has been shown to be as effective as the use of screened CMV-seronegative blood products in reducing the risk of CMV transmission.^{93–97} One caveat to this approach is that although the CMV infection rate is similar using CMV-seronegative products or leukodepletion, the incidence of invasive CMV disease with leukodepletion was found to be higher in one study.⁹³ The reason for this is unclear, and overall leukodepletion remains an effective and safe method for reducing the risk of CMV infection and disease resulting from transmission in blood products.

Transmission of CMV through a transplanted organ is a well-known occurrence after SOT. A CMV seronegative recipient of a kidney or liver from CMV seropositive donors has a 70–80% chance of developing primary infection.^{98–100} Using molecular typing methods, several studies have demonstrated that the CMV strain present in the recipient is identical to the strain from the donor.^{27,101} In part due to the immunosuppression associated with organ transplantation, CMV seropositive recipients of organs from seropositive donors can also experience reinfection despite the presence of natural immunity pretransplant.¹⁰²

CLINICAL MANIFESTATIONS

■ INFECTION IN IMMUNOCOMPETENT HOSTS

Symptomatic disease in otherwise healthy individuals is uncommon. Primary infection can result in a mononucleosis-like syndrome manifested by fever, lymphadenopathy, and peripheral blood lymphocytosis. While most cases of mononucleosis are due to infection with Epstein-Barr virus (EBV), CMV accounts for about 50% of EBV-negative cases.¹⁰³ Contrasting with EBV infection, pharyngitis and tonsillar exudates are less common in CMV mononucleosis.¹⁰³ Other

manifestations of symptomatic CMV infection include abnormal liver function tests, malaise, sweats, and jaundice.¹⁰⁴ Rare manifestations include colitis,^{105,106} pneumonitis,¹⁰³ hepatitis,^{107,108} Guillain-Barre Syndrome,^{109,110} meningoencephalitis,¹¹¹ myocarditis,^{112,113} and blood dyscrasias such as thrombocytopenia and hemolysis.^{114,115} The fact that CMV has endothelial cell tropism and has been linked to vasculopathy in cardiac transplant recipients has raised the possibility that CMV may be a factor in the development of atherosclerosis in the immunocompetent host.^{7–9} However, this hypothesis remains controversial.

■ CONGENITAL INFECTION

Approximately 1% of newborns in the United States are infected with CMV in utero.¹¹⁶ Of these, 7% will have symptomatic disease, or “cytomegalic inclusion disease.”¹¹⁷ It has been generally believed that fetal infection occurring from a previously immune mother is less severe than fetal infection occurring during primary maternal infection.^{118–120} However, reports documenting severe fetal disease in newborns born to seropositive mothers indicate that preexisting maternal natural immunity does not always protect the fetus from the disease.^{72,121–123} Manifestations of CMV inclusion disease include jaundice, hepatosplenomegaly, thrombocytopenia, and CNS involvement, such as microcephaly, chorioretinitis, hearing loss, and cerebral calcifications. In up to 20% of infants, cytomegalic inclusion disease is fatal. Among infants who do survive, many will have serious lifelong CNS sequelae, such as mental retardation, blindness due to optic atrophy, and sensorineural hearing loss. Most of the extra-CNS manifestations of inclusion disease resolve spontaneously.

Of the infants who are congenitally infected but do appear asymptomatic at birth, up to 15% will still manifest delayed sequelae such as mild developmental delay and hearing loss that may be bilateral and complete.^{124,125} The presence of CMV in the organ of Corti and in the neurons of the spiral ganglia as well as occasional CMV nuclear inclusions in cochlear cells point to CMV cytotoxicity as a plausible pathogenic mechanism for this syndrome.^{124,125}

CMV infection that occurs in the peri- or postnatal period differs significantly from congenital infection. Urinary titers of CMV in these infants are typically lower than that in congenitally infected infants, and the vast majority do not develop symptomatic disease.¹²⁶ Symptomatic infection, although rare in this setting, may resemble that of mononucleosis.¹²⁷ However, infants of CMV seronegative mothers who acquire CMV from blood transfusion from seropositive donors are at high risk for developing multisystem CMV infections with a high fatality rate.⁹² The use of CMV-seronegative blood products in this population dramatically reduced the morbidity and mortality associated with posttransfusion CMV.

■ INFECTION IN THE IMMUNOCOMPROMISED HOST

CMV disease is most commonly encountered in the immunocompromised host, particularly those who have undergone HSCT or SOT, or in those who have AIDS. While some manifestations of CMV disease are common to both the transplant population and the HIV-infected population, there are several significant differences in disease manifestations between these two groups (Table 25-1).

More than 90% of HIV-1-infected men are coinfecting with CMV.¹²⁸ Individuals with CD4⁺ counts less than 100 cells/mm³ are at the greatest risk for CMV disease, which in the majority of cases represents reactivation of latent virus. In the era prior to the routine use of HAART, CMV was the most common viral opportunistic infection in persons with AIDS.¹²⁹ Since the introduction of HAART in the 1990s, the incidence of CMV disease has fallen by more than 80%.¹³⁰ Retinitis was the most common form of CMV disease and typically occurred when CD4⁺ counts dropped below 50 cells/mm³.¹³¹ Less common manifestations of CMV disease in this population include polyradiculopathy characterized by ascending lower-extremity weakness, meningoencephalitis, esophageal ulcerations, colitis, and sclerosing cholangitis.

Several factors influence the development of CMV infection and disease after HSCT and SOT. Perhaps most important is the CMV serostatus of the donor and recipient. Primary infection in the seronegative SOT recipient is generally associated with higher rates of symptomatic infection and disseminated disease than reactivation of latent virus in a seropositive recipient, presumably due to the lack of any preexisting immunity in the seronegative recipient.^{132,133} The development of primary CMV infection has been noted in up to 79% of liver transplants and 58% of kidney or heart transplants in which the donor is seropositive and the recipient is seronegative.^{134,135} In the setting of HSCT, several studies have documented that CMV seropositivity of the recipient results in significantly increased overall posttransplant mortality compared to CMV seronegative recipients with a seronegative donor.¹³⁶ When the recipient is CMV seronegative, overall mortality is increased when the donor is seropositive compared to the situation where the donor is seronegative.¹³⁷ However, when the recipient is CMV seropositive, the effect of donor serostatus is uncertain. One large study failed to show an effect of donor serostatus on overall mortality,¹³⁸ while another showed increased mortality among unrelated transplants when the donor was CMV seronegative.¹³⁹ In this study, there was a trend toward a higher rate of death due to infectious complications among patients who received grafts from CMV seronegative donors ($P = 0.07$). This finding was hypothesized to be due to the potential protective effect of transferring CMV-specific immune cells in the seropositive graft.

Also critical to the development of CMV disease is the degree of immunosuppression. Among SOT recipients, the

Table 25-1. Common Manifestations of CMV Infection

Neonates
<ul style="list-style-type: none"> • Cytomegalic inclusion disease • Sensorineural hearing loss
Immunocompetent adults
<ul style="list-style-type: none"> • Mononucleosis-like syndrome
Solid organ transplant recipients
<ul style="list-style-type: none"> • Mononucleosis-like syndrome • Allograft rejection/dysfunction in the transplanted organ (hepatitis, pneumonitis, coronary stenosis/allograft vasculopathy, renal impairment) • Gastrointestinal disease (esophagitis, colitis)
Hematopoietic stem cell transplant recipients
<ul style="list-style-type: none"> • Pneumonitis • Gastroenteritis
HIV/AIDS
<ul style="list-style-type: none"> • Retinitis • Gastrointestinal (esophagitis, colitis, biliary tract disease) • Neurological (encephalitis, polyradiculopathy)

highest rates of CMV disease have been reported in lung and heart–lung recipients, and a higher rate of CMV disease is found in recipients of T-cell-depleted HSCT than in recipients of nondepleted stem cell product.^{140,141} Additionally, the transplant recipient is at particularly high risk of CMV reactivation during periods of potent immunosuppression that accompany graft rejection or graft-versus-host disease.

Almost any organ can be involved in CMV disease after SOT or bone marrow transplant. Manifestations of CMV disease common to both SOT and stem cell transplantation include pneumonitis, hepatitis, and colitis. Even in patients who do not develop any of these overt manifestations of CMV infection, seropositivity has been associated with an increased incidence of serious bacterial and fungal infections after bone marrow transplant.¹³⁷ These observations suggest that “indirect effects” of subclinical CMV infections may include immune suppression, a plausible hypothesis in light of the frequent reactivation in transplant recipients, and the large number of immune modulatory molecules expressed by CMV.

DIAGNOSIS

■ CULTURE

Growth of CMV in the diagnostic laboratory, usually in primary human fibroblast cells, takes several weeks and is laborious (Fig. 25-4A). The shell vial technique, in which monoclonal

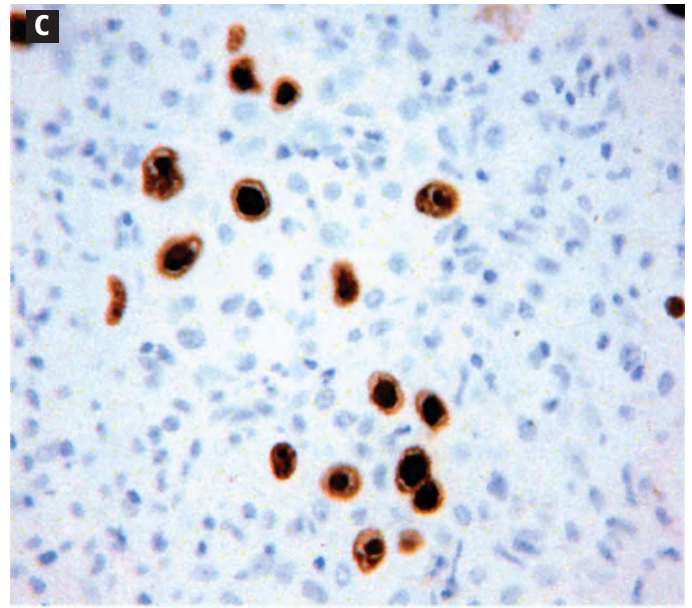
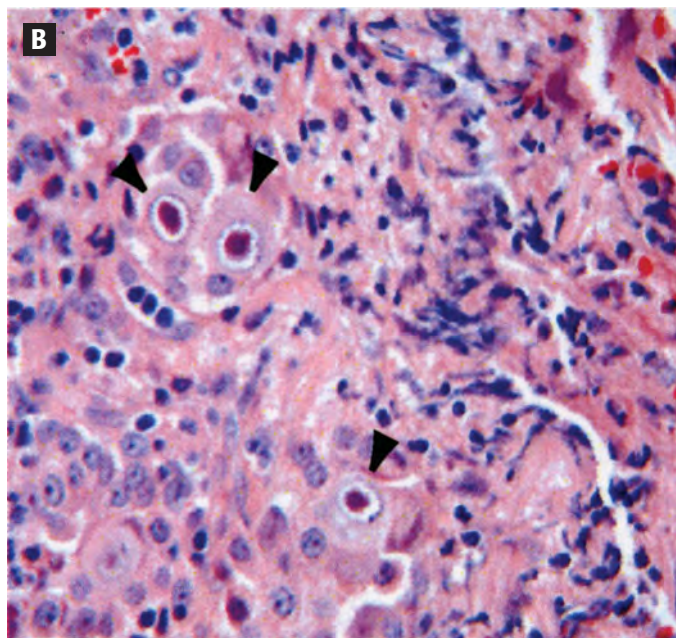
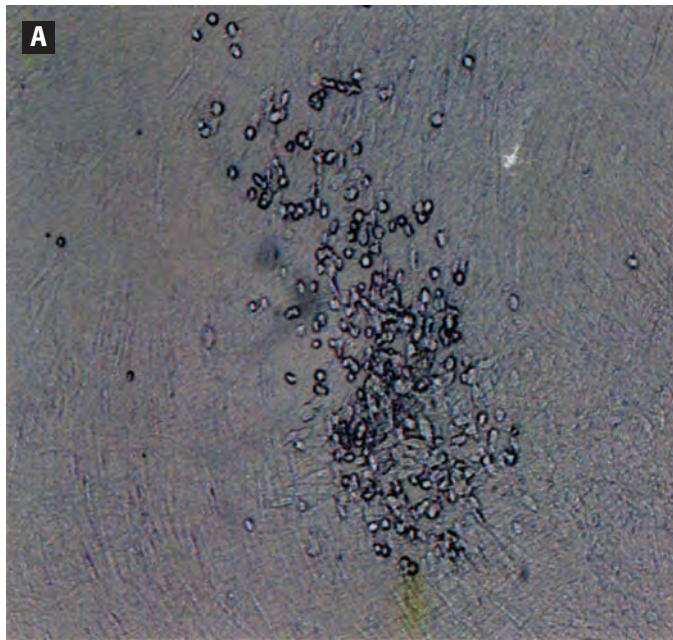


FIGURE 25-4. Cytopathology and histology of CMV infection. **A.** A CMV plaque appears by phase contrast microscopy as a cluster of rounded refractile cells surrounded by normal spindle-shaped fibroblasts 1 week after infection (10 \times). **B.** Hematoxylin and eosin (H&E) staining of a lung biopsy from a CMV-infected AIDS patient shows inflammatory infiltrates. Several cells display the characteristic “owls eyes” nuclear inclusions (arrowheads, 40 \times). **C.** Immunohistochemistry of the same lung biopsy shows many infected cells detected using a mixture of monoclonal antibodies directed against the IE1 and ppUL44 proteins (40 \times). (B and C were provided by Julie Randolph-Habecker and Robert Hackman, Fred Hutchinson Cancer Research Center.)

antibodies are used to detect CMV immediate-early proteins in cultured cells, can be performed within 18–24 hours after inoculation and is now widely used for rapid diagnosis of CMV in samples such as bronchoalveolar lavage (BAL) fluid.

■ ANTIGEN DETECTION

The detection of the CMV pp65 tegument protein in peripheral blood leukocytes using a monoclonal antibody offers a rapid, sensitive, and specific method of diagnosing CMV viremia. In this assay, peripheral leukocytes are spread on a glass slide and stained with a fluorescent antibody directed against pp65. The number of positive cells provides a rough estimate of the circulating viral load. When used in the

transplant setting, a positive CMV pp65 assay has been shown to predict the development of invasive disease. False negatives can occur in up to 10% of cases of CMV pneumonia and colitis. Additionally, since the assay relies on the detection of pp65 in circulating leukocytes, it is not reliable in patients with profound leukopenia. The predictive value of this assay has not been validated when performed on other clinical samples such as BAL fluid.

■ POLYMERASE CHAIN REACTION

The polymerase chain reaction (PCR) relies on the amplification of CMV DNA from blood or other tissue specimens. While the assay characteristics vary from center to center, this

method is the most sensitive method for detecting CMV, and it maintains a good degree of specificity. In addition, it is rapid, with results usually available within 24 hours, and can provide a quantitative measurement of CMV viral load in a sample. PCR has been shown to be an accurate predictor of CMV disease in transplantation, HIV, and fetal infection.¹⁴²

■ HISTOPATHOLOGY

The detection of CMV by shell vial, pp65 antigen, or PCR does not necessarily confirm CMV as the causative agent of a disease process. Thus, histopathology of biopsy samples is an important tool for diagnosing CMV invasive disease in situations where the diagnosis is otherwise unclear (Fig. 25-4). The presence of characteristic CMV “owl’s eye” nuclear inclusions in, for example, a tissue biopsy specimen strongly implicates CMV as an etiologic factor. The sensitivity of this approach can be enhanced by the use of immunohistochemical techniques to identify CMV antigens even when classic inclusions may not be evident.

TREATMENT AND PREVENTION

■ ANTIVIRAL AGENTS

Ganciclovir is a nucleoside analogue of guanosine that acts as a competitive inhibitor of deoxyguanosine triphosphate incorporation into viral DNA. A CMV gene, *UL97*, encodes a phosphotransferase that converts ganciclovir to ganciclovir monophosphate. Cellular enzymes then convert the monophosphate to the triphosphate form. The major toxicity of ganciclovir is myelosuppression, with neutropenia occurring in up to 16% of all patients receiving ganciclovir, and 30% of HSCT recipients.¹⁴³ Neutropenia often responds to dose reduction, and sometimes support with granulocyte-colony stimulating factor is required. Less common side effects include confusion, dizziness, headaches, nausea, vomiting, and diarrhea. Resistance to ganciclovir can arise as a result of mutations in the *UL97* gene or less commonly in the DNA polymerase (*UL54*) gene.

Valganciclovir is the valine ester of ganciclovir. After oral administration, valganciclovir is quickly absorbed and hydrolyzed to ganciclovir by intestinal and hepatic cells. The advantage of valganciclovir is that it has much greater bioavailability compared to oral ganciclovir (almost 70% compared to 6–8%), and pharmacokinetic studies have demonstrated that a daily 900-mg oral dose of valganciclovir results in blood levels equivalent to 5 mg/kg of intravenous ganciclovir.¹⁴⁴ Based on controlled trials,^{145,146} valganciclovir has been approved for induction and maintenance therapy of CMV retinitis in people with AIDS, and for the prevention of CMV disease in adult recipients of heart, kidney, and kidney-pancreas transplants. Side effects of valganciclovir are

similar to those of intravenous ganciclovir, namely leukopenia, neutropenia, diarrhea, fever, among others.¹⁴⁷

Foscarnet is a pyrophosphate analogue that binds directly to, and competitively inhibits, the CMV DNA polymerase. Unlike ganciclovir, foscarnet activity is not dependent on phosphorylation by the *UL97* gene product; thus, CMV that has acquired ganciclovir resistance due to *UL97* mutations will still be susceptible to foscarnet. Foscarnet has been used successfully for the treatment of most manifestations of CMV disease. Foscarnet has been shown to be equivalent to ganciclovir for the treatment of CMV retinitis and gastrointestinal disease in AIDS patients.^{148,149} Resistance to foscarnet can occur and is due to mutations in the CMV DNA polymerase (*UL54*) gene. Renal failure, hypocalcemia, hypomagnesemia, and hypophosphatemia are all common and potentially life-threatening consequences of foscarnet therapy. Thus, close monitoring of the patient on foscarnet is required.

Cidofovir is a cytosine nucleotide analogue that does not require phosphorylation by viral enzymes for antiviral activity. Cellular enzymes convert cidofovir to cidofovir triphosphate, which then inhibits the CMV DNA polymerase. Since cidofovir is not phosphorylated by the CMV *UL97* gene product, it is active against ganciclovir-resistant *UL97* mutants. However, some mutations in the DNA polymerase gene confer resistance to both ganciclovir and cidofovir.¹⁵⁰ The long half-life of cidofovir allows a once-per-week dosing schedule. The major toxicity with cidofovir is renal—uptake of the drug by the proximal renal tubular cells results in degeneration and necrosis of these cells. Since this effect is often irreversible and can lead to serious morbidity, cidofovir should be coadministered with probenecid, which reduces the uptake of cidofovir by renal tubular cells.

There is limited evidence for a role of high-titer CMV-immune globulin (Cytogam) in treating or preventing CMV infections.⁴⁷ In one trial, the combination of CMV-immune globulin and ganciclovir did reduce mortality in marrow transplant recipients with CMV pneumonitis compared to historical controls.¹⁵¹ Whether high titer immune globulin is superior to standard intravenous immunoglobulin (IVIG) for this indication is not known.

Fomivirsen is an antisense RNA compound that inhibits CMV replication by hybridizing with the CMV immediate early 2 (IE2) mRNA and consequently blocking its translation. Although approved for the treatment of CMV retinitis in patients with AIDS, it is not commonly used because of the availability of implantable ganciclovir and oral valganciclovir.

■ TREATMENT OF THE NEWBORN

Due to the potential long-term effects of congenital CMV infection, there has been considerable interest in determining whether treatment of CMV has a role in this setting.¹⁵² Intravenous ganciclovir, when administered to infants with

symptomatic CMV disease within 1 month of birth, was shown to reduce CMV viral load and possibly has a beneficial impact on auditory abilities in one study that was not placebo-controlled.¹⁵³ More recently, the effect of ganciclovir was evaluated in infants born with CMV CNS disease in a randomized trial.¹⁵⁴ Intravenous ganciclovir (6 mg/kg every 12 hours for 6 weeks) or no treatment was given to infants less than 1 month old who were born with symptomatic CMV CNS disease. Significantly fewer ganciclovir recipients had hearing deterioration at 6 months and 1 year compared to control patients. Additionally, ganciclovir recipients gained more weight and had a larger increase in head circumference during the first 6 months than did control patients. As significantly more episodes of neutropenia occurred in the treatment arm, and as ganciclovir is known to have both gonadal toxicity and carcinogenicity in animal models,¹⁴⁷ the decision to treat symptomatic infants requires balancing the potential benefits and risks. Ganciclovir is teratogenic¹⁴⁷ and thus should not be used during pregnancy. Current options for women who acquire primary or symptomatic secondary infection during pregnancy are limited.

■ PREVENTION

Several interventions can help prevent CMV infection in specific settings. CMV titers are high in semen and in cervical and vaginal secretions, suggesting that condoms are likely to prevent transmission between sexual partners. Indeed, condoms are effective barriers to CMV transmission in experimental systems.¹⁵⁵

As described above, serological screening or leukoreduction of blood products can reduce the incidence of transfusion-related CMV transmission. In the setting of SOT or HSCT, the selection of grafts from a seronegative donor when the recipient is also seronegative is beneficial. However, the shortage of solid organs and the difficulties in finding appropriated donors for HSCT often preclude this option. Thus, several interventions have been adopted to prevent CMV infection and disease in these settings. After HSCT, prophylactic and preemptive antiviral therapy strategies have been shown to effectively reduce the incidence of CMV disease posttransplant.⁴¹ In the realm of SOT, many centers use prophylaxis for high-risk transplants (D+/R-) and will use preemptive antiviral therapy in the D+/R+, D-/R-, and D-/R+ transplants.¹⁵⁶

The Institute of Medicine of the National Academy of Sciences recently placed CMV in its “highest priority” category for vaccine development.¹⁵⁷ A primary target population for such a vaccine would be young adults, especially seronegative women prior to childbearing age, in whom a vaccine would have the potential to reduce the risk of congenital CMV disease. A safe and effective vaccine could be used in other groups including seronegative day-care workers and

seronegative patients prior to transplantation. Several vaccine candidates have been tested in phase I studies or are under development including live, attenuated viruses based on the CMV (Towne strain), canarypox vectors expressing gB or pp65, soluble recombinant gB, and various DNA vaccines.¹⁵⁸ Earlier studies with the CMV (Towne) vaccine demonstrated partial protection of seronegative women exposed to seropositive infants and reduced severity of disease in seronegative recipients of kidneys from seropositive donors.^{159,160} Given that CMV persists even in the presence of an immune response and prior infection does not prevent reinfection with a new strain, development of an effective CMV vaccine will be a challenging goal.

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John W. Sixbey

DEFINITION

Herpesviruses are classified according to biologic characteristics into three subfamilies: the *alpha*-, *beta*-, and *gammaherpesvirinae* (see Chapter 23). The gamma herpesvirus subfamily, distinguished on the basis of establishing latent infection in lymphocytes, contains both the *Lymphocryptovirus* and *Rhadinovirus* genera defined by similarities in genome structure, gene organization, and relatedness of major viral proteins. These gamma herpesvirus genera include two members that infect humans and are implicated in oncogenesis. One of these, the Epstein-Barr virus (EBV, also called *human herpesvirus 4*) is the prototype *Lymphocryptovirus*. Kaposi's sarcoma associated herpesvirus (KSHV, or *human herpesvirus 8*) is a member of genus *Rhadinovirus*. In this chapter we emphasize select aspects of EBV biology as they may relate to sexual transmission and to clinical manifestations in the context of the general immunosuppression that accompanies HIV infections (for more general reviews, see refs. 1 and 2).^{1,2}

HISTORY

Denis Burkitt, a medical missionary to East Africa in the 1950s, first postulated an infectious agent as the cause for a common childhood tumor (Burkitt's lymphoma) based on the epidemiologic characteristics of this disease in equatorial Africa.³ Using lymphoma samples provided by Burkitt, Tony Epstein and his student, Yvonne Barr, established the first permanent human lymphocytic cell lines⁴ and by electron microscopy discovered a new herpesvirus with distinct antigenic and biologic characteristics.⁵⁻⁷ Paramount among these was the ability of this virus to confer unlimited growth potential to B lymphocytes in vitro.^{8,9} Seroepidemiologic studies by Werner and Gertrude Henle indicated that like other herpesviruses, EBV infection was widespread,^{10,11} providing an apparent incongruity of ubiquitous asymptomatic carriage of this first candidate human tumor virus. Global distribution and high seroprevalence suggested that the virus

might play a role in a very common disorder as well, and the fortuitous seroconversion of a technician in the Henle laboratory during the course of infectious mononucleosis led to the identification of EBV as the causal agent of this much studied lymphoproliferative syndrome.¹² Subsequent nucleic acid hybridization analyses have implicated EBV as an etiologic agent in nasopharyngeal carcinoma,^{13,14} Hodgkin's disease,¹⁵⁻¹⁷ unusual T cell lymphomas,^{18,19} and polyclonal B-lymphoproliferative disorders.^{20,21} Although historically much of EBV research has been focused on the oncogenicity of EBV latency proteins expressed in human tumors, strikingly little is understood regarding the natural history of EBV infection. A reexamination of events surrounding viral acquisition and shedding at mucosal sites draws attention to relatively new and unexplored areas of EBV biology: the pathologic contribution from EBV replication, reinfection consequent to second exposures or reactivation of endogenous virus, and genetic recombination of coinfecting EBV genomes.

EPIDEMIOLOGY

Antibody to EBV can be detected in 90–95% of the population by adulthood.¹⁰ Primary exposure often occurs in the first years of life, with seroconversion evident before the age of 5 years in 50% of children studied in the United States and Great Britain.^{22,23} In economically advantaged communities, primary infection may be delayed until adolescence or early adulthood,²⁴ at which time acquisition of virus produces the clinical syndrome acute infectious mononucleosis.

■ VIRAL SHEDDING AND TRANSMISSION

Oropharyngeal sites

After initial exposure, EBV establishes a latent infection that persists for the life of the host. The lifelong virus carrier state is accompanied by asymptomatic viral shedding that provides a readily available source of infectious virus for person-to-person

spread. Suspicion that infectious mononucleosis was related to an orally transmitted pathogen (hence the expression “kissing disease”²⁵) was confirmed by the demonstration of cell-free virus in throat washings and saliva of infectious mononucleosis patients.^{26,27} That intimate contact is required for transmission of virus was verified by epidemiologic studies wherein susceptible roommates of college students with acute infectious mononucleosis were shown to be at no greater risk for EBV seroconversion than the uninfected student population at large.^{28,29} In young children, the route may be more indirect, associated with smaller virus inoculums and inapparent symptomatology. After recovery from acute infectious mononucleosis, EBV can be detected readily in the oropharynx for at least 18 months.³⁰ In healthy seropositive adults followed prospectively over 15 months, 90% shed EBV at some point, as detected by the standard lymphocyte transformation assay, with 25% shedding virus on every testing occasion.³¹ Immunocompromised patients have still higher rates of viral shedding,³² and increased levels of EBV excretion into oropharyngeal secretions are characteristic of individuals infected by HIV-1.^{33,34}

Genital tract

Identification of EBV at oropharyngeal sites,^{26,27,30} together with the experimental infection of mucosal epithelium derived from normal human cervix,³⁵ raised the possibility of broader mucosal involvement including the genital tract. In fact, infectious EBV can be recovered from genital mucosa of women with acute infectious mononucleosis,³⁶ suggesting that virus is either conveyed from the oropharynx to distant mucosal sites by trafficking EBV-infected lymphocytes or that infection has been initiated by introduction of exogenous virus at that anatomic site. Transmissibility of genital virus is suggested by the successful isolation in the lymphocyte transformation assay of EBV from filtrates of cervical washings³⁶ as well as from vulvar ulcerative lesions.³⁷ Analogous to the persistent shedding of virus from oropharyngeal sites, EBV can also be recovered from the cervix of women without serologic evidence for recent EBV infection.³⁶ Indeed, the prevalence of EBV DNA in cervical samples from women attending sexually transmitted disease (STD) clinics ranges from 28% to 40% by polymerase chain reaction (PCR) analyses.^{38–40} A possible etiologic role for EBV in subclinical genital lesions was indicated by a study of koilocytotic lesions of the vulva in which EBV DNA was detected in almost half of vulvar biopsies at sites of acetowhite lesions after application of 3% acetic acid.⁴¹ In contrast, 11% of cell samples from normal vulvar mucosa contained EBV DNA.

In healthy, sexually active uncircumcised men, EBV DNA was detected by PCR in cells scraped from the coronal sulcus of the glans penis in 13% of study participants.⁴⁰ Forty-eight percent of EBV-seropositive men with urethral discharges

secondary to gonococcal infection had EBV DNA detected in their genital tract secretions,⁴² representing either lymphocyte-associated virus within the cellular inflammatory infiltrate or cell-free infectious virus. Although the transmissibility of cell-associated virus by the genital route remains to be determined, infection via transfer of latently infected cells has been shown to occur in other contexts. For example, the introduction of EBV-infected cells by blood transfusion^{43–45} or tissue transplantation^{46,47} causes both asymptomatic seroconversion and clinical disease.

Few studies to date have directly addressed sexual transmission of EBV or the possibility of acquiring classic infectious mononucleosis after genital tract infection. Sexual behavior was found to contribute to asymptomatic acquisition of EBV in a longitudinal study of 45 seronegative women 15–19 years of age, 22 of whom seroconverted within 5 years of study enrollment.⁴⁸ Risk of seroconversion increased with number of sexual partners and was greatest after acquisition of a new sexual partner, although rarely contemporaneous with the first exposure. In one instance, EBV DNA was detected in a cervical cytologic sample at the visit immediately preceding detection of serum antibodies; in 5 others, viral DNA was detected simultaneously with seroconversion. Cervical samples from women who seroconverted were EBV DNA positive on as many as seven occasions over greater than a 3-year interval, with four women still positive at the end of follow-up.⁴⁸ The continued presence of virus over prolonged sampling periods, together with a high EBV DNA copy number in cervical samples,^{48,49} makes sexual transmission of EBV highly probable. Similarly, a highly significant correlation between seropositivity for EBV, sexual intercourse, and an increasing number of sexual partners was found in a cross-sectional analysis of 1006 new University students.⁵⁰ In this study, two-thirds of infectious mononucleosis cases were statistically attributable to sexual intercourse, whereas only a tenth of asymptomatic primary infections were linked to sexual activity.

EBV GENOTYPES AND COINFECTION

Despite obvious epidemiologic implications of a genital distribution of EBV, direct sexual transmission has not been unequivocally shown. What may ultimately allow osculatory versus venereal routes of transmission to be distinguished are EBV genotypic markers used for tracking discordant strains of virus within individual subjects. Both primary infection and carrier states are now known to be more complex than previously thought, with both tissue compartmentalization and cyclic exchange of multiple EBV genotypes occurring at distinct anatomic sites within an infected host.^{51–53}

EBV isolates can be categorized broadly into two types now called *EBV-1* and *EBV-2* (formerly types A and B). Each is distinguished on the basis of polymorphisms in the genes

that encode the EBV nuclear antigens (EBNAs), specifically EBNA2, 3A, 3B, and 3C.^{54–56} EBNA2 differs more extensively between genotypes than the other EBNA proteins^{55,56} and is primarily responsible for the biologic differences between type 1 and type 2. Specifically, type 1 strains transform primary B lymphocytes *in vitro* with greater efficiency than type 2 EBV, resulting in a cell growth phenotype readily maintained in culture.^{57,58} Such polymorphisms in the EBNA genes generate immunologic responses that are both type-specific and cross-reactive. Although antibodies to EBNA2 and 3A are partially cross-reactive between types, the antibody responses to EBNA3B and 3C are largely type-specific.^{59,60} Similarly, both type-specific and cross-reactive cytotoxic T cell responses can be detected.^{61–63}

Once thought to be restricted in its geographic distribution,⁶⁴ EBV-2 (like EBV-1) circulates widely in all human populations.^{38,65,66} Coinfection with both EBV-1 and EBV-2 has been reported in from 9% to 27% of immunocompetent adults,^{38,65} suggesting either the simultaneous acquisition of both types during primary infection or reinfection on a second exposure. Although it has been long assumed that persistent carriage of EBV by a healthy host precludes second infections,⁶⁶ the independent acquisition of a second virus is suggested by a study of EBV genotypes in throat and genital washings of women at an STD clinic.³⁸ Not only were coinfections more common in the STD study population, perhaps reflecting multiple exposures, but disparate EBV types were found in the oropharynx versus genital tract of a single participant. Such anatomic segregation of types is consistent with two separate introductions of virus into the same host. Unlike the case with herpes simplex 1 and 2, neither EBV genotype showed a predisposition toward one specific anatomic location.

Coinfection with type 1 and type 2 EBV is especially apparent in immunocompromised patients^{38,67–69} such as recipients of bone marrow or organ transplants and HIV-1-infected individuals. The increased load of endogenous virus that accompanies immune suppression facilitates detection of the spectrum of resident virus in this clinic population. Moreover, immune impairment itself may render this group more susceptible to repeated infection from new viral exposures, whether in the form of administered blood products or multiple sexual partners. A high prevalence of EBV-2 in homosexual men has been suggested to indicate sexual transmission of that genotype.⁷⁰

In addition to the type 1 and type 2 classification of EBV, individual strains within the two major types can be distinguished by changes in EBNA1, BZLF1, and LMP1 gene sequences of EBV. EBNA-encoding genes contain repeat regions, the number of which varies between individual isolates. Such variability is visible on DNA blots as restriction fragment length polymorphisms or as size differences in EBNA proteins on immunoblots.^{71,72} Unlike with type

differences, however, presence of multiple strains does not necessarily reflect repeated infection, because intratypic diversity may also be generated within an individual by heterologous recombination between repeat sequences during replication of endogenous virus. Diversity in LMP1 coding sequences has provided consistent sequence variations that have been particularly useful for defining phylogenetically distinct strains of EBV.^{73,74} Strain-specific markers have been used to document multiple infections within a host, to track exchange of virus strains between tissue compartments and to monitor spread of EBV infection between patient and contact.^{51–53,71,75,76}

IMMUNOLOGY AND PATHOGENESIS

An elusive aspect of EBV biology is how a ubiquitous and persistent pathogen that normally achieves a natural rapport with its host may on occasion be highly pathogenic years after primary infection. Emerging possibilities that more fully acknowledge EBV opportunism in the context of the life-long carrier state include *de novo* infection of neoplastic tissue newly prone to infection by virus endogenous to the host as well as generation of viral recombinants that may have altered pathogenicity and tissue tropisms. New clinical settings characterized by enhanced viral exposure and immunosuppression,⁷⁷ when viewed against the traditional EBV diseases Burkitt's lymphoma and nasopharyngeal carcinoma, are informative with regard to EBV pathophysiology.

■ MUCOSAL DETERMINANTS OF EBV TROPISM

Consideration of EBV as a sexually transmitted agent highlights interactions between virus and cells at mucosal surfaces, where the major disease manifestations of the virus occur. In fact, it is only by viewing infection within the context of epithelial and lymphoid tissue interrelationships that a unified view of EBV pathogenesis emerges. The possibility of a regular exchange of virus between epithelium and circulating lymphocytes first became evident in studies of primary EBV infection, where the detection of EBV DNA and RNA in desquamated epithelial cells from throat and cervical washings indicated epithelial cell foci of EBV replication.^{36,78,79} Viral recombinants generated in oropharyngeal epithelium can be subsequently recovered in peripheral lymphocytes.⁸⁰ Despite the proclivity of EBV to remain latent in lymphocytes *in vitro*, virus transfer between cell types is almost certainly bidirectional. Initiation of virus replication is thought to occur in latently infected, circulating memory B cells concurrent with their differentiation into plasma cells.^{81,82} Mucosal seeding by trafficking lymphocytes has been demonstrated convincingly in an organ transplant recipient who developed oropharyngeal shedding of virus strains acquired from transfused blood.⁴⁵ The notion of the intercellular exchange of virus as a natural component of EBV's life

cycle is reinforced by findings of persistent replication in healthy oral epithelium of chronic carriers,^{83–85} marking it as one site of EBV egress and host-to-host spread, if not a source for reinfection of lymphocytes within the persistently infected host.

Alternate replication in B lymphocytes and epithelial cells switches tropism of the virus in a manner that has implications for spread both within and between hosts, virus originating in epithelial cells more efficiently infecting B cells and vice versa.⁸⁶ Preferential infection of B lymphocytes occurs via an interaction of the major viral glycoprotein gp350 with the cellular attachment receptor, the complement receptor type 2 (CR2 or CD21),⁸⁷ and of a trimeric EBV glycoprotein complex of gH, gL, and gp42 with the entry coreceptor, HLA class II.⁸⁶ Epithelial cells lacking CR2 and HLA class II are infected by as yet poorly understood mechanisms requiring glycoprotein complexes without gp42. Although both two-part and three-part complexes are normally found on the virus envelope, their ratio is skewed toward a gH/gL predominance after EBV replication in B cells, where newly synthesized gp42 interacts intracellularly with coreceptor HLA class II to deplete its representation on the viral envelope.⁸⁶

Cell-to-cell spread of virus in immune hosts may also be influenced by the presence of secretory antibody at mucosal surfaces. EBV-specific dimeric IgA facilitates uptake of EBV into epithelial cells via the basolateral polymeric immunoglobulin receptor while concurrently neutralizing infection of B lymphocytes by competing for the viral ligand of CR2.^{88,89} Entry into polarized epithelium is likely to be achieved by multiple and as yet incompletely understood routes, including interactions between viral BMRF2 and cellular integrins.^{90,91}

■ EPITHELIAL CELL-DERIVED RECOMBINANT EBV

Although lymphocyte culture has provided suitable models for study of EBV latency and virus-induced lymphoproliferation, systems permissive of EBV replication have not been available to address biologic issues raised by viral shedding at mucosal surfaces. EBV infection in AIDS patients has been particularly instructive by providing the opportunity to observe replicative EBV infection in the epithelial setting.⁷⁷ (Fig. 26-1A) shows a cross section through the epithelial lesion oral hairy leukoplakia, with abundant viral replication in the outer, more differentiated layers of epithelium. Unlike permissive epithelial cell infections with other herpesviruses, replication of EBV within this lesion is noncytolytic, possibly a consequence of the concurrent expression of both replicative and transforming EBV proteins within the cell.^{92,93} Viral gene products that extend cell survival include lytic cycle BHRF1, a homologue of Bcl-2 that is expressed at high levels in oral hairy leukoplakia, and latency gene LMP1 that can induce expression of the antiapoptotic cellular gene A20.^{94,95}

Expression of latency gene EBNA2 may contribute to yet a second distinguishing attribute of this lesion, coinfection with type 1 and type 2 EBV, and generation of intertypic and intratypic recombinants.^{68,80,96–101} By upregulating expression of attachment receptor CR2 on infected epithelial cells, EBNA2 may facilitate superinfection by multiple EBV genotypes in this replicative environment.¹⁰² Recent detection of type 1 and type 2 recombinants^{100,101,103} confirms not only coinfection of the human host with separate genotypes but also superinfection of a single cell by two distinct and replicating viruses. Moreover, now there is unequivocal evidence that epithelium-derived EBV recombinants can disseminate via lymphocytes,^{76,80,104} demonstrating not only their infectivity but also a role for epithelium in viral seeding of peripheral blood lymphocytes.

The larger issue is to what extent EBV biology in oral hairy leukoplakia reflects events in healthy virus carriers. EBV coinfection and recombination have also been described in the general population.^{38,65,80,96,101,103,105} More importantly, both intertypic recombinants and nontransforming variants of EBV generated by intratypic recombination appear to be transmissible between healthy hosts independent of the parental virus genotypes.^{96,103} Although the pathophysiologic significance of recombinant strains remains unclear, such genomic variability at mucosal sites may generate novel viral determinants capable of disturbing the usual virus-host balance in healthy carriers. For example, nontransforming virus has been implicated in a rare form of chronic active EBV infection in an 8-year-old child.¹⁰⁵ EBNA2-deleted variants, impaired in their ability to transform B lymphocytes in vitro, have been postulated to contribute to the genesis of a subset of Burkitt's lymphomas.^{96,106} Defective, rearranged EBV genomes identified in hairy leukoplakia⁹⁷ have the potential of enhancing replication of standard latent EBV genomes,¹⁰⁷ thereby inducing the exuberant viral replication characteristic of oral hairy leukoplakia. Furthermore, such defective genomes have been detected, in the absence of prototypical virus, in sporadic Burkitt's lymphoma and Hodgkin's lymphoma.^{108,109}

■ CELL-MEDIATED IMMUNE CONTROL IN CHRONIC EBV CARRIERS

The overall size of the EBV-infected B cell reservoir is largely controlled by CD8⁺, HLA class I-restricted, EBV-specific cytotoxic T lymphocytes (CTLs). Up to 5% of the total circulating CD8⁺ T cell pool may be committed to this single virus in the EBV-carrier state,¹¹⁰ indicating the critical role for T-cell surveillance in maintaining the host: virus balance. Impaired CTL responses in immunosuppressed patients such as transplant recipients or HIV-1-infected individuals^{32,111} leads to an expansion of the infected B cell population and potentially fatal lymphoproliferative disease. The contribution of virus-specific CTLs in immune regulation of EBV-induced

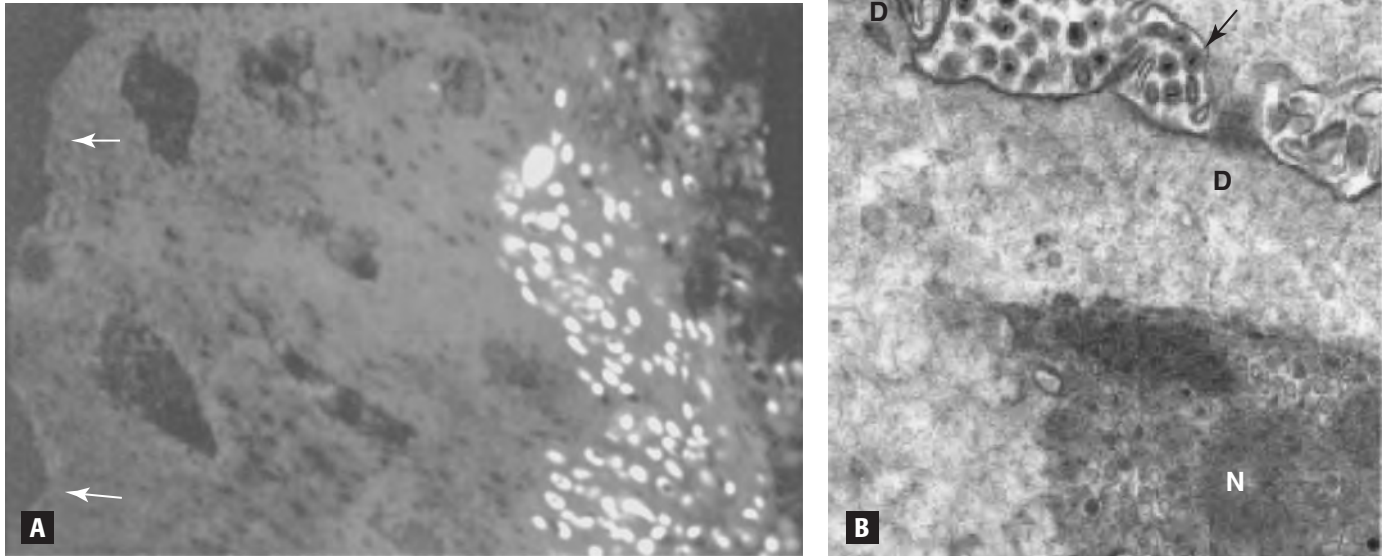


FIGURE 26-1. EBV replication in oral hairy leukoplakia of AIDS. **A.** A cross section of the mucosal lesion immunostained for EBV immediate-early antigen BZLF1 demonstrates replication in the upper layers of thickened epithelium. Arrows indicate the basal epithelial layer. **B.** Electron micrograph of interepithelial space showing abundant mature EBV virions (*arrow*). Nucleus (*N*) contains immature virus particles (*D*, desmosomes).

lymphoproliferation has been made clear by recent therapeutic interventions involving adoptive transfer of virus-specific T lymphocytes to restore immunity against EBV infection in bone marrow transplant recipients.^{112–114}

Of the nine EBV proteins expressed during latent infection in cultured lymphoblastoid cell lines, only a subset (EBNA3A, 3B, and 3C) provides what appear to be dominant CTL targets (with some responses also seen to EBNA1, EBNA2, EBNA-LP, LMP1, and LMP2).^{115,116} Apart from deficient CTL activity, downregulation of latent gene expression *in vivo* may also facilitate the escape of infected cells from immune destruction. Three patterns of latent gene expression (latency I, II, and III) first observed in cultured cells¹¹⁷ have parallels in EBV-associated tumors. In Burkitt's lymphoma (latency I), for example, only a single viral antigen is expressed, reducing tumor susceptibility to EBV-specific CTL surveillance.¹¹⁸ In contrast, immunoblastic B cell lymphomas (latency III) typical of immunocompromised patients express the full spectrum of EBV latent proteins and remain sensitive to CTL control if intact.

CLINICAL MANIFESTATIONS

INFECTIOUS MONONUCLEOSIS

Primary EBV infection in infancy or early childhood is usually subclinical, but when delayed until the second decade of life, it manifests as infectious mononucleosis in up to 50% of

patients. A self-limiting lymphoproliferative disease, the syndrome consists of fever, headache, pharyngitis, lymphadenopathy, and general malaise. Resolution of symptoms may take weeks to months, but primary infection is always followed by the establishment of a permanent viral carrier state. Diagnostic features of acute infection include the appearance of heterophile antibodies and a prominent atypical lymphocytosis, reflecting the unusually strong T-cell response elicited by virally infected B cells. Predominantly CD8+, the reactive T cells comprise both nonspecific and HLA-restricted EBV-specific cytotoxic T cells reactive to both EBV lytic and latent cycle antigens.¹¹⁰ The exaggerated nature of the T cell response suggests that the syndrome is largely immunopathologic in nature. The greater frequency of symptomatic infection in adolescence may relate not to age but rather to a larger inoculum of transmitted virus and the ensuing T cell reaction.

AIDS-RELATED MANIFESTATIONS OF EBV INFECTION

HIV-related immunosuppression disrupts the usual homeostasis achieved between EBV and host, increasing the risk for both reactivation of latent EBV and acquisition of coinfecting strains. Reduced immune control results in elevated levels of EBV in the oropharynx as well as blood of HIV-infected patients,^{33,34} similar to what has been described in transplant recipients.^{32,113} There is some evidence to suggest that episodes of EBV reactivation may have clinical consequences. Most EBV malignancies in the population at large

are preceded by antibody responses indicative of an enhanced level of viral activity^{119–121}; deregulation of the virus-host balance may favor emergence of a malignant cell clone. Medical consequences of the high EBV burden in AIDS are reflected in unique pathology as well as in the increased frequency of otherwise rare EBV diseases.

Oral hairy leukoplakia

Oral hairy leukoplakia is a hyperplastic EBV-induced mucocutaneous epithelial cell disease and the first pathologic manifestation attributable to replicative EBV infection,⁷⁷ making the lesion unique in EBV biology. It is seen in up to 25% of homosexual men with AIDS but has been reported as well in other immunocompromised patients and, rarely, healthy individuals.^{77,80} Clinically, the lesion is an asymptomatic, poorly demarcated keratotic area with a corrugated or “hairy” surface varying in size from a few millimeters to extensive lingual and oral mucosal involvement. Typically on the lateral borders of the tongue, the whitish, slightly raised lesion is often mistaken for thrush. Histopathologic features include a thickening of epithelium, with characteristic balloon cells resembling koilocytes, and a hyperkeratosis resulting in microscopic hairlike projections. An abundance of viral particles can be seen in the outer layers of epithelium (Fig. 26-1 B), consistent with the notion that EBV replication is linked to terminal differentiation of cells.^{35,78} Epithelial dysplasia is not a feature of these lesions, and malignant transformation of oral hairy leukoplakia has not been reported.

EBV-associated malignancies in AIDS

Non-Hodgkin’s lymphoma, an AIDS-defining cancer some 60 times more common in AIDS patients than in the general population,¹²² can be divided morphologically into Burkitt-like and immunoblastic lymphomas (see Chapter 76). Both have a higher association with EBV (30–40% and 75–80%, respectively) in AIDS than in non-AIDS groups.^{123,124} Tumors may carry either type 1 or type 2 virus,^{125–127} reflecting the relative prevalence of each genotype within the HIV-infected population. Burkitt’s lymphomas appear early in the course of AIDS, prior to profound immunosuppression, whereas immunoblastic lymphomas typically occur in late-stage AIDS when cellular immunity is compromised. The timing of immunoblastic lymphomas may be explained by their expression of latent viral proteins (type III pattern of EBV latency)¹²⁸ that in an immunocompetent host provide ample targets for EBV-specific cytotoxic T cells. Appearance of the malignancy coincidental with diminished immune surveillance suggests an opportunistic proliferation similar to post-transplant lymphoproliferative disease. A relatively new entity associated with patients infected by HIV is plasmablastic lymphoma, which occurs preferentially in the oral cavity. A variant of diffuse large B cell lymphomas, it has immunoblastic

morphology with a plasma cell phenotype and up to 80% of cases contain EBV.^{129–131} B cell associated antigens CD20 and CD45 are typically absent, but tumors strongly immunostain for plasma cell reactive antigens.

Two malignancies that are not associated with EBV in the general population but which regularly contain the viral genome in patients with HIV-1 infection are leiomyosarcoma^{132,133} and primary central nervous system lymphoma (PCNSL).^{134,135} The incidence of PCNSL has dramatically declined since the era of highly active antiretroviral therapy (HAART), a trend evident to some extent with all non-Hodgkin’s lymphomas.^{136–138} Leiomyosarcoma, a mesenchymal malignancy with smooth muscle differentiation, has been shown by in situ cytohybridization to contain EBV in affected muscle cells of both children and adults with HIV infection.^{132,133} Sites of occurrence can be unusual (e.g., epidural, laryngeal, adrenal) and multicentric.¹³⁹

Hodgkin’s lymphomas in the setting of AIDS contain EBV in 75–90% of the cases,^{140,141} reflecting the unusually high frequency in the HIV-infected population of mixed-cellularity and lymphocyte-depletion subtypes¹⁴² known to be most closely associated with EBV in the general population.^{15,16} Although not considered an AIDS-defining illness, Hodgkin’s lymphoma occurs with increased frequency in the setting of HIV infection.¹⁴³ The disproportionate distribution of subtypes and unfavorable clinicopathologic features make the entity distinct to AIDS.^{140,141}

Our understanding of the precise role of EBV in the biology of each malignancy remains rudimentary. Because EBV terminal repeat sequences are variably reiterated in each infectious particle, they provide a viral measure of clonality in infected cell populations.¹⁴⁴ The uniform number of terminal repeats found in tumor cells implies infection preceded clonal expansion. Since EBV was present at the genesis of the tumor, the virus has been deemed causal. Recent findings suggest an alternate interpretation for EBV clonality in EBV-associated malignancies that is consistent with the notion of infection as a sequel to malignant transformation, at which time EBV might provide additional growth or survival advantages.^{145,146} Chance infection of an emerging neoplasia by virus endogenous to the host is consistent with the characteristic sporadic association of EBV with any one cancer and a host environment made conducive to EBV replication by immunosuppression.

TREATMENT

The nucleoside analog acyclovir is ineffective in the treatment of latent EBV infection characteristic of viral-induced lymphoproliferation but, as a potent inhibitor of EBV DNA polymerase, can inhibit EBV replication. Although capable of blocking viral shedding from the oropharynx in infectious mononucleosis patients, the

drug does not reduce the load of latently infected B cells in the peripheral blood or affect the disease course. In contrast, acyclovir effectively resolves the permissive infection in oral hairy leukoplakia, although cessation of treatment often results in a recurrence of lesions within 1–4 months.^{147,148}

The advent of HAART has led to an improvement in prognosis of patients with AIDS-related lymphomas^{136–138} (see Chapter 76). Improved immune function has made patients better able to tolerate standard chemotherapeutic dosage regimens, with overall survival in most cases comparable to that of the general population of cancer patients.¹³⁸ EBV targeted therapies for EBV-positive tumors have shown promise in select patient groups, including some with HIV. Adoptive immunotherapy, successfully pioneered for the immunoprophylaxis and therapy of posttransplant lymphoproliferative disease,^{113,114} takes advantage of virus-specific markers on tumor cells as targets for infused EBV-specific cytotoxic T cells. Other strategies under consideration include pharmacologic modulation of EBV expression by 5-azacytidine, an inhibitor of DNA methyltransferase, with the intent of converting a tumor with limited viral antigen expression to one with a lytic or latency III phenotype amenable to immune recognition and destruction.^{149,150} In addition, the induction of the EBV lytic cycle in tumors by pharmacologic agents, when combined with ganciclovir, leads to conversion of the latter to its active cytotoxic form by EBV-encoded kinases, causing tumor cell death.¹⁵¹ Two studies, using low-dose hydroxyurea shown to induce EBV episomal loss from tumor cells in vitro, demonstrated good responses in three patients with EBV-associated PCNSL.^{152,153} Cidofovir, member of a promising newer class of antiviral molecules, the acyclic nucleoside phosphonate analogs, has shown an antitumor effect against EBV-transformed epithelial cells and lymphocytes in experimental animals.^{154,155}

PREVENTION AND CONTROL

Largely because of the global significance of EBV-related malignancies, concerted efforts toward vaccine development are underway.¹⁵⁶ One prototype subunit vaccine is based on the abundant viral envelope glycoprotein gp350 that binds the B-lymphocyte receptor CR2 and elicits neutralizing antibody against infectious virus.¹⁵⁷ Other strategies focus on the use of peptides derived from latent antigens to stimulate cytotoxic T cells central to the control of EBV-infected B lymphocytes.^{115,116} With respect to precautions in clinical settings, physical isolation of patients with acute EBV infections is not required. However, individuals with a recent history of acute EBV infection should not be selected as blood or tissue donors when possible because of the enhanced viral load accompanying primary infection.

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GENERAL PROPERTIES AND CLASSIFICATION

Papillomaviruses are a group of small DNA viruses that primarily induce epithelial cell proliferation, or papillomas, in higher vertebrates. Infections are strictly genus or species specific and there is considerable tropism among the viruses for particular anatomic sites. Viral particles are nonenveloped, have an icosahedral symmetry, and encapsulate a double-stranded circular genome of 7.9 kb that is associated with cellular histones (for more extensive reviews see Ref. 1). For some time papillomaviruses could not be efficiently propagated in tissue culture and so little was known about the virus life cycle. Early information about the function of viral genes came from studies using individual cloned genes in various cellular or in vitro assays. However, in recent years much progress has been made in propagation of the virus in organotypic raft cultures, allowing a clearer understanding of the viral life cycle and the role of individual viral proteins.²⁻⁸ Unlike most other virus groups, types are not based on antigenic diversity, but rather on DNA homology (see below). The genomes of over 100 human papillomavirus (HPV) types have been molecularly cloned and completely sequenced and partial sequences for potentially up to another hundred types have been detected by PCR-based assays.^{9,10} The sequences are available through Genbank.

More than 30 HPV types infect the genital tract. The consequences of infection with genital HPVs vary, and at least some of the variation is type-specific, as discussed in detail in Chapter 28. The genital HPVs have been grouped into high- and low-risk types, based on the potential of the infected cells to progress to cervical carcinoma.¹¹ For example, approximately 50% of invasive squamous cell cancers of the cervix (SCC) harbor the high-risk HPV 16, whereas only 1 of 932 SCCs collected worldwide contained the low-risk HPV 6.¹²

GENOME STRUCTURE AND FUNCTION

Sequence analysis of cloned viral genomes has shown that the genetic organization of all human and animal papillomaviruses is well conserved. The genomic map of HPV 16 is

depicted in a linear form in Fig. 27-1. All eight open reading frames (ORFs) are located on one strand of DNA, and accordingly, transcription of viral genes has been shown to use only one strand as template.¹³ The ORFs E6, E7, E1, E2, E4, E5 are designated as early, and L1 and L2 are late, based on the expression of only the early region in BPV-1 transformed cells, and expression of the late region in productively infected cells.^{14,15} E3 and E8 are not present in all genomes. They do not always code for viral proteins, although an E2^αE8 fusion protein has been reported for HPV-31.¹⁶ An approximately 850 bp segment between L1 and E6 is devoid of ORFs and has been variously designated as the noncoding region (NCR), upstream regulatory region (URR), or long control region (LCR). This region contains a number of cis-acting sequences necessary for viral DNA replication and the regulation of transcription. A detailed review of papillomavirus genome structure and gene expression can be found in Zheng and Baker.¹⁷

Transcription of the viral genome is very complex and produces many alternatively, and multiply, spliced RNAs, mostly in low abundance (Fig. 27-1 and reviewed in Ref. 13). Transcription initiates at several different promoters, though early and late genes seemingly share at least some of the same promoters. All of the early RNAs terminate at a polyadenylation site at nucleotide (nt.) 4215 and the late RNAs use a poly-A site at nt. 7321. Characterization of the mRNAs indicates that some genes, e.g., E7 or E5 are translated only from bi- or poly-cistronic messages, though the low-risk viruses have an additional promoter for expression of E7.¹⁸ An mRNA encoding L2 has not been unambiguously identified, though the L2 protein has been readily detected.^{14,19} Additionally, some ORFs are spliced together to encode fusion proteins, e.g., E1^αE4, while other ORFs encode multiple products, e.g., E2, E2C, E2M and E6, E6*, E6**. Thus, although all genital HPVs encode eight ORFs, the exact number of viral proteins that are expressed during infection is not known precisely.

Knowledge about the function of HPV gene products has increased in recent years but is still incomplete because of the

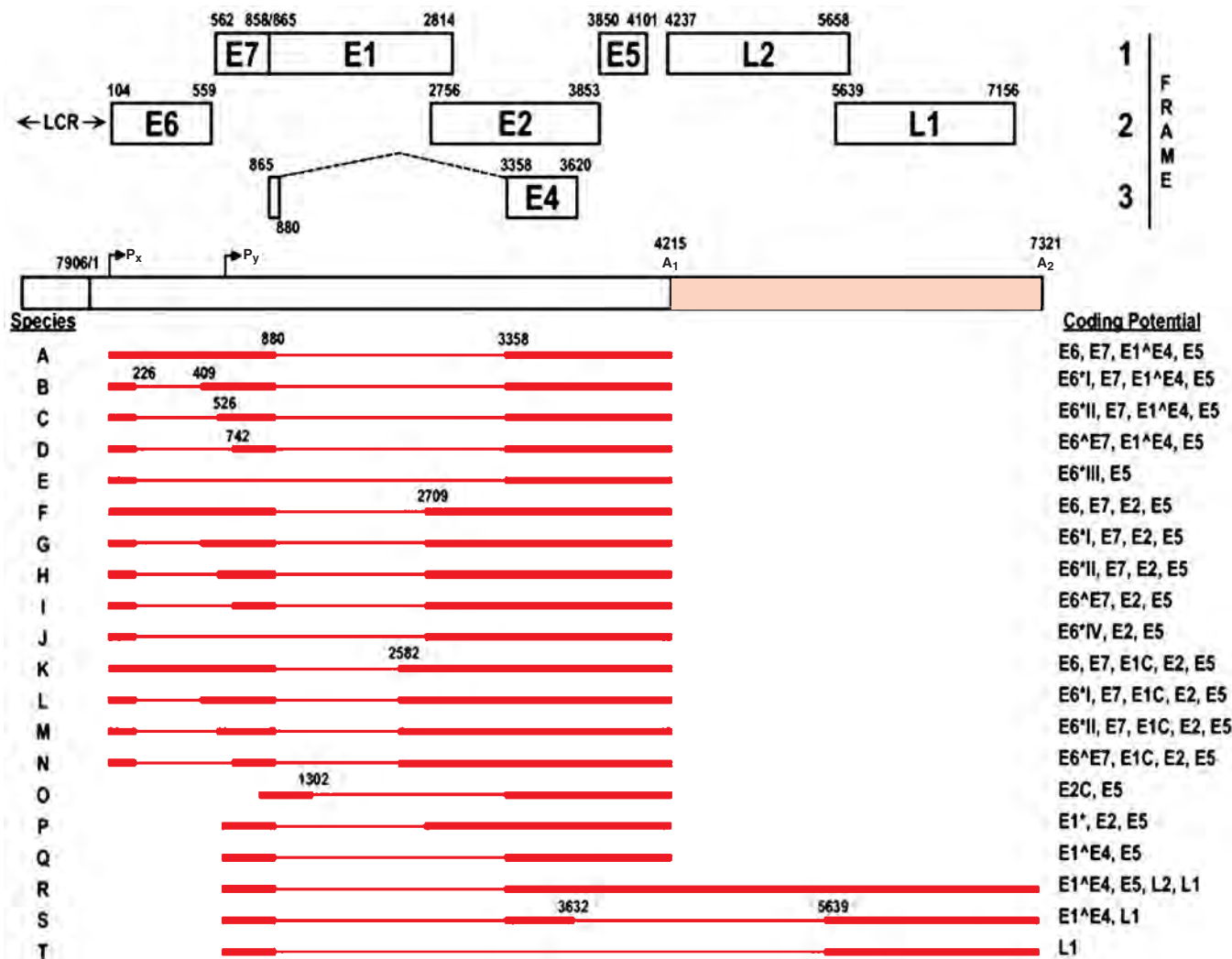


FIGURE 27-1. Genome organization and transcription. Genome structure and transcription map of HPV-16. The bracket line in the middle of the panel represents a linear form of the virus genome for better presentation of head-to-tail junction, promoters (arrows), and early (A_2) and late (A_1) polyadenylation sites. The open reading frames (ORFs) (open boxes) are diagrammed above the bracket and the numbers above each ORF are the nucleotide positions of the first nucleotide of the start codon and last nucleotide of the stop codons in the HPV-16 genome. The E4 ORF spans two exons and formation of the intact E4 ORF requires RNA splicing (dashed lines). LCR indicates a long control region. Below the bracket line are the reported RNA species derived from alternative promoter usage and alternative splicing. Exons (heavy lines) and introns (thin lines) are illustrated on each species of the RNA, with splice site positions being numbered by nucleotide positions in the virus genome. Although all early transcripts driven by early promoter P97 are illustrated with a 5'-end from nt. 97, multiple transcription starting sites in W12 cells have been mapped by 5' RACE at nt. 83 (frequency[F] 3), 91 (F2), 93 (F2), 94 (F1), 95 (F4), 96 (F8) (Carl C. Baker, unpublished data). Similarly, all late transcripts driven by differentiation-inducible promoter P670 are shown for convenience with a 5'-end from nt. 670, but the real 5' ends in W12 cells have been mapped by 5' RACE to nt. 682 (F4), 713 (F5), and 774 (F3) (Carl C. Baker, unpublished data). (Reprinted by permission from Zheng ZM, Baker CC. Papillomavirus genome structure, expression, and post-transcriptional regulation. *Front Biosci* 2006; 11: 2286–2302.)

limited ability to study HPV infections in cultured cells. Many of the HPV proteins interact with multiple cellular proteins and serve a variety of functions. [Table 27-1](#) summarizes information about the products encoded by the ORFs and their presumed functions, which will be discussed in more detail below.

VIRION STRUCTURE

Two proteins, the major capsid protein L1 and the minor capsid protein L2, form the HPV virion coat.^{20–22} In early studies, the three-dimensional structure of several papillomavirus

virions was determined by cryoelectron microscopy and image analysis^{23,24} as shown in [Fig. 27-2A](#). Capsids are ~60 nm in diameter and are composed of 72 pentameric capsomers arranged on a skewed icosahedral lattice with a triangulation number of 7 dextro. The shell, made of L1 protein, is ~2 nm thick and appeared much smoother on the internal surface than the external surface with a fairly contiguous density. Capsomers extended radially 6 nm from the shell and appeared as five pointed stars. Intercapsomer interactions were restricted to the shell. Twelve capsomers are pentavalent (contacting 5 neighboring capsomers) and 60 capsomers are hexavalent. The

Table 27-1. Characterization of Proteins Encoded by HPV ORFs

ORF	Proteins	Approx. Size	Functions	Refs.
E1	E1	68 kDa	Binds origin of replication; ATP-dependent helicase	137–149
	E1C	8 kDa	Unknown; encoded by several HPV mRNAs	
	E1N	23 kDa	Unknown; detected in BPV-1 transformants	
E2	E2	48 kDa	Site-specific (ACCN ₆ GGT) transcription factor; heterodimerizes with E1 to facilitate replication initiation	82,87–89,99,150,151–154
	E2C	28 kDa	Lacks transactivation domain; may function to inhibit E2	
E3		unknown	Only present in BPVs	
E4	E1 ^ E4	17 kDa and smaller processed forms	Very abundant protein; contains few codons of E1 Fused to E4; interacts with cytokeratins; can cause G2 arrest	190–198
E5	E5	10 kDa	Promotes proliferation through growth factor signaling pathways (low-risk); transforming activity in vitro	199–211
E5b		unknown	Only present in HPV 6, 11	
E6	E6	150 a.a.	Eliminates functional p53 (high-risk); alters transcription; activates hTERT	227–291
	E6*, E6**	40–60 a.a.	Unknown but may inhibit activity of E6; predicted in high-risk HPVs	
E7	E7	100 a.a. migrates 20 kDa (high risk)	Promotes proliferation by inactivating pRb and CKI function	292–352
E8	E8 ^ E2	28 kDa	Only present in BPVs, HPV 6, HPV 31	
L1	L1	55 kDa	Major capsid protein; sufficient for self-assembly into capsid, neutralizing epitopes	20–44
L2	L2	50–60 kDa, migrates as 72 kDa	Minor capsid protein, may function in viral entry and capsid assembly	20–44

capsomers are composed of five subunits of L1 with an axial dimple of 3 nm. The location of the minor capsid protein, L2, was not apparent in the image reconstructions. At a resolution of 3.5 nm, capsids or virus-like particles (VLPs) generated by self-assembly of L1 are identical to authentic HPV virions.²⁵

Several studies in recent years have refined the structure of the HPV virion. These studies have been facilitated by the development of methods to produce GST-tagged fusions of the viral capsid proteins in *E. coli*²⁶ and production of VLPs, which are empty shells of the viral capsid proteins. In particular, these studies have clarified interactions within and between capsomers. Two cysteines (175 and 428 in HPV16)

that may participate in formation of disulfide bonds and thus stabilize the virion have been identified.^{27,28} The crystal structure of the T = 1 HPV 16 L1 capsid has recently been described.²⁹ This was prepared using 12-pentamer “small VLPs” with deletions of the first few amino acids of the N-terminus and the last few amino acids of the C-terminus. Later an atomic model was developed by combining image reconstructions of cryoelectron microscopy of bovine papillomavirus with crystal structure coordinates from an HPV 16 L1 VLP.³⁰ Some nonconserved residues near the C-terminus are exposed on the capsid surface, and the L1 C-terminus of one capsomer “invades” a neighboring capsomer.

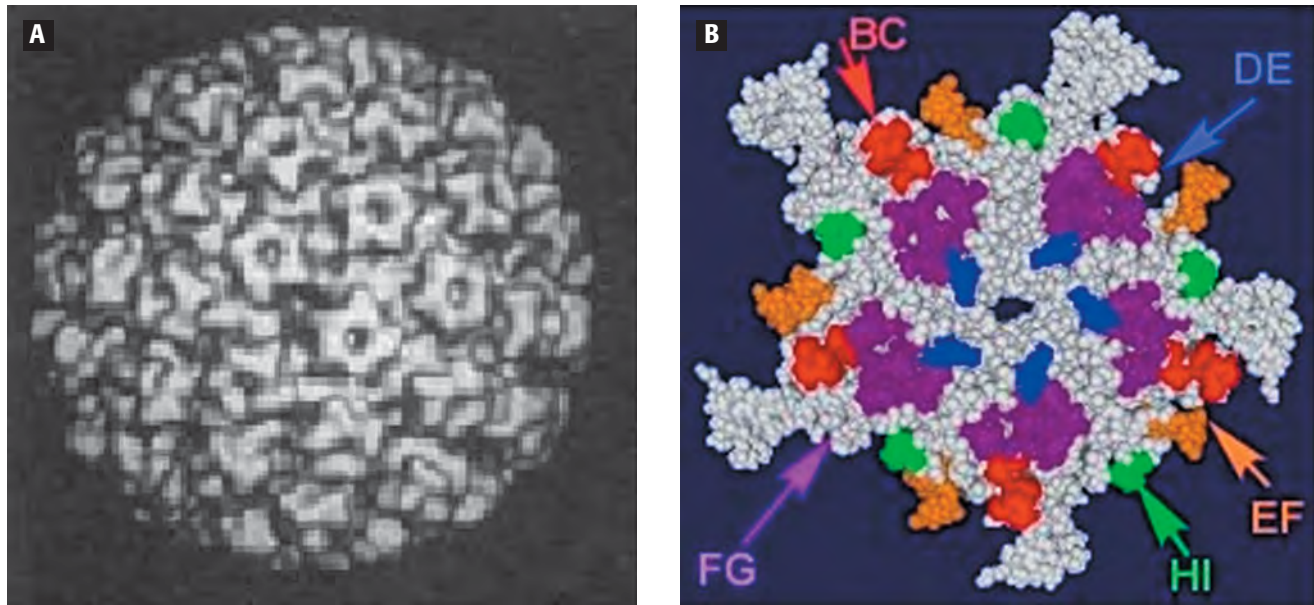


FIGURE 27-2. A. Structure of the HPV virion. A three-dimensional reconstruction of cryoelectron micrographs of a vaccinia virus-expressed HPV 1 capsid containing L1 and L2. (Reprinted by permission from Hagensee ME, Olson NH, Baker TS, Galloway DA. Three-dimensional structure of vaccinia virus-produced human papillomavirus type 1 capsids. *J Virol* 1994; 68(7): 4503–4505.) **B.** Molecular model of capsomer structure and hypervariable loops. Each loop is shown in a different color (Reprinted by permission from Orozco JJ, Carter JJ, Koutsky LA, Galloway DA. Humoral immune response recognizes a complex set of epitopes on human papillomavirus type 6 L1 capsomers. *J Virol* 2005; 79(15): 9503–9514.)

This structural information has been useful in elucidating the nature of HPV epitopes recognized in the immune response to HPV. Epitopes are generally characterized as being either linear, or dependent on sequence alone, or conformation-dependent. Five loops on the capsomer surface with hypervariable sequence between different HPV types have been identified and are designated by two letters as BC, DE, EF, FG, and HI in Fig. 27-2 B. A large proportion of the known antibodies to HPV recognize epitopes in one of these loops or incorporating multiple loops. The variability in these loops generally prevents antibodies to one HPV type from recognizing other HPV types. This has been studied by preparation of chimeric VLPs in which different parts of the L1 sequence for different HPV types have been exchanged. For example, the FG and HI loops are both important for binding of the H16.V5 monoclonal antibody, while the FG and DE loops have been linked to antibody H16.E70 binding.^{29,31–37} The C-terminal arm, also exposed on the virion surface, contains the epitope for the antibody H16.U4.³⁴

There is also some debate as to whether there is a single immunodominant epitope recognized in the immune response to HPV. In one early study, monoclonal antibodies against HPV 6, 16, 18, and 33 were used to block the reactivity of human sera with capsids of the corresponding HPV type. A single monoclonal antibody for each type blocked reactivity of most sera, suggesting the existence of a single dominant epitope.³² In contrast, in a later study mapping the epitopes on the surface of HPV 6 capsomers recognized by human sera using chimeric HPV 6 and 11 VLPs, Orozco et al. found that sera recognized a variety of different epitopes.³⁸

Another recent study used neutralization assays to test a panel of chimeric HPV 16 and 31 VLPs for their ability to block neutralizing activity of sera obtained from a University of Washington natural history study.³⁹ Some chimeric VLPs retained wild-type HPV16 ability to block neutralization, some had an intermediate activity, and some, like HPV 31, could not block neutralization. Transfer of neutralizing activity required sequences from more than one loop. These studies argue against the presence of an immunodominant epitope.

Finally, while in early studies the presence of L2 did not affect virion assembly or structure,²⁵ recent work suggests L2 can facilitate virion formation.^{40,41} Positively charged sequences on L2 are thought to interact with viral DNA and facilitate genome packaging.⁴² Finnen et al. analyzed assembly into complexes of HPV 11 L1 and L2 produced by coexpression in bacteria.⁴⁰ They identified an L1-binding domain consisting of amino acids 396–439 in the carboxy terminus of L2. At either pH 5.2 or 6.8, L1 + L2 assembled into $T = 1$ VLPs, while L1 alone assembled into either $T = 7$ or $T = 1$ VLPs at pH 5.2 but could not assemble into VLPs at pH 6.8. A widely cross-reactive neutralizing epitope near residue 108 has also been identified on the N-terminus of L2, suggesting that part of the L2 protein is exposed on the virion surface, possibly as a loop.^{43,44}

TAXONOMY AND PHYLOGENETIC RELATIONSHIP

Originally, the family *Papovaviridae* included the genus *Papillomavirus* and the genus *Polyomavirus*. However,

subsequent studies indicated that there is significant divergence between the papovaviruses and the papillomaviruses in virion diameter, genome size, transcriptional organization, and other aspects of their biology. They have therefore been reclassified as separate families by the International Committee for Taxonomy of Viruses. They are also now divided into different genera and further subdivided into species, consistent with the classification of other viruses.⁴⁵ The genetic relationships among HPV types have been examined by the construction of phylogenetic trees based on various segments of the genome (reviewed in⁴⁵ (Fig. 27-3). The genera are designated by the letters of the Greek alphabet, and the species are designated by a number. The genus alpha

papillomavirus contains the mucosotropic HPVs that infect the genital tract, as well as some HPVs that infect cutaneous epithelium. Viruses that fall within a species have the same biologic behavior. For example, HPV 16 and other types in the same species are a cause of cervical cancer, while HPV 6 and related types tend to cause warts.

Originally, HPV types were based on <50% homology as determined in liquid hybridization assays,⁴⁶ but DNA sequence data revealed more extensive homology among types. Based on criteria adopted by the Papillomavirus Nomenclature Committee, types are defined as having less than 90% homology of the aggregate E6, E7, and L1 ORF DNA sequences. A new type can only be assigned once the

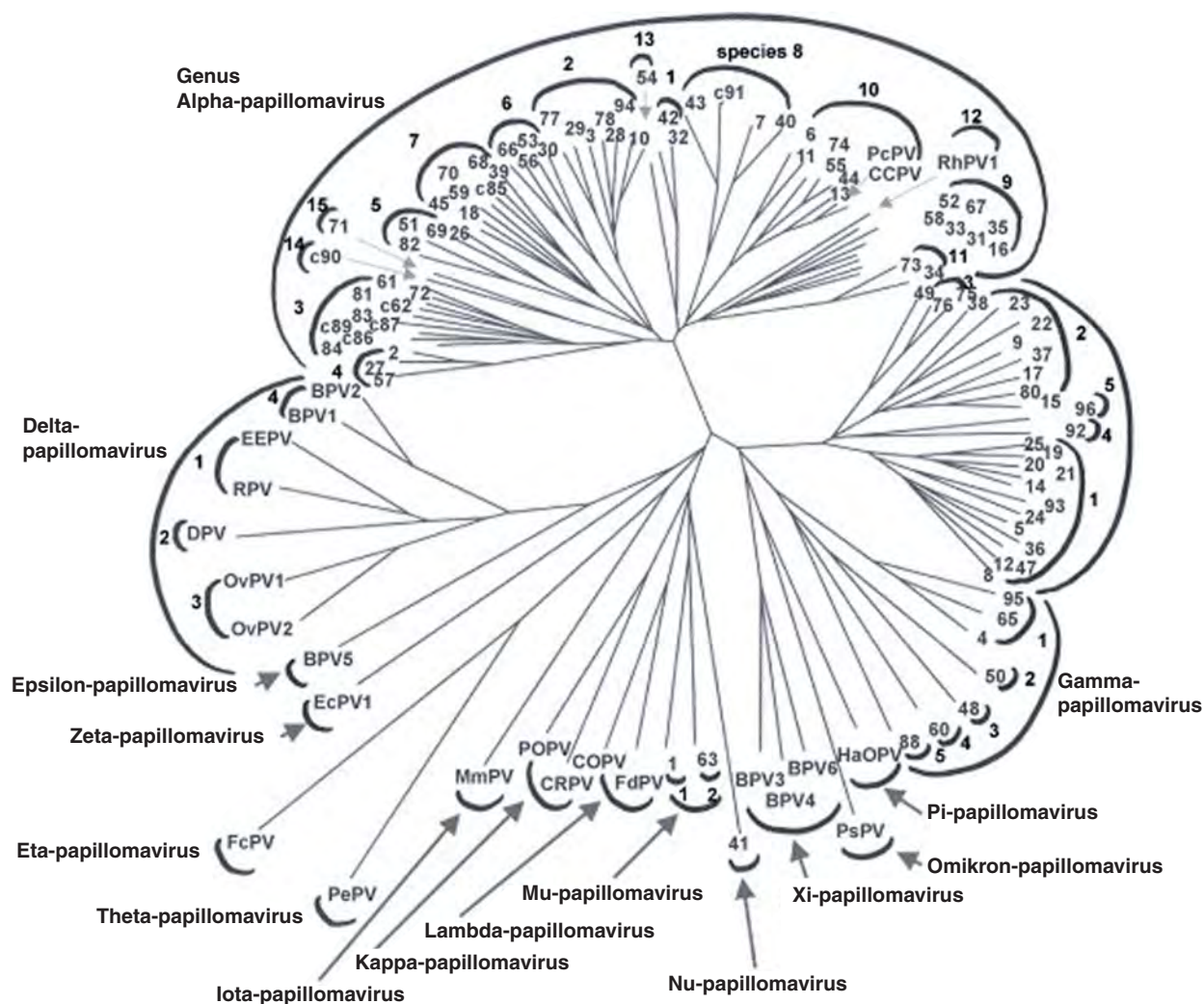


FIGURE 27-3. Phylogenetic tree containing the sequences of 118 papillomavirus types. The L1 ORF sequences were used in a modified version of the Phylip version 3.572 and based on a weighted version of the neighbor-joining analysis. The tree was constructed using the Treeview program of the University of Glasgow. The numbers at the ends of each of the branches identify an HPV type; c-numbers refer to candidate HPV types. All other abbreviations refer to animal papillomavirus types. For the meaning of each abbreviation, please refer to Table 3 in Ref. 51 (within Ref. 45 of this chapter). The outermost semicircular symbols identify papillomavirus genera, e.g., the genus alpha-papillomavirus. The number at the inner semicircular symbol refers to papillomavirus species. To give an example taken from the upper part of the figure, the HPV types 7, 40, 43, and cand91 together form the HPV species 8 in the genus alpha-papillomavirus. (Reprinted by permission from de Villiers EM, Fauquet C, Broker TR, Bernard HU, zur HH. Classification of papillomaviruses. *Virology* 2004; 324(1): 17–27.)

complete 7.9-kb genome has been cloned. HPV subtypes have between 2% and 10% sequence divergence and variants of a type have <2% divergence. The extent of intratypic variability may differ among types. For instance, there is no evidence of subtypes of HPV 16, with sequence variation running around 1%. On the other hand, a few subtypes of HPV 6 and HPV 45 have been found. Variants of a particular type are often grouped by geographical region of origin and ethnic groups, e.g., European, Asian American, North American, and African. While HPV types clearly vary in their biological properties, much remains to be learned as to whether subtypes or variants have distinct biological behavior. However, a number of studies have found some differences in the pathogenicity of different variants.^{47–49}

VIRAL LIFE CYCLE

It was initially difficult to study the life cycle of papillomaviruses because the full infectious life cycle could not be recapitulated *in vitro*. Viral infection or transfection of viral DNA into keratinocytes grown in monolayer cultures results in limited transcription and replication, without formation of infectious progeny, and a gradual loss of viral DNA.⁵⁰ Infectious virus has been produced in a xenograft system in which HPV 11 virus was used to infect fragments of tissue that were then implanted under the renal capsule of nude mice.⁵¹ Characterization of viral transcripts produced in the xenografts has provided a great deal of information about HPV 11 transcription.⁵² Analyses of naturally occurring lesions have provided complementary results. Viral transcripts have been analyzed in cell lines harboring episomal HPV genomes grown in monolayers or organotypic cultures.^{53,54} Upon induction of complete keratinocyte differentiation, viral DNA replication, late gene expression, and formation of viral particles were observed,^{55,56} confirming the dependence of viral gene expression on the differentiated state of the host cell. These *in vitro* observations are consistent with the restriction of vegetative HPV replication and formation of progeny to the most terminally differentiated layers of the epithelium. However, amplification of viral DNA and expression of the late gene *L1* has been reported in parabasal spinous layers of benign warts infected with HPV-1.⁵⁷

The introduction of HPV genomes into keratinocytes followed by differentiation in organotypic cultures provides a means to do genetic analyses.⁵³ This approach has been used for HPV 11,^{2,3} 16,^{4,5} 18,⁶ 31b,⁷ and 45.⁸ It has allowed development of a large body of new information on the expression of viral proteins and viral replication as described in subsequent sections. A recently described method for production of infectious HPV particles in 293TT cells without viral replication or epithelial cell differentiation should also allow many new studies.⁵⁸

ATTACHMENT, ENTRY, AND UNCOATING

Despite the exquisite species and cell-type specificity of HPV infections, studies with labeled viral particles have shown that HPVs bind promiscuously to a wide range of cell types.^{59,60} The inclusion of reporter DNA with the particles showed that entry also occurred in many cell types, indicating that the restriction of viral tropism is not due to a cell-type-specific receptor or coreceptor. The $\alpha 6$ integrin has been proposed as a candidate receptor,⁶¹ but this has not been substantiated by others.⁶² Shafti-Keramat et al. found keratinocytes lacking $\alpha 6$ integrin to be permissive for HPV 11 infection and have proposed syndecan-1 as the primary receptor.⁶² The L1 protein apparently mediates binding to the cell; VLPs containing L1 can only bind and can block binding of L1/L2 containing virions.⁵⁹

Several recent studies have provided new information about the mechanism of entry into the cell, translocation to the nucleus, and uncoating of the viral genome. Heparan sulfate proteoglycans, probably carried on syndecans, are important for binding to some target cells.^{62–65} Clathrin-mediated endocytosis is thought to allow entry of the virus, although one study has suggested that while HPV-16 and HPV-58 use this pathway for cell entry, HPV-31 uses caveolae-mediated endocytosis.^{66–68} A 23 amino-acid peptide at the amino terminus of L2 facilitates exit from the endocytic compartment.⁶⁹ The L2 C-terminus also has been reported to interact with the motor protein dynein, which may facilitate movement of the viral genome to the nucleus,⁷⁰ and the tSNARE protein receptor syntaxin 18,⁷¹ which helps mediate protein trafficking through the endoplasmic reticulum. The Hsp70 chaperone protein has been suggested as a mediator of uncoating.⁷² Disruption of interpentameric disulfide bonds is also required for viral particle disassembly.²⁷ Several studies have identified a potential role for interaction of HPV coat proteins with the Kap alpha 2 and Kap beta 1 nuclear import receptors.^{73–76} Day et al. have suggested that L2 is involved in chaperoning the viral genome to nuclear domain 10 (ND10) by a mechanism dependent on promyelocytic leukemia (PML) protein.⁷⁷ Finally, the kinetics of absorption and entry has been examined and found to be relatively slow.⁷⁸

TRANSCRIPTION OF VIRAL GENES

Transcription of HPV genes is tightly coordinated with the differentiated state of the cell, as evidenced by different RNA transcripts in different layers of the epithelium^{79,80} (Fig. 27-4). Expression of E1 and E2 is thought to occur in basal cells to maintain episomal replication of the HPV genome. Transcription of E6 and E7 is required to promote proliferation of parabasal cells, in order to provide the replication machinery for viral DNA replication. In the high-risk viruses, E6 and E7 transcription is directed from a single promoter,

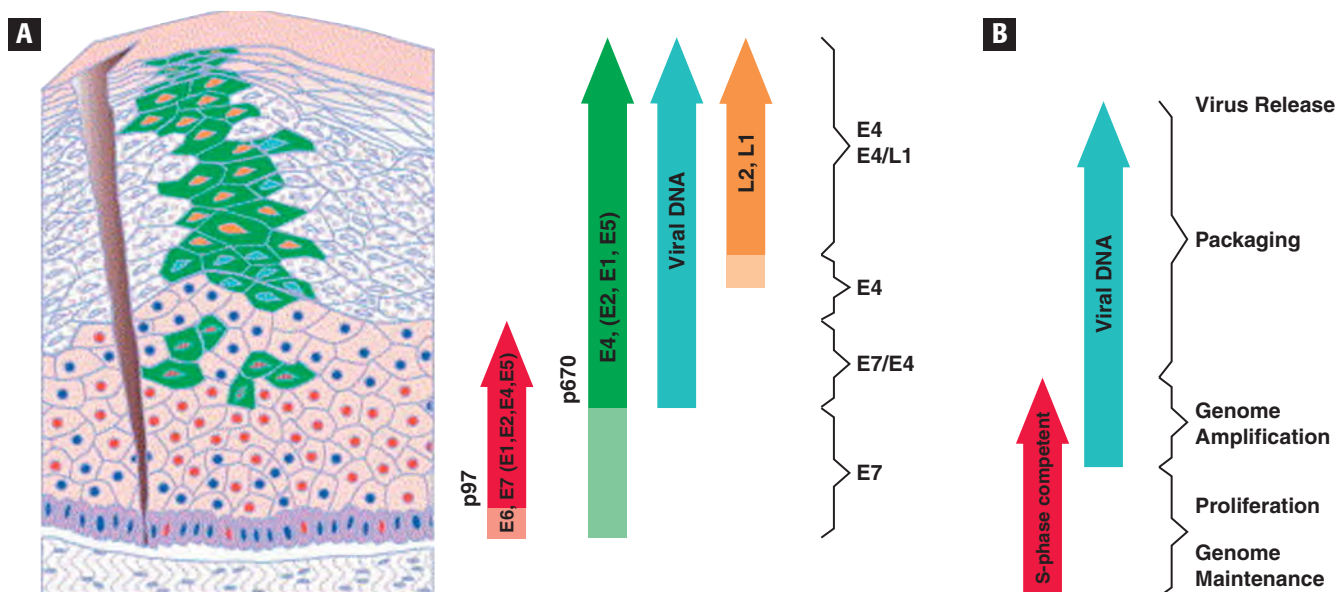


FIGURE 27-4. Life cycle organization during productive infection by HPV types from supergroup A. **A.** Diagrammatic representation of the skin to reveal the pattern of HPV16 gene expression as the infected cell migrates toward the epithelial surface. Other supergroup A viruses, such as HPV2 and HPV11, follow a similar pattern. After infection (in this case through a cut), the viral genome is maintained as a low copy number episome. During epithelial differentiation, the p97 promoter directs expression of the E6 and E7 genes necessary for S-phase entry (red). The p670 promoter is upregulated in the higher epithelial layers, and viral replication proteins (E1, E2, E4, E5) increase in abundance (green), facilitating amplification of viral genomes (blue). Changes in mRNA splicing allow E4 to persist into the upper epithelial layers where the viral capsid proteins (yellow) are found. **B.** Cells in the lower epithelial layers are S-phase competent. Viral genome amplification begins in these cells but ceases once the cells lose their ability to express S-phase proteins. Although amplified viral genomes can be detected throughout the upper epithelial layers, cells that are actively supporting genome amplification appear confined to a region where E7 expression coincides with the high-level expression of E4, and probably also, an increase in the abundance of E1 and E2. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.) (Reprinted by permission from Doorbar, J. The papillomavirus life cycle. *J Clin Virol* 2005; 32: S7–S15.)

p97 for HPV 16 and p105 for HPV 18,^{81,82} whereas the low-risk viruses use separate promoters for E6 and E7.⁸¹ However, transcription from other novel promoters has been reported for HPV-16,^{83,84} HPV 18,⁸⁵ and HPV 31b.⁸⁶

A basal level of transcription from the p97/p105 promoter is regulated by the keratinocyte-dependent enhancer in the NCR and can be repressed by binding of E2 to its cognate recognition sequences located adjacent to the p97/p105 TATA boxes.^{82,87} E2 has a role in repressing transcription from the viral promoter and its loss on viral DNA integration allows increased expression of the oncogenic proteins E6 and E7. E2 also activates transcription under some circumstances.⁸⁸ Variations in binding to four different E2 binding sites may contribute to transcriptional regulation.⁸⁹ Interestingly, the E8E2C protein of HPV-31 had an ability to repress transcription from a single promoter-distal E2 binding site. This activity was lacking in the full-length E2, suggesting that E8E2C has a role in regulating transcription.⁹⁰ E2 binds the general transcription factor TFIIB⁹¹ and is thought to directly inhibit HPV transcription at a step subsequent to binding of TBP or TFIID to the TATA box.⁹² It interacts with numerous other transcription factors and chromatin modification factors including CBP,⁹³ p/CAF,⁹⁴ C/EBP,⁹⁵ nucleosome assembly protein 1,⁹⁶ and Top BP1.⁹⁷ An interaction between bromodomain protein 4 and E2 is required for transcriptional activation

by E2.⁹⁸ Two crystal structure studies of the amino terminal transcription activation domain of E2 suggested that dimerization of E2 helps recruit distal transcription factors to the viral transcription complex⁹⁹ and that there is a high degree of overlap of regions important for transcription and replication.¹⁰⁰ Interestingly, E2 has been reported to repress transcription from the viral promoter in an integrated but not the episomal state.¹⁰¹ Another recent study indicates that both integration of HPV and loss of episomes expressing E2 is necessary for progression to cervical carcinogenesis.¹⁰² Transcription is also regulated through binding sites for numerous common cellular transcription factors such as YY1, SP1, AP-1, Oct1, NF1, and Brn-3a and other silencer and enhancer elements.^{2,103–107}

Some progress has been made in identifying changes in transcription factor binding involved in the switch from early gene to late gene expression. Viral late gene transcription is controlled by another promoter, p670 in HPV 16. A viral transcript expressed from this promoter and encoding the first few codons of E1 fused to the E4 ORF appears to be the major viral transcript in HPV-infected cells and specifies the viral protein designated E1^αE4.¹⁰⁸ Regulation of the E1^αE4 promoter is not well understood; however, this promoter appears to be used for transcription of the late gene products, L1 and L2, and both the capsid proteins and E1^αE4 are only

expressed in the most differentiated layers of the epithelium.¹⁰⁹ Binding activity of CCAAT displacement protein inhibits expression of HPV 6 E6, E7, and E1 but decreases on keratinocyte differentiation.¹¹⁰ Sen et al. carried out extensive analysis of cis regulatory elements within the region from nt. 7511–7762, known as the keratinocyte enhancer region of HPV 31.¹¹¹ Numerous changes in the complex of transcription factors binding to a given cis-regulatory element at different stages of the viral life cycle were identified. For example, one region was found to bind C/EBP β in undifferentiated cells but an NF-1-like factor bound C/EBP β in differentiated cells. The transcription factor hSkn-1a has been reported to displace YY1 to activate the p670 late promoter of HPV 16.¹¹² Recent work using array analysis found changes in binding of at least 36 HPV DNA-interacting factors over the course of differentiation and identified novel associations of HPV-16 promoter regions with C-Myb, Pax5, NFATx, and WT1.¹¹³ Interestingly, the C/EBP β transcription factor has been reported to activate transcription from the late promoter but to inhibit transcription from the early p97 promoter.¹¹⁴ The transition to late gene expression may require differentiation but not viral DNA amplification.^{115,116} In one study mapping the elements controlling transcription from the HPV 31 late promoter p742, Bodily and Meyers identified a 150-bp region in the E7 ORF as the core promoter and found that while sequences in the NCR can enhance expression from p742, they do not confer responsiveness to differentiation. The region containing the start site was dispensable for basal expression but required for differentiation response.¹¹⁶

Late gene expression is also governed at the level of usage of the polyadenylation site, since late mRNAs do not terminate at the early poly A site at nt. 4215, but continue to the site at nt. 7321 (see Fig. 27-1). Inhibition of late gene expression by use of the early poly A site has been linked to a combination of the AAUAAA sequence, binding of cleavage-stimulation factor and other factors, an enhancer element in the early region 3' UTR, and a negative regulatory element in the L2 ORF.^{117,118} A negative regulatory element in the 3' untranslated region of the *L1* gene is important for posttranscriptional control.¹¹⁹ This region contains several splice sites and binds numerous splicing factors.^{120,121} A splicing silencer in the L1 coding region¹²² and a splicing enhancer in the E4 coding region have been described that may regulate gene expression.¹²³ A region in the 3' end of HPV 16 early mRNAs that destabilizes mRNA and results in decreased protein levels has also been identified.¹²⁴

The effects of chromatin structure on viral gene expression have also been the subject of much recent work. The HMG-I(Y) architectural protein and the histone acetyltransferase p300/CBP have been identified as part of the HPV 18 enhanceosome.¹²⁵ The ability of E2 to activate transcription is inhibited by CpG methylation.¹²⁶ In the same study, the HPV 16 NCR was hypermethylated in undifferentiated cells

but hypomethylated in differentiated cells, suggesting one mechanism by which viral gene expression changes over the course of infection. Inhibition of histone deacetylase (HDAC) activity with trichostatin A preferentially upregulated HPV 11 promoter activity in the basal and parabasal layers of organotypic rafts.¹²⁷ A shift in DNAase 1 accessibility from the NCR near the E6 ORF in undifferentiated cells to a region between nt. 659 and 811 in differentiated cells was found by del Mar Pena and Laimins.¹²⁸ Interestingly, inhibition of deacetylation was not sufficient for late gene activation. There is some evidence for an association between genomic hypomethylation and carcinogenic progression.¹²⁹

Much recent work has been done in characterizing how different papillomavirus genes are expressed from polycistronic transcripts. Recent work suggests that for HPV-16 and 18, E7 is translated by translational reinitiation from spliced E6*I transcripts,¹³⁰ although a leaky scanning mechanism has also been reported.¹³¹ It should be noted, however, that expression of HPV 16 E7 from a monocistronic transcript has also been reported.¹³² Remm et al. describe expression of HPV-18 E1 by discontinuous ribosome scanning on an mRNA containing E6, E7, and E1.¹³³ A recent study suggests that control of viral gene expression is also regulated at the level of translation. Oh et al. found that HPV E7 expression was correlated with phosphorylation and inactivation of the translation inhibitor dIF4E:4E-BP1.¹³⁴

VIRAL REPLICATION

It is widely believed that papillomaviruses have two modes of replication—stable replication of the episomal genome in basal cells and runaway, or vegetative, replication in more differentiated cells to generate progeny virus. The initial stages of infection may involve limited amplification of the viral genome to maintain a stable but low copy number of viral genomes in basal cells. The origin of replication is located in the NCR and contains an AT rich region, a region with dyad symmetry repeats to which E1 binds, and an adjacent E2 binding sequence.^{135,136}

E1 is the origin-binding protein and has ATP-dependent helicase activity. It recognizes overlapping arrays of hexanucleotide sequence¹³⁷ to which E1 is proposed to bind sequentially,¹³⁸ finally binding the DNA as a double hexamer.¹³⁹ E1 also interacts with the cellular polymerase–primase complex,^{140,141} Rep A,¹⁴² and topoisomerase I.¹⁴³ It may disrupt chromatin structure by interaction with histone H1¹⁴⁴ and hSNF5.¹⁴⁵ Its activity is regulated by phosphorylation and interaction with CDK/cyclin complexes.^{146–149}

Although E2 is not absolutely required for replication *in vitro*, it strongly stimulates replication *in vitro* and is necessary for replication *in vivo*,^{150,151} presumably by recruiting other components to the preinitiation complex. Interestingly, in HPV 31 four binding sites for E2 have been characterized

and may cooperate to regulate viral replication.¹⁵² HPV E2 interacts directly with E1.^{153,154} Numerous studies have examined the regions of interaction with E1. In general, the carboxy-terminal regions of E1, including the ATP-binding domain, have been identified as important for specificity of interaction with E2,^{155–157} while the amino terminal domain of E2 is important for E1 interaction.¹⁵⁴ Interestingly, for bovine papillomavirus, there is an interaction between the DNA-binding domains of E1 and E2, as well as between the helicase domain of E1 and the transactivation domain of E2.^{158,159} It has been proposed that interaction between the DNA-binding domains prompts a bend in the DNA that facilitates the second productive interaction between the helicase and transactivation domains.¹⁶⁰ The x-ray crystal structure of the HPV 18 E2 activation domain bound to the E1 helicase domain suggested that E2 prevents hexamerization of E1 in part by preventing ATP binding.¹⁶¹ It has also been proposed that there is a sequential binding of E1 dimers to opposite faces of the double helix.¹⁶² E2 helps to recruit the E1 protein to the origin of DNA replication in a two-step process in which E2 is displaced at later stages of replication,¹⁶³ possibly through the action of the chaperone proteins Hsp70 and Hsp40.¹⁶⁴ The E1–E2 interaction has also been proposed to suppress nonspecific DNA binding activity of E1 and to increase high-affinity binding at the replication origin.^{165,166} Alternative mRNA splicing may also regulate the relative ratios of E1 and E2, which in turn helps control viral replication during different stages of the viral life cycle.¹⁶⁷ E2 is also thought to have a role in tethering of viral DNA to mitotic chromosomes, possibly through interaction with the cellular bromodomain protein Brd4.^{168,169} It has been reported that TATA-binding protein disrupts the E1–E2 interaction and inhibits replication, possibly facilitating a switch in the major role of E2 from replication to transcription.¹⁷⁰

Apart from the origin-dependent initiation of replication, all other factors required for viral replication are encoded by the cell. It is unclear what regulates the switch from episomal to vegetative replication, except that it may depend on factors only found in terminally differentiating cells. One study with BPV-1 found that episomal replication occurred in proliferating cells and extensive amplification of viral DNA only occurred in growth arrested cells.¹⁷¹ Two modes of episomal or maintenance replication have been proposed. The genome may replicate once per S phase or by a random-choice mechanism.¹⁷² The switch could be regulated in part by p53, which interacts with HPV-16 E2.¹⁷³ It has been reported that p53 inhibits amplificational replication, suggesting that HPV-mediated degradation of p53 could be important¹⁷⁴ and also that stable maintenance episomal replication of bovine papillomavirus is not sensitive to p53.¹⁷⁵

Changes in transcription factor binding to the HPV URR are likely to be important in regulating viral replication. The CCAAT displacement protein negatively regulates replica-

tion.¹⁷⁶ In one study of the role of different regions of the HPV 31 NCR on replication during different phases of the viral life cycle, Hubert et al.¹⁷⁷ found that disruption of binding sites for several transcription factors, including AP1 and Sp1, in the keratinocyte enhancer region could reduce replication levels. An analysis of the replication efficiency of constructs with chimeric NCRs derived from different HPV 16 variants showed that small changes in the NCR sequence affect replication levels and are responsible for the increased replication level of some American variants relative to European and African variants.¹⁷⁸ Differences in replication correlated with differences in expression of E1 and E2 and may depend on binding sites for transcription factors AP-1, Sp1, and YY1. It has also been reported that the YY1 transcription factor can directly bind and inhibit E2.¹⁷⁹

Disruption of a splice site at nt. 3295 of HPV 31 prevented episomal maintenance replication but allowed immortalization of a cell line with integrated copies of the viral DNA, suggesting a role for E1–E4 and E5 in replication. Using a simple differentiation system consisting of suspension of keratinocytes in methylcellulose, it was found that amplification of viral DNA correlated with expression of the viral protein E1–E4 and the cellular proteins involucrin and transglutaminase.¹⁸⁰ Amplification was not correlated with expression of keratin-10. The E8–E2C protein has also been reported to repress replication from extrachromosomal origins of replication.¹⁸¹

VIRUS ASSEMBLY AND RELEASE

It has been difficult to develop experimental models to study virus assembly or release. However, improvement of organotypic raft culture methods and methods for preparation of VLPs have provided some information. Viral particles have been observed in the nucleus of infected cells in the granular layer of the epithelium, where packaging of the genome likely occurs. There is no evidence that HPV infections are cytolytic; release of viral particles is a result of degeneration of desquamating cells. Changes in the morphology of the cornified cell envelope in HPV 11-infected cells, due to reduction in expression of loricrin, have been observed.^{182,183}

Several studies have examined the role of disulfide bonds in capsid and virion assembly.^{27,28} One study proposed that L2 facilitates virion formation at a step prior to disulfide bond formation and helps link viral DNA to the capsomers.⁴¹ This is also supported by experiments with organotypic raft cultures, in which HPV-31 mutant genomes lacking L2 were found to produce virions with a 10-fold reduction in the amount of encapsidated DNA.¹⁸⁴ The PML/ND10 nuclear subdomain may be a site of virion assembly. Using bovine papillomavirus, Day et al. showed that L1 and E2 can be recruited to the PML protein oncogenic domains¹⁸⁵ by L2. It has been suggested by Florin et al. that L1 and L2 translocate to the nucleus separately and that L2 induces reorganization of ND10 nuclear subdomains before

interacting with L1¹⁸⁶ and that the chaperone protein Hsc70 helps to translocate L2.¹⁸⁷ However, others have found that nuclear localization, but not PML localization, was required for L2 incorporation into VLPs.¹⁸⁸ Finally, the observation that a fraction of E1 and E2 show colocalization with ND10 structures may indicate some coupling between viral DNA replication and virion assembly.¹⁸⁹

FUNCTIONS OF E4

Numerous reports suggest that HPV E1^E4 plays a role in various aspects of the viral life cycle. Its expression causes collapse of the keratin intermediate filament network.^{190,191} Expression of E1^E4 also induces cell cycle arrest at the G(2)/M boundary.¹⁹² This arrest has been correlated with retention of Cdk1/cyclinB as well as Cdk2/cyclin A complexes in the cytoplasm and their sequestration to the cytokeratin network^{193,194} and is in some cases dependent on expression of Wee1.¹⁹⁵ It has also been reported to cause relocation of PML protein, suggesting a potential role in viral replication or assembly.¹⁹⁶ Mutational analysis suggested that E1^E4 has separable roles in how the virus affects differentiation, the level of amplification of viral DNA, and the proportion of cells in the suprabasal layer of a raft culture that synthesize DNA.^{197,198}

FUNCTIONS OF E5

The E5 protein also may have some role in cell cycle control and in some papillomaviruses such as BPV-1 it is a major transforming protein. HPV E5 has been reported to localize to the Golgi apparatus and the endoplasmic reticulum, as well as the plasma membrane.¹⁹⁹ HPV 16 E5 prevents maturation of the MHC class I and II antigens and sequesters the MHC complex to the Golgi apparatus.^{200,201} Interaction with the epidermal growth factor receptor (EGFR)²⁰² and enhancement of EGF signaling has also been described,²⁰³ possibly by inhibition of c-Cbl-1-mediated degradation of EGFR.²⁰⁴ Hyperplasia in transgenic mice expressing HPV 16 E5 was dependent on EGFR.²⁰⁵ Activation of EGFR has also been reported to lead to increased expression of vascular endothelial growth factor.²⁰⁶ However, in one recent study comparing E5 from BPV-1 and HPV-16, HPV-16 E5 could support anchorage-independent growth in soft agar, but unlike BPV-1 E5 did not induce focus formation or activate growth factor receptors, PI3 kinase or c-Src.²⁰⁷ The overexpression of E5 can either protect cells from²⁰⁸ or sensitize cells to²⁰⁹ apoptotic stimuli. In organotypic raft cultures with a mutant HPV 31 genome lacking E5, reductions in genome amplification and late gene expression were observed, as well as decreased expression of cyclin A and cyclin B, but no change in EGF receptor phosphorylation was observed.²¹⁰ In similar experiments with HPV-16, viral DNA amplification was observed but there was a subtle reduction in the number of suprabasal cells undergoing DNA synthesis.²¹¹

ROLE OF HPVS IN CANCER

A role for HPVs in the etiology of anogenital cancers has been firmly established based on a large number of molecular and epidemiologic studies. HPV DNA can be detected in nearly 100% cervical tumors.²¹² In one study, no significant variation in positivity was found among countries, though the rates of cervical cancer varied markedly.¹² The association of HPV with other genital tract tumors has been less well studied, and while the prevalence of HPV appears to be lower than in the cervix, consistently high levels of association have been reported.^{213,214} The epidemiological and clinical relationship between preneoplastic lesions and HPV-containing anogenital cancers will be discussed in Chapter 28; this section will focus on the biological characteristics of high-risk HPVs that lead to the development of neoplasia.

E6 and E7 are the two viral genes that are invariably retained and expressed in tumors,²¹⁵ and these two oncoproteins from the high-risk types, but not from low-risk types, are sufficient to immortalize cells in culture.^{216,217} Studies have shown that E6 and E7 can independently extend the life span of cells in culture, and together they efficiently immortalize human epithelial cells (reviewed in Ref. 218). E6 and E7 alone can immortalize cultured cells at a lower efficiency and this involves additional cellular changes. Immortalized cell lines are not tumorigenic when assayed in nude mice, but tumorigenic derivatives have been established spontaneously with long-term culture²¹⁹ or induced by carcinogen treatment.²²⁰ Tumorigenicity is accompanied with additional cytogenetic changes. Taken together the current evidence suggests that the high-risk HPV E6 and E7 oncoproteins provide several critical functions for the development of neoplasia (Fig. 27-5). Firstly, E7 disrupts the signal that normally prevents a cell from entering S phase once the cell has left the basal layer. The increased number of proliferating cells increases the number of cells that are available as targets for additional genetic alterations, or “hits,” that lead to neoplasia. Secondly, both E6 and E7 bypass damage-induced DNA checkpoints and other growth arrest signals. Inactivation of cell cycle checkpoints allows genetic instability, and the failure to eliminate cells that have undergone potentially deleterious changes contributes to the development of neoplasia. Thirdly, E6 activates the expression of telomerase, allowing the continued proliferation of cells²²¹ and blocks the apoptotic response. The development of invasive cancer, or tumorigenicity in animals, requires the activation of genes that favor penetration of the basement membrane, altered interactions with the matrix to permit growth in the stroma or other tissues, and new growth factor requirements. Additional cytogenetic changes accompany tumorigenicity. Inactivation of checkpoints allows the continued genetic instability that gives rise to the new genetic changes required for tumorigenicity.

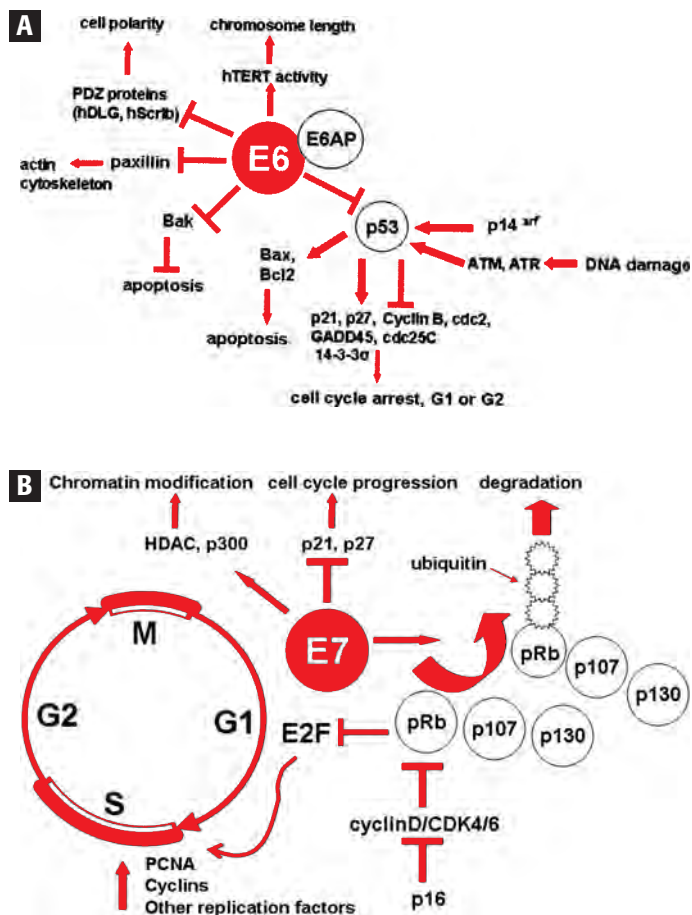


FIGURE 27-5. Role of HPV E6 and E7 in neoplasia. **A.** HPV E6 affects cell cycle progression by a number of different mechanisms. One of the most important is by causing proteasome-dependent degradation of the tumor suppressor protein p53 by the cellular ubiquitin ligase E6AP. In the absence of HPV E6, p53 activity is induced by various stresses including DNA damage, partly through the ATM and ATR kinases. This leads to activation (p21) or repression (cyclins, cdc2) of various genes leading to cell cycle arrest and to apoptosis. HPV E6 also causes activation of the catalytic *hTERT* component of telomerase and disrupts normal apoptotic response to DNA damage, in part by causing degradation of pro-apoptotic factors such as Bak. Finally, infection causes changes in the actin cytoskeleton and cell polarity by affecting the PDZ-domain-containing proteins and paxillin. **B.** HPV E7 affects cell cycle progression by causing proteasome-dependent degradation of the tumor suppressor protein pRb or the related pocket proteins p107 and p130 by an unknown mechanism. This allows expression of many genes required for entry into S phase and cell cycle progression including, but not limited to, proliferating cell nuclear antigen (PCNA) and cyclins. It also affects other factors important in cell cycle control such as the cyclin-dependent kinase inhibitor p21 and histone deacetylases.

Predictions about the role of HPV in neoplasia obtained from experimental studies are consistent with the natural history of cervical cancer. Among women who develop squamous intraepithelial lesions, the time from first detection of viral DNA to lesions is short, ~2 years, though factors like number of partners and infection with other STDs may influence the interval (reviewed in Ref. 222). Even mildly dysplastic lesions show an increase in proliferation and polyploidization. These changes result as a direct consequence of

expression of E6/E7. The median age of carcinoma in situ (CIS) in the United States is 29,^{223,224} indicating that approximately a decade has elapsed between the initial infection and severe dysplasia. CIS lesions are characterized by their aneuploid DNA content and thus reflect the genetic instability that accompanies prolonged expression of E6/E7. The preneoplastic lesions can regress spontaneously. One principle explanation for their regression is likely to be an effective immune response, and generalized T-cell deficiency has been associated with increased dysplasia (reviewed in Refs. 225 and 226). Other explanations may include the fact that some, perhaps most, alterations will be deleterious, resulting in cell death. The median age of invasive cervical cancer in the United States is 49, indicating that additional changes required for invasion and metastasis are acquired slowly over time.

FUNCTIONS OF E6

The genital HPV E6 proteins are approximately 150 amino acids in length and contain four cys-x-x-cys motifs involved in binding zinc.^{227,228} High-risk E6 is primarily localized to the cell nucleus and E6 proteins have activities that activate or repress various heterologous promoters.^{229–232} HPV 16 E6 binds to p53²³³ in concert with a cellular ubiquitin conjugating enzyme, E6AP, and targets p53 for degradation.²³⁴ Interestingly, the E6*I isoform has been reported to interfere with the ability of wild-type E6 to degrade p53.^{235–237} HPV 6 E6 has greatly reduced ability to bind p53 *in vitro*,^{233,238,239} it does not target p53 for degradation *in vitro*, and the intracellular level of p53 in cells expressing 6 E6 is unaffected.²³⁹ Sedman et al.²⁴⁰ found that mutant p53 could cooperate with 16E7 to immortalize human keratinocytes, suggesting that the inactivation of p53 might be the sole function of E6 in immortalization; however, inactivation of p53 was not required for E6 to immortalize mammary epithelial cells.²⁴¹ Using mutants of 16E6 that resulted in degradation of p53 but failed to immortalize human embryonic kidney cells in cooperation with 16E7, Nakagawa et al.²⁴² concluded that degradation of p53 was necessary but not sufficient for E6-mediated immortalization. However, in other reports immortalization without degradation of p53 has also been observed.^{241,243}

Another important function of HPV E6 is the activation of hTERT, the catalytic subunit of telomerase.²²¹ This activation is at least partly dependent on binding sites for the c-Myc and SP1 transcription factors in the hTERT promoter.²⁴⁴ Binding of c-Myc to the hTERT promoter has been detected by chromatin immunoprecipitation.^{245,246} However, the exact role of c-Myc is not yet clear, as telomerase activity does not clearly correlate with levels of c-Myc.^{244,247,248} E6 has also been reported to cause degradation of c-Myc.²⁴⁹ Induction of hTERT expression by HPV 16 E6 has recently been shown to also depend on the NFX-1 transcription factor.²⁵⁰ Two isoforms of NFX-1 have opposing effects on hTERT transcription.

A 91-kDa form represses telomerase transcription and is targeted by HPV 16 E6 for degradation via the E6AP ubiquitin ligase. A second 123-kDa isoform actually activates telomerase expression and is not targeted for degradation. In addition to hTERT, another important transcriptional target of E6 is transforming growth factor β -1.²⁵¹ The advent of microarray analysis has made possible identification of numerous genes involved in regulation of differentiation whose expression is effected by E6.²⁵²

HPV 16 E6 has been shown to bind many other cellular proteins that may have a role in induction of neoplasia. In addition to p53, E6 binds and inactivates the related protein p73.²⁵³ Other binding partners include BRCA1,²⁵⁴ the focal adhesion protein paxillin,²⁵⁵ the calcium binding proteins ERC-55 (E6BP)²⁵⁶ and fibulin-1,²⁵⁷ the E6TP RapGAP,^{258,259} the AP-1, TRIP-BR-1, and hADA3 transcription factors,^{260–262} minichromosome maintenance protein-7,²⁶³ several PML proteins,²⁶⁴ the Jak-STAT pathway regulator Tyk2,²⁶⁵ IRF-3,²⁶⁶ protein kinase N,²⁶⁷ and the GADD34/PP1 phosphatase complex that helps regulate the translation initiation factor eIF-2 α .²⁶⁸ E6 also binds and inactivates the histone acetyltransferase p300,^{269,270} which has been reported to impact expression of both p53²⁷¹ and hTERT.²⁷² A number of other binding partners contain a PDZ motif that binds to a short region at the C-terminus of high-risk E6 proteins. These include hDLG,^{273,274} hScrib,²⁷⁵ MAGI-1,²⁷⁶ and MUPP1.²⁷⁷ E6 causes degradation of many of these proteins, but their significance to the viral life cycle or to the induction of neoplasia is still unclear. In one study mutation of the PDZ binding domain of E6 did not affect the ability of E6 to immortalize human mammary epithelial cells.²⁴¹ Other studies suggest that the PDZ-binding domain does contribute to the oncogenic potential of E6.^{278–281} A number of these PDZ-domain proteins are involved in cell adhesion. Both the hDLG and hScrib proteins also bind the APC tumor suppressor.²⁸² The PDZ domain has also been reported to be responsible for activation of the NF κ B transcription factor by E6.²⁸³ In particular, this interaction is necessary for induction of the apoptosis-inhibiting protein cIAP. E6 also interacts with other proteins involved in regulation of both the intrinsic and extrinsic pathways of apoptosis, such as Bak²⁸⁴ and Bax,²⁸⁵ which it targets for degradation, as well as tumor necrosis factor²⁸⁶ and FADD.^{287,288} These studies showed that depending on the experimental conditions, E6 has been reported both to prevent apoptosis and to sensitize cultured cells to apoptotic stimuli.

Numerous studies have addressed the specific regions of interaction between E6 and its binding partners. The binding between E6 and p53 is dependent on residues in the zinc binding region in E6.^{238,239,289,290} Binding between E6 and E6AP is disrupted by a mutation of amino acids 9–13 of E6,²⁴⁷ although amino acids from 19 to 128 have also been suggested to be important.^{235,243} Recently a solution structure of HPV 16 E6 has been reported,²⁹¹ which suggested that many of the sites deemed crucial for p53 and/or E6AP binding may dis-

rupt the overall structure of E6. Their results mutating a large number of surface exposed residues only found F47 disrupting p53 binding and did not identify any residues that were critical for E6AP binding.

FUNCTIONS OF E7

The genital HPV E7 proteins are approximately 100 amino acids and contain two cys-x-x-cys repeats in the carboxy terminal half of the protein that binds zinc.²⁹² The amino terminal half of E7 shares two conserved regions of homology (CR1 and CR2) with the E1A oncoproteins of adenoviruses and with the polyomavirus T antigens. All of these oncoproteins bind to the retinoblastoma (Rb) tumor suppressor, p105Rb,²⁹³ and other Rb-related pocket proteins, such as p107 and p130,²⁹⁴ through a well-defined motif, LxCxE, present in CR2. This motif binds to a cleft between the A- and B-box portion of the Rb pocket in a manner also dependent on a conserved group of adjacent lysine residues.^{295,296} Binding to HPV E7 disrupts the interaction between Rb and E2F.²⁹⁷ This allows activation of numerous E2F-responsive genes necessary for transformation including, but not limited to, cyclin E,^{298,299} cyclin A,²⁹⁸ proliferating cell nuclear antigen (PCNA),³⁰⁰ and cdc25.³⁰¹ Expression of E7 also results in elevated levels of the cyclin-dependent kinase (CDK) inhibitor p16^{INK4A}.²⁹⁹

HPV 16 E7 binds Rb much more strongly both in vitro³⁰² and in vivo³⁰³ than does HPV 6 E7, and transformation activity parallels Rb binding activity. Interestingly, HPV 1 E7 has been shown to bind Rb with high affinity though it failed to transform cells.³⁰⁴ In that study, 1 E7 was not able to transactivate an E2F responsive promoter, suggesting that although 1 E7 bound Rb, it was not able to inactivate the tumor suppressor activity of Rb.³⁰⁵ It was subsequently found that HPV 16 E7 targets pRb and other pocket proteins for degradation by the ubiquitin-proteasome pathway.^{306–310} In contrast, HPV 1 E7 binds but does not degrade Rb.³¹¹ Several studies have shown that mutated 16 E7 proteins that were unable to bind to Rb were transformation deficient^{312–317} though one study has shown that immortalization of keratinocytes might not involve Rb binding.³¹⁸ Although Rb binding was required for transformation, a number of mutated E7 constructs were fully competent to bind Rb yet were still transformation deficient.^{316,317} HPV 16 E7 with a mutation of amino acid 2 from histidine to proline retains the ability to disrupt pRb/E2F complexes but is unable to degrade Rb or extend the life span of cultured cells.³⁰⁸ HPV 16 E7 targets all three pocket proteins for degradation. Interestingly, HPV 6 E7 has been reported to target p130 for degradation.³¹⁹

The mechanism by which E7 targets pRb for degradation is not yet known and requires binding of other cellular factors to E7. The stability of both pRb and E7 itself is dependent on ubiquitination and degradation by the proteasome, but the mechanisms may be different.^{306,307,309,310} E7 has also been

reported to interact with one component of the proteasome,³²⁰ although mutation of the binding site did not stabilize Rb. One possible candidate for involvement in E7 regulation of pocket protein stability is the SCF (Skp/cullin/F-box) E3 ubiquitin ligase. E7 is targeted for degradation by this multiprotein complex using the SKP2 F-box specificity factor.³²¹ SKP2 has been reported to interact with pRb but its role in pRb stability in the presence of E7 has not yet been conclusively shown.³²² SKP2 was also shown to target p130 for degradation.^{323,324} Darnell et al. found that overexpression of the serine proteinase inhibitor plasminogen activator inhibitor (PAI-2) could stabilize pRb by interaction of Rb with a novel Rb-binding motif, PENF, in PAI-2.³²⁵ They hypothesized that this interaction prevents pRb cleavage by some protease, possibly calpain, and that this cleavage may precede proteasomal degradation of pRb.

Although pRb binding and degradation through the CR1 and CR2 motifs is the most critical role of E7 in transformation, other cellular factors are also important and degradation of Rb alone cannot abrogate growth arrest in cultured cells.³⁰⁸ Mutations affecting the zinc fingers found in the carboxy terminal end of E1A and E7 have both been shown to be transformation deficient, suggesting that important factors also bind in this region. A number of E7-binding cellular factors are involved in regulation of gene expression through modification of histone acetylation levels. The amino terminal region of E1A oncoprotein can bind to p300,³²⁶ a CREB-related transcription factor.³²⁷ Recently, p300 binding activity has also been identified for E7,^{328,329} although the binding site was characterized as being in a more central region of E7 overlapping the pRb-binding domain. This interaction could contribute to transformation by affecting acetylation and expression of Rb/E2F target genes or by acetylation of Rb itself, as described for E1A.³³⁰ The difference in reported binding sites may also explain earlier work in which E1A constructs mutated in the p300-binding domain can complement E1A proteins mutated in the Rb-binding domain, while HPV 16 E7 constructs mutated in the Rb-binding domain could not complement E1A proteins mutated in the p300-binding domain.³³¹ E7 has also been reported to bind the pCAF acetyltransferase.³³² In contrast to this effect on acetyltransferases, E7 interacts with the members of the HDAC protein family³³³ and the Mi2 component of the NURD HDAC complex as well.³³⁴ Disruption of E7-HDAC binding interferes with maintenance of the HPV genome and the ability of E7 to extend the life span of cultured cells.³³⁵

Another important E7-interacting cellular protein is the CDK inhibitor p21, the inactivation of which is important for E7 abrogation of cell cycle arrest.³³⁶ Although E7 has been reported to increase p21 levels,^{337–339} it may inactivate it in part by changing its subcellular localization.³⁴⁰ Other important factors reported to interact with E7 that cannot be fully

discussed here include, but are not limited to, BRCA1,²⁵⁴ TATA box binding protein,³⁴¹ Oct-4,³⁴² the Rb associated factor p60,³⁴³ the Smad proteins,³⁴⁴ insulin-like growth factor binding protein 3,³⁴⁵ interferon regulatory factor-1,³⁴⁶ M2 pyruvate kinase,³⁴⁷ the MPP2 fork head domain transcription factor,³⁴⁸ AP-1,³⁴⁹ and the promyelocytic leukemia protein.³⁵⁰ Finally, phosphorylation of E7 by casein kinase II is important for its ability to facilitate S-phase entry³⁵¹ and may regulate binding of some of these interacting proteins.³⁵²

COMBINED FUNCTIONS OF E6 AND E7

Many studies have identified effects on cellular pathways linked to the combined expression of E6 and E7. Microarray studies are beginning to allow increasingly comprehensive examination of changes in gene expression in response to expression of HPV oncoproteins. One study using microarray analysis of organotypic raft cultures identified alterations in 1381 genes on expression of HPV E6 and E7.³⁵³ Interestingly, genes that were downregulated tended to be involved in protein translation. A cooperative effect of E6 and E7 has also been reported in downregulation of expression of TGF β -2³⁵⁴ and IL-8.³²⁹

Two other key pathways linked to both E6 and E7 are the Notch pathway and the pathway regulating EGF and angiogenic factors such as VEGF. Both upregulation^{355–357} and downregulation³⁵⁸ of the Notch1 pathway in association with progression to cervical cancer and expression of E6 and/or E7 has been reported. The discrepancies may be due to changes in subcellular localization³⁵⁷ and on the exact levels of expression in various experimental systems.³⁵⁶ Apoptosis is inhibited by this pathway through PI3K and Akt.³⁵⁹ In general, expression of E6 and E7 correlates with increased expression of VEGF and EGF, and there is a complex feedback mechanism whereby they regulate each others' expression.^{360–362}

The exact combination of the effects of HPV E6 and E7 necessary for immortalization and transformation, in particular whether p53 inactivation, telomerase activation, or both, is required, has also been the subject of a number of studies. Kiyono et al. found that disruption of the pRb/p16^{INK4A} pathway in combination with expression of hTERT was sufficient for immortalization of HMECs.²⁴¹ In some other studies it has been suggested that both degradation of p53 and E7 functions in addition to inactivation of p16^{INK4A} are required for immortalization.³⁶³ Some discrepancies may be accounted for by the fact that hTERT levels on overexpression are typically approximately 10-fold higher than those induced by hTERT. Park and Androphy have suggested that the requirement for p53 degradation depends on the presence of functional E7.³⁶⁴

Finally, several studies have addressed the relative roles of E6 and E7 in transgenic mice. These studies have identified distinct roles in progression and promotion of tumorigenesis.^{365–368} While E7 acted primarily at the promotion stage of carcinogenesis, E6 had a greater effect at the progression stage.

DISRUPTION OF CELL CYCLE CONTROL

In normal epithelium, proliferation is restricted to a few cells in the basal layer; suprabasal cells exit the cell cycle and undergo terminal differentiation. Experimental studies have shown that high-risk E7 prevents quiescence, resulting in proliferating cells throughout the epithelium.^{369,370} Although the molecular mechanism that imposes a G1 arrest on epithelial cells as they leave the basal layer is not fully known, both Rb and the CDK inhibitor (CKI) p21 have been implicated. p21 associates with the G1 cyclin/cdk complexes, preventing the phosphorylation of Rb and other critical targets required for progression into S phase.³⁷¹ The E7 protein is capable of uncoupling proliferation and differentiation, allowing cellular and viral replication in cells expressing differentiation markers.^{369,370,372} The mechanism likely involves both release of E2F and binding to p21^{cip1}.^{373–375}

Large hyperchromatic nuclei characteristic of polyploid nuclei are observed in cells engineered experimentally to express E7 or E6/E7, as well as in HPV-associated lesions. This observation suggests that the viral oncoproteins can disrupt the S/M checkpoint that ensures that S phase does not reinitiate without an intervening round of mitosis. Inactivation of p53 has been shown to disrupt the mitotic spindle checkpoint,³⁷⁶ and some studies have suggested that p21 is required for S/M coordination, though the mechanism is not known.³⁷⁷ Thus, E7 bypasses control of epithelial cell proliferation and both E6 and E7 may contribute to the development of polyploidy by disrupting the S/M checkpoint.

In response to DNA damage, cells arrest in the G1 and G2 phases of the cell cycle, presumably to allow time to repair the damage before initiating DNA synthesis or mitosis.³⁷⁸ Arrest in G1 is dependent upon the ability of a cell to induce p53, which results in the transactivation of a number of p53 responsive genes, the most critical of which appears to be p21^{cip1}.^{379,380} By binding to cyclin/CDK complexes, p21 inhibits progression from G1 into S phase. Induction of p21 also inhibits PCNA-dependent DNA replication, though short-range DNA synthesis required for repair is not affected.^{381,382} Other genes involved in DNA repair are also transactivated by p53. As an alternative to growth arrest, cells can undergo apoptosis in response to DNA damage. The decision as to which pathway to take is not completely understood but is influenced by cell type specific factors, the presence or levels of p53, and conflicting signals for growth proliferation and growth arrest (reviewed in Ref. 383; p53-inducible genes such as Bax can promote apoptosis). Additionally, as discussed above, E6 is also able to directly target components of the apoptotic pathway for degradation.

Both E6 and E7 are able to bypass DNA-damage-induced arrest by distinct pathways. Expression of HPV proteins interferes with a variety of mechanisms of DNA repair including nucleotide excision repair and repair of thymine

dimers.³⁸⁴ Elimination of p53 by HPV 16 E6 leads to low levels of p21 and efficient bypass of the DNA-damage-induced G1 checkpoint.^{385,386} Using mutated E6 proteins it was demonstrated that the ability to abrogate G1 arrest was completely correlated with E6-mediated degradation of p53.²³⁹ However, E6 has been reported to interfere with the fidelity of DNA end-joining by both p53-dependent and p53-independent pathways.³⁸⁷ E6 also interacts with the repair protein XRCC1 to disrupt single-strand break repair.³⁸⁸ The inability of HPV 6E6 to bypass a DNA-damage-induced growth arrest reinforces that 6E6 is not able to inactivate p53.

HPV 16 E7, but not 6E7, bypasses a damage-induced G1 checkpoint through mechanisms that are not completely understood.^{385,389,390} These effects have been thought to be independent of p53, but Song et al., using a combination of mice overexpressing E6 or E7 in p53 wild-type or null background, suggested that some effects of E7 are dependent on p53.³⁹¹ Inactivation of Rb by 16E7 obviates the requirement for cyclin D/cdk4 activity³⁹² and the subsequent release of E2F transcription factors from Rb activates the transcription of genes required for S phase, including cyclin E,^{393,394} which has been shown to be required for S phase entry.³⁹⁵ Accordingly, cyclin E has been shown to be elevated in E7 expressing cells.²⁹⁸ However, by analysis of mutations in the E7 C-terminus, inactivation and destabilization of pRb was shown to be insufficient for bypass of DNA-damage-induced growth arrest.³⁰⁸ Inactivation of growth arrest signals likely involves additional activities of E7 that include direct binding to CKIs.^{374,375,396} In particular, inactivation of p21 by E7 is important.³³⁶ Interestingly, Therrien et al. have reported that both global and transcription-coupled nt. excision repair were impaired in the presence of E6, while only global repair was disrupted in the presence of E7.³⁹⁷ An increase in levels of MDM2 has also been observed on expression of E7 in keratinocytes, which may contribute to the ability of E7 to abrogate to mitotic spindle checkpoint.³⁹⁸

Recent work also suggests further functions of HPV E2 in cell cycle disruption. E2 has been reported to directly interact with and regulate the stability and subcellular localization of E7.³⁹⁹ As discussed in an earlier section, E2 also interacts with p53. E2 expression induces apoptosis or senescence in a number of experimental settings.^{400–403} Interestingly, the ability of E2 proteins to interact with p53 and induce apoptosis varies between the high- and low-risk HPV types.⁴⁰⁴ The gene expression profile of cells undergoing E2-induced senescence has been analyzed and showed a downregulation of chromatin regulatory factors.⁴⁰⁵ E2 has also been reported to interact with E6 and to inhibit the ability of E6 to degrade PDZ-domain containing substrates.⁴⁰⁶

ADDITIONAL CELLULAR FACTORS

A great deal of interest has focused on the observation that integration of HPV sequences into the cellular genome

frequently accompanies progression to malignancy.^{407–409} Unlike retroviruses there is no specific integration site on the HPV genome, but the frequent disruption of the early region has been postulated to provide a means to increase E6/E7 gene expression by either eliminating transcriptional repression by E2⁴¹⁰ or exchanging the viral 3' end of the E6/E7 RNA which contains an RNA destabilizing element for a more stable 3' end encoded by cellular sequences.⁴¹¹ The chromosomal site into which HPV sequences integrate is nonspecific, or at least occurs on many different chromosomes. Integration of HPV genomes has been reported to occur preferentially at fragile sites,^{412–414} perhaps because the chromatin structure provides easier access for recombination complexes. Integration near matrix attachment regions has also been observed.⁴¹⁵ Some studies have found integrated HPV sequences in proximity to cellular protooncogenes.^{412,413,416} Interestingly, in one study of HPV-18 integration occurred near the *c-myc* protooncogene in 30% of cases.⁴¹⁷ Activation of *c-myc* on integration has also been reported.⁴¹⁸ A new potential tumor suppressor gene, APM-1, has been identified by cotranscription with HPV-68.⁴¹⁹ However, consistent activation of oncogenes as a consequence of HPV integration has not been demonstrated. A detailed review of known integration sites is found in Ref. 409. Although integration of HPV sequences into the cellular genome is a frequent feature of invasive carcinomas, it is not obligatory as some HPV 16-positive tumors retain only episomal genomes.^{420–422} In one study of the physical status of HPV-16, Arias-Pulido et al. found HPV-16 to be 61.9% episomal, 29.4% mixed, and 8.7% integrated in cervical CIS and 39.1% episomal, 45.7% mixed, and 15.2% integrated in invasive cervical cancers.⁴²³ It should be noted that the presence of high copy number episomes may prevent detection of integrated genomes. Extensive deletions of E1 and E2 were also found.

The identification of consistently observed chromosomal abnormalities in cervical carcinomas was initially hampered by the difficulty of obtaining a sufficient number of metaphases for karyotypic analyses. Early studies found that cervical carcinomas were frequently aneuploid or tetraploid and reported frequent alterations in chromosomes 1, 3, and 11.^{424–426} Loss of heterozygosity has also been reported for 3p.⁴²⁷ Comparative genome hybridization overcame the need for mitotic cells and identified overrepresentation of 3q as pivotal genetic change that marked the transition from severe dysplasia to invasive cancer.^{428,429} A phosphatidylinositol 3-kinase gene located in this region has been postulated to be important.⁴³⁰ A gain of 3q was observed in 1/13 severe dysplasias and in 9/10 invasive cervical cancers. In more recent work, alterations on many other chromosomes have been reported, including 2, 4, 5, and 10.^{431–433} Gain of chromosome 20q has been reported in several studies.^{434–436}

HPV immortalized human epithelial cells are generally not tumorigenic, but long-term passage in culture can spontaneously give rise to tumorigenic derivatives,²¹⁹ or they can be induced by treatment with carcinogens.²²⁰ These experimentally derived tumor cell lines have been used to identify genes that may be responsible for the conversion to malignancy. Cytogenetic changes that accompany the progression to tumorigenicity were studied in a HPV 18 immortalized cell line, 18–11.⁴³⁷ A striking but unstable aberration of chromosome 3 occurred very early after establishment of the cells in culture. Postcrisis, the length of the derivative 3 stabilized, but the long arm contained a complex rearrangement of other chromosomes. Concomitant with the development of tumorigenicity the *ETS2* oncogene, which maps to 21q22, was translocated to the derivative #3.⁴³⁸ A similar translocation of *ETS2* to 3qter was observed in the carcinogen-induced tumorigenic line. Importantly, cytogenetic analyses of cervical cancers have frequently reported changes in chromosome 3,⁴²⁶ suggesting that the model systems mimic authentic tumor development.

Some progress has been made in recent years toward understanding the mechanism by which HPV causes chromosomal instability. Overexpression of HPV-16 E6 causes premature mitotic chromosome segregation⁴³⁹ and chromosomal abnormalities, in particular formation of anaphase bridges, have been correlated with telomerase levels in E6-expressing cells.^{440,441} Expression of E6 and E7 has been linked to upregulation of a number of genes involved in regulating the G2-M phase transition, in particular *Plk1*, *Aurora-A*, *cdk1*, and *Nek2*⁴⁴² and the upregulation of *Plk1* has been linked to E6-induced tetraploidy.⁴⁴³ In early studies, it was found that HPV E6 and E7 cooperate to induce aberrant centrosome duplication and tetrasomy, although E7 alone, but not E6 alone, could cause the abnormalities.^{444,445} These abnormalities were an early event after infection and could be observed in organotypic raft cultures in which E6 and E7 were expressed from an HPV episome.^{446,447} Later work showed that both E6 and E7 could disrupt spindle checkpoint control and cause anaphase bridge formation.⁴⁴⁸

The same group has observed that while E7-induced abnormalities occur early in cells with a normal appearance, E6-induced abnormalities occur in multinucleated cells. Interestingly, the ability of E7 to induce centrosome abnormalities appears to be independent of its effects on pRb⁴⁴⁹ but dependent on CDK2.⁴⁵⁰ Finally, in one study numerical chromosomal abnormalities were observed with intermediate levels of E7 expression, while both numerical and structural abnormalities were observed on high levels of E7 expression.⁴⁵¹ Thus, while the mechanisms are not entirely understood, both E6 and E7 appear to contribute to the induction of chromosomal instability.

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Rachel L. Winer and Laura A. Koutsky

INTRODUCTION

At least 40 of the over 100 different human papillomavirus (HPV) types primarily infect genital epithelium.¹ The great diversity of HPV types reflects the ability of this group of viruses to exploit the different microenvironments of the largest organ in humans—the skin. To some extent, the epithelial tropism of different HPV types corresponds to different clinical manifestations (Table 28-1).¹⁻³ For example, HPV 2 and HPV 4 are often detected in common warts of the hands,⁴⁻⁶ HPV 6 and HPV 11 are most frequently detected in genital warts (condylomata acuminata),^{7,8} and HPV 16 or HPV 18 is detected in a high percentage of invasive cancers of the genital tract and anus.⁹⁻¹² While a restricted number of genital HPV types have been linked with cancer,¹³ most have been linked with development of squamous intraepithelial lesions (SILs) of the cervix, vagina, vulva, penis, or anus.¹⁴ In the future, genital warts, precancerous genital lesions, and genital tract cancers are likely to become less common, as the newly developed prophylactic HPV vaccines become more widely available.¹⁵

This chapter provides an overview of the epidemiology and clinical aspects of genital HPV infection. Results from the prophylactic HPV vaccine trials are also discussed. Chapter 27 covers the biology of the virus, Chapter 57 provides an overview of the epidemiology and clinical aspects of HPV-related genital cancers, and Chapter 58 reviews current concepts in cervical cancer screening.

DEFINITIONS

The majority of newly acquired genital HPV infections appear to be subclinical and asymptomatic. Clinically visible manifestations of HPV include warts that may be condylomatous, papular, flat, or keratotic in appearance. Subclinical infections may appear as flat “aceto-white” lesions that are visible with colposcopic magnification of epithelium that has been treated with a mild acetic acid (vinegar) solution, or as SILs that are diagnosed microscopically on the basis of

characteristic cytologic and histologic features.¹⁶ Low-grade SIL (LSIL), the cytological equivalent of histologically confirmed cervical intraepithelial neoplasia grade 1 (CIN 1), is the morphologic manifestation of vegetative viral replication. High-grade SIL (HSIL), the cytological equivalent of histologically confirmed cervical intraepithelial neoplasia grade 2 or 3 (CIN 2-3), including carcinoma in situ, is considered to be a precancerous lesion with a high potential for malignant transformation. If left untreated, HSIL often will persist for years, developing additional genotypic and phenotypic changes that eventually result in an invasive carcinoma.¹⁷

For some individuals, detection of HPV DNA in genital specimens is the only evidence of current infection. Many adults without clinical, microscopic, or molecular evidence of HPV infection have serum antibodies to specific HPV types, indicating past infection. However, because a portion of individuals with genital HPV infection do not develop antibody responses that can be detected using current assays, false-negative HPV serology results limit the value of serologic testing for prior HPV infection (see reviews by Carter and Galloway and Konya and Dillner).^{18,19}

HISTORY

Written descriptions of condylomatous warts of the genital tract and anus date as far back as the first century A.D. (see reviews by Oriel and Rosenbaum).^{20,21} Within the first decade of this century, the viral etiology of both common skin warts and genital warts was demonstrated.²² During the 1930s, work with the cottontail rabbit papillomavirus provided important clues as to the role of this family of viruses in the development of tumors.^{23,24}

Although the cytologic manifestations now known to be characteristic of cervical HPV infection were first described in 1956,²⁵ it was not until the 1970s that these cellular changes were attributed to HPV infection.^{26,27} Also during this decade, the genetic heterogeneity of HPVs was first demonstrated through use of molecular hybridization techniques.²⁸⁻³¹ Throughout the 1980s and 1990s, several

Table 28-1. Clinical Manifestations Associated with Different HPV Types

Clinical Manifestation	HPV Types
Skin lesions	
Plantar warts	1
Common warts	2, 4, 26, 27, 29, 57
Flat warts	3, 10, 28, 49
Butcher's warts	7
EV-associated lesions (benign or malignant)	5, 8, 9, 12, 14, 15, 17, 19–25, 36–38, 46, 47, 50
Genital	
Condylomata acuminata	6, 11
Noncondylomatous lesions and/or CIN	6, 11, 16, 18, 26, 27, 30, 31, 33, 34, 35, 39, 40, 42–45, 51–53, 56–59, 61, 62, 67–71, 73, 74, 81
Carcinoma	16, 18, 26, 31, 33, 35, 39, 45, 51–53, 56, 58, 59, 66–68, 73, 82
Nongenital mucosal	
Mouth (focal epithelial hyperplasia)	13, 32
Laryngeal papilloma	6, 11
Maxillary sinus papilloma	57
Carcinoma (head/neck/lung)	16, 18, 30

Adapted from De Villiers EM, Fauquet C, Broker TR, Bernard HU, Zur Hausen H. Classification of papillomaviruses. *Virology* 2004; 324(1): 17–27; de Villiers EM. Papillomavirus and HPV typing. *Clin Dermatol* 1997; 15(2): 199–206; Munoz N, Castellsague X, de Gonzalez AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. *Vaccine* 2006; 24S3: S1–S10.

epidemiologic and molecular studies provided firm evidence linking specific HPV types with the development of most genital tract and anal cancers.^{13,17,30,32–36}

PATHOGENESIS

HPVs are epitheliotropic, and replication that results in infectious progeny takes place in differentiating squamous epithelium.^{37,38} Viral DNA, but not structural (capsid) protein, can be detected in the lower layers of the epithelium.³⁹ Capsid protein and infectious virus are found in the superficial differentiated cell layers. HPV-infected epithelium characteristically has a hyperplastic prickle cell layer (acanthosis), with a stratum corneum consisting of only one or two layers of parakeratotic cells. The dermal papillae are elongated, and there is a sharp border with the dermis (Fig. 28-1). Koilocytes, which are mature squamous cells with a large,

clear perinuclear zone, may be scattered throughout the outer cell layers. The nuclei of koilocytes may be enlarged and hyperchromatic, and double nuclei are often seen.⁴⁰ Ultrastructural studies show virus in some of the cell nuclei. Although koilocytes are thought to represent a specific cytopathic effect of HPV, koilocytotic features are often subtle, and other cellular changes may mimic koilocytic changes. Thus, detection of koilocytes is not a sensitive or reliable predictor of cervical HPV infection.⁴¹

PREVALENCE AND INCIDENCE

■ PREVALENCE

The point prevalence of genital HPV infection detected by polymerase chain reaction (PCR)-based methods among populations of women with cytologically normal Pap smears

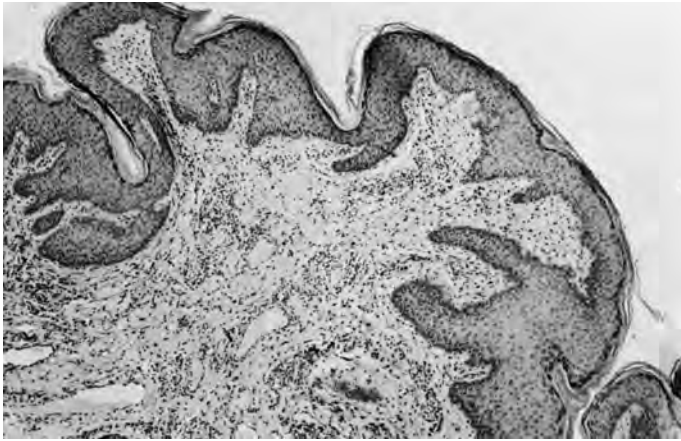


FIGURE 28-1. Biopsy of condyloma acuminatum, showing acanthosis, elongated dermal papillae, and sharp border with dermis. H&E stain (Courtesy of E. Stolz.)

has ranged from 1.5% to 44.3%,^{42–63} depending on the population studied and the sensitivity of the PCR assay used. In general, sexually active younger women are more likely to have HPV DNA detected in genital tract specimens than older women. HPV 16 appears to be the most common type among cytologically normal women, as well as the most common cancer-associated type.^{9,42,64–70} The worldwide distribution of HPV types detected in LSILs (from a worldwide meta-analysis⁷¹) and in cervical specimens taken from cytologically normal women (from an International Agency for Cancer Research (IARC) pooled analysis⁴²) is shown in [Table 28-2](#).

Genital HPV infection is also common in men, with prevalence estimates from studies using PCR-based methods ranging from 3.5% to 46.4% (see review by Partridge and Koutsky^{72–75}). In a population of university students, the prevalence of HPV infection in 213 male students was similar to the prevalence in 418 female students (28%).⁷⁶ In case–control studies of the male role in the epidemiology of cervical cancer in Colombia and Spain, cell samples for detection of HPV DNA were collected from the distal urethra and the external surface of the glans and coronal sulcus of the penis. In Colombia, 26% of husbands of 210 women with cervical cancer and 19% of husbands of 262 women without cervical cancer were positive for HPV DNA by PCR,⁷⁷ whereas in Spain, 18% of husbands of 183 women with and 4% of husbands of 171 women without cervical cancer were positive for HPV DNA.⁷⁸

Serologic assays for specific HPV types have been used to detect antibodies to virus-like particles (VLPs), which are conformationally correct viral capsids that have been synthesized from the L1 protein of the virus. Seroprevalence studies using VLPs as antigen suggest that, among women without clinically evident HPV-related disease, 2–43% have antibodies to HPV 16, and 9–25% have antibodies to HPV 6 or 11.^{8,52,79–87} The seroprevalence of other types, including

Table 28-2. Worldwide HPV DNA Prevalence of Types Commonly Detected in HPV-Positive Low-Grade Cervical Lesions and in HPV-Positive Cervical Specimens from Women with Negative Cytology

HPV type	HPV-Positive Low-Grade Cervical Lesions ^a	HPV-Positive Cervical Smears from Women with Negative Cytology ^b
16	26.6	19.7
31	11.7	7.5
51	10.9	4.0
53	10.1	1.2
56	9.7	7.1
52	8.8	5.3
18	8.6	7.2
58	8.5	7.6
66	8.5	4.1
6	8.1	1.4
39	7.8	4.3
33	7.6	5.8
59	6.0	2.9
35	5.9	5.9
45	4.9	5.6

^aMeta-analysis including 5,910 cases of HPV-positive low-grade cervical lesions from Europe (46.5%), North America (32.9%), South/Central America (14.8%), Africa (3.0%), and Asia (2.9%) (Clifford et al.⁷¹)

^bPopulation-based IARC pooled-analysis including 1,429 HPV-positive cervical specimens from Asia (34.9%), South America (34.4%), Europe (14.4%), and Sub-Saharan Africa (14.3%) (Clifford et al.⁴²)

18, 31, 33, 39, 58, and 59, has ranged from 9% to 23%.^{84,86,88} The wide range of seroprevalence estimates may be due in part to differences in populations surveyed and to use of different assays, capsid antigen preparations, or cutpoints for distinguishing seropositives from seronegatives. Whereas HPV DNA tends to be most prevalent in women under 25 years of age, seroprevalence tends to peak in women over 25 years of age.^{89–94} HPV antibodies are more commonly detected in women than in men.^{8,89,90,93,95–98} Data collected from the National Health and Nutrition Examination Survey between 1991 and 1994 suggest that 18% of women and 8% of men in the general U.S. population harbor antibodies to HPV 16.⁹⁵

■ GEOGRAPHIC DISTRIBUTION

Studies on the evolution of papillomaviruses (Chapter 27) suggest that the known HPV types have existed in nearly identical molecular form since humans first migrated out of

Africa.⁹⁹ Worldwide variations in the prevalence of genital HPV infection exist and are linked to regional variations in cervical cancer rates.^{51,100–111} Recent data also suggest that the distribution of HPV types detected in women varies by geographical region.^{9,42} For example, while HPV 16 is the most common type detected in invasive cervical cancers from all world regions, it is detected more frequently in cases from North America, Europe, and Australia than in cases from Asia, Africa, and South and Central America. Types 35, 52, and 58, on the other hand, are more commonly detected in the latter world regions.⁹ Similar patterns have been observed among cytologically normal women.⁴² Studies of invasive cervical cancers obtained from different regions of the world also suggest that variants of HPV types may segregate according to geography. Based on DNA homology, HPV 16 isolates have been classified into five major lineages, including Asian variants, American-Asian variants, European variants, African-1 variants, and African-2 variants.^{112,113} Compared to the HPV 16 prototype, non-European variants generally have greater nucleotide sequence divergence than European variants. Among European women with cervical cancer, European variants predominate, while African-1 and African-2 variants are more common in Africa.^{114–116} Non-European HPV 16 variants are associated with an increased risk of high-grade cervical or anal dysplasia and cervical cancer.^{114,115,117–122} Recent data also suggest that non-European variants of HPV 18 and HPV 52 are associated with an increased risk of cervical cancer.^{120,123–126} Other work has shown that variants of HPV 16 and HPV 18 appear to persist longer in a host whose race indicates an ancestral geographic distribution that was once shared with that of the variant. For example, European variants of HPV16 and HPV18 persist longer in white women, and African variants persist longer in African American women.¹²⁷

■ INCIDENCE

A population-based study in Rochester, MN, reported an incidence of genital warts of 1.06 per 1000 population in the late 1970s.¹²⁸ In Borås, Sweden, the incidence of genital warts was estimated to be 2.4 per 1000 population in 1990.¹²⁹ Among privately insured individuals in the United States, the age-adjusted incidence of genital warts ranged from 1.2 to 2.1 per 1000 population between 1998 and 2001.^{130,131} In all of these studies, genital warts incidence peaked at lower ages in women than in men. A recent study of female university students showed that most genital warts developed within 12 months after infection with HPV 6 or 11; overall, women developed genital warts within 3 years¹³² (Fig. 28-2).

Recent studies have estimated the incidence of subclinical HPV infections among women testing negative for HPV DNA at an enrollment visit. A comparison of 3-year cumulative incidence estimates from a population of 15–19-year-old

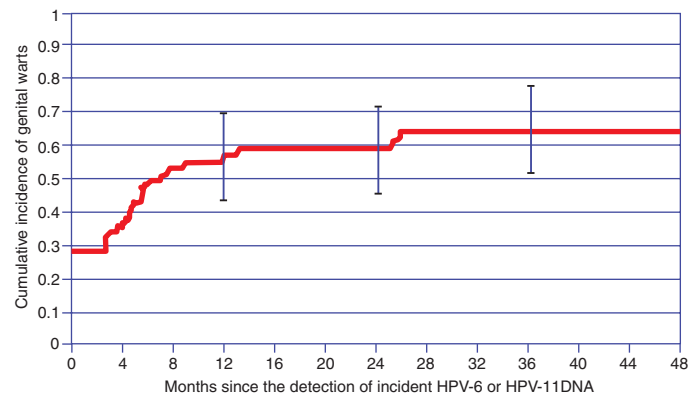


FIGURE 28-2. Kaplan–Meier survival analysis using detection of clinically visible genital warts as the outcome. Line represents proportion of women who developed clinically visible genital warts among women with incident HPV 6 or HPV 11 DNA infections ($n = 54$). (Adapted from Winer RL, Kiviat NB, Hughes JP, et al. Development and duration of human papillomavirus lesions, after initial infection. *J Infect Dis* 2005;191(5):731–738.)

females from the UK (44%)⁷⁰ and two populations of female university students from the United States (both 43%)^{66,133} shows that acquisition of HPV infections is common among sexually active young women. Higher rates have been reported among women attending family planning clinics.^{134,135} Studies enrolling women with a wider range of ages have reported age-related declines in HPV incidence,^{65,136–138} although secondary, minor peaks in incidence have been observed in older women.^{136,137} Incidence rates are generally higher for oncogenic HPV types than for nononcogenic types,^{65,66,70,133–136} and infection with multiple types is common.^{65,66,139,140}

Only a handful of studies have estimated the incidence of HPV infections in men. In studies of male soldiers, 13.8% of 250 Danish soldiers and 21.4% of 210 Mexican soldiers tested positive for HPV DNA after testing negative at an enrollment visit 6–8 months and 1 year earlier, respectively.^{141,142} At a Swedish STD clinic, 19.7% of 76 men testing negative for HPV DNA at enrollment tested positive at a follow-up visit an average of 3.5 months later.¹⁴³ In a small cohort of 85 male and 162 female STD clinic attendees with multiple sex partners, the incidence of HPV infection was similar for men (50.5 per 100 person years) and women (47.1 per 100 person years).¹⁴⁴

TIME TRENDS

In the United States, an eightfold increase in the age- and gender-adjusted incidence of genital warts was reported between the periods 1950–1954 and 1975–1978 (from 13 per 100,000 to 106 per 100,000).¹²⁸ During these years, rates of other STDs were increasing dramatically in Europe and North America and the population of sexually active young adults was also increasing.¹⁴⁵ Other data have shown 2.5–4.5-fold increases in the incidence of genital warts in the United States

and in Europe between the late 1960s and early 1980s.^{146–148} More recently, the age-standardized rate of new genital warts claims among privately insured individuals in the United States increased from 118 per 100,000 in 1998 to 205 per 100,000 in 2001.¹³⁰

TRANSMISSION

■ SEXUAL TRANSMISSION

Genital HPV infections are transmitted primarily through sexual contact. Sexual transmission of clinically evident HPV infection was noted in 1954, when Barrett et al.¹⁴⁹ reported on 24 women with genital warts who noticed the warts 4–6 weeks after their husbands had returned from the Far East. All husbands reported sexual contact with women while overseas, and all husbands had recently had penile warts. Oriol observed that 64% of 88 partners of individuals with genital warts developed warts, and newly developed warts were more infectious than older lesions.²¹ Other data supporting the sexual transmission of HPV include the fact that HPV DNA is rarely found in genital tract specimens of women who have not had vaginal intercourse.^{133,150–152} (HPV infections detected in women who have not had vaginal intercourse have been associated with reports of genital skin-to-skin contact,^{133,153,154} indicating that HPV is transmissible through nonpenetrative sexual contact.) In addition, studies among young women show a positive trend between increasing numbers of sex partners and increasing prevalence of genital HPV infection (see review by Xi and Koutsky⁵⁸). Positive associations between numbers of sex partners and HPV prevalence have also been observed among men, though less consistently (see review by Partridge and Koutsky⁷²). Recent longitudinal studies have demonstrated that HPV acquisition in young women is strongly associated with reports of new and recent sex partners,^{66,133,135,136,155–158} suggesting that the risk of genital HPV infection with each new sex partner is high. Unlike certain bacterial STDs,¹⁵⁹ genital HPV does not appear to require core groups (small segments of the sexually active portion of the population with very high rates of partner change) to sustain high rates of infection in communities throughout the world.¹⁵⁹

Concordance of specific HPV types among sex partners has been demonstrated. In studies using PCR-based methods, type-specific concordance has ranged from 23% to 65%.^{160–164} Concordance for the same HPV 16 variant has also been demonstrated.^{165,166} The transient nature of HPV infections and differences in the sensitivities of sampling methods for men versus women may explain why concordance rates are lower than may be expected.

Abrasion of the epithelial surface is likely to facilitate HPV infection within areas of stratified squamous epithelium. It is less clear, however, whether abrasion facilitates HPV

infection of metaplastic epithelium within the cervical transformation zone, where virtually all cervical cancers arise.

■ NONSEXUAL TRANSMISSION

The transfer of HPV by fomites is important in the transmission of skin warts;¹⁶⁷ whether this occurs with genital HPV types has not been well-evaluated. Digital transmission may occur. In a study of men and women with genital warts, 27% of subjects had the same HPV DNA types detected in genital samples and in finger brush samples.¹⁶⁸ Blood-borne transmission of HPV has not been reported.

Although rare, perinatal transmission does occur. As discussed in Chapter 81, a small minority of infants born to women with genital warts during pregnancy develop laryngeal papillomatosis,¹⁶⁹ and perinatal transmission appears to play a role in cases of condylomata developing within the first week of life.^{170–172}

SUSCEPTIBILITY TO HPV INFECTION

Some papillomavirus-related lesions such as focal epithelial hyperplasia and the macular–papular warts seen in individuals with epidermodysplasia verruciformis appear to be influenced by genetic predisposition.¹⁷³ Human leukocyte antigen (HLA) haplotypes may influence susceptibility to HPV infection and carcinogenic progression. Results from a longitudinal study suggest that HLA class II polymorphisms are involved in the clearance and maintenance of infection.¹⁷⁴ Furthermore, studies from different geographic regions have demonstrated a protective effect of the DRB1*13 allele against the development of high-grade neoplasia and cervical cancer (see review by Hildesheim and Wang¹⁷⁵). Results from studies exploring other polymorphisms in relation to carcinogenic progression have been less consistent.¹⁷⁶

Generally, an increased genital HPV prevalence has been observed among patients with immune-related disorders. Numerous studies have consistently demonstrated a high prevalence of HPV among HIV-seropositive populations of women^{177–192} and men.^{193–200} Studies have also shown increased HPV incidence^{178,201} and increased frequencies of infections with multiple HPV types²⁰² among HIV-infected individuals. One interpretation for the increased prevalence among HIV-seropositive individuals is that HIV-induced immunosuppression leads to reactivation of viruses that are otherwise undetectable. Renal allograft recipients are also at high risk of genital HPV infection, with recipients demonstrating a higher prevalence of HPV 16 or 18 DNA than control subjects.^{203–205}

RISK FACTORS

As noted above, many recent studies have demonstrated a strong and consistent association between increasing numbers

of new and recent sex partners and increasing likelihood of detecting HPV DNA in genital tract specimens. Characteristics of women's male partners are also important with respect to female HPV acquisition. In case-control studies, male partners of women with cervical cancer have reported higher numbers of female sex partners than male partners of control women without cervical cancer.^{77,78,161,206–209} In a cross-sectional study, Burk et al.¹⁵¹ examined the relationship between HPV infection among women and the behavioral characteristics of their regular male partners. The lifetime number of partners of the woman's male partners and duration of her sexual relationship were positively associated with HPV detection among women. Similarly, in a recent IARC pooled analysis, women who reported that their husbands had had extramarital sexual relationships (either before or during marriage) were more likely to test positive for HPV infection.²¹⁰ Data from longitudinal studies support these trends. It has been shown that the risk of female HPV acquisition is positively associated with women's estimates of her male partners' lifetime number of partners^{66,133} and that not knowing a male partner's prior sexual experience is also associated with an increased risk of acquisition.^{133,211} Furthermore, two recent studies of adolescent females noted that associations between increasing male partner age and likelihood of female HPV detection were likely reflective of the positive correlation between male partner age and prior sexual experience.^{211,212} An increased risk of HPV acquisition has also been associated with knowing a partner for less than 8 months before engaging in intercourse.¹³³ These data suggest that the better and longer a woman knows her male partner prior to intercourse, the lower her risk of becoming infected with HPV.

Male circumcision has also been investigated as a risk factor for HPV infection in both men and women, with conflicting results. A handful of studies have reported significantly lower HPV prevalence in circumcised men compared to uncircumcised men,^{142,213–215} whereas other studies reported no significant associations.^{76,216} One of these studies reported that circumcision was protective against prevalent HPV infections and repeat detection of prevalent infections at a 1-year follow-up visit, but not against new infections detected at follow-up.¹⁴² While circumcision status of male partners has not been associated with the risk of female HPV acquisition,¹³³ some,²¹⁵ but not all,^{206,208} case-control studies have reported that male partners of women with cervical cancer are less likely to be circumcised than those of control women.

Data on the association between smoking and HPV infection are inconclusive. Most studies have failed to link smoking to HPV detection in women and men.^{142,217–232} Several other studies have reported positive associations between increased detection of genital HPV infection and past^{216,233} or current smoking.^{55,94,216,234–238} In some cases, these associations were diminished after adjustment for numbers of sex

partners and other covariates.^{94,236,237} One study reported that the positive association between smoking and female HPV infection was restricted to HIV-positive women.²³⁹ In two other studies, significantly lower HPV prevalence was observed for former or ever smokers compared to women who had never smoked.^{240,241} A handful of prospective studies reported no significant associations between smoking and female HPV acquisition,^{66,155,156,236,237} whereas another prospective study of young women detected a significant positive association between current smoking and incident HPV infection, even after adjustment for measured sexual behavior variables.¹³³ It is unclear whether this finding reflects an actual smoking-related increase in HPV acquisition or if smoking is a marker of other unmeasured risky sexual behaviors.

Several lines of evidence suggest that HPV infection may be influenced by hormonal factors. Estrogen stimulation enhances expression of the HPV 16 E6 and E7 genes in SiHa cervical carcinoma cells.²⁴² Hormonal contraceptive (HC) use has been associated with condylomata acuminata.²⁴³ Anecdotal reports suggest that during pregnancy, when levels of estrogen and progesterone are high, condylomata acuminata increase in size in some women.²⁴⁴ The relationship of HC use to HPV infection is difficult to ascertain, given the strong correlation between HC use and sexual activity. Although some studies report an association between use of HCs and detection of HPV DNA independent of correlated variables such as sexual activities,^{133,222,237,245–247} most studies do not.^{48,95,105,156,219,220,224,226,230,233,234,236,240,248,249} Use of HC may represent a surrogate marker for sexual behavior that places a woman at high risk of genital HPV infection.

Some studies show a significantly higher HPV prevalence in pregnant women than in nonpregnant women^{229,250–253} and a decreasing prevalence post partum.^{250,252,254} The increased HPV detection rate among pregnant women may result from hormonal effects, since estrogens and progestagens show a steady increase during pregnancy and decrease post delivery. Alternatively, slight immune tolerance or local physiologic change during pregnancy may be responsible for the increased detection rates. It should be noted, however, that most studies failed to find a significant association between increased HPV prevalence and pregnancy.^{47,255–266} One methodologic difficulty in studies of the effect of pregnancy on HPV detection is lack of comparable controls.

NATURAL HISTORY

It is generally accepted that HPV infections in women are detected transiently, with most new infections becoming undetectable within 1 to 2 years.^{66,69,70,136} HPV 16 appears to persist longer than other HPV types.^{67,69,141,267} Little is known about HPV persistence in men, but studies testing men at two points in time suggest that a majority of HPV infections in men are also detected transiently.^{142,143,201} It is still not clear whether genital HPV infections are entirely eliminated by the host or

merely become suppressed at a level below detection, possibly through immunological mechanisms. Therefore, it should be noted that in epidemiological studies of HPV infection, the term “persistence” refers to persistent detection of infection rather than true viral persistence. A lack of consensus on what constitutes a persistent infection (for example, HPV positivity on two consecutive visits 6 months or 1 year apart) makes it difficult to compare results across studies.

After infection by HPV 16, serum antibodies develop in most women but they appear to develop slowly, and detection of HPV DNA and serum antibodies do not always coincide.^{268–270} Persistent detection of HPV DNA is associated with higher rates of HPV 16 seroconversion.²⁶⁹ A study of women attending a public university²⁶⁸ showed that, overall, 67% of women with incident HPV 16 infection and 94% of those with prevalent HPV 16 infection developed HPV 16 antibodies. In comparison, only 5% of women with incident genital HPV infection with other HPV types and 4% of those who were repeatedly negative for HPV DNA showed HPV 16 seroconversion. Importantly, among women with incident HPV 16 infection, the median time to seroconversion was 8.3 months. In another population of female university students, Ho et al.²⁷⁰ reported that the median time to seroconversion among women with incident HPV 16 infections was also 8.3 months. Seroconversion data among men with incident HPV 16 infections are not available.

Simultaneous coinfection with different HPV types has been commonly observed, but the effect of coinfection on type-specific persistence is unclear. Among populations of women, Rousseau et al.¹³⁹ reported that persistent detection of type-specific HPV DNA was unrelated to coinfection with other HPV types,¹³⁹ and Liaw et al.⁶⁷ reported that HPV 16 positivity did not affect the persistent detection of other HPV types. On the other hand, Ho et al.⁶⁶ reported that detection of multiple HPV types was a predictor of persistently detected infection. In a study of male soldiers in Mexico, Lajous et al.¹⁴² also reported that repeat detection of type-specific HPV DNA at two visits 1 year apart was positively associated with the number of types detected at the first visit.

It is currently unknown whether an initial infection with a specific HPV type confers immunity against reinfection with the same type of virus. A study by Xi et al.²⁷¹ characterized persistence of HPV 16 infection at the variant level. Seventy women who were repeatedly HPV 16 DNA positive two to eight times over an 8–32-month interval showed the same predominant variant at every visit. Sequencing of clones from a subset of specimens indicated that many women were infected by more than one variant but that only one major variant seemed to predominate over time, whereas minor variants appeared to be more transient. These results suggest that HPV 16 establishes a persistent infection in which a single variant predominates, while coinfection may result in minor populations of HPV 16 variants.

All HPV types are linked to the development of low-grade cervical SILs,¹⁶ whereas high-grade cervical SILs are usually positive for oncogenic HPV types.²⁷² In a cohort of young women in the United States, Moscicki et al.¹⁵⁵ reported that 15% developed LSIL within 3 years after initial HPV infection, and in the UK, Woodman et al.⁷⁰ reported that the 3-year cumulative incidence of any cytologic abnormality after initial infection was 33%. In another cohort of young women in the United States, Winer et al.¹³² reported that approximately 50% developed a low-grade lesion within 3 years after initial HPV infection (Fig. 28-3A). The latter study also reported that rates of lesion detection tend to increase with increased screening frequency, due to spontaneous regression of most low-grade lesions. Therefore, the shorter interval between follow-up visits (4 vs. 6 months) may explain why that study detected LSIL in a higher proportion of women. Half of newly detected low-grade lesions appear to regress within 6–9 months.^{70,132,273} It also appears that vaginal SIL is not uncommon among women with incident HPV infections. While less commonly detected than cervical SIL, one study reported that almost 30% of women with incident HPV infections developed vaginal SIL within 3 years (Fig. 28-3B), and the median duration of these lesions was less than 5 months.¹³²

Results from natural history studies suggest that LSILs are transient manifestations of productive HPV infections, whereas HSILs are cervical cancer precursor lesions. This is in contrast to the previously held theory that cervical carcinogenesis always follows a progression from persistent HPV infection to development of low- and then high-grade lesions. Several recent studies have shown that cervical high-grade lesions are a relatively early manifestation of HPV infections in young women. Woodman et al.⁷⁰ reported that the risk of high-grade lesions was highest in the first 6 months after initial HPV infection. It has also been shown that histologically confirmed high-grade lesions are common after infection with HPV 16 and 18 infections,^{132,274} with one study reporting that 27% of women with incident HPV 16 or 18 infections developed histologically confirmed CIN grade 2 or 3 within 3 years (Fig. 28-3C) and that the median time to development was 14 months.¹³² Along with data suggesting that long-term persistence (defined as repeated detection of the same HPV type on two visits at least 5 years apart) is similar for oncogenic and nononcogenic types (with the exception of HPV 16),²⁶⁷ these results suggest that persistence of oncogenic HPV DNA is more of a risk marker for underlying high-grade disease than a risk factor for developing high-grade lesions²⁷⁵ (see Chapter 57).

CLINICAL MANIFESTATIONS

Genital warts and HSIL are the two most common HPV-related clinical manifestations that require treatment. Although colposcopic examination and HPV DNA testing of genital tract

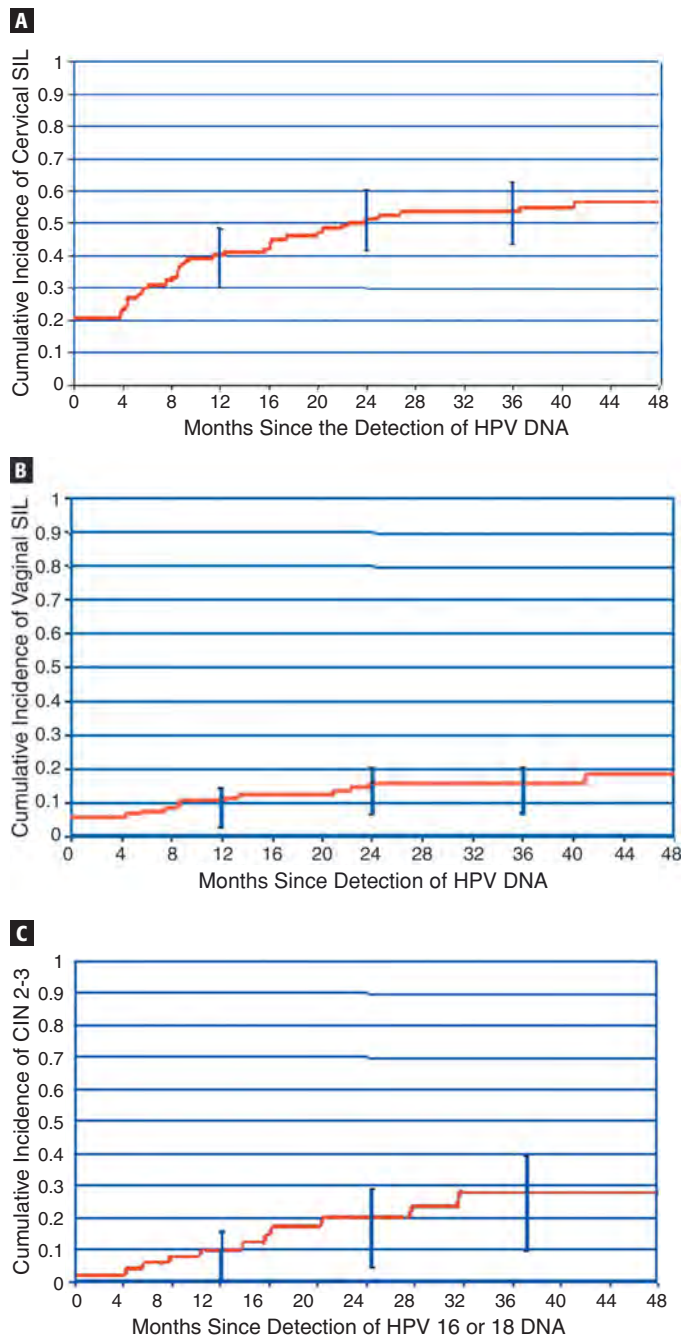


FIGURE 28-3. Kaplan–Meier survival analysis using detection of, **A.**, cervical SIL, **B.**, vaginal SIL, or, **C.**, biopsy-confirmed CIN 2–3 as the outcome. Lines represent proportion of women who developed the outcome among women with incident HPV DNA infections of any type ($n = 195$) or incident HPV 16 or 18 DNA infections ($n = 60$). (Adapted from Winer RL, Kiviat NB, Hughes JP, et al. Development and duration of human papillomavirus lesions, after initial infection. *J Infect Dis* 2005;191(5):731–738.)

epithelium would reveal SIL and HPV infection of the vagina, vulva, anus, or penis in a high proportion of sexually active adults, the clinical significance of SIL at sites other than the cervix (and perhaps the anus) is not clear. As discussed in Chapter 57, there is good support for the idea that high-grade cervical SIL represents an early stage in the development of

invasive cervical cancer. In the anal canal, the dentate line corresponds to a squamocolumnar junction similar to that of the cervix. Individuals who engage in anoreceptive intercourse are at increased risk of HSIL of the anus,^{193,195–199} and by analogy to the cervix they are at increased risk of invasive anal cancer. It has also been reported that the majority of anal cancers in women and homosexual men are positive for oncogenic HPV DNA.²⁷⁶ The clinical diagnosis and management of SIL and cancers of the genital tract is discussed in Chapter 58.

GENITAL WARTS

Individuals presenting with genital warts rarely report symptoms other than the appearance of new bumps or growths on their genitalia. Occasionally, patients will report itching, burning, pain, or bleeding. Some, perhaps most, individuals with genital warts never become aware of their presence. Women with external genital warts may report an abnormal vaginal discharge, which probably is due to a coexisting vaginal infection such as bacterial vaginosis and not HPV.²⁷⁷

Most genital warts occur on the penis, scrotum, urethral meatus, and perianal area in men and on the introitus, vulva, perineum, and perianal area in women. Less often, they may be found on the cervix and vaginal walls in women and the pubic area, upper thighs, or crural folds in both men and women.^{278–283} Because genital warts frequently occur with more than one lesion on one genital site and with lesions on different genital sites, it is important to examine the entire genitalia. Speculum exam for vaginal and cervical warts is recommended for women with external genital warts. Colposcopy is indicated for women with cervical warts, anoscopy for men and women with recurrent perianal warts and a history of anoreceptive intercourse, and urethroscopy for men with warts at the distal urinary meatus and terminal hematuria or abnormal urinary stream. Use of mild (3–5%) acetic acid solutions to detect “subclinical” HPV infections of the external genitalia is not recommended because the predictive value and therapeutic benefit of this procedure have not been established.

Condyloma acuminatum appearing on the lips, tongue, or palate is a rare manifestation of infection by genital HPV types.^{284,285} Some patients with oral condylomata will have concomitant genital or anal warts, and most give a history of oral sex. Although transmission of HPV by orogenital contact occurs, it is not a significant route of transmission.^{133,286,287}

The four morphologic types of genital warts are condylomata acuminata, which have a cauliflower-like appearance (Fig. 28-4); papular warts, which are flesh-colored, dome-shaped papules, usually 1–4 mm in diameter (Fig. 28-5); keratotic warts, which have a thick, crust-like layer and may resemble common skin warts or seborrheic keratosis (Fig. 28-6); and flat-topped papules, which appear macular to slightly raised (Fig. 28-7).^{22,26,283,288–292} In general, condylomas are most frequently detected on moist, partially keratinized

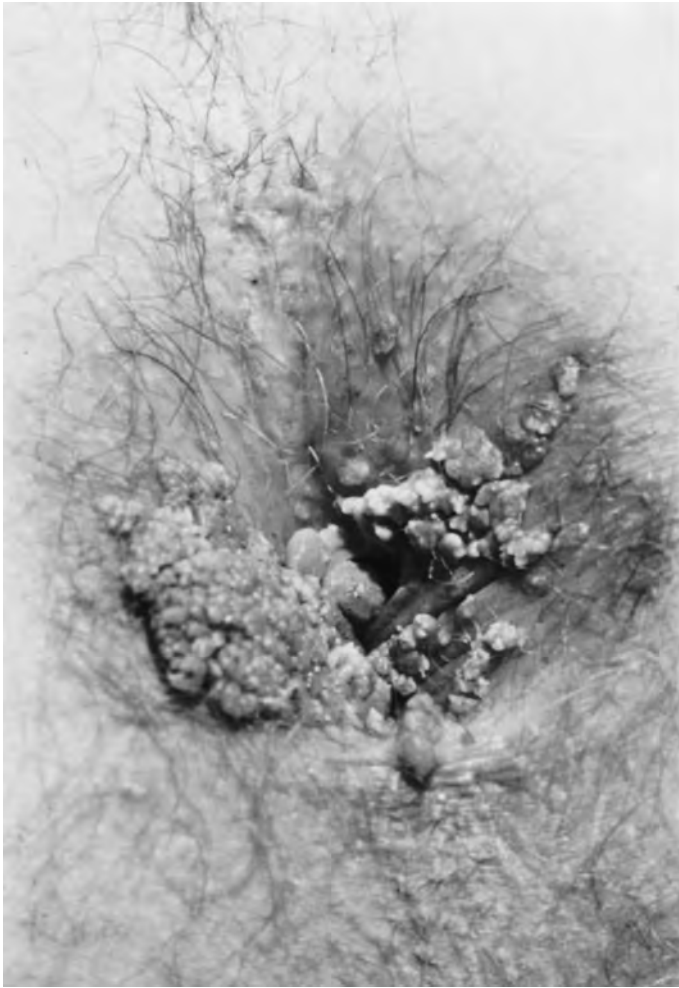


FIGURE 28-4. Anal condylomata acuminata. (Courtesy of E Stolz.)



FIGURE 28-5. Papular penile warts. (Courtesy of KR Beutner.)

epithelium, papular and keratotic warts on fully keratinized epithelium, and flat papular warts on either partially or fully keratinized epithelium. Regardless of morphology and anatomic location, most genital warts are caused by HPV 6 and to a lesser extent by HPV 11 and other HPV types.^{7,8,293,294} A variant of dome-shaped and flat-topped papules, often referred to as



FIGURE 28-6. Keratotic penile warts. (Courtesy of KR Beutner.)



FIGURE 28-7. Flat-topped macular warts. (Courtesy of KR Beutner.)

“bowenoid papulosis,” shows HSIL on histology and is usually hyperpigmented and positive for HPV 16 DNA.²⁹⁵

Some individuals, particularly those with reduced cell-mediated immunity due to HIV, immunosuppressive therapy, Hodgkin’s disease, or pregnancy, develop very large genital warts. On rare occasions, these large warts become locally invasive, destructive but nonmetastasizing tumors that are called giant condylomas or Buschke–Lowenstein tumors.²⁹⁶ These tumors are usually positive for HPV 6 DNA.

The differential diagnosis for genital warts includes papular anatomic structures such as skin tags (acrochordons), pearly penile papules, vestibular papillae, sebaceous (Tyson’s) glands, melanocytic nevi, and acquired papular lesions including molluscum contagiosum, Crohn’s disease, seborrheic keratosis, lichen planus, lichen nidus, and condyloma latum.^{297–303}

Macular or flat lesions considered in the differential diagnosis of genital warts include psoriasis, seborrheic dermatitis, circinate balanitis of Reiter’s syndrome, Bowen’s disease, erythroplasia of Queyrat on the glans penis, and HPV-associated squamous cell cancers.^{297,304,305} If the diagnosis of warts is questionable, a skin biopsy of the lesion may be performed.

MANAGEMENT

As noted above, the prevalence of genital HPV infection is high among sexually active adults, multiple epithelial sites may be infected, and multiple HPV types may be present. Diagnosis and treatment of subclinical genital HPV infections in young adults would be a monumental undertaking, and with the exception of HSIL, of unclear benefit but appreciable risk of scarring, hypo- or hyperpigmentation, and pain.^{306–308} Although the clinical and morphologic manifestations of HPV infection are usually cleared with treatment, it is likely that virus persists in at least a few epithelial cells in some individuals. Treatment of genital warts is usually effective at inducing a wart-free state and may reduce the amount of infectious virus present. Treatment of cervical SIL, particularly HSIL, reduces a woman's risk of invasive cervical cancer (see Chapter 58).

In most settings, patients with genital warts are examined and treated for other STDs. Their current sex partners are also offered examination and treatment for macroscopically visible warts and other STDs. These visits provide an opportunity to counsel and educate. Counseling sessions involve educating patients about their diagnosis, treatment options, probability of recurrences, relationship of HPV infection to cancers, and infectivity. Most patients with genital warts are contagious to uninfected sex partners.^{21,149} Treatment with clearance of warts probably reduces infectivity, but data addressing this issue are currently not available. Whether individuals with asymptomatic HPV infection are as contagious as patients with genital warts is unknown.

GENERAL PRINCIPLES OF TREATING GENITAL WARTS

Small warts of short duration (less than 1 year) respond better to therapy than large warts of long duration.²¹ Although there are no data to show that treatment reduces the probability of transmission, it might. Without treatment, genital warts may disappear, stay the same, or grow larger in size or number.^{309–314} Most genital warts are treated because they are aesthetically unpleasant. Clinical trials suggest that clearance rates are similar for the more widely accepted treatment modalities. Clearance rates have ranged from 23% to 94%.^{315–317} While development of new lesions at previously treated sites is common, posttreatment recurrence rates are not well defined, because few subjects have been studied and follow-up protocols have not been standardized. For example, in some studies a recurrence is defined as a new wart at the same site detected within a 6-month follow-up period, whereas in another study a recurrence is defined as new warts in the same anatomic area arising 2–4 months after initiation of therapy.

Choice of treatment is guided by patient preference, with consideration given to the patient's age and ability to comply with moderately complicated directions, to the location and

number of warts, and to the clinician's training. Several treatment sessions are usually required to achieve a wart-free state. Thus, time spent counseling patients as to the high probability of recurrence during the first 3 months of therapy and the need for multiple treatment sessions is important. There is no need to use expensive and toxic therapies as first-line therapy. Also, there are no data to support use of multiple rather than a single type of treatment on a single wart. Referral to a specialist is indicated for patients with extensive or refractory disease, cervical warts, or warts on the rectal mucosa.

Genital wart therapies are classified as patient applied or provider administered. Patient-applied treatments include podofilox (CondyloxTM) solution and gel, and imiquimod (AldaraTM) cream. To self-treat, patients must be able to identify and reach the warts and to follow the treatment application instructions. The provider-administered treatments include topical treatments—cryotherapy, podophyllin resin, trichloroacetic acid, or bichloroacetic acid; excisional treatments—curettage, electrosurgery, scissors excision, shave excision, or laser vaporization; or injectable treatments—interferon or 5-fluorouracil/epinephrine gel implant.

Podofilox 0.5% solution or gel is an antimetabolic agent purified from podophyllin resin. Unlike podophyllin, podofilox has a stable shelf life, does not need to be washed off after application, and is less likely to cause systemic toxicity.^{315,318,319} Treatment consists of twice-daily application by a cotton-tipped swab for 3 days followed by no treatment for 4 days for up to 4 weeks. Imiquimod 5% cream, which stimulates the production of interferon and other cytokines,^{320,321} is applied to warts with fingers three times per week (every other night) for up to 16 weeks. The treatment area is washed with mild soap and water 6–10 hours after application of imiquimod cream. For both of these patient-applied therapies, the prescribing clinician provides the first application, instructing the patient in proper use. Imiquimod and podofilox have not been approved for treatment of perianal, rectal, urethral, vaginal, or cervical warts. Safety for use in pregnant patients has not been established for either agent.

Cryotherapy, which destroys the wart and a small area of surrounding tissue through freezing, is recommended for small warts that are not extensive. One to six freeze–thaw cycles per wart per treatment session may be required. Most patients will require one to two treatment sessions per week for an average of 4–6 weeks. A cryoprobe, modified Q-tip, or fine spray is used to apply liquid nitrogen to each wart. Cryotherapy may be painful, and a local anesthetic is recommended unless only one or two small warts are being treated. Safety and efficacy are highly dependent on clinician's skills and training. Podophyllin resin, an antimetabolic plant compound, is applied to warts as a 10–25% solution in ethanol or tincture of benzoin and allowed to dry. One to four hours after treatment, the compound is completely washed off. It is applied to the warts by a clinician using a cotton-tipped swab once to twice a week for up to

6 weeks. Applications are limited to 0.5 mL or 10 cm² per treatment session to decrease the potential for systemic effects such as bone marrow depression. Podophyllin is not used in pregnancy. Trichloroacetic or bichloroacetic acid in 80–90% solution may be used to treat small moist warts. The solution is applied by the clinician to each wart. Treatment may be repeated weekly for up to 6 weeks. Due to the low viscosity of these solutions and risk of local irritation, care must be taken to reduce contact of the solution with surrounding normal epithelium. Some clinicians recommend the application of sodium bicarbonate (baking soda) to the uninvolved surrounding epithelium to remove unreacted acid.

Warts may be removed by curettage, electrosurgery, excision by scissors or scalpel, or laser vaporization. Local anesthetic is applied before the excisional procedure is performed. Simple office surgery is often used for extensive or large warts and for treatment of warts during pregnancy. Electrosurgery is contraindicated for patients with cardiac pacemakers or for lesions proximal to the anal verge.

Other treatments, including intralesion injection of interferon and 5-fluorouracil/epinephrine gel implants, have been shown to be as effective as the modalities discussed above in clearing warts that are small in number and size. Side-effect profiles and expense have limited the use of these alternative treatment modalities.^{322–324}

All wart treatments may cause mild local irritation and infrequently cause serious pain or systemic effects. If complete wart clearance is not achieved within 6 weeks for provider-applied therapies or at the end of the manufacturer's specified treatment schedule for patient-applied therapies, use of a different treatment, performance of a skin biopsy, or referral to a specialist is recommended.

FOLLOW-UP

After warts have cleared and possible complications of therapy have resolved, further follow-up of immunocompetent patients is not necessary. A follow-up visit scheduled 3 months after clearance, however, may be helpful for identifying recurrent warts and offering an additional opportunity for patient education and counseling. Furthermore, because genital wart recurrences are much more common in immunosuppressed patients, it may be helpful to provide these patients with repeated evaluations over an extended period of time. Annual cervical cytologic screening is recommended for women with or without genital warts, and the presence of genital warts per se is not an indication for cervical colposcopy.

PREVENTION

■ BEHAVIORAL INTERVENTIONS

Genital HPV infections are so prevalent and so often asymptomatic that risk of infection with one or more HPV types

appears to be high, even among individuals with relatively few sex partners. Nonetheless, there is epidemiological evidence to suggest that certain behavioral interventions could be effective in reducing HPV transmission and HPV-related morbidity. For example, the “ABC” (an acronym that stands for abstain, be faithful, use condoms) approach, an HIV prevention campaign that was successful in Uganda,³²⁵ could be useful in HPV prevention. Abstinence or lifelong mutual monogamy undoubtedly reduces risk of infection, since virgins are rarely positive for genital types of HPV DNA. Condoms are clearly effective in reducing the risk of genital transmission of HIV,³²⁶ but data on protection against other STDs, including HPV, are more limited.^{327,328} There is evidence that condoms protect some women from developing high-grade cervical neoplasia^{329,330} and invasive cervical cancer.^{208,331} Furthermore, in a recent clinical trial randomizing couples to either use or not use condoms, those randomized to use condoms exhibited significantly higher rates of regression of cervical neoplasia and penile lesions and were more likely to have cleared their HPV infections after 2 years.^{332,333} In another recent study of HPV-positive female adolescents, condom use was associated with shorter infection duration.³³⁴ Results from a recent prospective cohort study³³⁵ further suggest that condoms offer some protection against acquisition of new HPV infections. Eighty-two female university students were enrolled prior to or within 2 weeks before their date of first intercourse and followed at 4-month intervals. In addition, they recorded daily sexual behavior information into web-based diaries every 2 weeks. It was reported that women who used condoms for all sex acts in the 8 months prior to HPV testing were 71% less likely to acquire a new HPV infection than women who used condoms less than 5% of the time, even after adjustment for numbers of new sex partners and perceived numbers of male partners' previous sex partners. Specific features of the study design, including frequent longitudinal HPV testing, precise measurement of condom use frequency, and restriction to newly sexually active women, may explain why this study is the first to demonstrate a significant protective effect of condoms on HPV acquisition by females.³³⁵ It is not surprising, however, that some HPV infections were detected among women reporting consistent condom use, as HPV can be transmitted through nonpenetrative sexual contact with both male¹³³ and female¹⁵³ partners and imperfect condom use does occur.

■ PROPHYLACTIC HPV VACCINES

Two newly developed prophylactic HPV vaccines are showing considerable promise. Results from four published randomized controlled trials demonstrate with remarkable consistency that when administered to susceptible young women (15–26 years of age) prophylactic HPV vaccines provide

high-level protection (90% or better) from infection, persistent infection, and high-grade lesions caused by the targeted HPV type(s).^{274,336–342}

Both vaccines are composed of HPV type-specific L1 proteins that self-assemble into noninfectious, recombinant VLPs. One of the vaccines, Gardasil® (Merck & Co., Inc.), protects against HPV types 6, 11, 16 and 18 (quadrivalent) and the other, Cervarix® (GlaxoSmithKline), protects against types 16 and 18 (bivalent). HPV 16 and 18 cause about 70% of cervical cancers worldwide, and HPV 6 and HPV 11 cause about 90% of genital warts.^{8,68} Both vaccines, which are administered at 0, 1 or 2, and 6 months in a series of three 0.5-mL intramuscular injections, were developed to protect against HPV 16- and HPV 18-related genital disease, including cervical, penile, vulvar, vaginal and anal cancer, and precancerous lesions. In addition, the quadrivalent vaccine was developed to protect against HPV 6- and HPV 11-related diseases including genital warts and laryngeal papillomatosis.

Phase IIb trial data indicate that these prophylactic VLP-based vaccines are generally safe and well tolerated. Pain, redness, or swelling at the injection site was reported more often among vaccine recipients than among placebo recipients in the quadrivalent vaccine trial (86% vs. 77%) and in the bivalent vaccine trial (94% vs. 88%). Systemic adverse events including headaches, fatigue, and gastrointestinal symptoms were reported by a similar proportion of vaccine and placebo recipients in both trials: 69% in the quadrivalent vaccine trial and 86% in the bivalent vaccine trial. Findings from these trials also indicate that both vaccine formulations are highly immunogenic, with seroconversion rates to all targeted HPV types of over 98%.^{337,341}

Four to five years of follow-up showed high-level vaccine efficacy for preventing infection and cervical lesions among susceptible young women (i.e., women without PCR or serological evidence of prior infection by the targeted HPV types). The quadrivalent HPV 6/11/16/18 vaccine was 94% (95% CI 83%, 98%) effective in preventing persistent HPV 6/11/16/18 infection and 100% (95% CI 31%, 100%) effective in preventing HPV 6/11/16/18-related CIN.³⁴² The bivalent HPV 16/18 vaccine was 95% (95% CI 64%, 99%) effective in preventing persistent HPV 16 or 18 infection of the cervix, and 100% (95% CI 42, 100) effective in preventing HPV 16/18-related CIN.³³⁸ Results from a large phase IIb trial of monovalent HPV 16 vaccine ($n = 2391$) with 4 years of follow-up also showed high-level efficacy (100%, 95% CI 74%, 100%) for prevention of HPV 16-related CIN 2–3 among susceptible young women.²⁷⁴

These phase IIb trials also showed that vaccine-induced protection was robust. Women with relatively low levels of antibodies after vaccination appeared to be protected, and rare instances of possible break through infections did not appear to be correlated with low antibody titers. A portion of women enrolled in the trials did not receive all three doses of

vaccine within 6 months of the first dose, suggesting that there might be flexibility around the timing of vaccine administration. However, efficacy for less than three doses cannot be inferred, as the number of women who received only one or two doses was insufficient to determine efficacy for less than three doses.

In addition to trials of young women, other ongoing trials will assess vaccine safety, immunogenicity, and efficacy in different populations. Safety and immunogenicity have been evaluated in boys and girls 9–15 years of age (quadrivalent vaccine) or girls 10–14 years of age (bivalent vaccine). Both vaccines are generally safe and highly immunogenic in children. Trials of women over 25 years of age (both bivalent and quadrivalent vaccines) and of young men (quadrivalent vaccine) are ongoing. Other populations to be studied include infants, and immunocompromised children and young adults (e.g., those with HIV/AIDS, transplants, chronic immunosuppression, or autoimmune diseases).

Recent results from the phase III quadrivalent HPV 6/11/16/18 vaccine trials showed high-level efficacy (94% or better) for prevention of HPV 16- and HPV 18-related CIN 2–3 or worse, and prevention of HPV 6-, 11-, 16-, and 18-related CIN, vaginal intraepithelial neoplasia, vulvar intraepithelial neoplasia, and condyloma acuminatum in susceptible populations.³⁴³ Results from an interim analysis of the phase III bivalent 16/18 vaccine trials also showed high-level efficacy (90%) for prevention of HPV 16/18-related CIN 2–3 among susceptible women.³⁴⁴ Regulatory agencies in several countries including Australia, Canada, the European Union, Mexico, and the United States have approved the use of the quadrivalent HPV 6/11/16/18 vaccine. In the United States, the Centers for Disease Control and Prevention (CDC) Advisory Committee for Immunization Practices (ACIP) recommended that the approved vaccine be routinely administered to girls when they are 11–12 years old. The ACIP recommendation also allows for vaccination of girls as young as 9 years of age as well as vaccination of girls and young women 13–26 years of age.³⁴⁵ Australia approved the same HPV vaccine for girls and young women 9–26 years of age and for boys 9–15 years of age. The vaccine is not approved for use in pregnant women. Additional safety data, including data on pregnancy, fetal, and infant outcomes, are being collected in the on-going phase III trials and will continue to be collected in post-marketing surveillance studies after the vaccines are licensed and used in countries throughout the world.

Now that the prophylactic quadrivalent HPV 6/11/16/18 vaccine is commercially available, effective implementation strategies need to be developed. Key issues include how to provide public, provider, and policy maker education about the efficacy and safety of the vaccine; which age groups to recommend for routine and catch-up vaccinations; whether to vaccinate males as well as females; and how to make sure that women continue participating in cervical cancer screening programs. Even when

HPV vaccine coverage becomes widespread, cervical cancer screening will be needed, because cancer-causing HPV types that are not targeted by the vaccine will continue to circulate in the population and because the vaccine will not prevent cervical cancer among women with established HPV 16 or HPV 18 infections. Additional issues that are more acute in less developed countries are the cost of the vaccine, need for refrigeration and clean injection equipment, administration of three vaccine doses to adolescents who have limited access to clinical services, and cultural beliefs that involve sex and gender. As HPV immunization programs are implemented throughout the world, it will also be important to evaluate the duration of protection, need for a booster dose, and the impact of vaccination on the transmission dynamics and natural history of HPV types not included in vaccines.

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HISTORY AND DEFINITIONS

Although viral hepatitis is unquestionably an ancient disease, it is only in the past 40 years that an appreciation has emerged of the diversity of infectious agents capable of causing the clinical syndrome of acute hepatitis. The era of modern hepatitis virology began with the discovery of Australia antigen by Blumberg and associates in 1965 and the subsequent association of this antigen with hepatitis B.^{1,2} Knowledge in this area has since continued to expand rapidly, and at least five distinctly different human viruses (classified as hepatitis A through E) are now generally recognized to be causative agents of acute and/or chronic viral hepatitis (see [Table 29-1](#)).

Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV), and hepatitis E virus (HEV) all share a remarkable tropism for the liver despite profound differences in their physical structure, pathobiology, and epidemiology. Each of these viruses is a cause of clinically overt acute hepatitis associated with frank jaundice. The severity of the liver disease, which frequently accompanies acute infection with these viruses, generally distinguishes them from cytomegalovirus and Epstein-Barr virus, which typically cause much milder liver dysfunction during primary infections. Within the United States, almost all cases of acute hepatitis are caused by infection with HAV (51%), HBV (40%), or HCV (9%).³ These acute hepatitis virus infections cannot be distinguished from each other without serologic testing. Acute hepatitis represents a considerable disease burden within the United States, with an estimated 40,000–60,000 clinical cases occurring annually during the past 5 years. Only a fraction of these cases are reported to public health authorities, and a substantial number of additional infections do not come to medical attention because they are asymptomatic. Fulminant hepatic failure and death occur in a very small proportion of patients with acute hepatitis A or B, but these clinical endpoints are rarely associated with acute HCV infection in the United States.^{4,5}

The major burden of disease due to hepatitis virus infections stems from the chronic liver damage that occurs in individuals who develop persistent infections. The proportion of persons who become persistently infected is highly dependent on the infecting virus. Persistent infections with HAV are not well documented and may never occur. On the other hand, more than 50% of persons infected with HCV fail to clear the virus and most eventually develop biochemical and histologic evidence of chronic liver disease.⁶ HBV has an intermediate tendency to establish persistence, with the risk of persistent infection being highly dependent on the age at the time of infection and immunologic competence of the individual.

It is appropriate to focus attention on the hepatitis viruses in a textbook concerned with sexually transmitted diseases (STDs). Although these are systemic infections that are also commonly transmitted by other means, HBV is a sexually transmitted infection, and sexual activity may profoundly influence the risks for acquisition of HAV. To a lesser extent, sexual behavior may also influence the risk of infection with HCV and HDV. Vaccines are now available for the prevention of hepatitis B (and with it hepatitis D) and hepatitis A.⁷ These vaccines provide a unique means of prevention among STDs, and they should be used in populations at risk of these infections. This chapter will discuss the epidemiology and pathobiology of the hepatitis viruses and the use of hepatitis vaccines in populations at risk of STDs. Aspects of the management of patients with viral hepatitis are considered in Chapter 66.

HEPATITIS A

HEPATITIS A VIRUS

Physical characteristics and replication cycle

HAV is classified as the type species of the genus *Hepatovirus* of the family *Picornaviridae*. The virus is a small 27-nm, spherical, nonenveloped particle.^{8,9} Its RNA genome is single stranded, positive sense, and approximately 7.5 kb in length.

Table 29-1. Human Hepatitis Viruses

	Taxonomic Classification Virus Family (Genus) ^a	Genome ^b	"Viral" Envelope	Modes of Transmission ^c	Persistent Infection	Disease Associations ^d
Hepatitis A Virus ("infectious hepatitis")	<i>Picornaviridae</i> (<i>Hepatovirus</i>)	L/ss RNA 7.5 kb	No	ET ST PT (rare)	Extraordinarily rare if ever	AH, FH
Hepatitis B virus ("homologous serum hepatitis")	<i>Hepadnaviridae</i> (<i>Orthohepadnavirus</i>)	C/ds DNA 3.2 kb	Yes	HT ST NT	Common in infants and immunocompromised persons	AH, FH CH HCC
Hepatitis C virus ("post-transfusion NANB hepatitis")	<i>Flaviviridae</i> (<i>Hepacivirus</i>)	L/ss RNA 9.6 kb	Yes	PT ST (occasional) NT (occasional)	85% of all infected Persons	AH CH HCC
Hepatitis D virus ("delta hepatitis")	Unassigned genus (<i>Deltavirus</i>)	C/ss RNA 1.7 kb	Yes	PT ST (occasional)	Common if patient is an HBV carrier	AH, FH CH
Hepatitis E Virus ("enterically transmitted NANB hepatitis")	Unassigned genus (<i>Hepevirus</i>)	L/ss RNA 7.2 kb	No	ET	Never	AH, FH

^aVirus family (genus).

^bL, linear; C, circular; ss, single-stranded; ds, partially double-stranded; kb, kilobases.

^cDocumented modes of transmission: ET, enteric transmission; HT, horizontal transmission (see text); NT, perinatal transmission; PT, percutaneous transmission; ST, sexual transmission.

^dAH, acute hepatitis; FH, fulminant hepatitis; CH, chronic hepatitis and cirrhosis; HCC, hepatocellular carcinoma.

The genome organization includes a 5' nontranslated segment, ~734 bases in length,¹⁰ followed by a single long open-reading frame encoding a polyprotein of ~2227 amino acids, and a short 3' noncoding region that terminates in a 3' poly(adenylic acid) tract (Fig. 29-1). A small, genome-linked protein (VPg) is covalently attached to the 5' end of virion RNA. Genome-length cloned cDNA and RNA derived from it are infectious in cell cultures.¹¹

Within the infected cell, virion RNA acts as a messenger for synthesis of a large polyprotein, which is cotranslationally processed by the virus-specified 3C^{pro} proteinase into both structural and nonstructural proteins^{12,13} (Fig. 29-1). Three capsid proteins (VP1, VP2, and VP3, ranging from 222 to ~280 amino acid residues in length) have been demonstrated in purified virus preparations. Virion RNA also serves as template for (–)-strand RNA synthesis, which acts, in turn, as template for synthesis of more (+)-strand genomic RNA. This newly synthesized (+)-strand RNA is either used for further rounds of replication or packaged within the capsid proteins for export from the hepatocyte across the apical canalicular membrane into the bile. As with other picornaviruses, replication occurs in the cytoplasm of the infected cell and RNA transcription proceeds asymmetrically, with an excess of

(+)-strand molecules synthesized under direction of the virus-specified 3D^{pol} RNA-dependent RNA polymerase.⁸

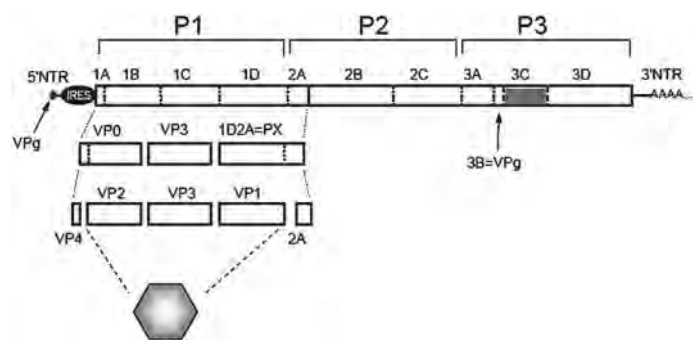


FIGURE 29-1. Genomic organization of HAV. The ~7.5-kb single-stranded (+)-sense RNA genome has a 5' untranslated region (5'NTR) approximately 740 bases in length, followed by a long open-reading frame (boxed region). The 5' terminus of the RNA is covalently linked to a small viral protein (VPg). There is a short 3' untranslated region, followed by a poly(adenylic acid) tail. Translation is under direction of an internal ribosome entry site (IRES), which is located within the 5'NTR. This leads to synthesis of a large polyprotein, which is cotranslationally processed by a viral proteinase (3C^{pro}) into capsid precursor proteins, VP0, VP2, PX (representing the P1 segment of the polyprotein), and a series of proteins, which are active in replication and which include the RNA polymerase, 3D^{pol} (P2-3 segments). "PX" in VP0 undergoes further cleavage to VP4 and VP1 following packaging of the viral RNA.

HAV may be propagated in cell cultures with reasonable efficiency. However, in most *in vitro* systems, HAV does not produce a cytopathic effect; there is no shutdown in host cell protein synthesis such as occurs with poliovirus infection. A variety of primate cell lines are permissive for HAV replication, but primary isolation of wild-type virus is difficult and frequently entails a period of several weeks (or longer) between inoculation of cell cultures and the first detection of viral antigen.^{14,15} Thus, virus isolation is not useful for diagnosis. Furthermore, virus yields from cell culture are relatively low. Nonetheless, the ability of this virus to be propagated in cell culture has made it possible to develop conventional formalin-inactivated vaccines (see below).

No significant antigenic differences have been found among strains collected from widely separated geographic regions.^{16,17} Substantial evidence suggests that the critical antigen(s) of HAV are conformationally determined and are thus “assembled” rather than “linear” structures determined solely by the primary amino acid sequences of the capsid protein. Analysis of HAV using neutralizing murine monoclonal antibodies indicates the presence of an immunodominant antigenic site on the virus capsid that is involved in antibody-mediated neutralization. Genomic sequencing of viral escape mutants selected during growth of the virus in the presence of neutralizing monoclonal antibodies has shown that such resistance can be conferred by substitutions at amino acid residues within VP3 and VP1, which contribute to this site.¹⁸ The conformational nature of the critical HAV antigens has prevented development of a vaccine, based on expression of antigen from recombinant cDNA.

Pathobiology

Chimpanzees, several species of marmosets, and New World owl monkeys are susceptible to HAV and may be infected by either oral or percutaneous inoculation of virus.^{19,20} Although disease in these primates is usually mild compared with symptomatic infections in adult humans, the course of the infection is otherwise very similar. Infection of the hepatocyte is central to the pathogenesis of hepatitis A. Studies with animal models have provided conflicting evidence for the replication of virus within the gastrointestinal epithelium, even though relatively large amounts of virus are present in feces from 1 to 4 weeks after exposure (Fig. 29-2). However, strong data support replication of the virus within crypt cells of the small intestine.²¹

Fecal shedding of the virus reaches its maximum just prior to the onset of hepatocellular disease, at which point the individual is probably most infectious. HAV, replicated predominantly within hepatocytes, is present in the bile and feces.²² Viral antigen also has been detected within the cytoplasm of hepatocytes, as well as within germinal centers of the spleen and lymph nodes and along the glomerular basement membrane in some primates.²³ There is an extended viremia that

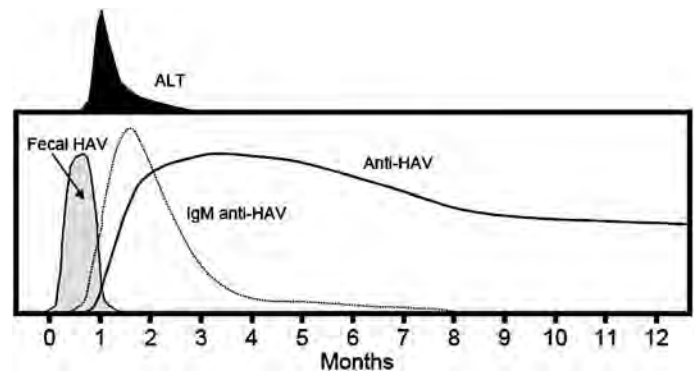


FIGURE 29-2. Typical clinical and virologic course of HAV infection. Temporal patterns are shown for the fecal excretion of HAV, the short-lived IgM-specific anti-HAV response, and the long-lasting total anti-HAV response. At the top is shown the serum ALT pattern, which reflects the acute liver injury associated with this infection.

persists for several weeks during the prodrome and early clinical phase of the illness; it roughly parallels the shedding of virus in the feces but is of much lower magnitude.²⁴ At the onset of hepatic inflammation in experimentally infected primates, the titer of infectious virus is greatest in liver, followed by feces, and then serum. The situation is likely to be similar in infected humans. Viral RNA may be detected in the feces for weeks after the onset of symptoms, but it is likely associated with only very low infectivity after the first 2 weeks of illness. Chronic fecal shedding of virus has not been observed. Epidemiologic studies noting the disappearance of HAV from closed populations with the passage of time argue against its existence.²⁵ Relatively prolonged shedding of the virus has been reported in infected premature infants²⁶ but has not been documented in other immunocompromised persons.

The mechanisms responsible for hepatocellular damage are poorly characterized. However, type A hepatitis appears to be due to an immunopathologic response to infection of the hepatocyte, rather than to a direct cytopathic effect of the virus. HLA-restricted, virus-specific, cytotoxic, CD8+ T cells have been recovered from the liver of persons with acute hepatitis A.^{27–29} Virus-specific cytotoxic T cells have been shown to secrete gamma interferon, which likely stimulates the recruitment of additional, nonspecific inflammatory cells to the site of virus replication within the liver.³⁰ A recent study found that patients with fulminant hepatitis A were more likely to have low or undetectable serum HAV RNA at presentation compared to those with a nonfulminant course, lending further support to the role of host immune response in hepatocellular damage.³¹

Immunity

Little is known about the innate immune response to HAV. However, like many other viruses, HAV has evolved mechanisms to block interferon-mediated innate responses.³² Protective immunity to HAV is conferred by antibody to the

virus (anti-HAV), which generally appears in the serum concurrent with the earliest evidence of hepatocellular disease (Fig. 29-2). This early antibody largely comprises IgM, although IgG may also be present shortly after the onset of symptoms.³³ IgG anti-HAV persists for life and confers protection against reinfection.³⁴ Reexposure of seropositive individuals may lead to increases in anti-HAV titer but is not associated with liver disease.³⁵ Both fecal and serum IgA anti-HAV have been described,³⁶ but the role of secretory immunity in protection against HAV infection appears to be very limited.³⁷ Both NK cell and virus-specific, HLA-restricted cytotoxic T-cell activities have been described.^{27,29,38} Along with the induction of interferon synthesis, such cellular effector mechanisms are likely to play an important role in clearing virus from the infected liver.

Transmission

With a few notable exceptions, the transmission of HAV between individuals is by the fecal–oral route, which includes sexual practices, such as oral–anal contact (see below). The potential for household transmission and even common-source outbreaks is enhanced by the large amounts of virus present in feces and the extraordinary physical stability of the virus.³⁹ Virus is concentrated from contaminated coastal waters by filter-feeding shellfish; hepatitis A may result if such shellfish are ingested inadequately or uncooked. In experimentally infected nonhuman primates, HAV has been detected in saliva during the incubation period.⁴⁰ However, transmission by saliva has not been demonstrated.

Percutaneous transmission of HAV has been documented with transfusion of blood and blood products, but such instances are relatively rare because the frequency of viremia (which only occurs during acute infection) is exceptionally low in blood donor populations. Nonetheless, outbreaks of hepatitis A have been reported among users of injection and noninjection drugs in Australia, Europe, and North America. In the United States, users of injected and noninjected methamphetamine have accounted for up to 48% of reported cases during certain outbreaks.^{41,42} In addition, injection-drug users (IDUs) have a higher prevalence of anti-HAV than the general U.S. population. Transmission among IDUs probably occurs through both fecal–oral and percutaneous routes. Although not widely appreciated, it seems likely that HAV is often transmitted percutaneously among IDUs who share paraphernalia for the preparation and injection of drugs.^{43–44} Viremia persists for several weeks during acute infection,^{24,40} and the exceptional physical stability of the virus (which exceeds that of HBV or HCV) would favor such transmission. Within the United States, the reported frequency of hepatitis A among such individuals has remarkably paralleled that of hepatitis B and hepatitis C, peaking in the late 1980s and since declining substantially.

■ EPIDEMIOLOGY

Population studies

The incidence of HAV infection is highly related to the current level of hygiene and sanitation, and the infection is most endemic in the less developed parts of the world, where poor socioeconomic conditions facilitate transmission of the virus. In the developed world and in some developing countries, the seroprevalence of HAV infection has declined, presumably because of improvements in hygiene associated with rising socioeconomic conditions.^{45,46} Because of this trend, the percentage of the adult population susceptible to the virus has undoubtedly increased and will probably continue to do so. In testing carried out as part of the third U.S. National Health and Nutrition Examination Survey between 1988 and 1994, anti-HAV was detected in 31% of Americans over 6 years of age.⁴⁷ The prevalence of antibodies increased with age and was higher among foreign-born immigrants (especially those of Mexican-American ethnicity). These results confirm and update earlier results showing that the prevalence of anti-HAV is related to age as well as socioeconomic factors within the United States.⁴⁸ The age-related nature of antibody prevalence in some Western countries appears to be due largely to a cohort effect created by the decreasing incidence of HAV infection. This general trend toward decreased incidence in developed countries pre-dated the introduction of hepatitis A vaccine but has likely been accelerated by it in countries that have embraced immunization.⁴⁶ By 2004, reported cases of hepatitis A had dropped to an all-time low in the United States, approximately 1.9/100,000 persons per year.⁴⁶

In contrast to the United States and other developed countries, most infections occur during early childhood in many developing nations,⁴⁹ often at an age at which specific symptoms of hepatitis A are minimal or absent (see below). In these countries with highly endemic infection, virtually the entire population has been infected and is immune by age 10.⁵⁰ In other developing countries, sanitary conditions have improved. Although transmission among young children is still common, a higher proportion of adolescents and adults remain susceptible and, when infected with HAV, are likely to develop symptomatic illness. The potential impact of this transitional pattern is typified by an epidemic of hepatitis A in Shanghai, which reportedly involved over 300,000 persons in early 1988.⁵¹

Endemic hepatitis A

The vast majority of HAV infections occur sporadically, presumably as a result of person-to-person spread of virus. Transmission occurs most frequently among close contacts, especially in households and extended family settings.⁵² Because the majority of children have asymptomatic or

unrecognized infections, they play a key role in HAV transmission and serve as a source of infection for others. In one study of adults without an identified source, 52% of their households included a child aged <6 years, and the presence of a young child was associated with HAV transmission in the household.⁵³ In studies in which serologic testing of the household contacts of adults without an identified source of infection was performed, 25–40% of contacts aged <6 years had serologic evidence of acute HAV infection (IgM anti-HAV).^{54,55} Recommendations to immunize children against hepatitis A in states having consistently increased incidence rates of the disease were made in the late 1990s and have been associated with dramatic reductions in disease incidence.⁴⁶

Sexual transmission

Hepatitis A, like other predominantly enteric infections, may be transmitted during sexual activity. However, the importance of sexual behavior in determining the risk of HAV infection varies widely among different populations. Sexual activity undoubtedly plays a greater role in the spread of HAV in industrialized nations, where most adolescents and adults are susceptible, than in developing nations, where HAV is highly endemic and most of the population is immune. Sexual activity also plays a greater role in the spread of HAV when sexual practices facilitate fecal–oral exposures. Thus, the risk for infection is particularly high among men who have sex with men (MSM).

Hepatitis A outbreaks among MSM have been reported frequently. Cyclic outbreaks have occurred in urban areas in the United States, Canada, Europe, and Australia and can occur in the context of an outbreak in the larger community.^{56–65} While some studies of these outbreaks identified specific sexual practices, such as higher numbers of partners and oral–anal contact, as risk factors for infection, other studies did not identify such associations.

Early seroprevalence studies also demonstrated an increased risk of HAV infection among MSM. In a study from Seattle, 30% of 102 MSM recruited from an STD clinic had anti-HAV antibodies, compared with only 12% of age- and socioeconomically matched heterosexual males.⁵⁶ The risk of previous infection was related to age, number of sex partners, and duration of homosexuality. In another study from San Francisco, 28% of MSM, aged 17–22 years, had serologic evidence of past infection.⁴⁴ Anti-HAV seropositivity was independently associated with Hispanic ethnicity, less than a high school education, and a history of more than 50 lifetime male sexual partners. Recent infection was documented in 3.3% of susceptible men. It was independently associated with insertive anal intercourse and the sharing of contaminated needles.⁴⁴ In the Seattle study,⁵⁶ an annual infection rate of 22% was observed when seronegative MSM were followed prospectively. Men reporting frequent oral–anal exposure were found to be at significantly

increased risk of becoming infected with HAV.⁵⁶ In retrospect, it is apparent that an epidemic of hepatitis A had occurred among MSM in Seattle at the time of this study. Most of the men who were studied had been homosexual for many years (mean = 12.4 years for those without anti-HAV). If the annual risk of acquiring hepatitis A were constant at 22%, the expected antibody prevalence would have been far greater than the observed 30%. This periodicity is further demonstrated by the results of seroprevalence studies of MSM conducted during the past 10 years, which have not consistently demonstrated an elevated prevalence of anti-HAV compared with a similarly aged general population.⁶⁶ An increase in the pool of susceptibles increases the probability of disease, when HAV is reintroduced into the community. Recent incidence data from the United States have shown highest hepatitis A rates among men aged 25–39 years.⁶⁷

An association between hepatitis A and sexual activity is more difficult to demonstrate in countries with moderate-to-high endemicity of infection. In a study carried out in Madrid, Spain, a region where hepatitis A is moderately endemic, there were no differences in the prevalence of anti-HAV in homosexual and heterosexual men.⁶⁸ At an average age of 28–29 years, 43–47% of these men were positive for anti-HAV antibodies.⁶⁸ However, a history of oral–anal contact was associated with anti-HAV seropositivity independent of sexual orientation.

Despite this evidence for sexual transmission of HAV, hepatitis A differs from most other STDs in at least two important ways. First, infection with the virus produces solid immunity so that symptomatic reinfection never occurs. Second, the infected individual is infectious for a relatively brief period of time. There is no prolonged carrier state. Although there has been little effort to formally model the sexual transmission of HAV, these facts suggest that several conditions may be required to sustain sexual transmission of HAV within a population. These include (1) a high degree of susceptibility among the population at risk, as defined by negative tests for anti-HAV, (2) sexual promiscuity, so that multiple partners may be exposed during the relatively brief period when virus is shed, and (3) sexual practices facilitating fecal–oral spread of virus. Epidemics of hepatitis A among urban MSM have generally included all of these elements. The sporadic nature of these outbreaks further suggest that introduction of virus into the sexually active population may be an additional requirement.^{56,60,62–64}

Although vaccination of children can result in fewer adult cases associated with contact with children, transmission among selected groups of adults can be sustained in the absence of transmission among children. Thus, within the United States, cases increasingly are concentrated among adults in identified high-risk groups, such as international travelers, users of illegal drugs, and MSM. The relatively high

disease rates among adult men younger than 40 years are a manifestation of this phenomenon.

■ CLINICAL MANIFESTATIONS OF HEPATITIS A

In the individual patient, acute illness due to HAV is indistinguishable from that due to hepatitis B or hepatitis C.⁶⁹ The incubation period of hepatitis A is relatively short, averaging about 4 weeks (Fig. 29-2). Under the age of 3 years, less than one in 10 infected children develop symptoms of hepatitis, whereas most infected adults are symptomatic.⁷⁰ Symptoms are often abrupt in appearance, although there may be a prodromal period of low-grade fever, malaise, headaches, and myalgias. Anorexia, nausea, and vomiting occur early in the illness, and diarrhea is not uncommon, especially among children.⁶⁹ The specific diagnosis of viral hepatitis, however, is often not suggested until the occurrence of dark urine or jaundice. Serum aminotransferase elevations are similar in magnitude to those seen in acute hepatitis B, although they generally do not persist as long. Most infected individuals will have normal aminotransferase levels by 6 weeks after the onset of symptoms, although 10–20% of cases may have minor enzyme abnormalities persisting for up to 3 months and occasionally longer.

Chronic viral hepatitis has not been documented to follow HAV infection, and there is no evidence of long-term persistence of the infection. However, it has been suggested that in rare instances HAV infection may trigger the onset of chronic autoimmune liver disease.⁷¹ Although jaundice may occasionally be prolonged for several weeks or more (“cholestatic hepatitis”), it is not indicative of severe hepatocellular disease and uniformly resolves with time.⁷² Occasional cases of “relapsing hepatitis A” have been noted. These patients have symptomatic and biochemical evidence of recurrent hepatitis, usually occurring within several months of acute type A hepatitis.^{72,73} The pathobiology of this condition is uncertain, but it always resolves without progression to chronic hepatitis. Hepatitis A accounts for less than 10% of all cases of fulminant hepatitis,⁷⁴ and the mortality in acute symptomatic hepatitis A is probably less than 0.1–0.2%. In an initial report from the U.S. Acute Liver Failure Study Group that included 354 patients enrolled between 1998 and 2001, 16 (4.5%) had hepatitis A.⁷⁵ A recent update that included 973 patients enrolled up to 2006 found that only 30 (3%) had hepatitis A (Lee WM, personal communications, September 2006). Several reports suggest that patients with underlying liver disease are more likely to develop fulminant hepatitis when infected with hepatitis A. Patients with acute liver failure due to HAV are more likely to recover spontaneously than those with acute liver failure due to HBV infection.

■ DIAGNOSIS OF HEPATITIS A

The diagnosis of hepatitis A rests entirely on serologic methods (Table 29-2). Anti-HAV is usually measured by solid-phase

enzyme-linked immunosorbent assay (ELISA). Absence of anti-HAV is strong evidence against current infection with HAV. However, the detection of anti-HAV in a patient with hepatitis does not prove infection is recent or responsible for current symptoms. A specific serodiagnosis requires the demonstration of IgM anti-HAV, which is present in virtually all patients with acute hepatitis A (Fig. 29-2). IgM anti-HAV may be detected by sensitive antibody-capture immunoassays for as long as 6 months after the onset of symptoms.^{33,76}

Table 29-2. Common Diagnostic Markers of Hepatitis Virus Infections

	Diagnostic Marker	Significance of Marker
HAV	Anti-HAV	Past or present infection, immunity to HAV
	IgM anti-HAV	Recent acute infection with HAV
HBV	HBsAg	Current acute or chronic infection with HBV
	HBeAg	High-titer HBV carrier, high infectivity
	HBV DNA	Current infection (quantitative measure of viremia)
	Anti-HBs	Immunity to HBV (vaccine or natural infection)
	Anti-HBc	Past or present infection with HBV
	IgM Anti-HBc	Recent acute infection with HBV
HCV	Anti-HBe	Reduced viral replication (except with precore mutants)
	Anti-HCV (ELISA)	Probable infection with HCV (~15% may have cleared infection)
	Anti-HCV (RIBA)	Recombinant immunoblot confirms screening ELISA
	HCV RNA	Definitive evidence of current infection (bDNA or RT-PCR assay)
HDV	Anti-HD	Active or recent infection with HDV

■ PREVENTION OF HEPATITIS A

Passive immunization

Immune globulin (IG), if administered within 2 weeks of exposure, is 80–90% effective in protecting against illness associated with HAV infection.⁷⁷ Infection is also probably prevented if IG is given soon enough after exposure. IG confers immediate protection against hepatitis A, while hepatitis A vaccine does not produce protective levels of antibodies to HAV until 2–4 weeks after active immunization (see next section). Thus, IG continues to have an important role in the management of exposed persons.^{78–80} Postexposure prophylaxis with IG (0.02 mL/kg intramuscularly) is recommended for household and sexual contacts of patients with hepatitis A.⁸⁰ Postexposure prophylaxis is generally not recommended in the setting of a common source outbreak, because such outbreaks are usually recognized only well into their course. IG has not been demonstrated to be effective in prevention of disease more than 2 weeks after exposure.

Active immunization

Whole cell inactivated vaccines have largely replaced IG for preexposure prophylaxis of hepatitis A.^{7,9} Hepatitis A vaccines contain formalin-inactivated viral particles that are produced in cell culture, purified, and adsorbed to aluminum hydroxide.^{81,82} Immunization elicits serum neutralizing antibodies (anti-HAV), which protect against both infection and disease.⁸³ At present, two similar vaccines are licensed in the United States for persons 12 months old or older: *Havrix* (GlaxoSmithKline Biologicals) and *Vaqta* (Merck). Both are produced from virus grown in infected human diploid fibroblasts. Each vaccine is available in adult and pediatric/adolescent formulations (for persons at least 18 years old, there is a combination hepatitis A and hepatitis B vaccine, *Twinrix* [GlaxoSmithKline Biologicals]). Comparative clinical trials of these vaccines have not been reported, but they appear to be comparable with respect to their clinical performance. Reactogenicity is relatively low and similar to that reported with hepatitis B vaccines. The most common adverse events include soreness at the site of intramuscular injection, which occurs in 21–56% of recipients. Fever has been reported in up to 4%.⁸⁴ Anaphylaxis, Guillain–Barré–Landry syndrome, and more obscure neurologic syndromes have been reported rarely. For adults over 17–18 years of age, both vaccines are given on a two-dose schedule, usually with 6–12 months intervening between doses. The package insert should be reviewed for specific details concerning administration.

Efficacy trials of hepatitis A vaccines have been limited to children, but it is reasonable to assume that similarly impressive results would be achieved in adults who develop comparable anti-HAV responses. In a randomized, placebo-controlled

trial, carried out among children aged 2–16 years, in Monroe County, New York, a single 25-U dose of *Vaqta* provided complete protection against symptomatic hepatitis A during a seasonal outbreak of disease (95% confidence interval was 87–100%).⁸⁵ The last case of hepatitis in an immunized child occurred 18 days after vaccine administration. Similar protection was observed in Thai children who had completed a primary immunization series with two 360 El. unit doses of *Havrix* (95% confidence interval = 74–98%).⁸⁶ Immunization also has been shown to prevent asymptomatic infection.⁸⁷

Hepatitis A vaccine is recommended for persons at increased risk of hepatitis A.⁸⁰ This includes MSM, injection and non-injection illicit drug users, international travelers to hepatitis A endemic regions, and others. The decision to use vaccine in any risk group should reflect the perceived risk, the potential severity of infection, and the cost of the vaccine. The Advisory Committee on Immunization Practices of the U.S. Public Health Service recently endorsed universal childhood immunization against hepatitis A within the United States.⁸⁰ This followed recommendations a decade earlier to immunize children aged 2 years and older in 17 states within the United States, where hepatitis A incidence was especially high, a recommendation that was followed by sharp overall reductions in the incidence of the disease, not only in children but also in adults.^{46,88} The presence of anti-HAV obviates the need for immunization in an individual, but serologic testing is not necessary prior to immunization. Preimmunization screening is not likely to be cost effective, unless the prevalence of antibody exceeds 30%, and, thus, is not warranted in most U.S. populations.

HEPATITIS B

■ HEPATITIS B VIRUS

Physical and chemical characteristics

HBV, a hepadnavirus, is one of a family of related DNA viruses infecting the livers of a variety of avian and mammalian species. The HBV virion (also known as the Dane particle) is a complex, double-shelled, 42-nm spherical particle, with an outer surface envelope surrounding a core structure containing a small DNA genome (Fig. 29-3). This genome is unique among human viruses in that it is a circular DNA molecule that is double stranded for 50–85% of its length, with a total genome length equivalent to double-stranded DNA of approximately 3200 base pairs^{89–91} (Fig. 29-4). The genomes of a number of HBV strains have been molecularly cloned and fully sequenced. The partially double-stranded DNA consists of a long strand, which is (–)-sense (i.e., antimesenger sense), and a shorter (+)-sense strand, which overlap at their 5′ ends (see Fig. 29-4).⁹² Within the (+)-strand, there are four overlapping, open-reading frames utilizing all three

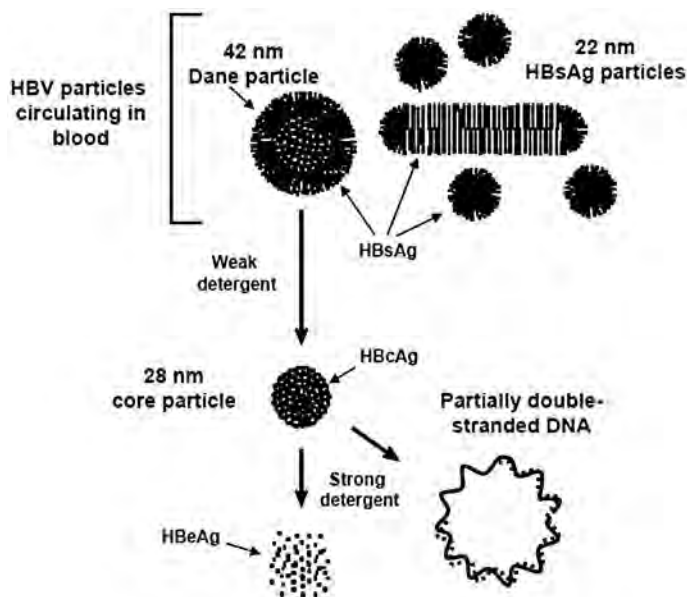


FIGURE 29-3. Structure of HBV. A variety of HBV particles are present in the blood of an infected person. These include the 42-nm-diameter infectious virion (Dane particle) and usually a much greater number of smaller, noninfectious, spherical or elongated HBsAg particles. Treatment of the Dane particle with weak detergent removes the surface envelope (HBsAg), leaving a smaller core particle (HBcAg). Stronger detergent treatment disrupts the core, releasing soluble HBeAg and the partially double-stranded DNA genome. (Modified from a figure courtesy of Dr. A.J. Cann, Leicester University.)

translation frames (i.e., encoding different amino acids from the same nucleotide sequences) (Fig. 29-4). Given the small size of the genome, this parsimonious use of the genomic DNA provides for a relatively large amount of genetic information. There are no segments of the DNA that are not translated into protein. The four open-reading frames encode a DNA polymerase/reverse transcriptase, the core protein (and the closely related precore protein, which is converted to the “e” protein by post-translational processing), a family of three surface envelope proteins with common carboxy termini (see below), and the “X” protein. This latter protein has been described to have numerous interactions with host cell proteins and is a nonspecific transactivator of host cell transcription.^{93,94} However, its precise role in viral replication and the pathogenesis of hepatitis B disease remains obscure.

The DNA genome of HBV replicates via reverse transcription of an intermediate RNA molecule (the “pregenome”), directed by the viral DNA polymerase/reverse transcriptase.⁹² The replication cycle of HBV thus resembles in gross detail that of the RNA-containing retroviruses, including the human immunodeficiency virus (HIV) (see Chapter 20). Indeed, the genomic organizations of these viruses bear some superficial similarities (Fig. 29-5). The principal difference in the replication cycles of these virus families lies in the fact that the DNA form of the HBV genome is packaged for export from the cell in virus particles, while it is the RNA form of the viral genome of HIV and other retroviruses that

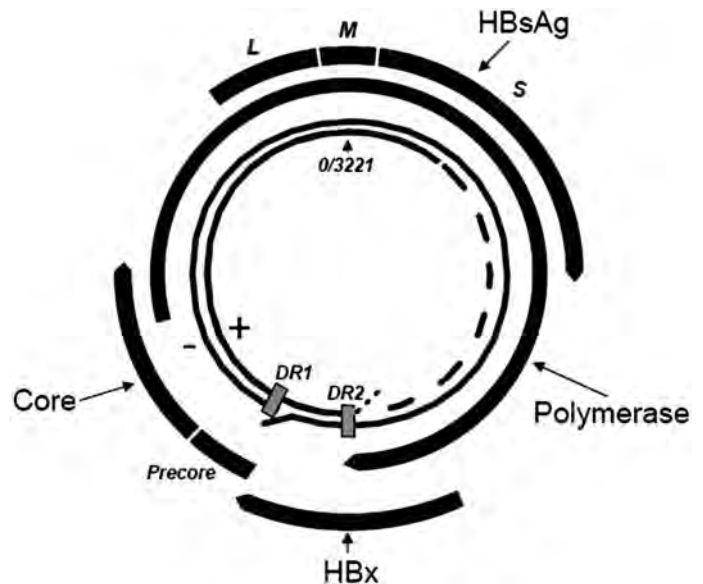


FIGURE 29-4. Organization of the circular 3.2-kb HBV genome. At the center of the figure is a schematic depicting the complementary linear full-length (–)-strand and partial (+)-strand DNAs, which are held in a relaxed circular conformation by the cohesive overlap formed by their 5′ ends. The solid lines represent DNA present within Dane particles, while the large dashed line represents the (+)-strand DNA segment that is synthesized following entry of the virus into the cell. Small boxes represent the two direct repeat elements (DR1 and DR2). The four overlapping open-reading frames are shown at the periphery: HBsAg (which encodes the L, M, and S envelope proteins), DNA polymerase/reverse transcriptase (pol), X, and core (which encodes both HBcAg and HBeAg).

is present in extracellular viral particles. The clinical significance of these similarities in the replication cycles of HBV and HIV is reflected in their shared sensitivity to antiviral suppression by certain nucleoside analog inhibitors of reverse transcriptase, such as lamivudine⁹⁵ (see Chapter 66).

In addition to the genomic DNA, the core of the HBV particle contains the DNA polymerase/reverse transcriptase, which also has an associated RNase H activity. Within the core particle, the DNA polymerase is active and in the presence of appropriate deoxynucleoside triphosphates will use the single-stranded, (–)-sense HBV DNA as a template to extend the (+)-sense molecule⁹⁶ (see Fig. 29-4). The major core protein is a 21-kDa molecule with specific antigenic activity (hepatitis B core antigen, or HBcAg). HBcAg is released from the intact virion by detergent treatment, which removes the surface envelope and leaves an intact 27-nm core particle. More vigorous disruption of the virus core releases an antigenically distinct, soluble viral antigen (HBeAg)⁹⁷ (Fig. 29-3). HBeAg is closely related to the core protein, as it is the product of proteolytic processing of the precore molecule and thus translated from the same reading frame.⁹⁸ The DNA sequence unique to the precore region encodes a signal sequence that directs the precore protein into a secretory pathway (see Fig. 29-4). During this process, both the amino terminal signal peptide and a carboxy terminal peptide are

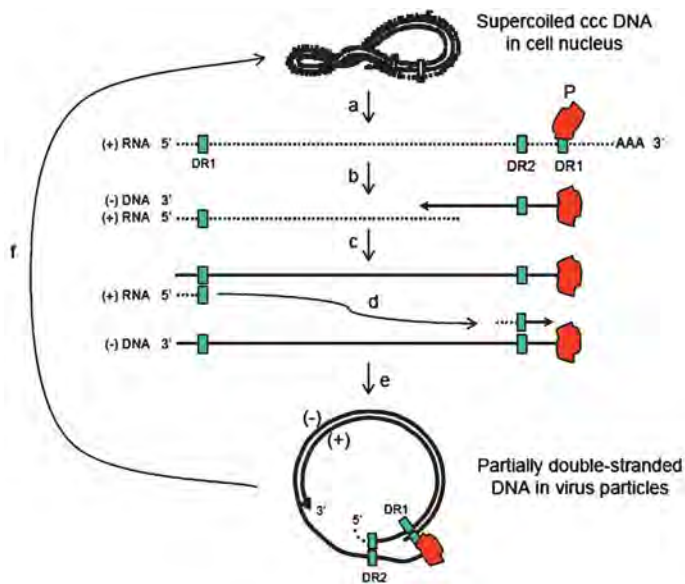


FIGURE 29-5. Schematic depicting the HBV replication cycle. The transcriptionally active form of the viral DNA is the completely double-stranded, supercoiled cccDNA that is present within the nucleus of the cell (shown at top of the figure) [1]. RNA transcription from cccDNA results in a greater-than-genome length (+)-strand “pregenome” pgRNA containing two copies of the DR1 direct repeat [2]. Protein-primed (P) reverse-transcription with associated degradation of the pregenomic RNA template is carried out by the viral DNA polymerase/reverse transcriptase and leads to production of genome-length (-)-strand DNA [3]. This occurs within immature core particles and is the step in replication that is blocked by lamivudine. Subsequent RNA-primed synthesis of the (-)-strand DNA [4] results in the partially double-stranded form of the genome found in mature virions [5]. Completion of DNA synthesis, removal of the primer moieties, and repair of the DNA strands lead to new cccDNA following infection of a subsequent cell by mature virions [6]. (Modified from a figure courtesy of Dr. A.J. Cann, Leicester University.)

cleaved from the precore protein to generate HBeAg. Thus, although the soluble HBeAg and particulate HBcAg have completely distinct antigenic specificities, these molecules have identical amino acid sequences throughout much of their length. The immune responses to these closely related molecules comprise very different Th-cell subsets.⁹⁹ Several lines of evidence suggest that the function of HBeAg may be to induce immune tolerance to HBV, thereby promoting viral persistence.¹⁰⁰

HBV variants with mutations within the precore region have been described.^{101–104} These precore mutants are unable to express HBeAg due to the presence of a stop codon within the precore region (see Fig. 29-4) but retain the ability to replicate and express the core protein (HBcAg). Precore variants usually emerge during the course of chronic HBV infection, around the time of HBeAg to anti-HBe seroconversion. De novo infection with precore variants is uncommon. Mutations in the basal core promoter region have also been described.¹⁰⁵ These mutations downregulate HBeAg production and are selected during the course of chronic HBV infection.

The surface envelope surrounding the virus core is a complex structure, containing as its major antigen a 24-kDa

glycoprotein (hepatitis B surface antigen, or HBsAg, also called the S protein, and previously known as “hepatitis associated antigen” or “Australia antigen”). An antigenic determinant common to all HBV strains (“a”) is associated with HBsAg. In addition, two pairs of mutually exclusive allelic antigens (“y” vs. “d,” “w” vs. “r”) have been defined.¹⁰⁶ Of the four possible major serotype combinations, only three (“ayw,” “adw,” and “adr”) have been found with any degree of frequency, and these occur in distinct, but possibly changing, geographic and demographic distributions. More recently, HBV has been classified, based on nucleotide sequences, into eight genotypes, A–H, the prevalence of which vary in different geographical regions.¹⁰⁷ Recent data suggest that HBV genotypes may play a role in determining the activity and risk of progression of liver disease, as well as response to interferon therapy.

In addition to HBsAg, the Dane particle contains two related proteins, large envelope (p39 and gp42) and middle envelope (gp33 and gp36), each of which exists as a doublet due to partial glycosylation. L, M, and S thus denote the large, middle, and small envelope proteins. These share in common the 226 amino acids of the S protein (HBsAg) at their carboxy terminus. They are coterminal translation products of the same open-reading frame but are produced from distinct mRNAs, in which translation is initiated from different in-frame AUG initiation codons^{89,90} (Fig. 29-4). The roles of the L and M proteins in the biology of HBV remain controversial, although both have been proposed to contain the virion receptor binding site. The inclusion of these antigens in future vaccines may result in improved immunogenicity (see below). HBsAg is usually produced in excess by infected hepatocytes, and, in most carriers of HBV, genome-free, subviral, 22-nm spherical or filamentous HBsAg particles greatly outnumber the genome-containing, infectious Dane particles in the blood (Fig. 29-3). These subviral particles, as well as the surface envelope of the Dane particle, also contain host cell-derived materials, including human albumin. While all three envelope proteins, L, M, and S, are expressed on the surface of Dane particles, only the small surface protein, S, is present in subviral particles.

Replication cycle of HBV

Attempts to propagate the virus in conventional cell cultures generally have not been successful. However, cells transfected with cloned HBV genomic DNA produce Dane particles, which are detectable by electron microscopy and infectious for chimpanzees.^{108,109} Such cells have been useful in dissecting the molecular steps in HBV replication and in assessing the response of HBV to candidate antiviral agents. However, no type of cultured cell is highly permissive for viral replication.

Early studies with the duck hepatitis B virus (duck hepatitis B virus, or DHBV) and subsequent work with HBV led to the conclusion that replication of this DNA virus proceeds via an

RNA genomic intermediate.⁹² This conclusion was based on the identification of immature intracellular core particles containing full-length RNA genomic intermediates and reverse transcriptase activity and the observation that synthesis of (–)-strand viral DNA is not inhibited by actinomycin-D (which typically blocks DNA-directed but not RNA-directed DNA synthesis). Current concepts concerning the replication of HBV may be summarized briefly as follows (Fig. 29-5).^{89–91} After attachment and penetration of the hepatocyte, synthesis of the incomplete (+)-strand of the gapped virion DNA is accomplished, possibly under direction of a cellular enzyme(s). Subsequent ligation of the gapped DNA (relaxed circle form) results in a fully double-stranded, covalently closed circular DNA (cccDNA), which exists as a supercoiled episomal form in the nucleus. This supercoiled episomal DNA does not replicate a DNA-dependent DNA synthesis mechanism and serves only a transcriptional role.¹¹⁰ Nonetheless, its amplification and persistence in the cell is central to the replication cycle of the virus. The cccDNA is the template for the subgenomic (+)-strand RNA transcripts encoding the envelope proteins, as well as a somewhat greater than full-length (+)-sense RNA pregenome (pgRNA). There is only a single poly(adenylic acid) addition site located within the core gene, and all the messenger RNAs are therefore 3′ coterminal. The core protein and the DNA polymerase are translated from pgRNA, while the X protein appears to be expressed from a unique transcript. The pgRNA serves a dual role, however, as it is also encapsidated within immature cytoplasmic core particles along with the DNA polymerase (reverse transcriptase). Within these immature core particles, the long (–)-sense DNA strand is synthesized by reverse transcription of the pgRNA, probably with concomitant degradation of the RNA directed by an associated RNase H activity. Subsequently, (+)-sense DNA is replicated from the full-length (–)-strand, but this process is often incomplete, resulting in a partially double-stranded DNA molecule encapsidated within the Dane particle as it exits the cell (Fig. 29-5).

The mechanism by which the cellular pool of supercoiled cccDNA is expanded is uncertain. It has been suggested that amplification might be the result of intracellular nuclear import of nucleocapsids¹¹⁰; alternatively, it might result from superinfection of the hepatocyte by additional virions. Either way, it is important to note that the maintenance of the cellular pool of supercoiled HBV cccDNA is not as dependent on the viral reverse transcriptase activity as are relaxed circular DNA forms of the genome. Thus, nucleoside analogs that are approved at present for the treatment of hepatitis B have no significant direct effect on cccDNA. Recent studies have shown that treatment with adefovir or pegylated interferon can decrease the pool of supercoiled cccDNA, but the effect on cccDNA is substantially less than the reductions in total HBV DNA.^{111–113} The resistance of cccDNA to nucleoside analogues that act primarily through inhibition of reverse

transcription of pgRNA and the long half-life of infected hepatocytes (and hence cccDNA) account for the high rate of viral relapse when treatment is stopped. Mathematical modeling estimates that it would take more than 10 years to eliminate cccDNA, even with nucleoside analogs that have a low propensity to generate drug-resistant mutants.¹¹¹ Thus, antiviral therapies for hepatitis B are suppressive rather than curative, much as acyclovir is not curative for genital herpes infections. During viral replication, double-stranded HBV DNA may become integrated at a low frequency into host chromosomal DNA. Unlike conventional retroviruses, however, this process is not obligatory for viral replication and appears to be a random event.

Pathobiology

The pathobiology of HBV infection is complex and incompletely understood.⁹¹ Following exposure, virus presumably gains access to the liver via the blood stream. HBsAg is found within the cytoplasm of hepatocytes, whereas HbcAg is usually restricted to the hepatocyte nucleus. There is evidence that HBV may also replicate within certain mononuclear cells of the bone marrow or blood,¹¹⁴ but the liver is the primary site of HBV replication. This tropism may result in part from the involvement of tissue-specific virus enhancer regions and promoters regulating HBV gene expression, the presence of virus-specific receptors on only certain cell types, or both. There is no evidence for replication of the virus at mucosal surfaces.

Acute hepatitis B

The majority of infections are self-limited (Fig. 29-6, top panel). HBsAg may appear in the blood as early as 6 days after percutaneous exposure, although this interval is usually from 1 to 2 months after mucosal exposure.¹¹⁵ Shortly afterward, circulating Dane particles, HBeAg, and DNA polymerase may be detected. This stage of detectable viremia is often brief. HBsAg synthesis is more abundant and typically more persistent, however, and it may be detected for up to 5 months or in some cases even longer.¹¹⁵ The first humoral immune response to the virus, consisting of IgM antibody to HbcAg (IgM anti-HBc), develops shortly after the appearance of HBsAg.^{116,117} Following the disappearance of circulating DNA polymerase and HBeAg, antibody to HBeAg (anti-HBe) may also be detected. Almost all (95–99%) healthy adults who are infected with HBV will eventually clear HBsAg from the circulation, and most, but not all, will develop antibody to HBsAg (anti-HBs). There may, however, be a delay of weeks to months prior to the first appearance of anti-HBs, even after the disappearance of HBsAg. During this so-called “window period,” anti-HBc and anti-HBe are the only serum markers of HBV infection. Symptoms of hepatitis usually develop after HBsAg has been circulating in the blood for 3–6 weeks and usually occur while HBsAg is still

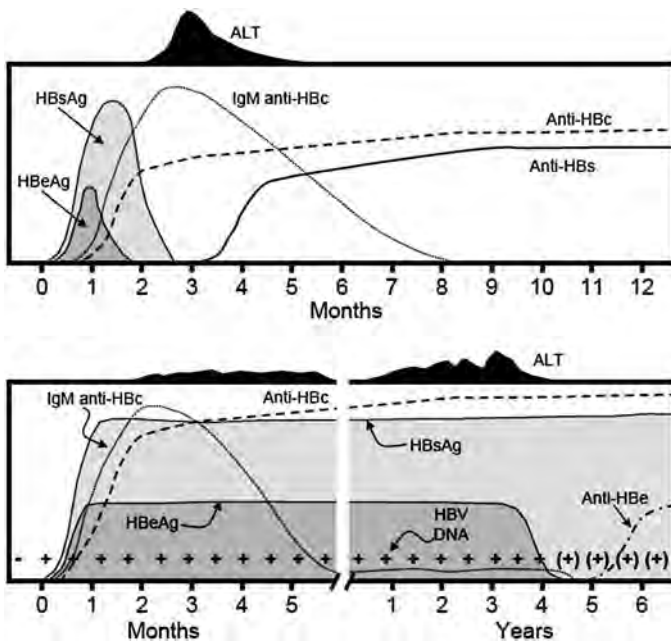


FIGURE 29-6. (Top panel) Typical virologic and serologic course of acute, self-limited HBV infection. (Bottom panel) Typical virologic and serologic course in a patient with chronic HBV infection, in which the infection is not cleared and persistent HBV infection becomes established. Clinical evidence of hepatitis (e.g., ALT elevation) is often very limited during the acute stages of such infections. Late clinical complications include cirrhosis, and hepatocellular carcinoma. Persistently infected patients with chronic hepatitis B can be distinguished from those with acute hepatitis B by the presence of high-titer IgM antibody to HBcAg in the latter. The degree of virus replication during the chronic phase of the infection is reflected in the presence of serum HBeAg and serum HBV DNA (not shown). Patients with chronic HBV may undergo a late HBeAg “seroconversion” event, in which HBeAg is lost and anti-HBe appears; most of these individuals will continue to have HBV DNA detectable at low levels, shown as “(+)”.

present (approximately 90% of patients). Symptoms may develop during the “window period,” however, or even after the appearance of anti-HBs. The appearance of anti-HBs signals the resolution of the infection. This antibody is protective against reinfection¹¹⁸ and represents responses against the S, M, and L envelope proteins. Anti-HBc and anti-HBs usually persist for years following infection, with anti-HBs conferring protection against reinfection on reexposure.

Chronic hepatitis B

A small proportion (1–5%) of infected adults fail to resolve the infection and become chronic HBsAg carriers (Fig. 29-6, bottom panel). Such individuals frequently have little or no evidence of acute liver disease when initially infected. Development of the chronic carrier state is more frequently seen in individuals who are immunocompromised (those with underlying HIV infection).¹¹⁹ Almost all infants who are infected neonatally become carriers. HBsAg may persist in the blood of these individuals for years in large and relatively constant amounts and may be associated with the presence of either HBeAg or anti-HBe.

Carriers who are positive for HBeAg usually have high serum HBV DNA levels¹²⁰; such carriers should be considered to be especially infectious.^{121,122} Chronic HBsAg carriers typically have very high titers of anti-HBc and usually do not have anti-HBs. Atypical individuals, however, may have both HBsAg and anti-HBs directed against a different HBsAg serotype.¹²³ These individuals should be regarded as infected, since the anti-HBs is not effective in neutralizing the infecting HBV serotype. Some individuals have isolated anti-HBc, with no detectable HBsAg or anti-HBs. These persons may be low-level HBV carriers with subdetectable levels of HBsAg or rarely HBV variants that are not detected by commercially available HBsAg assays. Most persons who are coinfecting with HCV or HIV and have isolated anti-HBc have low-level HBV infection.¹²⁴ Other persons with isolated anti-HBc have recovered from HBV infection but no longer possess detectable anti-HBs; such persons will develop anamnestic response when given HBV vaccine.¹²⁵ Rarely, persons with isolated anti-HBc are in the window phase of acute HBV infection and will test positive for IgM anti-HBc. Isolated anti-HBc may also be due to a false-positive test result.

While most persistent HBsAg carriers are asymptomatic and do not have evidence of significant liver disease, a minority has elevated serum aminotransferases and varying degrees of inflammation and fibrosis on liver biopsy. This histologic lesion may progress in some cases to cirrhosis. Coinfection with HCV or HDV and heavy alcohol consumption may accelerate progression of liver disease. The presence of HBeAg often correlates with high serum HBV DNA levels (up to 11 log₁₀ genome copies/mL) and active liver disease, and conversely seroconversion from HBeAg to anti-HBe in carriers with chronic hepatitis is frequently followed by normalization of aminotransferases¹²⁶ (Fig. 29-6, bottom panel). Along with clearance of HBV DNA, this is the desired endpoint in antiviral treatment of HBeAg-positive chronic hepatitis B (see Chapter 66) and has been shown to correlate with decreased risk of liver failure and improved survival.¹²⁷ Nonetheless, the use of sensitive assays for detection of HBV DNA has led to the recognition that HBV replication persists in most carriers after HBeAg seroconversion.⁹¹ The majority of carriers enter into an inactive carrier state after HBeAg seroconversion with typically low serum HBV DNA levels (<3 log₁₀ copies/mL) and normal aminotransferases. Approximately 4–20% of inactive carriers have one or more reversions back to HBeAg positivity. Among those who remain anti-HBe positive, 10–30% continue to have elevated aminotransferases and high HBV DNA levels (up to 9 log₁₀ copies/mL) after HBeAg seroconversion. Roughly 10–20% of inactive carriers may have reactivation of HBV replication and exacerbations of hepatitis after years of quiescence.^{128–131} Therefore, serial testing is necessary to determine if an HBsAg, HBeAg-negative carrier is truly in the “inactive carrier state” and life-long follow-up is required to confirm that the inactive carrier state is maintained.

Persistent high-level HBV replication and continued hepatic necroinflammation after HBeAg seroconversion is usually associated with the selection of precore and/or basal core promoter mutations. These HBV variants were initially reported in the Mediterranean countries and the Far East but are present worldwide, and their prevalence along with “HBeAg-negative chronic hepatitis” appears to be increasing. A recent study found that precore and/or basal core promoter variants were detected in roughly 30% of patients, with chronic HBV infection presenting to tertiary liver centers in the United States.¹³²

Because immunosuppressed patients are less likely to develop overt signs of hepatitis and because replication of large quantities of virus occurs in many completely asymptomatic carriers, it seems likely that the host immune response is intimately involved in the expression of liver disease. Much has been learned about this process from studies of transgenic mice expressing HBV proteins, as well as infected humans. HBV-specific cytotoxic T cells have been shown to be directed against epitopes within both the core and the surface proteins.^{133,134} The local expression of IFN- γ and other cytokines by these virus-specific CD8+ cytotoxic effector cells may serve to recruit monocytes and other inflammatory cell types to the site of infection. These appear to contribute significantly to the inflammatory process, but in a fashion that is less specifically directed than the CD8+ cells. Thus, hepatitis associated with HBV infection appears to be immune mediated, rather than a direct result of virus-induced cytopathology. These cellular immune responses play a central role in resolution of the acute infection. CD8+ cells have been shown to be capable of inhibiting a post-transcriptional step in virus replication.¹³⁵ Individuals who fail to develop an acute immune response leading to hepatitis following acute infection with HBV are probably more likely to go on to become chronic carriers than those who do develop hepatitis. However, it is interesting to note that long-term persistence of the viral DNA has been documented by sensitive assays even in individuals who have appeared to resolve the infection and who have robust cytotoxic T-cell responses.^{136,137} Thus, the virus may persist in individuals who have serologic recovery from acute HBV infection but be held in check by the immune system.¹³⁷

Liver cancer

There is a strong association between persistent HBV infection and primary carcinoma of the liver.^{138,141} Infection with HBV usually precedes the development of hepatocellular carcinoma by years, although the tumor occasionally develops during childhood. Integrated HBV DNA is present within tumor tissue in most individuals, but this is not always the case and there is no specific site at which the viral DNA is integrated into the host genome. Apparently random integration

of viral DNA may disrupt normal control of cellular growth and differentiation in some cases.^{142–144} However, it seems more likely that hepatocellular cancer usually develops as part of a multistep process, in which chronic inflammation, associated with hepatocellular regeneration and increased cellular proliferation, plays a prominent role. Free radicals produced as a product of the ongoing inflammatory response may cause damage to cellular DNA, ultimately contributing to the evolution of hepatocellular carcinoma. This is in line with recent data, suggesting that high serum HBV DNA levels and recurrent exacerbations of hepatitis are associated with an increased risk of hepatocellular carcinoma.^{130,145} A similar mechanism of carcinogenesis may account for liver cancer in patients who are infected with HCV, which does not replicate through a DNA intermediate and which thus never integrates its genetic information into the host cell genome (see below). Mutations within tumor-suppressor genes have been noted in many HBV-related hepatocellular carcinomas.^{146–148} An additional factor that may contribute to the oncogenic potential of HBV is the promiscuous transcriptional transactivating activity and multiple other suspected functions of the HBx protein.¹⁴⁹

The association of HBV with hepatocellular carcinoma is found worldwide. Although HBV-related hepatocellular carcinoma is a more significant problem in those countries where the HBsAg carrier rate is high in the general population, chronically infected people who emigrate from these countries contribute disproportionately to hepatocellular carcinoma rates in their adopted countries. Hepatocellular carcinoma is also being recognized as a major problem in MSM with HIV infection, although it appears that this is primarily due to coinfection with HCV rather than HBV.^{150,151} Nonetheless, it is increasingly clear that persons coinfecting with HBV and HIV have increased mortality from liver disease compared to those who are infected only with HBV or HIV.^{152,153} Not surprisingly, immunization with hepatitis B vaccine has been shown to reduce the risk of HBV-related chronic liver disease and hepatocellular carcinoma.^{154–156}

Immunity

Infection with HBV induces antibodies directed against each of the individual viral antigens: anti-HBs, anti-HBc, and anti-HBe (Table 29-2, Fig. 29-6). Of these, the antibody most clearly associated with protection is anti-HBs.¹¹⁸ Protection afforded by anti-HBs extends to all HBV serotypes, although HBV variants have been identified with potential “escape” mutations in the S protein.^{157,158} Some evidence suggests that the evolution of such escape mutations may contribute to vaccine breakthroughs in immunized infants who are born to HBV-carrier mothers. However, there is no evidence that the protective efficacy of HBV vaccines is decreasing as a result of these escape variants. The presence of anti-HBe in the blood of an HBsAg carrier generally correlates with reduced

infectivity,^{121,159} but there is no evidence that anti-HBe by itself has any protective effect. Although anti-HBs accounts for the protection afforded by immunization, it is very likely that memory T cells also contribute to durable immunity in those who have recovered from hepatitis B. A detailed discussion of the complex roles played by T-cell immunity to hepatitis B are beyond the scope of this chapter, but virus-specific T-cell responses probably contribute to both the liver injury associated with the infection and the control and eventual elimination of the virus.^{160,161}

Transmission

HBV is transmitted by percutaneous or permucosal exposure to blood or body fluids that contain blood. Blood is the major source of virus for transmission, and it may contain a very high titer of virus. HBsAg has been found in other serum-derived body fluids of infected individuals, including saliva, vaginal secretions, and semen, and the presence of Dane particles has been confirmed in saliva by electron microscopy.¹⁶² HBV DNA can be detected by nucleic acid hybridization in both saliva and semen of many HBeAg-positive carriers.^{163,164} Southern blot analyses have shown that the quantity of virus in saliva and semen is usually 1000-fold less than that present simultaneously in the blood but still may be as high as 10⁶ genome copies per mL.¹⁶³ HBV carriers with high serum titers of virus are more likely to have virus detectable in these secretions by these relatively insensitive methods. Most of this virus appears to be extracellular. Its presence in saliva and semen presumably reflects leakage from the circulation, and not the replication of virus at oropharyngeal or genital sites. Although studies directly examining the infectivity of various body fluids are limited, virtually any body fluid or secretion from an HBeAg-positive HBV carrier should be considered to be infectious.

Percutaneous exposures associated with HBV transmission have included receipt of blood transfusion or organ or tissue transplant from an infectious donor; IDU, including sharing of injection-preparation equipment; and frequent exposure to blood or needles among health-care workers. Transmission of HBV via transfusion of whole blood and blood components is rare because of donor selection procedures and routine testing of donors for HBsAg and anti-HBc¹⁶⁵ and has been eliminated via plasma-derived products through viral inactivation procedures. Among persons with bleeding disorders cared for at hemophilia treatment centers during 1998–2002 in the United States, no viral hepatitis infections, including HBV, were attributable to blood products received during that time.¹⁶⁶ HBV infection has also become a rare event in health-care workers since implementation of routine hepatitis B vaccination and use of standard precautions to prevent exposure to bloodborne pathogens.¹⁶⁷ Although the number of new cases of IDU-related hepatitis B declined dramatically

during the 1990s, the incidence of HBV infection among new injectors remains high, ranging from 10 to 31 per 100 person years.^{168–170}

Outbreaks of HBV infections among patients due to contaminated equipment used for therapeutic injections and other health care-related procedures continue to be identified in Western countries and contribute to a substantial burden of infection worldwide.¹⁷¹ In most cases, transmission resulted from noncompliance with aseptic techniques for administering injections and with recommended infection control practices designed to prevent cross contamination of medical equipment and devices. HBV transmission episodes related to tattooing and acupuncture have also been reported.^{172,173}

HBV is commonly transmitted from HBsAg-positive mothers to their infants at or near birth.^{121,159} As infected infants usually become chronic carriers, often for life, perinatal transmission of virus contributes disproportionately to maintenance of the carrier pool in areas of high HBV endemicity. The presence of maternal HBeAg or high serum HBV DNA level is associated with an increased risk of transmission of virus to the newborn.^{121,159} While intrauterine infection may occur, most infections are probably acquired at the time of birth. Transmission may be due to direct contamination of the infant's circulation with maternal blood at the time of delivery. Testing of cord blood for markers of HBV infection is not helpful in identifying infection in newborns. If the infant has no evidence of infection by the fourth month of life, he or she has a high probability of remaining free of infection subsequently. Infants who receive postexposure prophylaxis (HBIG and vaccine series) should be tested for anti-HBs and HBsAg at 9–15 months of age to confirm protection or detect "breakthrough" infections, which occur in a small proportion of immunized infants.¹⁷⁴ There is no epidemiologic evidence to incriminate breast feeding as a risk factor in transmission of the virus. Immunization is very effective in preventing maternal–infant transmission of HBV (see below).

Transmission of HBV from HBsAg carriers to their household contacts is well documented.¹⁷⁵ Follow-up studies of the susceptible household contacts of children with chronic HBV infection found that new HBV infections developed in 14–60% of their household contacts.^{176,177} Data from cross-sectional studies have demonstrated that household contacts of HBV-infected persons are more likely to have serologic markers of HBV infection (25–30%) than the household contacts of persons not infected with HBV (2–8%).^{178,179} When the chronically infected person was a child, serologic evidence of HBV infection was more common in other children in the household than in adults. These types of epidemiologic surveys suggested that "horizontal" transmission to young children was probably the most common means of transmission of this virus worldwide.¹⁸⁰ The exact mechanism by which this occurs is not known, however. Early

experiments demonstrated that HBV-containing serum was infectious when given orally to susceptible individuals,¹⁸¹ but the virus inoculum used in these studies included large amounts of exogenous protein, which may have protected the virus from inactivation by mucosal enzymes, gastric acid, or bile. Attempts to transmit HBV to susceptible nonhuman primates by oral administration of infectious saliva were unsuccessful, even though saliva transmitted infection when inoculated percutaneously.^{182,183} Such evidence suggests that the oropharynx is a relatively hostile portal of entry for HBV but is compatible with anecdotal reports that bites by infected individuals may transmit infection. It is probable that most “horizontal” transmission within families and among young children is due to inapparent percutaneous exposures to saliva or blood.¹⁸⁰ Such exposures may be relatively infrequent but apt to occur repeatedly over an extended period of close contact with a persistently infected carrier.

Among adults, sexual activity is one of the most frequent routes of transmission for HBV. Follow-up studies of the susceptible sexual partners of persons with acute hepatitis B demonstrated that HBV infection developed in 18–30%. Among susceptible spouses of persons with chronic HBV infection, the seroprevalence of HBV infection ranged from 25% to 59%. Homosexual and heterosexual activities with >1 partner in the previous 6 months were independent risk factors for acquiring acute hepatitis B.^{184,185} Historically, MSM were one of the groups at highest risk of HBV infection. Infection in this risk group was associated with receptive anal intercourse, increased numbers of sexual partners, and increased years of sexual activity^{186,187} (see below). Similar factors were associated with an increased risk of HBV infection among heterosexual men and women, including number of sexual partners, number of years of sexual activity, and history of other STDs.^{188,189} In addition, human semen has been shown to transmit infection when instilled into the vagina of susceptible gibbons.¹⁸³

■ EPIDEMIOLOGY

Population studies

The endemicity of HBV infection varies greatly worldwide and is influenced primarily by the predominant age at which infection occurs.^{121,190} Endemicity of infection is considered high in those parts of the world where at least 8% of the population is HBsAg positive, and 70–90% of the population has serological evidence of previous HBV infection. Almost all infections occur during either the perinatal period or early in childhood, which accounts for the high rates of chronic HBV infection in these populations. Risk of HBV infection continues after the first 5 years of life, but its eventual contribution to the high rate of chronic infection is less significant. Chronic infection with HBV is strongly associated with HCC,

and areas with a high endemicity of chronic HBV infection have the highest death rates from this neoplasm.

In areas of the world with an intermediate pattern of HBV infection, the prevalence of HBsAg positivity ranges from 1% to 7% and serological evidence of past infection is found in 10–60% of the population. In these areas, there are mixed patterns of infant, early childhood, and adult transmission.

In most developed parts of the world, including the United States and Western Europe, the prevalence of chronic HBV infection is <1%, and the overall infection rate is 5–7%. The highest incidence of acute hepatitis B is among young adults, and high-risk sexual activity and injectable drug use account for most cases of newly acquired hepatitis B.^{191–194} In the United States, heterosexual activity accounts for 40% of new hepatitis B cases, while MSM represent 15% of new cases. Among sexually active populations, current HBV infection data are limited, however. In a multicity survey of young (<30 years old) MSM, HBV prevalence ranged from 10% to 25%.¹⁹⁵ Among HIV-positive persons, the incidence of HBV infection was 13.3% among heterosexuals and 7.1% among MSM¹⁹⁶; prevalence of chronic infection was 3.9% among heterosexuals and 9.2% among MSM. Among HIV-positive heterosexual women with >10 lifetime partners, 48% had serologic evidence of HBV infection.¹⁹⁷

Sexually transmitted hepatitis B among MSM

Sexual transmission of HBV was first suggested by the occurrence of acute hepatitis B among sexual contacts of HBsAg carriers.¹⁹⁸ An increased prevalence of HBsAg and anti-HBs was noted subsequently among prostitutes and individuals attending venereal disease clinics.^{186,199–201} Overall, however, the most striking serologic evidence relating HBV transmission to sexual practices was found among MSM prior to the AIDS epidemic and subsequent educational campaigns promoting safe sex practices. Of over 600 New York City homosexual men who were solicited for study through recognized gay-oriented organizations and health clinics in the mid-1970s, 4.6% were found to be HBsAg carriers and 51.1% were found to have had past infection to the virus, as evidenced by HBsAg or anti-HBs positivity.¹⁸⁶ These men were predominantly Caucasians, under 40 years of age, and highly educated. Female homosexuals were not at increased risk for infection, as only 6.3% had anti-HBs and none were carriers. Of the gay men evaluated in this study, 23% gave a past history of viral hepatitis, and in these individuals the total seroprevalence rate was 65%. There was a high degree of correlation between numbers of previous sex partners and serologic evidence of past HBV infection. Of those with less than 10 sex partners during the previous 6 months, only 30.9% had been infected with HBV, compared with 60.5% of those with more than 10 sex partners.¹⁸⁶ The highest rates for HBsAg (7.5%) were found among men reporting predominant or exclusive

involvement in rectal intercourse, while those reporting oral–genital sex had significantly lower rates for both HBsAg (2.3%) and anti-HBs (39% vs. 51%). The duration of homosexual activity was also related to past HBV infection and was more important than age at the time of screening. Injection drug use did not appear to be an important variable. A high prevalence of HBV infection was documented among gay men in many other studies.^{187,200,202–205}

Several factors account for the high risk of HBV infection among MSM, which was noted in these early studies. One of the most important factors was the number of sexual partners. The typical homosexually active male frequenting Denver's steam baths in the late 1970s had eight different male sexual contacts per month.²⁰⁶ These contacts were largely anonymous and could total as many as 1000 over the lifetime of a gay man. In addition, the relatively high HBsAg carrier rate found among MSM in these studies meant that such anonymous sexual contacts often involved repeated exposure to HBsAg-positive partners. Schreeder et al.¹⁸⁷ estimated that the average openly homosexual male had 4.2 sexual contacts with HBsAg-positive men annually. However, these studies were conducted in the years immediately preceding licensure of the hepatitis B vaccine and the recognition of AIDS. During the mid-1980s, the adoption of safer sex practices by many MSM appears to have altered the epidemiology of HBV in this high-risk group. Although the overall incidence of hepatitis B increased within the United States from 1982 to 1988, the proportion of hepatitis B cases among men who were associated with homosexual activity fell from 30% to 12% in four sentinel counties studied by the Centers for Disease Control and Prevention.¹⁸⁹ In contrast, the proportion attributed to heterosexual contact increased from 10% to 20% among men and from 22% to 34% among women during this same period. Nonetheless, in a study published in 1995,²⁰⁷ serologic evidence of previous HBV infection among MSM living in high risk, inner-city neighborhoods of San Francisco, was positively associated with numbers of lifetime sexual partners, as well as non-white ethnicity, and a history of injection drug use in a sexual partner. In sharp contrast to homosexually active men, there are no data showing an increased risk of hepatitis B among gay women.

Receptive or insertive anal intercourse is a second important factor influencing the risk of acquisition of HBV among MSM.^{186,187} Nonspecific proctitis may result from receptive anal intercourse, and breakdown of normal mucosal barriers may facilitate transmission of virus. In one study, over a quarter of MSM had experienced rectal bleeding during a 4-month period. This was related both to the number of sex partners and to the participation in receptive anal intercourse.¹⁸⁷ In this same study, insertive oral–anal contact was also associated with HBV infection. In contrast, oral–genital or oral–oral contact between MSM had little apparent influence on the risk of becoming infected with HBV. These

findings were confirmed in a prospective study of homosexual men enrolled in the Multicenter AIDS Cohort Study.²⁰⁵ In this study, 19.8% of initially seronegative men seroconverted to HBV during a 30-month period. Insertive anal intercourse was the major risk factor identified for HBV seroconversion, raising the possibility that transurethral exposure may be important in acquisition of the infection.²⁰⁵ Based on a similar analysis of new HIV infections and a comparison of the prevalence of each virus, the investigators concluded that HBV is transmitted 8.6-fold more efficiently than HIV among homosexually active men.²⁰⁵

These data suggest that traumatic sexual practices that lead to small breaks in the skin and mucosa play a prominent role in the transmission of HBV, by facilitating exposure to virus in blood. In one survey, one out of five gay men reported rectal bleeding after intercourse and 9–16% had fissures, cracks, or tears in the rectum or anal skin over a 12-month period.²⁰⁸ In yet another study, 13 of 22 HBsAg-positive gay men were found to have rectal mucosal lesions, usually consisting of multiple, punctate bleeding points within 6 cm of the anal verge.²⁰⁹ HBsAg was identified in swab specimens from such lesions, as well as in swabs taken from apparently normal rectal mucosa and anal sphincters. HBsAg was identified in feces from these men, a finding that may, in part, explain the risk of infection associated with insertive oral–anal contact and anal intercourse.

Another important factor in the transmission of HBV among MSM is that HBsAg-positive homosexual men are often HBeAg positive. Approximately 65% of HBsAg-positive MSM are positive for HBeAg, while anti-HBe may be detected in 25%.^{210–212} In contrast, only about 10% of asymptomatic, HBsAg-positive blood donors are HBeAg positive. This difference most likely reflected relatively recent acquisition of the infection by many homosexually active men. The presence of HBeAg correlates with high replicative activity of the virus and is associated with an increased risk of heterosexual,¹⁷⁵ needlestick,¹²² and maternal–infant transmission of HBV.^{121,159} Thus, its frequent presence in homosexual men implies a high risk of infectivity. The titer of HBeAg correlates directly with the amount of virus present in semen and saliva.¹⁶³ Cellular immunodeficiency due to HIV in dually infected persons may result in higher levels of HBV viremia and enhanced potential for transmission.^{213–215}

Heterosexual transmission of HBV

Extensive evidence also supports the transmission of HBV by heterosexual contact. Sexual partners of HBsAg-positive carriers frequently have serologic evidence of HBV infection.^{175,198} In one study, either HBsAg or anti-HBs was found in 27% of spouses of HBsAg carriers but only in 11% of spouses of noncarrier controls.¹⁸⁶ Although nonsexual, household contacts of HBsAg carriers may also have serologic evidence of past HBV infection¹⁷⁵; the risk appears to be

greater for sexual partners of index cases. The sexual partners of individuals with acute hepatitis B are clearly at increased risk of acquiring infection, when compared with other members of the household. Mosley²¹⁶ reported that 18% of susceptible cohabiting spouses eventually became infected with HBV, whereas other family members generally did not. Similarly, Koff et al.²¹⁷ found that three of 13 sexual partners, compared with zero of 68 nonsexual domestic contacts, became infected with HBV in this setting. The risk of heterosexual transmission appears to be higher when the HBsAg-positive partner has detectable serum HBV DNA.²¹⁸ This is not surprising, since the amount of virus in saliva and semen is related to the magnitude of the viremia.¹⁶³ While it is likely that virus is transmitted by vaginal intercourse, it is difficult to assess the role of inapparent percutaneous or mucosal exposures resulting from the sharing of razors, toothbrushes, or other personal articles between partners. Available data do not support a major role for salivary exchange in the transmission of virus among sex partners.^{219,220}

In one study, the prevalence of HBV infection among white heterosexuals attending a clinic for STDs in Arizona, who were without other risk factors such as injection drug use, was related to numbers of previous sex partners.¹⁸⁸ Serum markers of HBV infection were present in 21% of those with five or more sex partners during the preceding 4 months, but in only 6% of those with fewer than five partners. A similar correlation existed for total numbers of lifetime sex partners, among both male and female clinic patients. In addition, a similar survey of heterosexual college students without other risk factors for HBV acquisition also demonstrated a positive correlation between numbers of previous sex partners and risk of HBV infection.²²¹ As many as 40–50% of cases of acute hepatitis B reported in the United States during the late 1990s were thought to be contracted through heterosexual exposure (Centers for Disease Control and Prevention, unpublished data).

Studies in a number of diverse populations, carried out at sites as diverse as San Francisco, California, and Mwanza, Tanzania, have confirmed a strong association between higher numbers of recent or lifetime sexual partners and the risk of HBV infection among heterosexual persons.^{207,221–224} Indeed, this association exists even among individuals with acute hepatitis B in Taiwan, a country with a very high overall prevalence of HBV infection.²²¹ In addition, an increased risk of HBV infection has been observed in heterosexual persons with a past history of STDs, particularly syphilis, but also gonorrhea or herpes simplex virus type 2 seropositivity.^{222–227} It is not clear whether this association is simply indicative of common risk factors for HBV and these other STDs, or whether it reflects an increased risk of transmission of HBV to persons who have active ulcerative genital lesions.

■ CLINICAL MANIFESTATIONS OF HBV INFECTION

Many adults infected with HBV probably have silent infections, which result in permanent and solid immunity. Only

one-third of seropositive homosexual men relate a past history of viral hepatitis.¹⁸⁶ However, in a placebo-controlled trial of an HBV vaccine conducted among homosexual men in New York City, 64% of infections in placebo recipients were associated with clinical evidence of disease.¹¹⁸ The onset of illness is generally more insidious than in hepatitis A, and evidence of hepatocellular disease resolves more slowly. The incubation period is usually from 40 to 110 days but may be shorter with large inoculum or percutaneous exposure and prolonged by administration of partially protective IG preparations.¹¹⁵ A small proportion (1% or less) of icteric adults develop acute hepatic failure, and about three out of four of these unfortunate patients will die as a result of their infection in the absence of liver transplantation.²²⁸ An initial report from the U.S. Acute Liver Failure Study Group, which included 354 patients enrolled between 1998 and 2001, found that 7.3% of cases were due to HBV.⁷⁵ A recent update that included 973 patients enrolled up to 2006 reported that the proportion of cases due to HBV remained steady at 7% (W.M. Lee, personal communication, September 2006). Fulminant disease may be more common following infection with pre-core mutants.²²⁹ Recent studies suggest that the risk of fulminant disease may depend in part on the HBV genotype.^{230,231} Infection with HDV may be the immediate cause of severe disease in many patients presenting with what looks like fulminant hepatitis B in countries where HDV infection is endemic (see below). As a rule, elderly patients tolerate acute hepatitis more poorly than younger individuals.

Approximately 15–20% of patients develop a transient serum sickness-like illness during the prodromal or early acute stage of hepatitis B.^{232,233} This syndrome is characterized by an erythematous macular or maculopapular, occasionally urticarial skin rash, polyarthralgia, and frequently frank arthritis. The arthritis may be migratory, is frequently symmetrical, and may involve both large joints of the extremities and proximal interphalangeal joints of the hands. Synovial fluid findings are variable, but leukocyte counts as high as 90,000 per cubic millimeter (often with a predominance of neutrophils) have been reported. Serum aminotransferases are usually elevated and may be the best clue to the proper diagnosis.

A striking feature of hepatitis B is the development of persistent infection. Out of 429 hospitalized patients with acute icteric hepatitis B, 43 became persistent carriers of HBsAg in one study.²³⁴ Overall, however, the frequency with which acute infection leads to the chronic carrier state is undoubtedly much lower, as these hospitalized patients represented a selected population. Among immunocompetent adults, progression to the chronic carrier state (HBsAg positive for >6 months) probably occurs in 1% or less. A follow-up study of American soldiers who were infected by administration of contaminated yellow fever vaccine in 1941–1942 suggested that long-term persistence after acute infection is a very rare

event in adults.²³⁵ The HBsAg carrier rate was only 0.26% in recipients of the contaminated vaccine who were studied 40 years after exposure to the contaminated vaccine. Up to a third of chronic HBsAg carriers develop histologic evidence of chronic hepatitis with fibrosis, while the remainder have a more benign disease characterized by minimal inflammatory changes on liver biopsy or no histologic changes at all.²³⁵ While chronic hepatitis B may progress to cirrhosis and death, spontaneous remissions can occur.²³⁶ On the other hand, reactivation of HBV replication and recurrence of active liver disease can occur either spontaneously or after immunosuppressive therapy. In addition, a wide variety of immunopathological conditions are associated with persistent circulating HBsAg, including generalized necrotizing vasculitis (polyarteritis nodosa),^{237–239} chronic membranous and membranoproliferative glomerulonephritis,²⁴⁰ and essential mixed cryoglobulinemia.²⁴¹ The latter condition, however, is much more frequently associated with hepatitis C.^{242,243}

■ DIAGNOSIS OF HEPATITIS B INFECTION

The diagnosis of HBV infection is based on serology (Table 29-2). Approximately 90% of patients with acute hepatitis B have detectable HBsAg, when they first present for medical care.¹¹⁷ This antigen may be detected by any of a variety of sensitive assay methods. Approximately 10% of patients with acute HBV infection are HBsAg negative, however, and these cases are more difficult to document. In such patients, anti-HBc is uniformly present, while anti-HBs may be found in some. Anti-HBs and anti-HBc generally persist for many years after acute infection; their presence is not diagnostic of acute hepatitis B. In contrast, specific tests for IgM anti-HBc have proven very useful in the diagnosis of acute infection. IgM anti-HBc is detected in almost all cases of acute hepatitis B and typically persists after acute infection for 6–24 months. While many chronic HBsAg carriers have persistent IgM anti-HBc, the titer is usually substantially lower than that found in acute infection, and it is usually not detected in commercial assays (thus preserving IgM anti-HBc as a specific marker for acute infection) except during severe exacerbations of chronic hepatitis. The IgM antibody is often 7S rather than 19S IgM in chronic carriers.²⁴⁴ The presence of HBeAg in an HBsAg-positive individual suggests a high degree of infectivity.^{121,122} Conversion of HBeAg to anti-HBe in a patient with chronic hepatitis B generally signals a resolution of hepatocellular disease (Fig. 29-6, bottom panel) and, in some cases, even heralds an end to the HBsAg carrier state.¹²⁶ However, it has become increasingly clear in recent years that HBV replication persists after HBeAg seroconversion.⁹¹ Serum HBV DNA levels even may be as high as 8–9 log₁₀ copies/mL in some patients. Recognition that HBV replication persists throughout the course of HBV infection, and that the balance between host immune response and

virus replication varies during the course of chronic HBV infection, is critical in the management of patients with chronic HBV infection.²⁴⁵

Quantification of serum HBV DNA is crucial in the evaluation and management of patients with chronic HBV infection and in the assessment of the efficacy of antiviral treatment. A major dilemma in the interpretation of serum HBV DNA levels is the determination of cutoff values used to define treatment indications and response. Given that sensitive tests show that HBV DNA may persist even in persons who have serological recovery from acute HBV infection and that low levels of HBV DNA may not be associated with progressive liver disease, complete viral clearance is an unrealistic treatment endpoint. An arbitrary value of 5 log₁₀ copies/mL had been chosen as a criterion for treating chronic hepatitis B.²⁴⁶ However, chronic hepatitis, cirrhosis, and hepatocellular carcinoma have been found in patients with lower HBV DNA levels. Also, some patients with chronic hepatitis B have fluctuating HBV DNA levels that may vary from undetectable to >10 log₁₀ copies/mL.²⁴⁷ Thus, serial monitoring of HBV DNA levels is more important than any single arbitrary cutoff value in determining the prognosis and need for treatment.

■ PREVENTION

Hepatitis B vaccines are highly effective and provide protection against hepatitis B (and hepatitis D), by stimulating the production of neutralizing antibodies against HBV (anti-HBs).⁷ Since homosexual men have historically had very high hepatitis B attack rates, early placebo-controlled clinical trials of these vaccines focused on this important risk group. Immunization was shown to reduce the incidence of hepatitis B among homosexual men by 90–95%,^{118,208,248} and to similarly protect health-care workers with frequent exposure to blood.²⁴⁹ Protection became evident within weeks of the first two doses of vaccine in homosexual males, even though the incubation period of hepatitis B is often 6 weeks or longer. These results suggest some degree of postexposure protection. In general, protection correlates with anti-HBs titers >10 mIU/mL.^{118,248} Immunization also prevents perinatal infection in infants born to HBsAg-positive mothers. For maximal benefit in this setting, it should be administered within 12 hours of birth, in combination with hepatitis B IG.²⁵⁰ Immunized infants appear to be protected against hepatitis B for at least 15 years.^{251,252}

Symptomatic hepatitis B has almost never been observed in immunized persons who develop anti-HBs responses >10 mIU/mL, even though anti-HBs may fall to nondetectable levels in up to 50% of such persons within 5–10 years.²⁵³ It is likely that continued protection against hepatitis B reflects the establishment of good immunologic memory by the vaccine. Some vaccine recipients may develop

anti-HBc, which is indicative of HBV infection, but they almost always do so in the absence of disease.^{208,253}

Subunit hepatitis B vaccines contain recombinant HBsAg produced in the yeast, *Saccharomyces cerevisiae*. These have replaced earlier, chemically inactivated, subviral particle vaccines that were produced from plasma collected from chronic HBsAg carriers (plasma-derived vaccine). Two single-antigen recombinant vaccines, *Recombivax HB*[®] (Merck) and *Engerix-B*[®] (GlaxoSmithKline Biologicals) are licensed for use within the United States. A combination vaccine including both hepatitis A and hepatitis B antigens (*Twinrix*[®], GlaxoSmithKline Biologicals) is also available for persons ≥ 18 years old, as are pediatric combination vaccines that include other pediatric vaccine antigens.^{254,255} Both single-antigen vaccines contain purified HBsAg particles adsorbed to aluminum hydroxide. Since 2000, neither vaccine has used thimerosal as a preservative.²⁵⁴ In general, the single-antigen vaccines are comparable to each other in terms of safety and efficacy and can be used interchangeably. However, the vaccines are provided in several different formulations and dosage strengths, making it essential that the package insert be carefully examined for details concerning administration. Hepatitis B vaccines are very safe.^{253,254,256} Adverse events are usually confined to mild injection site reactions (up to 22% of immunized persons), while fever and other systemic symptoms are only infrequently reported. Anaphylaxis is a rare but well-documented complication of hepatitis B vaccine, and it is important that epinephrine always be available for immediate use. There are anecdotal reports of Guillain-Barré-Landry syndrome in some recipients of early plasma-derived hepatitis B vaccines, although it is not clear whether the vaccine played a causal role in such cases.²⁵⁷ It does not appear to occur with increased frequency in recipients of the newer recombinant vaccines.²⁵⁴

A usual immunization course includes three doses of the vaccine. The final booster doses should be given at least 4–6 months after the initial, two-dose, primary immunization series, as this enhances peak antibody levels and ensures more durable protection. All three doses can be administered on an accelerated, monthly schedule in the hope of quickly stimulating immunity,^{258,259} but this may reduce final anti-HBs titers and thus the duration of protection and should be followed by a final booster dose at least 4–6 months later. Almost all healthy infants, children, or young adults who receive a series of three intramuscular doses of a recombinant hepatitis B vaccine develop protective levels of anti-HBs. Immunogenicity may be reduced in persons over 40 years of age or who are otherwise immunocompromised (including persons with asymptomatic HIV infection).⁷ Immunocompromised patients should receive larger doses of vaccine in anticipation of a poor response.

Current recommendations for use of hepatitis B vaccines center on a fourfold hepatitis B reduction strategy²⁵⁴

(Table 29-3). This strategy includes (1) universal vaccination of infants beginning at birth, (2) prevention of perinatal HBV infection through routine screening of all pregnant women for HBsAg and immunoprophylaxis of infants born to HBsAg-positive women, (3) routine vaccination of previously unvaccinated children and adolescents, and (4) vaccination of previously unvaccinated adults at risk of HBV infection.²⁶⁰ Anti-HBs testing is not routinely recommended following immunization (for exceptions refer to Refs.) and there are no recommendations for late booster doses of vaccine.

During 1990–2004, incidence of acute hepatitis B in the United States declined 75%.^{261,262} The greatest decline (94%) occurred among children and adolescents, coincident with an increase in hepatitis B vaccination coverage. This success can be attributed, in part, to the established infrastructure for vaccine delivery to children and to federal support for perinatal hepatitis B prevention programs. There are long-standing recommendations to vaccinate persons who report a history of multiple sex partners, treatment for an STD, and MSM. However, vaccine is rarely offered in settings that provide health care to adults. Results of several studies indicate that health-care practitioners do not routinely ascertain high-risk sex or drug histories from their patients and miss opportunities to inform and vaccinate persons at risk of hepatitis B.²⁶³ Even in settings that provide services specifically targeted to high-risk adults (e.g., STD treatment clinics, HIV counseling and testing sites, and drug treatment programs), hepatitis B vaccination is not offered routinely.²⁶⁴ Thus, new implementation strategies are needed to protect adults currently at risk of HBV infection. In settings where a high proportion of persons are likely to be at risk of HBV infection (e.g., STD/HIV testing and treatment facilities, drug-abuse treatment and prevention settings, health-care settings primarily serving MSM, and correctional facilities), universal hepatitis B vaccination is recommended for all adults who have not completed the vaccine series. In primary care and specialty medical settings, standing orders should be implemented to administer hepatitis B vaccination as part of routine services.

■ TREATMENT

Treatment is discussed in detail in Chapter 66. The major dilemmas in treatment of hepatitis B are when to start and when to stop. Every hepatitis B carrier is a potential candidate for treatment; the decision is whether treatment should be initiated at the time of presentation or whether the patient should be monitored and treatment deferred. Although six different therapies have been approved, standard and pegylated interferon-alpha, lamivudine, adefovir, entecavir, and telbivudine, none eradicate HBV. Thus, careful consideration of the

Table 29-3. Persons for Whom Hepatitis B Vaccination Is Recommended

- I. All infants
- II. All children and adolescents <19 y of age
- III. Persons at risk of infection by sexual exposure
 - A. Sex partners of hepatitis B surface antigen (HBsAg)-positive persons
 - B. All sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with >1 sex partner during the previous 6 months)
 - C. Persons seeking treatment for a sexually transmitted disease
 - D. Men who have sex with men
- IV. Persons at risk of infection by percutaneous or mucosal exposure to blood
 - A. Household and needle-sharing contacts of HBsAg-positive persons
 - B. Current or recent injection-drug users
 - C. Health-care and public safety workers with reasonably anticipated risk of exposure to blood or blood-contaminated body fluids
 - D. Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- V. Others
 - A. International travelers to areas with high levels of endemic HBV infection
 - B. Persons with chronic liver disease
 - C. Persons with HIV infection
- VI. Settings where hepatitis B vaccination is recommended for all adults
 - A. Sexually transmitted disease treatment facilities
 - B. Human immunodeficiency virus testing and treatment facilities
 - C. Facilities providing drug-abuse treatment and prevention services
 - D. Correctional facilities
 - E. Health-care settings primarily serving men who have sex with men
 - F. Chronic-hemodialysis facilities and end-stage renal disease programs

patient's age, severity of liver disease, likelihood of response, and potential adverse events is needed before treatment is initiated.²⁶⁵ Treatment is indicated if the risk of liver-related morbidity and mortality within the next 10–20 years is high, and there is high likelihood of achieving viral suppression during continued treatment or sustained viral suppression after a defined course of treatment. Treatment should be deferred if the risk of liver-related morbidity and mortality within the next 20 years and the likelihood of achieving sustained viral suppression after a defined course of treatment are low. Because of the

fluctuating nature of chronic HBV infection, continued monitoring is essential for risk assessment. In general, treatment should be initiated if there are elevated aminotransferases and/or moderate–severe hepatic inflammation. Recent studies from Taiwan suggest that treatment should also be considered in older patients (>40 years) who have persistently high serum HBV DNA levels (>4 log₁₀ copies/mL). However, most persons participating in these studies were infected at birth, and it is uncertain whether this recommendation is appropriate for persons with adult-acquired HBV infection.

In choosing which antiviral agent to use as the first-line therapy, consideration should be given to the safety and efficacy of the treatment, risks of drug resistance, the costs of the treatment, as well as patient and provider preferences, and, for women, whether they are likely to become pregnant in the foreseeable future. The advantage of interferon therapy is the finite duration and lack of emergence of specific drug-resistant mutations. The disadvantages include need for parenteral administration, frequent side effects, and costs. The oral nucleoside analogs have the advantage of ease of administration and safety. However, long durations of therapy are required and carry accompanying risks of drug resistance. For patients with HBeAg-positive hepatitis, treatment should be continued for at least 6 months after HBeAg seroconversion. For patients with HBeAg-negative hepatitis, the endpoint is unclear, as relapse is frequent even after serum HBV DNA has been undetectable for more than a year. Combination therapy seems to be a more logical approach, but none of the combination regimens tested to date is clearly superior.

For patients coinfecting with HIV, the decision on HBV treatment should take into consideration the need for HIV treatment. For patients who are not in need of highly active antiretroviral therapy (HAART), or who are already well controlled on a HAART regimen that does not include a drug with activity against HBV, pegylated interferon-alpha may be considered as a first-line treatment, given its limited duration. However, adefovir or entecavir may also be used in this setting. For HBeAg-negative patients, earlier initiation of HAART may be considered in view of the need for very long-duration HBV treatment. For patients in whom HAART initiation is planned, it is best to use a regimen that includes drugs with activity against HBV; the combination of emtricitabine and tenofovir as a single pill is well suited for this purpose.

DELTA HEPATITIS/HEPATITIS D

■ CLINICAL VIROLOGY

HDV is a defective virus that is absolutely dependent on simultaneous HBV infection for provision of its envelope proteins.²⁶⁶ Thus, HDV infects only patients with active HBV infection. The infectious HDV virion is a 35-nm particle found in the blood.²⁶⁷ It has an outer envelope consisting of HBsAg (produced by the helper HBV infection) and an amorphous core containing a viral protein, delta antigen (HDAG), complexed with a small, circular, single-stranded RNA molecule ~1.7 kb in length.²⁶⁸ This genomic RNA has a very high G+C content and extensive intramolecular complementarity, resulting in its assuming a rod-like, predominantly double-stranded secondary structure. Both genomic and antigenomic sense RNAs are present in the liver of infected individuals. Replication of the viral RNA is thought to occur by a “rolling circle” mechanism under the direction of a cellular

polymerase, with nascent RNA molecules being capable of autocatalytic cleavage and self-ligation. The delta antigen is a highly basic phosphoprotein, which forms oligomers and has RNA-binding activity.^{269,270} It is encoded by the antigenomic sense RNA, making HDV a negative-strand RNA virus. The provision of HBsAg, encoded by the HBV genome, is the only helper function required for HDV replication.

HDV infection may occur as a “coinfection” with acute hepatitis B in an individual who was previously susceptible to HBV, or as a “superinfection” in an HBV carrier.²⁷¹ Either type of infection may result in severe hepatitis with fulminant disease and death.²⁷² Coinfections are often marked by a biphasic serum aminotransferase response, while superinfections may be associated with transient (at times permanent) suppression of HBV replication markers. Those who survive acute coinfections usually go on to complete recovery and are not at increased risk of becoming chronic HBV carriers. On the other hand, HBV carriers surviving HDV superinfections frequently become carriers of HDV with clinically aggressive chronic liver disease.²⁷¹ The diagnosis of HDV infection is generally dependent on demonstration of antibody to HDAG (anti-HD), as this is the only widely available test (Table 29-2). Acute HDV/HBV coinfections are distinguished from HDV superinfection of a chronic HBsAg carrier by measurement of IgM anti-HBc, which is present in the former and absent in the latter. Indeed, persons presenting with what appears to be acute type B hepatitis, who lack this serum marker, should be suspected of having HDV superinfection.

■ EPIDEMIOLOGY OF HDV

HDV is found in the blood of anti-HD-positive HBsAg carriers, and the prevalence of anti-HD among American carriers is strongly associated with illicit injection drug use, hemophilia, or a history of multiple transfusions.^{273,274} Geographic differences in the distribution of HDV are striking, however, and anti-HD is significantly more prevalent among HBsAg carriers from middle-eastern and Mediterranean countries. Outbreaks of fulminant delta hepatitis with high mortality rates have been reported among the indigenous populations of Venezuela and other South American countries, possibly representing widespread superinfection of HBsAg carriers.²⁷⁵ The implementation of hepatitis B immunization programs, improvement in socioeconomic status, and education of IDUs have contributed to marked decreases in new cases of HDV infection in Mediterranean countries. However, HDV infection continues to be common in Eastern Europe and among indigenous populations in central and South America.

■ SEXUAL TRANSMISSION OF HDV

The extent to which HDV may be sexually transmitted remains unclear. HBsAg-positive homosexual men have a low

prevalence of anti-HD compared with other carrier groups, particularly IDU.^{273,276–278} Accordingly, compared with IDU, a smaller percentage of homosexual men presenting with acute HBsAg-positive hepatitis in Los Angeles were found to have anti-HD.²⁷¹ These men also had a lower overall mortality than IDU with acute hepatitis B, reflecting their lower frequency of HDV infection. Nonetheless, HDV coinfection was found in 14% of homosexual men from Los Angeles with acute HBsAg-positive hepatitis,²⁷¹ many of whom denied a history of transfusions or injection drug use. Another survey found anti-HD antibodies in 9–15% of HBsAg-positive homosexual men living in Los Angeles and San Francisco, but only 0–1% of HBsAg-positive homosexual men in Chicago and Pittsburgh.²⁷⁶ In the West Coast groups, the presence of anti-HD was correlated with numbers of previous sex partners, as well as injection drug use. In contrast, of 60 homosexual men with acute hepatitis B who were identified through the sentinel counties study of the Centers for Disease Control and Prevention, none had concomitant HDV infection.²⁷⁷ Thus, except for reports from the West Coast of the United States,^{271,276} HDV infection appears to be a relatively rare cause of hepatitis among homosexual men. A similar absence of HDV infection among homosexual men with HBV infection was observed in Sydney, Australia.²⁷⁸ Fewer studies have focused on the potential for heterosexual transmission of HDV. However, a multivariate analysis of patients with acute delta hepatitis in Italy, a country with a generally high prevalence of HDV infection among HBsAg carriers, identified a history of having had >2 sex partners in the preceding 6 months as a significant risk factor for acquisition of the disease.²⁷⁸

■ PREVENTION AND TREATMENT

Although it is generally uncommon, the severity of liver disease accompanying acute and chronic HDV infections makes the potential for sexual transmission of HDV a concern worthy of continuing attention. However, there are no specific means for prevention of HDV infection other than immunization with hepatitis B vaccine, which provides protection by preventing the helper virus infection required for HDV replication.

Interferon is the only treatment that has demonstrated efficacy in chronic hepatitis D. Two recent studies confirmed that pegylated interferon can suppress HDV replication; ribavirin did not provide any additional benefit.^{279,280}

HEPATITIS C

■ INTRODUCTION

HCV was identified and shown to be the cause of almost all cases of non-B post-transfusion hepatitis in the late 1980s.^{281,282} The virus establishes a persistent infection in the

majority of infected persons, many of whom develop evidence of chronic inflammatory liver disease.⁶ These chronically infected persons are at risk of cirrhosis, liver failure, and hepatocellular carcinoma.^{283,284} HCV infection accounts for 15% of acute viral hepatitis cases within the United States. However, it is by far the leading cause of chronic viral hepatitis and is present in over 40% of persons with chronic liver disease. The morbidity and mortality associated with HCV infection are due to its unique propensity to cause persistent infection in most persons, a feature that distinguishes this virus from other hepatitis viruses. The specific mechanisms underlying viral persistence are not known.

Although it has been controversial, the balance of evidence now favors the occasional sexual transmission of HCV. The risk of infection with HCV, like HBV, has been independently related to numbers of sexual partners in some STD clinic studies.^{226,285} Although the risk of HCV infection has been shown to correlate with numbers of partners and/or specific sexual practices in some studies of homosexual men,^{286,287} the risk of infection is overwhelmingly more closely tied to injection drug use.^{286,289} The transmission of HCV is much more frequently associated with risks for percutaneous exposure such as sharing of paraphernalia for preparing and injecting drugs among illicit IDUs than with specific sexual behaviors. Sexual transmission of HCV appears to occur with a much lower efficiency than sexual transmission of HBV,^{290,291} although the reasons underlying this difference are not understood.

■ HEPATITIS C VIRUS

HCV is classified within the genus *Hepacivirus* of the family *Flaviviridae*, in part because of a distant phylogenetic relationship with yellow fever virus and other classical flaviviruses. However, HCV has a number of unusual biological features that distinguish it from other flaviviruses. These include most notably the ability to establish persistent infections in the majority of infected persons. Much has been learned about the molecular virology of HCV and its interactions with host cells since the last edition of this textbook was published, and a complete description of these advances is well beyond the scope of this chapter. More detailed reviews can be found elsewhere.^{392,293}

Virus structure and replication

The RNA genome of HCV is a single-stranded RNA molecule that is messenger sense.²⁸¹ Negative-strand replicative intermediates of the viral RNA have been demonstrated in the liver and serum.²⁹⁴ However, until recently, little has been known of the replication cycle of HCV, because wild-type virus undergoes only very limited replication in any cell culture system studied to date. HCV replicates to low levels in primary chimpanzee hepatocyte cultures, and several B- and

T-cell derived lymphoid cell lines may be permissive for low-level HCV replication as well.^{295–297} Generally speaking, however, the level of replication is insufficient for biochemical characterization of the virus and its replication. Complete cDNA clones of the HCV genome were constructed following identification of the virus, and the infectivity of RNA transcribed from several of these was established by demonstrating hepatitis associated with viremia in chimpanzees who were transfected *in vivo* by direct intrahepatic injection.^{298,299} These clones have benefited many aspects of HCV research, including the search for more fully permissive cell culture systems. In 1999, the first subgenomic HCV RNA replicons that were competent for replication in human cells were described.³⁰⁰ These RNAs express the nonstructural proteins of the virus and contain authentic 5' and 3' termini; they undergo efficient autonomous amplification following their transfection into permissive cell culture. Replicons propelled the field forward and led to many studies that have usefully characterized various aspects of viral RNA replication. However, it was not until 2005–2006 that the first cell culture-infectious viruses were described; these remain limited to only two virus strains at present but show promise of revealing previously unrecognized features of the viral life cycle, including aspects of viral entry into cells, assembly, and release.^{301,302}

The positive-strand RNA genome of HCV has a relatively lengthy 5' nontranslated region of approximately 342 bases, which contains an IRES that directs the 5' cap-independent initiation of viral translation.³⁰³ This is followed by a long, open-reading frame encoding a single polyprotein (Fig. 29-7). The polyprotein undergoes cotranslational processing events, directed by both host cell and virus-encoded proteinases. Several cleavages directed by host cell signal peptidases produce a series of structural proteins, which include the nucleocapsid protein (core), two envelope glycoproteins (E1 and E2), and a small membrane-associated protein (p7). Signal sequences within the amino terminal third of the polyprotein direct the secretion of the envelope proteins into the lumen of the ER, while the nucleocapsid protein remains within the cytoplasm. E1 and E2 become heavily glycosylated within the ER and the Golgi; these proteins have strong ER retention signals, and details of the viral assembly and secretion process remain obscure.^{304,305} E2 contains a highly variable domain near its amino terminus (HVR-1 domain), which is likely to form an immunogenic loop on the surface of the virion and which may interact with neutralizing antibodies.^{306,307} As such, it may be analogous to the V3 loop of HIV-1. It may also play a role in determining the interaction of the E2 protein with CD81, a putative coreceptor important for viral entry into cells.^{308,309}

At least six nonstructural proteins are derived from the remainder of the polyprotein (Fig. 29-7). Each seems to have multiple functions, many of which are only partly

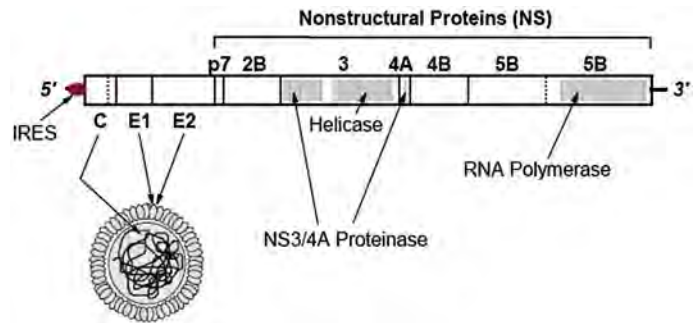


FIGURE 29-7. Organization of the 9.6-kb (+)-strand RNA genome of HCV. As in HAV (Fig. 29-1), the translation of a large polyprotein is directed by an IRES located within the 5' nontranslated RNA. This polyprotein is subsequently processed into the structural proteins, core (C), and the two envelope glycoproteins (E1 and E2), by cellular signal peptidase following translocation of part of the polyprotein into the endoplasmic reticulum. Following a *cis*-active cleavage directed by a cysteine proteinase activity spanning the NS2/NS3 junction, the NS3/4A protease directs further processing of the polyprotein, resulting in additional nonstructural proteins that are involved in viral replication. The major serine protease (NS3/4A) is a complex of NS3 and NS4A. NS3 also contains an RNA helicase, while NS5B possesses RNA-dependent RNA polymerase activity. These HCV proteins are targets of candidate antiviral drugs now in phase I/II trials.

understood. They include NS2, which includes in its C-terminal half a unique cysteine protease activity that spans the NS2B/NS3 junction and cleaves *in cis* at this site³¹⁰ and which also plays a role in viral assembly³¹¹; NS3, a serine protease/NTPase/RNA helicase responsible for the remaining processing events in the polyprotein^{312,313}; NS4A, an NS3 protease accessory factor that is intercalated into the structure of the mature NS3 protease and also anchors the NS3/4A complex to cellular membranes as well as to other viral proteins contributing to the replicase³¹⁴; NS4B, a hydrophobic protein that is responsible for reorganizing intracellular membranes into a “membranous web” that supports the replication of the viral RNA³¹⁵; NS5A, a multifunctional protein that appears to play roles both in interferon-resistance and replication of the viral RNA^{316,317}; and NS5B, the RNA-dependent RNA polymerase that forms the catalytic core of the replicase.³¹⁸ Many of these proteins have been shown to have important interactions with cellular proteins that promote the replication of the virus or contribute to the pathogenesis of the infection.²⁹³ Prominent among these interactions is the ability of the NS3/4A protease to proteolytically target key cellular signaling molecules required for interferon-mediated antiviral cellular defenses.³¹⁹

While interferon-based therapies are capable of curing many individuals with HCV infection, such treatment often fails and is associated with significant side effects (see Chapter 66). Thus, there has been strong interest in developing effective antiviral inhibitors of HCV replication. These have driven extensive studies of many of the nonstructural proteins, including high-resolution X-ray crystallographic analyses. The NS3/4A complex has been a

prime target for development of new small-molecule inhibitors of viral replication, and multiple candidate drugs are now in early phase I/II clinical trials. Some of these have shown remarkable clinical efficacy in short-term dosing studies.³²⁰ The same is true for inhibitors of the NS5B polymerase. Both allosteric (non-nucleoside) and active-site (nucleoside analog) inhibitors of NS5B have demonstrated promise as effective antiviral agents in early clinical studies. Although clinical experience remains very limited with either protease or polymerase inhibitors, antiviral drug resistance appears likely to be a significant risk with most, if not all, of these candidate therapies, which is not surprising, given the genetic diversity displayed by HCV strains, and will likely mandate the use of combinations of drugs in the future.

Genetic and antigenic heterogeneity

Different stains of HCV are classified as distinct “genotypes,” based on the extent of nucleotide sequence divergence.^{321,322} Genotype 1 is considerably more refractory to interferon therapy than non-1 strains, while spontaneous resolution of infection appears more common in genotype 3 infections.³²³ Otherwise, there is little evidence for differences in the pathogenicity of various genotypes. The genetic distance between some genotypes is large enough to suggest that there may be biologically significant serotypic differences as well. Preliminary analyses with recently developed virus neutralization tests, based on the use of cell culture infectious virus, suggest that there may be significant serologic differences between HCV genotypes, while earlier studies using pseudotyped viruses suggest extensive cross immunity.^{302,307} While early studies suggested that there is only low-level homologous protection when chimpanzees are challenged twice with the same strain of HCV,³²⁴ more recent studies have shown extensive protection against reinfection in chimpanzees, even with viruses from diverse genotypes.³²⁵

■ NATURAL HISTORY AND PATHOGENESIS OF HCV INFECTIONS

About 60–85% of all infections lead to virus persistence, and this is often associated with evidence of chronic liver disease (Fig. 29-8). After many years, this process may culminate in cirrhosis and liver failure, or the development of hepatocellular carcinoma. These end-stage events in chronic hepatitis C may claim as many as 10,000 lives annually in the United States.³²⁶

Acute hepatitis C

The primary cell type infected by the virus is the hepatocyte. However, there is some evidence for infection of lymphoid cells,³²⁷ and it is possible that this plays an important role in pathogenesis. Early studies in transfused individuals

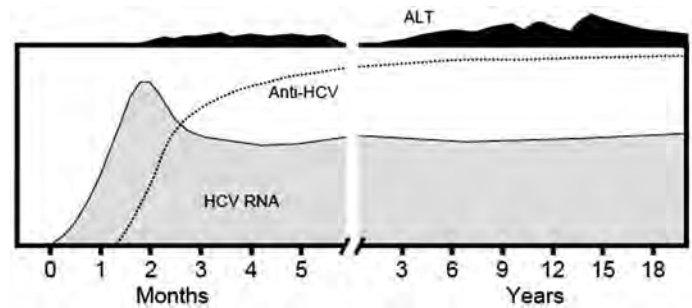


FIGURE 29-8. Typical virologic and serologic course of persistent HCV infection. Acute infection is often marked by little clinical evidence of hepatitis, despite the presence of relatively high levels of viral RNA in the blood that are detected by RT-PCR or sensitive bDNA hybridization assays. Anti-HCV detected by ELISA assays reflects specific antibody responses to a number of the viral proteins. Viremia is generally constant, while serum ALT levels can fluctuate significantly. The latter correlates poorly with the extent of histologic abnormalities in the liver. Late clinical complications include cirrhosis and hepatocellular carcinoma.

indicated that most HCV infections are associated with minimal symptoms and only rarely with identifiable jaundice.³²⁸ In contrast, patients presenting to physicians with acute hepatitis C are much more likely to be icteric.⁶ They represent only a small fraction of all acute infections. Quantitatively, virus replication appears to be greatest shortly after infection, with the magnitude of the viremia being highest during this period (Fig. 29-8). Clinical studies and analysis of experimentally infected chimpanzees have shown that the level of viremia declines with the appearance of antibody to viral proteins and T-cell-mediated immunity to HCV and, in most persons, remains constant at a relatively fixed level for many years thereafter.^{6,329} However, in a substantial minority of infected persons, these immune responses clear the infection, and viral persistence is not established. The clinical outcome of acute HCV infection is dependent on the vigor of both CD8⁺ and CD4⁺ T-cell responses to the infection.^{330–332}

Chronic hepatitis C

Approximately two-thirds of persons with chronic HCV infection go on to develop persistent or intermittent elevations in serum ALT levels.⁶ At liver biopsy, these individuals may have intrahepatic inflammation and fibrosis, the extent of which does not correlate with the magnitude of serum enzyme elevations. As many as a third of patients found to have chronic hepatitis C will ultimately develop cirrhosis^{6,284,333,334}; although it is not well defined, the fraction of all patients who are infected with the virus and progress to cirrhosis is undoubtedly far lower. Cirrhosis may be present within as little as 60 months of the initial infection but is identified typically in persons who have been infected for decades. Factors associated with disease progression include age at infection, regular alcohol consumption, coinfection with HIV

or HBV, and more recently obesity and insulin resistance.³³⁵⁻³³⁶ Some patients, usually with well-established cirrhosis, develop primary hepatocellular carcinoma.²⁸³ Chronic HCV infection is the most important etiology of hepatocellular carcinoma in western countries.

The major challenge to clinical investigators has been the discovery of specific markers that are predictive of progression of chronic hepatitis C to a clinically significant disease state. This remains an exceptionally difficult problem. There is no good correlation between biochemical markers and the extent of fibrosis or the presence or absence of cirrhosis. Indeed, many patients with cirrhosis have no obvious laboratory abnormalities.³³³ In addition, quantitative measurements of the viremia (“virus load”) are not useful in determining the extent of disease resistance.³³⁵⁻³³⁶ However, hepatitis C antibody-positive individuals who have normal ALT levels and who test persistently negative for viral RNA are at low risk of significant liver disease. A minority of all anti-HCV-positive individuals will fall into this category; some of these individuals may have false-positive tests, while others may have successfully cleared prior infection.

Destruction of the liver cell is probably not caused by direct cytotoxic effects of HCV infection, but rather by immunopathological mechanisms. Liver injury most likely results from the direct action of virus-specific cytotoxic T cells, as well as from secondary mediators of inflammation (such as gamma interferon) that are released as a result of the vigorous virus-specific T-cell response.^{161,329} Thus, T-cell-mediated responses have two effects on the disease process. They may suppress virus replication and lower the magnitude of viremia. However, in the absence of eliminating the virus altogether, cytotoxic T-cell responses also stimulate significant inflammation within the liver and are likely to be the proximate cause of inflammation, ALT elevation, and likely fibrosis.

Although both HCV- and HBV-related liver injury are immune mediated, the course of chronic HCV and HBV infections are different. Whereas chronic HBV infection is characterized by fluctuations in serum HBV DNA levels and exacerbations of hepatitis, chronic HCV infection usually progresses in a stepwise manner. Thus, assessment of the stage of hepatic fibrosis provides important prognostic information and is often used to determine the need for antiviral therapy. Because of the potential for complications and sampling error, many investigators have developed non-invasive models to predict hepatic fibrosis and/or cirrhosis, using routinely available laboratory test results, panels of special blood tests that include markers of liver inflammation and/or fibrosis, and most recently transient elastography.^{337,339} Some of these models have a fairly high degree of accuracy, but they are mostly designed to categorize patients as having mild versus advanced liver disease and do not differentiate among the different stages of fibrosis.

The frequency with which HCV infection leads to clinically overt liver disease has yet to be well established. In a retrospective cohort study of transfused individuals carried out in the United States, overall mortality was not increased in persons who had been infected with HCV 18 years earlier.³³³ Moreover, the risk of liver-specific mortality was only marginally increased in comparison with uninfected control subjects receiving equivalent numbers of transfusions. Although this study provides some level of comfort concerning this infection, this may be misleading. Most of the subjects were middle aged or older at the time of transfusion and subsequent infection with HCV and had other serious health problems such that 50% were no longer living after 18 years of follow-up. The impact of HCV infection may be quite different in individuals who are infected in the second and third decades of life and have many more years of life expectancy. Furthermore, when studied 18–20 years after their infection, as many as a third of the patients with transfusion-transmitted hepatitis C had elevated serum ALT activities indicative of chronic hepatitis. Moreover, among the patients from this group who underwent liver biopsy, approximately one-third had established cirrhosis.³⁴⁰

Consistent with this latter view, HCV is at present the leading cause of liver transplantation in the United States and an important overall cause of liver-related mortality. Concerns have been raised that HCV-associated mortality may increase significantly over the next two decades, as disease advances in large numbers of asymptotically infected persons who are at present in the third and fourth decades of life.³²⁶ Most of these persons probably acquired their infection due to limited injection drug use many years ago. Age-related seroprevalence data collected within the United States suggest that there has been a significant expansion of this pool of infected persons in recent decades.

Extrahepatic disease manifestations

Extrahepatic manifestations of HCV infection are relatively common and include most prominently glomerulonephritis and type II mixed cryoglobulinemia associated with vasculitis.^{243,341,343} Such individuals have circulating immune complexes containing viral RNA. Other potentially associated clinical conditions include porphyria cutanea tarda, sicca syndrome, and a variety of autoimmune diseases, as well as B-cell lymphoma. The pathogenesis of these conditions is poorly understood.²⁹³

■ DIAGNOSIS OF HCV INFECTION

Serologically, infection is marked by the presence of antibodies to several viral proteins: core, NS3, NS4, and NS5^{344,345} (Table 29-2). The presence of such antibodies may be detected by ELISA assays originally developed for

screening of blood donations. When such tests are found to be positive, confirmatory assays should be run to confirm the presence of infection. This usually involves detection of viral RNA in serum or plasma by a nucleic-acid-based diagnostic method such as RT-PCR,³⁴⁶ although a confirmatory recombinant immunoblot assay (RIBA) for antibodies is also available.³⁴⁷ The presence of antibodies to HCV signifies infection and not immunity. Positive reactions in assays for antibodies to E2 also correlate with serum RNA positivity³⁴⁸ and thus are not likely to reflect immunity. Quantitative RT-PCR assays and more sensitive qualitative RT-PCR and transcription-mediated amplification (TMA) tests for viral RNA are useful for assessing the replicative activity of the virus and for monitoring response to therapy (see Chapter 66).³⁴⁹ An international standard is used for determining quantity of circulating viral RNA and limits of detection of these assays.³⁵⁰ HCV genotype should be determined in all patients who are being considered for therapy.

■ EPIDEMIOLOGY OF HEPATITIS C

Transmission of HCV occurs by both percutaneous and mucosal exposures. Since transmission by blood and plasma-derived products has been eliminated by donor testing and inactivation procedures, the overwhelming risk factor in almost all studies in industrialized countries is a history of illicit injection drug use.³⁵¹ Because active HCV infections are highly prevalent among IDUs, exposure to HCV occurs early in the career of an IDU and is facilitated by sharing paraphernalia for the preparation of drugs with others, independent of sharing syringes and needles. Thus, HCV is one of the first infections contracted by most IDU. Percutaneous exposures such as accidental needlesticks are a source for infection among health-care workers, although the prevalence of infection in this group is usually similar to that of the background population. Like HBV, patient-to-patient transmission of HCV from unsafe therapeutic injections and other health-care procedures occurs in developed countries and contributes substantially to the disease burden in the developing world.^{352,353} HCV can remain viable on surfaces under ambient environmental conditions for at least 16 hours.³⁵⁴ Cosmetic procedures such as tattooing and body piercing have not been associated with an increased risk for HCV infection.³⁵⁵

In contrast to large or repeated direct percutaneous exposures to blood, sexual activity appears to be an inefficient means for transmission of this virus. Unlike HBV or HIV, MSM have not been shown to be at higher risk of HCV than heterosexuals, and sexual behavior is usually of secondary importance in determining the risk of HCV infection. However, there are a number of studies that relate sexual practices or numbers of sex partners to infection with HCV. In addition, recent outbreaks of hepatitis C

have been identified among MSM coinfecting with HCV and HIV.^{356–359} Maternal–infant transmission of HCV also occurs at much lower rates than with HBV but is increased when the mother is coinfecting with HIV.^{360–363}

Sexual transmission of HCV

Three general types of studies have attempted to document the sexual transmission of HCV. These include cross-sectional studies of populations at different levels of risk of acquiring STDs (such as MSM, prostitutes, STD clients, and blood donors), studies of sexual partnerships in which one partner is known to be infected with HCV, and case–control studies of individuals with acute hepatitis C. Each of these types of studies provides some support for the sexual transmission of HCV, but each also indicates that sexual transmission plays a limited role in determining the epidemiology of hepatitis C.

Osmond et al.²⁸⁶ studied 735 homosexual or bisexual men in San Francisco. They found HCV antibodies in only 4.6% of these men, while 81% had one or more markers of HBV infection. When percutaneous exposures were controlled for, the risk of HCV infection was marginally greater in those with >50 sex partners/year, or >25 oral- or anal-receptive partners. In contrast, HBV infection was much more strongly correlated with these risk factors.²⁸⁶ In a similar study, 2.9% of 1058 homosexual men included in the Pittsburgh arm of the Multicenter AIDS Cohort Study were found to be anti-HCV positive.²⁸⁷ Multivariate analysis found that injection drug use was the most important risk factor. However, seropositivity to HCV was significantly associated with a history of previous STD (syphilis and rectal gonorrhea) and anal receptive or insertive intercourse, but not numbers of sexual partners.²⁸⁷ These studies support a minor role for sexual transmission in determining the risk of HCV infection in homosexual men.

However, other studies have generated somewhat contradictory results. For example, Buchbinder et al.²⁸⁸ studied 435 gay men attending a municipal STD clinic in San Francisco. Five percent of non-IDUs were seropositive for HCV, whereas 25% of homosexually active IDUs were anti-HCV positive. There was no independent association between HCV infection and any sexual-risk factor on multivariate analysis.²⁸⁸ Another study of homosexual men carried out in Sydney, Australia, found 7.6% of homosexual men to be seropositive.²⁸⁹ Using a case–control approach, the risk of HCV infection was found to be independent of sexual practices or numbers of sexual partners. In fact, men without HCV infection were significantly more likely to have engaged in unprotected insertive or receptive oroanal intercourse. The only recognized risk factors for HCV infection in this study were injection drug use and infection with HIV-1.²⁸⁹

Taken in aggregate, these studies suggest that sexual behavior plays only a minor role in determining the risk of HCV infection among homosexual men and that sexual

transmission of the virus is relatively inefficient. Studies in prostitutes and other high-risk heterosexual populations generally confirm this impression.

In separate studies carried out in Taipei, Taiwan, and Fukuoka, Japan, HCV seroprevalence rates among female prostitutes ranged from 6% to 12%.^{364,365} The presence of HCV infection correlated with the length of time in prostitution and a history of syphilis. However, similar correlations were lacking among female prostitutes who were studied in Somalia.³⁶⁶ When non-IDU women attending an inner-city STD clinic in Miami were studied, 4.4% were seropositive for HCV, compared with 22% for HBV and 7% for HIV.²⁸⁵ Multivariate analysis indicated that HCV infection was more likely in women with >10 heterosexual partners in the preceding 5 years, those engaging in sexual practices more than once per week, and those with previous HBV or HIV infection.²⁸⁵ A similar study carried out in Baltimore confirmed the association between numbers of sex partners (i.e., having had >1 sex partner in the previous month) and HCV infection among non-IDU patients attending an STD clinic.²²⁶ In addition, this study found that the risk of infection was increased in men who reported a lack of condom use with sex during the month preceding their visit to the clinic.²²⁶ In general, the risk of HCV infection is generally greater in STD clinic patients who are over 29–30 years of age.^{226,291}

A number of studies have demonstrated that the rate of transmission of HCV within sexual partnerships is relatively low.^{367,372} For example, Osmond et al.³⁷¹ documented HCV infection in only two of 31 exposed female partners of infected hemophilic men, compared with zero of 81 partners of noninfected hemophilics. Similarly, Hallam et al.³⁷⁰ found only three of 104 long-standing sexual partners of infected hemophilic patients to be seropositive for anti-HCV. Each of the infected partners had other risk factors for infection. In another study, Eyster et al.³⁶⁸ found that female sexual partners of multitransfused men were approximately 8.5 times more likely to be infected with HIV than HCV if their partner was infected with either virus. In a STD clinic population, Thomas et al.³⁷³ demonstrated that the non-IDU female sexual partners of HCV-positive men were four times more likely to be infected with HCV than the female partners of HCV-negative men. No association was found for the male sexual partners of HCV-positive women. Thus, these studies document a low risk of male-to-female transmission within stable sexual partnerships. Fewer data address the issue of female-to-male transmission, but there is no evidence that transmission is increased in this direction.

It is possible, but not well documented, that HIV infection might increase the low risk of transmission of HCV within a sexual partnership. In a study of non-IDUs at risk of STDs, Lissen et al.³⁷⁴ reported HCV infection to be about twice as prevalent in stable, heterosexual partners of HIV-infected persons (9.2%) as in the partners of those without HIV infection (4.1%).

However, Eyster et al.³⁶⁸ found that only five of 164 female sexual partners of multitransfused men who were infected with both HIV and HCV were seropositive for HCV.³⁶⁸

Although these results indicate a relatively low rate of transmission of HCV within stable heterosexual partnerships, some studies have found that cohabiting sexual partners are at a significantly increased risk of infection compared to other household contacts of HCV-infected persons.^{375–377} This risk may be increased with older age and longer duration of marriage or sexual exposure.^{375,376} Furthermore, in at least one study, the results of nucleotide sequence analysis of virus present in blood support the interspousal transmission of HCV.³⁷⁵ Whether such infection occurs as a result of sexual intercourse or through other close, nonsexual contact remains uncertain.

Additional evidence for the occasional sexual transmission of HCV comes from a multivariate analysis of potential risk factors for HCV infection identified in a case-control study of blood donors in Sweden. HCV infection was independently correlated with injection drug use, blood transfusion, previous hospitalization, tattoos, and a history of previous STDs.³⁷⁸ Among those non-IDU who did not have a history of blood transfusion, the prevalence of antibodies to herpes simplex virus type 2 was significantly increased in those infected with HCV compared to those without HCV infection. A case-control study of blood donors in the United States identified a history of blood transfusion, injection drug use, intranasal cocaine use, and “sexual promiscuity” (defined as a history of STD, sex with a prostitute, and/or five or more partners per year) as significantly associated with HCV infection.³⁷⁹

All of the above studies are consistent with the notion that HCV may be sexually transmitted occasionally and that sexual behavior may influence the risk of HCV infection. However, because most of these studies were cross sectional in nature, the temporal sequence of the exposure relative to onset of infection was unknown. In case-control studies of acute hepatitis C conducted during 1978–1985, sex with a partner who had hepatitis or sex with >2 partners in the 6 months before onset of disease was independent risk factor for acquiring HCV.³⁸⁰ Among acute cases of hepatitis C reported in the United States during the 1990s, 15% had no risk factor other than sexual activity, of which two-thirds involved an anti-HCV positive sexual partner.³⁸¹ Most of these partner pairs were infected with HCV strains that were highly related, based on nucleic acid sequencing. The apparent inconsistencies in the risk of sexual transmission found between studies of persons with acute versus chronic hepatitis C might indicate differences in infectivity during the different phases of infection. The recent transmission episodes of acute HCV infection among HCV/HIV-coinfected MSM suggest that further investigation of this possibility might be worthwhile. However, it is clear from these studies that the sexual transmission of HCV is significantly less efficient than sexual transmission of HBV or

HIV, although there are insufficient data to quantify this risk for individual couples.

■ PREVENTION AND PATIENT COUNSELING

Prevention

Current understanding of protective immunity in hepatitis C is incomplete, but good evidence indicates that CD8+ memory T cells are essential for protection against persistent viral infection.^{293,382} Efforts to develop a recombinant HCV vaccine based on envelope proteins expressed in eucaryotic cells have met with limited success. Infection was prevented in immunized chimpanzees following challenge with a low-dose, homologous inoculum, and more recent studies suggest that immunization with envelope protein-based vaccines may reduce the risk of viral persistence, if not entirely prevent acute infection following challenge in the chimpanzee model.^{383–385} However, numerous technical difficulties hinder the commercial development of vaccines, including questions of efficacy and the presence of substantial genetic and probably antigenic heterogeneity among different HCV isolates. Although candidate vaccine have progressed to phase I clinical trials, it is unlikely that a vaccine will become available in the near future. Similarly, passive immunotherapy with pooled IG offers little promise of protection against HCV. Some early studies suggested that pooled IG might protect against disease if not infection.³⁸⁶ However, IG preparations that are currently in the market are made from plasma pools, from which donor units containing HCV antibodies have been excluded. Such preparations are less likely to be protective than the IG lots used in early studies of passive prophylaxis of non-A, non-B hepatitis. Nonetheless, a study in which chimpanzees received a special HCV IG (HCIG) preparation prior to challenge with virus demonstrated no protection against infection, despite a significant prolongation of the incubation period.³⁸⁷ Similarly, IG prepared from high-titered anti-HCV-positive plasma failed to prevent HCV reinfection after liver transplantation.³⁸⁸

Patient counseling

As indicated above, there is substantial evidence that HCV is only occasionally transmitted during sexual intercourse. Numerous partner studies demonstrate that the risk of transmission between individuals who are in a stable, monogamous relationship is quite low, although not completely absent. Thus, most experts do not routinely recommend the use of barrier prophylaxis by monogamous couples when one is found to be infected with HCV. Such a view is based in part on the absence of any data that condom usage would lower the already very low rates of transmission between sexual partners. On the other hand, many exposed individuals are relatively young, and there is clear evidence that HCV is a

significant pathogen, albeit with a long clinical latent period. Furthermore, as detailed above, virus transmission has been documented between cohabiting sexual partners. Thus, recommendations for or against the use of condoms in this setting cannot be undertaken lightly or with any great degree of certainty. It is most important that providers make available to patients appropriate information concerning the risk and potential consequences of HCV transmission during sex. The decision regarding the use of barrier prophylaxis must ultimately be made by the affected individuals. Persons with hepatitis C should be counseled to avoid exposing others to their blood and to limit their alcohol intake.³⁸⁹

■ TREATMENT

Treatment of chronic hepatitis C is discussed in Chapter 66. Currently approved treatment consists of a combination of pegylated interferon-alpha and ribavirin.^{390–392} Unless there are contraindications to the use of these treatments, patients with genotype 2 or 3 infection should be considered for treatment, given the high rate of sustained virologic response (70–80%) with a relatively short duration of treatment (24 weeks). Recent studies suggest that the duration of treatment may be further shortened to 12 or 16 weeks in patients with low pretreatment HCV RNA level or rapid virologic response (undetectable HCV RNA by week 4).^{393–394} Patients with genotype 1 infection are often recommended to undergo liver biopsy, in order to stage the extent of fibrosis prior to making a decision on treatment, because of the need for longer duration of treatment (48 weeks) and the lower rate of sustained virologic response (40–50%). However, patients who decline liver biopsies should not be denied treatment if they are otherwise appropriate candidates. Patients with HIV coinfection have lower rate of response but should be considered potential candidates for therapy due to the accelerated nature of the disease in coinfecting persons.^{395–396} Patients who have a long history of alcohol or drug abuse are more difficult to treat, but successful results have been reported with multidisciplinary approaches.

In recent years, rapid progress has been made in the development of small-molecule antivirals with activity against HCV.³⁹⁷ Both protease and polymerase inhibitors now in the clinic in phase I/II trials have shown substantial antiviral activity in chronically infected patients. Differences in sensitivity among HCV genotypes and the emergence of resistance appear likely to be significant issues in the future use of such antiviral drugs, suggesting that future treatment regimens will be based on combinations of agents, including interferon.

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DEFINITION AND HISTORY

Molluscum contagiosum is a benign papular condition of the skin, which is often sexually transmitted in adults. It is caused by the molluscum contagiosum virus (MCV), a member of the poxvirus family. Its characteristic appearance was first described in 1817 by Bateman, who labeled the disorder “molluscum,” a common term then for pedunculated lesions, and described it as “contagiosum” to signify its apparent transmissibility, which he felt was due to the “milky fluid” which could be expressed from the lesions.^{1,2} In 1841, Henderson and Paterson each described in this fluid cellular elements with large intracytoplasmic inclusion bodies (subsequently termed Henderson-Paterson, or molluscum, bodies), which they felt were responsible for causation and transmission of the disease.^{1,2} Subsequent reports of transmission of infection to humans by direct inoculation of lesion material supported an infectious etiology. The findings of tiny “elementary bodies” within the molluscum bodies by Lipschutz in 1911, and of disease transmission by a “filterable agent” by Juliusberg in 1905 and Wile and Kingery in 1919, suggested a viral agent.^{1,2} In 1933, Goodpasture demonstrated a marked similarity between the cellular inclusions and elementary bodies of molluscum contagiosum, fowl pox, and vaccinia and concluded that these infectious agents belonged to the same family of viruses.^{1,3} With the eradication of smallpox, MCV is the only human-specific poxvirus.⁴ Historically considered a minor clinical problem, molluscum contagiosum has become a common and often severe condition in patients with HIV infection.^{5–8}

BIOLOGY

MCV is a member of the family Poxviridae, subfamily Chordopoxvirinae, and the only member of the genus Molluscipoxvirus.⁹ Although never convincingly replicated in cultured cells, MCV has been purified from skin lesions.⁴ MCV is considered to be a poxvirus based on size, structure,

chemical composition, and physical and genomic characteristics.^{1,7,10–12} Ultrastructural studies of MCV reveal a particle similar to vaccinia virus, with which it has been most extensively compared: brick-shaped, approximately 300 × 220 × 100 nm in volume, with a biconcave viral core enclosed by an inner membrane and an outer envelope.^{1,10,13}

The viral genome consists of a single molecule of linear double-stranded DNA 190 kilobases long.^{10,11} Comparison of its sequence to that of other poxviruses indicates that it is among the most divergent of the poxvirus family.^{9,14} Although the majority of MCV genes are homologous to genes of variola and vaccinia, particularly those needed for transcription and replication, approximately one-third are unique to MCV and appear to mediate virus-host interactions.^{14,15} Many poxviruses encode proteins that help evade host immune defenses, often with homology to cellular genes from which they are likely derived, and those of MCV may be uniquely suited to infection restricted to the epidermis.^{16,17} Immune evasion genes of MCV that are homologues to cellular genes include an antagonist to the CCR8 chemokine (MC148),^{18,19} an IL-18 binding protein (MC54),²⁰ an MHC class I-like molecule that may interfere with viral antigen processing (MC80),²¹ CD150-like molecules that may alter antiviral signaling functions (MC2, MC161, MC162),²² a glutathione peroxidase that inhibits UV light- and peroxide-mediated apoptosis (MC66),²³ and inhibitors of tumor necrosis factor- α mediated apoptosis (MC159, MC160).^{24,25} Another viral gene that modifies virus-host interactions (MC13) inhibits vitamin D and glucocorticoid nuclear receptor transactivation, which may enhance viral growth by increasing keratinocyte proliferation (inhibited by both vitamin D and glucocorticoids) and blocking terminal differentiation (promoted by vitamin D).²⁶

Attempts at experimental cultivation of MCV have been frustrating and have limited the study of its life cycle.^{10,17} There is no well-established animal model of infection, and even human transmission studies have been only variably successful.^{1,2,11} MCV has been propagated in human foreskin

xenografts in athymic mice, offering hope of a model to test potential therapeutic agents; however, virions produced do not appear to be infectious and serial passage has not been successful.^{27,28} The virus cannot be grown in cell culture,^{10,17} a situation parallel to that of human papillomavirus (HPV). Virus derived from lesions will, however, cause functional changes in human primary fibroblast cells, inducing interferon production and induction of a characteristic cytopathic effect (CPE) with rounding of cells.^{1,2,10,29,30} Because these changes are associated with transcription of late as well as early viral genes, a low level of viral replication is likely; however, production of virions does not occur.³⁰ The inability to propagate virus in cultured cells has also limited characterization of MCV subtypes; however, based on DNA restriction endonuclease techniques four genomic subtypes have been identified, MCV 1–4, with evidence also of minor subtype variants (e.g., types 1v, 1vb, 1vc).^{10,31–36} The most common types, MCV-1 and MCV-2, are closely related in nucleotide sequence and genome organization, although their restriction maps differ substantially, in contrast to the restriction-site conservation seen with other poxviruses.¹⁰

EPIDEMIOLOGY

Characterization of the epidemiology of molluscum contagiosum has been limited by several factors. In most patients the lesions cause few problems and are self-limited.^{2,37–40} Thus, it is likely that many infected patients do not seek medical attention, and there are few population-based data concerning those who do, since molluscum contagiosum is not a reportable disease. Furthermore, the inability to cultivate MCV in cell culture has restricted studies of virus transmission, asymptomatic infection, and seroprevalence; thus, most epidemiologic studies rely largely on detection of characteristic lesions by physical examination.^{2,41}

Transmission of MCV occurs primarily by skin-to-skin contact by both sexual and nonsexual routes and is enhanced by warmth and humidity, with infection more common in underdeveloped and tropical climates.^{1,2,38–40,42,43} The suspicion that genital molluscum contagiosum is sexually transmitted is supported by indirect evidence, including lesion location (e.g., genital and pubic skin), a frequent history of contact with multiple sexual partners and prostitutes, the history and presence of other STDs, the presence of genital lesions in sexual partners, and peak ages of occurrence (20–29 years) that are similar to those of other STDs.^{2,38,39,44–46} There is no information about the efficiency of sexual transmission of MCV. The nonsexual form of the disease occurs primarily in children.^{47,48} It involves the face, trunk, and upper extremities and appears to be transmitted by direct contact with the skin of infected individuals and/or fomites.^{1,2,40,42,43} Infection has been associated with procedures causing skin

trauma (e.g., shaving, tattooing, and electrolysis)⁴⁹ and with contact with fomites, such as baths, gymnastic equipment and towels, and especially swimming pools, which have contributed to community outbreaks.^{1,2,40,42,43,50}

Data on rates of genital molluscum contagiosum are limited but suggest that incidence may be increasing. In the United States, a survey among private physicians demonstrated an 11-fold increase in visits by adults for molluscum contagiosum from 1966 to 1983,⁴⁴ although trend data since then are not available. In the UK, more recent data compiling trends in diagnoses made at genitourinary medicine (GUM) clinics indicate continued increases. Over the 10-year period from 1996 to 2005, the number of cases of molluscum contagiosum increased 134% in contrast to increases for first episodes of genital herpes and genital warts of only 13% and 12%, respectively. There was no increase in cases among men who have sex with men, suggesting that the rise is unlikely to be due to HIV-associated increases.⁵¹ Similarly, an STD clinic in India reviewed diagnoses among persons seen in the clinic in 1993–2000 compared to 1977–85 and found that while bacterial STDs decreased and genital warts were unchanged, genital herpes increased 80% and molluscum contagiosum increased 880%.⁵² Rates of nongenital molluscum contagiosum have been estimated from patients identified in dermatology clinics and in population-based surveys.^{2,40,42,43,47,48,53} While uncommon in North America and Europe, accounting for only 0.1–1.2% of patients attending dermatology clinics,⁴⁰ infection was noted during community surveys among villagers in Fiji and New Guinea in 4.5% and 7% of the population, respectively.^{40,43} Most cases were in children, and in surveys restricted to children in Fiji, New Guinea, and Japan, prevalence rates have ranged from 6% to 22%.^{40,42,43} Of interest, studies from dermatology clinics in developed countries indicate that a substantial proportion of cases in children (24–49%) have coexisting atopic dermatitis.^{54,55} Patients with HIV infection have prevalence rates ranging from 1.7% to 4.0%,^{56–58} while rates are even higher in those with clinical AIDS, ranging from 5% to 18%.^{59–62}

There are few data from population-based samples, although two recent studies have assessed incidence of cases of molluscum contagiosum seen by general practitioners in the Netherlands and in England and Wales, with similar findings. Both reported an annual incidence for all ages of 2.4/1000 and a cumulative childhood incidence (from 0 to 14 years of age) of 17%; incidence among adults was very low.^{47,48} Of interest, given the rise in cases in the UK GUM clinics, the study from England and Wales documented a 49% increase in incidence between 1994 and 2000. It has been speculated that the gradual rise in molluscum contagiosum could be due in part to the cessation of routine smallpox immunization following eradication, although the lack of serologic cross-reactivity between vaccinia and MCV makes such an explanation

unlikely.⁶³ A more plausible explanation, given the high proportion of patients with molluscum contagiosum who have atopic dermatitis, is the growing prevalence of the latter condition in developed countries.⁶⁴

Molecular epidemiologic studies indicate that MCV-1 occurs more commonly than MCV-2, although there is substantial geographic variability.^{7,10,33,34,55,65,66} There is no association between subtype and anatomic site, as there is for HPV and herpes simplex virus (HSV), or between subtype and lesion morphology. However, MCV-2 appears to occur more frequently in adults than in children, especially in those who are HIV-infected.^{10,33,65} Although mixed infections with both MCV-1 and MCV-2 and with subtype variants have been described, they are uncommon, and studies of family members with molluscum contagiosum and of multiple lesions from the same patient usually reveal identical subtypes.³⁴ Seroepidemiologic studies of MCV are limited and difficult to compare because of varying techniques and lack of adequate controls.^{1,2,43,55,67-70} Two recent studies have compared seroprevalence in those with active infection to control populations. Using a purified whole virus ELISA, Konya found a seroprevalence of 77% in those with lesions compared to 23% in population controls; among cases, seroprevalence did not vary by HIV status, but among controls it increased with age.⁶⁹ In contrast, using an ELISA based on the immunodominant 70-kd protein, Watanabe found a seroprevalence of 58% in cases but only 6% in healthy controls.⁷⁰ Current assays do not distinguish between antibodies to MCV-1 and MCV-2.⁶⁸

PATHOGENESIS, PATHOLOGY, AND IMMUNOLOGY

MCV has the most limited range of tissue tropism of any poxvirus. Infection occurs only in the epidermis, and dissemination does not occur even in profoundly immunocompromised hosts, as it can with vaccinia.^{10,11} MCV has a predilection for follicular epithelium and thus is uncommon on nonhair-bearing sites such as the palms, soles, and mucosa.⁷¹ Transmission is a result of skin inoculation, presumably following microscopic abrasions, and spread to “disseminated skin” sites probably occurs by external autoinoculation, with hematogenous or lymphatic spread unlikely.⁵ Although some poxviruses can establish persistent infection in cell culture, there is no convincing evidence of persistence *in vivo*, and the issue of persistence has not been clarified for MCV.¹¹ The high rate of infection in adults with AIDS raises the question of possible reactivation from subclinical infection in the setting of immunosuppression,^{6,7} supported by the finding of viral particles in skin adjacent to molluscum contagiosum lesions in persons with AIDS but not controls.⁷² However, the predominantly nongenital distribution of lesions in these previously sexually active persons suggests that reinfection is more likely. The

mechanism by which MCV stimulates basal cell proliferation and induces its benign tumors is not resolved. A protein homologous to epidermal and α -transforming growth factors identified in vaccinia and other poxviruses^{10,11} has not been found in MCV, although the possibility of an uncharacterized growth factor remains a consideration.¹¹

The pathologic changes induced by MCV infection are very characteristic^{1,2,17,73,74} (Fig. 30-1). Lesions consist of focal areas of hyperplastic epidermis surrounding cyst-shaped lobules that are filled with keratinized debris and degenerating molluscum bodies. In the basal layer, the nuclei and cytoplasm of the keratinocytes are enlarged and there is an increase in the mitotic rate. In the spindle layer, as a result of viral replication in the cytoplasm, cells begin to display cytoplasmic vacuolization, enlargement, and then replacement by eosinophilic compartmentalized globules, the molluscum bodies, which are contained in well-defined sacs and which compress the nuclei to the cell periphery.⁷⁵ In the granular layer, the molluscum bodies become more homogeneous with loss of their internal structural markings and are finally desquamated into the cystic lobules.^{1,2,73} Dermal changes are usually limited to stromal proliferation, although inflammation occurs in up to 20% of clinical lesions, with infiltration of the necrotic epithelium by lymphocytes, histiocytes, neutrophils, and occasionally multinucleated giant cells.^{1,2,73,76} In HIV infection, lesion histology may be atypical, with hyperkeratosis and verrucous changes.¹⁷

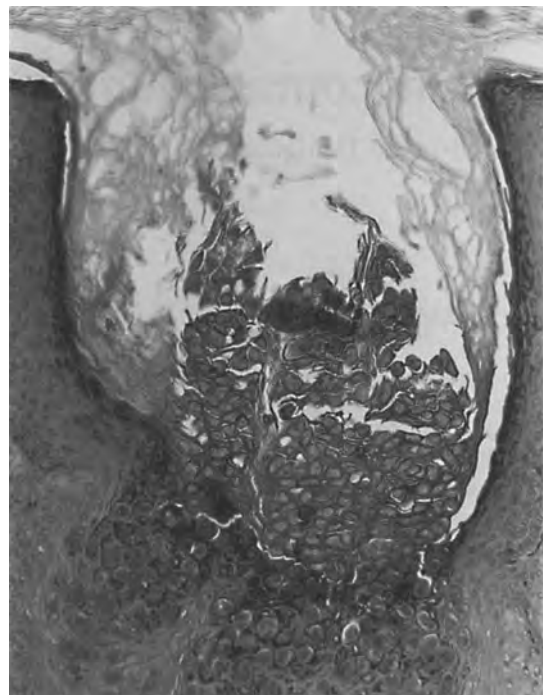


FIGURE 30-1. Biopsy of a molluscum contagiosum lesion showing an area of epidermal hyperplasia surrounding a cystic lobule. Keratinocytes in the upper epidermis as well as those desquamated into the lobule, demonstrate large, round intracytoplasmic molluscum bodies. Hematoxylin and eosin stain. (Courtesy of BA Werness.)

The importance of host immunity in the control of MCV remains poorly characterized. In the epidermis, the inflammatory infiltrate is usually minimal. While this has been ascribed to relative isolation from the immune system due to the superficial location of infection beyond the intact basement membrane and the sequestration of virions within the cytoplasmic sac,^{5,10,11,77} it is increasingly likely that the immune evasion mechanisms described above play an important role in this minimal inflammatory response.¹⁵ Epidermal inflammation occurs commonly after trauma, possibly as a result of disruption of these anatomic barriers, with a subsequent immune response which often precedes resolution of lesions.^{5,10} Additionally, the greater prevalence of lesions in children than adults suggests the acquisition of host resistance with age.^{40,43,47,48,53} Finally, the increase in rates and severity of infection in patients with AIDS indicates that intact cell-mediated immunity (CMI) is important in the control of MCV, as it is for vaccinia.¹¹ However, it is not clear whether a decrease in CD4 cells, Langerhans' cells, or another component of CMI is responsible for greater disease severity in AIDS.^{6,78} Despite the relatively high frequency of detectable antibody in those with clinical lesions,^{69,70} the role of humoral immunity in control of infection has not been defined.

CLINICAL MANIFESTATIONS

The incubation period of molluscum contagiosum averages 2–3 months, with a range of 1 week to 6 months.^{2,41} Most patients are asymptomatic, the diagnosis being made incidental to another problem. A minority of patients complain of itching or tenderness.^{2,38–40,79,80} Lesions begin as tiny papules which grow over several weeks to a diameter of 3–5 mm, occasionally enlarging to 10–15 mm, producing the “giant molluscum.”² The flesh-colored papules are smooth, firm, and dome-shaped, with a highly characteristic central umbilication from which caseous material can be expressed (Fig. 30–2). In adults, lesions most often occur on the thighs, inguinal region, buttocks, and lower abdominal wall and less commonly on the external genitalia and perianal region,^{2,7,81} a pattern contrasting with the distribution of genital warts. Children more typically develop lesions on the face, trunk, and upper extremities, often with a linear distribution suggesting autoinoculation by scratching; lesions on the palms, soles, and mucous membranes are rare.^{2,38,40,43,79} Lesions are usually more widespread in children than in adults, and while adults with genital disease rarely develop extragenital lesions, 10–50% of infected children have lesions in the genital region.^{40,80} The average duration of untreated disease is reported to be approximately 2 years, ranging from 2 weeks to 4 years; individual lesions usually resolve within 2 months.^{37,40,43,79} Recurrences after clearance occur in 15–35% of patients;^{37,40} whether these represent new infections or exacerbation of subclinical infections is unclear.⁷²



FIGURE 30-2. Penile molluscum contagiosum lesions in an immunocompetent host, with typical dome shape and central umbilication. (Courtesy of CAM Rietmeijer.)

The most frequent complication of infection, “molluscum dermatitis,” appears 1–15 months after the onset of lesions in up to 10% of patients.^{2,5,7,82} It consists of a sharply bordered eczematoid reaction 3–10 cm in diameter around an individual lesion, may involve only a portion of lesions, and usually disappears as the lesion resolves. Lesions of the eyelid may induce a unilateral conjunctivitis. The pattern is usually that of a chronic follicular or papillary conjunctivitis, but corneal changes with a punctate epithelial keratitis similar to that of trachoma can also occur.^{2,7} Other inflammatory conditions seen in association with molluscum contagiosum include folliculitis, sycosis barbae, erythema annular centrifugum, and pseudoleukemia cutis.^{2,7} Although it has been suggested that molluscum contagiosum lesions, like genital warts, worsen during pregnancy, there is little information on this issue.³⁹ Infection does not appear to affect the outcome of pregnancy, and while lesions have been reported in a child as young as 1 week old, no documented case of maternal-fetal transmission has been reported.³⁹

While normal hosts usually have 10–20 lesions, immunocompromised patients may develop hundreds of lesions.^{5–7,38–40} Widespread involvement of eczematous areas has been described in patients with atopic dermatitis and attributed to skin disruption, use of topical steroids, and/or an underlying immunologic disorder.^{79,83,84} Patients with frankly abnormal CMI are also at risk of developing extensive disease. Cases have been described in patients with sarcoidosis, epidermodysplasia verruciformis, lymphoma, and leukemia and in those receiving immunosuppressive therapy,^{2,5,7} although one review of molluscum contagiosum in children with

cancer indicated that the prevalence was no higher than in normal hosts.⁸⁵

In contrast, patients with HIV infection clearly experience an increased rate of infection. First noted in the early years of the AIDS epidemic,^{86,87} molluscum contagiosum in HIV-infected persons was recognized as a common opportunistic infection by the late 1980s.^{5-7,59-61} Both the prevalence and the severity of disease increase with advancing immunodeficiency,^{6,57,59-62} with lesions occurring in up to one-third of patients with CD4 counts of 100 cells/mm or lower.⁸⁸ The majority of lesions occur on the face and neck, especially in the beard area, where they are apparently spread by shaving; anogenital infection is relatively uncommon^{6,88} (Fig. 30-3). Outbreaks with extensive lesions are common, and giant molluscum lesions are noted in up to 10% of patients.⁶ Increased use of highly active antiretroviral therapy (HAART) would be expected to result in a reduction in molluscum contagiosum among persons with HIV infection. However, results to date comparing cohorts in the pre- and post-HAART eras have varied, with one demonstrating a reduction in prevalence⁸⁹ and several indicating no change.^{90,91} There is one recent report of an increase in molluscum following introduction of HAART,⁵⁸ although this may reflect a transient phenomenon related to increased lesion inflammation following HAART-induced improvement in immune function and enhanced lesion recognition. This phenomenon is considered to be part of the “immune reconstitution inflammatory syndrome” and molluscum is reported to be a common dermatologic marker of this syndrome.^{92,93}

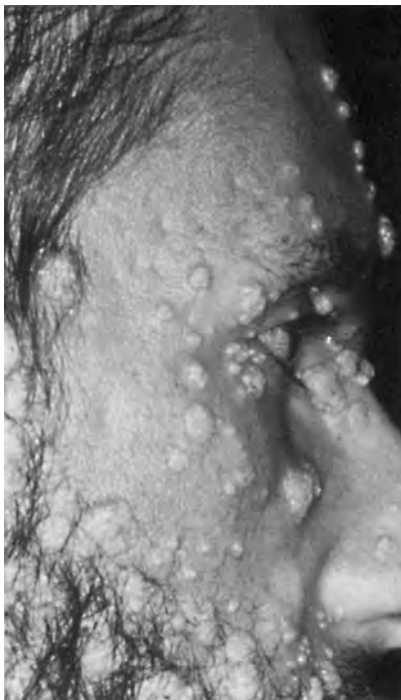


FIGURE 30-3. Severe facial molluscum contagiosum in a man with AIDS, with extensive involvement of the skin of the periocular and beard areas. (Courtesy of DL Cohn.)

DIAGNOSIS

The clinical diagnosis of molluscum contagiosum is usually made easily on the basis of the characteristic, pearly, umbilicated papules with caseous centers found on the face, trunk, extremities, or genital region.^{2,7,38,81} The use of a hand held magnification lens may be helpful in seeing the umbilication.⁷⁹ Lesions are most frequently misdiagnosed as common or genital warts or keratoacanthomas.^{2,7,38} Other considerations in the differential diagnosis include syringomas, plane warts, lichen planus, epithelial and intradermal nevi, sebaceous adenomas, histiocytomas, seborrheic and atopic dermatitis, basal cell epitheliomas, infection with HSV and varicella zoster virus, and lepromatous leprosy.^{7,38,79,94} In patients with HIV infection, basal cell carcinoma and disseminated fungal infections (e.g., cryptococcosis, penicilliosis, histoplasmosis) are also considerations.^{7,8} In atypical cases the diagnosis can be confirmed by demonstrating the pathognomonic enlarged epithelial cells with intracytoplasmic molluscum bodies on cytologic or histologic studies (see Fig. 30-1).^{2,7,8,38,74,79} Other diagnostic approaches include detection of MCV antigen by fluorescent antibody, viral particles by electron microscopy, and MCV DNA by PCR.^{36,41,95} Although not a diagnostic test, the CPE induced by MCV may be confused with that of HSV. Up to one-half of MCV lesions will induce CPE in cell culture,⁹⁶ and one laboratory reported that up to 10% of genital lesion specimens producing CPE were caused by MCV.⁹⁷

Additional diagnostic concerns include screening for other STDs in those with genital lesions^{38,46} and the possibility of an immunodeficiency, such as HIV infection, in those with widespread lesions. The issue of whether genital lesions in children should prompt a sexual abuse investigation is unresolved, although the presence of extragenital lesions suggests autoinoculation of the genital region, supporting a nonsexual route of transmission.⁹⁸

TREATMENT AND PREVENTION

Treatment of molluscum contagiosum is generally simple and accomplished by eradicating lesions with mechanical destruction or techniques to induce local epidermal inflammation.^{79,99,100} While therapy hastens resolution of individual lesions and may thereby reduce cosmetic concerns, autoinoculation, and transmission to others, the high frequency of recurrences and the benign and self-limited nature of the infection must be weighed against the pain and potential for scarring induced by destructive therapies, especially in children. Therapy is a higher priority in patients with many lesions, those whose lesions have persisted over time or are increasing, or those with large lesions.^{79,99,100}

Although few controlled studies have been performed,¹⁰¹ the simplest and most commonly recommended treatments are office-based techniques involving physical destruction of

lesions (e.g., excisional curettage, mechanical expression of the lesion core, cryotherapy, electrosurgery) or topical application of cytotoxic agents (e.g., cantharidin, trichloroacetic acid, retinoic acid, podophyllin).^{79,99,100,102} Because avoidance of treatment-associated pain is important in small children, topical agents or the use of local anaesthetics prior to destructive techniques is recommended. One large uncontrolled study of provider-applied cantharidin therapy in children reported a 90% clearance rate and 95% patient satisfaction.⁸⁰ Patient-administered therapies are also of growing interest. A randomized controlled trial of 0.5% podophyllotoxin cream reported a cure rate of 95% compared to only 16% with placebo.¹⁰³ There is also interest in topical imiquimod, an immune response modifier licensed for treatment of genital warts. A randomized controlled trial of 1% imiquimod cream (applied 3 times daily 5 days a week for 4 weeks) in primarily adolescent/adult males reported a cure rate of 82% compared to 16% in placebo recipients;¹⁰⁴ however, smaller studies of the currently licensed 5% preparation used less frequently in children have reported lower clearance rates.^{105–108} There are also reports of benefit with other patient-administered therapies including topical salicylic acid (alone or in combination with other agents such as povidone-iodine or acidified nitrite),^{109–111} silver nitrate paste,¹¹² and potassium hydroxide.¹¹³ Oral cimetidine may be useful as adjunctive therapy in patients with atopic dermatitis, but it is ineffective as monotherapy.⁹⁹

No therapy is very effective in immunocompromised patients because of the increased occurrence of new lesions.^{6–8} In HIV-infected patients, improvement of immune function following implementation of HAART has been associated with reports of dramatic improvement of molluscum lesions refractory to other therapy, usually with transient associated lesional inflammation suggestive of a local immune response.^{11–116} There are also case reports of responses in patients refractory to other treatments to therapy with topical imiquimod,^{105,117} pulsed dye laser,¹¹⁸ photodynamic therapy,¹¹⁹ or topical or parenteral cidofovir, a broad spectrum antiviral drug.^{89,120–122}

Recommendations regarding prevention of transmission include avoiding the sharing of bathtubs, bath towels, and sponges.^{79,99,123} While examination of sexual partners has been recommended in the past,^{2,7,38} there is no evidence to support this practice, and it is not currently recommended in the absence of another STI.¹⁰² Because of the widespread distribution of lesions, condoms do not appear to reduce the risk of sexual transmission.¹²⁴

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PART 6

Sexually Transmitted Bacterial Pathogens

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Julius Schachter and Richard S. Stephens

The chlamydiae are distinguished from all other microorganisms on the basis of a unique growth cycle (Fig. 31-1).¹ This cycle involves an alternation between two highly specialized morphologic forms, one adapted to an intracellular and the other to an extracellular environment. Because of this cycle, chlamydiae have been placed in their own order and family (*Chlamydiales*, *Chlamydiaceae*).² They are obligate intracellular parasites, and cannot be cultured on artificial media. Chlamydiae are restricted to an intracellular life style because they lack the ability to synthesize high-energy compounds, amino acids, vitamins, and cofactors. Thus, they depend on the host cell to supply them with ATP and necessary nutrients.

TAXONOMY

Chlamydia trachomatis, an important pathogen of humans, is one of several species within the genus *Chlamydia*.² A proposed division of the *Chlamydia* genus³ has not been generally accepted.⁴ An unfortunate consequence of the proposal has been the use of more than one genus name in the field. The properties of the four original species are shown in Table 31-1. *Chlamydia psittaci* is a common pathogen of avian species and domestic mammals, but only involves humans as a zoonosis.⁵ *Chlamydia pneumoniae* is a common respiratory pathogen of humans that has been implicated as a possible cause of coronary artery disease.⁶ *Chlamydia pecorum* is a pathogen of domestic animals.⁷ Some *C. psittaci* strains are sexually transmitted in their natural hosts, and one—the guinea pig inclusion conjunctivitis (GPIC) agent—may offer a potentially useful animal model for the study of sexually transmitted chlamydial infections.^{8,9}

C. psittaci, *C. pneumoniae*, and *C. pecorum* cannot be easily differentiated in the laboratory based solely on biochemical and phenotypic characteristics. Molecular techniques such as PCR or DNA hybridization or the use of monoclonal antibodies are required to differentiate the species. *C. trachomatis* is readily differentiated on the basis of two relatively simple laboratory tests (see Table 31-1). The simpler involves staining infected cells with iodine to determine whether the inclusions

contain glycogen: *C. trachomatis* inclusions do, while inclusions of the other species do not. The second and less reliable test involves testing for susceptibility to sulfonamides: *C. trachomatis* strains are susceptible and other chlamydiae are usually resistant. Each of these species contains many different strains possessing a variety of serologic and biologic properties. Unfortunately, their intracellular growth cycle has limited studies on the physiology of these organisms, and other markers for speciation have not been identified. The growing application of PCR in defining DNA sequences of genes, such as the 23S and 16S ribosomal RNA genes, coupled with phylogenetic analyses using a large database of chlamydial sequences, has enabled unequivocal markers of evolutionary relatedness.¹⁰ The use of DNA amplification based tests has become routine and found application for the identification

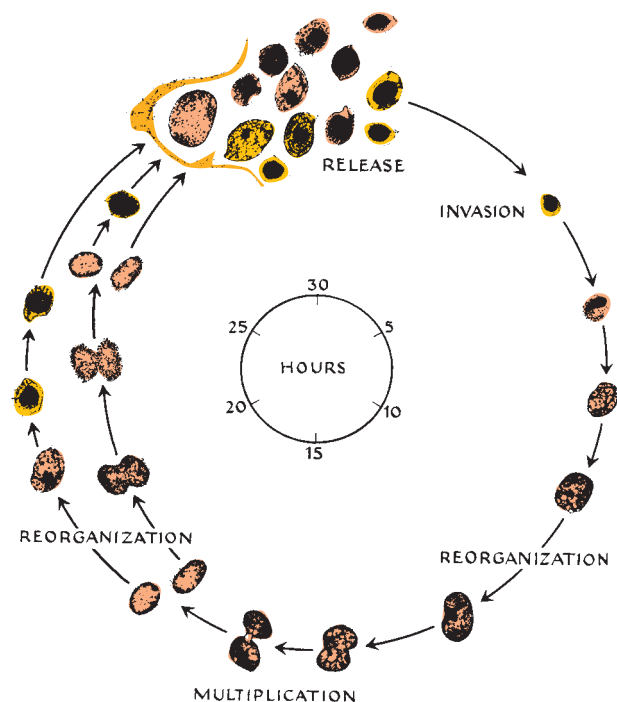


FIGURE 31-1. Growth cycle of the chlamydiae. (From Moulder JW. *The Psittacosis Group as Bacteria*. (CIBA Lectures in Microbial Biochemistry, 1963). New York: J Wiley, 1964, p. 95.)

Table 31-1. Usual Properties of *Chlamydia* spp

Property	<i>C. trachomatis</i>	<i>C. psittaci</i>	<i>C. pneumoniae</i>	<i>C. pecorum</i>
Sulfonamide susceptibility	+	–	–	–
Iodine-staining inclusions	+	–	–	–
Natural host	Human	Birds, lower mammals	Human	Sheep, cattle, swine

of strains, quantitation of chlamydial organisms and diagnostic detection.

The need for new tools for speciation is particularly acute within *C. trachomatis*. This species contains three biovars.^{2,11} The lymphogranuloma venereum (LGV) biovar causes LGV, a systemic STD (see Chapter 33). The trachoma biovar includes those strains causing the more common genital tract diseases (urethritis, cervicitis, salpingitis, infant diseases, etc.) and trachoma. Differentiation of those *C. trachomatis* trachoma biovar strains that cause genital infection from those that cause trachoma has been impossible until recently. It seems that these strains are identical except that the trachoma causing *C. trachomatis* do not produce a functional tryptophan synthase.^{12,13} This can be determined biochemically in tissue culture or by detecting the DNA sequence of the *trpA* gene. Thus, there is now an apparently stable biological marker to differentiate trachoma causing *C. trachomatis* strains from those isolated from the genital tract. The mouse pneumonitis (MoPn) biovar has now been placed in a separate species, *C. muridarum*. It does not infect humans and will not be discussed further in this chapter.

The trachoma and LGV biovars of *C. trachomatis* are related serologically but differ in the diseases they produce, in the type of cells they parasitize (in vivo and in vitro), in their experimental host range, and in a variety of other biological properties related to the infectious process (Table 31-2). The trachoma biovar has a very limited host spectrum in terms of susceptible cell types. In the natural host, it appears to infect only squamocolumnar cells; its strains are not efficient in infecting macrophages. LGV strains are more invasive and appear to be more efficient at replication in macrophages. Neither biovar will grow in polymorphonuclear leukocytes (PMNs). The basis for the biological differences between LGV and trachoma biovars is not yet understood despite analysis of the complete genome sequence for representatives of each.

HISTORY

Human diseases caused by *C. trachomatis* have been recognized since antiquity.¹⁴ Trachoma is described in Egyptian papyri. LGV was probably described by John Hunter in the eighteenth

century. The genital tract infections, such as nongonococcal urethritis and neonatal ophthalmia, caused by *C. trachomatis* were not recognized until it was possible to categorize these conditions following the identification of the gonococcus. With the introduction of ocular (Credé) prophylaxis with silver nitrate drops to prevent ophthalmia neonatorum and of culture and smear methods of diagnosing gonococcal infections, it became apparent that conjunctivitis in infants and urethritis in adult males both had nongonococcal forms.

C. trachomatis was first visualized in 1907 by Halberstaedter and von Prowazek in stained conjunctival scrapings taken from orangutans that had been inoculated with human trachomatous material. They quickly identified the typical intracytoplasmic inclusions, but initially they assumed that the organism was a protozoan. Shortly thereafter, similar inclusions were identified in human material from trachoma cases and then in conjunctival scrapings taken from infants with inclusion blennorrhoea. Inclusions were then found in the genital tracts of mothers of the affected infants and in the urethras of the fathers. In the first decade of the twentieth century, the presence of these inclusions was associated with nongonococcal urethritis.¹⁵

C. trachomatis was first isolated from patients with LGV.¹⁶ In the 1930s, the growth cycle of the LGV organism (as seen following intracerebral inoculation in mice and then in eggs) was noted to be similar to that found for the psittacosis organism, which had been isolated during the psittacosis pandemic of 1929–1930. The trachoma agent proved more difficult to recover, not being infective for mice. It was isolated by inoculation of embryonated hens' egg-yolk sacs by T'ang and associates in the 1950s.¹⁷ These results were soon confirmed by a number of research teams in different parts of the world. In retrospect, it is likely that a previous isolation claim by Macchiavello was probably valid, but it was not confirmed and the isolate was lost. The first isolate of *Chlamydia* (other than LGV agents) from the genital tract was made in 1959 by Jones, Collier, and Smith, who recovered *C. trachomatis* from the cervix of the mother of an infant with ophthalmia neonatorum.¹⁸ In 1964, chlamydiae were first recovered from the urethras of men epidemiologically associated with conjunctivitis cases.^{19,20}

Table 31-2. Properties of the LGV and Trachoma Biovars of *C. trachomatis*

Properties	LGV	Trachoma
I. Sulfonamide susceptibility	+	+
II. Iodine-staining inclusions	+	+
III. Host spectrum		
A. Natural host: humans	+	+
1. Mucosal surfaces	-	+
2. Lymphoid	+	-
B. Produce follicular conjunctivitis in subhuman primates	-	+
C. Lethal to mice (intracerebral)	+	-
IV. Growth in cell culture		
A. Form plaques	+	-
B. Marked enhancement by centrifugation	-	+
C. Infectivity enhanced by treating cells with DEAE	-	+
D. Infectivity reduced by treating cells with neuraminidase	-	+
E. Infectivity blocked by saturating cell surface with heat-killed homologous organism	-	+

For a number of years, there were very few groups actively pursuing the study of chlamydial genital tract infections. One of the reasons for this paucity of interest was the lack of a technology that lent itself to screening large numbers of specimens. All the early isolation studies (from 1960 to 1965) were performed using yolk-sac isolation procedures and thus were not clinically relevant because they could take up to 6 weeks to provide definitive answers. Dunlop and his colleagues at the Institute of Ophthalmology in London were the pioneering group that provided much of the impetus for continued research on chlamydial genital tract infections. In a series of studies, they found that a number of anatomic sites of the genitourinary tract could be infected with *C. trachomatis* and showed that approximately one-third of men with nongonococcal urethritis had the organism in their urethras.²¹⁻²³

A major technical breakthrough by Gordon and his colleagues in developing a tissue culture isolation procedure for *C. trachomatis* made it possible to (1) screen large numbers of specimens and (2) obtain the result of an isolation attempt in 48-72 hours, which made the laboratory diagnosis clinically useful.²⁴ Again, English workers were in the forefront of applying this test, and a number of research

groups in England independently published studies finding that one-third to one-half of men with nongonococcal urethritis had chlamydial infections.²⁵⁻²⁸ The clinical syndromes associated with these infections rapidly expanded.²⁹ These syndromes are listed in Table 31-3 and discussed in Chapters 32, 33, and 83.

Today, culture-independent tests have revolutionized chlamydia diagnostics. Commercially available antigen detection methods and nucleic acid hybridization tests, when introduced in the 1980s, largely replaced the technically more demanding isolation procedures. However the most important advance came from the introduction of nucleic acid amplification tests (NAATs) in the 1990s.³⁰ NAATs are far more sensitive than previously available diagnostic tests, and are highly specific, as well. Because they can be used with noninvasively collected specimens (such as first catch urines from either sex, or vaginal swabs), NAATs are well suited for screening as well as diagnosis. These specimens can be self-collected, making possible population-based screening, determination of incidence, as well as prevalence, and expansion of control programs to venues away from the traditional medical or STD clinics.

EPIDEMIOLOGY

■ SEXUALLY TRANSMITTED CHLAMYDIAL INFECTIONS

There appear to be two major modes of transmission of *C. trachomatis*. LGV, wherever it is found, appears to be always sexually transmitted. In industrialized western society, virtually all *C. trachomatis* infections are sexually transmitted. Men who acquire genital infection with non-LGV *C. trachomatis* strains usually develop nongonococcal urethritis 1–3 weeks postinfection. Because chlamydiae are obligate intracellular parasites and can only survive by a replicative cycle that results in death of the infected host cells, they must be considered to be pathogens at all times and are not part of the normal flora of the male or female genital tract. They do not always produce clinically apparent infections, however. For specific discussions of the epidemiology of these sexually transmitted infections, see Chapters 32 and 33.

If infective genital tract discharges are inoculated into the eye either during sexual activity or by hand to eye contact, conjunctivitis may develop.^{14,29,31} The disease caused by the trachoma biovar is called inclusion conjunctivitis, reflecting the diagnostic cytologic findings. In adults, it is an acute follicular conjunctivitis, which tends to follow a self-limited course. Keratitis and micropannus are common. Occasionally the disease persists beyond a few months and clinical features consistent with the diagnosis of trachoma may develop. Visual debility is rare. However, the regular appearance of corneal involvement (with the exception of Herbert's peripheral pits), similar to that found in classical trachoma, has led some workers to suggest that chlamydial infection of the eye represents a spectrum—from mild, self-limited, acute follicular conjunctivitis to chronic trachoma. The clinical picture is determined by the immunologic status of the host: previous exposure and hypersensitivity result in more severe disease, and reinfections or complicating bacterial infections interfere with spontaneous healing.^{14,29,31}

Infants exposed to *C. trachomatis* during passage through the infected birth canal may also acquire the infection and can develop a number of diseases, including conjunctivitis and pneumonia (see Chapter 83). At least 60–70% of exposed infants acquire chlamydial infection.³² Thus, both horizontal and vertical transmissions of *C. trachomatis* occur in industrialized society. Neither *C. pneumoniae* nor *C. psittaci* is sexually transmitted in humans.

ENDEMIC TRACHOMA

Child-to-child transmission is the most common method of chlamydial transmission in trachoma endemic areas.^{14,29,31,33}

In many developing countries, trachoma is endemic, and in some it is hyper- or holoendemic. Several hundred million people are known to be afflicted with trachoma, and millions

have been blinded. In holoendemic areas, children acquire the infection very early, either from persistently infected adults in their families or from exposure to other infected children. In some communities, all are infected by 2 years of age. Poor hygiene and unsanitary conditions contribute to the spread of the organism. Flies act as mechanical vectors in spreading infective ocular discharges. The disease begins as an acute mucopurulent conjunctivitis (often complicated by secondary bacterial infections) that becomes a chronic follicular keratoconjunctivitis, sometimes accompanied by a significant pannus (corneal neovascularization) formation and Herbert's pits.

In hyperendemic areas, active disease usually wanes when the children are 6–10 years old. Most of the children will be left with minor sequelae when the disease becomes inactive, and there will be no effect on vision. Some children with moderate to severe trachoma will develop badly scarred conjunctivae as a result of the necrosis of follicles. This scarring in the upper tarsal plate of the conjunctiva may with time result in distortion of the upper eyelid. The inturned upper lid margin causes the eyelashes to abrade and ultimately break down the corneal epithelium. It may take 25–30 years for this process to fully evolve, as the scars contract with age. Chronic, or recurrent infection, high-infectious load, and clinical severity are predictors of more severe sequelae.³⁴ The blindness seen in adults over 40 years of age usually reflect early childhood trachoma. In a hyperendemic area, age-specific blindness rates at age 60 may be 20% or more.³⁵

A major breakthrough in trachoma control has evolved from the introduction of azithromycin. Single-dose therapy with this drug has become the treatment of choice for genital tract infection.³⁶ It is effective in treating trachoma,³⁷ and community-wide treatment with azithromycin dramatically reduces chlamydial infection in the hyperendemic area.³⁸ This approach has been integrated into a single strategy for elimination of blinding trachoma as a public-health problem. This SAFE strategy has four basic components: surgery for the redirection of inturned eyelashes (entropion) and correction of trichiasis (where the eyelashes actually abrade the cornea); antibiotic treatment or using azithromycin for antichlamydial therapy; facial cleanliness; and environmental improvement.³⁹ Ultimately, these approaches have several long-term goals. The use of surgery is to prevent the development of blindness in those who already have lid damage from earlier chlamydial infection. The antibiotic treatment reduces chlamydial infection and facial washing, and provision of clean water and latrines are aimed at reducing further transmission of chlamydiae.

SEROVAR DISTRIBUTION

There are few studies aimed at determining the distribution of serovars in a community. Specific monoclonal antibodies

are available which can distinguish among the different serovars, but until this identification becomes more meaningful it will remain a research procedure. In trachoma endemic areas, there are usually only one or two serovars recovered in a community.^{31,40} Most infections within a household appear to be of the same serovar. The genital serovars (see Table 31-3) are not evenly distributed. L2 appears to be the most common of the LGV serovars, and the D and E serovars are the most commonly recovered trachoma biovars.⁴¹ The A and C serovars have never been recovered from the genital tract, but the B serovar, which is commonly associated with endemic trachoma, has also been shown to cause genital tract infection.

There appear to be no biological markers associated with the different serovars that would tend to make such typing relevant from either a clinical or a public-health viewpoint. It appears that the serotype of a strain has evolved independently from its biological background.⁴² However, a biological difference for strains isolated from trachoma patients has been identified. Isolates from trachoma patients lack a functional tryptophan synthetase gene, whereas isolates from the genital tract have a functional gene.^{12,13} This is independent of serovar as serovars A, B, and C each have a deficient gene, but serovar B strains isolated from the genital tract have functional gene.¹² The tryptophan synthase enzyme converts indole into tryptophan. Gamma interferon is an important host response to

chlamydial infection and is known to interfere with the completion of the chlamydial developmental cycle. Its action is thought to be due to tryptophan depletion. In vitro, the interferon's inhibitory effect in cell culture can be reversed by adding indole, if the chlamydiae possess a functional tryptophan synthase. This "indole rescue" was only observed with isolates of genital tract origin. This likely represents selection for a survival characteristic for the organism. The authors posit that presence of the enzyme will allow for productive infection in the genital tract where normal flora may produce indole, thus allowing the chlamydiae to escape the interferon effect.

Finer typing of *C. trachomatis* strains has been possible by genotyping the major outer membrane protein (MOMP) gene.^{43,44} This is the most variable of the genes among the serovars of *C. trachomatis*. It has four variable sequence regions that may reflect specific antigenic sites that are under selective immunologic pressures.⁴⁵ Use of a combination of monoclonal antibodies together with genotyping has verified that there are 18 major serovars of *C. trachomatis*, but because of nucleotide (usually coding amino acid) changes within serovars, multiple genovars can be detected. To date, the study of these genovars has had limited application. Efforts to associate specific genovars and serovars with more invasive disease or with more inflammatory changes have been equivocal. Genotyping has been replacing serotyping as an epidemiologic tool because it provides finer discrimination, and does not depend on isolation.

Table 31-3. Human Diseases Caused by Chlamydiae

Species	Serovar ^a	Disease
<i>C. psittaci</i>	Many unidentified serotypes	Psittacosis
<i>C. pneumoniae</i>	TWAR	Respiratory disease
<i>C. trachomatis</i>	L1, L2, L3	Lymphogranuloma venereum
<i>C. trachomatis</i>	A, B, Ba, C	Hyperendemic blinding trachoma
<i>C. trachomatis</i>	B, D, E, F, G, H, I, J, K	Inclusion conjunctivitis (adult and newborn), nongonococcal urethritis, cervicitis, salpingitis, proctitis, epididymitis, pneumonia of newborns

^aPredominant, but not exclusive association of serovar with disease. (Adapted from Schachter J. Chlamydial infections (in three parts). *N Engl J Med* 1978; 298: 428–435, 490–495, 540–549.)

BIOLOGY

DEVELOPMENTAL CYCLE

It is the developmental cycle of chlamydiae that sets them apart from all other bacteria. There are some differences in inclusion morphology within the chlamydiae, but all species appear to have essentially identical developmental cycles. The cycle may be divided into several steps: (1) initial attachment of the infectious particle, or elementary body (EB), to the host cell; (2) entry into the cell; (3) morphologic change to the reticulate particle, with intracellular growth and replication; (4) morphologic change of reticulate particles to EBs; and finally (5) release of the infectious particles.

The developmental cycle initially involves attachment to and penetration of EB to susceptible host cells.^{46,47} The infectious EB is relatively resistant to the extracellular environment but is not metabolically active. This particle changes to a metabolically active and dividing form called the reticulate body (RB, or initial body) at some time within the first 6–8 hours after entering the host cell. This reorganization process is poorly understood. EBs are approximately 350 nm in diameter and have an electron-dense center; RBs are approximately 1 μm in diameter and are not electron dense.

After reaching the RB stage, chlamydiae synthesize their own macromolecules—RNA, DNA, and protein—using the host-cell pool of precursors.⁴⁸ Glycogen is produced by all *Chlamydia*, but it accumulates within the inclusions of *C. trachomatis*, reaching levels detectable by iodine stain at approximately 30–48 hours postinfection.⁴⁹ The RB divides by binary fission from approximately 8 hours to 18–24 hours postentry. This is the stage of greatest metabolic activity, when the organisms are most sensitive to inhibitors of cell-wall synthesis and inhibitors of bacterial metabolic activity. Beyond 18–24 hours, the numbers of EB increase and this form appears to predominate, although both EB and RB are found in the mature inclusion.

The entire cycle takes place within a chlamydia-modified intracellular vacuole, which undergoes a large increase in size. As the RB multiplies, there is traffic of lipids from the *trans*-Golgi into the inclusion, although the biological significance of this finding is unknown.⁴⁹ At some time between 48 and 72 hours, the cell and vacuole rupture, releasing the infectious EBs. The RBs are not stable outside the host cell. Thus, as part of their unique growth cycle, the chlamydiae appear to have evolved two morphologic entities—the compact, stable EB, which successfully persists in the extracellular environment and is responsible for cell-to-cell and host-to-host transmission; and the highly labile RB, which is the metabolically active and vegetative form that is noninfective and does not survive outside the host cell.

EB Attachment

The initial contact of the chlamydial EB with the susceptible host cell may involve a specific receptor–ligand interaction, but no such structures have been unequivocally identified on either the EB or the host cell. The attachment process may involve specific receptor sites as trypsin treatment of host cells renders them resistant to infection⁴⁶ and mutant host cells have been selected that are resistant to attachment by chlamydiae.⁵⁰ Although the binding target is not known, the presence of these sites could determine which cells are naturally susceptible. For some strains, attachment may be charge dependent. DEAE-dextran pretreatment of cells leads to marked enhancement of attachment and entry of the trachoma biovar, but not of the LGV biovar.⁵¹ Treatment with negatively charged molecules such as heparin can inhibit chlamydial infectivity and elute EB from the surface of host cells. The attachment of *Chlamydia* to host cells and inhibition of phagolysosomal fusion are inhibited by specific antibody or by mild heat treatment of EB (56°C for 30 minutes).^{52,53} Monoclonal and polyclonal antibodies to several different chlamydial antigens (usually specific for variable sequence regions of MOMP, but also including some to other proteins) have been found to neutralize infectivity *in vitro* by inhibiting attachment for cells lacking antibody Fc receptors. The function of antibodies to these

antigens in naturally occurring infections is uncertain, but could contribute to protection from infection or reduce micro-biological spread to other tissues.

Cell entry

Once attached, the EB is rapidly internalized by the host cell. If a mixture of EB and *Escherichia coli* or yeast are presented to susceptible host cells, the chlamydiae will be preferentially ingested.⁵² Many of the cells that the chlamydiae infect are not considered phagocytes. Moulder has stressed the differentiation of host cells into professional and nonprofessional phagocytes and that chlamydiae induce phagocytosis by the nonprofessional phagocytes.⁵⁴ The mechanism of chlamydial uptake is not understood.

Ultrastructural studies on the entry of chlamydiae into susceptible cells suggest that they enter through clathrin-coated pits. This suggests that chlamydial entry is via a pathway similar to receptor-mediated endocytosis.⁵⁵ However, inhibitors of receptor-mediated endocytosis such as monodansylcadaverine or amantadine did not inhibit LGV biovar uptake in HeLa cells.⁵⁶ Entry may involve elements of receptor-mediated endocytosis process and may be chlamydia-directed by the secretion of chlamydial proteins into the host cell initiating an actin-based uptake mechanism.⁵⁷ Small GTPase cellular signaling events appear to serve the uptake process as activation of several members have been detected within minutes of chlamydial interaction with the host cell,⁵⁸ further implicating an important role for altering actin structure during the early infection stage. Once the chlamydiae penetrate the cell, they remain within an endosome throughout the growth cycle, and they specifically inhibit phagolysosomal fusion. Heat-killed or antibody-treated chlamydiae are not ingested at an enhanced rate and fail to inhibit phagolysosomal fusion. These two properties, induced phagocytosis and prevention of phagolysosomal fusion, are major virulence factors of this organism.

The EB is toxic. If the host cell ingests many particles (on the order of 100 EB), it may die with no resultant progeny.⁵⁹ Also, large concentrations of *Chlamydia* inoculated intravenously into mice will kill the animals; this “toxic death” appears to be a result of damage to the vascular endothelium. Chlamydiae do not produce an extracellular toxin.

Intracellular growth

The chlamydial particle enters the cell within an endosome and stays within that endosome through its entire developmental cycle. But phagolysosomal fusion does not take place.⁴⁷ The inhibitory signal is not associated with the RB, as after RBs are ingested there is fusion.⁶⁰ Inhibition is specific to the chlamydial phagosome, as fusion can take place in other phagosomes in the same cell.⁶¹ Following entry, chlamydiae modify the inclusion vacuole by secretion of a family of proteins that become associated with the vacuolar

membrane⁶² (see Fig. 31-2). Most of these proteins, called Incs, have no characterized function; however, IncA has been implicated with mediating fusion of vacuoles that harbor *C. trachomatis* organisms.⁶³ Interestingly, clinical isolates of *C. trachomatis* have been characterized that lack IncA expres-

sion and these strains form numerous inclusions within single cells following high-multiplicity infection (see Fig. 31-3).

Approximately 8 hours after entry into the cell, the EB has changed into an RB. The rigid structure of the EB is lost, and the RB is more permeable than the EB, allowing it to take up

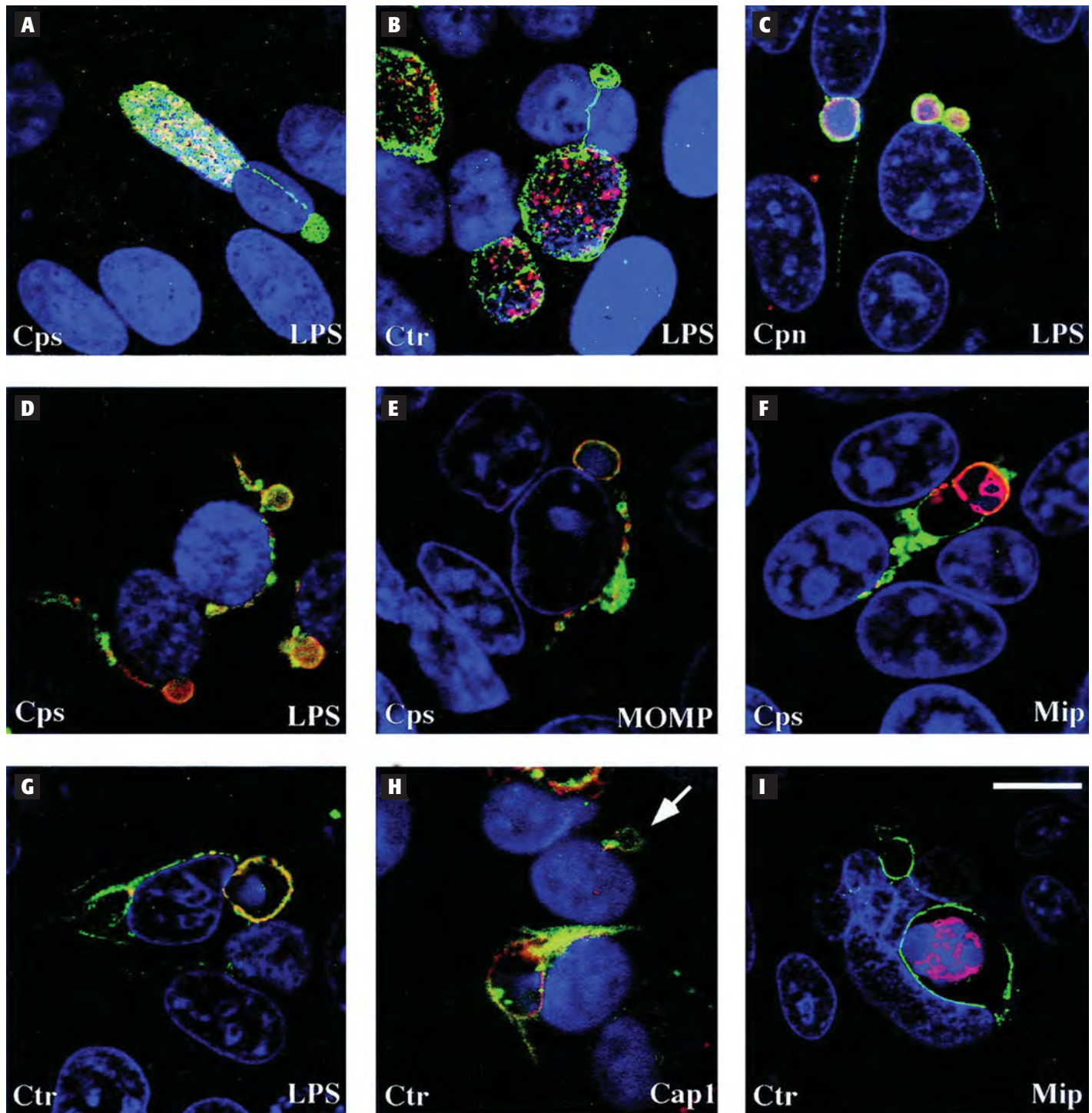


FIGURE 31-2. Antigen distribution within IncA-laden fibers of *Chlamydia*-infected cells cultured during standard growth conditions and in the presence of ampicillin. *C. psittaci* (Cps), *C. trachomatis* (Ctr), and *C. pneumoniae* (Cpn)-infected cells were cultured in MEM-10 (A to C) or MEM-10-containing ampicillin (D to I), prior to methanol fixation. All cells were labeled with anti-IncA antibodies (i.e., with fluorescein isothiocyanate). The antigens labeled with TRITC are depicted in the bottom right corner of each panel. Antigen colocalization was examined by using a confocal microscope. DAPI was used to label nucleic acids. The arrow in panel H shows the location of a vacuole embedded with chlamydial antigens that lack developmental forms. Bar, 8 μ m (for all images). (From Brown WJ, Skeiky YA, Probst P, Rockey DD. Chlamydial antigens colocalize within IncA-laden fibers extending from the inclusion membrane into the host cytosol. *Infect Immun* 2002; 70: 5860–5864.)

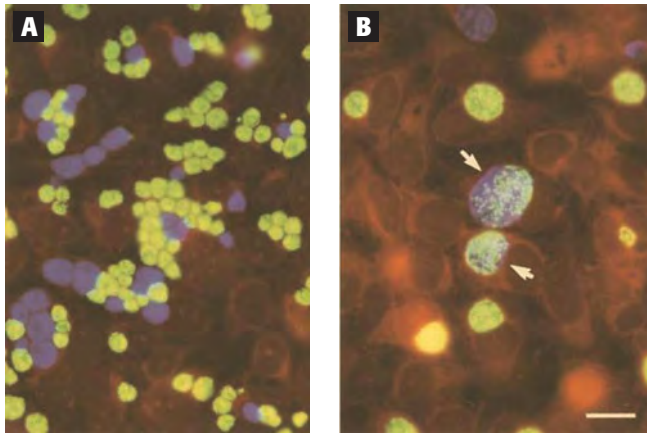


FIGURE 31-3. Dual infection of nonfusing, **A**, and fusion-competent, **B**, *C. trachomatis* strains cultured in HeLa cells and fixed for microscopy 30 h p.i. Within the nonfusing inclusions, serovar J_(s) (green developmental forms) and serovar K_(s) (blue developmental forms) remain segregated in individual vacuoles. Consistent with results of Ridderhof and Barnes⁶⁴, developmental forms of wild-type J (green) and K (blue) cells can be found within a single inclusion (arrows). The bar in panel B indicates 10 μ m for both panels. (From Suchland RJ, Rockey DD, Bannantine JP, Stamm WE. Isolates of *Chlamydia trachomatis* that occupy nonfusogenic inclusions lack IncA, a protein localized to the inclusion membrane. *Infect Immun* 2000; 68: 360–367.)

ATP and required nutrients. The inclusion and the RB act essentially as a reverse mitochondrion, with ATP and other nutrients entering the inclusion from the host cell.⁶⁵

The RBs divide by binary fission for approximately 20–24 hours. After that time, some of the RBs become EBs by a condensation process, which is not clearly understood. Condensation involves reorganization of the outer membrane envelope by incorporation of cysteine-rich proteins and by expression of DNA-binding proteins that compact the chromosome into the electron-dense nucleoid.^{66,67} Other RBs continue to divide. After replication of the RB, there is budding and blebbing of the outer membrane. Intermediate forms are also seen (see Fig. 31-1). The sequential synthesis of selected outer membrane proteins appears to reflect their putative function within the EB. Structural rigidity of the organism is maintained by disulfide bonds within the MOMP, which represents 60% of the outer membrane's weight.⁶⁸ The other cysteine-rich proteins of approximately 60 and 15 kDa are synthesized relatively late in the cycle.⁶⁹ The mature inclusion contains hundreds, even thousands, of EBs. The entire cytoplasm of the cell may be displaced by the inclusion. Throughout the infectious cycle, there is an inhibition of phagolysosomal fusion, and only at the very end is lysosomal enzyme activity noted.⁷⁰

MORPHOLOGY AND COMPOSITION

The chlamydiae are structurally complex microorganisms which possess cell walls and membranes quite analogous in structure to the cell walls of gram-negative bacteria⁷¹ (Fig. 31-4). Traces of muramic acid have been found in EB,

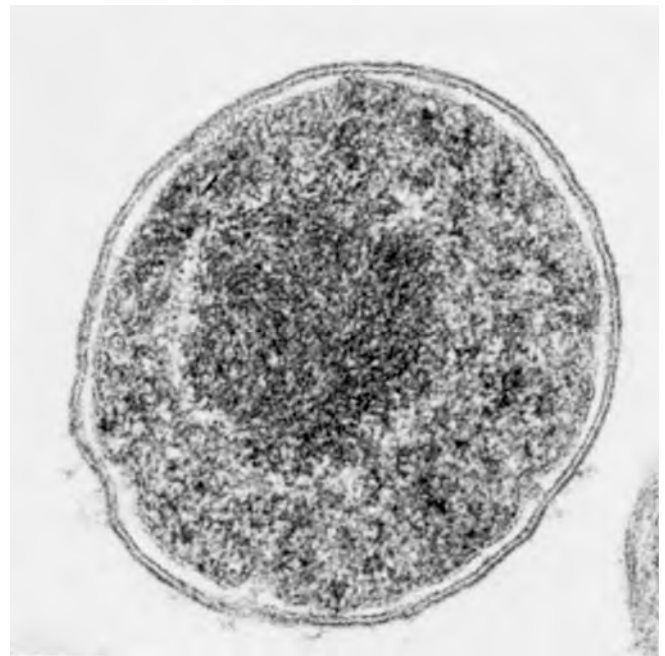


FIGURE 31-4. Electron photomicrograph of a thin section of a *C. trachomatis* EB (serovar L2/434). The trilaminar outer membrane (OM) and inner cytoplasmic membrane (IM) of the EB are shown at 118,000 \times magnification. (From Caldwell HD, Kromhout J, Schachter J. Purification and partial characterization of the major outer membrane protein of *Chlamydia trachomatis*. *Infect Immun* 1981; 31: 1161–1176.)

but in quantities inadequate to maintain structural integrity by a peptidoglycan layer.⁷² It is likely that the chlamydial cell wall is unique among bacterial species and probably represents a specialized structure compatible with the requirements of the chlamydial growth cycle.

The chlamydial cell wall consists of subunits approximately 20 nm in diameter arranged in a regular geometric pattern (Fig. 31-5).⁷¹ The outer membrane of *Chlamydia* contains the MOMP which is approximately 30% of the weight of the organism and approximately 60% of the weight of the outer membrane.⁷³ The size of this protein varies by serovar, with a molecular weight range of 38–43 kDa.⁷⁴ It is a porin⁷⁵ and also appears to be the major structural protein that functions in maintaining the structural integrity of the cell wall.⁷³ It is a cysteine-rich protein which is linked by disulfide bonds to itself and likely to two other proteins, of approximately 15 and 60 kDa, to maintain structural rigidity.^{76,77} MOMP is a transmembrane protein, with surface antigenic components responsible at least in part for serovar, serogroup, and species-specific serologic reactivity.^{78,79}

Although this statement is probably too simplistic, it is likely that the major structural changes that occur when the EB changes to an RB represent a reduction of intermolecular disulfide links within the EB outer membrane. RB outer membrane structure is in some respects similar to that of the EB, although with less disulfide bridging between MOMP and RB lacks the other cysteine-rich proteins.^{68,76} In the beginning

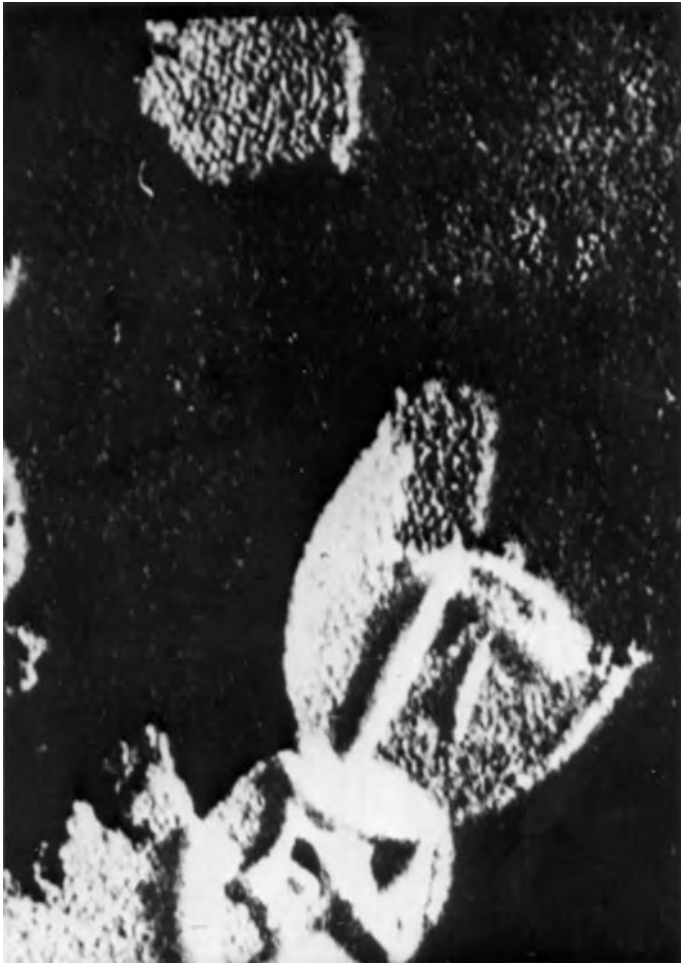


FIGURE 31-5. Fine structure of cell wall of meningopneumonitis organism. Shadowed preparation showing regular geometric arrangement of subunits approximately 20 nm in diameter. Approximately 75,000 \times magnification. (From Matsumoto A, Manire GP. Electron microscopic observations on the fine structure of cell walls of *Chlamydia psittaci*. *J Bacteriol* 1970; 104: 1332–1337.)

of the growth cycle, MOMP is reduced to the monomeric form, and it is found in the outer membrane throughout the chlamydial developmental cycle, whereas the other chlamydial proteins are synthesized later in the cycle.^{68,69,76} The synthesis of these other proteins is regulated at the transcriptional level so that they are expressed at the time the EB will form and are oxidized into the complex that is important for structural rigidity of the EB. Enzyme-mediated oxidation–reduction reactions are probably important in the differentiation of particle types.

Supporting the concept that the EB–RB transformation is partly dependent on reduction of disulfide bonds is the observation that reduced and alkylated MOMP functions as a porin.⁷⁵ EB in the presence of dithiothreitol showed increased glutamine oxidation, reduced infectivity, decreased osmotic stability, and staining characteristics of the RB.⁸⁰ This would be consistent with a structural change that is also important in the developmental cycle, as the outer membrane would be permeable to the nutrients required for RB metabolism.

The chemical composition of the organism appears to be approximately 35% protein and 40–50% lipid. Both RNA and DNA are found, although RBs, being metabolically active, have more RNA. The common group antigen, lipopoly saccharide (LPS), may be released from the particles by treatment with detergents such as deoxycholate.⁸¹

Electron micrographs have shown the regular arrangement of spikelike protuberances, which occur in only a limited area of the EB (Fig. 31-6).⁸² These projections are thought to be the type-III secretion apparatus. Type-III secretion systems are essential virulence determinants and function to deliver bacterial proteins into host-cell membranes or the host-cell cytoplasm. Only a few proteins (i.e., IncA and TARP) thus far have been shown to be secreted by this mechanism. However, given the probability of directing essential interactions with the host cell, identification and characterization of proteins delivered to the host cell by the type III secretion system promises to be a fertile research area.

Chlamydia appear to contain a number of penicillin-binding proteins.⁸³ The lack of muramic acid and peptidoglycan does not seem to jibe with the effects of penicillins. If one assumes that the ultimate effect of penicillin is the inhibition of cross-linking between tetrapeptide side chains of peptidoglycan, it would be reasonable to assume that chlamydiae have similar cross-linked tetrapeptides. These must link up with something other than peptidoglycan. Cycloserine, an inhibitor of tetrapeptide synthesis, is active against *Chlamydia* and its effect can be reversed by d-alanine, suggesting that such linkage occurs.⁸⁴

GROWTH AND CULTURE

Because chlamydiae are obligatory intracellular parasites, it is necessary to supply a living host cell to support their growth, although host protein synthesis is not required. Tissue culture isolation procedures have made chlamydial isolation clinically relevant. The organism can be recovered from patients in 48–72 hours, a time period consistent with other bacteriologic procedures. A number of cell lines have been used as host cells, and a variety of treatments—physical or chemical—have been employed to increase the susceptibility of these cells to chlamydial infection.^{14,85}

Modification of the host cells' charge by pretreatment of the monolayers with DEAE-dextran will enhance attachment by non-LGV *C. trachomatis* strains.⁸⁶ The single most important step in enhancing infection is centrifugation of the inoculum onto the tissue culture monolayer.^{24,87} With the exception of LGV strains, the *C. trachomatis* strains are not efficient at attaching to and infecting cells in vitro. Indeed, a convenient method of differentiating LGV from the trachoma biovar strains is to measure the enhancement of infectivity achieved with centrifugation, for it is minimal with the LGV strains (e.g., <eightfold) and increased by >10² for the non-LGV strains.

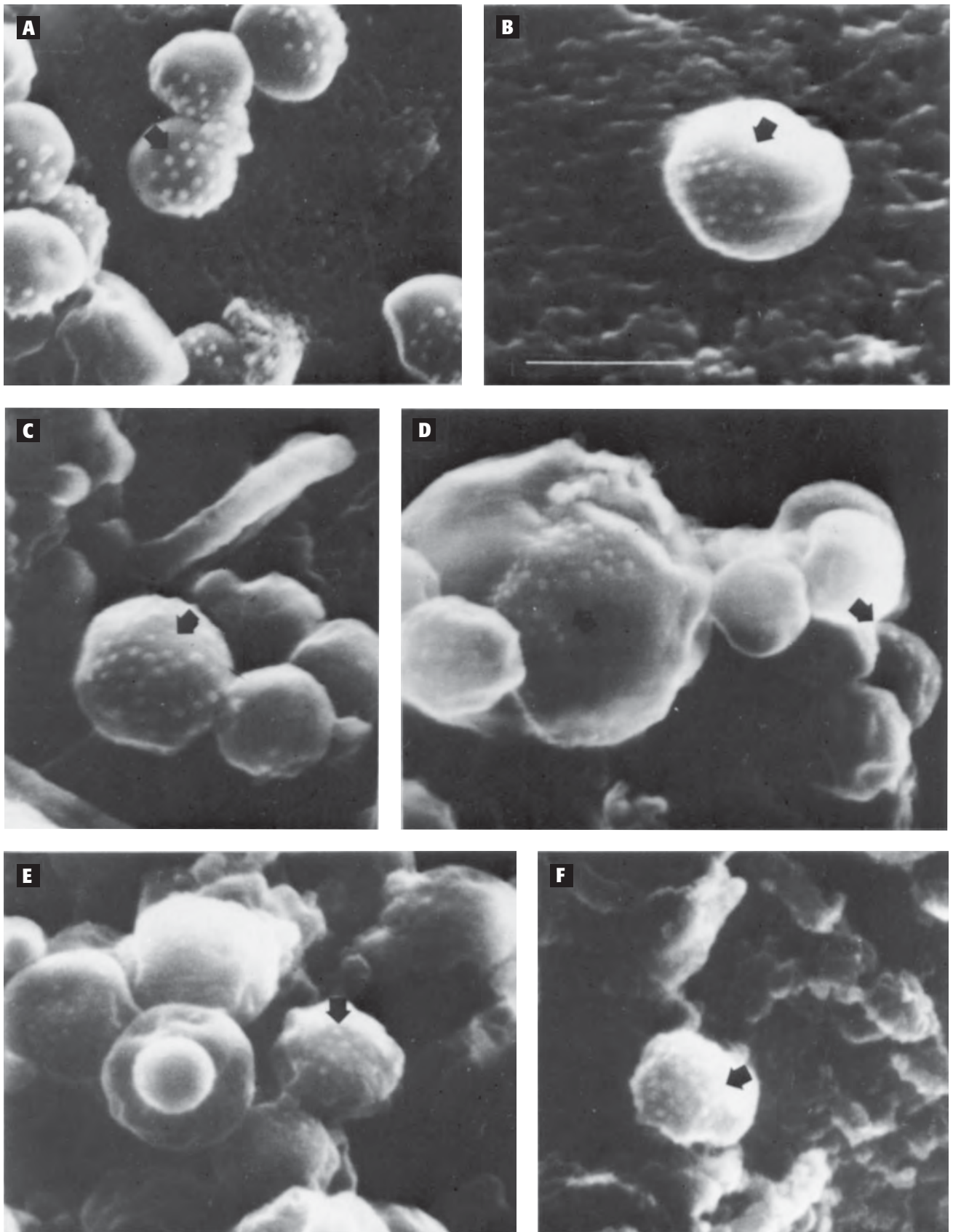


FIGURE 31-6. Scanning electron micrographs of two strains of *C. psittaci* and four strains of *C. trachomatis* settled onto L cells. **A.** *C. psittaci* (6BC). **B.** *C. psittaci* (feline pneumonitis). **C.** *C. trachomatis* (mouse pneumonitis). **D.** *C. trachomatis* (440L). **E.** *C. trachomatis* (G-17). **F.** *C. trachomatis* (UW-57). Arrows point to prominent arrays of projections. The bar in panel B represents 0.5 μm at 50,000 \times magnification. (From Gregory WW, Gardner M, Byrne GI, Moulder JW. Arrays of hemispheric surface projections on *Chlamydia psittaci* and *Chlamydia trachomatis* observed by scanning electron microscopy. *J Bacteriol* 1979; 138: 241–244.)

The growth of chlamydiae within the cell requires that the cell receives its essential nutrients. If the cell is starved, or if depletion experiments are performed with essential amino acids, some nutrients can be found to be growth limiting for chlamydiae, although often this reflects the requirements of the host cell more than those of the chlamydiae. The growth of *Chlamydia* in cell culture can be regulated by the amino acid concentration in the medium. Deprivation of the essential amino acids can render productive chlamydial infections to a nonproductive, persistent state. Addition of the required amino acids will then trigger growth of the chlamydiae.⁸⁸

The most commonly used procedure involves treatment of host cells with cycloheximide before or after centrifugation of the inoculum (see Chapter 52).⁸⁹ Synthetic abilities of the host cell are largely stopped by the action of cycloheximide, and under these conditions, *C. psittaci* required isoleucine, valine, and phenylalanine.⁹⁰ *C. trachomatis* appears to require histidine, while *C. psittaci* does not.⁹¹ Different *C. trachomatis* serovars can show different nutritional requirements.⁹¹ Cysteine is needed for the production of the cysteine-rich proteins that are important in EB rigidity. Cysteine deprivation will, in fact, prevent the final differentiation of EB from RB.⁹² The sensitivity of *Chlamydia* to amino acid concentrations may have important biological implications. The action of gamma interferon in reducing chlamydial replication and infectivity may be a direct result of reduced tryptophan levels in *Chlamydia*-infected cells.⁹³

RB harvested at 20 hours, but not EB purified from *C. psittaci* and *C. trachomatis* infected cells, can support ATP-dependent and antibiotic-susceptible synthesis of proteins. MOMP and 12.5 and 60 kDa cysteine-rich protein are produced at a lesser rate than is found in infected cells.⁹⁴ Chlamydiae are capable of incorporating carbon from glucose-6-phosphate, pyruvate, and isoleucine into a trichloroacetic acid insoluble fraction. This activity was shown using a mixture of EB and RB and is ATP-dependent.⁹⁵ Cyclic AMP inhibits chlamydial growth, and the action has been shown to be on the RB-to-EB transformation.⁹⁶ RBs appear to have a receptor protein for cyclic AMP.⁹⁷ Hormone levels may affect chlamydial growth and metabolism. Estradiol enhances the growth of *C. psittaci* and *C. trachomatis* in HeLa cells.^{98,99}

GENETICS

Technical considerations have prevented extensive genetic analysis of *Chlamydia*. Difficulties in developing a DNA transfer system and lack of suitable markers have restricted studies. Chlamydiae have one of the smallest bacterial genomes consisting of approximately 1.0–1.2 million base pairs, one-quarter of the size of most free-living bacteria such as *E. coli*.¹⁰⁰ All *C. trachomatis* serovars contain a 4.4-MDa plasmid.¹⁰¹ Functions of the plasmid genes are not known, although some of the gene products are expressed during

C. trachomatis infection in cell culture. Polypeptides encoded by these plasmids have been synthesized in an in vitro transcription translation system, and the polypeptides were not immunoreactive with antiserum prepared against chlamydiae,¹⁰² but antiserum from infected individuals will recognize some of the plasmid gene products.¹⁰³

Although basic chlamydial research has been hampered by the lack of genetic tools, the genomes of five chlamydial species have been sequenced and analyzed. These include strains of *C. trachomatis* and *C. pneumoniae*.^{104–108} Remarkably, pairwise comparison of all genes between these genomes reveals that 88–98% of the encoded genes are shared (see Fig. 31-7). The *C. trachomatis* serovar D and the *C. trachomatis* mouse pneumonitis (CtMoPn, Fig. 31-7) have almost complete identity in gene content; even more remarkable is that the order of their genes is identical. The genes shared by the chlamydiae define the basic phenotypic and biological attributes that are common to the chlamydiae. Of interest too are the minor differences that are simply sufficient to define tissue and host specificity. The fundamental knowledge being deciphered from these genome sequences has had a dramatic effect on the progress of chlamydial research by refocusing old hypotheses, raising new hypotheses, and enabling hypothesis testing.

PATHOGENESIS

The pathogenesis of any of the infections with *C. trachomatis* has not been elucidated. It is clear that LGV is a systemic infection involving lymphoid tissues. In vitro studies have shown that the organisms are capable of replicating within macrophages.¹⁰⁹ To date, all information suggests that non-LGV *C. trachomatis* strains have a very limited host-cell range in vivo. They appear to be almost exclusively parasites of squamocolumnar-columnar epithelial cells. Because they are obligate intracellular parasites and kill host cells at the end stages of their growth cycle, these chlamydial strains must

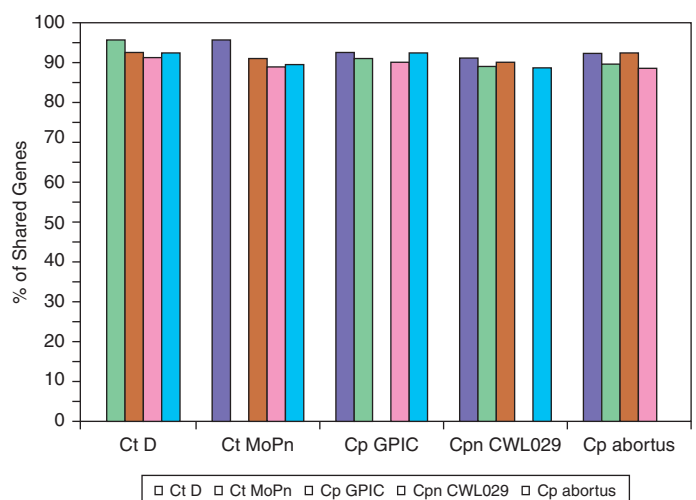


FIGURE 31-7. Level of shared genome content among chlamydial species.

cause some cell damage where they persist. There is little in vivo evidence for latency in the sense of persistence of non-replicating chlamydiae.¹¹⁰

The disease process and clinical manifestations of chlamydial infections probably represent the combined effects of tissue damage from chlamydial replication and inflammatory responses to chlamydiae and the necrotic material from destroyed host cells. There is an abundant immune response to chlamydial infection (in terms of circulating antibodies or cell-mediated responses), and there is evidence that chlamydial diseases are diseases of immunopathology.^{14,31,111,112}

There must be some sort of protective immune response to the organisms, because chlamydial infections tend to follow a fairly self-limited acute course, resolving into a low-grade persistent infection which may last for years. These infections may be activated by a variety of stimuli, of which steroids represent one class. Other reactivating agents are not yet known but must exist, as spontaneous exacerbations occur.¹¹³

LGV is a truly lymphoproliferative disease, and the other chlamydiae appear to be capable of causing a more localized lymphoproliferative response, in the sense that they can induce follicle formation in the mucous membranes. Although such a response is most well known for the conjunctiva (trachoma and inclusion conjunctivitis), follicular cervicitis and probably follicular urethritis (cobblestone appearance of Waelsch urethritis) are recognized entities. Follicles induced by *C. trachomatis* are authentic lymphoid follicles with germinal centers.

Trachoma has long been considered a disease in which reinfection is important.³¹ It has been speculated that hypersensitivity to chlamydial antigens explains the deleterious outcome observed after inadequate vaccination and the more severe disease seen after heterotypic infection.^{14,31} Resistance to reinfection appears to be predominantly serovar specific. In nonhuman primates, repeated (weekly) conjunctival instillation of *C. trachomatis* results in a disease with many of the manifestations of trachoma, including conjunctival scarring.¹¹⁴ Similarly, in an experimental salpingitis model, it was found that severe salpingitis in nonhuman primates was also in part dependent on previous exposure to chlamydiae.¹¹² A common pathologic end point of chlamydial infection is scarring of the affected mucous membranes. This is what ultimately leads to blindness in trachoma and to infertility and ectopic pregnancy after acute salpingitis. There is epidemiologic evidence that repeated infection results in higher rates of sequelae. Thus women identified with repeat infection have more acute salpingitis than those with single infections.¹¹⁵ From these epidemiologic studies, and the observational studies in trachoma, it is impossible to separate repeated discrete episodes of infection, from chronic, persistent infection as the precursor of severe late consequences.

The current prevalent theory is that much of the chlamydial disease is due to delayed hypersensitivity reactions to specific *Chlamydia* heat-shock proteins (HSPs).¹¹⁶ These

HSPs are similar to the HSPs of other organisms. HSP60 contains antigenic sites that are specific to chlamydiae, but it also has sites that are shared with mycobacteria and *E. coli*, and even with humans. It is clear that low-level infections can produce relatively high quantities of HSP60 and that women who suffer from tubal-factor infertility and ectopic pregnancy often have high levels of antibody to *Chlamydia* HSP60.^{117,118} It should be stressed that this is still a theory and direct proof from either human or animal studies has not been generated. It is conceivable that the observed reactions are just a proxy for another reaction, but these were identified because the HSPs are plentiful and highly immunogenic.

There are no satisfactory animal models for genital *C. trachomatis* infection. Nonhuman primates are susceptible to ocular and genital infections with the trachoma biovar. Much has been learned about the pathogenesis and immunity in ocular infections. Data suggesting that prior exposure is important in the poor outcome after oviduct infection have also been obtained in this model.¹¹² However, because of expense and difficulty of obtaining a large number of nonhuman primates, attempts have been made to develop models in smaller animals. The genital tract of female mice that have been treated with progesterone can be infected, and ascending infections can result in salpingitis and infertility.¹¹⁹ Some workers have attempted to exploit naturally occurring chlamydial infection in smaller animals. The *C. psittaci* GPIC agent and the mouse pneumonitis biovar of *C. trachomatis* are both capable of infecting genital tracts of their natural host.^{8,9,120} They are sexually transmitted and can cause tubal-factor infertility as a result of ascending infection in the female genital tract.^{121–123}

DIAGNOSIS

The diagnosis of chlamydial diseases is discussed in detail in Chapter 52.

ANTIMICROBIAL SUSCEPTIBILITY

There is no universally accepted protocol for testing the antibiotic susceptibility of *C. trachomatis*. A number of different procedures have been used, and the data in [Table 31-4](#) present the range of results obtained for inhibitory levels in tissue culture systems. The simplest procedures involve infection of cell culture with a standard inoculum followed by addition of an antibiotic-containing medium. After an appropriate incubation period, inclusion counts are performed, and the concentration of antibiotic resulting in 50% or 100% reduction in inclusion count is accepted as the minimum inhibitory concentration (MIC). This procedure tends to overestimate the activity of the drugs tested. A more rigorous test involves blind passage of inclusion-negative monolayers, in an effort to assure that the drugs in question actually

killed the *Chlamydia*. In this test, the minimum concentration where no inclusions are detected on passage is considered to be the minimal cidal level.¹²⁴

The most rigorous test of antimicrobial activity involves attempts to sterilize established infections in cell-culture systems. In this test, the tissue culture monolayers are infected with *C. trachomatis* for approximately 48 hours, and then different drug levels are added to the infected cell culture systems. After a subsequent 24-hour incubation period, the cell cultures are washed and passed to determine whether the chlamydiae have been eradicated. This procedure is likely to underestimate the effective levels of drugs, since the antibiotics are added after the time they would be most active. (That time is during active replication or metabolism, which peaks at less than 48 hours.) In addition, the technique suffers from technical objections concerning potential carryover of drugs into the second passage. This possibility is particularly present with those antimicrobials that are lipid soluble or that would have high intracellular penetration, as simple washing would not remove the drug from the monolayers and subsequent inoculum for the second passage.

C. trachomatis is susceptible to sulfonamides.² The organisms produce their own folic acid, and the enzymes in this synthetic pathway are susceptible to the action of the sulfonamides and to trimethoprim. Sulfonamides have been clinically effective in trachoma and LGV, but they are not used in treating most genital tract infections with *Chlamydia* because these drugs are not active against other organisms producing similar diseases.²⁹

Azithromycin is currently considered the drug of choice for treating chlamydial infection.¹²⁵ Aside from excellent in vitro activity, this drug demonstrates prolonged bioavailability, which permits single-dose administration, and it accumulates within cells. Single-dose therapy with azithromycin has been shown to be as effective as a week-long course of doxycycline in treating chlamydial infection, but likely results in much better compliance, especially in nonstudy situations. The drug is similar to erythromycin in in vitro assays with MIC <1.0 mg/mL.¹²⁶

Tetracyclines and erythromycin were formerly considered the drugs of choice in managing chlamydial genital tract infections. The organisms are highly susceptible in vitro and in vivo to the action of these antibiotics,^{29,124} and resistance to these drugs has never been shown to occur naturally. Although there are documented treatment failures where chlamydiae have been isolated from patients following treatment, the recovered agents have been found to be wholly susceptible to the antibiotics.

A phenomenon termed heterotypic resistance was first reported by Jones and colleagues¹²⁷ and has been more fully described by Somani and colleagues.¹²⁸ In this description, a small proportion of the chlamydia inoculum exhibits multiple drug resistance and this is manifested by persistent aberrant inclusions that are seen on subsequent passage. These isolates

Table 31-4. Minimum Inhibitory Concentration of Antimicrobial Agents for *C. trachomatis*

Drug	MIC (μg/mL or U/mL)
Rifampin	0.005–0.25
Tetracyclines	0.03–1
Azithromycin	0.03–1
Erythromycin	0.1–1
Ofloxacin	0.5–1
Ampicillin	0.5–10
Penicillin	1–10
Sulfamethoxazole	0.5–4
Clindamycin	2–16
Spectinomycin	32–100
Gentamicin	500
Vancomycin	1000

have poor survival characteristics in vitro and ultimately are lost, or cannot be successfully cultivated further. Attempts have been made to correlate heterotypic resistance with clinical treatment failures; however, studies by Suchland et al.¹²⁹ have shown that heterotypic resistance is actually a phenomenon that can be observed with any *C. trachomatis* isolate and is dependent upon inoculum size. Thus, it really does not represent clinically relevant antibiotic resistance, but is rather an artifact of the assay procedures and inoculum sizes used.

There is a suggestion that there may be some relative resistance to erythromycin and tetracycline, but there are no data to suggest that this has reached clinically relevant levels.^{127,130} Rifampin, which is highly active in vitro, has not been widely used to treat human chlamydial infections. Resistance to this drug can be readily developed by passage in the laboratory in the presence of low concentrations of the antibiotic.¹³¹ Rifampin-resistant mutants selected by serial passage at sub-MIC concentrations are still susceptible to rifalazil, a related drug.¹³² In vitro a combination of azithromycin and rifampin has been shown to be more effective against *C. trachomatis* than either drug alone. The emergence of resistance to rifampin in vitro is prevented by the presence of azithromycin, and the persistent inclusions and the presence of rRNA transcripts that may be seen when azithromycin is used alone were reduced by the presence of rifampin. This suggests that combination therapy may be more useful than monotherapy if new treatment approaches are needed.¹³³

Aminoglycosides are not active against *Chlamydia*, and this has led to their widespread use in controlling bacterial contamination in clinical specimens being tested for the presence of *Chlamydia*. Common antifungal drugs such as amphotericin B and nystatin are also inactive against *Chlamydia*, as are the nitroimidazoles used to treat *Trichomonas* infections.

Penicillins are active against *Chlamydia* in vitro, but they are generally not clinically useful. By analogy from animal studies, it has been calculated that levels on the order of 20–30 million units of penicillin per day would be required for antichlamydial activity in vivo. Cephalosporins are not active. Chlamydiae do have a cell wall similar to that of other bacteria, and its synthesis can be inhibited by penicillins, but only in the early phases of the growth cycle. Addition of penicillins to infected cells in vitro cannot be expected to show marked activity after 16–20 hours of infection, as at that stage active cell-wall synthesis is minimal. It is likely that one of the cell-wall inhibitors will ultimately be found to be clinically active against chlamydiae. There are now several studies showing that a week of amoxicillin at 500 mg three times daily is effective in treating chlamydial infection in pregnant women.

Many quinolones are active against chlamydia in vitro, but only ofloxacin has been clinically useful to date. In vitro, resistance can be selected for by passage at subcidal levels. Quinolone-resistant *C. trachomatis* had a serine to isoleucine substitution in the amino acid position 83 in GyrA.¹³⁴

IMMUNOLOGY

The biological role of antibodies or cell-mediated immunity (CMI) resulting from exposure to chlamydial antigens in either enhancing or protecting against disease or infection is not clear. Much of the difficulty in studying chlamydial antigens is due to technical problems in obtaining adequate quantities of organisms for the physicochemical fractionation procedures that are commonly used to study antigenic structure. Thus, these organisms are ideal candidates for study by modern techniques of molecular biology and genetics. What is clear is that the chlamydiae are highly complex organisms, which contain antigens of genus, species, subspecies, and serovar specificity.¹³⁵

The most easily detected antigen is the chlamydial group antigen, shared by all members of the genus. This antigen is responsible for the complement-fixing reactions that have been commonly used to diagnose psittacosis or LGV. Other, apparently protein, group antigens have been identified but not been characterized. The major genus-specific antigen has been identified as the LPS.¹³⁶

Chlamydial EB and RB contain an LPS antigenically similar to that of some gram-negative bacteria (*Acinetobacter calcoaceticus* and Re mutants of *Salmonella typhimurium*).

Chlamydial LPS demonstrates a positive limulus lysate test. It is structurally similar to the lipid A and KDO core of LPS from rough (Re) mutants of *S. typhimurium*.¹³⁷ Its chemical composition is also similar to that of *S. typhimurium* LPS, but it appears to contain a unique constituent, 3-hydroxydocosanoic acid.¹³⁸ Chlamydial LPS has two antigen sites. One is identical to that of *A. calcoaceticus* and *S. typhimurium*, and the other is *Chlamydia* specific.¹³⁹ *Acinetobacter* LPS can be used as the CF antigen for antichlamydial antibodies, but not all sera that are positive against the chlamydial antigen will react to the *Acinetobacter* LPS.¹³⁷

The antigens responsible for delayed hypersensitivity tests, such as the Frei test, which has been used in diagnosing LGV, have not been studied using modern techniques. The major antigen here is probably the LPS common group antigen because it is heat stable and sensitive to periodate. *C. psittaci* strains have been used successfully to prepare Frei antigens. There also appear to be specific antigens involved in delayed hypersensitivity responses, as more specific antigenic preparations can be developed by acid extraction from the crude group antigen.

Species-specific antigens appear to be shared by all members of a chlamydial species. They have been demonstrated by indirect hemagglutination, immunodiffusion with sonicated organisms, and crossed immunoelectrophoresis with solubilized organisms. MOMP has an important species-specific antigen.⁷⁸ Another species-specific antigen, common to *C. trachomatis*, has been purified to homogeneity by immunoabsorption with monospecific antibody.¹⁴⁰ It is pronase, heat sensitive, and of large molecular weight (1.55×10^5 Da). Antibody to this antigen is found in convalescent human sera from patients with LGV and those with high levels of antibody following other *C. trachomatis* infections.

The subspecies- or serovar-specific antigens are common only to selected strains within chlamydial species. These antigens have been the basis for a variety of serologic tests used for the classification of *C. trachomatis* isolates. They appear to be associated with the mortality observed following intravenous inoculation of mice with large quantities of viable chlamydiae. This death is termed a “toxic death” because it cannot be accounted for by multiplication of the organism; deaths occur within 24 hours, before a single cycle of replication can occur. The “toxic” effect of chlamydiae can be prevented by preincubation of the inoculum with hyperimmune serum. This “toxin” neutralization is strain specific and was first used to classify a variety of *C. psittaci* isolates.¹⁴¹ A similar approach was used with *C. trachomatis* isolates, and it was found that immunization of mice could prevent lethality from homotypic toxic challenge. A mouse toxicity prevention test (MTPT) was developed which yielded a number of specific *C. trachomatis* serovars.^{142,143} These serovars are identical to those shown by the microimmunofluorescence test (micro-IF).¹⁴⁴ The responsible antigens appear to be on the MOMP molecule.

Eighteen serovars prototypic strains of *C. trachomatis* have been characterized. A, B, and C serovars are usually associated with hyperendemic blinding trachoma in developing countries; D through K have been associated with oculogenital disease in industrialized societies; and L1, L2, and L3 are LGV serotypes. These serovars fall into two broad complexes (B and C) by micro-IF. Each complex shows extensive cross-reaction within the complex but little reaction with the other complex. Serovar-specific monoclonal antibodies are now available for typing purposes.

The MOMP is a porin and contains antigens of serovar, serogroup, and species specificity.^{78,145} Because of MOMP's important structural and antigenic role, studies of the gene responsible for its synthesis have been of particular interest. The gene encoding MOMP and its amino acid sequence is known for all serovars.¹⁴⁶ The sizes of MOMP fall between 39 and 42 kDa depending on the serovar. There are five conserved and four variable sequence regions within the genes, and each variable region is antigenic and surface exposed. The most variable segments are approximately 11 amino acids long and occur one each in the amino-terminal half and the carboxyl-terminal half of the MOMP. It is likely that these sites are responsible for subgroup- or serovar-specific antigenic reactivity. The species-specific site is located adjacent to one of the variable regions near the carboxyl-terminus. Minor genus-specific reactivity has also been shown.

MOMP and the 60–62-kDa and 12–15-kDa proteins may be copurified by sarkosyl extraction of EB. The 60–62-kDa proteins are important immunogens and often found as a doublet.¹⁴⁷ It is now clear that one of these is a cysteine-rich structural protein, while the other is a loosely bound HSP60. While MOMP appears to be the immunodominant antigen, there may be a more selective response to 60–62-kDa proteins. The latter proteins are surface exposed and have species-specific antigens. In contrast, the 15-kDa proteins are not on the EB surface. They contain antigens of species and biovar specificity.¹⁴⁸ A second porin with surface-exposed, species-specific antigens is PorB. This protein is significantly less abundant than MOMP and is also highly conserved and lacks the variable sequence regions observed for *C. trachomatis* MOMP.¹⁴⁹

Monoclonal antibodies directed against MOMP have been shown to be capable of neutralizing infectivity in cell culture and are protective against toxic effects seen in mice after intravenous inoculation of live EB. They can also neutralize infectivity for ocular infection in nonhuman primates.¹⁵⁰ Monoclonal antibodies against nonsurface subspecies, species-specific epitopes, or the LPS neither protected mice nor neutralized infectivity for the eye. The neutralization reactions usually appear to be serovar or serogroup specific.¹⁵¹ Antibodies to PorB also neutralize infectivity in tissue culture, but have not been tested in animal models.¹⁵²

The outer membrane of *Chlamydia* is a particularly interesting structure because in the EB it represents a target for immune attack. There have been a number of functions identified with putative protective antigens in the outer membrane. These functions, including host-cell attachment, enhanced phagocytosis, and phagolysosomal fusion inhibition, are all neutralized by specific antibody. Although a number of protein antigens have been identified, and MOMP and other proteins induce neutralizing antibody, no virulence antigen has been specifically identified.

CONTROL OF CHLAMYDIAL INFECTION BY THE HOST

In the majority of chlamydial infections, only a relatively small proportion of cells at affected sites are found to be infected. Because each inclusion releases hundreds of viable EB and relatively few nearby cells are infected, there must be control mechanisms that limit infectivity. The mechanisms are not clear, although T-cell functions are essential. Lymphokines have been shown to have an inhibitory effect on chlamydiae.¹⁵³ *C. trachomatis* is sensitive to alpha, beta, and gamma interferons.¹⁵⁴ The last of these appears to be most active. The lymphokine, which inhibits *Chlamydia* in human macrophages and in mice, has been identified as gamma interferon.^{155,156} The interferon appears to delay the developmental cycle so that the RBs persist for a longer period of time.^{157,158} This may result in persistent inapparent infection and may also play a role in immunopathogenesis. The mode of action appears to be the same as in other systems and involves depletion of tryptophan, making tryptophan unavailable to the chlamydiae.⁹³ The effect is reversible by addition of exogenous tryptophan.

It is likely that mechanisms such as the apparent effect of gamma interferon represent control of infection rather than protection against new infection. Antibodies may be involved in clearance and limiting infection.

IMMUNITY

Immunity induced by chlamydial infection is not well understood. It is clear that single infections will not result in solid immunity to reinfection. Multiple infections, homo- or heterotypic, are common. Unfortunately, the natural infection is not readily quantifiable in terms of inoculum size, and thus relative degrees of immunity may exist which are overcome with a sufficiently large challenge. Some immunity probably develops following initial or serial infection. In screening studies, younger women are found to have higher cervical infection rates than older women, who often have higher antibody levels. This speculation is also consistent with the observation that many isolate-negative individuals attending

STD clinics have IgM antibody to the organism.¹⁵⁹ This antibody could result from recent exposure and rapid resolution of the infection or its ablation by an immune response.

The only human chlamydial infection which has been subjected to extensive vaccine studies is trachoma. Unfortunately, these studies were performed without a sophisticated knowledge of the chlamydial immune response. These results have been summarized elsewhere.^{14,31} The results from field studies on vaccine trials and infection of human volunteers and nonhuman primates indicate that there is a short-lived relative immunity to reinfection with homotypic challenge.

Data from ocular infection with *C. psittaci* in guinea pigs and *C. trachomatis* in nonhuman primates suggest an important role for antibody in host defense.^{160–162} Antibody is capable of neutralizing chlamydial infectivity in cell culture. There are many possible modes of action. Antibody can inhibit attachment of the organism to the surface of a non-professional phagocyte, or result in failure to inhibit phagolysosomal fusion, or prevent a morphologic shift of the EB and RB by cross-linking surface proteins. Antibody may opsonize. Antibody that blocks attachment of *C. psittaci* to L cells enhances attachment to macrophages.¹⁶³

There are now many in vitro studies showing that immunization with purified, synthesized, or recombinant peptides can induce neutralizing antibodies. Synthetic vaccines have been developed, sometimes by artificially juxtaposing synthesized conjugates of T-helper sites with selected B-cell sites predicted to result in neutralizing antibody and finding that such antibodies are indeed generated. In some instances, these immunizing peptides have been linked by genetic manipulation and expressed in *E. coli*. While it has been relatively easy to induce neutralizing antibodies as assayed in vitro, vaccines that elicit neutralizing antibodies have so far failed to protect animals from subsequent challenge.

C. trachomatis do not appear to survive well in PMNs.¹⁶⁴ It is possible that antibody-enhanced phagocytosis plays an important role in clearance of infection and in resistance to reinfection. *Chlamydia* are rapidly internalized by human PMNs, and the majority are rendered noninfectious within 1 hour. Most of the EB are found in PMN phagosomes where lysosomal fusion has occurred.¹⁶⁵ The mechanism of killing by PMNs is not known, but it is likely that oxygen-dependent and oxygen-independent mechanisms are involved. Killing is still seen in the presence of inhibitors such as azide or cyanide.¹⁶⁴ Chlamydiae act as polyclonal stimulators of B-lymphocytes.¹⁶⁶ Stimulation can be effected in mice that are LPS nonresponders, suggesting that something other than the genus-specific antigen is responsible.

Leukocytes clearly play an important role in resistance to infection and in clearance of primary infection. T-cell deficient mice do not produce significant levels of antichlamydial antibody.¹⁶⁷ Lymphocyte transformation in vitro and delayed

hypersensitivity reactions are also T-cell dependent. They can be found in heterozygous mice and in mice who received thymus transplants, but are not observed in the nude athymic mouse.^{168,169}

Williams and colleagues have exploited the athymic mouse model of respiratory infection with the mouse pneumonitis biovar of *C. trachomatis* to dissect the immune response.^{167,169–171} Results of these studies have suggested a defense role for both antibody and CMI responses. Both CD4⁺ and CD8⁺ T cells have protective roles in animal models.¹⁷² The predominant evidence suggests that Th1-type cell responses involving CD4⁺ T-helper cells play an important role in protective immunity.^{173,174} However, the actual mechanism of immunity is unclear, and the demonstration that cytotoxic CD8⁺ T lymphocytes are capable of lysing chlamydia-infected cells suggests that these cells too could play a role.¹⁷⁵

VACCINE AND VIRULENCE FACTORS

Because surface antigens would be likely vaccine candidates, efforts to identify the factors responsible for attachment, enhanced uptake, and inhibition of phagolysosomal fusion and modification of host-cell functions will continue to be stressed. For *C. trachomatis*, neutralization of infectivity appears to be serovar specific. The only antigenic sites of that specificity that have been clearly identified are on MOMP; however, peptides or subcomponents of MOMP fail to protect by vaccination and effective neutralization based upon MOMP will likely require conformationally authentic MOMP or its mimic.¹⁷⁶ MOMP antigenic variation is not observed with most other species of chlamydiae and those such as *C. pneumoniae* may entirely depend on conformational determinants of MOMP for antibody reactivity.¹⁷⁷

The importance of T cells in immunity is a recurring theme. Both humoral and CMI responses are T-cell dependent. Identification of specific CD4 T-cell recognition sites may be crucial to understand the regulation of chlamydial immunity, especially at mucosal surfaces. Cytotoxic CD8 T cells can recognize and kill chlamydia infected cells,¹⁷⁵ and chlamydia-specific CD8 T cells promote resolution of infection in a murine model.¹⁷⁸

A real challenge with vaccine development will be generating immune responses that appear to be better than those that occur after natural infection. While much progress is being made on the microbiologic front, it is clear that considerable input from immunologists will be required to generate optimal methods for antigen presentation to enhance mucous-membrane immunity. Even if protective immune responses can be induced by a vaccine, the ultimate success of such a vaccine will depend, in part, on the antigenic stability of the organism. There is evidence of a high degree of immunologic variation within the variable regions of MOMP. Identification of high rates of DNA polymorphism

in the MOMP gene among prostitutes in Nairobi suggests the possibility of immune selection and evasion, which may present further problems for developers of a vaccine unless they discover alternative antigens that mediate protection.¹⁷⁹ Genomics have led to the discovery of several new virulence proteins that represent promising new opportunities for vaccine development.¹⁸⁰

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Walter E. Stamm

Since the early 1970s, *Chlamydia trachomatis* has been recognized as a genital pathogen responsible for an increasing variety of clinical syndromes, many closely resembling infections caused by *Neisseria gonorrhoeae* (Table 32-1). Because many practitioners have lacked access to facilities for laboratory testing for chlamydia, these infections often have been diagnosed and treated without benefit of microbiological confirmation. Newer, molecular diagnostic tests have in part now addressed this problem, making specific diagnosis much

more widely available. However, diagnostic tests are still not available to providers in developing countries. Unfortunately, many chlamydial infections, particularly in women, are difficult to diagnose clinically and elude detection because they produce few or no symptoms and because the symptoms and signs they do produce are nonspecific. The high prevalence of these infections in many parts of the world has thus resulted from inadequate laboratory facilities for their detection and eventual treatment, coupled with the nonspecific and minimal signs and symptoms chlamydial infections produce, the lack of familiarity clinicians have with these infections, and the lack of resources directed toward the development of programs for screening of high-risk patients, contact tracing, and treatment of infected partners.

Table 32-1. Clinical Parallels Between Genital Infections Caused by *N. gonorrhoeae* and *C. trachomatis*

Site of Infection	Resulting Clinical Syndrome	
	<i>N. gonorrhoeae</i>	<i>C. trachomatis</i>
<i>Men</i>		
Urethra	Urethritis	NGU, PGU
Epididymis	Epididymitis	Epididymitis
Rectum	Proctitis	Proctitis
Conjunctiva	Conjunctivitis	Conjunctivitis
Systemic	Disseminated gonococcal infection	Reiter's syndrome
<i>Women</i>		
Urethra	Acute urethral syndrome	Acute urethral syndrome
Bartholin's gland	Bartholinitis	Bartholinitis
Cervix	Cervicitis	Cervicitis, cervical metaplasia
Fallopian tube	Salpingitis	Salpingitis
Conjunctiva	Conjunctivitis	Conjunctivitis
Liver capsule	Perihepatitis	Perihepatitis
Systemic	Disseminated gonococcal infection	Reactive arthritis

EPIDEMIOLOGY

Chlamydial infections of the genital tract have a worldwide distribution and are prevalent both in the industrialized countries and in the developing world. The World Health Organization (WHO) estimated that 89 million new cases of genital chlamydial infections occurred worldwide in 2001.¹ In the United States, about 4–5 million cases of chlamydial infection occur annually at an estimated cost of \$2.4 billion dollars.² Since chlamydial infections first became a reportable disease in the United States in 1986, the number of reported cases in both men and women have increased each year (Fig. 32-1).³ The greater number of reported cases in women than men reflects current screening practices, which focus mainly on women. In 2004, 929,462 cases were reported, making *C. trachomatis* the most common reportable disease in the United States.³ However, only a minority of cases are actually reported. In selected countries and in parts of the United States where intensive chlamydia control programs have been instituted, dramatic reductions in prevalence have been observed. In Sweden, for example, the number of cases of *C. trachomatis* infection was reduced by more than 50% over a 7-year period, falling from 38,200 in 1987 to 13,600 in 1994.⁴ Similar declines have been seen in the Pacific Northwest (Region X in the

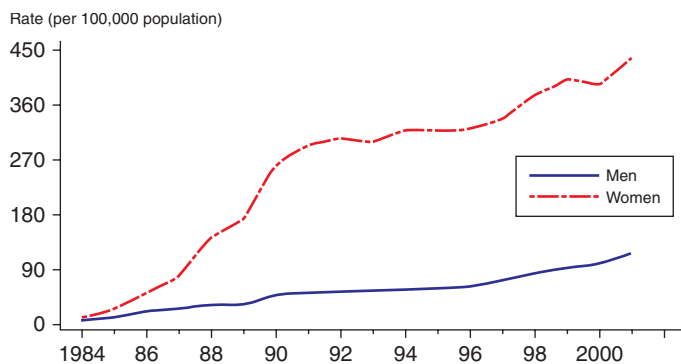


FIGURE 32-1. Reported cases of *C. trachomatis* infections in the United States by year and gender.

United States) and in Wisconsin after the institution of control programs. However, the prevalence of infection in these regions, namely, in Sweden, in Region X of the United States, and in Vancouver, British Columbia, Canada, has increased steadily each year since 1998 despite ongoing control program activities.^{4,5} This phenomenon is discussed in more detail under prevention below.

Chlamydial infections of the genital tract are primarily caused by serovars D, E, F, G, H, I, J, and K.⁵ A remarkably similar distribution of serovars has been observed worldwide, with the D, E, and F serovars (B class) being most prevalent and C class serovars less prevalent.⁶ Infections caused by the former serovars are also associated with higher inclusion counts and with young age.⁷ Among rectal infections in homosexual men, the D and G serovars are particularly prevalent for reasons as yet unexplained.⁸ Several studies have suggested that the F and G serovars may produce less symptomatic and/or less inflammatory infections than strains of other serovars.^{9,10} Paradoxically, variant F serotype strains have been seen more often in women with upper genital tract infection.¹¹

Using molecular analyses of the chlamydial MOMP, it has become increasingly evident that polymorphism within the MOMP gene is common among isolates from patients who are highly sexually active and frequently exposed to chlamydial infection.¹² Allelic polymorphism, thus, may produce antigenic variation that provides the organism with the ability to evade the immune response. Less antigenic variation in MOMP has been observed in strains isolated from less sexually active populations.¹³

INFECTIONS IN MEN

The prevalence of chlamydial urethral infection has been assessed in populations of men attending general medical clinics, STD clinics, adolescent medicine clinics, and student health centers and ranges from 3–5% of asymptomatic men seen in general medical settings to 15–20% of all men seen in STD clinics.^{5,14–17} Among military personnel, Podgore et al.

found an 11% prevalence of asymptomatic urethral chlamydial infection compared with a 2% prevalence of urethral gonococcal infection.¹⁸ Rates of chlamydial urethral infection of 13–15% have also been reported among sexually active boys attending adolescent medicine clinics.^{19,20} Among men, the prevalence and site of mucosal infection appear to be strongly correlated with both age and sexual preference. Of 1221 patients screened for urethral infection in an STD clinic, 5% of homosexual men and 14% of heterosexual men had positive urethral cultures for *C. trachomatis*, and in both groups prevalence decreased in each 5-year period from age 19 to age 39 years (Fig. 32-2). This striking age-related prevalence has been demonstrated repeatedly in both men and women; age is thus the most potent risk factor for *Chlamydia* in both genders. In other studies, both nongonococcal urethritis (NGU) and postgonococcal urethritis (PGU) were caused by *C. trachomatis* less frequently in homosexual than in heterosexual men.²¹ The prevalence of chlamydial infection generally has been higher in African Americans than in whites. In one screening study, 19% of nonwhite and 9% of white heterosexual males had urethral chlamydial infection.¹⁷ Evidence of chlamydial infection has been infrequent in sexually inexperienced populations of men.

Chlamydial infection is a cause of acute proctitis in homosexual men who practice receptive rectal intercourse without condom protection.^{22–24} Thus, both urethral and rectal chlamydial infections contributed to the high prevalence of serum antibody to *C. trachomatis* observed in homosexual men in the pre-AIDS era.

Pharyngeal infection with *C. trachomatis* has been demonstrated in 3–6% of men and women attending STD clinics and correlates with a history of recent orogenital contact.²⁵ Most such infections are asymptomatic. Among adolescents attending a teen clinic, only 1% were culture positive for *C. trachomatis* in the pharynx.²⁶ Earlier serologic studies suggesting an etiologic role for *C. trachomatis* in nonstreptococcal community-acquired pharyngitis have not been

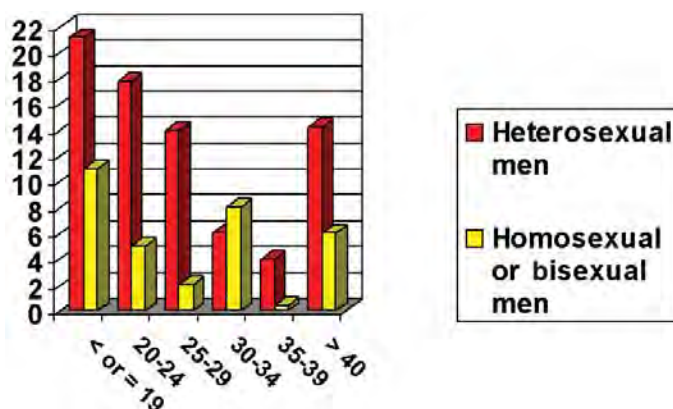


FIGURE 32-2. Prevalence of *C. trachomatis* urethral infection by age in men attending an STD clinic. Open bars = heterosexual men; solid bars = homosexual or bisexual men.

supported by more recent attempts to isolate *C. trachomatis* from patients with pharyngitis.^{27,28} The earlier serologic studies most likely were measuring antibodies against *Chlamydia pneumoniae*.

The overall incidence of *C. trachomatis* infection in men has not been well defined, since in most countries these infections are not officially reported, are not microbiologically confirmed, and often may be asymptomatic, thus escaping detection. In the United States, the number of reported cases of chlamydial infection in men is thought to be artifactually low because of the infrequent use of chlamydia diagnostic tests in men (see Fig. 32-1). Recent population-based studies in the community utilizing nucleic acid amplification tests (NAATs) suggest a prevalence of about 2% in younger (<24 years of age) men, with lesser prevalences in older men.²⁹

The transmissibility of genital chlamydial infections from females to males has not been extensively studied. In one study, male partners of women who had either chlamydial or gonococcal cervicitis were found to be infected with these agents 28% and 81% of the time, respectively.³⁰ Male partners of women with dual infections were also infected more often with gonorrhea than with chlamydia (77% and 28%, respectively).³⁰ Although this study suggests that *N. gonorrhoeae* is more transmissible than *C. trachomatis*, the differing lengths of incubation period of these two agents and differing efficiency of isolation from the urethra could explain the results. A more recent study by Quinn and colleagues utilized PCR rather than a culture to estimate rates of transmission and demonstrated that although 42% of male partners of infected women were urethral culture positive, 68% were PCR positive.³¹ The genotypes of the chlamydial strains were identical in both partners as well. This study suggests that transmission from men to women and from women to men may be equally efficient.

INFECTIONS IN WOMEN

The prevalence of chlamydial infection has been studied in pregnant women, in women attending gynecology or family planning clinics, in women attending STD clinics, in college students, and in women attending general medicine or family practice clinics in school-based clinics and more recently in population-based studies. Prevalence of infection in these studies has ranged widely from 3% in asymptomatic women in community-based surveys to over 20% in women seen in STD clinics.³¹⁻⁵³ During pregnancy, 3-7% of women generally have been chlamydia positive, although a 21% prevalence in a population of inner-city African American women and a 26% prevalence among pregnant Native American women have been reported.⁴⁶⁻⁴⁸ Demographic factors associated with an increased risk of chlamydial isolation in at least several studies include young age, nonwhite race, single marital status, use of oral contraceptives, and measures of sexual activity such as a

new partner or multiple sexual partners.^{31,35,44,45} The proportion of infected sexually active women has been highest for women aged 15-19 years and declines strikingly thereafter (Fig. 32-3). Sexually inexperienced populations (or women lacking the risk factors noted above) rarely exhibit chlamydial cervical infections. In a study evaluating a 50% sample of all sexually active Alaskan Inuit women living in remote villages, 114 (23%) of 493 had cervical infection with *C. trachomatis*.⁵³ As, in this study, has been demonstrated repeatedly that in sexually active populations in which little diagnostic testing and/or specific treatment is being used, the prevalence of infection may thus reach surprisingly high levels. This reflects the asymptomatic nature of chlamydial infection and the ability of the infection, when untreated, to persist for months or years.

The incidence of *C. trachomatis* genital infection has been defined in a few selected populations. Burstein and colleagues followed a cohort of 3860 women in Baltimore over 33 months and observed an incidence rate of 28/1000 person months in this largely African American inner-city population.⁴⁹ The increasing number of reported cases in the United States among women in recent years undoubtedly reflects increased use of diagnostic testing and more frequent screening of high-risk women (see Fig. 32-1).

As in men, transmissibility of chlamydia has also been poorly defined in women. A comparative study of partners of men with either chlamydial or gonococcal urethritis found

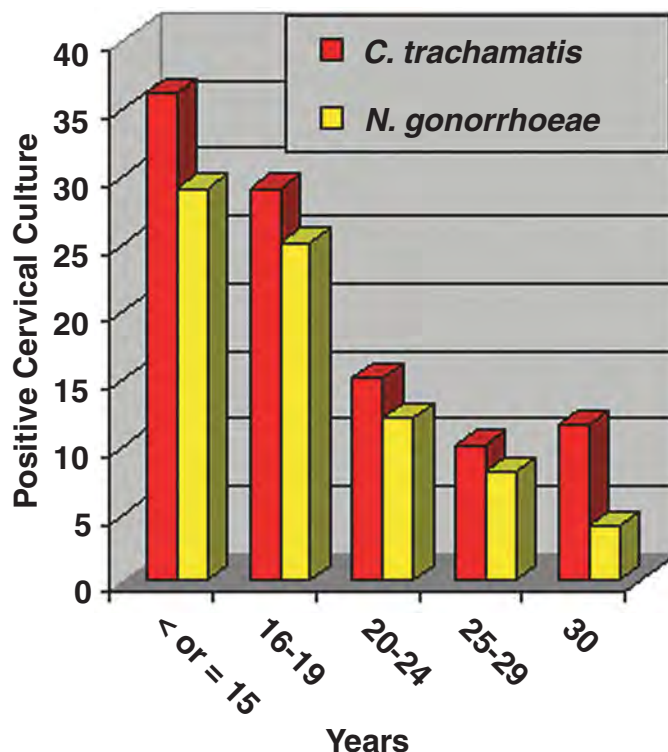


FIGURE 32-3. Prevalence of *C. trachomatis* and *N. gonorrhoeae* cervical infection by age in women attending an STD clinic. Open bars = *N. gonorrhoeae*; solid bars = *C. trachomatis*.

that these women were infected 45% and 80% of the time, respectively.³⁰ Among female partners of men with both infections, 45% had chlamydial infection and 64% had gonorrhea. Quinn and colleagues found that 57% of female partners of infected men were infected, as judged by culture, but 70% were positive, as judged by PCR.³¹

NATURAL HISTORY OF CHLAMYDIAL INFECTION

Several studies in the United States indicate that approximately 5% of neonates acquire chlamydial infection perinatally, yet antibody prevalence in later childhood before onset of sexual activity may exceed 20%.⁵⁴ The acquisition of infection during childhood has not yet been well documented but could occur from infected siblings (in whom infection acquired perinatally may persist for more than 1 year) or from parents or other adults via sexual abuse.⁵⁵ Childhood upper respiratory, eye, or middle ear infections with *C. trachomatis* might explain this rise in antibody prevalence between the neonatal period and adolescence, as could chlamydial genital infections acquired by children as a result of sexual abuse (see Chapter 72). Alternatively, cross-reacting antibody to *C. pneumoniae* strains producing upper respiratory infections during childhood could account for some or all of this apparent increase in the seroprevalence to *C. trachomatis* (see Chapter 15).

In adolescence, the incidence of culture-positive symptomatic genital chlamydial infections rises sharply, as does antibody prevalence. Asymptomatic infection also occurs commonly, and long-lived but unrecognized urethral, rectal, and cervical infections undoubtedly occur. Unrecognized, asymptomatic, or minimally symptomatic infections of the upper genital tract also occur and have been termed “silent salpingitis.” Both rectal and urethral infections contribute to the high antibody prevalence found in homosexual men.

Much remains to be learned about the natural history of genital infections owing to *C. trachomatis*, but, on the basis of knowledge of the natural history of trachoma and of limited studies of untreated men, nonpregnant women, and children, subacute and chronic asymptomatic infection of genital mucosal surfaces undoubtedly occurs commonly.^{32,56} Natural immunity in women, as measured by time to spontaneously clear infection, appears to take many months to develop.⁵⁷ The reported occurrence of chlamydial respiratory infection during immunosuppression suggests that impaired immunity may be followed by reemergence of symptomatic infection from a chronic latent focus.^{58,59} Recrudescence of ocular trachoma years after leaving an endemic area has also been shown to occur during topical cortisone therapy.⁶⁰ Current evidence indicates that chlamydial infection has not been a clinically apparent problem in AIDS patients.⁶¹

Similarly, the interactions between ocular trachoma, lymphogranuloma venereum (LGV), and non-LGV genital and perinatal infection have not been extensively studied in parts of the world where all of these strains are present in the same populations.⁶² It is not known, for example, whether the epidemiology or clinical manifestations of genital chlamydial infections are altered in LGV or trachoma endemic areas.⁶² Recent studies have called attention to the relatively high rate of recurrent infection with *C. trachomatis* in young, sexually active populations. In some studies, up to 20–30% of women have had evidence of recurrent infection within 6 months of an initial infection.^{63,64} Recurrent infections may be with the same or a different serovar or genotype.⁶³ Mixed infections with two or more strains are evident in 3–8% of more highly sexually active populations.⁶⁵ It is likely that recurrences may be caused either by exogenous reinfection from a new or untreated sexual partner or by failure to eradicate an original infection.

CLINICAL MANIFESTATIONS

Genital infections caused by *C. trachomatis* closely parallel those due to *N. gonorrhoeae* in terms of clinical manifestations (see Table 32-1). Both organisms preferentially infect columnar or transitional epithelium of the urethra, with extension to the epididymis; the endocervix, with extension to the endometrium, salpinx, and peritoneum; and the rectum. Both organisms can produce extensive subepithelial inflammation, epithelial ulceration, and scarring. Rarely, both organisms can produce systemic manifestations. In general, infections caused by *C. trachomatis* tend to be less abrupt in onset and are more often characterized by no symptoms or by milder symptoms than is the case for gonococcal infections.

INFECTIONS IN MEN

■ URETHRITIS

Although Koch's postulates have not been specifically fulfilled, persuasive evidence suggests that *C. trachomatis* causes 35–50% of NGU in heterosexual men. In the 1970s and 1980s, the frequency of chlamydial isolation in men with recent onset of NGU was remarkably consistent from study to study, despite differences in patient population and methodology.^{66–77} However, recent studies suggest that the proportion of NGU cases attributable to chlamydia may be declining in regions where chlamydia control programs have been in place.⁷⁸ When female partners of *C. trachomatis*-positive and *C. trachomatis*-negative men with NGU were examined, 60–75% of the former and 0–10% of the latter had chlamydial cervicitis, evidence that is consistent with

sexual transmission of *C. trachomatis* having resulted in NGU.^{72–75} Immunotyping (or, more recently, genotyping) of isolates from both partners has shown concordance of immunotypes or genotypes in most couples.³¹ Serum IgM antichlamydial antibody is found frequently in chlamydia culture-positive men with NGU but rarely in culture-negative men with NGU.⁷⁴ Finally, placebo-controlled treatment trials of men with NGU or therapeutic trials utilizing drugs such as spectinomycin, which have little effect on chlamydia, indicate that most men given placebo or ineffective therapy for *C. trachomatis* remain culture positive and symptomatic until effective treatment is given.^{75–77} Elimination of chlamydia thus coincides with resolution of symptoms. Although *C. trachomatis* has not been experimentally inoculated into the human urethra, baboons and chimpanzees develop chlamydial urethritis accompanied by serologic evidence of infection after urethral inoculation.⁷⁹

Clinically, chlamydia-positive and chlamydia-negative NGU cannot be differentiated on the basis of signs or symptoms.⁷⁶ Both usually present after a 7–21-day incubation period with dysuria and mild-to-moderate whitish or clear urethral discharge. Examination reveals no abnormalities other than the discharge in most cases; associated adenopathy, focal urethral tenderness, and meatal or penile lesions should suggest herpetic urethritis. Neither abnormal prostatic examinations nor prostatic inflammation has been convincingly linked to chlamydial urethritis.

C. trachomatis urethral infection is more often asymptomatic than gonococcal urethral infection, and, when symptoms occur, they are milder with chlamydial urethritis.^{17,80} However, most men with asymptomatic chlamydial urethral infection exhibit ongoing inflammation, as defined by persistent urethral leukocytosis (≥ 4 polymorphonuclear leukocytes [PMNs] per 1000 \times field) on Gram stains of urethral secretions or persistent pyuria in a first-void urine. Leukocyte esterase testing can also be used to identify patients with asymptomatic chlamydial urethritis.^{81,82}

PGU occurring in heterosexual men, like NGU, frequently results from infection with *C. trachomatis*.⁸³ These patients probably acquire gonorrhea and chlamydial infection simultaneously but, because of the longer incubation period of *C. trachomatis*, develop a biphasic illness if their original gonorrhea is treated with an agent that does not eradicate chlamydia. It is possible that acute gonococcal infection causes reactivation of a latent chlamydial infection, but there is little evidence to support this premise. Coinfection with these two agents occurs in from 15% to 35% of heterosexual men with gonorrhea but rarely in homosexual men. In areas where chlamydial control programs have been in place, the frequency of chlamydial coinfection among men with gonorrhea has declined to 5–10%. Of men infected with both chlamydia and *N. gonorrhoeae* who are treated with

penicillin, ampicillin, gentamicin, or spectinomycin, 80% or more develop symptomatic PGU or urethral leukocytosis without symptoms.^{66,68,83}

■ EPIDIDYMITIS

Berger and coworkers have shown that *C. trachomatis* causes most cases of what was previously termed idiopathic epididymitis in young, heterosexually active males.^{84,85} In these and subsequent studies, chlamydial and gonococcal epididymitis usually was associated with urethritis caused by *C. trachomatis* and/or *N. gonorrhoeae* in patients who were less than 35 years of age and sexually active, whereas patients with epididymitis who were older than 35 years generally had gram-negative bacterial infections and a history of urologic disease or instrumentation (see Chapter 53). Currently, about 70% of acute epididymitis in young, sexually active men appears to be attributable to chlamydial infection (see Chapter 53). Clinically, chlamydial epididymitis presents as unilateral scrotal pain, swelling, tenderness, and fever in a young male who often has associated chlamydial urethritis (NGU). The urethritis, however, may often be asymptomatic and evident only as urethral inflammation on Gram stain. Men with chlamydial epididymitis improve rapidly with tetracycline treatment, supporting the causal role of *C. trachomatis*.⁸⁵

C. trachomatis also produces mild epididymitis in monkeys after introduction of the organism into the vas deferens.⁸⁶ Antibody production, stimulation of cell-mediated immunity to chlamydial antigens, histologic findings, and subsequent recovery of *C. trachomatis* from the monkey's urethra support the causative role of *C. trachomatis* in this model.^{86,87} However, the epididymitis is mild, organisms have not been recovered from the epididymis, and the effects of repeated inoculation have not been studied. Thus, animal experiments have not yet elucidated the pathogenic mechanisms operative in chlamydial epididymitis.

Despite continued study, the role of *C. trachomatis* in causing nonbacterial prostatitis remains controversial (see Chapter 54). Mardh and coworkers reported that only 13% of patients with nonbacterial prostatitis had antibodies to *C. trachomatis* in serum or in expressed prostatic secretions, and none had positive cultures from expressed prostatic secretions.⁸⁸ They speculated that negative cultures could have resulted from the antichlamydial effects of spermine and zinc in prostatic secretions.⁸⁹ Nilsson reported recovery of *C. trachomatis* from the expressed prostatic secretions of 26 men with acute NGU, all of whom were considered to have cytologic evidence of prostatitis.⁹⁰ Bruce and colleagues also reported frequent isolation of chlamydia from urine, prostatic fluid, and prostatic expressate of men with nonbacterial prostatitis.⁹¹ However, these studies have not convincingly demonstrated the presence of chlamydia in the prostate itself, and the definition of prostatitis used is

disputed. Poletti and colleagues performed transrectal biopsies of the prostate in 30 men with known positive urethral cultures for *C. trachomatis* and a diagnosis of nonbacterial prostatitis based on prostatic tenderness or swelling on digital palpation; the organism was recovered from 10 of 30 prostatic specimens.⁹² These studies require confirmation and, taken together, are inconclusive regarding the role of *C. trachomatis* in nonbacterial prostatitis. Further studies should utilize a careful case definition (including cell counts in expressed prostatic secretions), conventional histologic studies, immunohistochemical study of biopsied tissue, serologic studies, sensitive molecular techniques to assess the presence of chlamydia (i.e., PCR and in situ DNA hybridization) in the prostate, and evaluation of response to therapy.

■ PROCTITIS

The chronic, indolent form of LGV that results from secondary spread of *C. trachomatis* of the LGV immunotypes from the genitalia to the rectum, usually in women, is discussed in Chapter 17. *C. trachomatis* of non-LGV immunotypes has also been isolated from the rectal mucosa of infants, heterosexual women, and homosexual men. The clinical manifestations of rectal infection in infants and adult women have not been studied extensively. The manifestations in homosexual/bisexual men are described in Chapter 69.

Prospective evaluation of homosexual men indicates that *C. trachomatis* of either the genital immunotypes D to K or LGV immunotypes can produce proctitis.^{22–25} The LGV immunotypes usually produce a primary ulcerative proctitis and a histopathologic picture of giant cell formation and granulomas similar to that seen in acute Crohn's disease. Non-LGV immunotypes produce milder infections, ranging from asymptomatic infection to symptomatic proctitis resembling gonococcal proctitis with rectal pain and bleeding, mucous discharge, and diarrhea. Most *C. trachomatis*-infected patients have abnormal numbers of PMNs in their rectal Gram stain, and, on sigmoidoscopy, those with symptoms exhibit friable rectal mucosa and often mucopus. In the pre-AIDS era, *C. trachomatis* appeared to be responsible for up to 15% of proctitis cases seen in homosexual males, and treatment with tetracycline promptly cured these patients.⁹³

■ REITER'S SYNDROME

Both Reiter's syndrome (urethritis, conjunctivitis, arthritis, and characteristic mucocutaneous lesions) and reactive tenosynovitis or arthritis without the other components of Reiter's syndrome have been related to genital infection with *C. trachomatis*. Studies of untreated men with characteristic Reiter's syndrome using the microimmunofluorescent (micro-IF) antibody assay indicate that preceding or concurrent infection with *C. trachomatis* is present in more than 80% of cases (see Chapter 61).^{94–96} Many men with Reiter's

syndrome also exhibit marked lymphocyte stimulation by chlamydial antigens in in vitro blastogenesis assays.⁹⁵ Fluorescein-conjugated monoclonal antibodies have been used to demonstrate what appear to be *C. trachomatis* elementary bodies in the joint fluid and synovial biopsies of patients with Reiter's syndrome, suggesting dissemination of chlamydial antigen beyond the mucosal site of entry in such patients.⁹⁷ However, viable chlamydia cannot often be recovered from the joint fluid or synovium of these patients, and demonstration of chlamydial DNA in the joint fluid/synovium has been reported by some groups but not by others.^{98–100} Cloned T cells from the synovium of patients with Reiter's syndrome have been demonstrated to recognize the chlamydial 57-kDa HSP and the chlamydial 18-kDa histone-like protein.¹⁰¹

Like postenteric (salmonella, shigella, and yersinia) arthritides, sacroiliitis, and spondylitis, Reiter's syndrome occurs with increased frequency in patients with the HLA-B27 haplotype.^{102–104} Class 1 HLA-B27 haplotype appears to confer a 10-fold increased risk of developing Reiter's syndrome, and 60–70% of persons with the syndrome are HLA-B27 positive.^{102–104} However, among a large series of HLA-B27-positive men with chlamydial urethritis, but with no other manifestations of Reiter's syndrome, none went on to develop Reiter's syndrome after onset of therapy with a tetracycline.¹⁰⁴

INFECTIONS IN WOMEN

■ CERVICITIS

Although many women with chlamydia isolated from the cervix have no signs or symptoms of infection, at least a third generally have local signs of infection on examination.^{105,106} Most commonly found are mucopurulent discharge (37% of women) and hypertrophic ectopy (19%). Hypertrophic ectopy refers to an area of ectopy that is edematous, congested, and bleeds easily (see Chapter 46). Cervical follicles can sometimes be visualized colposcopically in women with chlamydial infection of the cervix, but this finding has been uncommon in our experience and that of others.⁴¹ Paavonen et al. reported that colposcopic features of immature squamous metaplasia of the zone of ectopy are associated with chlamydial infection.¹⁰⁶ The number of PMNs in cervical mucus is correlated with chlamydial infection of the cervix. Brunham et al. reported that >10 PMNs per 1000× field was best correlated, although this criterion has been extensively debated.¹⁰⁷ Attention to careful collection of the specimen, and to selective counting of PMNs in cervical mucus, rather than in areas containing vaginal epithelial cells, is important. Based on clinical experience and cumulative studies published to date, a cutoff of >30 PMNs per 1000× field in Gram-stained smears of cervical mucus appears best correlated with chlamydial (or gonococcal) cervicitis. There appears to be a wide range of normal leukocyte values in

women without cervical infection, likely owing to the influence of the menstrual cycle, contraceptive practices, sexual activity, and other infections. Women who exhibit signs of chlamydial cervicitis (mucopurulent discharge and hypertrophic ectopy) yield greater numbers of chlamydial inclusion-forming units on primary isolation in tissue culture than women who have chlamydial infection without cervicitis.¹⁰⁸ Whether infections associated with cervicitis have been more recently acquired has not been established but may be the case.

The prevalence of *C. trachomatis* infection is greater in women with ectopy than in those without ectopy.¹⁰⁹ Ectopy may predispose women to chlamydial infection by exposing a greater number of susceptible columnar epithelial cells, making infection more likely on exposure. Alternatively, ectopy may increase the shedding of *C. trachomatis* from the cervix, or *C. trachomatis* infection of the cervix may cause ectopy. Cervical ectopy is normally present in 60–80% of sexually active adolescents and then declines in prevalence in the third and fourth decades. This may help explain the high prevalence of cervical chlamydial infections in adolescents. Oral contraceptives have also been associated with an increased risk of cervical *C. trachomatis* infection, probably because their use promotes ectopy; the increased risk appears to be limited to oral contraceptive users with ectopy.^{35,105}

Clinical recognition of chlamydial cervicitis depends on a high index of suspicion and a careful cervical examination. There are no genital symptoms that are specifically correlated with chlamydial cervical infection. As discussed previously, findings on examination suggestive of chlamydial infection include easily induced endocervical bleeding, mucopurulent endocervical discharge, and edema within an area of ectopy. The differential diagnosis of mucopurulent discharge from the endocervical canal in a young, sexually active woman includes gonococcal endocervicitis, salpingitis, endometritis, IUD-induced inflammation, or other causes (see Chapter 46). Gram stain of appropriately collected mucopurulent endocervical discharge from patients with chlamydial endocervicitis also usually shows greater than 30 PMNs per 1000× field, absence of gonococci, and only occasional other bacteria. Similarly, the observation of purulent (yellow or green)-colored cervical discharge on a cervical swab collected from such patients (a positive “swab test”; see Chapter 46) correlates with the presence of chlamydial and/or gonococcal infection.¹⁰⁷ Unfortunately, the majority of women with chlamydial infection cannot be distinguished from uninfected women either by clinical examination or by these simple tests and thus require the use of specific diagnostic testing.

Nearly all women with endocervical chlamydial infection have or develop antibodies to *C. trachomatis* in serum, as assessed by the micro-IF assay. Only 20–30% exhibit IgM antibody at the time of diagnosis, however, suggesting that many newly diagnosed cervical infections in women are not recent but long lived. Local cervical antibody has been

reported in only 30–50% of cases, but, in our experience, over 70% of culture-positive women have local antibody.¹⁰⁹ Sequential culturing of untreated women has demonstrated that chlamydial infection of the cervix may persist for weeks or months without development of symptoms or may spontaneously resolve.^{32,42}

The relation of chlamydial cervical infection to cytologic atypia, including reactive and metaplastic atypia and dysplasia, is discussed in Chapter 48. The cervical Pap smear frequently shows a characteristic pattern of inflammation in chlamydial infection, which can alert the cytopathologist and clinician to the need for further tests for chlamydia. The Pap smear itself, however, cannot be used as a sensitive or specific indicator of chlamydial infection of the cervix.

■ URETHRITIS

Screening studies in STD clinics suggest that of women cultured for *C. trachomatis* at both the cervix and the urethra, approximately 50% of positive women yield chlamydia from both sites and 25% from either site alone.^{36,37,72} Paavonen reported that women who had *C. trachomatis* in their cervix and urethra were more likely to complain of dysuria than women with cervical infection alone. Isolated urethral infection, without cervical infection, appears to increase in prevalence with age.³⁷ Case reports have previously suggested that symptoms of dysuria and frequency occur in women with chlamydial urethritis, pyuria, and no bacteriuria or other urinary pathogens, and a prospective evaluation of young women with the acute urethral syndrome (dysuria and frequency without bacteriuria of >10⁵ conventional uropathogens per mL of urine) has implicated chlamydia as an important cause of dysuria in young, sexually active women.^{36,110} Of 16 women with sterile pyuria, 10 had cultural and/or serologic evidence of infection with *C. trachomatis*, compared with less than 10% of women from the same population who lacked urinary symptoms or had coliform cystitis.³⁶ Women with chlamydial infection who were given placebo remained culture positive and symptomatic until given active antimicrobial therapy, whereas those given doxycycline improved rapidly.¹¹¹

Although urethral symptoms may develop in some women with chlamydial infection, the majority of female STD clinic patients with urethral chlamydial infection do not have dysuria or frequency. Even in women with chlamydial urethritis causing the acute urethral syndrome, signs of urethritis (urethral discharge, meatal redness, or swelling) are infrequent.³⁶ However, the presence of mucopurulent cervicitis in a woman with dysuria and frequency should suggest the diagnosis. *C. trachomatis* urethritis should be suspected in young, sexually active women with dysuria, frequency, and pyuria, especially if they have had a new sex partner within the last month or a sex partner with NGU. Other correlates of

chlamydial urethral syndrome include duration of dysuria of more than 7–10 days, lack of hematuria, and lack of suprapubic tenderness. An abnormal urethral Gram stain showing >10 PMNs per oil immersion field in women with dysuria but without coliform bacteriuria supports the diagnosis of chlamydial urethritis but is also found in women with gonococcal or trichomonal infection of the urethra.

■ BARTHOLINITIS

Like gonococci, *C. trachomatis* may produce an exudative infection of Bartholin's ducts. Davies et al. studied 30 women who had clinical evidence of Bartholinitis and isolated *N. gonorrhoeae* and *C. trachomatis* from the ductal exudate of 24 and nine women, respectively.¹¹² Of the nine chlamydia-positive women, seven had concurrent gonorrhea, but two were sex partners of men with NGU and had no evidence of gonococcal infection. Purulent infections of Bartholin's ducts may thus be owing to chlamydial infection, either alone or with concurrent gonococcal infection.

■ ENDOMETRITIS

Histologic evidence of endometritis, often with immunohistologic and/or cultural evidence of *C. trachomatis*, is present in nearly one-half of patients with chlamydial mucopurulent cervicitis and can be demonstrated in nearly all patients with chlamydial salpingitis. The presence of endometritis in patients with chlamydial cervicitis also correlates with a history of abnormal vaginal bleeding (see Chapters 50 and 64).

It is now clear that *C. trachomatis* infection is associated with endometritis.^{113–119} Mardh and coworkers first described two women from whom *C. trachomatis* was recovered by uterine aspiration, despite negative cervical cultures.¹¹³ Both women exhibited signs of salpingitis and had serologic evidence of chlamydial infection. Concomitant endometritis probably explains the menorrhagia and metrorrhagia often seen in women with salpingitis. These studies, like previous evidence gathered in monkeys infected with *C. trachomatis*, indicate that chlamydia cervicitis probably spreads through the endometrial cavity to reach the fallopian tubes.¹¹⁶ Subsequent studies have shown that chlamydial endometritis is characterized by infiltration of the endometrial stroma by plasma cells and infiltration of the endometrial superficial epithelium by PMNs. Besides nonpuerperal endometritis, Wager and coworkers have shown an association of intrapartum fever and late postpartum endometritis with untreated antenatal *C. trachomatis* infection.¹²⁰ Others have confirmed this association (see Chapter 64).

■ SALPINGITIS

The proportion of acute salpingitis cases due to *C. trachomatis* varies geographically and with the population studied. In

Sweden, Mardh and colleagues found that 19 of 53 women with salpingitis had chlamydial infections of the cervix and that of those with cervical infection who had laparoscopy, six of seven grew *C. trachomatis* in a culture from the fallopian tube.¹²¹ These authors found that 80% of 60 consecutive women with acute salpingitis had antibodies to *C. trachomatis*, with 37% exhibiting serologic evidence of acute chlamydial infection. Other serologic studies of women with salpingitis also suggest a prominent etiologic role of chlamydia.^{122–124} Studies in Seattle in women with laparoscopically confirmed salpingitis and histologically confirmed endometritis indicate that 80–90% have proven chlamydial or gonococcal infection, usually confirmed in the upper genital tract, with the proportion having either chlamydial or gonococcal infection being approximately equal.^{117,122} An interesting treatment study by Rees further supports the role of chlamydia in salpingitis.¹²⁵ Among 343 women randomly treated for gonorrhea with either penicillin or tetracycline, a significantly greater proportion of those who received penicillin went on to develop salpingitis; persistence of cervical *C. trachomatis* was associated with many but not all cases of salpingitis. As discussed in Chapters 49 and 50, and elsewhere, many cases of chlamydial salpingitis are associated with mild or absent symptoms or signs, despite progressive tubal scarring, resulting in pregnancy or infertility.^{126–130} Such studies have given rise to the term “silent salpingitis” attributable to chlamydia. Studies in animal models (see Chapters 49 and 50) also demonstrate the causative role of chlamydia in salpingitis and in the production of tubal scarring and infertility.^{131,132}

■ PERIHEPATITIS (FITZ-HUGH–CURTIS SYNDROME)

Since its original description by Fitz-Hugh and Curtis, perihepatitis occurring after or with salpingitis has been considered a complication of gonococcal infection. However, studies in the last 15 years suggest that chlamydial infection is, in fact, more commonly associated with perihepatitis than is *N. gonorrhoeae* (see Chapter 51), probably accounting for the majority of cases.^{133–135} Perihepatitis should be suspected in young, sexually active women who develop right-upper-quadrant pain, fever, nausea, or vomiting. Evidence of salpingitis may or may not be present on examination. A recent study has demonstrated that perihepatitis is strongly associated with extensive tubal scarring, adhesions, and inflammation observed at laparoscopy, as well as with high titers of antibody to the 57-kDa chlamydial heat shock protein.¹³⁶

OTHER CHLAMYDIAL INFECTIONS IN ADULTS

Since *C. trachomatis* causes a distinctive pneumonia syndrome in neonates (see Chapter 66), several studies have assessed the etiologic role of chlamydia in adults with pneumonia. Case reports and small studies suggest that *C. trachomatis* is an

occasional cause of pneumonitis in immunocompromised adults.^{137,138} Tack and coworkers isolated *C. trachomatis* from the lower respiratory secretions of five immunosuppressed patients with pneumonia and from one patient with acute bronchitis.¹³⁷ *C. trachomatis* was also isolated from the eye and nasopharynx and from bronchial brushings in three of these patients. However, none of these six patients developed serologic evidence of *C. trachomatis* infection, and all had concomitant cytomegalovirus infection. On the other hand, Meyers and coworkers demonstrated sustained IgM and IgG antibody rises to *C. trachomatis* in three patients who developed interstitial pneumonia after marrow transplantation, but lung tissue examined by culture and fluorescent antibody techniques from these patients and from 63 other transplant patients with idiopathic pneumonia provided no evidence of chlamydial infection.¹³⁸ More recently, histologic or cultural evidence of *C. trachomatis* infection could not be demonstrated in 48 lung biopsies from AIDS patients with pneumonia.⁶¹ Komaroff and coworkers reported serologic evidence of recent chlamydial infections in four out of 19 adults with community-acquired pneumonia not owing to other common bacterial or viral pathogens.¹³⁹ However, in retrospect, these likely represented antibodies to *C. pneumoniae* rather than to *C. trachomatis*. At this point, there is no evidence to suggest that *C. trachomatis* causes community-acquired pneumonia or other respiratory infections in adults.

C. trachomatis may on occasion produce culture-negative endocarditis, and serologic studies in one patient suggested that meningoencephalitis resulted from chlamydial infection.^{140–142} Other uncommon infections reported in adults, including peritonitis and postmenopausal vaginitis, have been attributed to chlamydia.^{143,144}

DIAGNOSIS

Chapter 74 discusses in detail the cytologic, cultural, antigen-detection, DNA hybridization, nucleic acid amplification, and serologic methods for diagnosis of *C. trachomatis* infections. Aspects relevant to deciding whom to test, what test to use, the collection of specimens, and the interpretation of results in adult patients are presented here.

Being an intracellular pathogen, *C. trachomatis* requires a cell culture system for propagation in the laboratory. Thus, cell culture was the gold standard test for the detection of *C. trachomatis* for years.⁶ However, its stringent requirements in terms of both technical expertise and specimen collection and transport make cell culture impractical in settings in which neither a cold chain nor a cell culture system can be maintained. Further, a carefully collected sample of columnar epithelial cells from the cervix or urethra is necessary, and specimens composed purely of polymorphonuclear cells or mucopurulent discharge are not adequate.⁶ For culture, specimens may be collected with a cotton-tipped swab (those with

wooden sticks should not be used, as they are inhibitory to chlamydia). For endocervical specimens, a cytobrush may result in an increase in the sensitivity of culture as more cells are collected.⁶ Specimens must be placed in specific transport media and refrigerated until they are inoculated within 24 hours onto cell culture plates.

Owing to the inadequacies, cost, and technical difficulties of cell culture, the development of nonculture tests has been a major research priority over the last 15 years. As a result, many nonculture diagnostic tests for *C. trachomatis* are now commercially available.^{6,145} The first of these tests used antigen detection, generally of chlamydia lipopolysaccharide (LPS) or MOMP, as a means of detecting chlamydial elementary bodies or antigens in genital specimens. The most widely used of these assays are the DFA and enzyme immunoassay (EIA) tests. In general, when obtained from the cervix, these tests detect between 60% and 85% of infections relative to culture.^{146,147} The DFA, when done by an experienced technician, has a sensitivity of 80–85%, but overall sensitivity depends both on the experience of the person performing the test and on collection of an adequate specimen.^{147,148} Sensitivity of the EIAs generally are in the range of 60–80%, compared with culture, and vary by assay (see Table 32-1).^{145–147,149} Although the DFA test is highly specific (>99%), the EIA requires a confirmatory assay with a blocking antibody or with DFA to eliminate false-positive results. Results of antigen detection tests can usually be obtained within 1–2 days. Several simplified rapid antigen detection tests that can be done on site and provide immediate results while the patient is in the clinic are also available. Unfortunately, the performance of these tests has been disappointing; most have yielded unacceptably low sensitivities relative to culture, and their use is discouraged until performance can be improved.^{147,150}

The advantages of all of the nonculture tests in comparison with culture are their ease of use in settings where transport or maintenance of specimens at colder temperatures is problematic or where cell culture is not available and their low cost. However, the hope that they might be useful as a noninvasive means of diagnosing chlamydial infection by testing urine has not been realized. The sensitivities of these assays when applied to urine have been unacceptably low, often in the 40–50% range, as compared with culture.¹⁵¹

The most exciting development in chlamydial diagnostic testing has been that of automated methods for the detection of amplified *C. trachomatis* DNA or RNA. Initially, the two most widely used methods were LCR and PCR, both of which were used for cervical, urethral, and urine specimens from males and females. The specificity of these tests has consistently been above 99%.^{6,147} Subsequently, the LCR assay was removed from the market because of problems with quality control. Another methodology, transcription-mediated amplification (TMA), amplifies chlamydial ribosomal RNA

and appears to have performance characteristics similar to LCR and PCR.¹⁵² PCR assays target nucleotide sequences on the plasmid of *C. trachomatis*, which is present in multiple copies within each elementary body. The TMA assay targets a ribosomal RNA sequence. The lower limit of detection of these tests is in the range of one to 10 elementary bodies (as compared to 10,000 elementary bodies for EIA). Further details of additional diagnostic test methods are discussed in Chapter 74.

In order to define the performance of these newer highly sensitive amplification tests, a new gold standard other than cell culture must be utilized. The best approach now that several amplification assays are available is to confirm one amplification assay by comparing it with a second or third similar assay. Using this approach, LCR when applied to first-catch urine (FCU; the first 10–30 mL of stream) has a sensitivity of approximately 90–96% for the detection of chlamydial urethritis in males, and 69–96% for chlamydial urethritis and/or cervicitis in females.^{153–157} Sensitivity of LCR performed on endocervical specimens has ranged from 81% to 100%.^{155,158,159} Compared with the performance of cell culture or antigen detection assays, LCR generally detected 15–40% more infected persons, with a concomitant increase in estimated prevalence of 4–5%. These studies were the first to indicate that a NAAT (LCR) performed on endocervical specimens was consistently more sensitive than culture and that its performance on FCU was sensitive enough to provide a means of noninvasive testing for the diagnosis of chlamydial infection of the urethra and the cervix in women.

The performance of PCR in the diagnosis of chlamydial infection has also been evaluated, relative to the expanded gold standard described above. Among males, its sensitivity when performed on FCU has generally been 87–100%.^{160–164} The test has detected up to approximately 40% more infections than urethral culture in some studies.¹⁶² Among females, PCR performed on FCU has demonstrated a sensitivity of 82–93%.^{162,165} Unexpectedly, performance of PCR on endocervical specimens has sometimes been variable, with sensitivities ranging from 60% to 92%.^{162–165} The presence of inhibitors in endocervical mucous is thought to be responsible for this variability in PCR sensitivity, in one study effecting a reduction of sensitivity of 15%.¹⁶⁵ Of the NAATs that are currently available, the GenProbe Aptima CT assay, which utilizes target capture and RNA amplification, appears to be the most sensitive and specific assay.

In addition to the use of first-void urine, the newer amplification tests may make it possible to use other novel specimens for the diagnosis of *C. trachomatis* infection. In women, self-collected swabs of the vaginal introitus are as sensitive and specific as cervical swabs for the diagnosis of chlamydial infection and may be the preferred specimen for either diagnosis or screening.

SEROLOGIC TECHNIQUES

Serologic tests have not been widely used for the diagnosis of chlamydial genital tract infections other than LGV. Several major problems have precluded their use. First, the baseline prevalence of antibody in populations of sexually active persons who are at risk of *C. trachomatis* infection is high, often ranging from 45% to 65% of persons tested. The high prevalence of seropositivity in culture-negative, asymptomatic patients presumably reflects either previous infection or persisting, chronic asymptomatic infection not easily detected with current assay techniques. Second, the lack of an abrupt onset of symptoms in many chlamydia-infected patients means that patients often are seen during periods when IgM antibody or rising or falling titers of IgG antibody cannot be demonstrated, and hence these serologic parameters of recently acquired infection often are absent. This particularly applies to women. Onset of symptoms is more abrupt in men with NGU, and seroconversion or IgM antibody can be documented in most men. Third, superficial genital tract infection (urethritis and cervicitis) generally produces micro-IF antibody titers in the range of 1:8 to 1:256, but rarely higher. Of men with NGU who were initially seronegative but later developed IgG antibody to chlamydia, 60% developed titers between 1:8 and 1:32, whereas 40% were between 1:64 and 1:256. Higher antibody titers (>1:256) have more often been seen in women with salpingitis and even higher titers (often >1:1024) in women with perihepatitis. Finally, cross-reacting antibody rises owing to *C. pneumoniae* may obfuscate serodiagnosis. These issues are discussed in more detail elsewhere in Chapter 31.

WHEN TO USE DIAGNOSTIC TESTING

All women suspected of having *C. trachomatis* genital infections on the basis of symptoms, signs, or exposure history, including women with suspected mucopurulent cervicitis, endometritis, pelvic inflammatory disease, acute urethritis, or acute proctitis, as well as women whose male partners have gonorrhea or NGU, should have specific diagnostic testing. As described in the preceding text, the diagnosis of many of these conditions is difficult to establish on clinical grounds alone, and the presence of a positive chlamydial test thus is of great value in confirming the suspected diagnosis. Although women in these categories should be empirically treated with antibiotics while test results are pending, the specific confirmation of *C. trachomatis* infection clarifies the diagnosis, improves the patients' understanding of their illness, probably enhances compliance with therapy, and facilitates management of sexual partners. Although "syndromic treatment" of women with chlamydia-associated syndromes (i.e., empiric treatment without testing) is an acceptable strategy, where

costs prohibit laboratory testing, the benefits attributable to testing argue for its use where affordable.

Second, unrecognized *C. trachomatis* infections should be identified by appropriate screening of asymptomatic women in high-risk groups.^{158,163,168} Universal screening of all women attending STD clinics or other clinics (e.g., family planning clinics, juvenile detention centers, and abortion clinics), where the prevalence of infection exceeds 10–12%, appears to be an effective and cost-efficient strategy.^{166–169} In other clinical settings where the overall prevalence of chlamydial infection is less than 5–6%, selective screening may be a more effective strategy. It has been recommended that all sexually active women under 25 years of age be screened, as well as older women who have specific risk factors, associated with chlamydial infections, including a new sexual partner, multiple sexual partners, and racial/ethnic backgrounds found to be at high risk in the local setting, and signs of cervicitis.^{147,168} Strong consideration should be given to screening all unmarried pregnant women and all pregnant women with one or more of these risk characteristics, especially adolescents.

In men, given both the relative paucity of serious complications that arise from *C. trachomatis* infections and the considerably greater proportion of infections that can be accurately diagnosed on clinical grounds alone, both specific diagnostic testing and screening for *C. trachomatis* infections should be given a lower priority than in women.¹⁶⁸ Thus, when resources limit the numbers of tests that can be done (e.g., in public health clinics), the tests available should be used primarily for diagnosis and screening in women. However, knowledge of the etiologic role of *C. trachomatis* in NGU has prognostic implications (>90% cure rate for patients positive for *C. trachomatis*, compared with 50% for those who are negative) and fosters the need for more aggressive identification and treatment of female partners. Specific diagnostic testing thus provides a number of benefits, even though infected men with symptoms or signs of urethritis should be treated empirically before the test results are known.

Up to one-third of heterosexual men with *C. trachomatis* urethral infection attending STD clinics lack symptoms of urethritis.¹⁷ Further, asymptomatic chlamydial urethritis is surprisingly prevalent (5–7%) among young men in inner-city high schools.¹⁷⁰ Screening of young men for asymptomatic *C. trachomatis* infection has been difficult because of the absence of a noninvasive and patient-acceptable diagnostic technique and because of the infrequency with which young men come into contact with health-care facilities. The availability of chlamydia testing on first-void urine using NAAT now makes screening of large numbers of young men possible in settings such as high schools or other clinics.¹⁶⁸ However, screening of sexually active asymptomatic young men has not been routinely recommended, as the health benefits of such screening for either heterosexual men or their partners have not been demonstrated and, in most areas,

implementation of screening in young women is incomplete.¹⁶⁸ Asymptomatic partners of women with mucopurulent cervicitis, pelvic inflammatory disease, or asymptomatic chlamydial infection should be screened and then given empirical therapy. The use of empirical therapy without specific testing foregoes an opportunity to identify still other sexual contacts who should be evaluated and treated and thus fosters continuation of the epidemic and reinfection of the patient. In homosexual men with suspected proctitis, *C. trachomatis* testing should be done to confirm the suspected diagnosis. Tables 32-2 and 32-3 summarize diagnostic criteria for various *C. trachomatis* infections in men and women, respectively.

THErapy

Although in vitro susceptibility testing for *C. trachomatis* has not been rigorously standardized, studies to date have found little strain-to-strain variation in minimum inhibitory concentrations of individual antimicrobials against chlamydia.⁶ The most active drugs against *C. trachomatis* in tissue culture are rifampin and the tetracyclines, followed by macrolides, sulfonamides, some fluoroquinolones, and clindamycin.⁶ Unlike gonococci, there has been no apparent emergence of antimicrobial resistance to *Chlamydia* isolated from humans. Tetracycline resistance has been observed in *C. suis* strains isolated from swine who had tetracycline in feed.¹⁷¹

The majority of clinical evidence regarding the effectiveness of various antimicrobials against *C. trachomatis* has been accumulated in men with NGU or gonococcal urethritis (Table 32-4). Two general principles have emerged from these studies: Penicillin, ampicillin, cephalosporins, and spectinomycin in single-dose regimens given for treatment of gonorrhea do not eradicate concomitant chlamydial infection, and 7 or more days of treatment with tetracyclines or macrolides eradicates *C. trachomatis* from nearly all men, at least as determined by short-term follow-up.^{172–182} However, chlamydial infection recurs 3–6 weeks after treatment in 5–10% of these men and cannot be clearly designated as reinfection or relapse. Most such recurrences are of the same immunotype as the original infecting strain, and nearly all cause recurrent clinical evidence of urethritis.

In men with NGU, trials using either placebos or agents such as spectinomycin, which are ineffective against *C. trachomatis*, have clearly established the greater effectiveness of specific antimicrobial treatment in eliminating both signs and symptoms of infection and in eradicating chlamydia. Clinical trials indicate that tetracycline hydrochloride, doxycycline, minocycline, triple tetracycline, erythromycin, and trimethoprim-sulfamethoxazole all achieve comparable clinical cure rates of approximately 85–95% in men with chlamydial NGU (see Chapter 52). Of the newer fluoroquinolones, ofloxacin and levofloxacin also have reported cure rates in this range,

Table 32-2. Diagnosis of *C. trachomatis* Infections in Men

Associated Findings	Clinical Criteria	Laboratory Criteria	
		Presumptive	Diagnostic
NGU	Dysuria, urethral discharge	Urethral GS with 5 or more PMN/high-power ($\times 1000$) field; pyuria on FVU	Positive culture or NAAT (urethra or FVU)
Acute epididymitis	Fever, epididymal or testicular pain, evidence of NGU, epididymal tenderness or mass	As for NGU	As for NGU; positive test on epididymal aspirate
Acute proctitis (non-LGV strain)	Rectal pain, discharge, bleeding; abnormal anoscopy (mucopurulent discharge, pain, spontaneous or induced bleeding)	Rectal GS with 1 or more PMN/high-power ($\times 1000$) field	Positive culture or NAAT
Acute proctocolitis (LGV strain)	Severe rectal pain, discharge, hematochezia; markedly abnormal anoscopy (as above) with lesions extending into colon; fever lymphadenopathy	Rectal GS with 1 or more PMN/high-power ($\times 1000$) field	Positive culture or NAAT complement fixation antibody titer

GS = Gram stain; PMN = polymorphonuclear leukocytes; NGU = nongonococcal urethritis; NAAT = nucleic acid amplification tests; FVU = first-void urine; LGV = lymphogranuloma venereum. Reproduced with permission from Stamm WE: Diagnosis of Chlamydia trachomatis genitourinary infections. *Ann Intern Med* 1988; 108: 710–717.

Table 32-3. Diagnosis of *C. trachomatis* Infections in Women

Associated Findings	Clinical Criteria	Laboratory Criteria	
		Presumptive	Diagnostic
Mucopurulent cervicitis	Mucopurulent cervical discharge, cervical ectopy and edema, spontaneous or easily induced cervical bleeding	Cervical GS with greater than 30 PMN/high power ($\times 1000$) field in nonmenstruating women	Positive culture or NAAT (cervix, FVU)
Acute urethral syndrome	Dysuria-frequency syndrome in young sexually active women; recent new sexual partner; often more than 7 days of symptoms	Pyuria, no bacteriuria	Positive culture or NAAT (cervix, or urethra or FVU)
PID	Lower abdominal pain; adnexal tenderness on pelvic exam; evidence of MPC often present	As for MPC; cervical GS positive for gonorrhea; endometritis on endometrial biopsy	Positive culture or NAAT (cervix, FVU, endometrium, tubal)
Perihepatitis	Right upper quadrant pain, nausea, vomiting, fever; young sexually active women; evidence of PID	As for MPC and PID	High-titer IgM or IgG antibody to <i>C. trachomatis</i>

GS = Gram stain; PMN = polymorphonuclear leukocytes; PID = pelvic inflammatory disease; MPC = mucopurulent cervicitis. Reproduced with permission from the *Annals of Internal Medicine*.

whereas ciprofloxacin has been associated with more frequent failures and should not be used for the treatment of NGU.^{183–185} Although relatively ineffective against *C. trachomatis* in vitro and when administered as a single dose, amoxicillin, when

given as 750 mg PO tid for 10 days, apparently eliminated chlamydia from six men with NGU followed for 24–48 days.¹⁷⁹ Pivampicillin in high dosage gave similar results.¹⁷² Although symptoms usually subsided as cultures became negative in

Table 32-4. Summary of Selected Studies Evaluating Oral Antimicrobial Treatment of *C. trachomatis* Urethritis in Men

Regimen	Efficacy ^a	Reference
Minocycline, 200 mg stat., then 100 mg q 12 h for 6 days	11/12 (92%)	175
Tetracycline, 500 mg qid for 7 days	35/35 (100%)	76
Erythromycin stearate, 500 mg q 12 h for 2 weeks	30/31 (97%)	176
Doxycycline, 200 mg for 2 days, then 100 mg for 12 days	50/52 (96%)	177
Deteclo, qd for 7 days	11/12 (92%)	173
Deteclo, qd for 21 days	16/16 (100%)	
Minocycline, 200 mg stat., then 100 mg bid for 6 days	39/40 (98%)	178
Rifampin, 600 mg qd for 6 days	52/53 (98%)	
Erythromycin stearate, 500 mg q 12 h for 15 days	27/30 (90%)	180
Lymecycline, 300 mg q 12 h for 10 days	21/24 (88%)	
Lymecycline, 300 mg q 12 h for 20 days	18/21 (86%)	
Pivampicillin, 750 mg tid for 7 days	19/22 (86%)	172
Doxycycline, 200 mg for 1 day, then 100 mg for 6 days	56/57 (98%)	194
Trimethoprim-sulfamethoxazole, 160 and 800 mg bid, respectively, for 10 days	18/20 (90%)	
Erythromycin, 500 mg bid for 10 days	18/23 (78%)	
Trimethoprim-sulfadiazine, 160 and 500 mg, respectively, in 1 tablet bid for 14 days	18/19 (95%)	75
Tetracycline, 250 mg qid for 7 days	21/24 (88%)	181
Tetracycline, 500 mg qid for 7 days	33/36 (92%)	
Rosaramicin, 250 mg qid for 7 days	38/42 (90%)	
Amoxicillin, 750 mg tid for 10 days	6/6 (100%)	179
Ciprofloxacin, 750 mg bid for 7 days	11/20 (55%)	185
Ciprofloxacin, 1000 mg bid for 7 days	13/18 (72%)	185
Doxycycline, 100 mg bid for 7 days	15/16 (94%)	189
Minocycline, 100 mg qd for 7 days	19/19 (100%)	189
Doxycycline, 100 mg bid for 7 days	23/23 (100%)	78
Azithromycin, 1 g single dose	27/30 (90%)	78
Doxycycline, 100 mg bid for 7 days	29/29 (100%)	187
Azithromycin, 1 g single dose	34/34 (100%)	187

^aStudies cited here generally performed chlamydia cultures before, just after, and 2–3 weeks following completion of treatment; efficacy, as expressed in this table, equals the number of patients with negative chlamydia cultures on visit 2 or 3 divided by the number of patients returning for follow-up visits 2 and 3. Eradication of chlamydia was usually, but not always, associated with clinical resolution of signs and symptoms.

these studies, the possibility cannot be excluded that latent chlamydial infection persisted after amoxicillin or pivampicillin treatment.

Azithromycin, with a half-life of 5–7 days, excellent intracellular and tissue penetration, and in vitro activity against *C. trachomatis* in the 0.25 µg/mL range, is an important, the only currently approved, single-dose agent for treatment of chlamydial infection.¹⁸⁶ Use of single-dose therapy is particularly attractive in potentially less compliant patients, such as adolescents or patients with few or no symptoms.^{186–189} However, individuals treated with azithromycin should still abstain from sex for several days after receiving therapy; earlier resumption of sexual activity with use of single-dose therapy could theoretically result in transmission of an unresolved infection to sex partners. Despite the greater cost of azithromycin as compared with doxycycline (\$9–15 vs. \$1–2), cost-effectiveness analyses support the hypothesis that the compliance assured with single-dose therapy may make it a more cost-effective therapy, particularly in patients with poor compliance.^{190,191} Wherever possible, directly observed single-dose therapy should be used, maximizing compliance. A recently published meta-analysis analyzed randomized clinical trials that compared azithromycin and doxycycline for *Chlamydia* genital infection and found equal efficacy (97% vs. 98%).¹⁸⁹

The recommended length of therapy for NGU using tetracycline or doxycycline has ranged from 7 to 21 days. However, in two studies in which 7 days of therapy were compared with 21 days of therapy with tetracycline or minocycline, no difference was found.^{174,175} Thus, there is as yet no evidence that prolongation of tetracycline or doxycycline therapy beyond 1 week is necessary, provided that sex partners are treated concurrently.

Fewer studies have assessed the effectiveness of antimicrobial treatment of uncomplicated cervical or urethral chlamydial infection in women (Table 32-5). Those data available suggest that tetracycline, 500 mg qid for 7 days, successfully eliminates *C. trachomatis* from the cervix through at least 3 weeks of follow-up.^{182,192–197} Erythromycin, when given as 500 mg PO qid for 7–14 days, is also effective as is ofloxacin, 200 mg PO bid. A small double-blind, placebo-controlled trial indicates that doxycycline, 100 mg PO bid for 10 days, successfully eliminated *C. trachomatis* from the cervix and urethra of women with the acute urethral syndrome.¹¹¹

Azithromycin given as a 1-g single dose was shown to be comparable to 7 days of doxycycline therapy for treatment of uncomplicated chlamydial infection of the cervix.¹⁸⁷ The advantages of single-dose directly observed therapy argue for its use in young women with uncomplicated cervical infection. Treatment options in pregnancy remain somewhat limited as neither doxycycline nor ofloxacin can be used. Erythromycin given as a 2-g daily dose achieves a cure in 84–94% of treated women, but up to half of women develop

significant gastrointestinal side effects and cannot complete the course of therapy.^{198–200} A 1-g daily dose for 7 days is better tolerated but less efficacious. The efficacy of azithromycin in pregnancy has now been studied sufficiently to recommend its routine use for treatment of *Chlamydia* in pregnant women.^{197,201} The recently published CDC treatment guidelines recommended a 1-g dose in this circumstance.¹⁹⁷ Alternatively, Amoxicillin 500 mg orally three times daily for 7 days can be used. Amoxicillin, which has a cure rate approximately equal to that of erythromycin, causes less frequent gastrointestinal intolerance.^{100,199,202} However, because the efficacies of all regimens in the pregnant patient may be low, a test of cure should be considered. Test of cure, if using NAATs testing, should be done at least 3 weeks after the end of treatment to minimize false-positive results.

Treatment of other chlamydia-related syndromes is discussed in individual chapters on salpingitis, epididymitis, and so forth.

PREVENTION

Since many chlamydial infections are asymptomatic, it has become clear that effective control must involve periodic testing of individuals at risk.¹⁶⁸ As the cost of extensive screening may be prohibitive, various approaches to defining target populations at increased risk of infection have been evaluated. One strategy has been to designate patients attending specific high prevalence clinic populations for universal testing. Such clinics would include STD, juvenile detention, and some family planning clinics. This approach, however, fails to account for the majority of asymptomatic infections, since attendees at high prevalence clinics often attend because of symptoms or suspicion of infection. Consequently, selective screening criteria have been developed for use in various clinical settings.^{204–208} Among women, young age (generally, <24 years) is a critical risk factor for chlamydial infection in almost all studies.¹⁶⁸ Other risk factors include the presence of mucopurulent cervicitis; multiple, new, or symptomatic male sex partners; and lack of barrier contraceptive use. These findings have given rise to criteria for selective screening of women. In some settings, screening based solely on young age (generally, <25 years) may be equally as sensitive as criteria that incorporate behavioral and clinical measures.^{209,210}

The effectiveness of selective screening in reducing the prevalence of chlamydial infection in women has been demonstrated in several ecological studies. In the Pacific Northwest, where extensive screening began in family planning clinics, in 1988 and in STD clinics in 1993, prevalence declined from 10% to 12% in the late 1980s and 4% to 5% in 1995.² Similar trends have occurred in association with screening programs elsewhere.^{211,212} However, Brunham et al. has pointed out that in British Columbia, Canada, as well as in

Table 32-5. Summary of Selected Studies Evaluating Antimicrobial Treatment of *C. trachomatis* Cervicitis in Women

Regimen	Efficacy ^a	Reference
Deteclo, 300 mg bid for 7 days	20/20 (100%)	192
Oxytetracycline, 250 mg qid for 14 days	49/50 (98%)	176
Oxytetracycline, 250 mg qid for 21 days	145/161 (90%)	182
Erythromycin, 500 mg bid for 15 days	13/17 (76%)	180
Lymecycline, 300 mg bid for 10 days	18/20 (90%)	
Lymecycline, 300 mg bid for 20 days	14/14 (100%)	
Trimethoprim-sulfadiazine, 160 and 500 mg, respectively, in 1 tablet bid for 14 days	15/15 (100%)	75
Doxycycline, 100 mg bid for 10 days	15/15 (100%)	
Doxycycline, 200 mg stat., then 100 mg bid for 9 days	55/58 (95%)	194
Erythromycin, 500 mg bid for 10 days	36/39 (92%)	
Trimethoprim-sulfamethoxazole, 160 and 800 mg, respectively, in 1 tablet for 10 days	37/40 (93%)	
Tetracycline, 500 mg qid for 7 days	21/22 (95%)	196
Erythromycin, 250 mg qid for 7 days	12/12 (100%)	
Sulfisoxazole, 500 mg qid for 10 days	8/8 (100%)	
Ciprofloxacin, 500 mg bid for 7 days	30/35 (86%)	193
Pivampicillin, 700 mg bid for 7 days	26/26 (100%)	195
Doxycycline, 100 mg bid for 7 days	17/17 (100%)	189
Minocycline, 100 mg qD for 7 days	16/16 (100%)	189
Ofloxacin, 300 mg bid for 7 days	26/28 (93%)	184
Doxycycline, 100 mg bid for 7 days	22/22 (100%)	184
Doxycycline, 100 mg bid for 7 days	72/73 (99%)	187
Azithromycin, 1 g single dose	78/78 (100%)	187

^aStudies cited here generally performed chlamydia cultures before, just after, and 2 to 3 wks following treatment efficacy, as expressed in this table, equals the number of patients with negative chlamydia cultures or visit 2 or 3 divided by the number of patients returning for those follow-up visits.

Region X in the United States, the low prevalence of infection in women screened for *Chlamydia* did not persist but rather was followed by rising prevalences each year since 1996.⁵ This trend after earlier reductions in prevalence is worrisome and suggests that the use of female screening may have limitations in terms of long-term value. Brunham et al. postulates that women identified by screening and treated may develop only partial immunity and remain susceptible to reinfection.⁵

Evidence that screening can effect a reduction in upper genital tract disease has recently been published. In a study in

Seattle, women in a large health-maintenance organization who satisfied selective screening criteria for chlamydial infection were randomized to one of two arms: an intervention arm in which women were tested for chlamydial cervical infection and a control arm characterized by standard care.²¹³ Subjects in the intervention (screening) arm experienced a marked reduction in the 1-year incidence of symptomatic PID, as assessed by clinical record review and patient report of symptoms compatible with PID (odds ratio, 0.44; 95% confidence interval, 0.20, 0.90). This finding was especially notable,

given that chlamydia prevalence in the study population was low (3.5%) and that chlamydia screening programs were already ongoing in the area.

The practical implementation of screening programs in settings with low-to-moderate *chlamydia* prevalence requires that the prevalence at which selective screening becomes cost effective relative to universal screening must be defined. Toward this end, a number of investigators have undertaken cost-effectiveness analyses. Most of these analyses have concluded that universal screening is preferred in settings with chlamydia prevalence above 3–7%.^{166–168,203} Depending on the criteria used, selective screening is likely to be more cost effective when prevalence falls below these numbers.

Among asymptomatic males, risk factors for chlamydial infection have been less extensively explored, and the effectiveness of screening programs targeting males is not known.¹⁶⁸

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Walter E. Stamm

Lymphogranuloma venereum (LGV) is one of the sexually transmitted diseases caused by *Chlamydia trachomatis*. A sporadic disease in North America, Europe, and Oceania, LGV is highly prevalent in parts of Africa, Asia, and South America. It is also known variously as *tropical* or *climatic bubo*,¹ *strumous bubo*,² *poradenitis inguinalis*,³ *Durand-Nicolas-Favre disease*,^{3,4} *lymphogranuloma inguinale*, and the *fourth*, *fifth*, or *sixth venereal disease*.⁵ LGV is preferred because it is less easily confused with granuloma inguinale.

LGV has a variety of acute and chronic manifestations. Three stages of infection, more or less analogous to those of syphilis, are recognized.⁶ The primary lesion of LGV is a small, generally painless genital papule that may ulcerate rapidly. The secondary stage is characterized by acute lymphadenitis with bubo formation (the inguinal syndrome) and/or acute hemorrhagic proctitis following rectal intercourse (the anogenitoretal syndrome) together with fever and other symptoms caused by systemic spread of infection. The vast majority of patients recover from LGV after the secondary stage without sequels, but in a few patients the persistence of *Chlamydia* in anogenital tissue incites a chronic inflammatory response and the development of genital ulcers, fistulas, rectal strictures, and genital elephantiasis. Antibiotic treatment during the secondary stage prevents these late complications, which otherwise may require surgical repair.

LGV is usually caused by one of the three serovars of *C. trachomatis*: L1, L2, and L3 (see Chapter 15). Other *C. trachomatis* strains occasionally have been isolated from infected tissue taken from patients who have symptoms compatible with genitoanorectal LGV.⁷⁻⁹

Throughout most of its history, LGV has been confused with other diseases, particularly with the lymphadenopathy of syphilis and genital herpes and the buboes of chancroid. Confusion was caused in part by the failure to recognize the common etiology of the different manifestations of LGV, which often were described as distinct clinical or pathologic entities. Durand, Nicolas, and Favre⁴ established the disease as a clinical and pathologic entity in 1913, and Phylactos

deduced a common etiology of climatic bubo and LGV in 1922,¹⁰ but a major diagnostic advancement in the study of LGV was the development of a "specific" skin test by Frei in 1925.¹¹ This test established the etiology of LGV proctocolitis and rectal stricture.¹² In 1930, LGV *Chlamydia* were isolated from buboes by intracerebral inoculation of monkeys,¹⁰ and LGV *Chlamydia* were grown in embryonated eggs in 1935.¹³ The latter achievement made possible the commercial manufacture of large amounts of standardized antigen for Frei tests and serodiagnostic tests.

The first effective drugs for treatment of LGV were the sulfonamides, which were introduced in the late 1930s.¹⁴ Although other drugs have since been developed for treatment of LGV¹⁵ and both serodiagnostic and molecular tests have been refined to give greater specificity, we still do not understand the pathogenesis of this disease.

A more detailed review of the history of LGV is a study in itself and will not be undertaken here. The monograph on LGV published by Stannus in 1933⁵ lists 933 references and, together with the excellent reviews published by Koteen in 1945¹⁶ and Favre and Hellerstrom in 1954,¹⁰ describes the historical evolution of the disease.

EPIDEMIOLOGY

LGV is a sporadic disease throughout North America, Europe, Australia, and most of Asia and South America. Occasional cases or clusters of cases suggest ongoing low-level transmission in these areas. It is endemic in east¹⁷ and west Africa,¹⁸ India,¹⁹ parts of Southeast Asia,²⁰ South America,²¹ and the Caribbean.²² Few countries require official notification of LGV cases, and the lack of standard diagnostic criteria renders reported cases somewhat suspect. Since 1950 no country in Europe has reported more than a few dozen cases of LGV annually,²¹ and the average for the United States was 595 cases per year, with slight increases during the wars in Korea and Vietnam.²³ By contrast, one municipal clinic in Ethiopia reports several thousand cases of acute LGV annually.¹⁷ Most of the reported LGV cases in

nonendemic areas occur in travelers who acquire the infection while visiting or living in an endemic area.²⁰ Like other sexually transmitted diseases, LGV is more common in urban than in rural areas, among the sexually active, and among the lower socioeconomic groups.²² Until recently, much of the reported epidemiology on LGV was based on cases diagnosed using clinical criteria or the results of serologic tests and/or Frei skin tests that were not specific for the disease.

Although cases of LGV are infrequent in Western Europe and the United States, recent outbreaks of LGV have been reported in homosexual and bisexual men many of whom are HIV positive and practice receptive rectal intercourse.^{24,25} Most such men have presented with acute proctocolitis and only a few have had the more classic ulcer and bubo associated with LGV. Most of the infections have been with L2 strains, some with a unique molecular variant of LGV.^{26,27}

Acute LGV is reported much more frequently in men than in women, with the ratio often reaching 5:1 or greater.²⁸ This is because symptomatic infection is much less common in women, who are usually diagnosed during early infection only if they develop acute proctocolitis or, less commonly, inguinal buboes. Late complications such as hyperplasia, ulceration and hypertrophy of the genitalia (esthiomene), and rectal strictures are reported to be more frequent in women than in men.^{16,24}

The frequency of infection following exposure is unknown. LGV is probably not as contagious as gonorrhea. Primary ulcerative skin lesions, urethritis, cervicitis, proctocolitis, and chronic ulcerations are probably the most infectious forms of LGV. Although supporting evidence is limited, the endocervix is apparently the most common site of acute infection in women. The cervix may remain infected for periods of weeks or months, as has been demonstrated for other serovars of *C. trachomatis*.²⁹ Congenital transmission does not occur, but infection may be acquired by the infant during passage through an infected birth canal.

PATHOGENESIS AND PATHOLOGY

Chlamydia cannot penetrate intact skin but gains entry through minute lacerations and abrasions. Laboratory-acquired infections following sonication and inhalation of highly concentrated LGV cultures have been reported.²⁷

LGV is predominantly a disease of lymphatic tissue.³⁰ The essential pathologic process is thrombolympangitis and perilympangitis with spread of the inflammatory process from infected lymph nodes into the surrounding tissue. The lymphangitis is marked by proliferation of endothelial cells lining the lymph vessels and the lymph channels in lymph nodes. Lymph nodes draining the site of primary infection rapidly enlarge and form small, discrete areas of necrosis surrounded by densely packed endothelial cells.³¹ The necrotic

areas attract polymorphonuclear leukocytes and enlarge to form characteristic triangular- or quadrangular-shaped “stellate abscesses.” Inflammation mats the adjacent lymph nodes together by periadenitis, and as the inflammation progresses, abscesses coalesce and rupture, forming loculated abscesses, fistulas, or sinus tracts.

The inflammatory process lasts several weeks or months before subsiding. Healing takes place by fibrosis, which destroys the normal structure of lymph nodes and obstructs lymph vessels. The resulting chronic edema and sclerosing fibrosis cause induration and enlargement of the affected parts. Fibrosis also compromises the blood supply to the overlying skin or mucous membrane, and ulceration occurs. In the rectum, this results in destruction and ulceration of the mucosa, transmural inflammation of the bowel wall, obstruction of lymphatic drainage, and formation of a fibrotic, inflammatory stricture. Numerous adhesions form that fix the lower part of the sigmoid and rectum to the wall of the pelvis and neighboring organs.^{31,32}

Although the primary pathologic process in LGV may be localized to one or two groups of lymph nodes, the organisms spread systemically in the bloodstream and can enter the central nervous system.³³ Dissemination and local extension of disease are limited by host immunity. Delayed hypersensitivity (as evidenced by positive skin tests) and LGV-specific *Chlamydia* antibody can be demonstrated 1–2 weeks after infection.³⁴ Chlamydial cytoplasmic inclusions can also be demonstrated within tissue phagocytes early in the course of infection.¹³ Host immunity ultimately limits chlamydial multiplication but may not eliminate these organisms from the body, and a state of chronic infection ensues.¹⁵ Viable *Chlamydia* has been isolated from late lesions as long as 20 years after initial infection.³⁵ Persistence of LGV in tissues or repeated infections by the same or related serovars of *C. trachomatis* may be important in developing systemic disease.³⁶ It is of interest that repeated subcutaneous or intravenous injections of Frei antigen were used to treat LGV in the 1930s with some success,³⁷ possibly by desensitizing the host to *Chlamydia*. Molecular and cellular aspects of pathogenesis are addressed in Chapter 31.

CLINICAL MANIFESTATIONS

■ PRIMARY LESION

The primary lesion of LGV may take one of four forms: a papule, an ulcer or erosion, a small herpetiform lesion, or nonspecific urethritis.²⁸ The most common is the nonindurated herpetiform ulcer that appears at the site of infection after an incubation period of 3–12 days or longer.^{10,24,38,31} It may be asymptomatic and inconspicuous (although occasionally multiple and deeply erosive). It is found in 3–53% of patients,^{39,40} heals rapidly, and leaves no scar.^{28,31} The most common site of occurrence in men is the coronal sulcus,

followed by the frenum, prepuce, penis, urethral glans, and scrotum.¹⁰ In women it appears most commonly on the posterior vaginal wall, the fourchette, the posterior lip of the cervix, and the vulva.^{6,10,39} If located intraurethrally, the ulcer or erosion may cause nonspecific urethritis with a thin, mucous purulent discharge.^{16,20} Other uncommon types of primary lesions are balanitis³⁸ and nodular ulcerations.^{10,16,31} Following rectal intercourse acute colitis or proctocolitis is often seen as the main manifestation of primary infection. Increasingly, this presentation is the primary form seen in nonendemic countries.

Primary LGV lesions in men may be associated with a lymphangitis of the dorsal penis and formation of a large, tender lymphangial nodule, or *bubonulus*.¹⁰ Bubonuli may rupture and form draining sinuses and fistulas of the urethra as well as fibrotic, deforming scars at the base of the penis.⁴¹ Lymphangitis is very often accompanied by local and regional edema, which may produce varying degrees of phimosis in men and genital swelling in women³⁸ (Table 33-1).

Cervicitis and urethritis are probably more common manifestations of primary LGV than reported statistics indicate.³⁸ Urethritis is usually asymptomatic and follows a mild course. Cervicitis may extend locally and could conceivably cause perimetritis or salpingitis. Additional studies using modern molecular diagnostics would be valuable to assess the

prevalence of LGV chlamydial infection at the urethral and cervical sites.

■ INGUINAL SYNDROME

Inflammation and swelling of the inguinal lymph nodes are the most common manifestations of the secondary stage of LGV in men^{20,24} and are the reason that most patients seek medical attention.²⁸ Other lymph nodes may be involved; the likelihood of such involvement depends on the location of the primary lesion (Table 33-2). The incubation period for this manifestation is 10–30 days, but it may be delayed for as long as 4–6 months after infection.^{35,39} It is important to note that LGV can also present as an acute systemic febrile infection without apparent lymph node localization or tissue reaction at the point of infection.

The inguinal bubo is unilateral in two-thirds of cases^{16,24} (Fig. 33-1). It begins as a firm, slightly painful mass that enlarges over 1–2 weeks. The inguinal bubo was described by William Wallace⁴² in 1833:

The skin becomes red and is then found to be adherent to the surface of the tumour, over which it could be previously moved. The bubo then for the most part increases with rapidity; the pain becomes of a throbbing kind; some degree of fever sets in, marked by an acceleration of pulse, an increase of heat, loss of appetite, imperfect sleep, with a general feeling of indisposition.

The constitutional symptoms associated with inguinal buboes may be associated with systemic spread of *Chlamydia*. During this stage of infection, LGV organisms have been recovered from the blood and the cerebrospinal fluid of patients both with and without symptoms of meningoencephalitis and abnormal cerebrospinal fluid.^{33,43,44} Other manifestations of systemic spread are hepatitis,^{45,46} pneumonitis,²⁸ and possibly arthritis.⁴⁷ Erythema nodosum,

Table 33-1. Lesions of Lymphogranuloma Venereum

Early	Late
<i>Inguinal syndrome</i>	
Primary genital lesion(s)	Genital elephantiasis
Genital ulcers	Genital ulcers
Inguinal buboes	
Bubonulus	
<i>Anorectal syndrome</i>	
Proctitis	Rectal stricture
	Lymphorrhoids
	Perirectal abscesses
	Anal fistula
<i>Other</i>	
Urethritis	Frozen pelvis
Cervicitis	Infertility
Salpingitis	
Parametritis	
Conjunctivitis	

Table 33-2. Site of Primary LGV Infection Determining Subsequent Lymphatic Involvement

Site of Primary Infection	Affected Lymph Nodes
Penis, anterior urethra	Superficial and deep inguinal
Posterior urethra	Deep iliac, perirectal
Vulva	Inguinal
Vagina, cervix	Deep iliac, perirectal, retrocrural, lumbosacral
Anus	Inguinal
Rectum	Perirectal, deep iliac



FIGURE 33-1. Early inguinal syndrome of LGV showing superficial, primary preputial erosion, dorsal penile lymphangitis, and right inguinal bubo.

erythema multiforme, and eyeground changes (papillary edema) are also reported.^{16,38,44}

As the bubo enlarges, the male patient complains of severe pain in the groin. He may walk with a limp, bent at the waist in an attempt to limit pain. Within 1–2 weeks the bubo becomes fluctuant, and the skin overlying the bubo takes on a characteristically livid color (“blue balls”) that predicts rupture of the bubo.²⁴

Rupture through the skin usually relieves pain and fever.^{16,44} Numerous sinus tracts are formed that drain thick, tenacious, yellowish pus for several days or weeks with little or no discomfort.⁴⁸ Healing takes place slowly, leaving callous and contracted scars in the inguinal region. The disappearance of the inguinal bubo usually marks the end of the disease in men, and the majority suffer no serious sequelae.^{24,49} Bubonic relapse occurs in about 20% of untreated cases.⁴⁹

Only about one-third of inguinal buboes become fluctuant and rupture; others slowly involute and form firm, slowly resolving inguinal masses without undergoing suppuration.^{16,24} In about 20% of cases, the femoral lymph nodes are also affected and may be separated from the enlarged inguinal lymph nodes by Poupart’s ligament; this process creates the “sign of the groove” that is said to be pathognomonic for LGV²⁸ (Fig. 33-2). Simultaneous involvement of the deep iliac lymph nodes occurs in about 75% of cases and may cause formation of a large pelvic mass that, fortunately, seldom suppurates.^{38,44} Extragenital primary lesions produce lymphadenitis and bubo formation in the lymph nodes draining the lesions; these extragenital buboes do not differ symptomatically or pathologically from inguinal buboes.¹⁶



FIGURE 33-2. Early inguinal syndrome of LGV showing a small vesicular primary lesion and bilateral inguinal lymphadenitis with cleavage of the enlarged right inguinal and femoral lymph nodes by the inguinal ligament, the characteristic “groove” sign.

In large studies of LGV in women, only 20–30% present with the inguinal syndrome.^{24,50} About one-third of female cases without proctitis, however, complain of lower abdominal and back pain, especially when supine.⁴⁴ This symptom is characteristic of involvement of the deep pelvic and lumbar lymph nodes and may be mistaken for acute appendicitis²⁸ or a tubo-ovarian abscess.^{16,44} Numerous adhesions may form, fixing the pelvic organs together.⁴⁴

Other infectious diseases causing inguinal lymphadenitis and bubo formation are plague, tularemia, cat scratch disease, and tuberculosis. More common causes of inguinal lymphadenitis without suppuration, which are frequently misdiagnosed as LGV, are genital herpes, syphilis, chancroid, and Hodgkin’s disease.³⁸ Small skin lesions on the feet or lower extremities may cause significant inguinal adenopathy with bacterial superinfection, usually staphylococcal or streptococcal. In nonendemic areas, however, the syndrome is most frequently mistaken for an incarcerated inguinal hernia⁵¹ or lymphoma.⁵²

■ ANOGENITORECTAL SYNDROME

The subacute manifestations of this syndrome are proctocolitis and hyperplasia of intestinal and perirectal lymphatic tissue (lymphorrhoids). The chronic or late manifestations are perirectal abscesses, ischio-rectal and rectovaginal fistulas, anal fistulas, and rectal stricture or stenosis.^{22,38}

In men, the rectal mucosa can be inoculated directly with *Chlamydia* during receptive anal intercourse or by lymphatic spread from the male posterior urethra. In women, the rectal mucosa can also be inoculated directly with during anal intercourse, or it can be secondarily infected by migration of infectious vaginal secretions or by lymphatic spread from the cervix and posterior vaginal wall. The vast majority of

patients with the anorectal syndrome are women or homosexual men.^{50,53–57}

The early symptoms of rectal infection are anal pruritus and a mucous rectal discharge caused by local or diffuse edema of the anorectal mucosa. The mucosa becomes hyperemic and friable after a period of several weeks and bleeds easily when traumatized.^{53,56,57} Multiple, discrete, superficial ulcerations with irregular borders appear on the mucosa and are gradually replaced by granulation tissue. A chronic inflammatory process invades the bowel wall, and noncaseous granulomas and crypt abscesses form.^{53,56} With secondary bacterial infection of the rectal mucosa, the discharge becomes mucopurulent. If left untreated, the granulomatous process progressively involves all layers of the bowel wall. The muscle layers are replaced by fibrous tissue.^{32,53} In women the rectovaginal septum may be eroded and a rectovaginal fistula may be formed.⁵⁴ Contraction of the fibrous components of the granulation tissue over a period of months or years causes partial (stricture) or complete (stenosis) blockage of the rectum.^{32,53,54}

Early symptoms of proctocolitis include fever, rectal pain, and tenesmus.^{16,22,54} The lower left quadrant of the abdomen is tender, and the pelvic colon may be palpably thickened. The rectal mucosa feels granular on digital examination, and movable, enlarged lymph nodes may be palpated immediately under the bowel wall.⁵⁴ There are no pathognomonic sigmoidoscopic findings. The inflammatory process may be localized to one segment of bowel or may occur at several different levels concurrently, but it is usually limited to that portion below the peritoneal reflection.^{22,32,54}

Additional symptoms that occur with rectal stricture are varying degrees of constipation, passage of “pencil” stools, attacks of ileus with colic and abdominal distension, and weight loss.^{24,38,53,58} The stricture usually forms 2–5 cm above the anocutaneous margin, where the perirectal lymphatic tissue is the richest.^{22,54} It is usually annular or tubular in shape⁵⁸ and its proximal margins are granular (Fig. 33-3). If the palpating finger can be introduced through the aperture of the nondistensible and rigid stricture, the mucous membrane above it has a normal consistency.⁵⁴ By contrast, the mucous membrane below the stricture generally shows ulcerative and granulomatous proctitis, which makes the digital examination very painful.²⁴ Although the stricture is often very narrow, complete bowel obstruction (rectal stenosis) is rare but strictures may cause bowel perforation and peritonitis, which is the usual cause of death in LGV.^{38,59}

The rectal mucosa below the stricture and the skin around the anus are frequent sites for the formation of perirectal abscesses and anal fissures.^{55,58} These may also occur as the only manifestation of chronic anogenitoretal LGV. Obstruction of the lymphatic and venous drainage of the lower rectum produces perianal outgrowths of lymphatic tissue that grossly resemble hemorrhoids but are called *lymphorrhoids*⁶⁰ or *perianal condylomas*.⁵⁸ Histologically, these anal

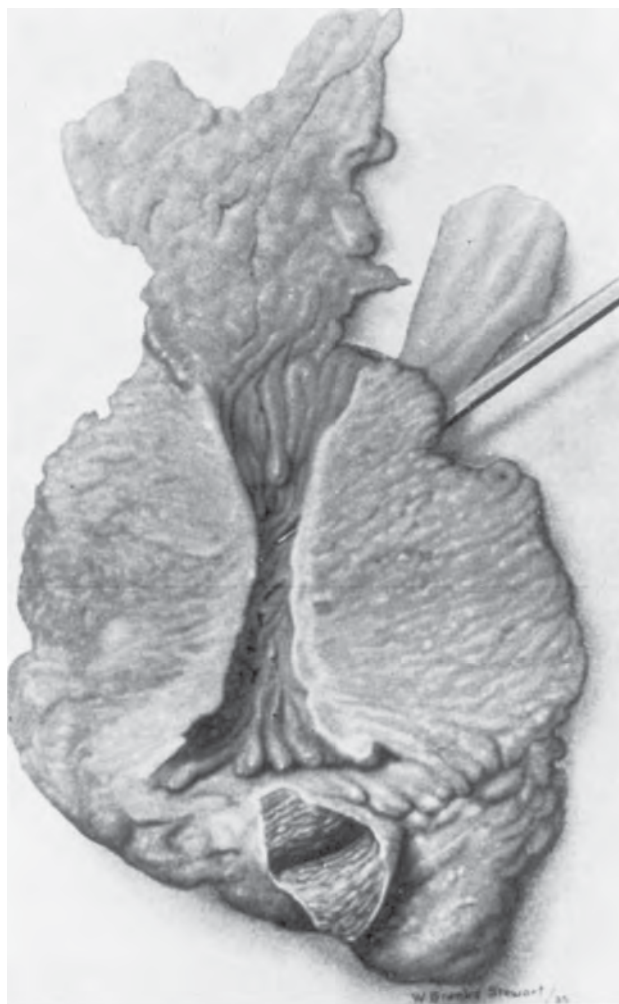


FIGURE 33-3. Necropsy specimen of an LGV rectal stricture containing an ileosigmoidal fistula. (With permission from Lichtenstein LL. Rectal stricture: A clinical analysis of 58 cases with observations on 154 Frei-positive cases of lymphogranuloma inguinale. *Am J Surg* 1936; 31: 111.)

tags are composed of dilated lymph vessels with perilymphatic inflammation.^{16,24}

The clinical and histologic picture of early LGV proctocolitis is very similar to that seen in inflammatory bowel disease,^{61,62} and there has been considerable debate in the medical literature concerning a possible etiologic role for LGV in regional ileitis (Crohn's disease) and ulcerative colitis.⁶³ Schuller et al.⁶⁴ demonstrated specific LGV antibody in the sera of 38 of 55 patients with Crohn's disease, but subsequent studies showed no serologic evidence of *Chlamydia* infection in either Crohn's disease or ulcerative colitis.^{65–67}

Several groups have isolated non-LGV *C. trachomatis* serovars from male homosexuals with proctocolitis.^{9,56,57} The sigmoidoscopic and biopsy findings in these patients differ from those found in LGV infections; the inflammatory process is not as intense or as invasive as that caused by LGV serovars, and hypertrophic mucosal “follicles” predominate. Infection of the rectum with non-LGV strains generally

produces a far milder illness than does LGV, with lack of progression to suppurative sequelae or fibrosis.

The rectal stricture of LGV may resemble that caused by trauma, actinomycosis, tuberculosis, schistosomiasis, and malignancy.^{22,38,58} It is most frequently mistaken for rectal cancer, and a biopsy should be taken to exclude this diagnosis. The incidence of rectal cancer in patients with LGV rectal stricture has ranged from 2%⁶⁸ to 5%.⁶⁹

■ ESTHIOMENE

Esthiomene (Greek, “eating away”), a primary infection affecting the lymphatics of the scrotum, penis, or vulva, may cause chronic progressive lymphangitis, chronic edema, and sclerosing fibrosis of the subcutaneous tissues of these structures.^{24,50} This results in induration and enlargement of the affected parts and, ultimately, in ulceration. In the earliest stages, the ulceration is superficial, but it gradually becomes more invasive and destructive. The vast majority of patients with esthiomene are women, and many authorities prefer to restrict the use of the term to this sex.

Chronic ulcerations are extremely painful. In women, they are most common on the external surface of the labia majora, on the genitocrural folds, and on the lateral regions of the perineum³⁸ (Figs. 33-4 and 33-5). The edema may extend from the clitoris to the anus and interfere with normal function. Urethral and vaginal^{16,24,50} stenoses and fistula formation have been reported.

OTHER MANIFESTATIONS

There is a tendency for women to develop papillary growths on the mucosa of the urethral meatus; these growths cause dysuria, frequency, and urinary incontinence with some perimeatal ulceration.⁵⁰ Penile, scrotal, or perineal sinuses may develop with or without urethral stenosis.^{18,50} Coutts³⁸ refers to this symptom complex as the *urethro-genitoperineal syndrome*.

Penoscrotal elephantiasis appears from 1 to 20 years after infection.³⁸ It may affect only the prepuce, the prepuce and the



FIGURE 33-4. Esthiomene of late lymphogranuloma venereum in a woman.



FIGURE 33-5. Elephantiasis of the labia and clitoris in a woman with late lymphogranuloma venereum. (Courtesy of M.I. Unit, Ibadan University, Nigeria.)

penis, the scrotum alone, or all the male external genitalia. The genital tissue is indurated and often deformed. The scrotum may reach monstrous size, but this is unusual.²⁴ Other conditions such as filariasis and mycosis must be considered in differential diagnosis.

Follicular conjunctivitis, often accompanied by lymphadenitis of the maxillary and posterior auricular nodes,¹⁶ can occur at any stage of LGV. The conjunctiva is infected by autoinoculation of infectious genital discharge. This condition may be analogous to Parinaud's oculoglandular syndrome.³⁸

Primary LGV lesions of the mouth and pharynx can occur as the result of fellatio or cunnilingus. This results in lymphadenitis of the submaxillary or cervical lymph nodes.²⁶ Cases of supraclavicular lymphadenitis with mediastinal lymphadenopathy and pericarditis have also been reported.^{70,71} Coutts⁴⁷ has recovered LGV from the gallbladder wall (in cases of chronic cholecystitis) and from fibrous perihepatic (in cases of Fitz-Hugh-Curtis syndrome), abdominal, and pelvic adhesions.

Erythema nodosum and other skin manifestations occur in about 10% of LGV cases during the early stages of infection.¹⁰ Their appearance may be precipitated by surgical

manipulation of infected lymph nodes.¹⁶ The malnutrition associated with rectal stricture was a frequent cause of pella-gra in the preantibiotic era.²⁴

DIAGNOSIS

Mild leukocytosis with an increase in monocytes and eosinophils frequently accompanies early bubonic and anogenitoretal LGV.^{20,22,25} A more significant polymorphonuclear leukocytosis is found routinely in patients whose LGV buboes are superinfected with pyogenic bacteria.¹⁶ The only other clinical laboratory abnormality found with regularity is an elevated gamma globulin concentration due to an increase of IgA, IgG, and IgM immunoglobulins.¹⁷

The diagnosis of LGV is usually based on (1) a positive Frei skin test, (2) a positive complement-fixation (CF) or other serologic test for LGV, (3) isolation of LGV *Chlamydia* from infected tissue and secretions in mice, embryonated eggs, or tissue culture, (4) histologic identification of *Chlamydia* in infected tissue, or (5) demonstration of *Chlamydia* by polymerase chain reaction (PCR) or other nucleic acid amplification test (NAAT) in infected secretions or tissues.^{72,73,74} Although histopathologic changes in LGV are not unique, they are sufficiently distinct to differentiate LGV buboes, bubonuli, and rectal strictures from similar lesions caused by other sexually transmitted agents.^{24,31,75}

■ FREI TEST

While the Frei test is no longer produced commercially or used widely, it is of historical interest given its very important role in many early studies of LGV. The original Frei test antigen used pus obtained from unruptured buboes, diluted in saline, and sterilized by heating.¹¹ Not only was the risk of bacterial or viral contamination of this antigen considerable, but it could easily be inactivated by overheating, and standardization of its potency was impossible.⁷⁶ Nevertheless, a positive test in a patient with clinical findings compatible with LGV generally indicated present or past infection. The successful culture of LGV in large amounts in the yolk sacs of chick embryos led to the commercial manufacture of a standardized skin test antigen (Lygranum) in 1940.⁷⁷ The test consisted of intradermal injections of 0.1 mL Lygranum into the skin of one forearm and a similar volume of control yolk sac material into the other forearm. The test was read at 48 hours, and a positive result was the development of a papule at least 6 × 6 mm in the principal diameter, provided the papule produced by the control was 5 × 5 mm or smaller. The same antigen was also used in complement-fixation serodiagnostic tests for LGV⁷⁸ after Melczer and Sipos⁷⁹ demonstrated the complement-fixing property of LGV in 1937.

The Frei skin test usually becomes positive after the appearance of buboes 2–8 weeks after infection.^{10,16,80} In the older

literature it was said that the Frei test was positive in about 95% of patients with bubonic LGV and in about 90% of those with ulcerative genital elephantiasis.⁶ The lack of sensitivity in the early stages of LGV is a distinct disadvantage.⁴⁶

Since the Frei antigen is common to all *Chlamydia*, the specificity of a positive reaction has limited its diagnostic usefulness, particularly in the past two decades, when the prevalence of other chlamydial infections has risen considerably.¹⁵ The Frei test usually remains positive for several years and possibly for life despite treatment.^{80,81} Commercial manufacture of Frei antigen was discontinued in 1974.

■ COMPLEMENT-FIXATION SEROLOGIC TEST

CF antibody test is more sensitive and turns positive earlier than the Frei test.^{16,38,43} There is no correlation between the CF antibody titer and the intensity of the Frei reaction,^{16,82} although in a given patient there is often close agreement between the two.⁸⁰ Like the Frei test, the CF test may result in cross-reactions in infections caused by other chlamydial infections, and the antibody may persist in high or low titer for many years.^{80,83} In general, active LGV infections have CF titers of 1:64 or greater,^{28,80,82–84} but high CF titers are occasionally found in asymptomatic patients and those with other chlamydial infections. Titers below 1:64 in a patient suspected of LGV on clinical grounds should be interpreted with caution.

Although a rise in CF titer of two or more dilutions may occur in early LGV,⁸² most patients with documented LGV initially have high CF titers that show little difference between serum specimens obtained during acute infection and at 6 weeks into convalescence.^{46,82} Variations in CF titer can also be caused by changes in both the concentration of test antigen and the test procedure.

■ MICROIMMUNOFLUORESCENT (MICRO-IF) ANTIBODY TEST

The micro-IF test is considerably more sensitive and specific than the CF test^{34,85,86}; although the micro-IF antibody reacts broadly with other *C. trachomatis* strains,⁸⁵ it is usually possible to demonstrate the antigenic type of the infecting strain by its pattern of reactivity in the assay.^{9,17,34} In LGV, acute-phase serum usually contains very high titers of micro-IF antibody.^{9,17,56} The major disadvantage of the micro-IF test is that it is technically very demanding and is hence used primarily in a few specialized research laboratories. It is not routinely available commercially.

■ ISOLATION OF LGV

Chlamydia can be isolated from infected tissue or secretions by inoculation of mouse brain, yolk sac, or tissue

culture.^{15,16,87,88} The recovery rate depends on the method used and the source of the inoculum. Bubo pus is the most practical clinical material to obtain and inoculate.²⁸ Wall et al.⁸² compared the recovery rate from bubo biopsy or pus in mice and yolk sac; *Chlamydia* were cultured from 85% of patients, with a higher recovery rate in mice (98%) than in yolk sac (78%). Other studies report much lower recovery rates.^{46,89}

For the past 25 years, HeLa-229⁹⁰ and McCoy¹ tissue-culture cell lines have been used to isolate LGV *Chlamydia*. The reported recovery rate from buboes, genital tissue, or rectal tissue ranges from 24% to 30%,^{17,34,46} which is lower than that reported for nongonococcal urethritis.^{15,88}

■ CYTOLOGY

The elementary and inclusion bodies of *Chlamydia* can be visualized both outside and inside cells in secretions and infected tissues by using Giemsa, iodine, and fluorescent antibody staining methods.^{38,88,91} Cytology has not been very successful for the diagnosis of LGV³¹ often because of the frequent contamination of specimens by bacteria and other artifacts.

■ NUCLEIC ACID AMPLIFICATION TESTS

PCR technology was the first NAAT used to detect “signature” *C. trachomatis* nucleic acid specific for the organism in cases of urethritis, cervicitis, salpingitis, and other syndromes caused by this agent.

A prospective study of an epidemic of LGV in the Bahamas in 1990⁹² involving 47 consecutive patients with genital ulcers seen at an STD clinic in Nassau demonstrated the advantage of the PCR test for diagnosis of LGV in an area where other causes of genital ulcers and lymphadenopathy, including HIV, are common. For non-LGV chlamydial infections, several different types of NAAT tests have been shown to be more sensitive and specific than chlamydial culture when used on urethral, cervical, vaginal, and urine specimens (see Chapter 31). More limited data indicate that NAAT tests can also be used on rectal swab specimens for testing *Chlamydia* although none of the assays have been FDA approved for this indication. As currently configured, the NAAT assays do not differentiate LGV and non-LGV chlamydia.

OTHER DIAGNOSTIC PROCEDURES

Various radiologic procedures have been used in LGV. Lymphography demonstrates the extent of lymph node involvement but does not outline buboes or reveal specific changes.⁹³ Rectal strictures caused by LGV are said to be characteristic when seen on barium enema and quite different from cancer: The LGV stricture is elongated, in contradistinction to the stricture produced by cancer; it produces little alteration in the mucosal pattern of the bowel; and it has a

tendency to form fistulas that tend to reenter the lumen of the rectum.^{94,95}

TREATMENT

A number of different drugs have been used to treat LGV, but few regimens have been studied in controlled clinical trials. A major problem in evaluating a given drug is the relative lack of criteria by which efficacy can be measured.⁹⁶ The natural history of LGV is highly variable and spontaneous remission is common.^{44,49}

Sulfonamides were the first drugs to show efficacy in LGV by promoting reduction in the size of buboes and healing of fistulas.^{14,75,97} However, lesions were not sterilized despite many months of therapy,¹⁴ and CF titers often showed little or no change.⁹⁸ In experimentally infected mice, 20% remained infected with LGV despite the most extensive sulfonamide therapy.⁹⁷

Penicillin and streptomycin were also found to be ineffective, although penicillin has some activity against *Chlamydia* in vitro.⁹⁷ The next antibiotics used were the tetracyclines, which proved to be quite effective in the management of the primary and secondary stages of LGV.^{49,83,99} Similar effectiveness was found with chloramphenicol,⁹⁶ erythromycin,¹⁰⁰ minocycline,¹⁹ and rifampin.¹⁰¹ The regimens currently recommended by the Centers for Disease Control are doxycycline 100 mg twice a day for 21 days or erythromycin 500 mg four times a day for 21 days. Some experts recommend 1 g of azithromycin once weekly for 3 weeks, but this has been little studied.

■ BUBONIC LGV

Greaves et al.⁴⁹ attempted the only comparative treatment study of bubonic LGV. The relative effectiveness of oral chlortetracycline, oxytetracycline, chloramphenicol, or sulfadiazine was compared with patients treated symptomatically with aspirin. The tetracyclines and chloramphenicol were given in a dosage of 500 mg qid for 14 days following a loading dose of 1 gm. Sulfadiazine was given in a dose of 2 gm initially, followed by 4 gm daily in divided doses for 10–28 days. The relative effectiveness of each drug was measured by the duration of inguinal adenopathy and the occurrence of bubonic relapse, sinus formation, or skin lesions after completion of therapy. Unfortunately, the average number of patients treated with each drug was 6.5, which limits the statistical validity of the results.

The duration of the bubo after treatment was same in all drug-treated groups and was not significantly shorter compared with the duration of the bubo in those given symptomatic therapy. Although specific chemotherapy had only a minimal effect in shortening the duration of the bubonic lesion (31 vs. 69 days), there was a more frequent occurrence of complications among the symptomatically treated control group. There was a marked reduction in CF antibody titer in

drug-treated patients which suggests that the amount of LGV present in infected tissues was reduced, if not eliminated. Other workers have shown that lymph nodes that were proved to be infective before tetracycline were found to be negative after therapy.¹⁰²

Minocycline, in a loading oral dose of 300 mg followed by 200 mg bid for 10 days, has been used with success to treat acute bubonic LGV and a limited number of cases of proctitis.¹⁹ Only limited information is available on treatment of LGV with erythromycin.¹⁰⁰

Although oral azithromycin in a 1-gm oral dose has been proven effective for treatment of chlamydial urethritis and cervicitis, its effectiveness in treating LGV is not known. Whereas it may prove to be effective for treatment of LGV in shorter courses, such short-course therapy should not be used until further supporting evidence is available.

Fever abates and patients usually experience prompt relief of bubo pain and tenderness and feel much improved 1–2 days after starting antibiotics.^{17,20} The bubo seldom suppurates after therapy begins, but fluctuant buboes may require frequent needle-and-syringe aspiration to prevent rupture.¹⁷

■ ANOGENITORECTAL LGV

Banov⁵³ reported the immediate and long-term effects of chlortetracycline, oxytetracycline, chloramphenicol, and erythromycin in cases of rectal stricture. Criteria used to compare the different drugs were subjective, the patients were not randomly assigned treatments, and the dosage schedules were variable. With the exception of erythromycin (only three cases studied), all drugs were effective. Apparently these drugs reduced the inflammatory edema of the rectal stricture but had no effect on scar tissue. In contrast to bubonic LGV, antibiotics had no immediate effect on the titer of CF antibody. No case of anal or rectovaginal fistula was cured by drugs alone.

The response of proctocolitis to antibiotics is usually dramatic. Symptoms are completely relieved and the rectal mucosa heals within a few weeks after treatment.^{22,56} However, occasional tetracycline treatment failures in proctocolitis have been reported.^{22,57}

SURGICAL TREATMENT

Surgical treatment of the acute inguinal syndrome should be limited to aspiration of fluctuant lymph nodes and occasional incision and drainage of abscesses.²² Before the advent of sulfonamides, surgical extirpation of buboes was recommended,^{22,25} although it was probably a prominent factor in the development of postoperative elephantiasis of the genitals by further blocking normal lymphatic drainage.³⁹ Under antibiotic coverage there is little risk that incision or aspiration of fluctuant buboes will lead to formation of sinuses.^{20,51}

Spontaneous resolution of a fibrous LGV rectal stricture never occurs, but the inflammatory process and the diameter of the stricture may be improved dramatically by antibiotic treatment.^{22,53} Dilatation of the stricture using elastic bougies under direct vision may be necessary but poses a significant risk of bowel perforation. It should be limited to soft, short strictures not extending above the peritoneal reflection and should be abandoned if the stricture splits easily or if bleeding occurs.²²

A variety of different surgical procedures may be required for advanced rectal stricture. The indications for operation are bowel obstruction, persistent rectovaginal fistula, and gross destruction of the anal canal, anal sphincter, and perineum.²² Plastic operations on the vulva, penis, and scrotum may be required for esthiomene and genital elephantiasis.³⁸ None of these procedures should be attempted without antibiotic treatment, and if possible, antibiotics should be given for several months before the decision to perform surgery is made.¹⁰³

PREVENTION

Prevention of LGV in nonendemic areas is predicated on identification and treatment of sexual contacts of proved or suspected cases. These contacts should receive prophylactic antibiotic treatment if recently exposed to infection so as to prevent reinfection as well as to eliminate a potential reservoir. The increasing prevalence of anorectal LGV in male homosexuals in Western Europe and the United States should be kept in mind when a young male presents with symptoms of proctocolitis.

Control of LGV in endemic areas presents a formidable problem.

The use of condoms and other safe sexual practices as outlined in Chapters 93–95 are the main prevention avenues to pursue.

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P. Frederick Sparling

Neisseria gonorrhoeae (gonococci) is the etiologic agent of gonorrhea and its related clinical syndromes (urethritis, cervicitis, salpingitis, bacteremia, arthritis, and others). It is closely related to *Neisseria meningitidis* (meningococci), the etiologic agent of one form of bacterial meningitis, and relatively closely to *Neisseria lactamica*, an occasional human pathogen. The genus *Neisseria* includes a variety of other relatively or completely nonpathogenic organisms that are principally important because of their occasional diagnostic confusion with gonococci and meningococci.

This chapter is concerned principally with the microbiology, genetics, and pathogenicity of gonococci. Chapter 35 is concerned with the clinical syndromes caused by gonococci and their treatment in adults; infections in children are discussed in Chapter 83. A discussion of the syndrome of urethritis in men is discussed in Chapter 59, and gonococcal and other related syndromes of the lower and upper genital tracts in women are discussed in Chapters 55 and 56.

HISTORY

Gonorrhea is one of the oldest known diseases of humans. There have been many reviews of the history of this disease, one of the best of which is the monograph by R.S. Morton.¹ Gonorrhea undoubtedly was known to the authors of the Bible. The Book of Leviticus describes a person with urethral discharge. Proclamations that infected persons were to keep themselves from others for 7 days may indicate that they already knew that the mean incubation period was 7 days. Biblical authors cautioned about transmission to social contacts and also about women copulating with afflicted men.

Hippocrates wrote extensively of gonorrhea in the fourth and fifth centuries B.C. He called acute gonorrhea “strangury” and understood that it resulted from “the pleasures of Venus.” The Roman physician Celsus was well aware of gonorrhea and its complications, and was known to catheterize patients suffering from urethral stricture. In the second century, Galen coined the word *gonorrhea*, by which he meant “flow of

semen.” Other early Greco-Roman physicians prescribed various treatments for gonorrhea, including sexual abstinence and washing of the eyes of the newborn.

Knowledge of gonorrhea and other sexually transmitted diseases in Europe was scant until near the end of the Dark Ages. The term *clap*, which is still commonly used to refer to this disease, first appeared in print in 1378. The derivation of the word *clap* is unclear but possibly refers to the Les Clapier district of Paris in which prostitutes were housed in the Middle Ages. European writings of the late Middle Ages make it clear that the disease was associated with sexual intercourse.

After the arrival of syphilis in Europe in the late fifteenth century, considerable confusion existed regarding the relation between gonorrhea and syphilis. Great surgeons such as Ambroise Paré (sixteenth century) and John Hunter (eighteenth century) considered syphilis and gonorrhea to be different manifestations of a single disease. Hunter’s conclusions were the result of a famous experiment in which he inoculated himself with material from a patient with gonorrhea; he acquired syphilis as a result. Distinction between these diseases was first clearly achieved by Philippe Ricord, but real understanding was only achieved after Neisser’s description of *N. gonorrhoeae* in 1879 and Leistikow’s and Löffler’s cultivation of the organism in 1882.

The twentieth century brought new, safe, highly effective therapy for gonorrhea, replacing the sometimes horrific therapies used for centuries, including urethral astringents, soundings, and other mechanical devices. Sulfonamides were first introduced in 1936 and penicillin in 1943 for gonorrhea therapy. The second great development of the twentieth century concerned the revolution in our understanding of the pathogenic mechanisms of this fascinating organism, which started with the demonstration by Kellogg and his colleagues in 1963 that there are differences in virulence of gonococci with different colonial morphology.² These developments enable better understanding of how gonococci cause repeated infections in the same individual and may lead to development of an effective vaccine.

EPIDEMIOLOGY

■ TRANSMISSION

Humans are the only natural host for gonococci. Gonococci survive only a short time outside the human body. Although gonococci can be cultured from a dried environment such as a toilet seat up to 24 hours after being artificially inoculated in large numbers onto such a surface, there is virtually no evidence that natural transmission occurs from toilet seats or similar objects. Gonorrhoea is a classic example of an infection spread by contact: immediate physical contact with the mucosal surfaces of an infected person, usually a sexual partner, is required for transmission. (The single exception is the occasional epidemic among prepubescent females living together and sharing bath towels and similar objects.)

■ STRAIN TYPING

For epidemiologic studies, it is useful to differentiate one strain from another. Several techniques have been developed that can be used successfully for this purpose.

Auxotypes

A relatively cumbersome system for differentiating gonococcal strains based on their ability to grow on chemically defined media was developed that classified strains as to whether they could grow without certain amino acids, purines or pyrimidines, or other specific nutrients.³ A strain unable to grow on chemically defined media lacking proline was designated Pro⁻, and a strain unable to grow without arginine was Arg⁻. Naturally occurring gonococcal isolates exhibit remarkable diversity in their biosynthetic capacities, probably reflecting the biochemically rich environment of their human host, which provides the organisms with most of the compounds needed for growth. The auxotyping system was used successfully in a variety of epidemiologic studies.⁴ The Arg⁻ Hyx⁻ (hypoxanthine⁻) Ura⁻ (uracil⁻), or AHU⁻, auxotype typically was associated with multiple other properties, including resistance to killing by normal human serum; propensity for causing asymptomatic male urethral infection; increased likelihood for causing bacteremia; and others.⁵ The auxotyping technique is not widely used in clinical laboratories today.

Serotyping

Investigators tried to develop a practical serotyping scheme for decades. A useful and formerly widely available technique for this purpose was based on monoclonal antibodies specific for various epitopes on outer membrane protein I (P.I, or Por).⁶ Por occurs in two immunochemically distinct serogroups: P.I.A and P.I.B, each of which is an allelic form of the *porB* gene. By employing a set of monoclonal antibodies against P.I.A strains and another set against P.I.B strains, one

can subdivide each of the serogroups into a wide variety of serovars (e.g., P.I.A-6, P.I.B-1), differing in their ability to react with certain members of the panel of monoclonal antibodies. Many dozens of specific serovars have been defined by these techniques.^{4,6} By a combination of auxotyping and serotyping with anti-Por monoclonal antibodies, gonococci can be divided into over 70 different strains; the number may turn out to be much larger. The technique is now little used because of exhaustion of the supply of the crucial monoclonal antibodies. It has been replaced largely for research purposes by hybridization with sets of specific oligonucleotides for variable loops of the *porB* gene, or by DNA sequencing of *porB* ("porin genotyping"), which serves much the same purpose.^{7,8} The technique has been used to follow evolution of strains in communities over time⁹ and also to document mixed infection by different strains.⁸

Antimicrobial susceptibilities

Another method to strain type gonococci is based on antimicrobial susceptibilities. This may be employed as an adjunct to the *porB* genotyping scheme, but by itself it is of little use.

Genotyping

Although it is impractical to undertake full genomic sequencing, it is possible to use various tools of molecular biology to rapidly assess differences in DNA sequences. Several techniques have been tried, most of which are no longer considered useful. A technique termed Opa typing used *opa*-based PCR primers to generate DNA from each of the approximately 11 *opa* genes. These were then subjected to restriction enzyme digestion, and the resultant pattern of restriction fragment length polymorphisms (RFLP) was used to compare identities of strains.¹⁰ Used in conjunction with other strain-typing systems, Opa genotyping offered additional and powerful resolving power. The most sophisticated technique for research purposes compares the DNA sequence of a variety of housekeeping genes (multilocus sequence typing, or MLST), which are not thought to be subjected to evolutionary pressures by the immune response to infection.⁹ The same technique has proven very useful in studies of the epidemiology of meningococcal infection,¹¹ but it is only employed by large research groups. Pulsed field gel electrophoresis (PFGE) is another research tool for differentiation of strain differences.

BIOLOGY

■ COLONY MORPHOLOGY

Gonococci are gram-negative diplococci, nonmotile and non spore forming, which characteristically grow in pairs (diplococci) with adjacent sides flattened. In 1963, Kellogg showed that gonococci occur in multiple colony types when grown

on a clear agar medium and viewed with obliquely transmitted light.² Small convex glistening type 1 and type 2 colonies were easily distinguished from the larger, flatter type 3 and type 4 colonies. The small colonies are now known to be piliated and are designated P⁺; large colonies are nonpiliated (P⁻) (Fig. 34-1). Colony types are variable, and although fresh isolates from patients usually are P⁺, unselected transfer in vitro

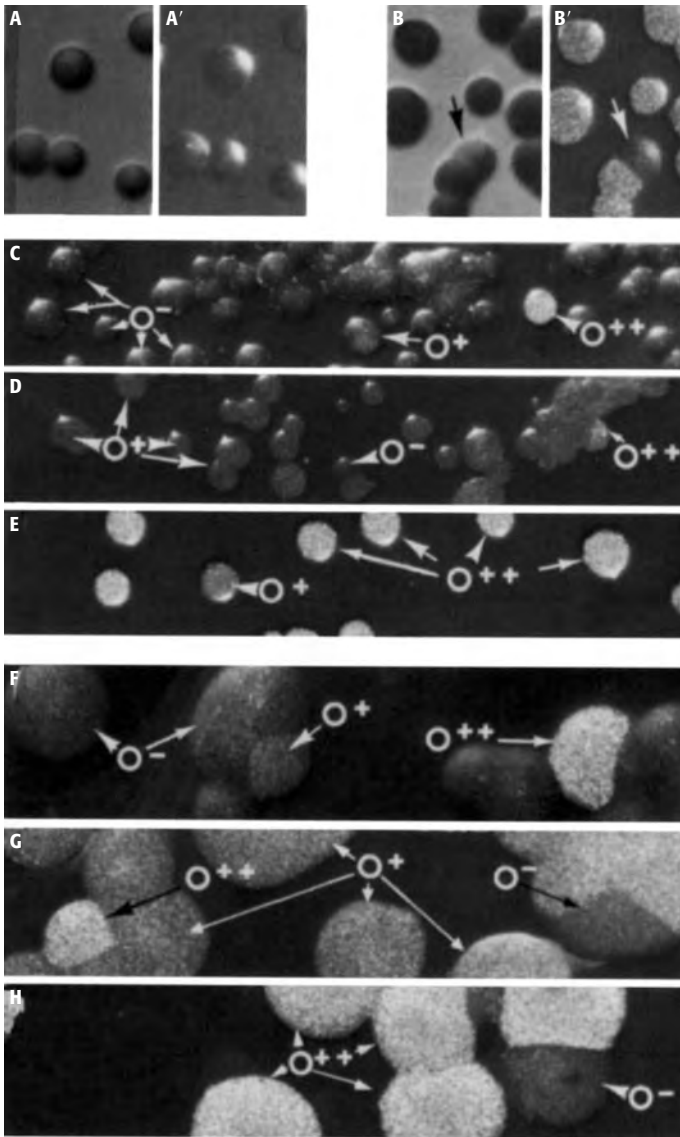


FIGURE 34-1. Gonococcal colonial morphologies. A variety of sizes and forms are present in gonococci cultivated on clear medium, in vitro. Small colonies with darkly rimmed borders (A–E) contain heavily piliated organisms, whereas large colonies (F–H) are constituted of nonpiliated gonococci. Colonies of both piliated and nonpiliated organisms display variation in their color and opacity characteristics. Use of a diffusing substage reflector allows visualization of colony color (A and B) and is depicted here for very light (A) and very dark (B) colonies. Use of a polished substage mirror allows differentiation of colonial opacity variants (A', B', C–H). Transparent colony (O⁻) populations are regularly “contaminated” by variants of intermediate (O⁺) or marked (O²⁺) colonial opacities (C). Similarly, O⁻ and O²⁺ colonies are found in O⁺ preparations (D), and colonies of lesser opacity (O⁻ or O⁺) appear in O²⁺ colony populations (E). These variants can also be found in otherwise homogeneous O⁻ (F), O⁺ (G), and O²⁺ (H) populations of nonpiliated gonococcal colonies. (Courtesy of J. Swanson and L. Mayer.)

usually results in conversion to P⁻.^{2,12} Some P⁻ colonies are capable of subsequent reversion to P⁺. Using human male prison volunteers as experimental subjects, Kellogg and his coworkers showed that after 69 in vitro passages, P⁺ “type 1” colonies retained virulence but the P⁻ “type 4” colonies did not.²

A second type of morphologically visible colonial variation concerns relative opacity of the colonies when viewed through a low-power microscope on clear media in appropriate lighting.^{13,14} Opaque (Op) colonies are darker and more granular than transparent (Tr) colonies (see Fig. 34-1). The Op and Tr colony types undergo rapid reversible variations in vitro. The biochemical basis of the opaque–transparent colony variation is owing to variation in expression of a family of outer membrane proteins formerly designated protein II (P.II) but now designated Opa; Op colonies contain cells expressing Opa, whereas most transparent colonies contain cells that are not expressing Opa.¹⁵

MEMBRANE STRUCTURE

When gonococci are viewed in cross section by transmission electron microscopy (TEM), they are seen to have a typical gram-negative outer membrane overlying a relatively thin peptidoglycan layer and cytoplasmic membrane. Meningococci contain a true polysaccharide capsule that is important to virulence, whereas gonococci lack such a structure. Frequently small blebs of outer membrane may be seen in TEM. Unlike *Escherichia coli* and many other enteric bacteria, gonococci are prone to release fragments of membrane into their surrounding environment; this may deliver toxic membrane components to distant sites and antigenic fragments that bind host antibodies.

Pili

The most important parts of the gonococcus from the pathogenic point of view concern surface molecules that are involved in attachment to, or invasion or injury of, the host or that serve as targets for host immune defenses. Among the best-studied surface molecules are pili. Viewed by electron microscopy, pili are arranged in individual fibrils or fibrillar aggregates and cover virtually the entire outer cell surface of the organism (Fig. 34-2). Fibrillar pili actually are polymers composed of perhaps thousands of a subunit of about 18 kDa. A great deal is now known about the structure of the pilin subunit, as assessed by x-ray crystallography.¹⁶ Pili are known to increase adhesion to host tissues.¹⁷ The cell receptor for binding pili is under intense study and subject to some dispute; it may involve the CD46 molecule.^{18,19}

Antigenic and phase variation

Pili undergo two types of variations at relatively high frequency: antigenic variation, in which strains shift the

antigenic type of their pilus; and phase variation, in which strains switch between P^+ and P^- states. Immune sera raised in animals against a single purified pilus react relatively weakly with pili prepared from unrelated clinical isolates.²⁰ The pilus expressed by a single gonococcal strain is known to be able to undergo extensive antigenic variation, either during passage on agar plates, during growth in subcutaneous chambers implanted into experimental animals, or during natural infection of

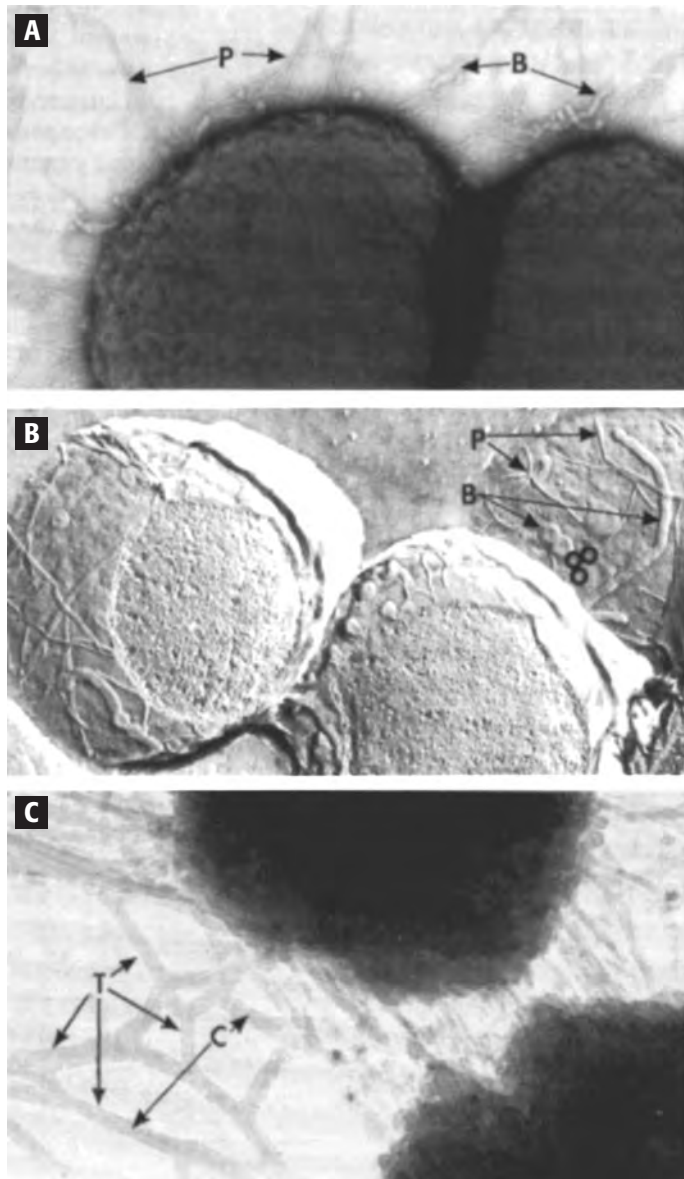


FIGURE 34-2. Electron microscopic appearances of gonococcal surface constituents. Different methods of preparing gonococci for electron microscopic examination yield strikingly different views of these organisms' surface constituents. In negatively stained preparations (A), pili (P) appear as thin (approx 8 nm) structures that are clearly differentiated from evaginated blebs (B) of the outer membrane. These blebs occur as elongated, sausage-like forms or as small vesicles. The actual surfaces of gonococci have a rugose appearance that is poorly resolved in this micrograph. After freeze-fracture freeze-etching (B), both pili (P) and outer membrane blebs (B) are seen lying against the organisms' surfaces. The "pebbled" appearance of the gonococcal surface is punctuated by pits (examples encircled). (Courtesy of J. Swanson and L. Mayer.)

humans.²¹⁻²³ The genetics of pilin variation, and the DNA sequence of expressed pili in several strains are well established.²³⁻²⁶ There is a common N-terminal region and several variable domains in the midportion or carboxy terminus of the protein (Fig. 34-3). Several relatively invariant or common regions are scattered amid the variable domains, including two cysteines at amino acids 121 and 151 that form a disulfide bridge. The amino terminus is nearly identical in all type 4 pilus expressing bacteria, including gonococci, meningococci, and several other organisms including *Bacteroides nodosus*, *Moraxella bovis*, and *Pseudomonas aeruginosa*.

Molecular mechanisms

The mechanisms of pilus phase (P^+) \leftrightarrow (P^-) and antigenic (P^+_{α}) (P^+_{β}) variation have been studied extensively. There are one or sometimes two complete pilin genes on the chromosome.²⁵⁻³⁰ The intact gene "expression site" contains an intact promoter region and ribosome-binding site and encodes an unusual short 7 amino acid signal sequence and the 159–160 amino acids of the mature pilin subunit. There are six to eight "silent" regions scattered at various locales around the chromosome. Each silent locus contains various amounts of pilin sequences, but lacks a promoter region, and the 5' end of the pilin structural gene. In some of these silent sites, there are many different copies of incomplete pilin gene sequences arranged in a head-to-tail tandem repeat order, and many of these variant copies of pilin sequences are slightly different from each other. Nonreciprocal recombination events may move one of these silent variant copies of pilin sequence into the expression site, resulting in expression of an antigenically variant but fully functional pilus (antigenic variation). On occasion, the variant copy of silent pilin DNA encodes a faulty peptide that when expressed results in a pilin that cannot be processed, assembled, secreted ("long pilin"), or anchored ("small" or secreted pilin) into a mature pilus, and the cell becomes P^- as a result.²⁸ Reversion back to a P^+ state in these instances occurs when a functional pilin sequence is moved from another variant silent copy into the expression site, replacing the faulty pilin sequences (phase variation) (Fig. 34-4).

Movements of pilin sequences between the silent and the expression sites are mediated by the homologous sequences

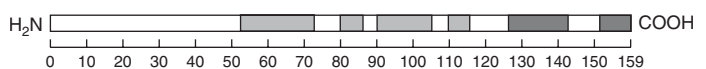


FIGURE 34-3. Schematic diagram of variability of pilin structure as revealed by DNA sequencing of expressed *pil* genes in multiple clinical isolates of a single epidemic strain. In the semivariability regions (hatched), single amino acid substitutions were found. In the hypervariability regions (black), there frequently were insertions or deletions of one to several amino acids. White areas are constant regions. Results are typical of those found in vitro in three laboratory strains. Numbers refer to amino acid residues of mature pilins. (From Sparling PF, et al. *J Infect Dis* 1986; 153: 196).

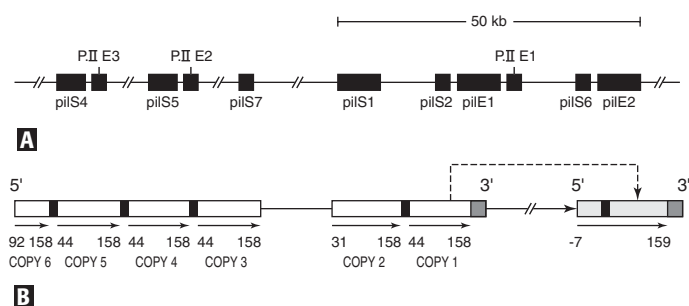


FIGURE 34-4. Molecular basis of pilus variations. In **(A)** the approximate chromosomal organization of known loci for pilin (*pil*) or opacity proteins (*opa*, or P.II) is shown. In strain MS11, there are two complete (“expression”) *pil* genes (*pilE1*, *pilE2*) and multiple incomplete (“silent”) loci (e.g., *pilS1*) containing copies of the 3′ end of *pil* genes. In some instances, *opa* (P.II) genes are adjacent to *pil* loci (e.g., P.II E1), each encoding a complete Opa protein. In **(B)** is shown the organization of one silent locus (*pilS1*), which contains six slightly variant copies of the 3′ end of *pil* genes. Numbers below the bars indicate pilin amino acids encoded by the DNA. Solid bars or striped areas indicate constant regions in or around the *pil* genes; other constant DNA regions are omitted for simplicity. The dotted line and arrow refer to movement by recombination of DNA from one silent copy into an expression locus (*pilE1*), which is facilitated by homology between the constant regions. This may result in phase or antigenic variation, as described in the text. (Adapted principally from data of Haas R, Meyer TF. *Cell* 1986; 44: 107.)

that flank or are located at intervals within the pilin DNA at the silent and the expression sites and depend on a functional recombination system.³¹ Occasionally a recombinational event results in deletion of the entirety of the 5′ and upstream regions of the structural gene in the expression site.³² When this happens, the organism becomes permanently nonpiliated since the necessary information to restore the pilus expression site is not contained within any of the silent copies.

Existence of three promoters for each pilin structural gene (*pilE*) suggests complex mechanisms for transcriptional control of pilus expression.³³ Indeed a *pilA pilB* sensor regulator system has been described that either induces or represses expression of *pilE*; it is not yet known which environmental factors affect the activity of this system.³⁴ An additional factor (integration host factor, or IHF) was described that also affects transcription of *pilE*.³⁵ Presumably, these complex systems serve to provide fine control of the amount of expressed pili, although the biological advantage of such controls is unclear.

Pilus-associated proteins

A very active area of research concerns the structure and function of a number of pilus-associated proteins.³⁶ One of them, designated PilQ, is a major outer membrane protein composed of 12 subunits, through which the assembled pilus fibril passes from inside to outside the bacterial outer membrane; it is thus a member of the secretin class of proteins.^{37,38} Recent evidence shows that PilQ also is a porin, through which antibiotics, transforming DNA, and heme pass under certain conditions.^{37,38} PilC is a hydrophobic outer membrane protein that is the

product of two genes (*pilC1* and *pilC2*), each of which produces slightly different forms of the protein. In the presence of a fully assembled pilus fibril, PilC apparently is bound to the pilus, and may be the adhesin that binds gonococci to the host cell.^{39,40} PilT is a minor protein that serves to retract the assembled pilus, thereby giving the cells their characteristic twitching motility,⁴¹ and serving to pull gonococci closer to the host cells to which they are rather loosely attached by the initial contact by pili. This in turn triggers several changes in the host cell, and promotes host cell survival.⁴² Other minor pilus associated proteins are involved in assembly and expression of pili.

Porin protein (Por)

When outer membrane proteins are examined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), the most prominent protein is a 34–36-kDa protein formerly designated P.I but now designated Por. Por is exposed on the surface of the outer membrane and in its native state in the membrane is a trimer.⁴³ It is physically proximate to the lipooligosaccharide (LOS) and also to reduction modifiable protein (Rmp).^{44,45} Por fulfills many functions for the gonococcus, including forming an anion-specific channel through the lipid-rich outer membrane.^{46,47} Por exists in two major chemically and immunologically distinct classes designated P1.A and P1.B; a given strain produces one or the other, but never both. They are the product of the *porB* gene; a separate *porA* gene which is expressed in meningococci is a pseudogene (mutant, not expressed) in gonococci.

The DNA sequence of multiple *porB* genes has been determined.^{48,49} The amino acid sequence and predicted structure is similar to that of porin proteins in other gram-negative bacteria. Comparison of the sequence of P1.A and P1.B proteins reveals certain regions that are common to both proteins and others where there is considerable variation.⁵⁰ The regions of variability represent areas of antigenic diversity. The P1.A and P1.B proteins are products of allelic variants of a single *porB* locus.⁵⁰

Opacity proteins

The opacity-associated protein family designated Opa (formerly protein II, or P.II) comprises a family of closely related proteins involved in cell adhesion that share the property of heat modifiability.^{13–15} These proteins vary in size from about 24 to about 28 kDa and when heated to 100°C take on a different conformation and exhibit a higher apparent molecular mass in SDS-PAGE. A given strain has the capacity to produce at least 10 different variants of the Opa family, as judged by sizes and antigenic properties of the expressed Opa proteins.⁵¹ A strain may express none of these or up to four or five different members of the Opa family simultaneously.⁵¹ The Opa family undergoes both phase variations ($Opa^+ \leftrightarrow Opa^-$) and antigenic variation ($OpaA \rightarrow OpaB \rightarrow OpaC \rightarrow \dots$), analogous to pilus variations.

Some Opa proteins promote adherence of cells in a colony and also promote adhesion of gonococci to neutrophils and epithelial cells.^{52,53} Most Opa proteins result in increased colony opacity, whereas all Opa⁻ clones are transparent. The very high frequencies in variation of Opa proteins can easily be seen by examining colony morphologies under appropriate lighting; many colonies exhibit sectors varying in opacity, which reflects the variability in expression of Opa (see Fig. 34-1).

Mechanisms of Opa variations

The genetic basis for phase and antigenic variation of the Opa family is now quite well understood and is different from that used to control the expression of pilus proteins. When Southern hybridizations are performed with the cloned *opa* gene, up to 12 *opa*-related restriction fragments of chromosomal DNA are visualized, indicating that there is a family of *opa* genes in the chromosome.⁵⁴⁻⁵⁷ Each of the *opa* genes is a complete gene with its own promoter, and each is transcribed into RNA at all times.^{55,56} Variation in expression of these genes is achieved by varying the number of an identical pentameric (CTCTT) repeat unit located immediately downstream from the ATG start codon, within the DNA that encodes the hydrophobic signal sequence, and upstream from the sequences coding for the mature structural protein.⁵⁵⁻⁵⁷ When the number of these repeat units is evenly divisible by three (e.g., 9, 12, 15, ...), the gene is translationally in-frame and an Opa protein is expressed. Any other number of the pentameric repeat (e.g., 8, 10, 11, 13, 14, ...) results in transcription of a gene that is translationally out-of-frame, and no Opa is expressed. The number of the pentameric repeat undergoes high-frequency variation, and this results in regulation of expression at the level of translation. Each *opa* gene contains two hypervariable domains, which may recombine with similar domains in other *opa* loci. Thus variable expression of *opa* genes results in antigenic variation, because of differences in structures encoded by different *opa* genes.

Reduction modifiable protein

All pathogenic *Neisseria*, including all gonococci, contain an antigenically conserved Rmp protein (formerly designated Protein III, or P.III) of about 30–31 kDa that is characterized by its altered apparent molecular mass on SDS-PAGE under reducing conditions. The structural gene *rmp* was cloned and sequenced.⁵⁸ This protein is of interest in pathogenesis because many blocking antibodies that prevent serum bactericidal activity are directed against this antigen, as discussed in the following.

H.8 Proteins

A monoclonal antibody (MAb) designated H.8 reacts with a conserved antigen found on all gonococci and meningococci, and on *N. lactamica* and *Neisseria cinerea*, but not on other

nonpathogenic *Neisseria*.⁵⁹ In gonococci and meningococci, there are at least two proteins containing an H.8 MAb-binding epitope. One is a lipoprotein containing five imperfect repeats of the peptide AlaAla-Glu-Ala-Pro (AAEAP) at the N-terminal region and an azurinlike sequence at the C-terminal region.^{60,61} The azurins are copper-containing proteins that may be involved in electron transport. The second H.8 MAb-binding protein does not have azurin-related sequences and is made up primarily of 13 repeats of the AAEAP peptide. The azurin protein Laz is involved in defense against oxidative stress and copper toxicity.⁶²

Iron- or oxygen-repressible proteins

Although all of the proteins discussed in the preceding with the possible exception of pili are expressed under all growth conditions, a variety of other proteins are expressed only under certain conditions, including iron starvation, anaerobic growth, or other limited-growth situations.⁶³⁻⁶⁶ The iron-repressible proteins (Irpcs) include a 37-kDa protein and several in the approximate range of 65 to over 100 kDa.^{63,64,67} The 37-kDa protein is designated ferric-binding protein (Fbp) because it contains iron and is involved in iron transport.⁶⁸ Virtually all gonococci and meningococci express an antigenically conserved Fbp.⁶⁹ A 70-kDa protein formerly designated FrpB on the outer membrane also is common to virtually all gonococci and meningococci. It has been renamed FetA in recognition of its function in low-affinity binding of the phenolate siderophore ferric enterochelin.⁷⁰ Gonococci do not produce siderophores, and the precise role of FetA in gonococcal physiology is unclear. Many of the other Irpcs are receptors for iron ligands, either for transferrin (Tf), lactoferrin (Lf), or hemoglobin (Hb).⁷¹⁻⁷³ These receptors bind ligand (either Tf, Lf, or Hb) with great specificity, and binding is required before iron is stripped from the ligand and transported into the cell. Unlike FetA, which is composed of a single integral outer membrane protein, the Tf, Lf, and Hb receptors are composed of a loosely surface-tethered lipoprotein and an integral membrane protein that appear to work together; the function of all of the iron-ligand receptors is dependent on transmission of energy to the outer membrane receptor by the inner membrane protein TonB.⁷⁴

Virtually all gonococci produce a functional Tf and Hb receptor, although about half of gonococci do not produce a functional LF receptor.⁷² The Hb receptor undergoes phase variation in expression (either translationally “on” or “off”) by means of slipped-strand mispairing of a short DNA repeat within the *hpuA* gene, analogous in mechanism to that employed by Opa proteins in their phase variation.⁷⁵ Women are more likely to express a Hb receptor in the expressed “on” phase in the first 2 weeks of the menstrual cycle, as compared to the latter half of the cycle or to isolates from men, suggesting that availability of Hb in the form of menstrual blood is a

selective advantage to gonococci in vivo.⁷⁶ Studies in male human volunteers established that either of the Tf or Lf receptors is essential for experimental infection of the anterior urethra^{77,78}; presence of both the Lf and Tf receptors imparts a selective advantage in the male urethra.⁷⁸ Thus both the Tf and Lf receptors appear to be functionally important to mucosal infection. It is unclear what advantage is imparted by loss of the Lf receptor; there appears to be some advantage to loss of the Lf receptor under certain circumstances, since there is evidence of horizontal transmission of a unique deletion of the *lbpAB* genes among clinically isolated gonococci.⁷⁸

*Iga*₁ proteases

All gonococci and meningococci but not other nonpathogenic *Neisseria* produce a protease that recognizes both serum and secretory IgA₁ (but not IgA₂) as a substrate.⁷⁹ There are two genetically and biochemically distinct variants of the gonococcal IgA₁ protease, and there is a correlation between auxotype, Por serogroup, and the class of IgA₁ protease expressed by the strain.⁸⁰ Each of the IgA₁ proteases cleaves IgA₁ at the hinge region, resulting in release of Fab and Fc fragments.⁷⁹ Since secretory IgA is the principal arm of antibody-mediated defenses at mucosal surfaces, the *Neisseria* IgA₁ protease presumably is important in inactivation of mucosal immune defenses. Surprisingly, loss of IgA₁ protease limits ability of gonococci to grow within epithelial cells, apparently because IgA₁ protease normally cleaves an intracellular protein (LAMP1) involved in phagosomal compartmentalization.⁸¹ Loss of IgA₁ protease does not reduce infectivity of gonococci for human volunteers (personal communications, J. Cannon, M. Cohen, et al.).

IgA₁ protease is synthesized as a precursor protein of about 169 kDa, and then is proteolytically cleaved twice to create a 45-kDa outer membrane protein and the mature 106-kDa IgA₁ protease molecule. The 45-kDa protein forms a channel through the membrane that allows export of the IgA₁ protease to the exterior.⁸²

Lipooligosaccharide

All gonococci express LOS on their cell surface, similar to the lipopolysaccharide (LPS) of other gram-negative bacteria. Gonococcal LOS contains a lipid A moiety and a core polysaccharide consisting of ketodeoxyoctanoic acid (KDO), heptose, glucose, galactose, and glucosamine, and/or galactosamine.⁸³ The two-dimensional structure of gonococcal LOS is now well established.⁸⁴ Unlike other gram-negative bacteria, gonococci do not express a long polymeric sugar attached to this core, and thus the gonococcal LOS is considerably smaller than typical LPS of other bacteria. By both chemical and immunologic criteria, there is intrastrain and interstrain variation in the nature of the core sugar antigens of LOS.^{83,85,86} A single strain may make up to six variants of

LOS, varying in apparent molecular mass from 3 to 7 kDa. Since the core sugars of LOS form antigens that are important in immune bactericidal reactions, phenotypic variation of these antigens may be pathogenically important.^{87,88} Gonococci with “short” LOS are serum sensitive but able to invade eukaryotic cells, whereas gonococci with “long” LOS are serum resistant but noninvasive.^{89–92} Many genes involved in LOS core sugar assembly undergo high-frequency phase variation by a mechanism similar to that involved in *opa* variations.⁹³ The terminal lacto-*N*-neotetraose (LNN_T) moiety on gonococcal LOS mimics the structure of certain human glycosphingolipids, which may help immune evasion.⁸³

Variation in LOS core sugar chain length has several important implications for pathogenesis. Gonococci vary in their ability to undergo sialylation of LOS (addition of host neuraminic acid to LOS by means of a bacterial sialyltransferase), because the site of sialylation is on a near-terminal LOS sugar that is variably expressed.^{89,94} “Short” LOS is unable to be sialylated, whereas full-length LOS is readily sialylated.^{90–92} Sialylated gonococci are at least partially protected (“masked”) from antibodies against both LOS and the closely neighboring Por molecule.⁹⁵

Other surface structures

Gonococcal peptidoglycan is similar to that of other gram-negative bacteria, containing a backbone of muramic acid and *N*-acetylglucosamine, but is rather unusual in the degree of its *O*-acetylation.⁹⁶ This may be relevant to the susceptibility of peptidoglycan fragments to biodegradation and to its inflammatory and other biological properties.⁹⁷

Gonococci do not express a true polysaccharide capsule despite several early reports to the contrary. Gonococci do produce a surface polyphosphate, however, that may serve some of the functions of a polysaccharide capsule, including provision of a hydrophilic and negatively charged cell surface.⁹⁸ Gonococci also bind charged polyanions including DNA to certain Opa proteins, which alters the surface charge of the cell and also the ability to be killed by normal human serum.⁹⁹ Gonococcal structures involved in pathogenesis are summarized in [Table 34-1](#) and shown in [Fig. 34-5](#).

■ METABOLISM

Gonococci have complex growth requirements.³ They utilize glucose, lactate, or pyruvate as sole sources of required carbon but cannot use other carbohydrates.³ This forms the basis for the carbohydrate utilization tests used for decades to speciate neisserial organisms. When grown in media supplemented with serum, they exhibit different outer membrane proteins and altered attachment to human neutrophils.¹⁰⁰ The factor that seems to stimulate these phenotypic variations is lactate.¹⁰¹ Human neutrophils release lactate as an end product of metabolism, with the result that gonococci growing in vivo

Table 34-1. Some Gonococcal Structures Involved in Pathogenesis

Structure (Abbreviation)	Function in Infection
Por	Insertion into host cell membranes Target for bactericidal, opsonic antibodies
Opa	Adherence
Rmp	Target for blocking antibodies
Pili	Adherence Resistance to neutrophils
Lipooligosaccharide	Tissue toxin Target for bactericidal, chemotactic antibodies
Peptidoglycan	Tissue toxin
Iron-repressible proteins	Iron uptake from transferrin, lactoferrin, hemoglobin
IgA ₁ protease	(?) Escape from mucosal IgA ₁

might encounter lactate as a principal carbon source.¹⁰¹ All gonococci (as well as other *Neisseria*) rapidly oxidize dimethyl- or tetramethyl-phenylenediamine, and this turns colonies pink and then black, forming the basis of the oxidase test.

Gonococci are capable of growth under anaerobic conditions if nitrite is provided as an electron acceptor.¹⁰² Their growth is stimulated by 5% gaseous CO₂ or if additional bicarbonate is added to liquid or solid growth media. They produce abundant catalase, which undoubtedly helps to promote growth in the presence of otherwise toxic peroxides, but unlike most aerobes they do not produce appreciable amounts of superoxide dismutase. It has been postulated that they grow in vivo under relatively anaerobic conditions,⁶⁵ although they ordinarily are grown in vitro under aerobic conditions.

Growth media

Gonococci do not tolerate drying and ordinarily must be plated onto appropriate media immediately on sampling patient secretions. As an alternative, gonococci may be put into one of several available transport media, in which they survive for up to 24 hours prior to being plated on definitive culture media. Growth is optimal at 35–37°C in a 5% CO₂ atmosphere, at a pH of about 6.5–7.5. When grown at relatively low pH (6.0–6.5), outer membrane composition is altered; below pH 6.0, no gonococci survive. (Vaginal secretions are

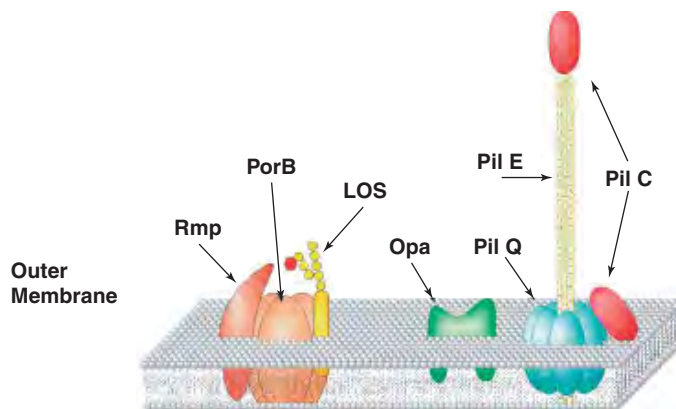


FIGURE 34-5. Illustration of gonococcal outer membrane depicting many of the antigens described in the text. Rmp, reduction modifiable protein; Por B, porin protein; LOS, lipooligosaccharide—the branched and phase variable LOS polysaccharide chain is depicted as being bound by sialic acid, designated by a red hexagon; Opa, opacity protein; PilQ, pilin accessory protein Q, a secretin through which the assembled pilus extrudes; PilE, pilin, the subunits which are assembled into the alpha helical pilus fibril; PilC, the outer membrane protein PilC, which is proposed to be presented by the pilus fibril as a tip adhesin. (Courtesy of C.E. Thomas.)

quite acidic, but gonococci grow in the endocervix, where the pH is neutral.) Although certain nonpathogenic *Neisseria* grow at room temperature, gonococci do not grow well below 30°C, and they do not survive above 40°C.

A complex growth medium is required. Ordinarily this is in the form of either chocolate agar or similar complex agar containing inorganic iron and supplemental glucose, vitamins, and cofactors. Many less fastidious microorganisms also found in the same ecological niches (pharynx, cervix, and rectum) grow more readily than gonococci, and relatively selective media have been devised that use antibiotics to inhibit growth of nonpathogenic *Neisseria*. Vancomycin, colistin, and nystatin were widely used for this purpose, but some gonococci are quite sensitive to the concentrations of vancomycin used in the selective media. Other formulations now have been developed in which vancomycin is replaced with lincomycin or other antibiotics.

GENETIC SYSTEMS

There are two principal systems for performing genetic analysis of gonococci: transformation and conjugation. There are no known bacteriophages for gonococci (or meningococci), and a drug-resistance transposon system that functions well within the gonococcus has not been discovered. No presently available transposon is suitable for generalized chromosomal mutagenesis of the gonococcus. Seifert and colleagues developed a shuttle mutagenesis system that is extremely useful for genetic studies, in which a chloramphenicol acetyltransferase gene *cat* (or other antibiotic-resistance genes) replaces β -lactamase (penicillinase) in a derivative of the transposon Tn3.¹⁰³ Other analogous shuttle mutagenesis systems have been developed.¹⁰⁴

Transformation

Gonococci are quite unusual in their constitutive expression of competence for transformation by exogenous DNA. In competent gonococci, virtually every cell is competent at all stages of growth, quite unlike many other transformable species in which competence is restricted to certain phases of the growth cycle. However, only piliated (P⁺) gonococci are competent for transformation.¹⁰⁵ The association between competence for transformation and expression of pili suggests that pili are involved directly in recognition or entry of transforming DNA. Mutations in *pilE* or in certain pilus-accessory genes dramatically reduce competence for transformation.¹⁰⁶ DNA enters through the secretin protein PilQ³⁷ and requires not only Pili but also PilT and PilC.

Although most P⁺ gonococci are highly competent, they only take up their own (homologous) DNA into the cell.^{107,108} The structural basis for specificity in recognition of homologous DNA is uncertain. A 10 base pair sequence was described that is largely responsible for selective entry.^{109,110}

Because gonococci are piliated (competent) in vivo and are highly autolytic and release transforming DNA in a biologically active form, transformation may be used in nature to transfer genes between different gonococcal strains.¹¹¹ This might be important in transfer of chromosomal antibiotic-resistance genes or pilin silent genes, among others. Indeed, Spratt has shown that gonococci probably are transformed in nature by DNA from other species, creating novel hybrid genes; this probably is important to evolution of the species, which exhibits a plastic, nonclonal structure.^{112,113} A complete genomic map of the gonococcal chromosome (strain FA1090) is available. Sequencing of other strains showed that there are blocks of DNA, not present in the genome of FA1090, apparently acquired by horizontal exchange from other bacterial species.¹¹⁴ These genetic or pathogenicity islands probably contribute to the ability of certain gonococci to invade host cells, secrete DNA, and other properties.¹¹⁴

Conjugation

Many gonococci contain a 36-kb conjugal plasmid that efficiently mobilizes sexual transfer of certain other non-self-mobilizable plasmids such as the 4.5- or 7.2-kb penicillinase (Pc^r) plasmids.^{115,116} The 36-kb conjugative plasmids also mobilize their own transfer with high efficiency, but they do not detectably mobilize chromosomal genes for transfer between gonococci.¹¹⁷

Mutagenesis

Although gonococci are highly variable in certain properties (particularly expression of pili, Opa, and LOS), they are relatively nonmutagenic. They are very susceptible to ultraviolet light but lack photoreactivation and error-prone repair systems and do not undergo ultraviolet mutagenesis under

ordinary conditions.¹¹⁸ A gonococcal *recA* gene has been cloned and mutated.¹¹⁹ The gonococcal *recA* mutants show reduced frequencies of chromosomal transformation and of pilin antigenic variation, as expected.³¹

Restriction and modification systems

Gonococci are known to contain multiple restriction endonucleases and their corresponding methylases.¹²⁰ Transformation by plasmid DNA is markedly reduced when plasmids are introduced into gonococci across restriction barriers, but chromosomal transformation seems to be little influenced by restriction barriers.¹²¹ Gonococci have DNA methylases for which there is no corresponding restriction endonuclease, which suggests that DNA methylation might be important to other biological functions including gene regulation.¹²⁰

Plasmids

Many gonococci contain a 36-kb conjugal plasmid. Slightly larger derivatives of the 36-kb plasmid have been isolated that contain the tetracycline resistance (Tc^r) *tetM* transposon.¹²² A variety of gonococcal β -lactamase (penicillin resistant, Pc^r) plasmids have been isolated and characterized. The two most frequent plasmids are either about 5.3 or 7.2 kb.¹²³ The Tc^r and Pc^r plasmids are discussed in the following under "Antimicrobial Susceptibility."

Most gonococci also contain a 4.2-kb plasmid of unknown function (*cryptic plasmid*). The DNA sequence of this plasmid has been determined.¹²⁴ Occasional gonococci can be isolated that do not contain the freely replicating (cytoplasmic) 4.2-kb cryptic plasmid, but they appear biologically normal.¹²⁵

■ PATHOGENESIS

Clinical correlations

Consideration of clinical manifestations of gonorrhea suggests many facets of the pathogenesis of the infection. Since gonococci persist in the male urethra despite hydrodynamic forces that would tend to wash the organisms from the mucosal surface, they must be able to adhere effectively to mucosal surfaces. Similarly, since gonococci survive in the urethra despite close attachment to large numbers of neutrophils, they must have mechanisms that help them to survive interactions with polymorphonuclear neutrophils. Since some gonococci are able to invade and persist in the bloodstream for many days at least, they must be able to evade killing by normal defense mechanisms of plasma, including antibodies, complement, and transferrin. Invasion of the bloodstream also implies that gonococci are able to invade mucosal barriers in order to gain access to the bloodstream. Repeated reinfections of the same patient by one strain

strongly suggest that gonococci are able to change surface antigens frequently and/or to escape local immune mechanisms (Table 34-2).¹²⁶ The considerable tissue damage of fallopian tubes consequent to gonococcal salpingitis suggests that gonococci make at least one tissue toxin or gonococci trigger an immune response that results in damage to host tissues.¹²⁷ There is evidence to support many of these inferences.

Model systems

Studies of pathogenesis are complicated by the absence of a suitable animal model. A variety of animal models have been developed, each of which has certain utility, but no animal model faithfully reproduces the full spectrum of naturally acquired disease of humans. Considerable evidence about antigenic variation and interactions with neutrophils has been obtained from inoculation of subcutaneous chambers in guinea pigs or other animals. Gonococci survive in the female genital tract of mice for up to several weeks, which has provided the basis to demonstrate the importance of many gonococcal gene products to local mucosal infection in the mouse.¹²⁸ However, the mouse model lacks many of the critical receptors including complement receptor 3 (CR3), CD46, and the carcinoembryonic antigen related family of cell adhesion molecules (CEACAM, or CD66) found on

human tissues¹²⁹ and thus does not fully reproduce the physiology of human infection. The mouse model has been used for studies of immunogenicity of various vaccine candidates,¹³⁰ and for early studies of experimental vaccines. The best model system for many in vitro studies is organ culture of human tissues, particularly the fallopian tube system exploited successfully by McGee and colleagues.¹²⁷ Cultures of human cells including primary male urethral epithelial cells¹³¹ provides means to study attachment and invasion.

Investigators have used male human volunteers for critical studies of pathogenesis.¹³² Evidence in human volunteers confirms high frequency of in vivo variation of LOS, pili, and Opa,^{23,132,133} and the apparent necessity of expression of either a transferrin or lactoferrin receptor.^{77,78} Expression of full-length LOS appears essential for maximal infectivity.¹³⁴ These studies in human volunteers are hopefully the prelude to efficient, rational, and safe tests of gonococcal vaccine candidates, although after at least two decades of intense research, no vaccine candidates are on the horizon.

Adherence

Two adherence ligands are well documented to be important: pili and Opa. Porin and LOS are also involved in adherence. Different adherence ligands are involved in binding different receptors, which vary in their presence in different human cells and organs. Piliated gonococci adhere better to human columnar epithelial cells than to squamous cells and to human cells better than to nonhuman cells. Isolated pili adhere in vitro, and certain pilus antigenic variants exhibit selective ability to attach to particular cells under defined conditions in vitro.¹³⁵ Antibodies against pili decrease adherence of piliated gonococci to epithelial cells and red blood cells.^{136–138} Similar evidence supports the role of Opa proteins in adherence: gonococci expressing certain Opa proteins adhere better than Opa⁻ (transparent) gonococci to various cells, and a monoclonal antibody raised against one Opa protein inhibits adherence.^{52,53,138} Antigenic variation of both pili and Opa may be biologically advantageous not only for escape from specific immune responses but also by providing specific adherence ligands for attaching to different niches in vivo.¹³⁹ There are claims for the importance of CD46 for adherence mediated by pili, although this is quite controversial,^{18,19} and both CEACAM and heparin-like glycosaminoglycans have been identified as host-cell receptors for Opa.^{140,141} Studies from Apicella's laboratory have shown that CR3 is a receptor in female genital cells and tissues for binding both pili and PorB¹²⁹; another important receptor is the asialoglycoprotein (ASGP-R) for binding LOS. The interactions between various adhesins and their receptors, and the consequences for attachment and invasion of various cells, have been reviewed recently.¹²⁹

Table 34-2. Mechanisms for Evasion of Host Defenses

Antigenic variation

Pili

Opa

Los

Blocking antibodies (serum-bactericidal resistance)

Rmp

Antibody cleavage

IgA₁ protease

Antigen release

Membrane blebs

Intracellular growth

(Facilitated by Por; certain Opas; short LOS)

Molecular mimicry (LOS)

Sialylation (serum-bactericidal resistance)

Pilus adhesins

Polyclonal sera raised against synthetic pilin peptides were studied for ability to block adherence of two unrelated P⁺ gonococci to epithelial cells, and only sera against pilin peptides from amino acids 41 to 50 and 69 to 84 were effective.¹⁴² These peptides are from relatively invariant regions of pilin.¹⁴³ However, many monoclonal antibodies that recognize specific or unique epitopes on pilin are more active in blocking adherence than monoclonal antibodies directed at common epitopes, which suggests that the pilin domain(s) involved in adherence actually are in variable region(s).¹³⁸ This is consistent with pilus vaccination studies of human volunteers, in whom protection extended only to the homologous isolate from which the pilus vaccine was prepared.¹⁴⁴

In *E. coli* and other gram-negative bacteria, pili (or fimbriae) are associated with increased adherence, but the adhesin is not the pilin subunit but rather a minor pilus-related protein.¹⁴⁵ Difficulties in identifying the gonococcal pilus adhesin might be owing to focusing research efforts entirely on pilin subunits. Gonococci contain several pilus-related proteins other than pilin.¹⁴⁶ At least one of these (PilC) has been proposed to be an adhesin independent of pili.^{39,40} PilC undergoes high-frequency phase variation in its expression, like so many gonococcal cell surface molecules. PilC may be located on the tip of the pilus and may be a tip-adhesin since antibodies against PilC decrease adherence.³⁹ PilC seems to play an important but still not fully defined role in gonococcal attachment.

Opa undoubtedly are important in infection since almost all isolates taken from patients are opaque or Opa expressing; the only exception is isolates taken from the female cervix near menses when most isolates are transparent.¹⁴⁷ Binding (adherence) to host cells is facilitated in an additive fashion by both Opa and Pili. Once host cells have bound an Opa⁺ Pil⁺ gonococcus, they appear to undergo increased expression of the ASGP cell-surface receptor for gonococcal LOS, thus presumably increasing the force and perhaps the frequency of attachment of other gonococci.¹⁴⁸

Interactions with leukocytes

Gonococci were formerly referred to as *Neisseria intracellulare* because Gram-stain smears from human infections sometimes showed neutrophils covered with gonococci, which were assumed to be inside the cell. Pili are known to increase adherence of gonococci to human polymorphonuclear neutrophils, but they also increase resistance to phagocytosis and killing. In contrast to nonpiliated gonococci, which are readily ingested and killed by neutrophils, piliated gonococci attach well but are ingested relatively poorly.^{149,150} Antipilus antibodies increase phagocytosis (“opsonization”).^{151,152} Thus pili increase epithelial cell adherence and decrease neutrophilic killing, and antipilus antibodies block

epithelial adherence and increase phagocytic killing. Attachment to neutrophils is also increased by certain members of the Opa family.^{53,129,153}

The majority of gonococci taken up by neutrophils are killed, but at least 2% of gonococci survive ingestion by neutrophils.^{154,155} Work in Smith's laboratory has identified a 20-kDa gonococcal protein that seems to play an important role in resistance to intracellular killing by neutrophils.¹⁵⁶ Porin acts to inhibit phagosome maturation and inhibits neutrophil function, and down-regulates expression of the opsonin-dependent receptor CR3.¹⁵⁷ Porin also modifies myeloperoxidase-mediated oxidative killing.¹⁵⁸

Neutrophils possess both oxidative and nonoxidative methods for killing intracellular bacteria. Oxidative killing depends on enzymes contained within the specific and non-specific granules of neutrophils, whereas the nonoxidative mechanisms depend on a variety of cationic or basic lysosomal proteins. Gonococci are sensitive to damage by the oxidative products generated intracellularly during the neutrophilic respiratory burst, but are also killed efficiently by neutrophils from patients with chronic granulomatous disease that lack the oxidative killing mechanism.¹⁵⁹ One neutrophilic protein involved in nonoxidative killing of gonococci is cathepsin G.¹⁶⁰ Gonococci containing certain alterations in penicillin-binding proteins show increased susceptibility to cathepsin G, which may explain the clinical observation that gonococci with low-level chromosomal resistance to penicillin are uncommonly isolated from the bloodstream.¹⁶⁰

Invasion

Biopsies from patients with gonorrhea show gonococci partially embedded within the cell surface (Fig. 34-6). Gonococci also can be seen within the epithelial cell, sometimes surrounded by cellular membranes. Shaw et al. employed a continuous culture of a human endometrial carcinoma cell to study variables affecting gonococcal invasion in vitro and found that invasion was increased when gonococci were grown in an iron-supplemented medium.¹⁶¹ Other laboratories confirmed this observation.¹⁶² Gonococci adhere selectively to mucus-secreting nonciliated cells of the fallopian tube and are gradually engulfed by pseudopods and engulfed by the host epithelial cell.^{127,163–165} Gonococci appear to be able to multiply and divide intracellularly, although they do not invade laterally between cells.^{127,166} Eventually some gonococci exit from the basal surface of the cell by a process termed exocytosis.¹⁶⁶ Once inside the epithelial cell, gonococci are immune to attack by antibody, complement, or neutrophils; their ability to survive to some degree inside epithelial cells suggests that they might be considered facultative intracellular parasites. As discussed in the preceding and subsequently, invasion also is favored by expression of P.I.A and certain Opa proteins and also by expression of “short” (nonsialylated) LOS.

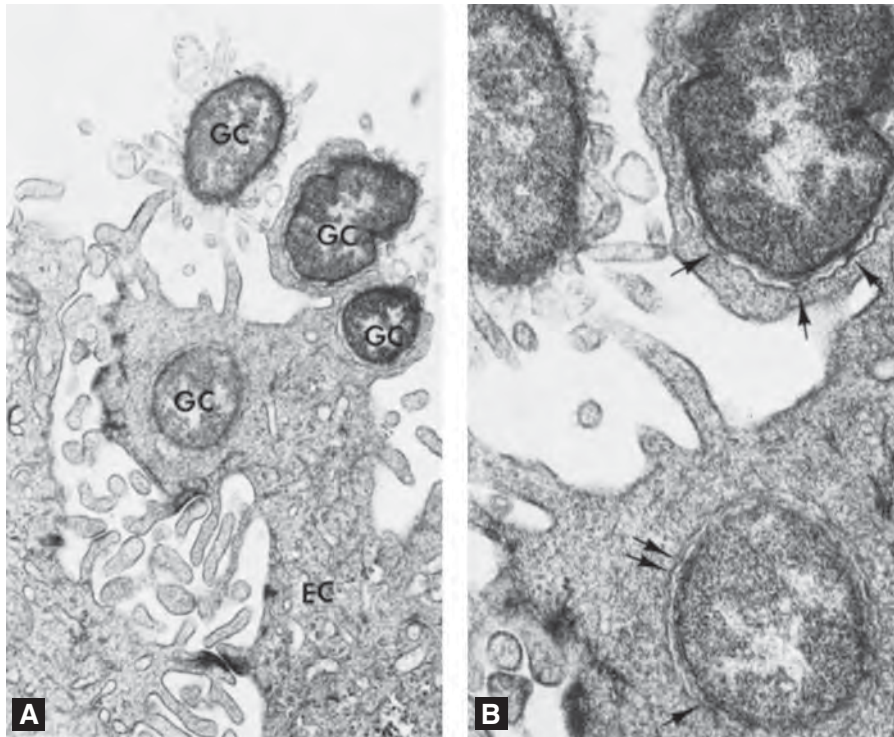


FIGURE 34-6. Gonococcal–epithelial cell relation in cervical biopsies from a woman with acute gonorrhea. One of the exocervical epithelial cells (EC) seen in this electron micrograph (**B** is an enlarged portion of **A**) has closely adherent gonococci (GC). Some of the bacteria appear to be partially or completely endocytosed by the epithelial cells. Pili are not visible in this thin section and, in general, are usually difficult to visualize in thin-section preparations. Note the close apposition of gonococcal outer membrane and epithelial cell plasmalemma (arrows) and the apparent enfolding of the bacteria by the host’s cervical cells. (Courtesy of D. Eschenbach and K. Holmes.)

Is Por a “trigger” for invasion?

Invasion is associated with a variety of cell-signaling events, and changes in epithelial cell morphology, as summarized recently.¹²⁹ Several observations suggest that Por may play a role in invasion. Incubation of radiolabeled gonococcal membranes or whole bacteria with red blood cells results in transfer of the gonococcal porin from the bacterial cell surface into the red cell membrane.¹⁶⁷ No other protein is translocated into the red cell membrane. Using phospholipid bilayers or so-called black lipid membranes to quantitate rates of transfer of porin protein, Lynch et al. showed that gonococci containing P.IA transfer Por into membranes more readily than gonococci containing P.IB.¹⁶⁸ Since gonococci with P.IA are more likely to cause disseminated disease than gonococci with P.IB (see Chapter 35), these results are consistent with the hypothesis that translocation or spiking of host cells by Por may be an important step in invasion of the host cell. Por translocation is accompanied by calcium flux and other changes in host-cell physiology.¹⁶⁹ Once inside the cell, Por associates with mitochondria¹⁷⁰ and either potentiates or depresses apoptosis, depending on the cell system studied.^{169–172} Porin channel activity is regulated during gonococcal growth in intact epithelial cells.¹⁷¹

Tissue damage

Gonococci produce a variety of extracellular products that might damage host cells including enzymes (phospholipase, peptidases, and others), but no true extracellular protein

toxin has been identified. Tissue damage appears to be owing to two structural components of the cell surface: LOS and peptidoglycan.

Although gonococci do not attach to ciliated cells of fallopian tubes in organ culture, diminished beating of cilia is evident within hours after infection.¹²⁷ Electron micrographs demonstrate extrusion of ciliated cells, even though attached gonococci are only visible on adjacent nonciliated cells (Fig. 34-7). Similar effects are evident after purified gonococcal LOS is added to the fallopian tube model.¹⁷³ The toxic portion of LOS almost certainly is the lipid A portion, as would be expected.¹⁷³ Perhaps damage to ciliated cells results when membrane blebs containing lipid A are released from gonococci attached to nonciliated cells.

In addition to the unequivocal evidence that lipid A is a tissue toxin for gonococcal infections, there is also excellent evidence that fragments of the cell wall or peptidoglycan are capable of inducing damage in the human fallopian tube organ culture model.¹⁷⁴ Gonococcal peptidoglycan fragments also may be involved in the pathogenesis of inflammatory arthritis after bacteremic disease,¹⁷⁵ similar to the role of peptidoglycan fragments in a well-studied animal model of post-streptococcal arthritis.¹⁷⁶

Dissemination

Serum resistance. The ability to resist the killing activity of antibodies and complement in normal human serum is closely related to the ability of gonococci to cause bacteremic illness with or without septic arthritis. A complex literature has evolved relating to the mechanisms of gonococcal resistance to serum antibodies and complement.



FIGURE 34-7. Scanning electronic microscopy studies of normal, uninfected human fallopian tube mucosa showing (A) ciliated cells and nonciliated cells (the latter are covered with microvilli) and (B) human fallopian tube mucosa 20 hours after infection with a piliated clone of *N. gonorrhoeae*. In (B) note morphologically intact ciliated cells (far right and top), two sloughing ciliated cells (center), and gonococci attached almost exclusively to the microvilli of nonciliated cells but not attached to a sloughing ciliated cells, $\times 4000$ magnification. (With permission from McGee ZA, et al. Pathogenic mechanisms of *Neisseria gonorrhoeae*: Observations on damage to human fallopian tubes in organ culture by gonococci of colony type I or type 4. *J Infect Dis* 1981; 143: 413.)

Most gonococci isolated from the bloodstream of patients are resistant to killing by serum from normal previously uninfected volunteers, whereas approximately two-thirds of isolates from mucosal infections are sensitive to killing by normal human serum.⁵ Presumably the bactericidal activity of normal human serum for many gonococci results from previous exposure to common antigens shared by gonococci and other commensal bacteria. The nature of these common antigens and the bacteria on which they are carried are unknown.

Some gonococcal isolates are resistant to normal human serum on first isolation from mucosal surfaces, but rapidly lose serum resistance on *in vitro* cultivation. This probably is owing to sialylation of full-length LOS *in vivo*, which results in phenotypic serum resistance. Nearly every isolate from patients with bacteremic disease exhibits stable serum resistance *in vitro*, which strongly suggests that unstable (phenotypically reversible) serum resistance is not biologically relevant to clinical gonococcal bacteremia.⁵ The remainder of this discussion refers to stable (genotypic) serum resistance or serum sensitivity.

In normal human serum, the principal bactericidal activity against serum-sensitive gonococci is found in the IgM fraction.^{87,177} Bactericidal antibodies of the IgG class also occur in pooled human serum globulins or in convalescent sera. The antigens against which bactericidal complement-fixing antibodies are directed include LOS, although IgM and IgG bactericidal antibodies apparently recognize different epitopes on LOS.⁸⁷ Equal amounts of the complement “attack complex” are bound to the surface of both serum-sensitive and

serum-resistant gonococci, suggesting that serum-resistant gonococci somehow are able to resist the otherwise lethal action of a fully formed complement attack complex.^{178,179}

The interaction between serum antibodies, complement, and antigenic targets on LOS is complicated by the presence in many individuals of other non-complement-fixing IgG antibodies that recognize epitopes on Rmp. These *blocking antibodies* inhibit the ability of otherwise bactericidal IgM antibodies in normal human sera to effectively recognize their target on LOS.^{177,180} The killing activity of sera frequently depends on the balance between non-complement-fixing blocking antibodies and complement-fixing bactericidal antibodies. Presumably the close physical proximity between Rmp and LOS accounts for the ability of anti-Rmp antibodies to block access of other antibodies to LOS. Recent evidence suggests that Rmp may be important not only for resistance to the bactericidal effects of human serum (and therefore for invasiveness) but also for successful transmission to the mucosal surfaces of sexual partners. Women with preexisting antibodies to Rmp were more likely to acquire infection from their infected partners than were other women who lacked antibodies to Rmp.¹⁸¹ Presumably, antibodies to Rmp in genital secretions blocked otherwise protective antibodies in genital secretions.

The structure of Por is also important to serum resistance. Early work established several genetic loci that were important to serum resistance (*sac-1*, *sac-3*), and each was very tightly linked to the *por* structural gene.¹⁸² Subsequent genetic studies showed that creation of intragenic *por* hybrids, in which a

crossover event occurred within *por*, markedly altered serum bactericidal resistance.⁵⁰ Thus the *sac* loci may well have represented alterations of *Por*, undetectable by the means available when those studies were conducted. Subsequently, two serum factors that inhibit complement deposition and activation have been identified that bind to particular surface-exposed loops of *Por*: C4bp and factor H, conclusively documenting the role of *Por* in serum bactericidal resistance.^{183,184} Species-specific ability to bind C4bp helps to determine whether gonococci are able to infect different animal hosts.¹⁸⁵

Chemotaxis

Serum resistance of gonococci may also relate to the pathobiological potential of infection at mucosal sites. Serum-resistant gonococci that cause bacteremia frequently cause asymptomatic relatively noninflammatory infections at the mucosal surface; this correlates with their relative inability to trigger a chemotactic response for neutrophils. In contrast, serum-sensitive isolates that rarely cause bacteremic disease but that frequently cause a marked inflammatory response at the mucosal surface elicit a much stronger chemotactic response *in vitro*.¹⁸⁶ Antibodies that elicit the C5 a-dependent chemotactic response are directed against LOS antigens.¹⁸⁶ Since severe pelvic inflammatory disease is correlated with relatively high-level sensitivity to serum killing *in vitro*, local tissue damage may reflect the ability of some gonococci to trigger a chemotactic response, resulting in increased local inflammation and tissue damage.¹⁸⁷

DIAGNOSIS

Diagnostic procedures are discussed fully in Chapter 35, but the principles can be outlined briefly here.

The standard procedure for diagnosing symptomatic disease in men with urethritis is the Gram stain. In asymptomatic men or in women with genital infection, the Gram stain is less useful, however, and cultures or nucleic acid amplification tests (NAATs) are necessary. A variety of NAATs have been developed, and they are the principal means of diagnosing gonococcal infection in most clinics in the United States at present.¹⁸⁸ Cultures are particularly useful whenever one is considering the possibility of an antibiotic-resistant gonococcal strain. Lack of culture in most locations has the effect that antibiotic sensitivity testing is rarely carried out except in certain locations that are part of the nation-wide gonococcal isolate sensitivity profiling (GISP) network established by the Communicable Diseases Center.

A variety of tests were developed to detect gonococcal antigen in genital secretions, including enzyme immunoassays with polyclonal sera against gonococcal antigens, monoclonal antibodies against gonococcal antigens, and a *Limulus* amoebocyte gelation test for lipid A, but none of these is in current use. Unfortunately, good diagnostic serologic tests have never been developed. Approximately one-half of infected persons

develop antipilus antibodies in serum during convalescence, but the sensitivity of the test is not sufficiently high for its use in high-prevalence populations, and the specificity is too low to use as a screening test in low-prevalence populations. A unique test that once had clinical promise used competent piliated gonococci as a test system to detect gonococcal transforming DNA in patient secretions.¹⁸⁹ The principle of this test was that gonococci can be transformed only by their own DNA and that virtually every gonococcal infection leaves residual amounts of biologically active transforming DNA in the environment. It has never been developed as a clinically useful test however.

■ ANTIMICROBIAL SUSCEPTIBILITY

Gonococci are inherently quite sensitive to antimicrobial agents, compared with many other gram-negative bacteria. However, there has been a gradual selection for antibiotic-resistant mutants in clinical practice over the past several decades, first by accumulation of chromosomal mutations that generally resulted in low-level resistance to penicillins and tetracyclines, and subsequently plasmids that mediate relatively high-level Pc^r and TC^r . The consequence of these events has been to make penicillin and tetracycline therapy ineffective in most areas. Antibiotics such as spectinomycin, ciprofloxacin, and ceftriaxone generally are effective but more expensive than penicillin G and tetracycline. Resistance to ciprofloxacin emerged in SE Asia and Africa in the past decade and has spread gradually throughout much of the world. The epidemiologic trends in prevalence of antibiotic-resistant gonococci and proper treatment of antibiotic-susceptible and antibiotic-resistant gonococcal infections are discussed in Chapter 35. The biochemical and genetic basis for antibiotic resistance is discussed in this chapter.

Penicillin

Isolates obtained in the 1940s typically were inhibited by 0.01 $\mu\text{g}/\text{mL}$ penicillin G or less. A gradual increase in prevalence and extent of resistance to penicillin occurred over the subsequent several decades; this was shown to be owing to the accumulation of several independent chromosomal mutations that affect cell surface structure. Three genetic loci resulting in low-level resistance to penicillin have been well studied.¹⁹⁰ One of them (*penA*) results in alteration of penicillin-binding protein two (PBP2), decreasing the affinity of PBP2 for penicillin. The gene for altered gonococcal PBP2 was cloned and sequenced, with the interesting suggestion that it might be the result of gene transfer from another related species in nature, leading to a hybrid PBP2.¹¹² The other loci (*mtr* and *penB*) result in low-level resistance to many antibiotics in addition to penicillins. The *mtrR* locus has been shown to encode a repressor of an *mtrCDE* efflux-pump that, when fully expressed,

reduces intracellular concentrations of antibiotics.^{191–193} The *penB* locus involves point mutations of *porB*, the structural gene for the major porin protein, altering net entry of antibiotics through the porin channel when the *mtr* mutation of the efflux pump also is present.⁴⁸ Introduction of *penA*, *mtr*, and *penB* into a sensitive gonococcal strain results in an increase in the minimum inhibitory concentration (MIC) of penicillin G from 0.01 to about 1.0 µg/mL. There have been a number of reports of gonococci with chromosomally mediated resistance to penicillin in which the MIC for penicillin is 2–4 µg/mL.¹²⁶ This fourth-step mutation was recently shown to be due to a point mutation in the secretin protein PilQ.³⁸

In 1976, a new type of gonococcal resistance to penicillin was first documented: the production of β-lactamase owing to the presence of plasmids that encoded production of a TEM-1 type of β-lactamase.¹⁹⁴ The first Pc^r (penicillinase-producing) gonococci contained either a 5.3- or a 7.2-kb plasmid. These two Pc^r plasmids are very closely related, and each carries approximately 40% of the common gram-negative μ-lactamase transposon Tn2.^{195,196} Based on the molecular structure of the gonococcal and *Haemophilus ducreyi* Pc^r plasmids, there is strong suspicion that gonococci acquired the Pc^r plasmids from *H. ducreyi*.^{197,198} The gonococcal Pc^r plasmids can be mobilized efficiently by the 36-kb gonococcal conjugal plasmid, helping to explain how Pc^r plasmids are spread to new gonococcal strains.¹⁹⁹

Tetracycline

Resistance to tetracycline also has increased owing either to the additive effects of several chromosomal mutations or to acquisition of a Tc^r plasmid. Chromosomal loci mediating low-level resistance to tetracycline have been designated *mtr*, *penB*, and *tet*; two of these also are involved in low-level, non β-lactamase mediated Pc^r.¹⁹⁰ The chromosomal *tet* gene encodes the 30 S ribosomal protein S10.²⁰⁰ In aggregate, these three loci result in an increase in the tetracycline MIC from about 0.25 to 2–4 µg/mL. Much higher levels of resistance (tetracycline MIC ≥ 64 µg/mL) are found in gonococci containing a 38-kb Tc^r plasmid, which is a derivative of the 36-kb conjugal plasmid. Hybridization studies show that the Tc^r plasmid contains *tetM*, which is carried on a transposon found in a variety of gram-positive and gram-negative microorganisms including many genital pathogens (*Gardnerella*, *Ureaplasma*).¹²² The Tc^r plasmids contain *tetM* in a position that does not inactivate conjugal function, and Tc^r gonococci can transfer this plasmid as well as Pc^r plasmids efficiently into other antibiotic-sensitive gonococci. The mechanism of resistance mediated by *tetM* involves production of a cytoplasmic protein that protects ribosomes from the action of tetracycline. Resistance to penicillins and tetracyclines remains common in most parts of the world.^{201,202}

Spectinomycin

For many years, there were only rare reports of gonococci exhibiting high-level resistance to spectinomycin (Spc), but in areas where this antibiotic has been used frequently because of the prevalence of Pc^r gonococci, Spc^r isolates are more common.²⁰³ Single-step, high-level resistance to Spc can be obtained relatively easily in the laboratory, and biochemical and genetic studies of Spc^r mutants and of naturally occurring Spc^r isolates show that they are virtually identical. The genetic locus *spc* maps within a cluster of chromosomal ribosomal genes and results in alteration of the ribosomal target on which Spc acts.¹⁹⁰

Other antibiotics

Streptomycin (Str) is not frequently used for therapy of gonorrhea at present, but many gonococci exhibit high-level resistance to Str. A locus for resistance to Str (*str*) maps near *spc*, and both are closely linked to those for resistance to tetracycline (*tet*), rifampin (*rif*), and others.¹⁹⁰

Resistance to nalidixic acid and related DNA gyrase inhibitors is obtained easily in the laboratory with mutation frequencies of approximately 1×10^{-8} . In contrast, Spc^r mutants arise with a frequency of about 1×10^{-10} to 1×10^{-11} . Resistance to fluoroquinolones is increasing, and now has become a general problem in many areas of the world.^{204,205} Resistance to fluoroquinolones is due either to mutations in *gyrA* or *parC*.^{205–207}

HOST-IMMUNE RESPONSE

Naturally acquired gonococcal infection results in serum antibodies against many gonococcal antigens including Pil, Por, Opa, Rmp, and LOS.^{208,209} As would be expected, serum antibody responses are greater in patients who have bacteremia or salpingitis than in those who have uncomplicated mucosal infection. Studies of mucosal secretions demonstrate that uncomplicated genital infection often results in serum and mucosal IgA and IgG antibodies against the homologous isolate,^{210,211} although some studies found a very poor local antibody response and almost complete lack of inflammatory cytokines IL-1, IL-6, and IL-8.²¹² The duration of the serum and mucosal antibody responses after natural infection are quite brief, however.²¹⁰ There is an innate response at the mucosal surface, with production of certain defensins.²¹³

Cytokine responses in experimental and natural gonorrhea are generally less than in other genital infections.²¹² The paucity of immune response is consistent with the ability of gonococci to dampen the response, as has been suggested for many other bacterial and viral pathogens. Work from two research groups has shown that gonococci expressing certain members of the Opa family do down regulate immune responses by T cells²¹⁴ and B cells,²¹⁵ although the mechanisms may be different in the different target cells. In B cells,

there appears to be an apoptotic response,²¹⁵ whereas in T cells there is no apparent cell death.²¹⁴ This is a very exciting recent development, and in combination with the well-worked theme of antigenic variation, provides entirely plausible reasons for the inability of local uncomplicated natural infection to result in an effective protective immune response.

There also is a cellular immune response to natural gonococcal infection, although the cellular immunology of gonorrhoea has been studied much less extensively than the humoral response.

VACCINES

The principal efforts to stimulate protective immunity to date have focused on use of P.I as an antigen. Intramuscular or subcutaneous inoculation with purified Pil results in both serum and mucosal antibodies that have antiadherence and opsonizing properties.^{136,144,151} Limited in vitro studies of male volunteers vaccinated with a single antigenic type of pilus showed that there was partial protection against urethral challenge with the homologous strain.²¹⁶ Although the level of protection was modest, with only a 10–30-fold increase in the 50% infectious dose, this conceivably could result in clinically significant protection. Unfortunately, challenge of vaccinated volunteers with a heterologous strain resulted in no protection (C.C. Brinton, presented at the International Pathogenic *Neisseria* Meeting, Montreal, 1982). A single antigenic type of pilus was used to vaccinate American military in a clinical trial, with the perhaps expected result that there was no protection against the diverse antigenic types of gonococci found in clinical practice.¹⁴⁴ It remains possible that a polyvalent pilus vaccine would be more effective or that a common pilin domain or pilus-related protein antigen will be discovered that is more broadly protective against mucosal and/or systemic gonococcal infection.

Other vaccines (including PorB and TbpA/B) are also under active investigation.²¹⁷ Advantages of the recombinant partial protection against reinfection by the same Por serovar was demonstrated in a large study in Africa.²¹⁸ However, this result was not confirmed in another differently designed study.²¹⁹ Studies of recombinant PorB and genetic vaccines expressing PorB in the mouse model of genital gonorrhoea have not shown protection (W. Zhu, C.-J. Chen, C. E. Thomas, A. Jerse, P.F. Sparling, et al., unpublished studies). A genetic vaccine composed of *porB* expressed from a Venezuelan Encephalitis virus replicon particle (VRP-PorB) showed some protection in the same model, but it appeared to be entirely due to the proinflammatory Th1 response elicited by the VRP vector, and not due to the expressed PorB (W. Zhu, C.-J. Chen, C.E. Thomas, R. Johnston, N. Davis, A. Jerse, and P.F. Sparling, unpublished data).

Understanding of the pathogenesis of gonorrhoea is now quite extensive. There is reason for some hope that this new

information can be translated into protection against this common and sometimes serious infection. It remains for the future to determine whether this hope can be realized. Few are working on a vaccine for gonorrhoea, and no vaccine is in immediate sight.

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HISTORY

The major clinical manifestations of gonorrhea in men were described in ancient Chinese, Egyptian, Roman, and Greek literature as well as in the Old Testament.¹ The current term for the clinical syndrome referred to as gonorrhea (Greek, “flow of seed”) is attributed to Galen (130 A.D.), who is said to have believed that the urethral exudate in males with gonorrhea was semen. However, there is little recorded evidence of awareness that urethral discharge in men was linked with morbidity for women until relatively recently. In 1879, *Neisseria gonorrhoeae* was demonstrated by Neisser in stained smears of urethral, vaginal, and conjunctival exudates,² making the gonococcus the second identified bacterial pathogen following the discovery of *Bacillus anthracis*. *N. gonorrhoeae* was first cultured in vitro by Leistikow in 1882, and effective antimicrobial therapy in the form of sulfonamides was first applied in the 1930s.³ In 1962, the availability of Thayer-Martin medium⁴ greatly facilitated the diagnosis of gonorrhea and may have contributed to subsequent increases in numbers of cases of gonorrhea reported in women. Since the mid-1960s, knowledge of the molecular basis of gonococcal–host interactions and of gonococcal epidemiology has increased to the point where it is amongst the best described of all microbial pathogens.

N. gonorrhoeae initially infects noncornified epithelium, most often of the urogenital tract and secondarily of the rectum, oropharynx, and conjunctivae. It is an exclusively human pathogen, which is transmitted primarily by sexual contact or perinatally. Infection most often remains localized to initial sites of inoculation. Ascending genital infections (salpingitis, epididymitis) and bacteremia, however, are relatively common and account for most of the serious morbidity due to gonorrhea. These complications are most common in populations that lack ready access to effective diagnosis and therapy.

EPIDEMIOLOGY

■ INCIDENCE

Relatively few countries have reporting systems that permit accurate estimation of true gonorrhea incidence. [Figure 35-1](#) shows the reported annual incidence of gonorrhea in the United States, Canada, and Sweden from 1970 through 2005.^{5–7} Gonorrhea is rare in Canada and much of Western Europe and, despite recent declines in reported cases, remains relatively common in the United States as well as in much of the developing world. In the United States, recent changes in gonorrhea incidence reflect the influence of multiple, sometimes opposing, trends for members of certain risk groups. At least part of the decline in gonorrhea in developed countries (including the United States) has been attributed to the impact of behavioral changes made to reduce risks of infection with human immunodeficiency virus (HIV). However, these changes have not occurred uniformly within the population. Although national data are not available, studies from several North American and European cities^{8,9} suggest that gonorrhea rates in homosexual or bisexual men declined precipitously in the 1980s and 1990s, but has again increased early in the twenty-first century⁵; it is not clear that rates in other groups have changed substantially. In addition, U.S. gonorrhea rates appear to have changed more for whites than for blacks and more among older age groups than in the young.⁵

The incidence of gonorrhea varies with age ([Fig. 35-2](#)). Seventy-five percent of reported cases in the United States in 2005 occurred in persons aged 15–29 years, with the highest rates occurring in the 15–19-year-old group. The incidences in 15–19-year-old and 20–24-year-old women were 625 and 581 cases per 100,000 population, respectively. However, it is estimated that only about 50% of 15–19-year-old women in the United States were sexually experienced, compared with

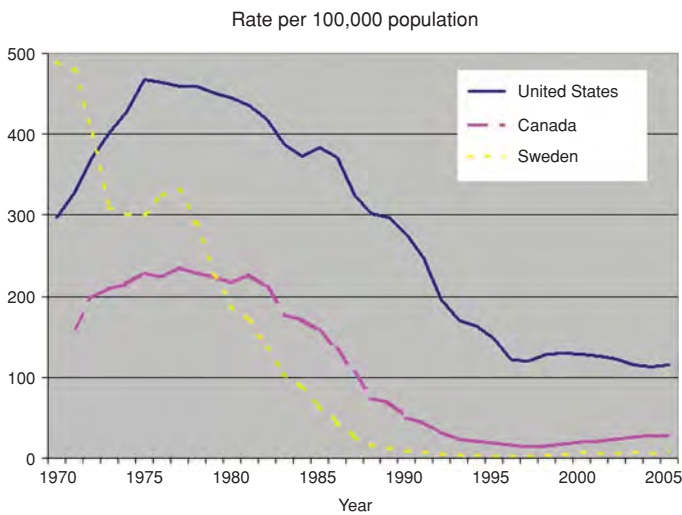


FIGURE 35-1. Reported annual incidence of gonorrhea in the United States, Canada, and Sweden, 1970–2005.

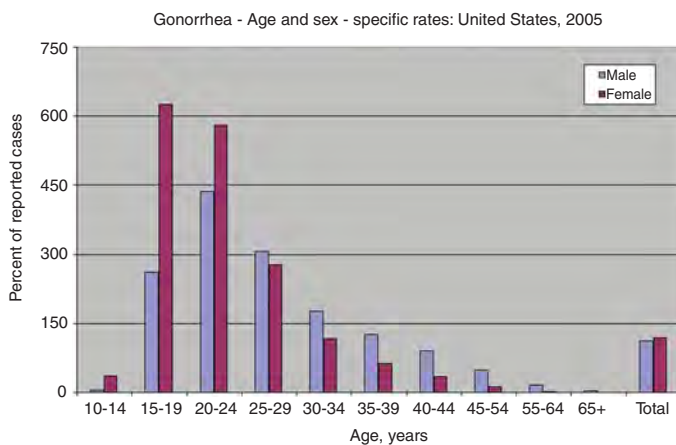


FIGURE 35-2. Age and sex distribution of reported cases of gonorrhea in the United States, 2005.

over 90% of the 20–24-year-old group. Thus, despite similar overall rates, the reported incidence of gonorrhea was almost twice as high for sexually active adolescents as for sexually active women in the 20–24-year-old group.⁵

In the United States in 2005, reported cases of gonorrhea were more than 18-fold higher in African Americans than in whites, a difference only partly explained by greater attendance of nonwhites at public clinics, where reporting is more complete than in other health care settings.^{5,10} Other demographic risk factors for gonorrhea include low socioeconomic status, early onset of sexual activity, unmarried marital status, and a history of past gonorrhea.^{10,11} Studies in Seattle documented that about 25% of sexually active 16–18-year-old black females living in low socioeconomic level urban census tracts in 1986–1987 acquired gonorrhea each year.¹² Since 1980s, illicit drug use and prostitution have also become increasingly associated with enhanced risk of gonorrhea, syphilis, and probably other sexually transmitted diseases

(STDs) as well. In the past decade, male homosexuality has become less associated with gonorrhea because of changing sexual practices among many homosexual men as a consequence of concerns regarding AIDS. Despite this trend, the incidence of gonorrhea in men who have sex with men (MSM) may still be higher than in exclusively heterosexual persons.¹³

The incidence of gonorrhea in the United States is seasonal: the highest rates occur in late summer, whereas the lowest are in late winter and early spring, with nadirs tending to be about 20% lower than peaks.^{10,14,15} The antimicrobial susceptibility of *N. gonorrhoeae* appears to fluctuate similarly,¹⁵ possibly as a consequence of seasonal variation in antibiotic usage. Seasonal variations in sexual activity, access to health care, changing commitments in schedules of the young individuals at highest risk for gonorrhea, or other factors also may be involved in these seasonal fluctuations.

The efficiency of gonorrhea transmission depends on anatomic sites infected and exposed as well as the number of exposures. The risk of acquiring urethral infection for a man following a single episode of vaginal intercourse with an infected woman is estimated to be 20%, rising to an estimated 60–80% following four exposures.¹⁶ The prevalence of infection in women named as secondary sexual contacts of men with gonococcal urethritis has been reported to be 50–90%,^{16,17} but no published studies have carefully controlled for number of exposures. It is likely that the single-exposure transmission rate from male to female is higher than that from female to male, in part because of retention of the infected ejaculate within the vagina. The risk of transmission by other types of sexual contact is less well defined. Gonorrhea transmission through insertive or receptive rectal intercourse presumably is relatively efficient, and pharyngeal gonorrhea is readily acquired by fellatio.^{18,19} Transmission of pharyngeal infection to other sites has been thought to be rare, but in one study this route of exposure accounted for 26% of urethral gonorrhea in MSM.¹³ It is possible that changing sexual practices among MSM in response to AIDS, specifically an increasing frequency of oral sex and decreased anal intercourse, have changed the population attributable risk of oral sex for urethral gonorrhea.

In women, use of hormonal contraception may increase the risk of acquiring gonorrhea,^{20,21} and use of the diaphragm has a protective influence.²² Transmission by fomites or through nonsexual contact is extremely rare, but may account for rare cases of gonorrhea in infants.

Symptoms and the behavioral response to them also influence the transmission of gonorrhea. Previous reports saying that 80% of women with gonorrhea were asymptomatic were most often based on studies of women who were examined in screening surveys or referred to STD clinics because of sexual contact with infected men.²³ Symptomatic infected women who sought medical attention were thus often excluded from

such surveys. However, as might be expected, more than 75% of women with gonorrhea attending acute care facilities such as hospital emergency rooms are symptomatic.²⁴ The true proportion of infected women who remain asymptomatic undoubtedly lies between these extremes. Appreciation of symptomatic infection in infected women is more difficult than in men because the clinical syndromes may be mistakenly attributed to other infectious processes, including urinary tract or vaginal infections.

Asymptomatically infected males and females contribute disproportionately to gonorrhea transmission, because symptomatic individuals are more likely to cease sexual activity and seek medical care. However, the presence of urogenital symptoms does not ensure that transmission will not occur. In a study of patients attending STD clinics in Baltimore, 38% of men and 46% of women presenting for symptom evaluation reported continued sexual activity after the onset of the symptoms that brought them to the clinic.²⁵ The reasons for continued sexual activity despite the presence of symptoms may include the relative lack of severity of symptoms early in the course of disease, denial, and for women, the nonspecificity of urogenital symptoms. The observation that many transmitters of gonorrhea (and other STDs) do not spontaneously cease sexual activity and seek care emphasizes the importance of taking active steps to bring the partners of infected persons to treatment.

Asymptomatic infections occur in men as well as women, and the percentage of infected men who are asymptomatic probably varies with duration of infection. In a cohort of 81 men who acquired urethral infection at a defined time, the mean time to development of symptoms was 3.4 days, and only 2 (2.5%) remained asymptomatic for 14 days²⁶ (Fig. 35-3).

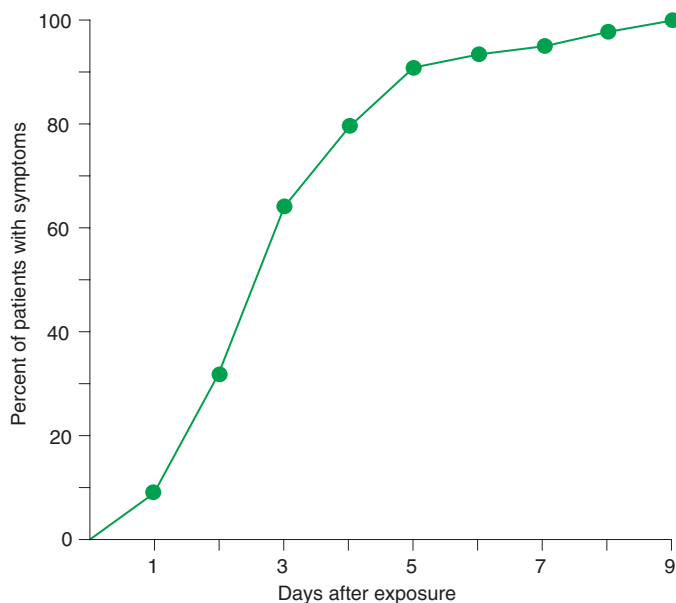


FIGURE 35-3. Incubation period in 44 men with symptomatic gonococcal urethritis. (From Harrison WO, et al. A trial of minocycline given after exposure to prevent gonorrhea. *N Engl J Med* 1979; 300: 1074.)

Although this study was performed in a geographic area where the strains of *N. gonorrhoeae* most likely to cause asymptomatic urethral infections were uncommon, the incidence of asymptomatic urethral gonococcal infection in the general population also has been estimated at approximately 1–3%.²⁷ The prevalence of asymptomatic infection may be much higher, approaching 5% in some studies, because untreated asymptomatic infections may persist for considerable periods.

PREVALENCE

The prevalence of gonorrhea within communities tends to be dynamic, fluctuating over time, and influenced by a number of interactive factors. Mathematical models for gonorrhea within communities suggest that gonorrhea prevalence is sustained not only through continued transmission by asymptotically infected patients but also by “core group” transmitters who are more likely than members of the general population to become infected and transmit gonorrhea to their sex partners.^{28–30} Although members of the core group described in these mathematical models share a number of characteristics including geographic clustering (usually within inner cities) and low socioeconomic status, the core group actually comprises a number of heterogeneous subgroups whose membership may change over time. These include persons with repeated episodes of gonorrhea, those who fail to abstain from sex despite the presence of symptoms or knowledge of recent exposure, and patients who practice high-risk behaviors such as illegal drug use, prostitution, or prostitute patronage.^{12,25,29} Finally, because the core group is defined primarily on behavioral grounds, membership in a core group is not a stable characteristic of an individual, but may change over time. Several studies have provided empirical observations that support mathematical models of core-group transmission.^{12,25,29}

While providing the focus for continued endemicity of gonorrhea, core groups are not solely responsible for gonorrhea prevalence within communities. In terms of social behavior, disease prevalence is due to infections transmitted by both core-group and non-core-group members, the interaction between these two groups, and the movement of patients from one group to another. These factors fluctuate with changes in normative social behavior, disease-control efforts, and other epidemiologic factors. At present, gonorrhea prevention and control efforts are heavily invested in the concept of vigorous pursuit and treatment of infected core-group members and asymptotically infected individuals. Because about 40% of asymptotically infected men and many women who are asymptomatic indeed have clinical findings compatible with gonorrhea,^{24,27} patient education designed to modify the behavior or response to mild symptoms also is an important albeit largely unexplored

part of gonorrhea control. In addition, however, efforts to access the often-difficult-to-reach core-group transmitters are needed to assist in gonorrhea control. Mathematical models of core transmission theory suggest that because gonorrhea transmission is not 100% efficient, and because spontaneous cures occur, without hyperendemic transmission by core-group members, gonorrhea prevalence would decline, perhaps ultimately to zero.^{28,30}

EPIDEMIOLOGIC CORRELATES OF GONOCOCCAL TYPES

A number of methods for gonococcal typing have been developed, as discussed in Chapter 31. Auxotyping,³¹ protein I-serotyping,³² and the two used in combination have been used most widely to study gonococcal epidemiology. Auxotyping classifies gonococci on the basis of stable nutritional requirements for a variety of amino acids and nucleosides, alone or in combination.³¹ Examples of common auxotypes are strains that require arginine (Arg), proline (Pro), uracil (U), methionine (M), or Arg, hypoxanthine, and uracil (AHU) for growth. Gonococci requiring none of the substrates are termed *prototrophic* (Proto) or are referred to as *wild type* by some authors. Protein I serotyping is based on the stable antigenic diversity of protein I, the protein present in largest quantity in the gonococcal outer membrane.³² Protein I is divided into two mutually exclusive classes, protein IA and protein IB, each of which can be further subdivided into serovars in coagglutination assays using panels of protein IA- or protein IB-specific monoclonal antibody reagents. Each serovar is designated by its protein I type (IA or IB) and a numeral based on its coagglutination pattern (e.g., IA-4, IB-3). Using both auxotyping and serovar analysis, gonococci can be divided into a large number of auxotype/serovar (A/S) classes (e.g., AHU/IA-1, Pro/IB-3, Proto/IB-12), providing a highly discriminative tool for study of gonococcal epidemiology.³³ In recent years, however, the antibodies for protein I (Por) serotyping have largely been exhausted and are no longer available. Strain typing based on differences in Por can now be accomplished in certain laboratories based on the DNA sequence of the *por* gene (“genotyping”),³⁴ as discussed more fully in Chapter 34.

Relatively large numbers (>50) of gonococcal A/S classes usually are present in most communities simultaneously,^{33,35} and new strains can be detected over time. The distribution of isolates within A/S classes tends to be uneven, with a few A/S classes contributing disproportionately to the total number of isolates. These predominant A/S classes generally persist within communities for months or years. In most studies, many more A/S classes are detectable only intermittently or even only once during a sampling interval and then not detected again. The factors that determine which

A/S classes will become predominant and which will be seen only transiently may include biologic characteristics of the strain or the host. Alternatively, epidemiologic factors such as transmission by commercial sex workers or drug users and importation by travelers may be important.

By allowing individual strains of *N. gonorrhoeae* to be tracked, A/S classification has helped elucidate how gonococci are introduced and spread in communities. For example, during a 12-week study of consecutive patients with gonorrhea seen at a Seattle STD clinic,³³ 489 isolates were collected from 390 patients. These isolates could be divided into 57 different A/S classes. Some A/S classes were isolated only from heterosexual men and women (e.g., AHU/IA-1, AHU/IA-2), whereas others were isolated almost exclusively from homosexual or bisexual men (e.g., Arg/IB-2, Proto/IB-20). During the study, one strain (Proto/IB-3) was not detected until week 6 and over the next 2 weeks was isolated from 1 woman, 1 homosexual man, and 10 heterosexual men. During the next few weeks, isolates of this A/S class from heterosexual men continued to far outnumber those from women, and over the subsequent year, this strain became one of the predominant gonococcal A/S classes throughout the city. Interviews of the patients infected by the Proto/IB-3 strain early in the outbreak identified one infected female who acknowledged over 100 different sexual partners over the preceding 2 months, suggesting that she may have played an important role in the introduction and establishment of this gonococcal strain in the community. Thus the Proto/IB-3 strain may have become common in Seattle not because of specific biologic factors but because of its chance of transmission to members of a core population by a high-frequency transmitter.

Some gonococcal strain types are associated with specific clinical manifestations of disease³⁵. In Seattle during the early 1970s, AHU/IA-1 and AHU/IA-2 strains caused more than 90% of asymptomatic urethral infections in men³⁶ and the majority of cases of disseminated gonococcal infections (DGIs).³⁷ However, these A/S classes were less common in symptomatic men and in women with gonococcal salpingitis.³⁸ AHU/IA-1 and AHU/IA-2 strains grow more slowly than many other gonococci, are particularly susceptible to the penicillins and tetracyclines, and tend to be resistant to the complement-mediated bactericidal activity of normal human serum.³⁹ Since the 1970s, the prevalence of AHU/IA strains in Seattle has diminished markedly, as have the numbers of cases of DGI and asymptomatic urethral gonorrhea in men.⁴⁰ These changes occurred shortly after institution of contact tracing for gonorrhea and with routine treatment of asymptomatic male sexual partners of infected women. Thus it seems that AHU/IA strains may have accumulated in the population because of their ability to cause asymptomatic infection in men. When this selection pressure was reduced through partner notification and treatment of asymptomatic men, the prevalence declined.

PATHOLOGY

In adults, only mucous membranes lined by columnar or cuboidal, noncornified epithelial cells are susceptible to gonococcal infection. The initial event in gonococcal infection is the adherence of *N. gonorrhoeae* to mucosal cells in a process mediated by pili, Opa, and perhaps other surface proteins.^{41,42} In fallopian tube organ culture models, the organism is then pinocytosed by the epithelial cells, which transport viable, sometimes dividing gonococci from the mucosal surface to subepithelial spaces.^{43,44} Simultaneous with attachment of gonococci to nonciliated epithelial cells, gonococcal lipooligosaccharide (endotoxin) impairs ciliary motility and contributes to destruction of surrounding ciliary cells.⁴⁴ This process may promote further attachment of additional organisms. Progressive mucosal cell damage and submucosal invasion are accompanied by a vigorous polymorphonuclear leukocytic response, submucosal microabscess formation, and exudation of purulent material into the lumen of the infected organ. In untreated infections, polymorphonuclear leukocytes are gradually replaced by mononuclear cells, and abnormal round cell infiltration has been reported to persist for several weeks or months after gonococci can no longer be isolated.⁴³ The molecular mechanisms of gonococcal invasion and infection are more fully discussed in Chapter 34.

CLINICAL MANIFESTATIONS: UNCOMPLICATED GONOCOCCAL INFECTIONS

Despite the focus of many patients and even some clinicians on symptomatic local infections, clinical gonorrhea is manifested by a broad spectrum of clinical presentations including asymptomatic and symptomatic local infections, local complicated infections, and systemic dissemination. Figure 35-4 estimates the relative proportion of individuals with each of the major clinical syndromes and shows the interrelations between them in a simplified form.

URETHRAL INFECTION IN MEN

Acute anterior urethritis is the most common manifestation of gonococcal infection in men. The incubation period ranges from 1 to 14 days or even longer; however, the majority of men develop symptoms within 2–5 days, as was the case in 36 (82%) of 44 men with uncomplicated gonorrhea in one of the few studies in which the time of exposure could be clearly defined²⁶ (see Fig. 35-3). The predominant symptoms are urethral discharge or dysuria. Although initially scant and mucoid or mucopurulent in appearance, in most males the urethral exudate becomes frankly purulent and relatively profuse within 24 hours of onset^{43,44} (Fig. 35-5). Dysuria usually begins after onset of discharge. Variable degrees of

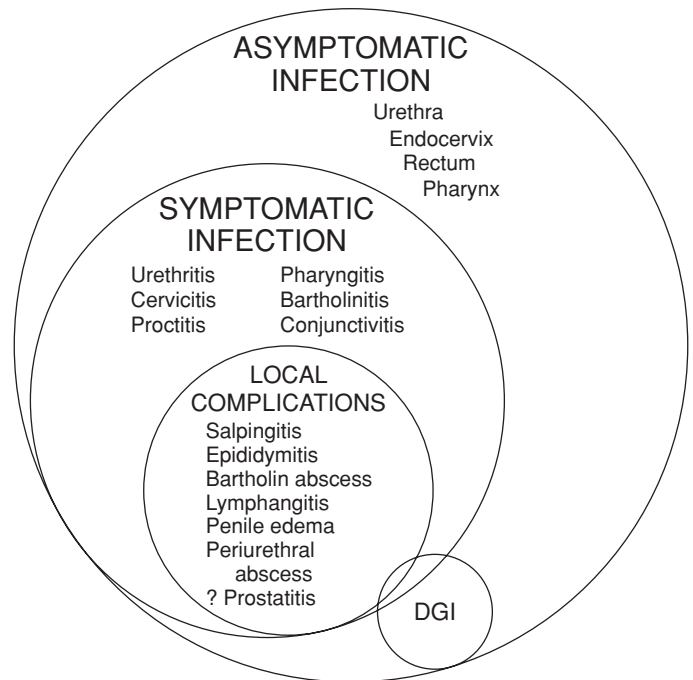


FIGURE 35-4. Clinical spectrum of gonococcal infection (DGI, disseminated gonococcal infection).

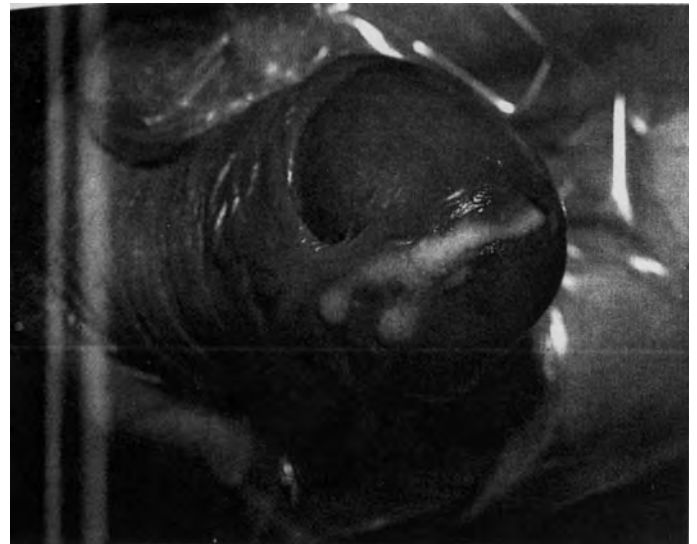


FIGURE 35-5. Purulent urethral discharge and penile edema in a patient with gonococcal urethritis.

edema and erythema of the urethral meatus commonly accompany gonococcal urethritis. Approximately one-quarter of patients develop only a scant or minimally purulent exudate, grossly indistinguishable from that associated with nongonococcal urethritis,^{45,46} and a minority never develop overt signs.^{27,28} The severity of symptoms is partly determined by the infecting strain of *N. gonorrhoeae*,⁴⁴ as discussed above. Without treatment, the usual course of gonococcal urethritis is spontaneous resolution over a period of several weeks, and before the development of effective antimicrobial therapy, 95%

of untreated patients became asymptomatic within 6 months.⁴³ Subsequent asymptomatic carriage of *N. gonorrhoeae* may occur but probably is exceptional.

Complications of gonococcal urethritis include epididymitis (see Chapter 60); acute or chronic prostatitis (see Chapter 61); so-called posterior urethritis, which may be associated with stranguria and urinary urgency; seminal vesiculitis; and infections of Cowper's and Tyson's glands. These have been documented infrequently using modern diagnostic techniques and are now rare in industrialized societies.

UROGENITAL INFECTION IN WOMEN

The endocervical canal is the primary site of urogenital gonococcal infection in women. Urethral colonization is present in 70–90% of infected women,^{47–49} but is uncommon in the absence of endocervical infection. However, after hysterectomy, the urethra is the usual site of infection.⁵⁰ Infection of the periurethral (Skene's) gland or Bartholin's gland ducts is also common, but probably is rare in the absence of endocervical or urethral infection.

The incubation period for urogenital gonorrhea in women is less certain and probably more variable than in men, but most who develop local symptoms apparently do so within 10 days of infection.^{51,52} The most common symptoms are those of most lower genital tract infections in women (see Chapter 55) and include increased vaginal discharge, dysuria, intermenstrual uterine bleeding, and menorrhagia, each of which may occur alone or in combination and may range in intensity from minimal to severe.^{24,53} Although the physical examination may be normal, many infected women have cervical abnormalities that include purulent or mucopurulent cervical discharge, erythema and edema of the zone of ectopy, and mucosal bleeding that is easily induced by swabbing the endocervix.⁵³ Purulent exudate occasionally may be expressed from the urethra, periurethral glands, or the Bartholin's gland duct (Fig. 35-6). The clinical assessment of women for gonorrhea is often confounded, however, by the nonspecificity of these signs and symptoms and by the high prevalence of coexisting cervical or vaginal infections with *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Candida albicans*, herpes simplex virus, and a variety of other organisms (see Chapter 55).

The manifestations of gonorrhea during pregnancy are not significantly different from those in nonpregnant women except that pelvic inflammatory disease (PID) is probably less common and pharyngeal infection appears to be more prevalent than in nonpregnant women.⁵⁴ Reported complications of genital gonorrhea in pregnancy include spontaneous abortion, premature rupture of fetal membranes, premature delivery, and acute chorioamnionitis (see Chapter 80), as well as ophthalmia neonatorum, pharyngeal infections, and other syndromes in the newborn (see Chapter 82).

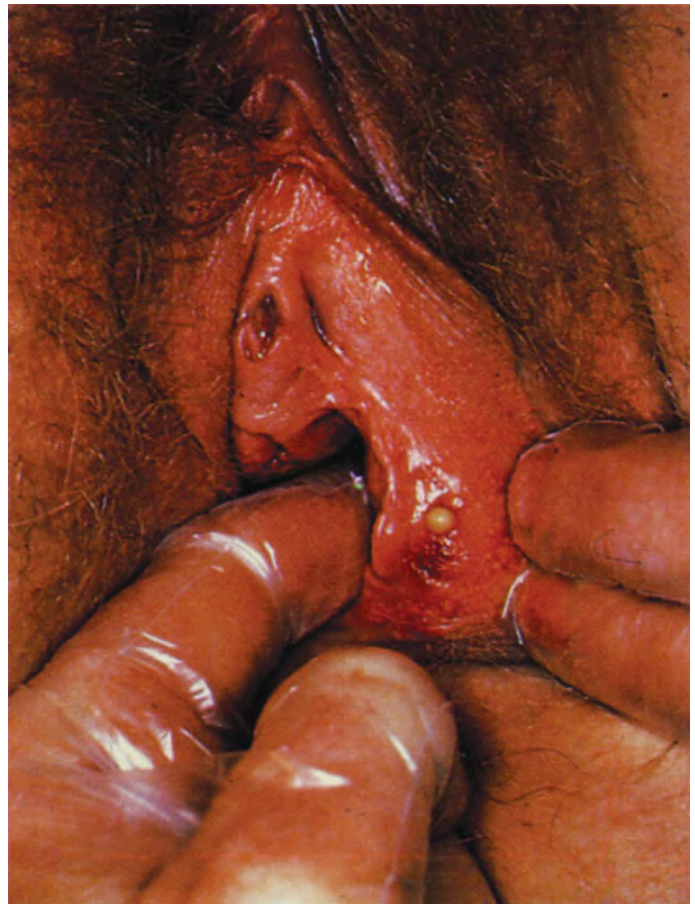


FIGURE 35-6. Purulent exudate expressed from the Bartholin's gland duct of a woman with gonococcal Bartholin's gland abscess. (From JA Davies et al. Isolation of *Chlamydia trachomatis* from Bartholin's ducts. *Br J Vener Dis* 1978; 54: 409.)

RECTAL INFECTION

The rectal mucosa is infected in 35–50% of women with gonococcal cervicitis and is a frequent site of infection in homosexual men; it is the only site of infection in approximately 5% of women with gonorrhea and 40% of homosexually active men studied prior to recognition of the HIV epidemic.^{47–49,55–59} In a study of MSM in 1993 and 1994, rectal infection was documented in 26 (25%) of 105 men infected at any anatomic site.¹³ In women, rectal gonorrhea is usually asymptomatic, although some cases, especially in MSM, are associated with overt proctitis. Among MSM, rectal gonorrhea is due to direct inoculation through receptive rectal intercourse. In contrast, most rectal infections in women occur without acknowledged rectal sexual contact and are assumed to result from perineal contamination with infected cervical secretions. The prevalence of rectal infection in women is positively correlated with the duration of endocervical infection,⁵⁶ further supporting the thesis that infection is usually due to perineal contamination by cervicovaginal secretions. Rectal infection occurs rarely, if ever, in strictly heterosexual men.

Many rectal infections are asymptomatic. When present, the symptoms of rectal gonococcal infection range from minimal anal pruritus, painless mucopurulent discharge (often manifested only by a coating of stools with exudate), or scant rectal bleeding, to symptoms of overt proctitis, including severe rectal pain, tenesmus, and constipation.^{56–58} External inspection of the anus only occasionally shows erythema and abnormal discharge, but anoscopy commonly reveals mucoid or purulent exudate (often localized to the anal crypts), erythema, edema, friability, or other inflammatory mucosal changes.⁵⁷ Several studies have suggested that fewer than 10% of rectal gonococcal infections in men and women are symptomatic, but many of these studies may have ignored or failed to elicit more subtle or ill-defined symptoms. Moreover, most studies have been affected by sample bias, failing to distinguish among patients being screened for gonorrhea, those attending spontaneously because of symptoms, and those responding to epidemiologic investigation of infected partners. One study⁵⁷ found that among MSM examined because they were sexual contacts of men with gonorrhea, 87 (57%) of 152 infected men had rectal symptoms, compared with 66 (41%) of 162 men from whom *N. gonorrhoeae* was not isolated ($p = 0.01$). However, infection with other pathogens was not investigated. A prospective study that was controlled for the reason for the visit showed that while a history of recent exposure to a sexual partner with gonorrhea was common in asymptotically infected patients, in patients attending the clinic for other reasons, *N. gonorrhoeae* was isolated from 31 (27%) of 114 symptomatic men but from only 6 (9%) of 64 asymptomatic men ($p < 0.01$).⁵⁸

PHARYNGEAL INFECTION

Among patients with gonorrhea, pharyngeal infection occurs in 3–7% of heterosexual men, 10–20% of heterosexual women, and 10–25% of homosexually active men. In studies performed prior to the AIDS era, the pharynx was the sole site of infection in less than 5% of patients irrespective of gender or sexual orientation.^{18,56,60–62} Among MSM, shifting prevalence of pharyngeal and rectal infection, as well as other published data, suggests that the frequency of fellatio has increased while the frequency of anal intercourse has declined in response to the HIV/AIDS epidemic. Gonococcal infection is transmitted to the pharynx by orogenital sexual contact and is more efficiently acquired by fellatio than by cunnilingus.⁶³

Anecdotal reports suggest that gonococcal infection may cause acute pharyngitis or tonsillitis and occasionally is associated with fever or cervical lymphadenopathy, but over 90% of pharyngeal infections are asymptomatic.^{18,60,61} Evaluation of pharyngeal symptoms is confounded, however, by the intriguing observation that among clients of STD clinics, sore throat and perhaps overt pharyngitis are correlated with a

history of fellatio but not with isolation of *N. gonorrhoeae* or other sexually transmitted organisms.^{18,63} Cunnilingus has not been associated with pharyngeal symptoms.

The clinical and epidemiologic significance of pharyngeal gonococcal infection may be greater than previously appreciated. The occasional occurrence of symptomatic pharyngitis and a possible increased risk of DGI in persons with pharyngeal gonorrhea¹⁸ are countered by the usual absence of symptoms and a spontaneous cure rate that approaches 100% within 12 weeks of infection.^{64,65} In addition, the transmission of pharyngeal gonorrhea to sex partners has been thought to be inefficient and relatively rare. However, in one study,¹³ 17 (26%) of 66 MSM with urethral gonorrhea acknowledged insertive oral sex but not insertive anal sex in the preceding 2 months. In this study, insertive oral sex was independently associated with both the urethral gonorrhea (odds ratio of 4.4, 95% confidence interval of 1.4, 9.4). Thus, pharyngeal infections may now be an important source of urethral gonorrhea in MSM.

UNCOMPLICATED INFECTION OF OTHER SITES

Gonococcal conjunctivitis is rare in adults; it is most often seen in patients with concomitant anogenital gonorrhea, presumably due to autoinoculation.⁶⁶ Accidental conjunctival infection has been emphasized as a hazard for laboratory personnel working with *N. gonorrhoeae*.^{67,68} An outbreak of 13 cases of gonococcal conjunctivitis was attributed to the cultural practice of ocular irrigation with urine.⁶⁹ Although usually described as a severe infection with a high risk of sequelae, mild or asymptomatic conjunctival gonorrhea infection occurs as well.

Primary cutaneous infection with *N. gonorrhoeae* has been reported rarely^{70–72} and usually presents as a localized ulcer of the genitals, perineum, proximal lower extremities, or finger. In many reports, simultaneous infection with other etiologic agents such as herpes simplex virus, *Haemophilus ducreyi*, and other pyogenic organisms was not excluded, and primary gonococcal infection could not be differentiated from secondary colonization of a preexisting lesion. Gonococcal infection of a congenitally patent median raphe duct of the penis is an uncommon but well-documented occurrence.⁷¹ Such infections usually occur in patients with anogenital gonorrhea, but exceptions have been reported.⁷²

DIFFERENTIAL DIAGNOSIS OF UNCOMPLICATED GONORRHEA

In males, gonococcal urethritis usually causes more florid signs and symptoms than nongonococcal urethritis and has a more abrupt onset, more prominent dysuria, and a urethral

discharge that is more profuse and more purulent in appearance.^{45,46} Additionally, the incubation period for gonorrhea usually is shorter than that of nongonococcal urethritis. Nonetheless, there is sufficient overlap in all these features that clinical differentiation is sometimes unreliable and must be corroborated by laboratory tests.⁴⁵ For the diagnosis of urogenital infection in women and for anorectal or pharyngeal infections, clinical differentiation of gonococcal from other causes is even less reliable than for urethritis in men, and laboratory diagnosis is mandatory. Nonetheless, a careful history and use of clinical predictors of infection for directing presumptive therapy in populations at increased risk are appropriate and desirable because expeditious therapy is likely to reduce complications and reduce further transmission of infection. Differential diagnosis is discussed more completely in Chapters 55, 56, and 59–61.

COMPLICATED GONOCOCCAL INFECTIONS

■ LOCAL COMPLICATIONS IN MEN

In men, the most common local complication of gonococcal urethritis is epididymitis (see Chapter 60), a syndrome that occurred in up to 20% of infected patients prior to the availability of modern antimicrobial therapy.⁴³ At present, the most common causes of acute epididymitis in patients under age 35 are *C. trachomatis*, *N. gonorrhoeae*, or both organisms.⁷³ Patients with acute epididymitis tend to present with unilateral testicular pain and swelling, and most patients with gonococcal epididymitis have overt urethritis when they present.

Penile lymphangitis, sometimes associated with regional lymphadenitis, is an uncommon minor complication of gonococcal urethritis, as is penile edema (“bull-headed clap”), a syndrome that also may accompany nongonococcal urethritis or genital herpes.⁷⁴ The pathogenesis of penile edema is unclear; swelling resolves with successful therapy and most such patients lack palpable cords or other clear signs of penile thrombophlebitis or lymphangitis. Postinflammatory urethral strictures were common complications of untreated gonorrhea in the preantibiotic era but are now rare.⁴³ Many such strictures, however, probably were related to repeated infection or due to the caustic urethral irrigations used for treatment, and stricture is rare today if effective systemic antimicrobial therapy is instituted promptly. Periurethral abscesses also are rare.

■ LOCAL COMPLICATIONS IN WOMEN

Pelvic inflammatory disease

In acute PID, the clinical syndrome comprised primarily of salpingitis, and frequently including endometritis, tubo-

ovarian abscess, or pelvic peritonitis is the most common complication of gonorrhea in women, occurring in an estimated 10–20% of those with acute gonococcal infection.^{75,76} PID is the most common of all complications of gonorrhea, as well as the most important in terms of public-health impact, because of both its acute manifestations and its long-term sequelae (infertility, ectopic pregnancy, and chronic pelvic pain). Patients with gonococcal salpingitis usually present with various combinations of lower abdominal pain, dyspareunia, abnormal menses, intermenstrual bleeding, or other complaints compatible with intraabdominal infection.⁷⁷ On physical examination, these patients usually are found to have lower abdominal, uterine, or adnexal tenderness, cervical motion pain, abnormal cervical discharge, and sometimes an adnexal mass or tubo-ovarian abscess.⁷⁷ Gram-stained smears of cervical secretions may show gram-negative intracellular diplococci. However, as in women with uncomplicated gonococcal cervicitis, the Gram stain is negative in 40–60% of women with gonococcal PID. Other findings that may or may not be present include fever, leukocytosis, elevation of the erythrocyte sedimentation rate, and increased levels of C-reactive protein.⁷⁷ Women with gonococcal salpingitis often appear more acutely ill than women with nongonococcal salpingitis, are more often febrile (74 vs. 22%), and are more likely to present during the first 3 days of symptoms (32 vs. 15%).⁷⁷ Despite the apparently greater clinical severity of gonococcal PID, laparoscopic studies show that the severity of tubal disease is similar in women with gonococcal or nongonococcal salpingitis.⁷⁷ The pathophysiology, differential diagnosis, and clinical spectrum of acute salpingitis are more fully discussed in Chapter 56.

Apart from PID, Bartholin’s gland abscess is the most common urogenital complication of gonorrhea in women. *N. gonorrhoeae* was isolated from the Bartholin’s gland ducts of 52 (28%) of 183 women with urogenital gonorrhea, 10 of whom (6%) had enlargement and tenderness of the gland.⁷⁸ Other bacteria, including *C. trachomatis*, are responsible for many cases of bartholinitis, but tests for gonococcal infection are indicated for all women with this syndrome.

■ SYSTEMIC COMPLICATIONS: DISSEMINATED GONOCOCCAL INFECTION

Disseminated gonococcal infection, usually manifested by the acute arthritis-dermatitis syndrome, is the most common systemic complication of acute gonorrhea. The syndrome has been estimated to occur in 0.5–3% of patients with untreated mucosal gonorrhea, although the higher estimates were made in settings where the prevalence of gonococcal isolates likely to disseminate was high.^{79–81} DGI results from gonococcal bacteremia and is most often manifested by acute arthritis, tenosynovitis, dermatitis, or a combination of these findings. Patients with these clinical manifestations

are often stratified on the basis of culture results into proven, probable, and possible DGI.⁸² Patients with positive cultures from blood, joint fluid, skin lesions, or otherwise sterile sources constitute less than 50% of DGI cases and are considered to have proven DGI.^{79–82} In more than 80% of DGI patients, *N. gonorrhoeae* may be cultured from the primary mucosal site(s) of infection (anogenital or pharyngeal cultures) or from a sexual partner^{79–82}; in the absence of positive blood or other sterile-site cultures, these patients are usually referred to as having probable DGI. Patients with an appropriate clinical syndrome and the expected response to therapy but with negative cultures for *N. gonorrhoeae* are referred to as having possible DGI. However, recognition of patients with DGI is sometimes delayed, or even overlooked, because of the wide variety of clinical findings associated with this syndrome and the mistaken assumption that patients with gonococcal bacteremia have genitourinary signs and symptoms, high fever, marked leukocytosis, or other signs of clinical toxicity.

The most common clinical manifestations of DGI are joint pain and skin lesions. Although the “classic” skin lesion of gonococcal dermatitis is a tender, necrotic pustule on an erythematous base, in many patients skin lesions also may evolve from, or present as, macules, papules, pustules, petechiae, bullae, or ecchymoses.^{79–82} The skin lesions tend to be located on distal portions of the extremities and usually number fewer than 30.^{80,82} Many patients with gonococcal dermatitis have arthralgia or tenosynovitis early in the disease, and frank arthritis with effusion tends to occur somewhat later. Approximately 30–40% of patients with DGI have overt arthritis.^{79–82} Any joint may be involved, although DGI most often involves wrist, metacarpophalangeal, ankle, and knee joints. Synovial fluid cultures are rarely positive in patients with synovial fluid leukocyte counts of less than 20,000 per mm³, whereas cultures are often positive in patients with more than 40,000 white blood cells per mm³.^{81,82} The manifestations of gonococcal arthritis and differentiation of this process from other acute arthritides are more fully discussed in Chapter 67.

Proving infection in patients with DGI is sometimes difficult. The bacteremia associated with DGI is not continuous, and positive blood cultures become less common as the duration of clinical signs and symptoms increases. Overall, only 20–30% of DGI patients have positive blood cultures.^{79–82} In some areas, AHU/IA-1 and AHU/IA-2 strains of *N. gonorrhoeae* cause most cases of DGI; these strains also tend to be associated with asymptomatic urogenital infection, increased susceptibility to penicillin G, and resistance to the complement-mediated bactericidal activity of normal human serum.^{80,81} Although most gonococci isolated from patients with DGI exhibit such “serum resistance,” isolates from patients with suppurative arthritis are less resistant than those from patients with tenosyn-

ovitis or dermatitis.^{81,83} These organisms also are more likely to be inhibited by the concentrations of vancomycin contained in selective media for gonococcal isolation from mucosal sites (e.g., modified Thayer-Martin medium) and by the sodium polyanethiosulfonate anticoagulant used in many blood culture media.^{84–86} These problems may be overcome through the use of alternative media; however, use of alternative media is relatively uncommon because of lack of knowledge of their availability. In addition, DGI is often not included in the differential diagnosis of acute, asymmetric arthritis or dermatitis in young, sexually active patients because of the erroneous expectation that patients with DGI are likely to have signs and symptoms of urogenital infection. Mucosal infection in patients with DGI often is asymptomatic. All these problems contribute to underdiagnosis.

DGI is probably more common in women than in men.^{79–82} In most cases, bacteremia probably begins soon after infection; in about half of the women with DGI, the onset of symptoms occurs within 7 days following menstruation.^{79–82} Several studies also have cited pregnancy and pharyngeal gonorrhea as risk factors for DGI.^{18,79–82} Deficiency of complement either due to inherited complement deficiency or due to episodic complement deficiency in association with clinical flares of other diseases such as lupus erythematosus may predispose individuals to gonococcal or meningococcal bacteremia.^{80,81,87} Only a small percentage of patients with DGI, however, have complement deficiency syndromes, and routine screening of DGI patients for complement deficiency is probably not indicated. Such screening should be performed, however, in patients with second episodes of systemic gonococcal or meningococcal infection.^{81,87}

The characteristic response to appropriate antimicrobial therapy has been interpreted as evidence of DGI in patients from whom *N. gonorrhoeae* could not be isolated.⁸² Over 90% of patients are subjectively improved within 48 hours of initiating therapy, and more than 90% of febrile patients become afebrile over the same period.⁸² DGI due to PPNG⁸⁸ or gonococci with chromosomally mediated antibiotic resistance⁸⁹ has become apparent with failure to respond clinically to penicillin therapy; ceftriaxone or other antibiotics with proven activity against antibiotic-resistant gonococci should be used rather than penicillin for all patients with suspected DGI.

Gonococcal endocarditis and meningitis

Gonococcal endocarditis is an uncommon complication of gonococcal bacteremia, occurring in an estimated 1–3% of patients with DGI.^{79,80} Nonetheless, recognition of gonococcal endocarditis among patients with DGI is essential because of the possibility of rapidly progressive valvular

damage with life-threatening consequences. The aortic valve appears to be infected most often in patients with gonococcal endocarditis, and in the preantibiotic era, most patients died of aortic valve incompetence and acute heart failure within 6 weeks.

Fewer than 25 cases of gonococcal meningitis have been reported. Case reports of this complication describe patients with typical presentations of acute bacterial meningitis, usually without typical findings of DGI.^{90,91} *N. gonorrhoeae* is indistinguishable from *N. meningitidis* on Gram's stain of cerebrospinal fluid.

MENINGOCOCCAL INFECTIONS

Several reports have documented that infection or colonization with *N. meningitidis* may occur at all mucosal sites compatible with sexual transmission. Although rare in comparison with gonorrhea, meningococcal infections may mimic nearly all the clinical manifestations of gonorrhea. Pharyngeal colonization with *N. meningitidis* was documented in 17.2% of 2224 patients attending an STD clinic from 1970 to 1972,¹⁸ a rate comparable with that in the general population.⁹² However, subgroups of patients attending STD clinics have been found to have differing rates of carriage. Among 398 STD clinic patients with gonorrhea, *N. meningitidis* was isolated from the oropharynxes of 44 (52%) of 85 MSM, compared with 58 (19%) of 313 heterosexual men and women ($p < 0.0001$). In addition, *N. meningitidis* was isolated significantly less frequently from heterosexual African Americans than from heterosexual whites ($p < 0.0001$).⁹³ These prevalences parallel the relative frequencies with which these population groups acknowledge oral sex (MSM > heterosexual whites > heterosexual African Americans).⁹⁴ Other investigators reported a similar prevalence (42.5%) of pharyngeal meningococcal colonization in 815 homosexual men attending an STD clinic.⁶²

Genital and anorectal colonization with meningococci also occurs. In studies conducted in STD clinics in the 1970s, the prevalence of urethral colonization with *N. meningitidis* was 0.2–0.4% in heterosexual men, but was up to 1% in MSM.^{95–98} In MSM, meningococci accounted for 15 (13%) of 114 urethral isolates of oxidase-positive, gram-negative diplococci, compared with 4 (1.1%) of such 368 urethral isolates from heterosexual men.⁹⁸ Similarly, 37 (21%) of 175 such isolates from the rectums of MSM were *N. meningitidis*.⁹⁸ In women, the prevalence of cervical, urethral, or rectal colonization with *N. meningitidis* was similar to that of urethral infection in heterosexual men.^{92,95–98} However, in London, England, in the late 1980s, meningococci were isolated from only 11 (0.2%) of 5571 urethral specimens in MSM, and only 4% of oxidase-positive, gram-negative diplococci were *N. meningitidis*.⁹⁹ In the same study, no meningococci were isolated from almost 25,000 urethral or cervical specimens

from women or heterosexual men. Thus, it is likely that the prevalence of anogenital meningococcal colonization varies geographically and over time. All suspicious anorectal or urethral isolates from homosexual men, as well as pharyngeal isolates from all patients, should be tested to distinguish *N. gonorrhoeae* from *N. meningitidis*.

The pathogenicity of anogenital meningococcal infection and the frequency with which it produces clinical disease are unclear, and no systematic studies have been performed to determine its mode of acquisition or the prevalence of infection in the sex partners of colonized patients. However, 50–80% of meningococcal isolates in this setting are serogroupable and hence presumably pathogenic; serogroups B, C, X, and Y account for most anogenital isolates.^{62,93,95,96} Several case reports have linked meningococcal isolation to urethritis, epididymitis, vaginal discharge, acute salpingitis, and DGI-like syndromes.^{40,92,95,96,99–102} Therapy has not been formally studied, but symptomatic rectal or genital meningococcal infections have been cured in small numbers of patients receiving treatment with regimens recommended by the Centers for Disease Control and Prevention (CDC) for gonorrhea. Thus, the preponderance of evidence suggests that genital meningococcal infection sometimes is sexually transmitted and, when detected, should be managed in the same manner as gonorrhea.

LABORATORY DIAGNOSIS

The laboratory diagnosis of gonococcal infections depends primarily on identification of *N. gonorrhoeae* at infected sites by microscopic examination of stained smears, by culture, or increasingly by immunochemical or genetic detection of the organism. Principals of several techniques are discussed in Chapter 34 and details of several techniques, and particularly culture, are included in Chapter 52.

■ IDENTIFICATION OF *NEISSERIA GONORRHOEAE* IN SECRETIONS

Culture

While culture for *N. gonorrhoeae* detection from urogenital sites has been supplanted, in large part by nonculture methods in North America and Western Europe, isolation remains the diagnostic standard for gonococcal infections and continues to be used in many locations. Currently available antibiotic-containing selective media (e.g., modified Thayer-Martin medium) have diagnostic sensitivities of 80–95% for promptly incubated specimens, depending in part on the anatomic site being cultured (Table 35-1). For urethral specimens from symptomatic men, cultures on selective and nonselective media are equally sensitive, because the concentration of gonococci in the urethra usually exceeds that of other

Table 35-1. Frequency of Isolation of *Neisseria Gonorrhoeae* by Site from Patients with Uncomplicated Gonorrhea^a

	<i>N</i>	Total Positive Number (%)	Only Site Positive, Number (%)
<i>Women^b</i>	162		
Endocervix		155 (96)	75 (46)
Anal canal		62 (38)	3 (2)
Pharynx		35 (22)	4 (3)
<i>Heterosexual men^c</i>	177		
Urethra		177 (100)	166 (94)
Pharynx		11 (6)	0
<i>Homosexual men^d</i>	355		
Urethra		205 (58)	146 (41)
Anal canal		177 (50)	109 (31)
Pharynx		62 (17)	18 (5)

^aAnalysis limited to patients for whom all indicated sites were cultured; single cultures on modified Thayer–Martin medium were used.

^bWomen who had undergone hysterectomy were excluded.

^cData from Handsfield HH, et al. Correlation of auxotype and penicillin susceptibility of *Neisseria gonorrhoeae* with sexual preference and clinical manifestations of gonorrhoea. *Sex Transm Dis* 1980; 7: 1.

^dData from Handsfield HH, et al. Correlation of auxotype and penicillin susceptibility of *Neisseria gonorrhoeae* with sexual preference and clinical manifestations of gonorrhoea. *Sex Transm Dis* 1980; 7: 1; Tice AW, Rodriguez VL. Pharyngeal gonorrhoea. *JAMA* 1981; 246: 2717.

flora. In contrast, selective media are preferred for culturing the endocervix, rectum, and pharynx, where other, less fastidious bacteria often outnumber *N. gonorrhoeae*.^{85,86} The highest yield from all sites probably results when both selective and nonselective media are inoculated simultaneously with specimens obtained using separate swabs.^{4,85,103,104} However, the incremental yield is small, and this procedure is not sufficiently cost-effective to be recommended for routine use.

For women, single cultures on most selective media detect 80–90% of endocervical infections.^{47,48,85,104} Although the urethra, Bartholin's gland ducts, and Skene's glands are commonly infected, they are rarely the sole site of infection in women with intact cervixes and therefore are not usually cultured. In women who have undergone hysterectomies, however, urethral culture gives highest yield.⁵⁰ *N. gonorrhoeae* may be isolated from the anal canal of 35–50% of women with gonorrhoea, and this is the sole site of infection in up to 5%.^{47,48,55} Similarly, the pharynx is infected in about 5–20% of women with gonorrhoea, but is the sole site of infection in fewer than 5%.^{18,47,48} The increased yield from sampling sites in addition to the cervix results in part from reduced sampling error. Thus the proportion of women found to have a positive culture from the anal canal or pharynx alone might be still lower if duplicate endocervical specimens were cultured routinely.^{85,104} Accordingly, for women, cultures of the urethra,

accessory gland ducts, anal canal, and pharynx should be considered optional, depending on symptoms, sites exposed, culture methods employed, and available resources.

The sites to be cultured in men also depend on sexual orientation and the anatomic sites exposed. For symptomatic heterosexual men, culture of urethral exudate alone is usually sufficient, but pharyngeal cultures may be useful for men with pharyngitis who practice cunnilingus or for men who have performed cunnilingus with a woman known to have gonorrhoea.¹⁸ Although screening of asymptomatic men for urethral gonorrhoea has been recommended in the past, in many areas the prevalence of the AHU/IA strains that cause most asymptomatic infections has declined, and the yield of culture may be low enough to permit discontinuation of this practice. For example, at the Seattle-King County STD clinics in 1993 and 1994, *N. gonorrhoeae* was isolated with urethral cultures from only 6 (0.12%) of 5179 men who had no symptoms of urethritis, no discharge on examination, and were not contacts of women with gonorrhoea (authors' unpublished data). Similarly, only 34 (1%) of 3271 men seen at a Birmingham, AL, STD clinic between January 1, 1994 and June 30, 1995 with positive cultures for *N. gonorrhoeae* were not treated at the time of their initial presentation to the clinic (authors' unpublished data). Among MSM, the rectum is infected almost as frequently as the urethra, although the actual

yield depends on patients' specific sexual practices.^{59,62,104} Isolated pharyngeal infection occurs in about 5% of infected homosexual men.^{13,18,59,61,105} Although gonococcal urethritis is common, asymptomatic urethral infection is rare in this population.^{59,62} Thus, in screening asymptomatic MSM for whom all three sites are potentially exposed, anorectal culture gives the highest yield, and pharyngeal cultures are desirable. However, these issues have not been thoroughly reexplored since the mid-1980s, when many urban homosexually active men made major changes in sexual behavior in response to the AIDS epidemic.

Several reports have documented failure of vancomycin-containing selective culture media to support growth of vancomycin-sensitive gonococci.^{84,106} The prevalence of such strains is highly variable, but in 1970s it accounted for up to 30% of gonococcal isolates in some geographic areas.^{84,86,106} The ability to culture these organisms also is inoculation dependent, with greater inhibition occurring with smaller inocula.^{84,86,106}

Stained smears

Gram's stain, methylene blue, acridine orange, and several other dyes have been used to prepare clinical material for microscopic examination for gonococci, but Gram's stain has been the most extensively studied. For examination of clinical material, a smear is considered positive for gonorrhea when gram-negative diplococci with typical morphology are identified within or closely associated with polymorphonuclear leukocytes (Fig. 35-7); it is considered equivocal if only extracellular organisms or morphologically atypical intracellular gram-negative diplococci are seen; and it is considered negative if no gram-negative diplococci are present. Nonpathogenic *Neisseriaceae* other than *N. meningitidis*, which are morphologically indistinguishable

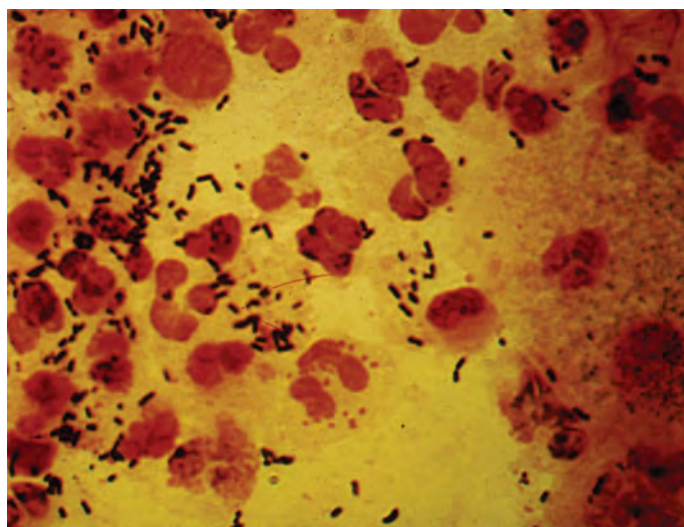


FIGURE 35-7. Gram-stained smear showing polymorphonuclear leukocytes with intracellular gram-negative diplococci in urethral exudate from a man with gonococcal urethritis ($\times 1000$).

from *N. gonorrhoeae*, are generally not cell associated. *Acinetobacter* spp are bipolar-staining gram-negative bacilli that, contrary to earlier reports, are easily distinguished from *N. gonorrhoeae* by experienced microscopists. Table 35-2 shows the sensitivity and specificity of Gram-stained smears for various categories of genital and rectal infection relative to isolation of *N. gonorrhoeae*.

For evaluation of men with symptoms or signs of urethritis, the urethral smear is sufficiently sensitive and specific that additional testing may be considered optional for routine care.¹⁰⁷ In some settings such as for monitoring of antimicrobial susceptibility, culture remains an important initial step. The performance of stained smears and culture likewise each depend in part, however, on specimen collection technique and the experience of the microscopist. Smears from the endocervix or rectum are less sensitive than those from the urethra, although positive smears of properly collected specimens are highly specific when examined by experienced personnel, and they facilitate expeditious therapy of infected patients, especially when the index of suspicion is high.^{75,107,108} On the other hand, in most clinical settings where the prevalence of gonorrhea is relatively low even among women with cervicovaginal complaints, the yield and predictive value of stained smears of cervical secretions, and thus the utility of the test, is low. Stained smears should be used as an adjunct to, but not replacement for, more specific tests. The sensitivity of anorectal smears for evaluation of patients with symptoms of proctitis is enhanced when the exudate is obtained by direct visualization using an anoscope rather than blindly,¹⁰⁹ even though anoscopy does not apparently improve the sensitivity of culture.¹¹⁰ Smears are not commonly obtained from the urethra or accessory gland ducts of women, but should be performed if abnormal exudate is expressed or the patient has had a hysterectomy. The Gram's stain smear has not been studied in pharyngeal gonococcal infection, but is generally believed to be both insensitive and nonspecific; it is not recommended.

Nonculture diagnostic techniques

A major impediment to use of culture for gonorrhea diagnosis in many clinical settings are the time, expense, and logistical limitations such as specimen transport to laboratories for testing, a process that may take several days and result in temperature variation or other circumstances that can jeopardize culture viability.¹¹¹ In recent years, reliable nonculture assays for gonorrhea detection have become available and are being used increasingly. In 2001, it was estimated that about 25 million tests for gonorrhea diagnosis were performed in the United States, of which approximately over 75% were nonculture tests.¹¹² Given that these tests are likely somewhat more sensitive than culture for diagnosis of urogenital infection, their continuing promotion by manufacturers, and the fact that specimens collected for gonorrhea diagnosis with these tests also can be frequently

Table 35-2. Sensitivity and Specificity of Gram-Stained Smears for Detection of Genital or Anorectal Gonorrhea

Site and Clinical Setting	Sensitivity ^a	Specificity ^b
<i>Urethra</i>		
Men with symptomatic urethritis	90–95	95–100
Men with asymptomatic urethral infection	50–70	95–100
<i>Endocervix</i>		
Uncomplicated gonorrhea	50–70	95–100
Pelvic inflammatory disease	60–70	95–100
<i>Anorectum</i>		
Blind swabs	40–60	95–100 ^c
Anoscopically obtained specimens	70–80	95–100 ^c

^aSensitivity—percent of patients with positive cultures who have positive Gram-stained smears.

^bSpecificity—percent of patients with negative cultures whose Gram-stained smears also are negative.

^cThe studies showing 95–100% specificity for anorectal smears did not report whether meningococcal infection was distinguished from gonorrhea. Until further data are available, a positive anorectal smear should be considered highly specific for either gonococcal or meningococcal infection.

Source: Data from Handsfield HH, et al. Asymptomatic gonorrhea in men: Diagnosis, natural course, prevalence and significance. *N Engl J Med* 1974; 290: 117; Jacobs NF, Kraus SJ. Gonococcal and nongonococcal urethritis in men: Clinical and laboratory differentiation. *Ann Intern Med* 1975; 82:7; Thin RN, Shaw EJ. Diagnosis of gonorrhea in women. *Br J Vener Dis* 1979; 55: 10; Barlow D, Phillips I. Gonorrhea in women: Diagnostic, clinical, and laboratory aspects. *Lancet* 1978; 1: 761; Wallin J. Gonorrhea in 1972: A 1-year study of patients attending the VD unit in Uppsala. *Br J Vener Dis* 1974; 51: 41; Rothenberg RB, et al. Efficacy of selected diagnostic tests for sexually transmitted diseases. *JAMA* 1976; 235: 49; Wald ER. Diagnosis by Gram stain in the female adolescent. *Am J Dis Child* 1977; 131: 1094; William DC, et al. The utility of anoscopy in the rapid diagnosis of symptomatic anorectal gonorrhea in men. *Sex Transm Dis* 1981; 8: 16; Deheragoda P. Diagnosis of rectal gonorrhea by blind anorectal swabs compared with direct vision swabs taken via a proctoscope. *Br J Vener Dis* 1977; 53: 311.

used to simultaneously test for *C. trachomatis*, their utilization is likely to continue to increase. At the same time, there is an increasing need for culture-based regional monitoring of gonococcal antimicrobial susceptibility to guide therapeutic choices (see below).

Nonamplified DNA probe tests (e.g., Gen-Probe Pace 2) are often used as nonculture tests for gonorrhea. Compared to culture, this test, based on a single-stranded DNA probe designed to hybridize to *N. gonorrhoeae* rRNA, has sensitivities of 89–97% and specificity of 99%, has performed comparably

to culture on selective media, and is often available for costs similar to culture.^{113–115}

More recently, nucleic acid amplification tests (NAATs) for gonorrhea diagnosis have become widely available.^{116,117} Assays based on polymerase chain reaction (PCR), transcription-mediated amplification (TMA), and other nucleic acid amplification technologies have been developed. As a group, commercially available NAATs are more sensitive than culture for gonorrhea diagnosis and specificities are nearly as high as for culture. NAATs have additional advantages of providing performance similar to that of urogenital swabs when voided urine or, for women, vaginal swabs are used as specimens. This simplified specimen collection has permitted gonorrhea screening for men and women in settings where genital examinations are impractical, but disease prevalence may be high. In addition, like the nonamplified tests mentioned above, a single specimen collected for most NAATs can be tested for both *N. gonorrhoeae* and *C. trachomatis*. Although not currently approved for these specimens, studies underway evaluating the performance of NAATs for diagnosis of pharyngeal and rectal infection suggest that they will perform well at nonurogenital sites of infection.

Fluorescein-conjugated antibodies have occasionally been employed to detect *N. gonorrhoeae*, but this method has not proved sufficiently sensitive or specific for routine use.¹¹⁸ Immunologic or biochemical detection of gonococcal antigens or metabolic products, including surface proteins, endotoxin, and oxidase or other enzymes, also has been investigated in the past but currently seem less promising than nucleic acid detection.

Collection of clinical specimens

Urethral exudate from men may be obtained by passage of a small swab 2–4 cm into the urethra²⁸ or by collecting the first 15–30 mL of voided urine.^{118,119} Although the latter method obviates the discomfort of passing a urethral swab or loop, collection and culture of urine are time consuming, depend in part on the ability of the patient to provide a proper specimen, and require prompt processing for culture because the urine from some individuals is rapidly bactericidal for *N. gonorrhoeae*.¹²⁰ Similar specimen handling and transport have far less effect on NAAT performance. For collection of endocervical specimens, the cervix should be cleansed of external exudate or vaginal secretions and a swab inserted 1–2 cm into the external os and rotated gently for up to 10 seconds.¹²¹ When personal or logistic constraints preclude speculum examination, a vaginal specimen may be obtained by a clinician or the patient using a swab or a tampon.¹²² With this technique, the sensitivity of NAATs are excellent, whereas there is a modest reduction in culture sensitivity and a marked reduction in the sensitivity of Gram-stained smears.

Nucleic acid amplification assays have been studied for clinical specimens from sites other than the urogenital tract. Emerging data suggest that most currently available NAATs are substantially more sensitive for gonorrhea detection than conventional culture. The specificity of NAATs for diagnosis of extragenital gonorrhea is slightly less than that for culture, although the most appropriate gold standard for nonculture diagnosis remains an area of controversy which may impact performance estimates.

Anorectal specimens from patients without symptoms of proctitis may be obtained by blindly passing a swab 2–3 cm into the anal canal, using lateral pressure to avoid entering any fecal mass. If gross fecal contamination of the swab occurs, it should be discarded and another specimen obtained. For symptomatic patients, anorectal specimens should be obtained under direct vision using anoscopy, which increases the sensitivity of the smear.^{109,110} Pharyngeal specimens are obtained by swabbing the posterior pharynx, including the tonsillar areas and faucial pillars.

SEROLOGIC DIAGNOSIS

Serologic tests have been developed to detect antibodies to *N. gonorrhoeae* or its components using complement fixation, immunoprecipitation, bacterial lysis, immunofluorescence, hemagglutination, latex agglutination, enzyme-linked immunoabsorbance, and other techniques.¹²³ Many of these methods have proved useful for studies of the immune response and pathogenesis of gonorrhea. However, most reported serodiagnostic tests have sensitivities of about 70% and specificities of about 80% for patients with uncomplicated gonorrhea and thus are not useful for screening, case finding, or diagnosis, or other clinical purposes in the United States.^{124,125}

THERAPY OF GONOCOCCAL INFECTIONS: ANTIMICROBIAL SUSCEPTIBILITY OF *N. GONORRHOEAE* AND DEVELOPMENT OF RESISTANCE

While the majority of gonococci remain susceptible to a variety of antimicrobial agents, selection of strains with relative or absolute resistance is readily accomplished both in the laboratory and in the real world, and in vivo development of resistance continues to dictate changes in recommended therapy for gonorrhea. The prevalence of resistance varies geographically, and it is important to know the sensitivities of isolates from the region in which one practices. In general, the resistance is mediated through either the cumulative effect of chromosomal mutations or by single-step acquisition of plasmids that encode for high-level resistance. Since many patients with gonorrhea are treated syndromically and formal agar dilution

MIC determination for *N. gonorrhoeae* is time consuming and not widely available, recommendations for gonorrhea therapy usually only consider regimens with efficacy of 95% or greater.¹²⁶ To accomplish this, both the United States and the World Health Organization use sentinel surveillance systems (see below) to monitor susceptibility and guide their gonorrhea treatment recommendations.

Prior to the mid-1930s, when sulfanilamide was introduced, gonorrhea therapy involved local genital irrigation with antiseptic solutions such as silver nitrate or potassium permanganate.^{3,43} By 1944, however, many gonococci had become sulfanilamide resistant, and infection persisted in about one-third of patients treated with maximal doses. Fortunately, in 1943 the first reports of the near 100% utility of penicillin for gonorrhea therapy were published,¹²⁷ and by the end of World War II, as penicillin became available to the general public, it quickly became the therapy of choice. Since then, continuing development of antimicrobial resistance by *N. gonorrhoeae*^{128,129} led to regular revisions of recommended gonorrhea therapy. From the 1950s until the mid-1970s, gradually increasing chromosomal penicillin resistance led to periodic increases in the amount of penicillin required for reliable therapy. Similar trends in MICs were also observed for macrolide and tetracycline antibiotics, the other two major antibiotics used at the time.¹²⁹ In 1976, however, strains of *N. gonorrhoeae* with high-level penicillin resistance due to plasmid-mediated β -lactamase production were reported initially as having originated in West Africa and the Far East.¹³⁰ Thus, for the first time, through single-step plasmid acquisition, gonococci had become impervious to clinically useful doses of penicillin. About 10 years later, gonococci with high-level, plasmid-mediated resistance to tetracycline were first described,¹³¹ further reducing the utility of the tetracycline family of drugs for gonorrhea treatment. As a consequence, by the late 1980s, penicillins and tetracyclines were no longer recommended for gonorrhea therapy.

In addition to resistance to penicillin, tetracyclines, and erythromycin, in 1987, clinically significant chromosomally mediated resistance to spectinomycin—another drug recommended for gonorrhea therapy—was described in U.S. military personnel in Korea.¹³² In Korea, because of the high prevalence of PPNG, in 1981, spectinomycin had been adopted as the drug of choice for gonorrhea therapy. By 1983, however, spectinomycin treatment failures were beginning to occur in patients with gonorrhea, and over the next 2 years, the prevalence of spectinomycin-resistant *N. gonorrhoeae* increased. Following recognition of the outbreak of spectinomycin-resistant gonococci in Korea, ceftriaxone became the drug of choice for treatment of gonorrhea in U.S. military personnel in that country.¹³² Sporadic cases of spectinomycin-resistant gonorrhea have been reported elsewhere, but such strains remain rare in the United States, possibly related to relatively low utilization of this relatively expensive therapeutic agent.^{133,134}

Beginning in 1993, fluoroquinolone antibiotics were recommended for therapy of uncomplicated gonorrhea in the United States. These drugs were effective in single-dose, oral regimens, were unrelated to β -lactam antibiotics and thus could be administered to persons with penicillin allergy, and were well tolerated. These appealing characteristics contributed to their extensive use for gonorrhea therapy over the subsequent decade. By 2007, however, U.S. antimicrobial surveillance revealed that the prevalence of gonococcal strains with diminished fluoroquinolone susceptibility had exceeded 5% nationally, sparing no region and with particularly high prevalences in Hawaii, in the Western U.S., and among MSM nationwide. As a result, in 2007 the CDC opted to no longer recommend fluoroquinolone antibiotics for therapy of uncomplicated gonorrhea. This change meant that ceftriaxone and other cephalosporin antibiotics had become the sole class of antibiotics recommended as first-line therapy for gonorrhea.

In 1986, as the problems of antimicrobial resistance in *N. gonorrhoeae* in the United States were becoming apparent, the CDC reinstated sentinel surveillance of the antimicrobial susceptibility of *N. gonorrhoeae*.¹³⁵ In 2005, data from the systematic monthly testing of gonococcal isolates from 27 U.S. cities demonstrated that nearly 20% of isolates have one form or another of antimicrobial resistance.¹³⁶ The CDC sentinel surveillance system continues to document the substantial geographic diversity of antimicrobial-resistant *N. gonorrhoeae*.^{135,136}

CHOICE OF TREATMENT REGIMENS FOR *N. GONORRHOEA*

The choice of antimicrobial agents for gonorrhea therapy is influenced by a variety of factors in addition to the antimicrobial activity of drugs for *N. gonorrhoeae*.¹³⁷ Pharmacokinetic studies demonstrated that serum levels of penicillin equal to or greater than three times the MIC of the infecting strain of *N. gonorrhoeae* for 8 hours were needed to reliably cure uncomplicated infection¹³⁸; similar relationships between antimicrobial pharmacokinetics and gonococcal susceptibility are presumed to be operative for other antimicrobial agents. In general, single-dose, observed therapy is preferred for gonorrhea in order to overcome problems of patient compliance. In addition, the choice of antimicrobial agents for therapy is influenced by the probability that patients with acute gonococcal infection are coinfecting or have been exposed recently to other STD agents. Among coinfecting agents for patients with gonorrhea in the United States, *C. trachomatis* is preeminent. Up to 10–20% of men and 20–30% of women with acute urogenital gonorrhea are coinfecting with *C. trachomatis*.^{10,46,76,139–141} In addition, substantial numbers of women with acute gonococcal infection have simultaneous *T. vaginalis* infections. For several decades,

it was recommended widely that therapy for gonorrhea would also be effective against incubating syphilis. However, more recent data suggest that incubating syphilis is relatively rare in gonorrhea patients in the United States and the choice of treatment has no measurable effect on the frequency of syphilis.¹⁴² However, activity of selected agents against *Treponema pallidum* may remain an important consideration in some settings. Similarly, in Africa and other areas where chancroid is prevalent, patients may have been exposed to *H. ducreyi* at the time of contraction of gonorrhea.

Since 1985, the treatment recommendations published by the CDC for the United States have recommended single-dose therapy with medications effective for eradication of *N. gonorrhoeae*, followed by therapy expected to eradicate *C. trachomatis* infections (currently either azithromycin or doxycycline). This approach has been shown to be effective for the therapy of both the infections.^{139,140}

For over two decades, ceftriaxone—a third-generation cephalosporin—has been the most reliable single-dose regimen used for gonorrhea worldwide.¹⁴¹ The dose of ceftriaxone currently recommended for therapy of uncomplicated gonorrhea by the CDC is a single intramuscular injection of 125 mg,^{140,143} although in some settings 250 mg, the lowest unit dose commercially available, continues to be used. Either dose is highly effective for rectal and pharyngeal, as well as genital, gonorrhea.¹⁴⁴ Although a small percentage (<1%) of patients treated with ceftriaxone fail antimicrobial therapy, clinically significant ceftriaxone resistance has not been reported through 2005.^{136,141} The major drawbacks of ceftriaxone therapy for gonorrhea are the requirement for parenteral administration and the potential (albeit low) for reactions of patients allergic to β -lactam antibiotics. Cefixime, an orally absorbed cephalosporin with MICs for *N. gonorrhoeae* that are similar to ceftriaxone, provides a useful oral alternative to parenteral ceftriaxone and also was recommended by the CDC for gonorrhea in its 2006 *STD Treatment Guidelines*.¹⁴¹ However, at the time of writing, cefixime tablets are not commercially available in the United States.¹⁴¹

In 1984 a report was published describing the utility of norfloxacin, the first widely available fluoroquinolone antibiotic for treating gonorrhea.¹⁴⁵ Enthusiasm for gonorrhea therapy with earlier quinolones (nalidixic acid and rosoxacin) had been tempered by the tendency of gonococci to rapidly become resistant to the former and by the unacceptable neurotoxicity (primarily vestibular) of the latter.¹⁴⁶ Since that time, a number of other newer fluoroquinolones, including ciprofloxacin, ofloxacin, levofloxacin, and several others, have been evaluated as single-dose regimens with promising results.^{142,146} However, as early as 1988, there were reports of quinolone resistance among gonococcal isolates from the Philippines¹⁴⁷ and Southeast Asia, where some quinolone antibiotics are inexpensive and widely available, and by the mid-1980s quinolones were no longer reliable in

some Pacific and Asian countries. By 2006, surveillance in the United States showed that the prevalence of quinolone-resistant gonococci had increased to exceed 5% in heterosexual men and 35% among MSM, leading the CDC in 2007 to no longer recommend this class of antibiotics for therapy of uncomplicated gonorrhea.¹⁴⁸

Thus, there are currently few well-studied therapeutic alternatives to ceftriaxone for gonorrhea treatment. Limited data and ongoing studies suggest that cefpodoxime, cefuroxime, or other oral cephalosporins may be effective alternatives to ceftriaxone. A single 2-g dose of azithromycin has also been found to be effective for gonorrhea therapy,¹⁴⁹ although gastrointestinal side effects (nausea, vomiting) are relatively common with this regimen and there is reason for concern for the potential for *N. gonorrhoeae* to rapidly develop clinically significant resistance.

Each of the currently recommended treatment regimens has specific advantages and disadvantages that should be used to individualize therapy for gonorrhea. For example, single-dose oral regimens are desirable in terms of convenience and reduced risk for needle-stick exposures in health-care workers. For treatment of MSM with gonorrhea, the ceftriaxone regimen is preferred over other regimens. The strains of gonococci that occur in homosexual men are more likely to harbor the antibiotic resistance mutation (mtr),¹⁵⁰ which makes these organisms somewhat more resistant to antibiotics and thus results in higher treatment failure rates when alternate regimens are used. Similarly, while efficacious for anogenital gonorrhea, spectinomycin hydrochloride often fails to cure pharyngeal gonorrhea¹⁵¹ and is not recommended in homosexual men. Moreover, spectinomycin is not readily available in the United States at present. Finally, particularly in settings such as public clinics where large numbers of patients are treated and funds are limited, cost considerations may lead to choice of one agent over another.

In addition to currently recommended regimens for treatment of uncomplicated gonorrhea, there are a substantial number of other antibiotics that have been demonstrated to be effective for gonorrhea therapy.^{141,149} However, compared with the CDC-recommended ones, these drugs may not have any advantage over recommended regimens.¹⁴¹

FOLLOW-UP

Because all recommended regimens have cure rates that approach 100%, repeat cultures for test of cure are no longer recommended for all patients with gonorrhea.¹⁴¹ However, test-of-cure often is warranted if an atypical regimen is used or if medication compliance is uncertain. Even when recommended regimens are used, as for persons with chlamydial infections, 10–20% of heterosexual men or women treated for gonorrhea become reinfected in the next several months.¹⁵¹ Thus, a diagnosis of gonorrhea identifies a person at increased

risk for reinfection. As a result, rescreening for acquisition of gonorrhea or other STDs is now recommended for persons with gonorrhea approximately three months following their initial diagnosis.¹⁴¹

MANAGEMENT OF SEX PARTNERS

Most authorities recommend treatment of all recent sex partners of patients with gonorrhea, prior to the availability of culture results, in order to prevent complications and curtail the transmission (“epidemiologic treatment”).^{141,152} The definition of *recent* depends on the clinical and epidemiologic settings; in most instances, all partners exposed within the preceding 60 days prior to the onset of symptoms or to diagnosis of the index case should be treated. For patients with asymptomatic gonococcal infection, however, extending contact tracing to may prove useful for prevention efforts. There is considerable evidence that expedited partner therapy is beneficial to partners and the index case as well (see Chapter 54).

PREVENTION

Properly used condoms provide a high degree of protection against acquisition and transmission of genital infection.^{26,153} The diaphragm and cervical cap also may reduce transmission and acquisition of endocervical infection.^{20,154,155} Topical spermicidal and bactericidal agents have been shown recently to clearly reduce the probability of infection by both *N. gonorrhoeae* and *C. trachomatis* in patients using these gels. However, nonoxynol-9 containing spermicides have been shown to increase risk for HIV infection in studies conducted in high-risk women (commercial sex workers); hence nonoxynol-9-containing spermicides are no longer recommended for STD prevention.^{20,21,142} Urinating, washing, and douching after intercourse are assumed by many to be beneficial in prevention of gonorrhea, but controlled data are lacking. In addition, certain practices such as douching are now increasingly being associated with harmful outcomes. Prophylactic administration of antibiotics immediately or soon after sexual exposure clearly reduces the risk of infection (see Chapter 51).²⁶ However, this practice is likely to select and facilitate transmission of antibiotic-resistant strains of *N. gonorrhoeae*. In addition, except in very high-risk settings, routine antibiotic prophylaxis is unlikely to be cost-effective.

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Syphilis and related infections have long fascinated clinicians and scientists who marvel at the ability of the fragile bacterial agents of these diseases to cause lifelong infection in the untreated host. The nature of the waxing and waning clinical course, the ability of the bacteria to evade the host immune response for decades, and the refractory nature of the bacteria to manipulation *in vitro* have been the topics of research for decades, without resolution today. Nonetheless, much has been learned about the *Treponema*, and the molecular genetic tools that have been developed have had a marked impact on our knowledge of these organisms. This chapter reviews our current understanding of these organisms and the mechanisms employed by the bacteria and the host in the intimate interactions that we call infection.

CLASSIFICATION

The treponemes are members of the family Spirochaetaceae within the order Spirochaetales. This family includes several important human pathogens (e.g., the agents of syphilis and the endemic treponematoses, Lyme disease, and relapsing fever), animal pathogens, as well as symbionts. A second family, Leptospiraceae, includes the agents of leptospirosis; a proposed third family, Brachyspiraceae, includes several species associated with gastrointestinal illness in humans and other mammals. All members of the Spirochaetales are characterized by their spiral shape, corkscrew motility, and the existence of periplasmic flagella (endoflagella); their phylogenetic relationships have been extensively investigated by 16S rDNA analysis.^{1,2} All members of the genus *Treponema* are thought to be host-associated, with a wide variety of natural hosts including humans and other primates, rabbits, cattle, dogs, and termites. An extensive review of the pathogenic treponemes has recently been published.²

■ TREPONEMAL PATHOGENS OF HUMANS

Treponemal infections of major public health importance include venereal syphilis (called syphilis hereafter), yaws, and

bejel (“endemic syphilis”). Three morphologically identical subspecies of *Treponema pallidum* have been classified as the agents of these infections: *T. pallidum* subsp. *pallidum* (syphilis), *T. pallidum* subsp. *pertenue* (yaws), and *T. pallidum* subsp. *endemicum* (bejel). *T. carateum* is the agent of pinta, a related treponemal infection that is rarely reported today. This uncultivable treponeme is thought to be very closely related to the *T. pallidum* subspecies listed above and should probably be listed as a fourth subspecies of *T. pallidum*. Each of these infections is transmitted by direct contact: usually sexual contact for syphilis and skin-to-skin or mucous membrane contact for yaws, pinta, and bejel. All cause early skin or mucous membrane lesions, followed by disseminated and sometimes recurring lesions and chronic asymptomatic infection, occasionally leading to disfiguring and destructive late manifestations after many years. These infections are described more fully in Chapters 37 and 38.

Many phylogenetically distinct treponemes have been identified in the gingival pockets of persons with periodontal disease.^{3,4} This very common condition is characterized by a shift in the oral flora from gram-positive to gram-negative, by chronic or recurring gingival inflammation, and alveolar bone resorption with loss of dentition. Although periodontal disease is characterized as polymicrobial, approximately 40% of bacteria found in periodontal pockets are treponemes.⁵ A number of oral treponemes can be cultivated *in vitro*, and the best-studied oral treponeme is *T. denticola*. A group of non-cultivable oral treponemes, called PROS (pathogen-related oral spirochetes), have some antigenic similarity to *T. pallidum* and have been highly associated with several types of periodontal disease.^{6–8}

■ RELATED ANIMAL PATHOGENS

Several treponemal infections have been recognized in non-human mammals. A natural venereal infection of rabbits is caused by *T. paraluisuniculi*, a noncultivable treponeme that is morphologically identical, yet antigenically distinct from *T. pallidum* but is not infectious for humans.^{9–12} Another

treponeme was isolated from baboons in Guinea, a yaws-endemic region, and was determined by immunological studies to be more closely related to *T. pallidum* subsp. *pertenue* than to *T. pallidum* subsp. *pallidum*^{13,14}; recent work has shown that this treponeme is genetically distinct from the three known *T. pallidum* subspecies.¹⁵ One study suggests that this organism is infectious for humans.¹⁶

A newly identified group of treponemes, including *T. brennaborensis*, is highly associated with papillomatous digital dermatitis (PDD) and ulcerative mammary dermatitis in cattle and sheep.^{17–20} Like periodontal disease, these polymicrobial infections are primarily associated with anaerobic gram-negative bacteria and a preponderance of treponemes. The PDD treponemes are closely related genetically to oral treponemes.²¹

■ INTESTINAL TREPONEMAL SYMBIONTS

Several symbiotic treponeme species have been identified in digestive tracts of cattle and termites. In both cases, these organisms appear to be important for host nutrition. Members of a widely diverse treponemal flora in the hindgut of termites²² have H₂/CO₂-acetogenesis and dinitrogen fixation capabilities that contribute to the health of their hosts.²³ In cattle, organisms such as *T. saccharophilum* are thought to be important in the digestion of ingested plant material.

GENETICS OF TREPONEMES

■ TREPONEMA PALLIDUM GENOME

Perhaps because of the inability to culture *T. pallidum* in vitro, *T. pallidum*, Nichols strain, was one of the first bacteria for which the genome sequence was determined.²⁴ This achievement in 1999 opened the door to understanding the metabolic capabilities of *T. pallidum* and spawned a number of molecular studies of potential virulence factors. The circular chromosome contains 1,138,006 base pairs containing 1041 predicted open reading frames, making its genome approximately one-fourth the size of *Escherichia coli*. The lack of metabolic capability revealed in the *T. pallidum* genome sequence is consistent with the strong host-dependence of this organism for survival. Although there is still no method for genetic modification of *T. pallidum*, the availability of the genome sequence has largely overcome the problem of obtaining large numbers of treponemes from infected animal tissues by permitting targeted amplification and identification of genes of interest. This has greatly facilitated studies of individual genes, gene families, and metabolic pathways.

■ COMPARATIVE GENOMICS

In addition to *T. pallidum*, the genome of *T. denticola* has also recently been sequenced.²⁵ The genome of this cultivable

organism is 2.5 times larger than *T. pallidum* and contains genes for much of the metabolic machinery lacking in *T. pallidum*. Comparative analysis of these genomes suggests that the divergence of these two treponeme species was very ancient compared to that for other bacterial groups. Although two-third of *T. pallidum* genes have homologues in the *T. denticola* genome, there is very little synteny. Minimal genome sequence (limited primarily to 16S DNA sequence) is available for the noncultivable oral treponemes; these fall across the phylogenetic spectrum, but many are closely related to *T. vincentii* and *T. medium*.²⁶

In the 1950s, a “nature versus nurture” debate raged in which Hudson²⁷ and Hackett²⁸ argued whether the clinical differences among the treponemal infections were due to genetic versus environmental factors, respectively. Recently, a molecular approach has been used to compare gene sequences from the three *T. pallidum* subspecies. The gene sequences for some of the major antigens and proteins of the subspecies have demonstrated either complete identity (TpN15,²⁹ TpN17³⁰) or minor changes (*tpf-1*,³¹ 16S rDNA,³² and Tp92³³) between the *pallidum* and non-*pallidum* (*pertenue*, *endemicum*) subspecies. For some molecular signatures, rapid restriction site analysis of coding (glycerophosphodiester phosphodiesterase³⁴) and noncoding³⁵ regions can be used to differentiate the *pallidum* from non-*pallidum* subspecies, but none of these molecular targets can be used to differentiate *T. pallidum* subsp. *pertenue* from *T. pallidum* subsp. *endemicum*.

More dramatic differences between the *pallidum* and non-*pallidum* subspecies were identified through examination of a family of putative virulence factors (the *T. pallidum* repeat [Tpr] family of proteins, discussed again below). At one locus, *tprD*, the non-*pallidum* subspecies and approximately 50% of the tested *pallidum* strains have a sequence (called *tprD2*) that differs significantly from the *tprD* sequence present in the Nichols strain genome sequence³⁶; the remaining 50% of *pallidum* strains have the Nichols *tprD* sequence. It was subsequently found that the *tprD*-containing strains have an identical sequence at the *tprC* locus, while the *tprD2*-containing strains have *tprC* sequences that differ significantly from each other and from the Nichols prototype *tprC/D* sequence.³⁷ Even this major sequence difference, however, could not be used to identify *T. pallidum* subsp. *pertenue* versus *T. pallidum* subsp. *endemicum*, and the “nature versus nurture” debate was unresolved.

Newly published data¹⁵ show for the first time that the three subspecies can be differentiated by molecular signatures within the *tpr* family. The functional significance of these sequence differences is not yet known but may involve tissue tropism or invasive capability, two characteristics that distinguish syphilis from the nonvenereal treponemal infections. This and several other analyses^{33,34,38} have also demonstrated that *T. paraluisuniculi* is more distantly related compared to

the three subspecies of *T. pallidum*. Although molecular differences have been defined among the three subspecies, the specific genes and gene products responsible for different clinical diseases (see Chapter 38) have not been identified.

Rothschild³⁹ suggests that *T. pallidum* subsp. *pertenue* was the most ancestral of the three subspecies and was present in Africa at the time of the origin of modern humans; the two remaining subspecies are suggested to have evolved from *pertenue*, with the *pallidum* subspecies evolving in the New World (the Columbian theory) within the past 2000 years. Baker and Armelagos⁴⁰ revised the Columbian theory and proposed a scenario in which *T. pallidum* subsp. *pallidum* (venereal syphilis) evolved in Europe within the past 500 years. More recently, Armelagos and colleagues⁴¹ reviewed the molecular literature on the pathogenic treponemes and concluded that there is a no molecular distinction among the subspecies. In contrast, Gray et al.³⁸ performed an extensive comparison of six *tpr* genes (*tprC*, *D*, *I*, *K*, *G*, and *J*) from multiple strains of each of the *T. pallidum* subspecies, demonstrating that there is clear molecular evidence to support the existence of the three subspecies and suggesting that the divergence of the three subspecies was distant in time, certainly not within the past 500 years as proposed by Baker and Armelagos.⁴⁰ Investigation of additional genes and additional strains will be needed to resolve these divergent views.

STRUCTURE AND PHYSIOLOGY OF TREPONEMES

■ CELL STRUCTURE

Treponemes are motile spiral-shaped bacteria that are seen by darkfield or phase contrast microscopy but they are difficult to visualize by routine light microscopy because their long and very thin dimensions (approximately 10–14 μm in length and 0.1–0.2 μm in diameter) place them below the resolution of the light microscope. Their cell architecture is similar to gram-negative bacteria, in that they have a cytoplasmic membrane, a thin peptidoglycan cell wall, and a periplasmic space underlying the outer membrane. The motility organelles are termed periplasmic flagella or endoflagella (EF) because they are located within the periplasmic space. A cross section of *T. pallidum* is shown in Fig. 36-1; the EF are readily visible in the periplasmic space. Approximately three EF filaments are inserted at each end of the treponeme and they wrap around the cell body toward the center of organism.

The outer membrane of *T. pallidum* differs from most gram-negative bacteria in two major respects: it lacks lipopolysaccharide (LPS)^{42,43} and it has a dearth of integral membrane proteins.^{44,45} Immunological studies have suggested that binding of antibody to the surface of *T. pallidum* is very limited and requires long incubation periods.^{46–48} It

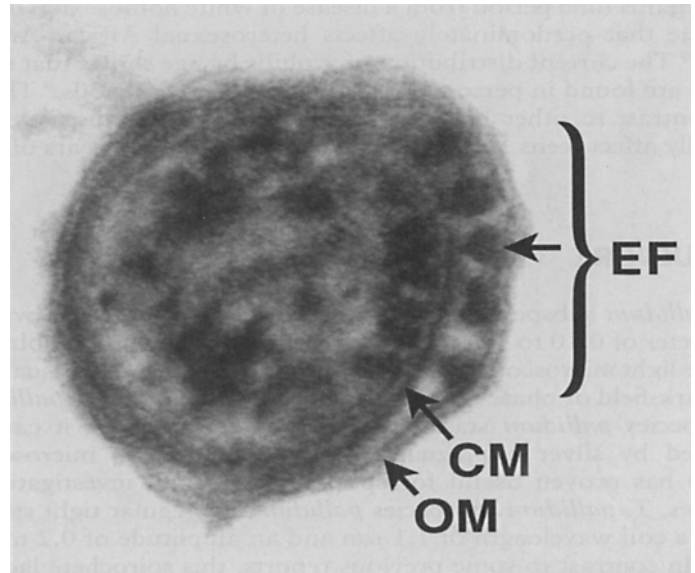


FIGURE 36-1. Cross section of *T. pallidum* subsp. *pallidum* showing the outer membrane (OM), endoflagella (EF), and cytoplasmic membrane (CM). (Courtesy of Steven J. Norris.)

had been suggested that the surface of the bacterium is covered by a mucopolysaccharide “slime layer”^{49,50} or by host-derived proteins,⁵¹ thus blocking the binding of specific antibodies to surface antigens.⁴⁷ An alternative explanation resulted from freeze–fracture electron microscopy studies from two laboratories: these studies independently showed that the number of visible “particles” (thought to represent integral outer membrane proteins) on the surface of *T. pallidum* was significantly lower (by 90%) compared to cultivable treponemes and other spirochetes.^{44,45} This finding led to the coining of the term “stealth pathogen” to describe the relative antigenic inertness of the *T. pallidum* surface.⁵² In contrast, the inner membrane contains numerous visible particles (see Fig. 36-2). Although the number of surface antigens may be small in *T. pallidum*, there is ample functional evidence that such antigens exist, and a number of surface-exposed proteins have been proposed. Several of these are discussed below in the discussions of attachment to host cells and antigenic variation. The search for surface-exposed proteins has been significantly hampered by the exquisite fragility of the *T. pallidum* outer membrane and there continues to be controversy in the field about the identity of such proteins.

■ MOTILITY

T. pallidum is actively motile, moving with a corkscrew motion, with bending and flexing, but with little translational movement. These characteristics are used to differentiate *T. pallidum* from other treponemes during darkfield microscopic examination of specimens from patients with suspected syphilis. The structure of *T. pallidum* EF is unique, consisting of four gene products: FlaA (outer sheath) and three flagellar

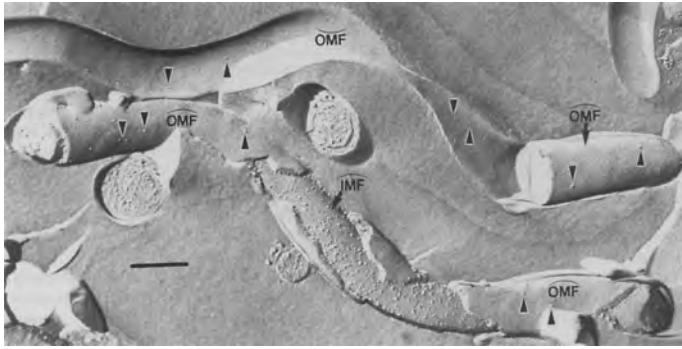


FIGURE 36-2. Membrane architecture of *T. pallidum* subsp. *pallidum*, as demonstrated by freeze–fracture electron microscopy. The concave and convex outer membrane fracture (OMF) faces, corresponding to the outer and inner leaflets of the outer membrane, respectively, contain a very low concentration of intramembranous particles (*arrowheads*). In contrast, the convex inner membrane fracture (IMF) face, corresponding to the inner leaflet of the inner membrane, has a high concentration of intramembranous particles. (Courtesy of Eldon M. Walker.)

core proteins, FlaB1, FlaB2, and FlaB3.²⁴ Studies of nonmotile EF knock-out mutants of cultivable treponemes indicate that the helical shape of the treponeme is maintained even when the EF are not produced.⁵³ Motility of the treponemes is enhanced by increased viscosity of the medium, suggesting that the bacteria are capable of motility in body fluids in the eye and joints. Motility results from the rotation of the EF from their insertion points, similar to flagella from other bacteria, and is mediated by a rotary motor apparatus. An important role for motility in syphilis pathogenesis has long been suspected but has not been rigorously proved because there is no genetic system for creating nonmotile EF mutants in *T. pallidum*.

■ CHEMOTAXIS

Most motile bacteria have chemotactic capability, and *T. pallidum* is no exception. Approximately 5–6% of the genome is devoted to genes associated with directed (chemotactic) movement.⁵⁴ Interestingly, the genomes of *T. pallidum* and other pathogenic spirochetes, including *Borrelia burgdorferi*, are predicted to contain orthologs of the well-recognized CheW–CheR chemotaxis components. The chemotaxis machinery is thought to assist *T. pallidum* as it navigates throughout the body during dissemination, and recent microarray studies indicate that a number of chemotaxis genes are upregulated during early active syphilis infection.⁵⁵

METABOLISM AND SURVIVAL IN VITRO

Studies of the metabolism of *T. pallidum* have been hampered for many years by contaminating rabbit tissue that was contained in *T. pallidum* suspensions. It was not until the publication of the *T. pallidum* genome that investigators fully appreciated the metabolic limitations of the organism.

Although *T. pallidum* contains the genes for the complete Embden–Meyerhof pathway, it lacks genes for the Krebs cycle and lacks the heme proteins involved in electron transport.²⁴ This suggests that *T. pallidum* is able to generate only two molecules of ATP per glucose molecule through glycolysis, compared to 36–38 molecules for bacteria with “complete” metabolic capability, perhaps accounting for its significantly slower growth rate (generation time of ~30–33 hours,^{56,57} compared to *E. coli*’s 30 minutes). Furthermore, *T. pallidum* lacks the genes required to synthesize most amino acids, purines, pyrimidines, and lipids *de novo*. As expected for an organism with such limited biosynthetic capability, there are 18 putative transport systems including ATP-Binding Cassette (ABC) transport systems.²⁴ The predicted targets of *T. pallidum* transporters include amino acids, carbohydrates, and cations. *T. denticola*, which has much more complete metabolic machinery, has 106 ABC transporter systems compared to four for *T. pallidum*.²⁵ Many of *T. denticola*’s transporters appear to be specific for amino acids, consistent with the high number of proteases produced by *T. denticola*, suggesting that proteolysis of host tissue may provide a major source of nutrients (via amino acid fermentation) for that organism.

It has long been recognized that *T. pallidum* survival is diminished in atmospheric oxygen, and most cultivation attempts in the past 30 years have employed reduced-oxygen conditions in recognition of the microaerophilic nature of the organism. Aerotolerant bacteria have enzymes, such as superoxide dismutase, catalase, or peroxidase, which can protect them from the toxic effects of oxygen radicals. The genome sequence confirmed that *T. pallidum* lacks genes for these enzymes,²⁴ thus explaining its sensitivity to oxygen. However, the organism survives better in microaerophilic rather than anaerobic conditions, and several other genes for oxygen protective enzymes were identified. Hazlett and colleagues⁵⁸ described neelaredoxin, which reduces superoxide to peroxide, and proposed a scheme in which alkyl hydroperoxide reductase C reduces the peroxide to water (substituting for the activity of catalase). Neelaredoxin is thought to be regenerated by reduction with rubredoxin. Rubredoxin is then reduced by NADH oxidase, the only *T. pallidum* enzyme to require molecular oxygen and perhaps accounting for the microaerophilic nature of *T. pallidum*. Although this pathway appears to provide some level of protection against oxygen toxicity, it is likely less effective than superoxide dismutase and catalase.

Many attempts have been made to cultivate *T. pallidum* in vitro. Limited success was described by Fieldsteel and colleagues in 1981⁵⁹ in which *T. pallidum* was shown to undergo limited multiplication (up to a 50-fold increase or five generations) during coculture with rabbit epithelial cells under reduced oxygen concentration with dithiothreitol. Although others have reproduced these findings,^{60,61} significant

advances have not been reported, and it is still not possible to achieve multiplication after subculture. The inability to cultivate *T. pallidum* is a major stumbling block in research on syphilis, as the development of tools for genetic manipulation of the organism requires cultivation.

NATURAL HISTORY OF SYPHILIS

The natural history of syphilis is described in detail in Chapter 37, but a brief discussion is warranted here as a context for the following discussion of animal models and pathogenesis of syphilis.

Syphilis is a chronic infection that progresses over decades, with alternating active clinical disease (primary, secondary, and tertiary stages) and asymptomatic periods (called latency).

■ EARLY SYPHILIS

Infection occurs by direct, usually sexual, contact with an infectious lesion (i.e., primary chancre or secondary mucocutaneous lesions). The bacteria are thought to penetrate intact mucosal surfaces⁶² or via microscopic abrasions of skin where they multiply locally with a generation time of ~30 hours. Within the first hours-to-days of infection, some organisms gain access to the circulation (including lymphatics) and disseminate widely, often including the central nervous system (CNS) and, in pregnant women, the fetus. The primary lesion, called a chancre, appears at the site of infection and is caused by the host cellular infiltration triggered by the presence of large numbers of treponemes; regional lymphadenopathy is common. The chancre resolves without treatment (see “Acquired Immunity and Bacterial Clearance” section) and the untreated individual may manifest the secondary stage after a period of weeks to several months or, in some cases, concurrently with the healing of the primary lesion. The secondary stage is characterized by skin lesions (usually a maculopapular rash) on the trunk, extremities, palms and soles, as well as mucous membrane lesions (mucous patches) and hypertrophic lesions in moist body crevices (condylomata lata). These are often accompanied by systemic lymphadenopathy. The rash and lymphadenopathy resolve spontaneously due to the host’s immune response. Less common symptoms and signs of secondary syphilis include alopecia, subclinical or clinically apparent hepatitis, and uveitis; symptomatic or asymptomatic CNS involvement is common during this stage. After resolution, patients enter the latent stage. Secondary lesions may reappear, usually during the first year of infection, and latent (asymptomatic) syphilis of <1-year duration is called “early latent” syphilis.

■ LATE SYPHILIS

Late syphilis (>1-year duration) is asymptomatic (“late latent” stage) in most untreated individuals. The bacterial

burden, though systemically distributed, is thought to be relatively low. Even in the preantibiotic era, most untreated persons with syphilis failed to develop further clinical manifestations during the remainder of their lives.⁶³ This observation, coupled with the reversion to seronegativity in the cardiolipin-based tests available at the time, led some to postulate that spontaneous cure occurs in a proportion of persons with untreated late latent syphilis. There is no microbiological evidence for cure, and some VDRL nonreactive persons develop tertiary syphilis. Therefore, it should be assumed that infection is chronic in untreated individuals. Late active disease (termed “tertiary syphilis”) ultimately appeared in ~30% of infected persons in the preantibiotic era and was most frequently manifested as gummatous tissue destruction, cardiovascular involvement (aortitis, aortic aneurysm), or symptomatic late neurosyphilis (tabes dorsalis, paresis, optic atrophy).⁶³

ANIMAL MODELS OF TREPONEMAL INFECTIONS

The rabbit is the standard experimental model for syphilis, although other mammals, including nonhuman primates, can be infected with *T. pallidum* subspecies.⁶⁴ Whereas the mouse is the preferred experimental host for many infections, *T. pallidum* fails to induce disease in this animal although organisms can be recovered from tissues of inoculated mice.⁶⁵ There is reportedly some host “preference” among the *T. pallidum* subspecies, and hamsters appear to be better hosts for subspecies *pertenue* and *endemicum*^{64,66} in terms of the development of clinical disease. *T. carateum* will grow only in nonhuman primates.⁶⁷

The rabbit is the most widely used animal model because infection results in disease that closely resembles human infection in terms of clinical manifestations, histopathology, and immune responses. Intradermal infection of rabbits results in development of chancres that enlarge, ulcerate, and heal as in humans. If the backs of such rabbits are kept clipped, a proportion of animals will subsequently develop disseminated lesions that mimic human secondary syphilis. Disseminated lesions will also appear on the clipped back following inoculation by the intravenous route, although immunologically this is considered a disseminated primary infection. Organisms are most readily propagated by intratesticular infection, and bacteria can be extracted from testis tissue during peak orchitis. Rabbits, like humans, have persistent latent infection (demonstrated by the ability to isolate *T. pallidum* from rabbits that have been infected for years), although symptomatic tertiary disease is not recognized. Extensive pathological studies of rabbits with longstanding syphilis suggested a number of abnormal findings; however, the specificity of these findings to syphilis is unclear.

Nonhuman primates are the only species in which symptomatic tertiary syphilis has been described.⁶⁸

Congenital syphilis, a major cause of human neonatal morbidity and mortality worldwide, has been replicated in guinea pigs and rabbits in limited studies.^{69–71}

PATHOGENESIS AND IMMUNE RESPONSES

■ ATTACHMENT, INVASION, AND DISSEMINATION

One of the requirements for infection is the attachment of the pathogen to host cells. *T. pallidum* readily attaches to eukaryotic cells and has been demonstrated to be fairly promiscuous in its attachment to a variety of cell types,^{72–74} perhaps reflective of its ability to disseminate to and infect many tissues. Bacterial adhesin(s) and the cognate eukaryotic cell surface receptor(s) have not been identified for *T. pallidum*, although it is recognized that immune serum (collected from infected rabbits) will inhibit attachment of the organisms to eukaryotic cells in vitro.^{73,74} This area of research was inactive for two decades until recent work by Cameron and colleagues^{75,76} applied molecular and informatics approaches to identifying adhesins of *T. pallidum*. Through their work, the individual proteins that specifically bind the extracellular matrix (ECM) components laminin⁷⁵ and fibronectin⁷⁶ have been identified and characterized. Fibronectin and other ECM molecules are frequently used by bacterial pathogens as an early step in attachment in which the ECM molecules, which also have cell-binding domains, serve as a bridge between the host cell and the bacterial cell. Fibronectin and laminin are widely distributed in serum and in tissues and may play a role in the ability of *T. pallidum* to disseminate. Laminin is also abundant in the basement membranes that lie beneath endothelial and epithelial cells, and the ability of *T. pallidum* to bind to laminin may facilitate initial infection through the epithelial surfaces and dissemination by guiding bacterial migration into the vasculature. Specifically, Tp0155 and Tp0483 bind to fibronectin,⁷⁶ and Tp0751 binds to laminin.⁷⁵ In each case, antibodies raised against the recombinant proteins effectively inhibit binding of *T. pallidum* to the respective ECM component in vitro. Antibodies to these proteins are also induced by active infection, demonstrating that the proteins are expressed in vivo, and it is assumed that antibody-mediated inhibition of binding may also occur in the host after the acquired immune response develops. The demonstration that these proteins function in attachment of *T. pallidum* to ECM implies that they are surface exposed on the intact treponeme. While formal proof of their outer membrane location has not been provided, the existing data are most consistent with surface exposure. Other than the ECM-binding proteins, no other putative *T. pallidum* adhesins have been identified at the molecular level.

It is well recognized from the clinical course of syphilis that early and widespread dissemination occurs. The organism can rapidly pass through intact genital mucosa⁶² and can be identified in regional lymph nodes within hours of intratesticular inoculation in rabbits.⁷⁷ In vitro models have demonstrated *T. pallidum* traversing an endothelial monolayer via intercellular junctions,⁷⁸ although this may not be the only route. It is widely assumed that the active motility of the organism is essential for invasion and dissemination; this is supported by the fact that 5–6% of the *T. pallidum* genome is devoted to putative chemotaxis and motility-related genes.

■ INNATE HOST RESPONSE

The role of the innate immune response to infections has become an area of intense research in recent years. The previously held belief that the primary defensive function of epithelial surfaces of the body was to serve as a passive physical barrier to pathogens has been modified by the recognition that toll-like receptors (TLR) can be expressed on many epithelial surfaces (reviewed in 79). In response to common pathogen components (e.g., LPS, lipoteichoic acid, CpG DNA, flagellin), epithelial cells can be triggered to produce proinflammatory cytokines and chemokines. These serve to attract professional antigen presenting cells (APC) that also express TLR, thus amplifying the proinflammatory signal in the host.

Unlike most gram-negative bacteria, *T. pallidum* lacks LPS^{42,43} and thus does not activate cells through TLR4. Radolf and coworkers showed that the lipid portions of treponemal lipoproteins (e.g., Tp47, Tp15, Tp17) serve to activate cells through TLR2/TLR1 heterodimers.^{80–82} Because these lipoproteins are not on the surface of *T. pallidum*, the organisms may be able to escape immediate detection by the innate immune system, thus providing time for initial multiplication and dissemination. Although we know that an inflammatory response is eventually triggered by *T. pallidum*, the precise mechanics of signaling are still unresolved. Lipoproteins may be released from dying treponemes in vivo, thus allowing their interaction with TLR2 on the surface of epithelial, endothelial, or APC. Invasion of tissues by *T. pallidum* would also bring the bacteria into direct contact with dendritic cells, macrophages, and other known APC, which would ingest and process the antigens, thus releasing the lipoproteins for recognition by TLR expressed inside the phagocytic vacuole. In either case, APC containing *T. pallidum* antigens travel to the draining lymph nodes where T lymphocytes initially become sensitized. These *T. pallidum*-sensitized T cells then traffic to the sites of infection and high bacterial concentration, thus establishing a potent and very effective acquired immune response.

■ ACQUIRED IMMUNITY AND BACTERIAL CLEARANCE

Syphilis is a disease in which the clinical manifestations appear to be caused by the inflammatory and immune responses rather than by any direct cytotoxic effect of *T. pallidum*. Extraordinarily high ratios of *T. pallidum* to mammalian cells are necessary for any evidence of direct cytotoxicity in vitro,⁸³ and the genome of *T. pallidum* does not contain orthologs of known bacterial toxins. The induration of the primary chancre is due to the infiltration of the site by large numbers of lymphocytes and macrophages; the tissue destruction seen in the ulceration of the primary chancre and in late gummatous syphilis is due to endothelial proliferation in local capillaries, with occlusion of the lumen resulting in localized tissue necrosis. Similarly, in congenital syphilis, damage to the fetus is not apparent until the fetal immune response is sufficiently mature to respond to the presence of the bacteria.⁸⁴ As mentioned above, the inflammatory effects of *T. pallidum* are mediated primarily by the lipid moiety of the lipoproteins (e.g., Tp47, Tp17, Tp15). Numerous *T. pallidum* antigens, including the lipoproteins listed above, the endoflagellar proteins (e.g., FlaA, FlaB1, 2, 3), and the Tpr protein family (e.g., TprA-TprL), have been shown to stimulate T-cell responses, including interferon-gamma (IFN- γ) production, in the rabbit model.^{85–87}

■ BACTERIAL CLEARANCE

Studies of experimental syphilis have shown that T-cell infiltration occurs as early as day 3 following infection and continues to increase in magnitude in parallel with *T. pallidum* numbers.^{88,89} Macrophages next infiltrate the site and, within days of significant macrophage infiltration, the number of treponemes in the tissue declines precipitously (termed “bacterial clearance”). With smaller inocula or in natural infection in humans, the same process occurs, albeit with a longer time frame.

The observations that bacterial numbers decline rapidly after macrophage infiltration, coupled with the demonstration that macrophages can phagocytize opsonized *T. pallidum* in vitro,⁹⁰ strongly suggest that the major mode of bacterial clearance and lesion resolution is phagocytosis of treponemes by macrophages.^{88,89} Subsequent studies by Baker–Zander and coworkers demonstrated that *T. pallidum* are killed following ingestion by macrophages in vitro,⁹¹ and that this is dependent upon the presence of opsonic antibody. Interestingly, a small subpopulation of treponemes escapes active clearance in early lesions and Baker–Zander demonstrated that these surviving organisms are refractory to phagocytosis.⁹² This resistance may be due in part to antigenic variation, discussed below.

The T lymphocytes that infiltrate early syphilitic lesions in humans^{93–96} and rabbits^{96a} include both CD4⁺ and CD8⁺ cells. The cytokine profile of the cellular infiltrates, in rabbits^{96b} and humans,⁹⁷ is skewed very heavily toward the Th1 type,

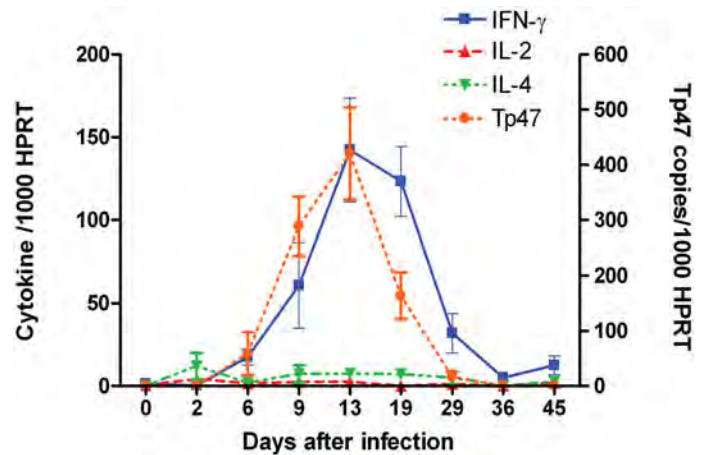


FIGURE 36-3. Quantitation of interferon-gamma (IFN- γ), interleukins 2 and 4, and *T. pallidum* (represented as Tp47) during progression and healing of chancres in rabbits, as measured by quantitative reverse transcriptase polymerase chain reaction. Copies of message for cytokines and Tp47 are normalized to 1000 copies of a housekeeping gene, hypoxanthine phosphoribosyl transferase (HPRT). IFN- γ is the most abundant cytokine and its level parallels the bacterial load, as measured by Tp47. (Unpublished data).

with IFN- γ predominating. IFN- γ production parallels the bacterial number in syphilis lesions (Fig. 36-3). Little to no IL-4 (a Th2 cytokine) is produced. IFN- γ can be produced by both CD4⁺ and CD8⁺ lymphocytes, and IFN- γ is consistent with the hypothesis that activated macrophages are the primary effector cell in the resolving early lesion.

The presence of both activated T lymphocytes and macrophages at the site of an ulcerative lesion (primary chancre) may explain the well-recognized association of syphilis with higher rates of acquisition and transmission of HIV.^{98–100} HIV has been isolated from swabs of genital ulcers, including primary syphilis chancres.^{101,102} Stimulation of macrophages by treponemal lipoproteins upregulates both HIV-1 gene expression¹⁰³ and expression of CCR5 (a coreceptor for HIV) on peripheral blood mononuclear cells.¹⁰⁴

■ ANTIBODIES IN SYPHILIS

Antibodies are produced during syphilis infection, and detection of antibodies is a major tool in diagnosis and screening for syphilis. As described in Chapter 63, serodiagnosis of syphilis is based upon antibodies to lipid antigens in the VDRL and RPR (so-called “nontreponemal”) tests and to predominantly protein antigens in the FTA-ABS, TPPA, and TPHA (“treponemal”) tests. The functions of the antibodies measured by these tests are not known, except that anti-VDRL antibodies can opsonize *T. pallidum* for phagocytosis by macrophages and, thus, comprise a portion of the opsonic capacity of immune serum.¹⁰⁵

An early serological test for syphilis (the “*T. pallidum* immobilization,” or TPI, test) measured the ability of serum

antibodies to render *T. pallidum* immobile in the presence of complement.¹⁰⁶ Bishop and Miller demonstrated that antibodies and complement can neutralize, or render noninfectious, *T. pallidum* following a long incubation in vitro,⁴⁸ although molecules that are the targets of these immobilizing and neutralizing antibodies have not been defined. Recent work by Blanco and coworkers demonstrates, for the first time, that a monoclonal antibody with specificity for a phosphorylcholine moiety putatively located on the surface of *T. pallidum* is highly effective in immobilizing and neutralizing *T. pallidum*.¹⁰⁷ It should be noted that phosphorylcholine is a component of the VDRL/RPR lipid antigen mentioned above that induced opsonic antibody. The role of immobilizing and neutralizing antibodies in the infected host is unclear. It is recognized that there are large numbers of circulating treponemes in the host during early syphilis, even after the development of measurable immobilizing antibody. Further, the successful immunization studies of Miller (described below) demonstrated complete protection of immunized rabbits against *T. pallidum* challenge even in the absence of measurable immobilizing antibody.¹⁰⁸

The identities of protein targets of opsonizing antibody remain controversial and are embroiled in the discussion about the nature of outer membrane proteins in *T. pallidum*. Centurion-Lara¹⁰⁹ and colleagues reported that TprK (TP0897) is a target of opsonic antibody, but Hazlett et al. failed to reproduce these results.¹¹⁰ Cameron and coworkers provided evidence that Gpd (Tp0257)¹¹¹ and Tp92 (TP0326)³³ are located in the outer membrane and are targets of opsonic antibody, but Shevchenko et al. reported that GPD (called GlpQ in their report) is entirely subsurface.¹¹² Thus, although it is well recognized that opsonizing antibodies are induced by infection, the identities of their specific molecular targets is unclear at this time.

■ EVASION OF HOST IMMUNITY AND ESTABLISHMENT OF LATENT INFECTION

Despite the dramatic clearance of billions of treponemes from early syphilitic lesions and the development of opsonizing, neutralizing, and immobilizing antibodies, syphilis is a chronic infection in which treponemes persist in the host for decades. Administration of large quantities of high-titer antibodies from infection-immune rabbits only partially protects recipients from infectious challenge.^{113–116} A number of hypotheses have been proposed to explain this persistence, including localization within host cells,¹¹⁷ masquerading by coating the bacterial surface with host proteins,⁵¹ relative lack of surface exposed protein antigens,^{44,45,52} and specific or generalized immunosuppression.^{118,119} Of these, only the relative lack of surface proteins is currently considered to be a major factor in persistence. As discussed above, *T. pallidum* does have a paucity of integral outer membrane proteins and

lacks LPS. Thus, it can effectively avoid triggering an immediate inflammatory response, and discernible cellular infiltration (even in immunized animals) occurs only in response to a large bacterial number ($\geq 10^6$). Thus, the organism has evolved very successful mechanisms for evading the immune response.

One of the most intriguing discoveries in syphilis pathogenesis is the recent description of antigenic variation in *T. pallidum*. The gene encoding TprK, a putative target of opsonic antibody, was demonstrated to have seven sequence-variable regions (V regions); this sequence variation was demonstrated between *T. pallidum* isolates and even within a given isolate.^{120,121} Subsequent studies by Centurion-Lara elegantly demonstrated that the mechanism of sequence variation is gene conversion, with new sequences being derived from discrete donor sites elsewhere in the genome.¹²² Development of clonal populations of *T. pallidum* (with a homogenous *tprK* sequence) permitted the demonstration that sequence change occurs at a very rapid rate in some strains, and that accumulation of variant sequences within a host is more impressive in the setting of specific immunity.^{122,123}

Correlative immunological studies by Morgan and coworkers clearly demonstrated that the V region peptides are the targets of infection-induced antibodies, while the intervening constant regions of the protein are T-cell epitopes.¹²⁴ LaFond et al. demonstrated that anti-V region antibodies are exquisitely specific, and that even minor changes in amino acids can abrogate reactivity of the antibodies.¹²⁵ Thus, changing the amino acid sequence of the antibody epitope even slightly permits the bacterium to escape the activities of anti-TprK antibodies that are induced during infection. This antigenic variation mechanism likely permits some treponemes to escape the local bacterial clearance during resolution of early lesions and contributes to the long-term survival of *T. pallidum* during latent syphilis and chronic infection.

■ PROTECTIVE AND LONG-LASTING IMMUNITY

Antibodies and specifically sensitized T lymphocytes can be demonstrated even after many years of infection, suggesting a significant long-term memory response, persisting after penicillin therapy. The role of this immunological memory in prevention of reinfection is unclear. STD clinicians recognize that individuals can have multiple episodes of syphilis. Thus, infection per se does not produce lifelong immunity to reinfection. Controlled studies in the rabbit model have demonstrated that the degree of acquired resistance to reinfection is dependent upon the length of the initial syphilis infection: rabbits infected with *T. pallidum* for 3–6 months, then treated with penicillin, are resistant to symptomatic reinfection with that same strain of *T. pallidum*, while those infected for shorter periods before treatment are susceptible to reinfection.^{48,64} Cross-immunity between strains is less complete,

even following long-term infection.⁶⁴ Infectious challenge of rabbits with untreated latent infections does not result in symptomatic reinfection. Protective immunity was examined in humans by Magnuson and coworkers¹²⁶ who inoculated prisoners at Sing Sing Prison with the Nichols strain of *T. pallidum*. Those subjects who had been treated for syphilis in the past were susceptible to infectious challenge: symptomatic reinfection or increase in antibody titer was seen in those previously treated for early syphilis and in half of those previously treated for late latent syphilis. The only individuals who showed no change following infectious challenge were five persons with *untreated* late latent syphilis and half of those previously treated for late latent syphilis. These studies demonstrate that immunity to syphilis is very slow to develop, is often incomplete except in untreated syphilis, and may be strain specific.

Grassy and colleagues, using modeling methodology, recently proposed that the periodicity of syphilis epidemics is due to developing immunity that appears after “recovery from syphilis.”¹²⁷ The definition of “recovery from syphilis” is key to the validity of this hypothesis. If “recovery” means those patients who have been treated for latent syphilis, then the level of established immunity in most individuals would be dependent upon duration of infection prior to treatment and would, in many cases, be insufficient to prevent reinfection, particularly with a different strain of *T. pallidum*. If, on the other hand, “recovery” indicates those in whom early lesions have resolved and who now have *untreated* latent infection, developing immunity may in fact contribute to reduced susceptibility to symptomatic reinfections. These individuals would be “dead ends” in terms of transmission. This situation is somewhat reminiscent of the hypothesis of Brunham et al.¹²⁸ regarding immunity in chlamydia: does prompt identification and treatment of chlamydia infections within a population prevent the development of meaningful immunity to reinfection in that population? The very long duration of syphilis infection needed to develop functional immunity suggests that a situation similar to that being postulated for chlamydia might also be relevant to syphilis.

IMMUNIZATION AND LIKELIHOOD OF A VACCINE

■ PROOF OF CONCEPT

The slow establishment of significant immunity during natural infection suggests that development of a vaccine for syphilis is likely to be a very difficult endeavor. In the pre-molecular era, numerous investigators (reviewed in 129) used standard approaches to antigen preparation (e.g., formalin-fixation and heat-killing) in the hope of creating an effective syphilis vaccine. None of these vaccines was successful,

probably because immunity is largely dependent upon an effective cellular immune response rather than the antibody-focused response induced by killed organisms. In now-classic studies, however, Miller¹⁰⁸ hypothesized that there is a fragile, low concentration of protective antigen on the surface of intact *T. pallidum* and that this antigen must be preserved for effective immunization. He attenuated *T. pallidum* by exposure to high levels of gamma-irradiation and, coupled with a strenuous immunization schedule (60 intravenous inoculations of motile, freshly irradiated *T. pallidum* over a 37 week period), was able to demonstrate complete and long-lasting immunity in rabbits to inoculation with the immunizing strain of *T. pallidum*. These studies serve as proof of concept for development of a syphilis vaccine and provide encouragement to those investigators who are searching for an effective immunization protocol.

Many issues remain for development of a human vaccine, including the question of cross-protection among strains, the impractical nature of the attenuation and immunization protocol used by Miller, and the contamination of *T. pallidum* suspensions with rabbit tissue because of the need to propagate *T. pallidum* in rabbits. Today’s investigators are examining the effectiveness of immunizing with purified single antigens or antigen combinations in the hope of overcoming these difficulties. To date, these studies have resulted in partial protection at best.

■ RECOMBINANT PEPTIDE ANTIGENS

Since the advent of recombinant DNA technology, syphilis researchers have produced recombinant *T. pallidum* proteins in *E. coli* and have immunized rabbits using a variety of adjuvants. Many of these studies were unsuccessful and are unpublished; others yielded partial protection (resulting in infection following challenge of immunized rabbits but with significant alteration in lesion development compared to control infections). None has provided complete protection. Recent studies, summarized in the review by Cullen and Cameron,¹³⁰ demonstrate that those proteins with putative outer membrane localization and surface exposure (e.g., TprK, Tpr subfamily I members, ECM-binding proteins, Tp92) are generally most successful in inducing measurable, though not complete, resistance to infection. In many of these immunized animals, erythema and induration (“lesions”) developed at the challenge sites but they contained few or no demonstrable treponemes, and the lesions failed to progress to ulceration. If a similar “partially protective” vaccine were to be approved for use in humans, it would not protect the host from infection but might impact syphilis transmission by limiting treponeme burden and ulceration. Efforts are continuing to modify antigens, adjuvants, and immunization protocols to increase the level of protection achieved.

■ LIPIDS AS IMMUNOGENS

Lipid antigens have long been recognized in syphilis and have served as the basis for the original Wassermann test as well as for the VDRL and RPR tests that are currently used for serodiagnosis. The outer membrane of *T. pallidum* contains a paucity of integral membrane proteins, and the lipid membrane comprises the majority of the surface that is exposed to the host. Antibodies raised against the cardiolipin-lecithin-cholesterol VDRL antigen are opsonic, and animals immunized with this antigen are partially protected against infection with *T. pallidum*.¹⁰⁵ The antiphosphorylcholine monoclonal antibody described by Blanco¹⁰⁷ has very potent treponemicidal activity in vitro and in vivo. While these results may suggest the use of lipid antigens in a future syphilis vaccine, care must be taken to ensure that autoimmune responses are not induced. This is particularly important because *T. pallidum* lacks the capability to synthesize its own lipids and derives its membrane lipids from the host. Thus, immune responses resulting from lipid immunization may be misdirected to affect normal host tissue.

CONCLUSIONS

Just as syphilis has fascinated and perplexed clinicians for centuries, the causative agent, *T. pallidum*, continues to challenge investigators who strive to unravel its mysterious nature. Significant challenges lie ahead in terms of in vitro cultivation, genetic manipulation, identification of surface antigens, and the means for inducing protective immunity. Each of these goals is formidable, and the shrinking number of investigators who devote their research efforts to syphilis does not bode well for major advances in *T. pallidum* research. Despite this, the availability of the genome and the development of a number of new molecular methodologies have resulted in significant new information in the past 10 years. However, until an effective syphilis vaccine is developed, control of syphilis will continue to depend on reduction of risk-taking behavior, prompt identification and tracing of contacts, and the continued efficacy of penicillin therapy. Unfortunately, without new tools, the same tired approaches may yield the same high levels of infection that have been seen globally for the past 50 years.

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INTRODUCTION

Syphilis is one of the most fascinating diseases of humans. Untreated infection typically evolves through several stages, termed primary, secondary, and tertiary, each separated for variable times by no clinical evidence of infection, which is termed latency. The interval between primary and secondary stages typically is only weeks to a few months, but the interval between secondary stage and tertiary syphilis typically is many years. This remarkably variable and long-drawn-out course raises many unanswered questions about the nature of the host–parasite interaction. These issues are discussed in Chapter 36 by Lukehart, and the natural history of the disease in studies from the preantibiotic era is discussed in more detail in earlier editions of this book.¹

The disease has been of great historical importance not only for the practice of medicine but also because of its effect on many persons who played important roles in the history of the Western world. It was an extremely common infection only a few decades past, with prevalence in various autopsy series in the first half of the twentieth century of 5–10%.^{2,3} In certain groups of low socioeconomic status studied in the prepenicillin era, syphilis affected 25% or more of the U.S. population. Widespread use of antibiotics after World War II reduced the incidence of early syphilis to manageable proportions, and recognized new cases of late syphilis decreased. However, late syphilis (particularly neurosyphilis) remains an important problem in the Western world, and congenital syphilis is an occasional problem as well. Syphilis remains a very common problem in many other parts of the world, especially Southeast Asia and sub-Saharan Africa. Since syphilis is also an important risk factor for HIV transmission throughout the world,⁴ this ancient disease still is highly deserving of our complete attention.

ORIGINS

■ THE COLUMBIAN THEORY

Syphilis was epidemic in late fifteenth-century Europe, and the early stages apparently were often unusually severe by

contemporary standards. The rapid spread and considerable effects of the disease throughout Europe in the last decade of the fifteenth century caused it to be termed the Great Pox, in contrast to another scourge, smallpox. The disease received its present name from the poem by Fracastoro in 1530 about the afflicted shepherd, Syphilis. The late complications of syphilis were recognized early and were frequently mentioned by many Elizabethan authors.

The late fifteenth-century European epidemic coincided with the return of Columbus from America in 1493, causing many to assume that the disease was acquired from natives in the West Indies and carried back to a nonimmune (and therefore particularly susceptible) population in Europe. Certainly, if this did occur, conditions were ripe for rapid transmission, because Europe was engaged in wars at that time, and the movement of the troops and their camp followers created a perfect vehicle for rapid spread of a sexually transmitted disease. On the other hand, there are Biblical and ancient Chinese writings that are consistent with descriptions of late cutaneous syphilis, although other illnesses such as tuberculosis or leprosy could have caused similar descriptions to be written. An illness suggestive of syphilis apparently was not described in early American natives. These and other considerations led some to speculate that venereal syphilis did not arise suddenly in Europe after 1493 but may have been endemic already, only to become more widespread and severe as a consequence of the wars that coincided with the return of Columbus and his men.

TRANSMISSION

The disease is usually acquired by sexual contact, with the obvious and important exception of congenital syphilis, where the infant acquires the infection by transplacental transmission of *T. pallidum*. Transmission by sexual contact requires exposure to moist mucosal or cutaneous lesions of primary or secondary syphilis. Patients with untreated disease may apparently recover only to relapse over a period of up to 2 years. Therefore, a person may be able to transmit syphilis during the first year or two of untreated infection.

The rate of acquisition of syphilis from an infected sexual partner during a single sexual contact has been estimated at about 30%, based on a placebo-controlled study of the efficacy of various antibiotics in aborting syphilis in known contacts within the previous 30 days of patients with primary or secondary syphilis.⁵ The dose of the rabbit-adapted Nichols strain of *T. pallidum*, which infects 50% of human volunteers by intracutaneous inoculation, is about 60 organisms, similar to that for rabbits.⁶ If the ID₅₀ for humans of native or “street strains” of *T. pallidum* on mucosal surfaces is similar, exposure to a relatively few organisms suffices to initiate infection. Syphilis is a systemic disease; treponemes spread via the blood stream beginning during the incubation period,⁷ and women may transmit infection to their fetus in utero shortly after onset of infection.⁷ Transmission to the fetus in utero has been documented as early as the ninth week of pregnancy.⁸ Women remain potentially infectious for the fetus for many years, although the risk of infecting a fetus declines gradually during the course of untreated illness; after about 8 years there is little risk even in the untreated mother.

EPIDEMIOLOGY

Reported syphilis peaked in the Western world in the years around World War II but declined dramatically thereafter, coincident with the general availability of penicillin. In the United States, a significant resurgence of early syphilis occurred in the 1980s, owing to successive waves of disease, first in homosexual males and then in drug-abusing persons. The peak of this epidemic occurred in 1990 and was followed by a steady decline in primary and secondary syphilis, as well as congenital syphilis. Between 1991 and 1995, total reported U.S. cases of primary and secondary syphilis declined from 43,500 to 17,000 and, by 2000, to 6000. Almost all states recorded decreases; incidence remained highest in the south and, nationwide, among African Americans. This decline in early infectious syphilis led some to speculate about elimination of syphilis. Such speculation was not new, but, once again, it proved to be premature, given the increases that followed in subsequent years. A national syphilis elimination effort was launched in 1999, focused on African American heterosexuals in the southern United States.

Between 2000 and 2004, there was a resurgence of early syphilis in the United States, with 8000 cases in 2004, mainly due to an increase in men who have sex with men (MSM).⁹ Rates remained highest in the southern states and, especially, among African Americans, where they were five times higher than among whites. This increase coincided with outbreaks of acute HIV infection among college-age men who used the Internet as a means to contact sex partners.¹⁰ In some cities, coincident acute HIV and early syphilis outbreaks were noted in MSM, and behavioral data showed that rates were highest in HIV patients who were taking

antiretroviral therapy.^{11,12} The conclusion was inescapable that MSM were adopting riskier behaviors, perhaps in the belief that HIV was now a treatable disease. Public health authorities were urged to adopt Internet-based interventions targeted at MSM.¹⁰

Rates of infectious syphilis are higher in many other areas of the world than in Western Europe and the United States. For instance, rates of early syphilis rose dramatically in the 1990s in certain cities of the former USSR, attributed to a breakdown in public health systems.¹³ Infectious syphilis is relatively common in much of sub-Saharan Africa, and in Southeast Asia, including China; the World Health Organization (WHO) estimates that about 4 million new cases occur yearly in each of Southeast Asia and sub-Saharan Africa.¹⁴ Syphilis has resurged in China in recent years and is now epidemic.¹⁵ The prevalence of syphilis in the population in some African communities is 5–10%. Clearly, this infection has not disappeared in the antibiotic era, as some thought it would.

■ EPIDEMIOLOGIC TREATMENT OF CONTACTS

Because *T. pallidum* has a relatively long doubling time, approximately 33 hours for each cell division, the incubation period before onset of infectious lesions is relatively long also, averaging 3 weeks, but extending as long as 90 days. This allows a window of opportunity for treatment of sexual contacts exposed within the past 90 days to partners with early syphilis (early latent and primary and secondary syphilis), which practice has been crucial to controlling syphilis in the United States. As incidence wanes, resources allocated to public health personnel for finding and treating named contacts often have been cut back, resulting in waves of disease. In less affluent countries, there are few funds for such epidemiologic tracing initiatives, which may help to explain, in part, national disparities in incidence and prevalence of syphilis.

THE STAGES OF SYPHILIS

■ PRIMARY

The initial lesion of syphilis is a papule that appears at the site of venereal contact, 10–90 days (average 3 weeks) after exposure. The papule grows to a size of 0.5–1.5 cm in diameter and after about a week ulcerates, producing the typical chancre of primary syphilis, a round or slightly elongated ulcer, 1–2 cm across, with an indurated margin (Fig. 37-1). The ulcer has a clear base, without an exudate. It is remarkable that genital ulcers of 1–2 cm in diameter are painless; this feature contributes importantly to the natural history of the infection. Modest enlargement of inguinal lymph nodes, frequently bilaterally, is observed in the majority of patients who have genital lesions. Although



FIGURE 37-1. Primary syphilitic chancre of the penis. Note the rolled edges of the ulcer, the indurated button-like appearance, and the clean ulcer base.



FIGURE 37-3. Primary chancre of the tongue.



FIGURE 37-2. Primary perianal chancre in a homosexual man.

solitary lesions are often thought to be typical, multiple lesions frequently occur. Primary lesions in nongenital sites are particularly likely to have an atypical appearance, especially in the anal area (Fig. 37-2).

Because of their venereal origin, primary syphilitic chancres most frequently occur in the genital, perineal, or anal area; however, any part of the body may be affected (Fig. 37-3). Most chancres are found on the penis of men and on the labia, fourchette, or cervix of women. Therefore, syphilis is usually diagnosed in its primary stage in heterosexual men. In contrast, because the chancre is not visible in women and is also painless, syphilis is often not diagnosed in women until the secondary stage. The same applies to chancres in the anus or rectum, which are particularly common in homosexual men. Although these lesions may cause pain on defecation or rectal bleeding, becoming confused with hemorrhoids or even a neoplasm, they often go unnoticed, as do those on the labia and cervix.

In the absence of treatment, syphilitic chancres heal spontaneously within 3–6 weeks. The immune mechanism for healing is obscure but presumably involves both cellular and humoral mechanisms (see Chapter 36).

Differential diagnosis

As a general rule, syphilis should be considered as a possible cause of any ulcerating lesion of the genitalia or other erogenous zone and in any cutaneous area exposed to infectious lesions. Differentiating a syphilitic chancre from chancroid, the lesion caused by *Haemophilus ducreyi*, may be impossible on clinical grounds, although a great degree of tenderness, a jagged border, a yellow exudate, or striking inguinal lymphadenopathy, especially if the overlying skin is thin and shiny, is suggestive of chancroid. A chancre that is smaller, but otherwise indistinguishable from that caused by syphilis, may be transiently present in lymphogranuloma venereum. Simple trauma to the penis or a fixed drug eruption may cause lesions resembling a chancre. It is usually not a problem to distinguish lesions of herpes simplex virus (HSV) infection from those of syphilis, because HSV produces multiple small lesions on which a vesicle might be seen. However, coinfection by *T. pallidum* and HSV may occur, and secondary bacterial infection of a limited vesicular eruption may produce coalescent lesions that can be confused with syphilitic chancres. Moreover, recurrent HSV may present with a single ulcer. Even experienced clinicians are not able to diagnose the etiology of genital ulcer on clinical grounds alone, with more than 60–70% accuracy.

In some regions of the world, genital ulcer may also be due to *Calymmatobacterium granulomatis*, the cause of Donovanosis. A multiplex single-tube polymerase chain reaction (PCR) assay has been devised to diagnose genital ulcers, including *T. pallidum*, HSV, *H. ducreyi*, and *C. granulomatosis*, with good specificity but less than optimal sensitivity.¹⁶

■ SECONDARY

Within a few weeks or months (or less commonly, coincident with the primary lesion) a variable systemic illness develops, characterized by low-grade fever, malaise, sore throat, headache, adenopathy, and cutaneous or mucosal rash.

Evolution of secondary lesions is a manifestation of widespread hematogenous and lymphatic dissemination of *T. pallidum*, as evidenced by the infectious transfer of disease to susceptible animals with blood, lymph nodes, liver biopsy, and cerebrospinal fluid (CSF).⁷ At least 25% of patients with secondary syphilis have abnormal CSF, with increased cells, protein and presence of *T. pallidum* by animal transfer or PCR.¹⁷ This spread to the central nervous system is not usually accompanied by neurological signs, and standard therapy for early syphilis in persons without HIV infection appears equally effective for patients with or without abnormal CSF, as discussed below, under treatment.

The initial finding in disseminated syphilis is an evanescent copper-colored macular rash that is usually overlooked by the patient and not observed by the physician. A few days later, a symmetric papular eruption appears, involving the entire trunk and the extremities, including palms of the hands and soles of the feet. The papules are red or reddish brown, discrete, and usually 0.5–2 cm in diameter. They are generally scaly, although they may be smooth, follicular, or, rarely, pustular. Except for the involvement of palms and soles (Fig. 37-4), syphilis may be difficult to distinguish from pityriasis rosea or psoriasis. Vesicles and bullae do not occur except in congenital syphilis of the newborn, although pustular lesions are seen on the palms or soles. Circular (annular) lesions occur on the face of dark-skinned persons. Hypo- or hyperpigmentation may be seen. Alopecia occurs in some cases. Mucosal lesions, either small, superficial, ulcerated areas with grayish borders that resemble painless aphthous ulcers or



FIGURE 37-4. Secondary syphilitic rash on palm and sole.

larger gray plaques, also are common (Fig. 37-5). Erosive gastritis has been documented in rare instances.

Condyloma lata is a term used to describe large, raised, whitish or gray lesions found in warm, moist areas. These lesions were originally described as a manifestation of secondary syphilis, resulting from the effects of local skin breakdown in warm, moist areas; most frequently, the axilla and groin were involved (Fig. 37-6). Today, it is more common to observe condyloma in an area adjacent to a primary chancre, generally in the perineum or around the anus, possibly resulting from direct spread of treponemes from the primary lesion. These lesions appear before or soon after the appearance of the generalized lesions of secondary syphilis.



FIGURE 37-5. Mucus patches involving the tongue in secondary syphilis.

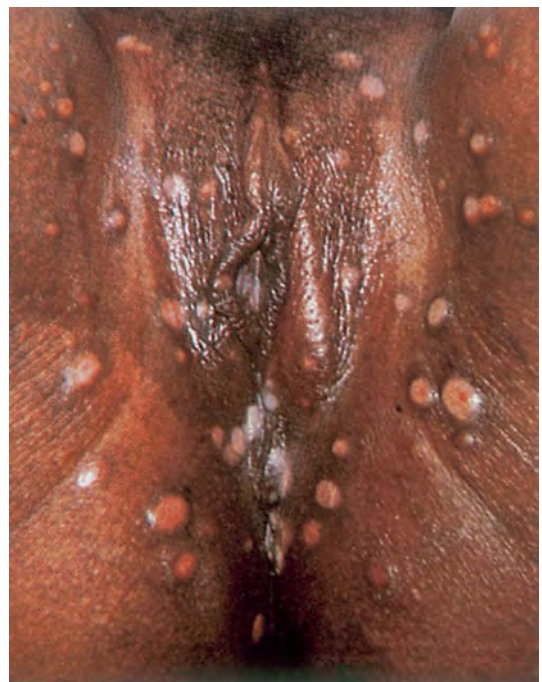


FIGURE 37-6. Perivulvar and perianal condyloma latum in secondary syphilis.

Secondary syphilis is a systemic disease, and interest in the dermatologic manifestations should not blind the physician to the presence of other symptoms, such as malaise, sore throat, headache, weight loss, low-grade fever, or muscle aches. Pruritus is not uncommon, and it may be severe. Lymph node enlargement is present in the majority of patients. In one prospective study, 75% of infected persons had palpable inguinal nodes, and 38% had axillary, 28% posterior cervical, 18% femoral, and 17% epitrochlear nodes.¹⁸ Periosteal inflammation was said to be clinically apparent in one-fourth of cases in the pretreatment era, with the skull, tibia, sternum, and ribs being involved most often. In a more recent study, technetium bone scan found lesions in a measurable proportion of cases, but these were asymptomatic; symptomatic bone involvement occurs only very rarely. Subclinical hepatitis can be detected by laboratory studies revealing elevated liver enzymes (particularly alkaline phosphatase) in about one-fifth of cases and is supported by histologic findings; occasionally, symptomatic hepatitis results.²⁰

Circulating immune complexes are uniformly present in secondary syphilis, and their deposition is thought to play a prominent role in the pathogenesis of syphilitic lesions. When iritis, anterior uveitis, and glomerulonephritis or nephrotic syndrome occur in secondary syphilis, they are probably mediated entirely by deposition of complexes.^{17,21}

Differential diagnosis

The skin rash of secondary syphilis may be confused with pityriasis rosea, psoriasis, especially if it is scaly, erythema multiforme, or a drug eruption. The sore throat, fever, and adenopathy suggest infectious mononucleosis and similar syndromes, including acute HIV infection. In this setting, clinical hepatitis and jaundice occasionally may be observed. The meningitis of secondary syphilis suggests many other causes of lymphocyte-predominant aseptic meningitis, as discussed below under syphilis of the central nervous system. Unless lesions are present on the palms or soles, any cause of a generalized papular eruption may be confused with secondary syphilis. It may be difficult to diagnose syphilis in its secondary stage once the disease is considered, but far more commonly, the physician has simply forgotten to entertain the diagnosis. For these reasons, serological tests for syphilis should be included in evaluations of sexually active adults who have a generalized skin eruption, and syphilis and acute HIV should be considered in any mononucleosis-like syndrome.

LATENCY

By definition, persons with historical or serological (see below) evidence for syphilis who have never received treatment for this disease and who have no clinical manifestations are said to have latent syphilis. The diagnosis of latency formally requires examination of the CSF to rule out asymptomatic neurosyphilis, although most clinicians do not do a lumbar

puncture in every patient with probable latent syphilis, as discussed below. Latency has been somewhat arbitrarily divided into early latency and late latency, on the basis of the time when untreated individuals are likely to have spontaneous mucocutaneous (infectious) relapses. In the Oslo study of untreated syphilis at the turn of the twentieth century, secondary relapses occurred in 25% of patients whose infection had become latent, with most relapses occurring in the first year.²² The U.S. Public Health Service therefore defines early (potentially infectious) latency as 1 year from onset of infection.

TERTIARY

The principal morbidity and mortality of syphilis in adults in past years were due to the late manifestations of illness involving the skin, bones, central nervous system, or viscera, particularly the heart and great vessels. There may be an interval of 1 to over 20 years from the acute infection to clinical onset of the late or tertiary stages of disease, long after the lesions of early syphilis have been forgotten. Studies in the preantibiotic era suggested that about one-third of untreated infections were followed by tertiary complications, of which neurosyphilis was most common, but gummas and cardiovascular disease were also prevalent.²² In the antibiotic era, all but neurosyphilis are now curiosities in the developed world, probably because of the effects of intermittent antibiotics on the development of gummas and cardiovascular disease.

SYNDROMES OF TERTIARY SYPHILIS

Tertiary syphilis occurs in many clinical syndromes, most conveniently divided into three main groups: neurosyphilis, cardiovascular syphilis, and late benign syphilis.

NEUROSYPHILIS

Abnormalities in the CSF have been noted in 13% of patients with untreated primary syphilis, and 25–40% of patients with untreated secondary syphilis.^{23,24} *T. pallidum* has been demonstrated by animal inoculation or PCR in the CSF of 15–40% of patients with untreated primary and secondary syphilis, even in the absence of other abnormalities.^{7,18,25}

After the initial spirochetal invasion of the CNS during early syphilis, untreated infection may resolve spontaneously, persist as asymptomatic syphilitic meningitis, or progress to symptomatic acute syphilitic meningitis. Progression of early asymptomatic or symptomatic meningeal infection may lead to meningovascular syphilis (usually 5–12 years after primary infection) or the later forms of neurosyphilis such as tabes or paresis (usually 18–25 years). The progression often represents a continuum of changes rather than a series of discrete steps. It is unclear why some patients never develop neurosyphilis in the absence of treatment, whereas others do.

Table 37-1. Classification of Neurosyphilis

Asymptomatic	31 ^a
Early	
Late	
Meningeal	20
Acute syphilitic meningitis	6
Meningovascular	11 ^b
Cerebral	
Spinal form	3
Parenchymatous	48
General paresis	12
Tabes dorsalis	30
Taboparesis (mixed)	3
Optic atrophy	3 ^c
Gummatous	1
Cerebral form	
Spinal form	
Total	100

^aDistinction between early and late asymptomatic syphilis could not be made.

^b"Deafness," comprising 1% of cases in Merritt et al.²⁶, was included in this category.

^c"Optic neuritis," comprising 3% of cases in HH Merritt et al.²⁶, was included in this category.

Data from Merritt HH, et al. *Neurosyphilis*. New York: Oxford, 1946.

A helpful scheme for classifying syndromes of CNS syphilis as seen in the preantibiotic era was provided by Merritt and colleagues (Table 37-1).²⁶ Although this classification emphasizes individual forms of neurosyphilis, features of several of the entities commonly coexist, producing, for example, combinations of meningitis and vasculitis or tabes and paresis.

Early neurosyphilis: asymptomatic

By definition, there are no clinical manifestations of asymptomatic neurosyphilis; rather, this condition is defined by the presence of abnormalities in the CSF in the absence of other findings of neurologic disease. The usual abnormalities include 10–100 WBC/mm³ (nearly all of which are lymphocytes), a protein of 50–100 mg/dL and, in 90% of cases, a reactive nontreponemal antibody (Venereal Disease Research Laboratory [VDRL]) test in the CSF. Blood serology (VDRL or rapid plasma reagin [RPR]) is usually but not invariably positive.

The likelihood of finding CSF abnormalities in persons with untreated syphilis increases until 12–18 months after initial infection, and the likelihood that neurosyphilis will develop increases in proportion to the extent of the abnormalities.²⁷ Conversely, a completely normal CSF examination after 2 years of latent untreated syphilis affords reasonable assurance that neurosyphilis will not develop. Thus, because asymptomatic neurosyphilis tends, in the absence of therapy, to resolve or to progress, its frequency tends to decrease with the passage of time.²⁸ In the absence of treatment, 87% of persons who had persistent CSF abnormalities for 5 years after infection went on to develop neurosyphilis.²⁹

Acute syphilitic meningitis

Acute syphilitic meningitis was relatively rare even before antibiotics became available, accounting for 6% of all cases of neurosyphilis.²⁶

Symptoms and signs. The incubation period in the majority of patients with syphilitic meningitis is less than 1 year. In about one-quarter of these patients, meningitis is the first clinical manifestation of syphilis. A small percentage of patients still have a secondary rash at the time of the meningitis.³⁰ The clinical presentations of acute syphilitic meningitis may be divided into several patterns, but these categories overlap extensively. The principal neurologic manifestations include cranial nerve palsies (seen in 40% of cases) and signs of increased intracranial pressure. The involvement of multiple cranial nerves, particularly the third, sixth, seventh, and eighth, is consistent with an extensive basilar meningitis. Sensorineural deafness occurs in about 20% of patients, commonly in association with other cranial nerve palsies.³¹ Deafness is often preceded by tinnitus and may develop rapidly, for example, over 1 or 2 weeks. The hearing loss primarily involves higher frequencies; vestibular involvement is uncommon. Involvement of the eighth cranial nerve may be an isolated finding, and the CSF may be entirely normal. Thus, early acquired syphilis is a cause of potentially reversible, rapidly progressive, or sudden sensorineural deafness and must be considered in diagnosis, even in the absence of clinical findings of secondary syphilis or of overt lymphocytic meningitis.

Acute syphilitic meningitis was relatively common in patients who received inadequate doses of antisiphilitic therapy. Ehrlich documented this association and called the condition neurorecurrence. In the 1990s, this same constellation of symptoms and signs was noted in HIV-infected patients, especially after penicillin treatment, leading to the concept that such disease occurred after treatment of immunologically normal hosts with inadequate antimicrobials or treatment of immunocompromised hosts with ordinarily excellent antibiotics.

Acute syphilitic hydrocephalus was seen in one-third of the cases of syphilitic meningitis reported by Merritt et al.³⁰

Symptoms usually develop 3–7 months after primary infection, but they can appear as many as 6 years later. The principal symptoms and signs are those of increased intracranial pressure; fever is only low-grade or may be absent.

Laboratory findings. The CSF changes include elevated pressure, mononuclear pleocytosis of 10–200 cells per cubic millimeter (but occasionally as high as 1000–2000 cells per cubic millimeter), elevated protein concentration (up to 200 mg/dL), elevated globulin level, and a modest reduction in glucose in 45% of cases. The VDRL test on CSF is reactive in most but not all cases. Patients with isolated involvement of the eighth cranial nerve are likely to have a normal CSF with a nonreactive VDRL test.

Pathologic changes. The inflammatory process involves not only the meninges but also the ependyma (granular ependymitis). The meningeal infiltrate consists of lymphocytes and plasma cells located particularly in perivascular spaces. Progressive inflammatory changes produce an endarteritis, which may result in thrombosis, vascular occlusion, and cerebral infarction. This process underlies the focal cerebral signs (aphasia and hemiplegia) and seizures that occur in some patients with acute syphilitic meningitis. Acute syphilitic hydrocephalus develops as a result of obstruction, by organizing exudate, of CSF flow either from the posterior to middle cranial fossa (communicating hydrocephalus) or from the fourth ventricle (obstructive hydrocephalus). Cranial nerve abnormalities result from compression by basilar exudate and fibrous organization or as a consequence of increased intracranial pressure.

Diagnosis and differential diagnosis. Diagnosis of acute syphilitic meningitis is based on the clinical picture of aseptic meningitis, and reactive blood and CSF serology. A history of a recent chancre or secondary rash or the presence of generalized lymphadenopathy may suggest the diagnosis, but meningitis may be the first clinical manifestation of syphilitic infection, especially in HIV-infected patients.

Differential diagnosis includes the various causes of a lymphocytic meningitis, including enteroviruses, HSV, HIV, other spirochetes (*Leptospira* or *Borrelia* [Lyme disease]), mycobacteria, fungi, drug reactions, malignancy, and autoimmune diseases. Syphilis is likely to be accompanied by reactive serology, which does not, a priori, exclude any other diagnosis. Each of these other conditions may have some unique epidemiologic, clinical, and laboratory features pointing to the correct diagnosis. Acute syphilitic hydrocephalus may suggest the diagnosis of brain tumor, and the presence of low-grade fever and signs of increased intracranial pressure might raise the question of brain abscess.

The clinical features, particularly the distinctive skin lesion, and epidemiology of Lyme disease serve to distinguish it from secondary syphilis. When Lyme disease occurs in the absence of extrameningeal findings, the distinction between the two

processes becomes more difficult. The sera and CSF of patients with the neurologic involvement of Lyme disease have been said to be nonreactive in nontreponemal tests.³² However, 11% of patients with Lyme disease have a reactive fluorescent treponemal antibody (FTA) test after absorption (ABS) with nonvirulent treponemes (FTA-ABS).³³ Furthermore, patients with syphilis show serologic reactivity with *Borrelia burgdorferi*: five of 18 patients with various stages (primary, secondary, latent, and late) of syphilis had positive ELISA tests for Lyme disease, and 11 had positive FTA tests.³² Utilizing the clinical and epidemiologic features of the two diseases as well as VDRL reactivity and *B. burgdorferi* antibody testing of serum and CSF, distinction between the two spirochetal diseases usually can be made. Western blots may help to resolve serological ambiguity.

Meningovascular syphilis

Vascular neurosyphilis may involve any part of the central nervous system.³⁴ The common denominator is infarction secondary to syphilitic endarteritis. The process is almost invariably a meningovascular one, stemming from the chronic meningitis that underlies all forms of central nervous system syphilis. In the series of Merritt et al., 10% of patients had this form of neurosyphilis.²⁶ This disease usually occurs 5–12 years after initial syphilitic infection, which is earlier than the occurrence of paresis or tabes, and most patients are 30–50 years of age. Cerebrovascular neurosyphilis may occur concurrently with, or progress to, general paresis or tabes and may be accompanied by Argyll Robertson pupils in the absence of these complications.

Symptoms and signs. The most common manifestations are hemiparesis or hemiplegia (83% of cases), aphasia (31%), and seizures (14%). Among 241 patients with neurosyphilis studied at the Medical College of Virginia, adult-onset seizure disorders were prominent in 24%.³⁵ The most common involvement, by far, is the territory of the middle cerebral artery, but any other artery on occasion may be occluded.

The onset of symptoms may be abrupt. However, about 50% of patients have premonitory symptoms of headache, dizziness, insomnia, memory loss, or mood disturbances lasting for weeks or months, probably consistent with diffuse arterial involvement. Psychiatric manifestations (personality and behavioral changes and slowing of mentation and speech) may be so prominent as to suggest the diagnosis of general paresis initially, until the onset of a stroke syndrome.^{26,34}

Laboratory findings. Serum RPR is positive in meningovascular syphilis. The CSF VDRL test is positive in most but not all cases, and there is a lymphocytic pleocytosis in the CSF. Angiographic changes include diffuse irregularity and “beading” of anterior and middle cerebral arteries and segmental dilatation of the pericallosal artery.³⁶ In contrast to the short, irregular sites of atherosclerotic disease, the areas of arterial narrowing in cerebrovascular syphilis tend to be

longer and smoother. Vascular neurosyphilis, rather than atherosclerosis, is also suggested when angiographic changes occur in the supraclinoid portion of the internal carotid artery and the proximal portions of the anterior or middle cerebral arteries, in the absence of stenotic changes at the carotid bifurcation. Computed tomography (CT) shows low-density areas with variable degrees of contrast enhancement, consistent with multifocal infarctions. Magnetic resonance imaging shows focal regions of high signal intensity on T2-weighted sequences, compatible with foci of ischemia.³⁷

Pathologic changes. The characteristic histologic changes of the arteritis of cerebrovascular neurosyphilis consist of infiltration by lymphocytes and plasma cells of the vasa vasorum, the adventitia, and, ultimately, the media of large- and medium-sized arteries. Occlusion of the vasa vasorum results in destruction of the smooth muscle and elastic tissue of the media. Concentric proliferation of subintimal fibroblasts narrows the lumen progressively until it is occluded by thrombus formation.

Diagnosis and differential diagnosis. The possibility of meningovascular syphilis should be considered when cerebrovascular accidents occur in a young adult, especially one who has none of the usual risk factors such as uncontrolled hypertension or findings suggestive of embolic cardiac disease. In the older age group, the diagnostic problem is compounded by the greater likelihood of coexisting cerebral atherosclerosis, which may also be responsible for a stroke, even though the patient has, e.g., meningal (asymptomatic) neurosyphilis.

Differential diagnosis includes other causes of stroke syndromes such as hypertension (lacunar strokes), atherosclerotic vascular disease, cerebral emboli, or various types of cerebral vasculitis. Angiographic changes in cerebral vessels in systemic lupus erythematosus may be indistinguishable from those of syphilitic arteritis, and those in polyarteritis nodosa may be somewhat similar.

Meningovascular syphilis of the spinal cord

Meningovascular syphilis of the spinal cord consists principally of syphilitic meningomyelitis (the most common form) and spinal vascular syphilis (acute syphilitic transverse myelitis).³⁸ Spinal syphilis has always been rare, representing only about 3% of cases of neurosyphilis. It is almost always associated with cerebral involvement, but the disease of the cord may be preeminent. The basic underlying process is chronic spinal meningitis, which may result in parenchymatous degeneration of the cord directly or as a result of vascular thrombosis.³⁸

Symptoms and signs. Syphilitic meningomyelitis usually occurs after a latent period of 20–25 years. The onset is gradual. The earliest symptoms are weakness or paresthesias of the legs, progressing to paraparesis or paraplegia, which is often

asymmetric. Urinary and fecal incontinence and variable sensory disorders (pain and paresthesias) in the legs are prominent. On examination, the legs are weak and spastic, and deep tendon reflexes are hyperactive; ankle clonus is present. The most frequent sensory abnormalities are loss of position and vibratory sense in the lower extremities, with a sensory level in about one-third of patients. The clinical picture may be more complex when meningomyelitis develops in the course of tabes or general paresis, or when spinal artery thrombosis supervenes, changing the spastic paraparesis to a flaccid paraplegia. The classic manifestations of spinal vascular syphilis are those of a transection of the spinal cord, usually at a thoracic level, with abrupt onset of flaccid paraplegia, a sensory level on the trunk, and urinary retention.

Laboratory findings. Blood serologic tests are regularly positive and CSF examination discloses the same abnormalities seen in other forms of syphilis (including a positive VDRL test), except in burned-out or old, treated cases.

Diagnosis and differential diagnosis. The diagnosis of syphilitic spinal thrombosis is made when flaccid paraplegia develops abruptly in a patient who has consistent CSF abnormalities and reactive blood and CSF serologies. Other causes of acute transverse myelitis must be distinguished.

General paresis

General paresis (also known as paretic neurosyphilis, dementia paralytica, and general paralysis of the insane) is a meningoencephalitis associated with direct invasion of the cerebrum by *T. pallidum*. The clinical illness is a chronic process that evolves over many years and declares itself in middle-to-late adult life. This form of late syphilis develops 15–20 years after initial infection. Prior to World War II, patients with this disease made up 5–10% of all first admissions of psychotic patients to psychiatric hospitals.^{39,40} Although this disease is now rare, it accounted for 10% of cases of neurosyphilis in the first two decades of penicillin therapy.⁴¹

The clinical picture is that of a combination of psychiatric manifestations and neurologic findings that may mimic almost any type of psychiatric or neurological disorder. The illness is commonly insidious in onset but may occasionally become suddenly evident. The early features are usually of a psychiatric nature, and the course of illness is that of a dementing process (Table 37-2). As the disease progresses, these symptoms are magnified and others appear, including defects in judgment, emotional lability, delusions, and inappropriate social or moral behavior. Grandiose delusions and megalomania, although dramatic manifestations, occur in only 10–20% of cases.⁴² Depression may be the predominant presenting feature and the most common initial diagnosis in patients with paresis.⁴¹ Adult-onset seizures, noted in 15–20% of patients, may be the initial manifestation of paresis.⁴² Although rare,

Table 37-2. Symptoms of General Paresis

Early	Late
Irritability	Defective judgment
Memory loss	Emotional lability (depression, agitation, and euphoria)
Personality changes	Lack of insight
Impaired capacity to concentrate	Confusion and disorientation
Carelessness in appearance	Delusions of grandeur
Headache	Paranoia
Insomnia	Seizures

Data from Merritt HH, et al. *Neurosyphilis*. New York: Oxford, 1946.

congenital syphilis may present with a paresis-like picture in adolescence, resulting in poor performance in school and behavioral abnormalities.

The most common neurologic findings in general paresis are pupillary abnormalities; flattening of the facial lines, tremors of the lips, tongue, facial muscles, and fingers; and impaired handwriting and speech. Pupillary abnormalities are common in paresis and may be present in other forms of neurosyphilis. The pupils may be large, unequal, and sluggishly reactive to light and accommodation. Over the course of months, normal pupils may change to the Argyll Robertson type defined by the following characteristics: (1) the retina is sensitive (i.e., the eye is not blind); (2) the pupils are small and fixed and do not react to strong light; (3) the pupils react normally to convergence accommodation; (4) mydriatics (atropine) fail to dilate the pupils fully; and (5) the pupils do not dilate on painful stimuli. Argyll Robertson pupils are observed more frequently in tabes than in paresis.

The duration of untreated paresis ranges from a few months, in cases of sudden onset, to 4 or 5 years until death. Uncommonly, spontaneous but transitory remissions have occurred. The shorter the duration and the milder the symptoms at the institution of therapy, the better is the prognosis.

Communicating hydrocephalus has complicated a few cases of general paresis and may account for either lack of clinical improvement or progressive deterioration after treatment.⁴³ The patients have had gait apraxia, akinetic mutism, incontinence, and pyramidal tract signs along with severe dementia. Isotope cisternograms have shown early ventricular entry of the radionuclide and absence of parasagittal radioactivity. CSF shunting has produced immediate improvement in several cases.

Laboratory findings. Nontreponemal serologic tests of blood and CSF are usually but not invariably positive in cases of paresis.^{26,42,44} Other CSF findings are typical of those in neurosyphilis. The CSF may be normal in a patient whose neurosyphilis has been arrested by treatment.

Specific antitreponemal antibody tests of CSF, such as FTA-ABS or micro-hemagglutination assay for *T. pallidum* (MHA-TP), have been studied as a tool to diagnose neurosyphilis in cases in which the CSF VDRL is nonreactive.⁴⁵⁻⁴⁷ These tests are more sensitive, but they may be reactive as a result of diffusion of serum immunoglobulins into the CSF; for this reason they should probably not be done routinely, although some advocate their use of these to help rule out neurosyphilis.⁴⁸⁻⁵⁰

Another approach is to examine intrathecal antibody synthesis of antitreponemal antibodies using the CSF-IgG index, obtained by dividing the CSF to serum IgG ratio by the CSF to serum albumin ratio. A result >0.7 is indicative of IgG synthesis within the CNS, but this finding is consistent with a variety of infectious or inflammatory processes.^{51,52} Better evidence for intrathecal antitreponemal antibody synthesis may be obtained if the CSF:serum ratio of *T. pallidum* hemagglutination assay (TPHA) is at least four times higher than the corresponding ratio for some other unrelated but ubiquitous antibody, such as adenovirus hemagglutinating antibody. CSF *T. pallidum*-specific IgM antibody levels have been studied for their utility in diagnosing CNS syphilis^{53,54} but have not found widespread use in practice. An increase in proportions of B cells in CSF may help diagnose neurosyphilis.⁵⁵ A PCR test on CSF for *T. pallidum* has been reported to be modestly sensitive and specific diagnosing neurosyphilis^{18,56} but, to date, has not been applied in clinical practice.

Computerized tomography in parenchymatous neurosyphilis may show extensive regions of decreased attenuation of the cerebral white matter, particularly in the frontal lobes and paraventricular areas of the parietal lobes, together with enlargement of cortical sulci and associated ventricular dilation; such changes are similar to those seen in demyelinating disorders.⁵⁷ Cortical atrophy and multiple areas of hypodensity in both cerebellar hemispheres and in the brainstem, consistent with infarctions, may also be seen. Multiple nodular enhancing lesions were observed at the base of the brain in one patient with meningovascular syphilis and cleared completely within 3 months after a 10-day course of intravenous penicillin.⁵⁸ Both enhancing lesions (gummas) and generalized cortical and subcortical atrophy have been observed in patients with neurosyphilis.⁵⁹

What should the physician conclude concerning an older adult with a history of prior treated early syphilis who years later has a reactive serum treponemal test, atypical neurologic or psychiatric findings, and CSF abnormalities such as minimal pleocytosis and slightly elevated protein with a negative CSF VDRL? Is this a patient whose treponemal test reactivity

merely represents prior infection and whose current neurologic syndrome has a nonsyphilitic etiology, or does he/she have active neurosyphilis in the absence of serum and CSF VDRL reactivity? This may be a very difficult diagnostic dilemma.

Pathologic changes. Grossly, the brain in general paresis shows varying degrees of thickening of the meninges, consistent with chronic meningitis and fibrosis. Cerebral atrophy is prominent, particularly in the frontal pole and the tips of the temporal lobes. Demyelination of cerebral white matter is often present. Granular ependymitis, formed of whorls of subependymal astrocytes, is characteristic.

Diagnosis and differential diagnosis. The diagnosis is based on the clinical picture, which is readily recognizable in its full-blown form but is more difficult to define when atypical or incomplete, together with characteristic spinal fluid abnormalities. Moreover, other diseases including alcoholic brain disease may mimic paresis, and if they occur in a patient with positive serologies for syphilis, a mistaken diagnosis of paresis may be made. The findings on CT scan, the presence of pupillary changes, and a history of alcohol abuse are helpful in correct diagnosis. Hallucinations are prominent in delirium tremens but are rare in general paresis.

Tabes dorsalis

In the prepenicillin era, tabes dorsalis accounted for about one-third of patients with neurosyphilis. Among several hundred patients with neurosyphilis treated in neurologic clinics in Poland from 1956 to 1965, tabes was the most frequent diagnosis (44%), although in the majority; the process appeared to have “burned out,” that is, the disease no longer progressed and CSF abnormalities were absent, either spontaneously or as a result of the incidental use of antibiotics.⁶⁰ In a study of late complications of syphilis involving about one-third of the population of Finland between 1963 and 1968, 66 cases of neurosyphilis were identified; of these, two-thirds involved tabes dorsalis.⁶¹ In the 1960s, 30 cases of neurosyphilis (10 of tabes) were seen in one regional neurological center in England over a 3.5-year period. Over the next 8.5-years, only 16 cases, including four of tabes, were encountered.⁶² This condition is now a rarity in most of the developed world.

Symptoms and signs. The onset of symptoms of tabes occurs in the majority of untreated patients after a latent period of 20–25 years. The early clinical features are lightning pains, paresthesias, diminished deep tendon reflexes, and poor pupillary responses to light. In more advanced stages, other symptoms and signs become prominent (Table 37-3). Lightning pains are sudden paroxysms of severe stabbing pains lasting for a few minutes at a time. These pains usually occur in the lower extremities but may be felt anywhere. They may occur at long intervals or may persist in attacks lasting

Table 37-3. Symptoms and Signs of Tabes Dorsalis

	Percent
Symptoms	
Lightning pains	75
Ataxia	42
Bladder disturbances	33
Paresthesias	24
Visceral crises	18
Visual loss (optic atrophy)	16
Rectal incontinence	14
Signs	
Pupillary abnormalities	94
Argyll Robertson pupils	48
Absent ankle jerks	94
Absent knee jerks	81
Romberg's sign	55
Impaired vibratory sense	52
Impaired position sense	45
Impaired touch and pain sense	13
Ocular palsies	10
Charcot's joints	7

Data from Merritt HH, et al. *Neurosyphilis*. New York: Oxford, 1946.

for several days at a time. Treatment with carbamazepine or related drugs may be effective.⁶³ Paresthesias are frequently felt on the legs or trunk. Hyperesthesia may be present in the areas involved by lightning pains; such areas may serve as trigger zones that precipitate bouts of pain when touched.

Visceral crises are related to lightning pains, tending to recur in attacks of marked severity that may mimic acute surgical emergencies. The most common form is a gastric crisis consisting of intense epigastric pain, nausea, and vomiting. Intestinal crises (abdominal pain and diarrhea), rectal crises (painful tenesmus), and laryngeal crises (pain in the larynx, hoarseness, and stridor) are rare.

Loss of vibration sense and inability to feel passive movement in joints are among the first detectable signs. Other sensory abnormalities include loss of deep pain perception and development of patchy areas of hypalgesia and hypesthesia over the trunk and extremities. Knee and ankle reflexes are almost always reduced or absent, whereas muscle strength is usually well preserved until the late stages. Plantar responses are flexor; Babinski's reflex indicates the coexistence of meningovascular

syphilis, general paresis, or some unrelated disorder of the CNS. Ataxia of gait is evident, and results of heel-to-shin and finger-to-nose testing are abnormal. In addition to the broad-based, stamping gait, which becomes worse when patients try to walk in the dark, abnormal findings include diminished vision owing to optic atrophy, Charcot's joint (unstable, painless, uninflamed, and markedly enlarged joint with overproduction of bone owing to repeated trauma to this anesthetic structure, especially involving the knee), and mal perforans (a painless penetrating trophic ulcer on the plantar surface at the base of a toe). The spine (particularly the lumbar spine) may be the site of Charcot changes, characterized by dense irregular sclerosis, large parrot-beak osteophytes, scoliosis, and disk-space narrowing. Although the lesion itself is painless, distressing pain may be produced by impingement of the hypertrophic bone or by a disk protruding on posterior nerve roots.

Sluggish pupillary reactivity to light is an early finding in tabes; true Argyll Robertson pupil is a later feature of the disease. Involvement of cranial nerves (particularly the second, third, and sixth) is often overlooked in tabes. Primary optic atrophy appears as sharply defined, grayish white optic disks with conspicuous physiologic cupping, visible lamina cribrosa, and narrowed retinal arteries. If untreated, visual loss progresses to irreversible blindness over months to years. Ptosis and flabbiness of facial muscles probably contribute in a large measure to the so-called tabetic facies. Divergent strabismus may also result from third cranial nerve palsy. Oculomotor weakness is attributed to basilar meningitis, accounting for its occasional improvement after penicillin therapy. Eighth cranial nerve involvement (hearing loss with or without accompanying vestibular abnormalities) is not uncommon.

The time from the onset of tabes to the development of ataxia may be 6 months to 25 years; the longer the duration of the preataxic phase, the slower the subsequent course. In the prepenicillin era, far-advanced tabes was observed with complete incapacitation owing to joint deformity, loss of bladder control, blindness, ataxia, and deafness. Tabes may burn out with time, even in the absence of treatment. Lightning pains may persist even when early treatment has been successful; their presence, therefore, does not indicate continued syphilitic infection. Antibiotic treatment cannot reverse the extensive changes of advanced disease.

Laboratory findings. The laboratory findings in tabetic neurosyphilis are variable, depending on the stage of tabes, whether partial or full treatment has been administered in the past and whether the process has spontaneously burned out. In the prepenicillin era, negative blood serologic reactions were reported in 12–42% of cases. In a 1972 study of seven patients with long-standing tabes, the blood nontreponemal serology was negative in six patients, all of whom had been treated repeatedly but continued to have lightning pains and other manifestations of tabes.⁶³

The CSF findings among 100 patients with tabes, including a large number of patients with old, arrested cases, were (1) lymphocytic pleocytosis in 50% (practically all untreated cases), (2) elevated protein concentration (45–100 mg/dL) in 50%, and (3) reactive nontreponemal serologic test in 72%.²⁶

Diagnosis and differential diagnosis. A clinical diagnosis of tabes is most likely in a patient with lightning pains and ataxia who exhibits findings of absent deep tendon reflexes, Argyll Robertson pupils, and a positive Romberg sign. Early and atypical cases present greater problems in diagnosis, and only the results of serologic testing and spinal fluid examination may lead to the correct diagnosis. A mixed clinical picture of taboparesis may also be a source of diagnostic confusion.

Differential diagnosis includes a variety of neurologic disorders. Although knee and ankle jerks may be lost in meningovascular syphilis of the spinal cord, lightning pains and pupillary changes are not usually present; ultimately, hyperactive reflexes and extensor plantar responses develop. Adie's syndrome (absent deep tendon reflexes and myotonic pupil) can be distinguished from tabes by the fact that the pupil is not miotic. This syndrome also lacks the lightning pains and ataxia of tabes; serologic tests are negative and CSF examination is normal. Diabetic neuropathy may mimic tabes (diabetic pseudotabes) by producing sluggish pupillary reactivity, ptosis, pains, and ataxia and by absent deep tendon reflexes. However, in diabetic and other types of peripheral neuropathy, the pain is burning in character rather than shooting, as is typical of tabes, and the serologic findings are negative. Combined system disease is similar to tabes in producing ataxia and bladder disturbances, but lightning pains are not a feature. Extensor plantar responses are found in combined system disease but not in tabes.

Optic atrophy and ocular syndromes

Syphilitic optic atrophy, which often is seen in tabes, may appear as an isolated manifestation of neurosyphilis.⁶⁴ Other ocular manifestations may also be the first sign of neurosyphilis, including uveitis; clinicians suspecting late syphilis should inspect the eyes carefully and refer patients for ophthalmologic evaluation including slit lamp examination. The usual symptoms of optic atrophy are those of progressive visual loss involving first one eye and then the other. As in cases of tabes, CSF abnormalities are usually present in the untreated patient. Optic atrophy may also result from prior syphilitic optic neuritis. The visual evoked response may make it possible to distinguish primary from postneuritic optic atrophy on the basis of a normal latency in the former.⁶⁵ Penicillin treatment can usually prevent further progression of visual loss.

Gummas of the nervous system

Cerebral gummas. Intracerebral gummas are extremely rare.²⁶ The features are those of a cerebral neoplasm, brain abscess, or tuberculoma. CSF findings are the same as in other forms of neurosyphilis but include increased CSF pressure. CT scan may reveal a low-density nonenhancing area, and angiography may show a hypervascular blush zone surrounding the focal area of gummatous necrosis.⁶⁶ The diagnosis may only be made when the patient is operated on for a suspected intracranial mass lesion. Recent literature contains anecdotal accounts of cerebral gummas, mostly in HIV-infected persons.⁶⁷

Atypical presentations of neurosyphilis in HIV infection?

As the incidence of neurosyphilis has continued to decline in the antibiotic era, atypical presentations of this disease have been noted.^{35,68,69} One reason may simply be decreased familiarity with the full range of manifestations of neurosyphilis. It is also possible that the clinical features and the course of neurosyphilis have been modified by antibiotic treatment of intercurrent illnesses during the latent stage of syphilis, or by concomitant presence of HIV infection. In a retrospective study, 1.5% of all patients attending a clinic for HIV-related disease had been diagnosed as having neurosyphilis.⁷⁰ Holtom et al. screened 312 entrants to an AIDS clinic and found 71 with reactive RPR and MHA-TP tests.⁷¹ Of these, 33 consented to have a lumbar puncture; three (10%) had reactive VDRL in the CSF. Thus, prevalence of neurosyphilis was at least 1% (three of 312). Dowell et al. found that when 13 asymptomatic HIV-infected patients with serum RPR $\geq 1:4$ submitted to a lumbar puncture, the CSF VDRL was reactive in seven (54%); five of these subjects had increased white blood cells in their CSF and six had elevated protein, as well.⁷² Since many clinics that provide care for HIV-infected patients find that 5–10% of all patients have serum RPR reactive at $\geq 1:4$, these data are all consistent with a prevalence of asymptomatic neurosyphilis exceeding 2% in HIV-infected patients.^{71,72}

Neurosyphilis often occurs in persons whose HIV infection has not yet progressed to cause AIDS.⁷³ The diagnosis of HIV infection may be made first when a patient presents with neurosyphilis. Considering its rarity in the non-HIV-infected population, the diagnosis of neurosyphilis should strongly suggest the coexistence of HIV infection. Failure to treat asymptomatic neurosyphilis in HIV-infected persons may be followed by progression to symptomatic neurosyphilis, generally manifesting itself as a cerebrovascular accident. Recognition of the rapid progression to meningovascular syphilis in HIV-infected persons was probably the first recognition of the coexistence of these diseases.⁷⁴ Anecdotes of the dangers of progression to neurosyphilis after apparently adequate penicillin therapy of HIV-positive patients are not uncommon, although large treatment studies of HIV-positive and HIV-negative subjects have not found differences in

clinical response overall.¹⁸ Serological responses may be slower or less complete in patients with HIV.^{18,75,76}

■ CARDIOVASCULAR SYPHILIS: CLINICAL MANIFESTATIONS OF ACQUIRED CARDIOVASCULAR SYPHILIS

Syphilis of the cardiovascular system becomes clinically manifest after a latent period of 15–30 years. Most patients are between 40 and 55 years of age at onset, and men are affected three times as often as women. Reasons for the male predominance are unclear, and some have speculated that susceptibility was increased in persons undergoing hard physical labor for prolonged periods. There really is no clear evidence as to why some develop neurosyphilis, others develop cardiovascular syphilis, and others—the majority of untreated patients—never develop symptomatic late disease. Penicillin and other antibiotics appear to have nearly eliminated late cardiovascular syphilis, even in AIDS patients. It is unclear why this is so.

Cardiovascular syphilis may lead to aortic aneurysms, aortic insufficiency, coronary artery stenosis, and, rarely, myocarditis. Its clinical presentation is characterized by the functional disorder resulting from cardiac involvement, and, at times, it may be difficult to distinguish cardiovascular syphilis from other more common varieties of cardiac disease.⁷⁷

Pathology and pathophysiology

The cardiovascular system is not clinically affected in the early stages of syphilis, but older pathology studies suggest that such involvement was common in tertiary-stage disease.⁷⁸ However, clinical manifestations of cardiovascular syphilis occurred in only 10% or less of patients with tertiary disease. Aortic, coronary ostial, valvular, and myocardial lesions have been described, but aortitis was the most common lesion, accounting for the majority of clinical manifestations.^{79–81}

T. pallidum presumably spreads to the heart during the early stages of syphilis, possibly via the lymphatics, and the organisms lodge in the aortic wall, where they remain dormant for years. The spirochetes appear to have a predilection for the vasa vasorum of the aorta, particularly the proximal aorta, producing transmural inflammatory lesions resulting in endarteritis of these vessels. The proximal portions of the coronary arteries near the ostia sometimes are involved by the obliterative endarteritis. This inflammatory process, which is rich in perivascular lymphocytes and plasma cells, continues for years, long after evidence of early syphilis has passed. This suggests that the lesions of late cardiovascular syphilis have an immunologic basis, as has been proposed for other forms of tertiary syphilis.

Although the initial insult is primarily to the small nutrient vessels of the aorta, all three layers of aortic wall are affected by

the process. Probably because of obliteration of the lumen of the vasa vasorum, the aortic media develops patchy necrosis with subsequent focal scarring. The medial destruction is also associated with the destruction of the important elastic tissue of the media, which sets the stage for subsequent aortic dilation and aneurysm formation. The adventitia, which contains the prominently inflamed vasa vasorum, undergoes fibrous thickening. The overlying aortic intima becomes diffusely diseased, with atherosclerotic changes involving virtually the entire intimal surface of the affected aorta. The extensive plaque formation has been described as “tree barking,” and the calcification accompanying these complicated atherosclerotic plaques accounts for the eggshell calcification of the proximal aorta that is often evident radiographically (Fig. 37-7).

Aortic aneurysm

Syphilitic aneurysms, the most common manifestations of tertiary syphilis, virtually always involve the thoracic aorta, particularly the ascending aorta immediately at and above the sinuses of Valsalva. Over 60% involve the ascending portion of the thoracic aorta; 25% involve the transverse arch.⁸² Rarely, syphilitic aneurysms of the innominate artery present with cerebral emboli.⁸² These aneurysms are typically fusiform or saccular in type. Syphilitic aneurysms do not dissect, probably because of the medial scarring and wall thickening of the chronic inflammatory process.⁷⁹

Characteristically, syphilitic aneurysms remain asymptomatic for many years, before they are detected. Symptoms

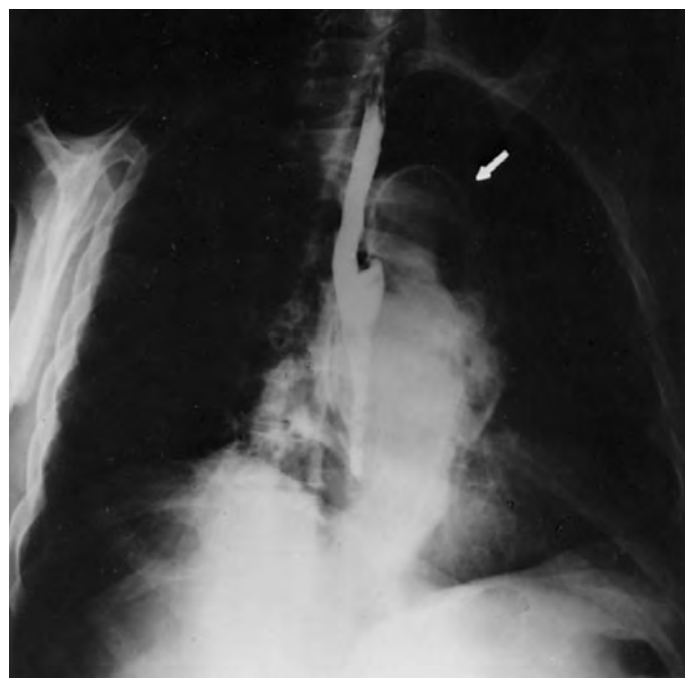


FIGURE 37-7. Chest radiograph, after barium swallow, of a 56-year-old man with a history of incompletely treated syphilis. Marked calcification can be seen within the aneurysm of the ascending aorta (arrow). (Courtesy BW Gayler.)

eventually develop when an aneurysm encroaches on surrounding structures or ruptures. In some cases, aneurysms erode through the chest wall and present as a chest wall mass. More typically, the patient presents with persistent chest pain or with symptoms of a mass lesion compressing adjacent structures, such as hoarseness from recurrent laryngeal nerve pressure. A rare presentation may be with the superior vena cava syndrome and, in association with cough, dyspnea, dysphagia, and hemoptysis, may be misdiagnosed as lung cancer.⁸³ If aortic insufficiency is not present, there may be no detectable abnormalities on cardiac examination. The chest radiograph may be normal or show a mediastinal mass with typical eggshell calcification outlining the aneurysm (see Fig. 37-7). This finding, however, may also be seen in severely atherosclerotic aortas or aortas from patients of advanced age and is not specific for syphilis. The precise definition of the aneurysm is achieved by aortic root angiography.

Management is largely dictated by symptoms. If a patient presents with evidence of an expanding aneurysm or with chest pain or symptoms of encroachment on adjacent tissue, surgical resection would be appropriate therapy.

Coronary artery disease

The coronary arteries may be primarily involved in syphilis, but almost always only the ostia or the most proximal few millimeters of the coronary arteries are affected. The pathogenesis of the coronary arterial disease is an obliterative endarteritis. When the luetic process significantly narrows the coronary ostia, it may lead to ischemic heart disease, including angina pectoris or sudden death.⁸⁴ Ordinarily, the acute coronary occlusion would involve such an extensive mass of left ventricular myocardium that the patient would not likely survive long enough to evolve a clinically apparent myocardial infarct. The diagnosis of syphilitic coronary disease should be considered in a patient who has been shown, by coronary angiography, to have isolated right or left main coronary ostial narrowing without atherosclerosis in the rest of the coronary tree and who has a history of syphilis or other signs of cardiovascular syphilis.

Aortic regurgitation

Pure aortic regurgitation without stenosis formerly was a common cardiovascular manifestation of syphilis, occurring in roughly 30% of patients with tertiary syphilis of the cardiovascular system. Aortic regurgitation appears to be due to aortic root dilation with stretching of the aortic valve, leading in many cases to widening of the aortic valve commissures, thickening of the aortic valve leaflets, and a variable amount of aortic valve incompetence.⁷⁹ The degree of insufficiency may range from mild to severe and largely determines both the clinical course and its management.

Physical findings of luetic aortic insufficiency include diastolic blowing along the lower left sternal border, increased aortic second sound, and if the aortic insufficiency has been severe enough, a prominent left ventricle that is both hypertrophied and dilated. A tambour-like quality of the second heart sound has been commonly described in syphilitic aortic valve disease, probably owing to the aortic root dilation. If aortic stenosis also is present, the cause is highly unlikely to be syphilitic.

The differential diagnosis of chronic pure aortic insufficiency (i.e., without a component of stenosis) includes healed infective endocarditis, congenitally malformed valves, Marfan's syndrome, ankylosing spondylitis, Reiter's syndrome, trauma with cusp dehiscence, or aging and aneurysm in a sinus of Valsalva. Cardiovascular syphilis can usually be distinguished from these other conditions by findings including aortic root disease, a tricuspid aortic valve with normality of the other cardiac valves, and the absence of stigmata of metabolic and connective tissue diseases.

Management of syphilitic aortic insufficiency is dictated by the symptoms and hemodynamic status of the patient. Congestive heart failure and chest pain are indications for valve replacement. Unfortunately, symptoms often develop at a time when the heart has already been hypertrophied and dilated, and, despite valve replacement, a secondary valvular myocardiopathy remains. Technical aspects of surgery for syphilitic aortic insufficiency are generally no more difficult than for rheumatic valvular disease; the area of the sinuses of Valsalva and the most proximal aortic root tend to be scarred and thickened and therefore provide a good foundation for valve implantation. The state of the aorta should be carefully assessed both before and after valve replacement. Progressive thoracic aortic dilatation can occur after aortic valve replacement for syphilitic aortic valve disease and may require surgical repair, as well.⁸⁵

■ LATE BENIGN SYPHILIS

Late benign syphilis or gumma is a proliferative granulomatous inflammatory process that may be destructive of affected tissues. Most lesions occur in the skin and the bones, with a lesser frequency in the mucosae and certain of the viscera, muscles, and ocular structures. In some ways, the classification is misleading, since gumma of the myocardium, brain, spinal cord, or trachea with stenosis may be anything but benign.⁸⁶

Incidence

In the preantibiotic era, gummas were common, but, for unclear reasons, in the United States, they became much less common in the decade before the introduction of penicillin and all but vanished by 1960. A critical review of the Oslo study, originally conducted in the late nineteenth century, showed that 15.8% of 1147 patients "sooner or later" developed

late lesions of the skin, mucous membranes, or bones and joints.²² Twenty-five percent of men and 35% of women had recurrent episodes.²² In contrast, a search of medical records at Vanderbilt University and Nashville General Hospitals by the late Dr. Rudolph Kampmeier disclosed only a single case during a 15-year period in the 1970s and 1980s. The literature post-1990, however, contains scattered anecdotes of gummatous lesions of many organs (brain, bones, skin, and others) mainly in HIV-infected persons.^{87–89} Thus, physicians still must be aware of this relatively rare form of syphilis.

Pathogenesis

The gumma is thought to represent an inflammatory response to a few organisms. The demonstration of *T. pallidum* in lesions was difficult; animal inoculation rarely was successful, and silver stains usually were unrewarding. The best evidence in support of hypersensitivity was provided by Magnuson et al., who inoculated volunteers in Sing Sing Prison with the Nichols strain of *T. pallidum*. Gummas developed only in persons with a history of previous syphilis.⁶ Magnuson et al. concluded that superinfection in a sensitized patient may explain gumma formation.

Pathology

Syphilitic inflammation is generally relatively mild but chronic, and slow destruction of tissue leads to eventual fibrosis. The early inflammatory nodule has a granulomatous character closely resembling the lesion of tuberculosis. Grossly, gummas are nodules that may be found in any tissue or organ and may vary from microscopic size to many centimeters in diameter. The necrotic material in the larger nodules is of a gummy consistency, hence the term gumma. The histologic picture shows coagulative necrosis surrounded by lymphocytes and mononuclear cells; multinucleated giant cells appear only rarely. The lesion is encapsulated by proliferating connective tissue, with vascularized connective tissue extending outward from the necrotic area. When the skin or mucous membrane is involved, an ulcer develops. Deep scarring accompanies the healing of gummas.

Clinical manifestations

The presence of any chronic inflammation, tumefaction or tumor, or destructive lesion of any tissue or organ of the body suggests that syphilis be considered in the differential diagnosis.

Skin. Two forms may appear: a nodular or noduloulcerative and a solitary lesion.

Nodular and noduloulcerative lesions. The nodular lesion is a deep indurated nodule that varies from pinhead to pea size and is brownish red in color. The multiple nodules are distributed

usually in an arciform pattern with predilection for the face, the scapular and interscapular areas, and the extremities. They may remain for weeks or months and may heal without breaking down but still may show scarring. If nodular lesions break down to the noduloulcerative form, they heal leaving an atrophic noncontractile scar (Figs. 37-8 and 37-9). If untreated, they will heal, but over time (up to years) new nodules appear at the margins of the previous site, advance in a serpiginous fashion, and may eventually cover by scar an area as large as the whole back. These lesions resolve promptly with effective treatment.

The solitary gumma. The solitary gumma is a subcutaneous process that involves the skin secondarily. It is more common on the thighs, buttocks, shoulders, forehead, and scalp. As it becomes necrotic, it has the characteristics of a “cold abscess,” as in other granulomatous diseases. It may drain through one or more areas (Fig. 37-10).

Skeleton. Tertiary syphilis of bones was about as common as gumma of the skin. Although the gumma is a destructive process, it may be hidden by the osseous or periosteal reaction. The radiographic manifestations include periostitis,

gummatous osteitis, and sclerosing osteitis. The clinical characteristics include pain (especially nocturnal), tenderness, swelling, bony tumor, stiffness, and limited motion. Less common symptoms are heat, redness, and draining sinuses. Gumma of skeletal muscle is recognized by biopsy or by resolution of the tumor under therapy.

Recognition of skeletal involvement by congenital syphilis may come late in life; one of the authors (M.N.S.) has seen an elderly patient who presented with fractures of the leg bones thought to be secondary to osteomyelitis until it was recognized that periosteal elevation typical of congenital syphilis was seen in many long bones as well as the cranium.

Upper respiratory tract, mouth, and tongue. Gummatous osteitis of the nasal bones, hard palate, and nasal septum, as well as perichondritis of the latter used to be relatively common (Figs. 37-11 and 37-12).

Digestive system. The clinical picture of the rare gumma of the esophagus suggests carcinoma. Esophagoscopy may reveal an ulcer, tumor, or stricture. Gastric syphilis may mimic either a malignant or a benign gastric ulcer clinically and radiologically. Gumma of the liver was the most



FIGURE 37-8. A. Nodular syphilid. **B.** Characteristic residual scars from noduloulcerative syphilis. (From Kampmeier RH. *Essentials of Syphilology*. Philadelphia: Lippincott, 1943.)

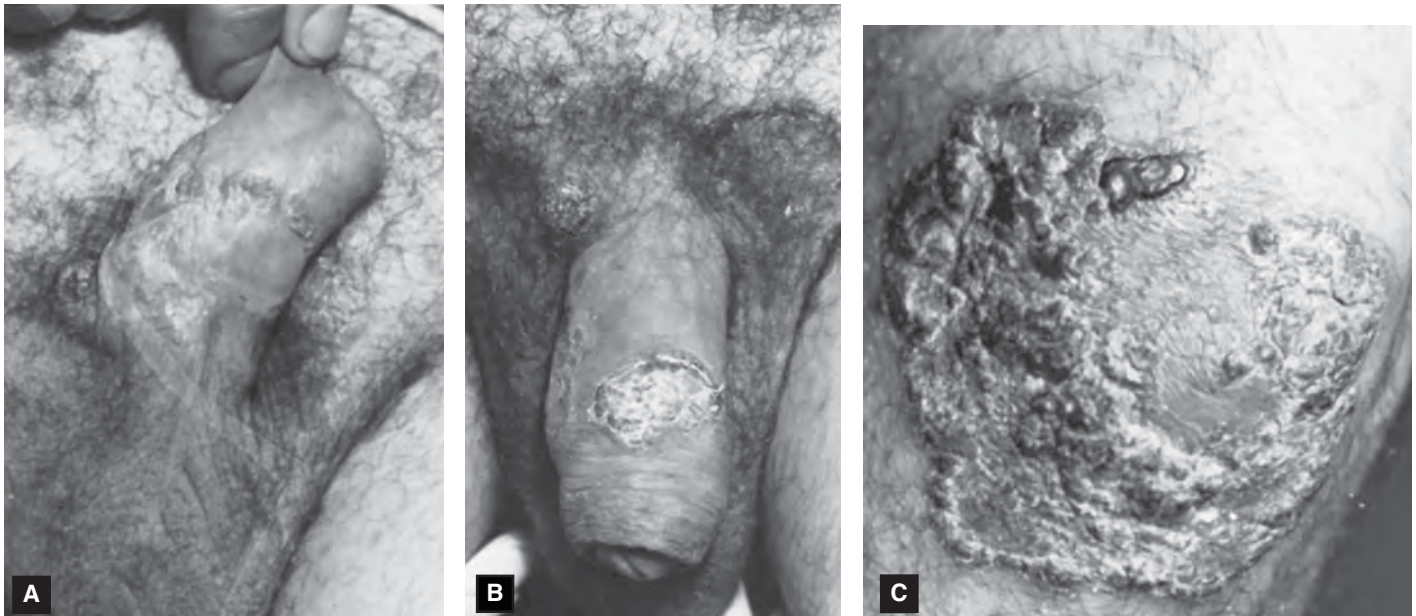


FIGURE 37-9. **A.** Nodular syphilid on inferior side of the penis. **B.** Nodular syphilid of the pubic area and solitary gumma on dorsum of the penis. **C.** Nodular syphilid of the knee. There were signs of aortic incompetency. (From Kampmeier RH. *Essentials of Syphilology*. Philadelphia: Lippincott, 1943.)



FIGURE 37-10. Ulcerating solitary gumma of skin of 12 months' duration. Note scarring from spontaneous healing. Accompanying solitary ulcers on each shoulder and on the leg, 4–8 cm in diameter, began as pimples 7 months previously. (From Kampmeier RH. *Essentials of Syphilology*. Philadelphia: Lippincott, 1943.)

frequent type of gastrointestinal tertiary syphilis. Some patients remain asymptomatic. However, there may be symptoms of low-grade fever, weight loss, and epigastric pain and tenderness.

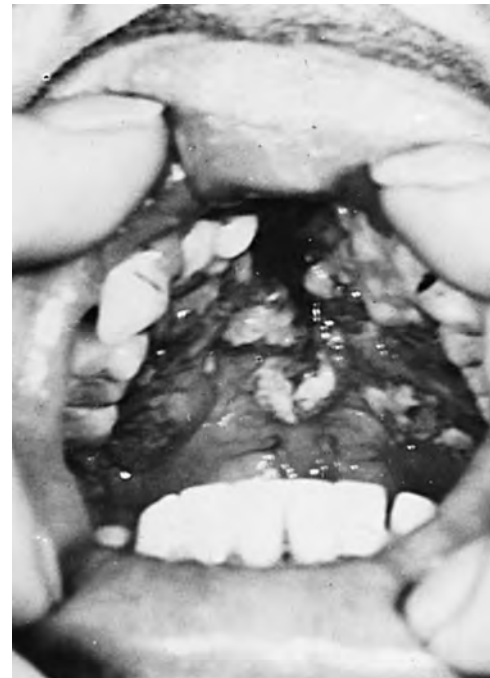


FIGURE 37-11. Osteitis of hard palate with perforation. (From Kampmeier RH. *Physical Examination in Health and Disease*. Philadelphia: Davis, 1970.)

Myocardium. Myocardial gummas, especially of the left ventricle and commonly asymptomatic, have been reported on occasion. Rarely, complete heart block resulted from gummatous involvement of the atrioventricular bundle.



FIGURE 37-12. Disease of the cartilaginous nasal septum.

DIAGNOSIS

The principal challenge in diagnosing syphilis is remembering to include it in the differential diagnosis.

■ DARKFIELD EXAMINATION

The most specific and sensitive method for verifying the diagnosis of primary syphilis is the finding of treponemes with characteristic appearance by darkfield microscopic examination of fluid obtained from the surface of the chancre. *T. pallidum* is slender, actively motile with sudden bending motions, and has pointed tips and about 16 coils. This test result is nearly always positive if a good specimen is provided to an experienced observer, provided that there has been no prior therapy with antibiotics or application of ointments that render the reading difficult. If no exudate is present, abrading the chancre and adding a drop or two of saline yields an adequate specimen. False-positive readings do not occur if trained observers are doing the study, even if the material has been obtained from oral lesions. Although treponemes can be detected in secondary lesions, it is much more difficult to prepare the sample, and almost no one uses

this technique for diagnosis in secondary syphilis, except in cases of condyloma lata. Darkfield examination has no place in diagnosing late syphilis.

■ CULTURE

No method has been developed for culture outside of animals, despite years of trying by many investigators. *T. pallidum* can be grown in animals, and isolation in rabbits has been used in test of clinical materials¹⁸ (see Chapter 36).

■ MOLECULAR AMPLIFICATION

PCR-based tests have been developed and used in research studies to diagnose either the invasion of the CSF^{18,90} or the cause of genital ulcers,¹⁶ but they are not available for routine clinical use.

■ SEROLOGICAL TESTS

Serologic tests for syphilis fall into two broad categories. Those in the first category, initially described by Wassermann 100 years ago, measure antibody to diphosphatidylcholine or cardiolipin, a component of mammalian cell membranes that is incorporated and, presumably, modified by *T. pallidum*. Subsequent modifications include the VDRL test, developed at the Centers for Disease Control and Prevention, and the RPR. The VDRL test is the test that is still done on CSF, whereas the RPR is a card assay that tests for anticardiolipin antibody in serum. The level of antibody is reported as the greatest dilution of CSF or serum at which the test is still positive. In general, the height of the RPR antibody correlates with the activity of the syphilitic infection.

The second category of serologic tests for syphilis is the one that detects surface-exposed proteins of *T. pallidum* after adsorption to remove cross-reacting antibodies to common, shared bacterial antigens. Until the late 1970s, the standard test was the FTA-ABS. This test was highly specific for *T. pallidum* and very sensitive but required a fluorescent microscope and highly trained personnel. It has largely been replaced by a card assay that uses hemagglutination as the endpoint (MHA-TP or TPHA). A variation on this test now widely used is the *T. pallidum* particle agglutination test. These tests are reported without titration, and the result is positive or negative. Once this antibody appears, it usually persists for life; thus, a positive test indicates present or prior infection with *T. pallidum*. A Western blot test has been studied as an additional method to validate specificity⁹¹ but is not widely used.

Historically, serologic tests for antibody to cardiolipin have been called nontreponemal or nonspecific, whereas those to surface-exposed proteins have been called treponemal or specific tests. Antibody to cardiolipin is, in some senses, an autoantibody, which explains chronic (>6 months) positivity of this test in certain autoimmune diseases, including lupus

erythematosus and the antiphospholipid syndromes—and in the aged. Antibody to cardiolipin also appears transiently (<6 months) in other acute infections, most notably EB virus infection and chicken pox—and after immunizations.

In primary syphilis, the RPR is positive in about 80% of patients at the time they come to medical attention, often at a relatively low level ($\leq 1:16$). The MHA-TP is positive in about 90% of such patients. In secondary syphilis, the RPR is always positive and at titers $\geq 1:16$, as is the MHA-TP. In latency, the titer of anticardiolipin antibody falls, although the test is likely to remain positive at a low level. In neurosyphilis, the RPR rises in some, but not all forms, as noted above. The RPR may also be positive at only a low level in cardiovascular syphilis, because weakening of the aortic wall may continue after active disease has burned itself out. In gummatous disease, the RPR is positive at a high level, as might be expected from the immunologic nature of the reaction.

It is important to understand that, although these serologic tests are both sensitive and specific, they are likely to support but not establish a diagnosis of syphilis. For example, a positive MHA-TP with a negative RPR in a patient with a genital ulcer could be consistent with syphilitic chancre. But the MHA-TP may remain from a prior syphilitic infection, and the genital lesion may be due to another organism altogether, e.g., *H. ducreyi*. The same may apply even if both tests are positive. This is why the search for treponemes by darkfield examination should be undertaken whenever possible, even though it is time consuming and requires trained personnel, and why tests should be routinely done for other causes of genital ulcer. A high-titered MHA-TP in the presence of a skin rash strongly supports a diagnosis of secondary syphilis. Nevertheless, *the most reliable use of the MHA-TP test is to use a negative result to exclude the diagnosis of anything other than the earliest stage of primary syphilitic infection.* A negative MHA-TP excludes the diagnosis of syphilis in a patient with a rash that might be secondary infection (so does a negative or low-titer RPR, although the prozone phenomenon rarely may give a false-negative reaction) and also excludes the possibility that neurologic or cardiovascular disease may be syphilitic.

Since, as noted above, RPR reactivity reflects activity of disease, levels are expected to subside after treatment, and the results of this test are followed in order to assess the efficacy of such therapy. After treatment for primary or early secondary syphilis, the RPR generally returns to nonreactive over a period of 1–2 years. The longer the disease persists before treatment, the more likely it is that the test will remain positive at a low level throughout life—the so-called serofast state. Treatment of latent or late syphilis generally is followed by persistence of a positive RPR.

The serofast state may indicate that treatment failed to eradicate treponemes from the body. Treponemes may persist in lymph nodes and the CNS of treated patients and experimental animals.^{92,93}

SYPHILIS AND HIV INFECTION

Few published data support the contention that the manifestations of primary and secondary syphilis are altered by HIV infection, and, in fact, prospective studies provide results that refute this notion. In contrast, concurrent HIV infection, whether before or after a diagnosis of AIDS has been made, appears to have an impact on neurologic involvement in syphilis.⁹⁴ Cases of therapeutic failures have been described after conventional doses of penicillin for primary or secondary syphilis. Numerous individual case reports have documented the apparently rapid progression of early syphilis to neurosyphilis, manifested as meningitis or cranial nerve defects (most commonly optic neuritis or deafness).^{94–97} The term “quaternary neurosyphilis” has been revived to describe necrotizing encephalitis in an HIV-infected patient.⁹⁸ In many cases, concurrent HIV infection has been documented for the first time only when neurologic complications appeared. Risk of neurosyphilis is increased substantially—three- to fivefold—in HIV-infected patients with RPR titers $\geq 1:32$ or in whom CD4 counts are <350 .⁹⁰

TREATMENT OF SYPHILIS

■ PRIMARY OR SECONDARY SYPHILIS, NO HIV INFECTION

A single dose of 2.4 million units of benzathine penicillin appears to produce a clinical cure of primary or secondary syphilis. For patients who are unable to take penicillin, ceftriaxone (1 g) intravenously or intramuscularly every day for 10 days^{99–102} should provide identical results. Tetracycline 500 mg, four times daily or doxycycline 100 mg twice daily for 14 days¹⁰³ may be just as effective. Azithromycin has been used successfully^{104–107} to treat syphilis and has the advantage of apparently being curative in primary- and secondary-stage illness after a single oral dose of 1 or 2 g, even in HIV-infected patients.¹⁰⁶ However, clinical failures after single-dose azithromycin therapy have been noted on the West coast of the United States,¹⁰⁸ which has been correlated with mutation of the ribosomal RNA target for macrolide antibiotics.^{109,110} As of early 2007, the prevalence of resistance to azithromycin among *T. pallidum* isolates is largely unknown, due to lack of routine testing for resistance, but the extent of documented resistance suggests that use of azithromycin is unwise.¹¹¹

With successful antibiotic treatment for primary or secondary syphilis, lesions disappear within days and the RPR test returns to negative over 1 to 2 years in nearly all cases, declining more slowly in secondary disease. Serologic failure must be differentiated from recurrent (new) infections after treatment for the initial infection. The rarity of tertiary

syphilis in the United States in the past three decades argues that, in practice, recommended doses of penicillin have been remarkably successful in curing syphilis. Some patients who are cured of their secondary syphilis retain low-grade VDRL or RPR reactivity throughout life (serofast state), which does not respond to repeat therapy with the same or other antibiotics.

Patients who fail therapy, as measured by clinical relapse or a fourfold or greater rise in RPR titers, should be retreated, usually with benzathine penicillin in a dose of 2.4 MU IM weekly for 3 weeks. Their HIV status should be rechecked, and a lumbar puncture should be strongly considered.

After treatment for primary or secondary syphilis, about one-third or two-thirds of patients, respectively, have a reaction characterized by chills, fever, arthralgias, headache, and transiently increased prominence of lesions. This is called a Jarisch–Herxheimer reaction (discussed in more detail below).

■ LATENT SYPHILIS, NO HIV INFECTION

Latent syphilis presents a problem. The diagnosis is based on a reactive RPR and MHA-TP tests in an asymptomatic subject. In the majority of instances in the United States today, this serologic result reflects previously treated rather than active infection. The official recommendation in the 2006 Treatment Guidelines from the CDC¹¹² is that a single injection of benzathine penicillin, 2.4 million units, be given in early latent syphilis (less than 1 year), but that three injections be given at weekly intervals for late latent syphilis or syphilis of unknown duration.

An important question is whether to perform a lumbar puncture in every patient with presumed latent syphilis, in order to exclude asymptomatic neurosyphilis. In cases where suspicion of untreated or inadequately treated syphilis is high, lumbar puncture should be done. An alternative approach is to do no spinal tap unless neurological disease is present, treating with three doses of benzathine penicillin at weekly intervals, a therapeutic regimen that once was standard for neurosyphilis and in which failures were documented very infrequently. Careful follow-up is mandatory.

The response of latent syphilis to therapy is difficult to assess. Since the patient is free of symptoms, the only possible response, barring the appearance of symptomatic tertiary syphilis, is a change in serologic test results. The RPR titer often remains unchanged (serofast state), or it may decline, but it usually does not return to negative. Rising titers suggest therapeutic failure, in which case a CSF examination must be done and the patient must receive either a repeat of the initial therapy or a more aggressive therapy, as for instance intravenous penicillin for neurosyphilis (see below).

■ TREATMENT OF PRIMARY AND SECONDARY SYPHILIS IN HIV-INFECTED PATIENTS

Most reports show that HIV infection does not markedly affect response to benzathine penicillin therapy.¹¹² Concomitant use of probenecid to boost serum levels after oral amoxicillin therapy did not improve response to therapy of early syphilis, regardless of HIV status.¹⁸ The U.S. Public Health Service continues to recommend a single dose of 2.4 million units benzathine penicillin in this situation.¹¹²

Concern remains, however, that benzathine penicillin may not prevent the progression to early neurosyphilis in HIV-infected persons, based on numbers of individual cases in which treatment of primary or secondary syphilis with benzathine penicillin was followed by rapid progression to neurosyphilis, along with evidence of persisting treponemes in the CSF of HIV-infected patients after treatment.^{92,113–115} Those who recommend a single dose of benzathine penicillin state that the percentage of treated cases that fail is so small that they cannot recommend an increased penicillin dose for everyone. Some authorities, in contrast, believe that minimum therapy for primary or secondary infection without neurologic involvement in HIV-infected patients should be three doses each of 2.4 million units benzathine penicillin at weekly intervals.¹¹² However, there are no data to show that progression to neurosyphilis, the principal concern in this situation, is reduced by the more aggressive therapy.¹⁸ The same may be said for injection of 2.4 million units daily of procaine penicillin plus oral probenecid 500 mg every 6 hours or of 1 g ceftriaxone daily for 10 days.^{76,101} There are no data to support use of doxycycline in this situation. Azithromycin appears to be equally efficacious in HIV—positive and negative—subjects,^{105,106} but worries about azithromycin resistance raise serious concerns, as discussed above. Additional reservations about the macrolides stem from the facts that the evidence favoring their use in syphilis never was strong and they plainly do not readily cross the blood–brain barrier. Clearly, careful serological and clinical follow-up after treatment is especially important in the patient with early syphilis who is also HIV infected.

■ TREATMENT OF LATENT SYPHILIS IN HIV INFECTION

Unlike the situation in non-HIV-infected persons, a substantial proportion (5–50%) of HIV-infected persons who have no clinical signs of syphilis, but who have a positive RPR, especially if the titer is $\geq 1:8$, has CSF abnormalities that suggest the diagnosis of neurosyphilis.^{99,116} Accordingly, in such cases, lumbar puncture is highly desirable. Odds of finding evidence of neurosyphilis on examination of CSF are increased about sixfold in HIV-infected persons if their RPR is $\geq 1:32$, and about threefold if the CD4 count is < 350 cells/mm.^{3,90} If CFS analysis is negative, three doses of

benzathine penicillin can be given. If it is positive and there are no other evident causes, treatment should be given for neurosyphilis. If a lumbar puncture cannot be done, many practitioners favor treatment as if neurosyphilis were proven to be present.

■ TREATMENT OF NEUROSYPHILIS, NO HIV INFECTION

The introduction of penicillin in the 1940s strikingly simplified the therapy and improved the outcome of neurosyphilis. At first, repeated intramuscular injections of aqueous penicillin were administered every 3–4 hours for a total dosage of 2–3 million units over a period of 8–16 days. By the early 1950s, it was apparent that the administration of 6–10 million units of penicillin (as either procaine penicillin G or procaine penicillin in oil with aluminum monostearate) over a period of 18–21 days produced a good therapeutic response in over 90% of cases. In the occasional patient who did not respond, another course of penicillin at a higher dose was usually successful in arresting the infection.

Among 765 patients treated with varying dosages of penicillin (2.4 to more than 9 million units) for asymptomatic neurosyphilis, only one subsequently went on to develop symptomatic disease and was considered an unequivocal treatment failure.¹¹⁷ Similarly, the results of penicillin therapy of acute syphilitic meningitis have been very good, with clearing of the CSF changes and lack of progression to parenchymatous neurosyphilis. In one series of cases, spinal fluid findings indicated that the disease was arrested in each of 462 patients with various forms of neurosyphilis treated in this fashion.¹¹⁸ Early reports of results of penicillin treatment of paresis indicated a relatively low rate (6% to less than 20%) of failure of response in the CSF, of clinical progression, or of late complications.¹¹⁹ Among a group of 58 hospitalized patients with paresis treated with one or more courses of penicillin, 26 (45%) improved and were discharged from the hospital; this result indicates that this form of neurosyphilis is not hopeless, particularly when treatment is instituted as soon as clinical symptoms become evident, but response to therapy is by no means assured.^{35,120} In a multicenter study involving treatment of over 1000 patients with paresis, a total penicillin dosage of 6 million units was judged to be adequate.¹²¹

The prognosis of tabes dorsalis is variable, and the disease can be compatible with long life. About 4–10% of untreated cases become spontaneously arrested at an early stage. In the prepenicillin era, treatment improved or arrested the clinical course in over 80% of cases. However, in view of the nature of the underlying pathology, disappearance of many of the clinical findings would not be expected. Similarly, many of the residual signs and symptoms may persist after penicillin therapy. The most satisfactory therapeutic results are achieved in early cases of tabes, in which the CSF findings are markedly abnormal.

As a result of this clinical experience, for several decades treatment with 7.2 million units of benzathine penicillin G (2.4 million units intramuscularly weekly for three doses) was regarded as adequate for all forms of neurosyphilis. Clinical failures were almost unheard of. The recommended dosages for the treatment of all forms of late syphilis were initially designed to maintain serum spirochetal levels of 0.031 unit or more per milliliter.¹²² Studies in the late 1960s and early 1970s showed that 2.4 million units of benzathine penicillin produces serum levels $\leq 0.5 \mu\text{g/mL}$. Because levels in CSF are probably no more than 2% of serum levels, spirochetal levels may not be achieved in the CSF of patients receiving this medication.¹²³ The principal reason for concern was the description of cases, in which treatment for early syphilis was followed by development of neurosyphilis.^{124,125} In retrospect, these cases probably reflect early neurosyphilis (see above) in patients who were HIV infected; HIV infection had not yet been recognized at the time some of these cases were described.

As a result of these considerations, the Centers for Disease Control and Prevention 2006 Treatment Guidelines¹¹² no longer recommend benzathine penicillin to treat neurosyphilis, instead recommending use of intravenous aqueous penicillin G 18–24 million units daily for 10–14 days or intramuscular procaine penicillin G 2.4 million units plus probenecid 500 mg by mouth four times daily for 10–14 days. This dosage of procaine penicillin is very painful. Some authorities recommend that either treatment should be followed by benzathine penicillin weekly for 3 weeks because of the concept that duration of therapy may be as important as intensity. In Europe and the UK, recommendations are somewhat different, including in the UK primary use of intramuscular procaine penicillin plus oral probenecid, or as a first alternate, oral amoxicillin plus oral probenecid, with intravenous penicillin G as a second alternative.¹²⁶ Results appear to be equally good, but lack of suitable clinical trials limits conclusions that can be drawn. It should be emphasized that some authorities continue to recommend three doses of benzathine penicillin, 2.4 million units at weekly intervals to treat neurosyphilis in the absence of HIV infection.

In patients with penicillin allergy, options are limited. One may try to desensitize the patient in a hospital environment, with preparations for possible anaphylaxis.¹¹² Ceftriaxone penetrates the CSF and has good activity in early syphilis. A retrospective study observed patients for 6–24 months after treatment with 10–14 days of daily IV ceftriaxone, which appeared curative in six of seven with documented neurosyphilis.⁷² The use of 1 versus 2 gm of ceftriaxone each day did not appear to have any impact on the outcome. Thus, in a penicillin-allergic patient, ceftriaxone might be considered, although there is still a 10% chance of cross reaction with ceftriaxone.

Follow-up

Clinical (including CSF) examination should be done 3 months after antibiotic treatment of patients with neurosyphilis and then at 6 month intervals, until the CSF findings return to normal.¹¹² Thereafter, reevaluation should be performed annually for several years. This is particularly important in patients who have been treated with alternative antibiotics, because limited data are available on the long-term efficacy of such therapeutic programs.

Normalization of CSF values may be taken as a reliable sign of antimicrobial efficacy of therapy. Failure of CSF cell count or VDRL to return to normal 1 year after completion of therapy may lead to retreatment, although there may be no further benefit. The recommendation by the CDC to seek advice from an expert sounds reassuring, but there is no consensus among experts as to what, if anything, should be done.

A true failure of therapy may rarely occur, in which an initial normalization of CSF findings is followed by relapse; in such cases, repeat therapy needs to be given. If relapse has not occurred during a period of 2 years after therapy, the patient can generally be regarded as cured.

■ TREATMENT OF NEUROSYPHILIS IN HIV-INFECTED PERSONS

The best regimens to treat neurosyphilis in HIV-infected persons are not certain. There are anecdotal reports of failure of benzathine penicillin to eradicate early neurosyphilis in HIV-infected patients treated for primary or secondary syphilis,¹²⁵ and there is consensus¹¹² that benzathine penicillin therapy is not indicated for neurosyphilis in HIV-infected patients, as discussed above. Intravenous penicillin is the standard of therapy, as in non-HIV-infected persons. Nonrandomized studies of patients treated with 18–24 million units of penicillin daily showed that some patients relapsed and several others had no apparent response during a relatively short time of follow-up.^{127,128} Response to therapy, as measured by time to return of CSF VDRL to normal appears slower in HIV-infected persons.¹²⁹ Careful follow-up is required after therapy.

■ ROUTINE CSF EXAMINATION IN HIV-INFECTED PERSONS WHO HAVE SEROLOGIC EVIDENCE FOR SYPHILIS?

Should the CSF be examined in every patient who has early syphilis and concurrent HIV infection? In the past, CSF abnormalities including the presence of treponemes were found in up to 40% of patients with early syphilis, yet did not require an altered approach to penicillin therapy. In a study of “enhanced therapy” (oral amoxicillin plus probenecid, as compared to standard benzathine penicillin), response to therapy was essentially the same in HIV-infected and HIV-uninfected

persons, even though treponemes were observed in CSF in 25% of patients before therapy.¹⁸ This argues against routine lumbar puncture in early syphilis, regardless of HIV status, but many experienced clinicians in the United States and UK advocate lumbar puncture regardless. One must be aware that CSF abnormalities may be present owing to the HIV infection itself, although a CSF WBC count of over 20 cells/mm³ supports the diagnosis of neurosyphilis.⁹⁰ Favoring the routine use of lumbar puncture in HIV-infected persons who have latent syphilis of any duration (e.g., defined by a reactive serum RPR \geq 1:4 without clinical signs of syphilis) is the observation that a substantial proportion may be found to have evidence of active neurosyphilis.^{71,72} Furthermore, repeated CSF analysis provides a means for following the results of treatment. However, repeated determinations of serum RPR may give equivalent insight into response or failure; lumbar puncture could then be reserved for those patients who have clinical or serological evidence for failure or for relapse.

Thus, there is not a clear answer to the question. A lumbar puncture certainly should be done in patients who have symptoms or signs consistent with neurosyphilis, and in any stage of infection when a patient does not show an appropriate serologic response to therapy.

Follow-up

Repeated, close evaluation is required for HIV-infected patients who have evidence of neurosyphilis. Recommendations¹¹² to do follow-up serum and CSF studies at 3-month intervals should be followed. There is enough questions about the efficacy of any recommended treatment and sufficient likelihood of a relapse, even if initial therapy appears to be effective that a substantial sense of insecurity should characterize the approach of the treating physician to his or her patient.

■ TREATMENT OF LATE SYPHILIS OF THE CARDIOVASCULAR SYSTEM AND LATE BENIGN SYPHILIS

There are no data in the modern era regarding the best antibiotic treatment of late syphilis of the cardiovascular system or of the other organs affected by “late benign” syphilis. In general, guidelines for late latent syphilis also pertain to late syphilis of the cardiovascular system and also late benign syphilis.

Late benign disease was approaching the vanishing point in the era before penicillin, and this trend was enhanced by the efficacy of penicillin therapy for early syphilis. There are no controlled studies of penicillin in any large series of patients. In 1948, Tucker reviewed the results of penicillin therapy in 50 patients, with either skin or bone disease at the Johns Hopkins Hospital clinics,^{130,131} and concluded that satisfactory results were obtained in approximately

90% by the administration of a single course of penicillin. In a 1976 review of the literature on the treatment of late benign syphilis, St John¹³² found no subsequent therapeutic trials and accepted Tucker's recommendation of treatment with "at least two million units of penicillin if not more."

■ TREATMENT OF THE PREGNANT PATIENT

A pregnant patient with primary or secondary syphilis should be treated with penicillin in the same dosages as in a nonpregnant patient. For any pregnant patient with primary or secondary syphilis who is allergic to penicillin, it seems reasonable to consider ceftriaxone, although series of cases showing efficacy have not been described. Moreover, there is a risk of cross-allergic reaction in the order of 10%, and a risk of fetal loss if there is an allergic reaction. The 2006 guidelines from the CDC do not endorse either ceftriaxone or azithromycin in pregnancy because of lack of data.¹¹² Pregnant women with penicillin allergy should be referred to a specialist for desensitization to penicillin. Erythromycin should not be used because it does not reliably cure an infected fetus.¹³³ Tetracyclines likewise should not be used in this case because of fetal toxicity. Special care in follow-up is mandatory for both mother and child after treatment during pregnancy, since failure to prevent congenital syphilis by treating pregnant women with penicillin is well documented.¹³⁴

■ JARISCH–HERXHEIMER REACTIONS

After treatment for primary or secondary syphilis, about one-third or two-thirds of patients, respectively, have a reaction characterized by chills, fever, arthralgias, headache, and transiently increased prominence of lesions. This is called a Jarisch–Herxheimer reaction and is owing to the release of treponemal constituents. The onset is within 4–6 hours after treatment, and it subsides within 24 hours. The symptoms may be impressive in their severity; in one small group of 35 cases in which temperatures were monitored by rectal probe, two patients had peak temperatures $\geq 103^{\circ}\text{F}$.¹³⁵ The Jarisch–Herxheimer reaction is not dependent on type or dose of antibiotic used and should not be mistaken for a penicillin allergy. Jarisch–Herxheimer reactions are not an indication for discontinuance of treatment; most reactions can be managed by reassurance of the patient and aspirin or ibuprofen. Some authorities in Europe and the UK recommend concomitant short-term prednisone therapy in certain situations, particularly neurosyphilis, to avert inflammatory consequences of treatment, but this is not recommended in the U.S. guidelines.

FOLLOW-UP

Serologic tests should be repeated at 6-month intervals in non-HIV-infected persons to document the return to a neg-

ative RPR. Most patients with early syphilis will revert to VDRL or RPR negativity within 12 months, although a small proportion may remain positive at low titer ("serofast"). Therapy of latent or late syphilis may be followed by low titer seropositivity in a higher proportion of patients, and persisting low titer but stable VDRL or RPR in the face of normal clinical status does not indicate need for retreatment. It is important for the health provider to be aware of variability in testing kits and readers, such that a twofold difference is common in the absence of any change. This explains why repeated tests to document a trend are recommended.

In those situations in which cure is not so certain—patients receiving therapy other than penicillin, infants treated in utero, and HIV-infected persons—follow-up must be especially rigorous. Serologic responses and, where indicated, clinical observations should be checked every 3 months for 1 year and at 6-month intervals for at least another year.

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André Meheus and Francis J. Ndowa

Treponemal infections include venereal syphilis and the endemic (nonvenereal) treponematoses (i.e., yaws, endemic syphilis, and pinta). The similarities between the clinical manifestations of the various treponemal diseases are remarkable. They all have initial lesions followed by more extensive secondary manifestations, and they all exhibit the phenomenon of latency. In general, virtually any lesion produced by the three endemic treponematoses also may be produced by venereal syphilis.^{1,2}

The immune-response pattern in syphilis and the non-venereal treponematoses is similar. This complicates the interpretation of reactive serologic tests for syphilis (both nontreponemal, e.g., VDRL and treponemal tests, e.g., TPHA) in patients who have lived in areas where endemic treponematoses are still prevalent.

Small genetic differences have been identified between the causative organisms of venereal syphilis and the endemic treponematoses^{3,4}; so far none of these variations can distinguish the subspecies, but breakthroughs in research are forthcoming which finally might resolve whether they are all the same or different organisms (Sheila Lukehart, Personal communication, 2005).

GLOBAL EPIDEMIOLOGY AND CONTROL

■ HISTORICAL CONTEXT

Since its creation in 1948, the WHO made the fight against the endemic treponematoses a major priority. In close collaboration with UNICEF, in the period 1952–1964, the global endemic treponematoses control program (TCP) was launched, and it became a real success story: More than 50 million patients were treated with long-acting penicillin in 46 countries, reducing the overall disease prevalence by more than 95%. The control strategy subsequently was changed from a vertical program to one that was integrated into basic health services, and it was felt that this approach would cope with the remaining “last cases” in the community until eradication was achieved. Global eradication did not occur, however,

and a number of transmission foci remained. By the end of the 1970s, resurgence of endemic treponematoses had occurred in many areas, and the World Health Assembly of the WHO alerted the international community.⁵

In the early 1980s, renewed control efforts were implemented in a number of countries (such as seven West African countries: Benin, Côte d’Ivoire, Ghana, Mali, Burkina Faso, Niger, and Togo). But again, the final blow to the endemic treponematoses was not given.

BARRIERS TO CONTROL AND ERADICATION

Barriers to sustaining control efforts up to eradication are as follows⁶:

There is a perception by health decision makers that these diseases are already fully under control.

The economic impact is not evident; mainly children are affected.

The diseases are not fatal.

Foci of diseases are mainly in remote, rural, poor populations (often ethnic minority groups).

Health services in areas affected are inadequate or absent; political commitment has not been translated in implementation of primary health care (PHC).

Single disease programs are not “fashionable.”

The infections are not a threat to industrialized countries and to the leading classes in urban areas of the developing world.

The main motive for dealing with these diseases and working toward eradication is humanitarian, to protect children and communities from the crippling, invalidating, and disfiguring sequelae and, through endemic treponematoses control, to develop effective health services for remote and poor communities.

A comprehensive overview of the global epidemiology of the endemic treponematoses goes back to the early nineties.⁷ As reporting has become more and more incomplete, national and local statistics are increasingly unreliable.

Articles in the scientific literature have now become the major but very fragmented source of information.

ESTIMATION OF THE BURDEN OF DISEASE⁸

The population at risk is estimated at 34 million (mainly infants, children, and to a lesser extent, adolescents and young adults). They all live in the developing countries, with 21 million of them living in the so-called least developed countries (LDCs) (Fig. 38-1). The regions most affected are Africa and Southeast Asia, with some residual foci in Central and South America, the Middle East, and the Pacific Islands. The total number of cases (infectious, latent, and old cases) is estimated globally at 2.6 million, and infectious cases are estimated at 460,000, of which there are 400,000 cases in Africa. The prevalence of infectious cases is used for evaluating endemic treponematoses control programs. When infectious cases no longer appear in a geographic area, that area enters the consolidation phase of the control program. If serosurveillance indicates that transmission no longer occurs, then the disease can be considered eradicated. The number of disabled persons due to endemic treponematoses is estimated at 260,000 globally.

YAWS

Yaws, also known as framboesia, pian, or buba, is caused by *Treponema pallidum* subspecies *pertenue* (*T. pertenue*). Although *T. pertenue* has not been grown on artificial culture media, it has been grown successfully in rabbits and hamsters.

■ EPIDEMIOLOGY

Transmission of yaws occurs through direct contact with an infectious yaws lesion. It is usually contracted in infancy

or childhood. Indirect transmission by flies (*Hippelates pallipes*) has been suggested. Congenital transmission does not occur. In sparsely dressed populations, transmission is obviously facilitated by close bodily contact when children are playing or sleeping together.

Yaws occurs primarily in the warm, humid, tropical areas of Africa, South America, the Caribbean, Southeast Asia, and some Pacific Islands. Typically, yaws, like the other endemic treponematoses, is confined to populations with low standards of hygiene in remote areas with little or no health care; yaws is a disease found “at the end of the road.”⁹⁻¹³

■ CLINICAL FEATURES

As in syphilis, the clinical manifestations of yaws are divided into early- (which includes primary and secondary lesions) and late-stage disease.¹⁴

Early-stage disease

Skin. An initial lesion develops at the point of entry of the treponeme (often the lower extremities) after an incubation period of 10–45 days or longer. Systemic spread of the treponemes probably occurs during the incubation period. The initial lesion assumes a variety of appearances but usually progresses over a period of several weeks from a small papule to a proliferative papilloma, which exudes serum that is rich in treponemes and therefore highly infectious. The lesion may persist for 3–6 months and may ulcerate as a result of bacterial superinfection. The initial lesion heals spontaneously, often leaving a scar.

A first crop of secondary lesions may develop before the initial lesion has healed but may not appear for 1–2 years.

Characteristic secondary lesions are the large, raised papillomas and papules from which exudation of highly infectious serum is a feature; in addition, a wide variety of lesions may appear on the skin and oral mucous membranes. Early lesions of the palms and soles include hyperkeratotic or squamous macular lesions, which may be combined with a papilloma. If such papillomas develop on the soles of the feet, walking becomes very painful, and the patient adopts a crablike gait (crab yaws). During the first 5 years of infection, there may be one or several relapses of early yaws lesions, separated by latent periods of variable duration. Each crop of secondary lesions may persist for more than 6 months; the lesions heal spontaneously and do not leave scars.

Change in climate may influence the number and distribution of early skin lesions. In the dry season, fewer lesions may be present, and they tend to be of the macular or papular type; papillomas tend to occur in the more humid body areas such as the axillae and anal folds.

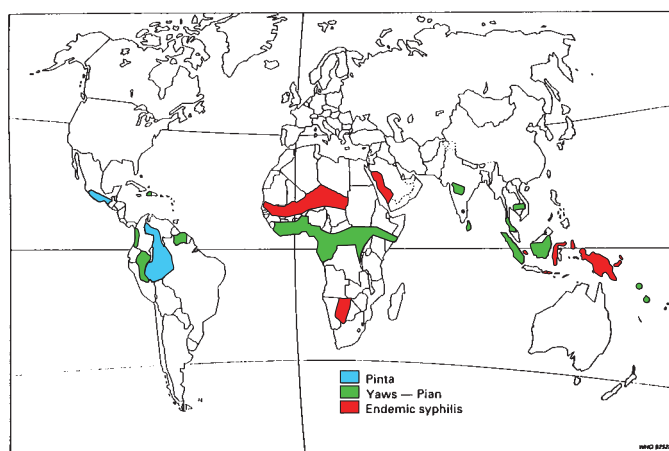


FIGURE 38-1 Geographic distribution of the endemic treponematoses since the early 1990s.

Bone. Many patients with yaws experience bone pain, which becomes worse at night and may be accompanied by pathologic bone changes. Osteoperiostitis may involve the long bones and the bones of the hands and feet and presents as a polydactylitis of the fingers and goundou, a hypertrophic osteitis of the nasal process of the maxilla.¹⁵ The etiology of goundou and saber tibia is still uncertain, but both conditions are commonly seen in yaws endemic areas.

Late-stage disease

Late active yaws lesions develop in about 10% of patients 5–10 years after the initial infection. Treponemes are microscopically scanty or absent in late lesions. Late lesions may involve the skin and subcutaneous tissues, including the skin of the palms and soles, the mucosae, and the bones and joints. In all these lesions, tissue destruction resulting in ulceration is common:

Gummas may involve the skin and the subcutaneous tissues or may be secondary to an underlying osteitis.

Hyperkeratosis of the soles and palms may result in atrophic skin and contractures of the fingers (ghoul hand). Gangosa (rhinopharyngitis mutilans) is a destructive ulceration of the palate and nasal septum leading to collapse of the nose.

Juxtaarticular nodules are lumps of fibrous tissue that develop in the subcutis in the vicinity of joints, with a strong predilection for the sacrum, elbows, greater trochanter, capitulum fibulae, and malleolus externus.

The skin tends to react to trauma with pigmentary changes (hypopigmentation).

It is generally accepted that neurologic and cardiovascular complications and sequelae do not occur in yaws.

ENDEMIC SYPHILIS (BEJEL, DICHUCHWA)

Endemic syphilis is caused by *T. pallidum* subspecies *endemicum* (*T. endemicum*). Transmission occurs via infectious lesions on the skin and mucous membranes, often through the use of common feeding utensils. It is essentially a disease of hot, dry countries and used to be endemic in rural communities of the Middle East, Bosnia, Bulgaria, and Botswana, from where it is now practically eradicated. However, major foci still exist in the Sahelian region of Africa.¹⁰

CLINICAL FEATURES

Early-stage disease

Primary lesions are seldom seen. Patches on the mucous membranes, angular stomatitis, and papules and macules favoring the moist areas of the body are the most typical manifestations. Condylomata lata often occur and are

comparable with those in yaws and venereal syphilis. Unlike venereal syphilis, however, the eruption may persist for many months or even years. In the early stage, a painful osteoperiostitis may occur, similar to the osteoperiostitis in yaws.¹⁶

Late-stage disease

Infections of skin, bones, and cartilage may lead to severe destruction, especially of the nose and palate (gangosa). On the skin, gummatous ulcers are characteristic. Periostitis with bone pain and gummas have been reported. Neurologic and cardiovascular involvement has not been reported, nor has congenital transmission.¹⁶

PINTA (CARATE, MAL DE PINTO)

Pinta is caused by *Treponema carateum*. It is the most benign of the endemic treponematoses; the skin is the only organ affected. Transmission most probably occurs through direct skin contact; the disease is mainly transmitted in childhood. Pinta is now confined to native populations living in the remote rural areas of Central and South America (e.g., the Amazon basin).^{16,17}

CLINICAL FEATURES

Early-stage disease

After an incubation period of several weeks, initial lesions will appear in the form of an itchy erythematous papule, which may progress to an erythemasquamous plaque on the uncovered parts of the body accompanied by local lymphadenopathy. These lesions disappear spontaneously. In the secondary stage, widespread rashes or multiplication of papules develops. The lesions may persist for years and remain darkfield-positive for treponemes. Generalized lymphadenitis is common.

Late-stage disease

The late stage is characterized by pigmentary changes typical of pinta. At first, there are round, oval, or irregular patches of hyperpigmentation, ranging in color from reddish-purple to slate blue; later, achromic patches and skin atrophy develop. Pruritus is marked. These color changes are not necessarily synchronized, and patients may show the various stages simultaneously. A congenital form is not known.

ATTENUATED ENDEMIC TREPONEMATOSES

In areas of reduced transmission, the clinical manifestations of the endemic treponematoses can be much milder (few or even a single lesion of short duration) or most of the infected subjects can be fully asymptomatic.²

In the Gambia, 9.3% of pregnant women were syphilis serology positive; children up to 14 years old of these seropositive mothers showed no signs of congenital syphilis, and perinatal, infant, or child deaths were not higher than in children of seronegative mothers; no clinical signs of yaws or endemic syphilis were found, indicating the asymptomatic nature of the infection.^{18,19} Similar observations were made in neighboring west African countries.^{10,20}

TREATMENT OF THE ENDEMIC TREPONEMATOSES

The WHO recommends that patients and their contacts receive long-acting benzathine penicillin, 1.2 mU in a single intramuscular injection; children less than 10 years of age should be given half this dose.¹ Resistance to penicillin has not yet been proven, but reports from areas as far apart as Papua New Guinea and Ecuador suggest reduced effectiveness of penicillin in yaws patients.^{11,21} Distinction between relapse, reinfection, or true resistance has not been possible, but nevertheless, some experts suggest doubling the recommended penicillin dosage.

Benzathine penicillin at the recommended dose will cure early lesions and prevent the development of destructive late lesions but often does not lead to seroreversal. Tetracycline, doxycycline, and erythromycin, at doses appropriate for venereal syphilis, are alternatives in patients allergic to penicillin. Tetracycline (including doxycycline) is not recommended for pregnant or breast-feeding women and children under 12 years old. About management of patients coinfecting with HIV, as yet, no information is available.

MAJOR ISSUES FOR RENEWED ACTION

Control strategies for the endemic treponematoses are well established and remain largely unchanged. Major issues to stimulate renewed action are as follows⁸:

1. A single, cheap, and effective measure to stop transmission of these infections is available (single-dose injection of a long-acting penicillin); treponemes may not yet have developed resistance to penicillin, but this could occur.
 2. These infections are resurging and reemerging in large areas of the developing world, particularly in the poorest countries.
 3. Global elimination and ultimately eradication are feasible.
 4. Characteristics of at-risk populations are often remote, end-of-the-road, ethnic minorities who are not covered at all or highly underserved by health services.
 5. Endemic treponematoses control can be used to establish or strengthen PHC and to dramatically increase confidence in and the use of health services. A high degree of community participation in control activities is assured nearly everywhere.²²
- The new paradigm for the twenty-first century is poverty alleviation. Elimination of the endemic treponematoses in combination with other health initiatives and in a context of strengthening the health system would significantly contribute to this noble goal.

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Stanley M. Spinola

Haemophilus ducreyi is a gram-negative coccobacillus that causes chancroid, which is characterized by painful genital ulcers and inguinal lymphadenitis. Chancroid is endemic in resource-poor countries and is a marker of poor public health infrastructure. Like other agents of genital ulcer disease (GUD), chancroid facilitates both acquisition and transmission of HIV-1.¹ Clinical data and mathematical models suggest that chancroid contributes substantially to the HIV-1 pandemic in sub-Saharan Africa and Asia.¹⁻⁴

HISTORICAL CONTEXT

Chancroid, or soft chancre (*ulcus molle*), may have been present in human populations from the time of the ancient Greeks.⁵ Several excellent review articles detail the history of the disease, the isolation of *H. ducreyi*, and controversy in its role in causing genital ulcers.⁵⁻⁸ In brief, Leon Bassereau distinguished chancroid from syphilis, or hard chancre, in 1852. In the 1890s, Augusto Ducrey identified short, compact bacteria by weekly autoinoculation of pus from infected ulcers to the skin of the forearm in patients but was unable to grow the organism on artificial media. In 1900, the organism was isolated on blood agar plates by Benzacón and colleagues, who fulfilled Koch's postulates by experimental inoculation, infection, and reisolation of the organism from humans. Intradermal skin tests and animal and human models of infection were developed in the first half of the twentieth century.⁶ However, there was no standard or selective media on which to grow the organism from clinical specimens. When the type strain (CIP 542) was established in 1975, three of four strains examined lacked outer membranes, indicating that several gram-positive organisms had been mistakenly classified as *H. ducreyi*.⁹

A major breakthrough in the study of *H. ducreyi* was the development of selective media using commercially available reagents by Hammond and colleagues in the late 1970s.^{10,11} Isolation of *H. ducreyi* from clinical specimens fostered epidemiological studies that showed the link between chancroid and HIV-1 acquisition, which prompted

studies on pathogenesis, host responses, diagnostics, therapy, and eradication.

TAXONOMY, GENOME, AND STRAIN CLASSIFICATION

H. ducreyi is a strict human pathogen and there is no known environmental or animal reservoir.⁵ The organism is a fastidious, facultative anaerobe that was classified as a *Haemophilus* species because of its microscopic appearance, requirement for X factor, and biochemical properties.^{5,7} However, by 16S rRNA sequence analysis, *H. ducreyi* is not found in the *Pasteurellaceae* cluster that includes *Haemophilus sensu stricto* species such as *H. influenzae* and *H. aegyptius*.¹² *H. ducreyi* is grouped with the *Actinobacilli* in a distant cluster, which does not contain other organisms of high pathogenic potential for humans.¹²

The genome of *H. ducreyi* strain 35000HP (HP, human passaged),^{13,14} was sequenced by Munson and colleagues (www.microbial-pathogenesis.org). The genome is composed of a single 1.7-Mb chromosome¹⁵ and contains 1693 putative open reading frames (ORFs). The closest homologues of 66% of the ORFs were found in the sequenced genomes of *Haemophilus influenzae* or *Pasteurella multocida* as determined by BLAST analyses.^{16,17} Substantial homology is observed for many genes, but there is little conservation of long-range gene order in the chromosome when *H. ducreyi* is compared to these species. The genes encoding several *H. ducreyi* toxins such as hemolysin and the cytolethal distending toxin (CDT) are absent from the *H. influenzae* and *P. multocida* genomes,^{16,17} which is not surprising given that these organisms are somewhat distant taxonomically. Interestingly, the genome of *H. ducreyi* lacks the repetitive DNA motifs that promote slip-strand mispairing resulting in phase variation (on-off switch) of virulence genes, a mechanism that plays a critical role in the pathogenesis of *H. influenzae* and gonococcal infections.^{18,19}

Clinical isolates of *H. ducreyi* form a homogeneous DNA hybridization group and share many of the same surface antigens, suggesting that there is limited diversity within the

species.^{5,20} There appear to be at least two circulating classes of the organism, which express different immunotypes or variants of several outer membrane proteins²¹ and different proteomes.²² Compared to class I strains, represented by the prototype 35000HP, class II strains express a more truncated LOS, grow more slowly on agar plates, and may be underreported.²¹ Clinical isolates can also be distinguished by restriction fragment length polymorphism of ribosomal DNA,²³ and multiple ribotypes may circulate in endemic areas or in outbreaks.^{24,25}

EPIDEMIOLOGY

Chancroid is endemic in regions of Africa, Asia, and Latin America where syndromic management of GUD is emphasized, and where diagnostic tests for *H. ducreyi* are not routinely performed.¹ UNAIDS and WHO estimate that the annual global prevalence of chancroid is six million cases, based on the prevalence of syphilis and the relative percentage of syphilis and chancroid in GUD cases among STD clinic attendees in whom an etiology has been established.²⁶ Because the data are problematic, WHO does not include chancroid in their global estimates of prevalence of sexually transmitted infections (STIs). In industrialized nations, chancroid is now rare,^{27,28} but sporadic outbreaks do occur.^{1,29–31}

When selective media became available in the 1980s, several features of chancroid epidemiology became apparent. In endemic areas and in outbreaks in industrialized nations, infected men frequently reported intercourse with commercial sex workers (CSWs), who either had symptomatic GUD or internal ulcers that were painless, and who continued sex work without seeking treatment.^{1,30,32} Lack of circumcision was associated with infection in men.⁵ In outbreaks in the United States, additional risk factors for acquisition included exchange of drugs for sex, crack cocaine use, or sex with a partner who used cocaine.^{25,29,30} In endemic areas, the male to female ratio of chancroid was 3:1, and in sporadic outbreaks the ratio was as high as 25:1.⁵

In the 1990s, Multiplex PCR (M-PCR) (Roche Diagnostic Systems, Branchburg, NJ), which simultaneously amplifies DNA targets from *H. ducreyi*, *T. pallidum*, and HSV-1 and HSV-2, replaced culture as the most sensitive method to detect *H. ducreyi*.^{31,33–35} By M-PCR, the percent of chancroid in GUD cases among patients attending STD clinics in various countries is shown in Table 39-1,^{27,29,31,33–43} which also includes studies that used investigator-designed reagents.^{28,44,45} Most of the GUD cases were in men. The prevalence of chancroid in GUD cases was 0–5% in the United States, Peru, Europe, Thailand, and China^{27,28,37,38,41} except in outbreak situations.^{29,31} At the end of the 1990s, several studies suggested a trend toward lower chancroid and higher HSV prevalence in endemic areas, likely due to syndromic

management for bacterial agents of GUD and reactivation HSV in patients coinfecting with HIV-1.^{35,36,43} These PCR-based studies showed that mixed infections with *H. ducreyi* and HSV, syphilis, or all three agents were common, occurring in 17.4% (95% confidence interval [CI], 13.1–21.5%) of the 1007 proven chancroid cases. Mixed infection likely accounts for the variable clinical presentation of chancroid described below and chancroid treatment failures. By M-PCR, the proportion of patients with no microbiologic diagnosis for GUD was initially as low as 6%.³³ Overall, no etiology was found in 25.8% (95% CI, 22.3–29.2%) of the 4461 GUD cases listed in Table 39-1, suggesting that PCR-based tests perform less well in field studies than in research settings or that agents other than those tested might be responsible for some cases of GUD.

CLINICAL MANIFESTATIONS

H. ducreyi is thought to enter the host through breaks in the epithelium that occur during intercourse.^{5,6} *H. ducreyi* infects mucosal epithelium, keratinized stratified squamous epithelium, and regional lymph nodes.^{5,11} Erythematous papules form at each entry site within several hours to days and evolve into pustules in 2–3 days. Papules and pustules are usually not painful, and only a small number of patients recall having these stages.⁵ After a few days to 2 weeks, the pustules ulcerate and patients typically have 1–4 painful ulcers. Patients generally do not seek medical attention until they have had ulcers for 1–3 weeks, probably about 3–5 weeks after acquisition.^{5,11,46}

Natural ulcers are classically described as very painful and nonindurated with ragged edges⁵ (Fig. 39-1). The ulcer base may be covered by a yellow or gray necrotic purulent exudate, and the ulcer frequently bleeds when scraped. However, the classic presentation of chancroid occurs in a minority of patients,⁴⁷ and chancroidal ulcers may be indistinguishable



FIGURE 39-1. Typical culture-proven chancroidal ulcers in an HIV seropositive man. (Photograph provided by Professor David Lewis.)

Table 39-1. Chancroid Prevalence in GUD by PCR

Regions	Year	No.		% Patients with Chancroid	Reference
		M	F		
Dakar, Senegal ^a	1992	41	5	56	44
New Orleans, Louisiana	1992–94	298	E	22	31
Lesotho	1993	69	36	56	33
Durban, Johannesburg & Cape Town, SA	1994	538	E	32	35
Pune, India	1994	277	25	28	34
Carletonville, SA	1993–94	232	E	69	36
Jackson, Mississippi	1994–95	111	32	39	29
Lima, Peru	1994–95	63	E	5	37
Santo Domingo, DR	1995–96	81	E	26	37
Chiang Mai City, Thailand	1995–96	8	30 ^b	0	38
Kingston, JA	1996	252	52	24	40
Ten Cities, United States	1996	351	165	3	27
Amsterdam, The Netherlands ^a	1996	221	151	1	28
Antananarivo, Madagascar	1997	139	57	33	39
Carletonville, SA	1998	186	E	51	36
Lilongwe, Malawi	1998–99	94	43	30	43
Dar es Salaam & Mbeya, Tanzania ^a	1999	54	48	21	45
Shanghai & Chengdu, PRC	2000	204	23	0	41
Durban, SA	2000	438	149	10	42

M, males; F, females.

^aStudies that did not use M-PCR; E, excluded.

^bCSWs.

from syphilis and genital herpes. Lesions in men are usually localized to the external and/or internal surfaces of the foreskin, the frenulum, and the coronal sulcus or penile shaft (Fig. 39-1).⁵ The majority of lesions in women are at the vaginal entrance (Fig. 39-2).⁵ In women, asymptomatic carriage is rare.⁴⁸ However, infected women may have internal vaginal and cervical ulcers that are painless. Perianal lesions occur in women who report anal intercourse.¹¹ Lesions also occur in nearby areas such as the thighs and buttocks or at distant sites.^{5,11} Extragenital skin lesions are thought to be due to autoinoculation.^{5,11}

Ten to forty percent of patients with chancroid have suppurative inguinal lymphadenopathy or buboes⁵ (Fig. 39-3). *H. ducreyi* can be recovered from buboes,^{5,49} but how the organism traffics to lymph nodes is unclear. *H. ducreyi* does not cause bacteremia. In vitro, the organism dies at temperatures above 35°C, and temperature sensitivity likely precludes spread via the blood stream.²⁰

In the preantibiotic era, chancroid could persist for 3–4 months and cause giant ulcers and erosion of the infected area until incision and drainage and topical therapies were given.⁶ Chancroid also caused fibrosis of the foreskin, leading to phimosis or autoamputation.^{5,6}



FIGURE 39-2. Chancroidal ulcer of the fourchette in a female.



FIGURE 39-3. Left-sided inguinal bubo in a patient with a culture-proven chancroidal ulcer. (Photograph provided by Professor David Lewis.)

PATHOGENESIS AND HOST RESPONSES

■ NATURAL INFECTION

Information on pathogenesis and the host response to *H. ducreyi* is limited to a few cross-sectional studies on patients who present with ulcers. Chancroidal ulcers contain

a superficial zone of polymorphonuclear leukocytes (PMNs) and necrotic tissue, and a perivascular and interstitial mononuclear cell infiltrate that consists of macrophages, T cells, and small clusters of B cells.^{50–53} The T cells express the memory marker CD45RO, and similar numbers of CD4 and CD8 cells are present. A diffuse infiltrate of Langerhans cells is also present in the dermis. Thus, the histopathology of natural infection consists of two major components: a PMN infiltrate that coalesces at the ulcer base to form an abscess and a dermal infiltrate of T cells and macrophages that resembles a poorly formed granuloma. The combination of an abscess and a granuloma is an unusual histopathology for a bacterial pathogen. *H. ducreyi* is found at the ulcer base and associates with PMN and fibrin, consistent with results from human inoculation experiments.^{54,55,55a}

Peripheral blood mononuclear cells (PBMCs) from HIV seronegatives with chancroid exhibit proliferative responses to several *H. ducreyi* antigen fractions, while PBMCs from HIV seropositives are less responsive.⁵⁶ Patients with chancroid have increased levels of soluble IL-2 receptors in urine and serum⁵⁷ and have significantly higher levels of antibody to *H. ducreyi* antigens than noninfected controls or patients with other STIs.^{58–62} Antibody responses occur after 2–3 weeks of ulcerative symptoms, likely 4–5 weeks after inoculation.⁴⁶ Sera from chancroid patients are not bactericidal.⁶³

Whether natural infection with *H. ducreyi* confers immunity to subsequent exposure has never been studied directly. In the weekly autoinoculation experiments performed by Ducrey, serial ulcers were maintained for up to 15 weeks.⁵ In outbreaks of chancroid, thought to be due to one strain, patients have had up to three recurrences.^{11,64} The data suggest that natural infection with *H. ducreyi* does not confer protective immunity to repeated exposures in those who form ulcers.

■ HUMAN INOCULATION EXPERIMENTS

Much of what is known about *H. ducreyi* pathogenesis in humans is derived from experiments in which bacteria are inoculated into nongenital skin of human volunteers.^{26,65,66} Experiments done in the 1940s suggested that infection was safe.^{67,68} Placement of 10^6 *H. ducreyi* onto intact upper arm skin does not cause disease.⁶⁵ A 1.9-mm puncture wound, which allows bacterial delivery into the epidermis and deep dermis, is sufficient to initiate papule formation. Whether a more shallow abrasion would be effective is unknown. The estimated infectious dose is between 1 and 100 CFU.^{69,70} Papules develop within 24 hours of inoculation and either spontaneously resolve or evolve into pustules 2–5 days later. Pustules enlarge and generally become mildly pruritic and painful in 7–14 days of observation. The human volunteer model simulates the first 2 weeks of chancroid but does not provide information about later stages.

Within 24 hours of inoculation, micropustules are present in the epidermis.⁵⁵ By 48 hours, the bacteria are seen in the epidermal micropustules and in the dermis where they colocalize with PMNs, macrophages, collagen, and fibrin.⁵⁵ The relationships between *H. ducreyi* and host cells are maintained throughout the papular and pustular stages. The bacteria are predominantly extracellular, and the infiltrating PMNs and macrophages fail to ingest the organism. The bacteria do not colocalize with keratinocytes, fibroblasts, laminin, or fibronectin. Evasion of phagocytosis and phagocytic killing is a major mechanism of bacterial survival in the first 2 weeks of infection and likely extends to the ulcerative stage.^{55a}

In addition to the intraepidermal pustules, a dermal infiltrate of mononuclear cells is recruited within 24 hours of infection.⁷¹ The mononuclear cells consist primarily of macrophages and T cells that are predominantly CD4 memory cells.⁷² The histopathology of experimental infection is nearly identical to that of natural infection except that CD4 and CD8 T cells are present in equal numbers in chancroidal ulcers.^{26,50}

■ BACTERIAL EFFECTS ON OUTCOME

Putative virulence determinants of *H. ducreyi* include LOS structures that are similar to those found in *N. gonorrhoeae* and mimic human glycosphingolipids, secreted products or toxins, pili, iron-regulated proteins and receptors, and outer membrane proteins.^{5,20,66} Isogenic mutants have been made in many genes encoding putative virulence determinants by allele exchange.^{73,74} In mutant-parent comparison trials in human volunteers, many mutants were able to initiate papule formation. Mutants that do not make sialylated or paragloboside-like lipooligosaccharide (LOS), hemolysin, CDT, or both hemolysin and CDT, fine tangled pili, the major outer membrane protein, superoxide dismutase C, or the porin proteins (OmpP2A and OmpP2B) formed pustules at rates similar to the parent⁶⁶ (unpublished observations). Possible reasons as to why these mutants were virulent are discussed elsewhere.⁶⁶ Whether these gene products contribute to ulcer formation or lymphadenitis cannot be tested in humans, due to safety concerns.

Certain mutants were unable to form pustules. These included those that lack expression of the hemoglobin receptor (HgbA), the peptidoglycan-associated lipoprotein, an outer membrane protein that is the major known determinant of serum resistance (DsrA), an intact *flp* locus, two large supernatant proteins (LspA1 and LspA2), and an outer membrane protein involved in adherence to collagen (NcaA)^{66,75,76} (unpublished). The exact cause for attenuation of these mutants in vivo is not known, but the DsrA mutant should have been killed by serum that transudates into the wound. The HgbA mutant may not have replicated due to its inability to acquire heme. The *pal* mutant has an unstable outer

membrane, but is serum resistant and evades phagocytosis in vitro⁷⁷ (unpublished observations). The *flp* locus is required for microcolony formation and also resembles type IV secretion systems, which play an important role in the secretion of virulence factors in other species.⁷⁵ The LspA1 and LspA2 double mutant is unable to resist phagocytosis and to inhibit the uptake of secondary targets by phagocytic cell lines.⁷⁸ The LspA1 and LspA2 double mutant likely is unable to resist uptake and killing in vivo. The attenuation of the NcaA mutant likely underscores the significance of adherence to collagen in vivo.

■ HOST EFFECTS ON OUTCOME

No data directly address whether there are differences in host susceptibility to acquisition or to progression of disease in natural chancroid. However, in the preantibiotic era, a variant of chancroid called “chancre mou volant” was described in which spontaneous healing of the ulcer occurred in 5–6 days.⁶ Spontaneous healing of ulcers was also reported in later outbreaks,¹¹ but its frequency and basis is unknown.

In the human infection model, the most significant predictors of outcome are gender and host. Men and women form papules (become infected) at similar rates, but the odds ratio of men developing pustules is 2.8-fold (95% CI, 1.6–5.0) that of women⁷⁰ (unpublished observations), consistent with the male to female ratio of ulcerative disease in endemic areas. The outcomes of multiple infected sites within a subject tend to be similar, suggesting that there is an overall host effect on the sites.⁷⁹ In reinfection experiments, some hosts repeatedly resolve all inoculated sites while others repeatedly form pustules, suggesting that some hosts are able to overcome the antiphagocytic properties of the organism.^{79,80} Interestingly, there are no differences in the ability of isolated PMNs or macrophages from people who formed pustules on successive experimental infections and those who resolved on successive experimental infections to take up 35000HP in vitro.⁷⁹ These data suggest that the complex environment—dendritic cells, T cells, macrophages, and PMNs—at the site of infection within each subject modulates outcome.

■ OTHER PATHOGENESIS MODELS

H. ducreyi attaches to and invades human keratinocytes and fibroblasts in vitro,⁸¹ but the relevance of these findings to human infection is unclear given the results of the human inoculation experiments.⁵⁵ *H. ducreyi* binds to type I and type III collagen, fibrinogen, fibronectin, and laminin in vitro⁸² (unpublished observations) but only binds to collagen and fibrin in vivo.⁵⁵ *H. ducreyi* resists uptake and inhibits uptake of opsonized secondary targets by phagocytic cell lines,^{78,83,84} consistent with the evasion of phagocytosis observed in humans.

Rabbit, swine, murine, and primate models for chancroid have been developed, and a detailed comparison of these models to the human model is presented elsewhere.⁶⁶ A major difference among the models is that the infectious dose in humans is between 10^1 and 10^2 CFU, while the infectious doses in the animals range from 10^4 to 10^7 CFU. *H. ducreyi* replicates to 10^4 – 10^6 CFU in human pustules⁸⁵ and is cleared in swine.^{86,87} Lesions in mice develop in response to lipooligosaccharide (LOS), not replicating bacteria.^{88,89} In contrast to the human model,^{79,80} infection in animals evokes serum antibody responses and perhaps most importantly provides protection against repeat exposure.^{87,90} Bactericidal activity develops in the serum of swine that are repeatedly infected, and passive transfer of swine immune serum protects against infection.⁸⁷

DIAGNOSIS, CULTURE, AND DETECTION

Diagnostic tests for chancroid were reviewed recently by Lewis.⁹¹ In brief, microscopy of exudates and antigen detection are neither sensitive nor specific enough to be clinically useful. Serology is only useful for prevalence studies.^{46,62} Culture and PCR-based tests are the cornerstones of diagnostic testing.

The standard culture media for *H. ducreyi* consists of two plates, one containing gonococcal agar base, 2% bovine hemoglobin, and 5% fetal calf serum (GC-HgS), the other containing Mueller-Hinton agar base with 5% chocolate horse blood (MH-HB).⁹² These media are supplemented with 1% CVA enrichment or 1% IsoVitalX to provide L-glutamine and vancomycin (3 $\mu\text{g}/\text{mL}$) to prevent overgrowth of gram-positive organisms. GC-HgS, which contains fetal calf serum, is expensive. Gonococcal agar base supplemented with 5% Fildes extract and 5% horse blood (GC-FHB) is 82% as sensitive as the dual media and is a reasonable alternative for resource poor settings.⁹³ Transport and other media preparations are described elsewhere.^{91,94,95}

Cultures are obtained by swabbing the base of the ulcer vigorously with a dry or moist cotton swab that becomes saturated with pus, which is immediately inoculated on the plates. Plates should be incubated for 48–72 hours in moist candle-extinction jars. The organism grows at 35°C, but optimal growth occurs at 33°C.⁹⁶ *H. ducreyi* is identified as a small yellow–grey colony that can be pushed intact across an agar surface. Gram stain shows pleomorphic gram-negative rods that are in short chains, pairs, or schools of fish. Colonial morphology and the characteristics of the Gram stain are likely due to tight intercellular adherence, whose basis is unknown (Fig. 39-4).⁵ Biochemically, the organism requires X factor but not V factor for growth, is oxidase positive by the tetramethyl-*p*-phenylenediamine method, but is otherwise inert.^{5,92} V factor independence is plasmid mediated, and in some strains the plasmid is integrated into the chromosome.⁹⁷

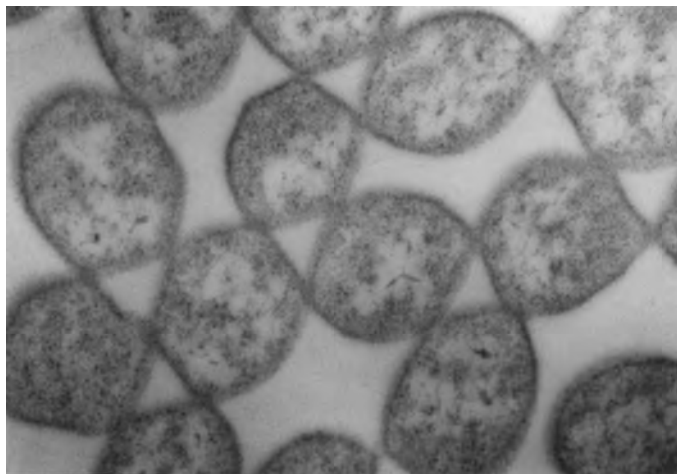


FIGURE 39-4. Transmission electron micrograph of a thin section of a colony of *H. ducreyi* stained with uranyl acetate. Note the areas of intercellular adhesin that result in the colonial characteristics described in text.

The Roche M-PCR assay has a resolved sensitivity of 95–98% and a specificity of 99.6% for *H. ducreyi*.^{31,33} Compared to M-PCR, the clinical diagnosis of chancroid is neither sensitive (range, 52–75%) nor specific (range, 52–75%) and has poor positive predictive value even in endemic areas.^{34,37,39,40} Compared to M-PCR, the resolved sensitivity for the dual culture system is approximately 75%.^{31,33} Unfortunately, M-PCR is not commercially available and requires special training and equipment, and culture is the only reliable diagnostic test available for most clinical settings.

In nonendemic regions, most STD clinics do not routinely test GUD patients for chancroid.²⁹ In practice, the diagnosis of chancroid is typically made by exclusion of HSV and syphilis. If patients with GUD and inguinal lymphadenitis or treatment failures for primary syphilis appear in a community, public health authorities should be notified so that diagnostic testing can be initiated. Even in endemic regions, routine screening of GUD patients for chancroid may not be cost effective given the changing epidemiology of the disease. A reasonable approach may be to use culture or PCR-based tests to screen a limited number of GUD patients when chancroid is suspected and provide syndromic management if chancroid is found. PCR-based tests may also be used to develop syndromic treatment algorithms based on the local prevalence of HSV, syphilis, and chancroid.⁴³

ANTIBIOTIC RESISTANCE AND THERAPY

Currently, little is known about the global prevalence of antibiotic resistant *H. ducreyi*, since few centers perform cultures and determine antimicrobial susceptibilities.⁹⁸ To complicate the issue further, there is no standard method for determining susceptibility.²⁰ Suggestions for using agar

dilution techniques are presented elsewhere,^{20,99} and Etest may be an acceptable alternative.¹⁰⁰

The history of antibiotic resistance in *H. ducreyi* parallels that of *N. gonorrhoeae*. Many *H. ducreyi* isolates have plasmid-mediated resistance to ampicillin, chloramphenicol, tetracyclines, and sulfonamides.^{5,98,101} These plasmids are homologous to R factors found in *Neisseria* and *Haemophilus* species and gram-negative enteric organisms.⁵ Some clinical isolates of *H. ducreyi* have a mobilizing plasmid that can transfer itself and antibiotic resistance plasmids to other species.⁵ Strain 35000HP contains a 49-kb integrated conjugative resistance element (ICE) that is a member of a family of conserved genomic islands with a shared evolutionary origin found in some *H. influenzae* strains and strains of many diverse bacterial species.¹⁰² ICE usually contains antibiotic, metal, and antiseptic resistance genes and other accessory genes.¹⁰² These elements were likely responsible for the widespread emergence of ampicillin, chloramphenicol, and tetracycline resistance in many bacterial species in the 1970s. However, no antibiotic resistance gene is present in the 35000HP ICE. Trimethoprim resistance, whose mechanism is unknown, became widespread in the 1990s.^{20,98} A few *H. ducreyi* isolates were also reported to be resistant to erythromycin; fortunately, these observations were not replicated.²⁰ Quinolone resistance does not appear to be widespread.^{20,98,99}

Clinically, chancroid is successfully treated with macrolides, quinolones, and third-generation cephalosporins. Current treatment recommendations by the Centers for Disease Control and Prevention (CDC) include single dose azithromycin 1 g orally or ceftriaxone 250 mg intramuscularly, ciprofloxacin 500 mg orally twice a day for 3 days, or erythromycin base 500 mg orally three times a day for 7 days.¹⁰³ In general, most of these regimens have cure rates greater than 90%. In a small, randomized trial, a single-dose of ciprofloxacin (500 mg) and the 3-day regimen produced cure rates that were similar.¹⁰⁴ A larger double-blinded placebo-controlled clinical trial showed that single-dose ciprofloxacin was comparable to a 7-day course of erythromycin.¹⁰⁵ Thus, a single dose of ciprofloxacin seems to be a reasonable alternative to the 3-day regimen. Although single-dose ceftriaxone is highly effective in some settings,¹⁰⁶ one study in Kenya showed that bacteriologic failure occurred in approximately 30% of patients treated with this regimen.¹⁰⁷ Failures occurred in both HIV seropositive and seronegative patients.

The recommended azithromycin and erythromycin containing regimens are equally effective.¹⁰⁸ A low-dose erythromycin regimen (250 mg three times a day for 7 days) was as effective as the standard 500 mg regimen in one study.¹⁰⁹ The MIC of azithromycin for *H. ducreyi* is low (range, 0.0005–0.004 µg/mL), and azithromycin persists in tissues due to its long elimination half-life of 7.5 days.¹¹⁰ In human inoculation experiments, a single 1 g dose of azithromycin

prevents the development of disease for approximately 2 months in volunteers who are challenged weekly.¹¹⁰ Thus, azithromycin may provide both therapeutic and prophylactic value.

In evaluating antibiotic regimens, one must distinguish between bacteriologic and clinical cure.¹¹¹ Even if *H. ducreyi* is eradicated, ulcers may persist if HSV or syphilis is present and not treated. Within 1 week of treatment, the ulcers should be less tender and there should be no purulence. Most ulcers heal in 2 weeks, but large ulcers may take up to 4 weeks to epithelialize.¹¹¹

With the recent lack of antibiotic development, no comparative treatment trials have been published since 1999. Open label use of a single dose (5 g) thiamphenicol, a chloramphenicol derivative, in 1171 cases of chancroid resulted in a cure rate of 98.8%.¹¹² However, these cases were diagnosed by exclusion of syphilis and positive Gram stains of exudates, not by culture or PCR. Thiamphenicol and chloramphenicol are both substrates for chloramphenicol acetyl transferase,¹¹³ and thiamphenicol should not be effective in treating chloramphenicol-resistant *H. ducreyi*.

Buboes may be treated by incision and drainage or needle aspiration, which frequently needs to be repeated.⁴⁹ In a randomized study comparing these modalities, incision and drainage was preferable⁴⁹ and the time to healing was 1 week to 10 days.

INTERACTIONS BETWEEN *H. DUCREYI* AND HIV-1

■ ACQUISITION AND TRANSMISSION OF HIV-1

In case-control studies in areas endemic for chancroid and HIV, the relative risk of acquiring HIV infection for patients with GUD ranged from odds ratios of 3–18.2.^{114–116} Per individual sexual act, GUD is estimated to enhance HIV acquisition by 4–23-fold; the exact magnitude of the cofactor effect is difficult to estimate due to confounding variables.^{3,4,117} In serodiscordant couples, GUD in an HIV positive person enhances the relative risk of viral transmission per coital act twofold, after adjustment for viral load.^{117,118} Simulation models estimate that GUD may have accounted for the acquisition of 40–80% of HIV infections in Africa in the 1990s.³

Disruption of epithelial barriers is likely a major mechanism underlying viral acquisition, as is the recruitment of T cells and macrophages expressing the CD4 receptor. In human inoculation experiments, lesional macrophages have significantly increased expression of CCR5 and CXCR4 and lesional CD4 T cells have significant upregulation of CCR5, compared to monocytes and CD4 T cells in peripheral blood.¹¹⁹ However, upregulation of coreceptors has not been studied in natural infection. HIV-1 is shed from coinfecting ulcers.¹²⁰ In coinfecting persons, *H. ducreyi* may cause local

viral replication by recruitment and subsequent activation of CD4 CD45RO cells and macrophages that are latently infected with HIV-1, but this hypothesis has not been tested.

■ CLINICAL FEATURES OF COINFECTION

In the early 1990s, case reports indicated that patients who are HIV seropositive have atypical presentations of chancroid.^{121,122} These reports were written when it was thought that *H. ducreyi* was intracellular and that cell-mediated immunity was a critical host defense mechanism, hypotheses that were not substantiated in the human challenge model. No further case reports have appeared in the literature. Interestingly, the histopathology of chancroidal ulcers in HIV seropositives and seronegatives is indistinguishable.^{51,52}

Reports from Africa on persons coinfecting with HIV and chancroid also indicated that coinfecting individuals have a greater number of ulcers that persist for longer periods and do not heal as readily after antibiotic treatment as patients infected with *H. ducreyi* alone.^{20,52} Antibiotic treatment failures were reported in HIV seropositives for what were suboptimal regimens even in HIV seronegatives.¹⁰⁷ Subsequent studies failed to show differences in antibiotic treatment efficacy in HIV seropositives and seronegatives for single-dose azithromycin or ciprofloxacin regimens.^{105,123,124} Treatment failure of chancroid in HIV seropositives is likely due to coinfection with herpes simplex virus and does not represent failure to eradicate *H. ducreyi*.¹⁰⁵ Taken together, the data suggest that the effect of HIV on the histopathology, clinical course, and treatment of chancroid is minimal.

Immune activation may also cause systemic viral replication. HIV-infected female sex workers with clinically diagnosed GUD of undetermined etiology have statistically significant higher HIV viral loads than female sex workers who do not have GUD.¹²⁵ Men with urethritis and HIV plus GUD of undetermined etiology in a chancroid endemic country have lower CD4 counts and higher viral loads than HIV-infected men with urethritis without GUD.¹²⁶ These studies are difficult to interpret because they are not longitudinal and contain many confounding clinical variables.

TRANSMISSION DYNAMICS AND THE CASE FOR ERADICATION

As is discussed in Chapter 3, for an STI to remain endemic in a population, the reproductive rate ($R_0 = \beta cD$) must be ≥ 1 . For *H. ducreyi*, the average duration of infectiousness (D) is estimated to be 4 weeks or 0.08 years based on the facts that *H. ducreyi* can be recovered from surface cultures of experimental papules and pustules, which represent the first 2 weeks of infection,¹⁴ and that medical attention is sought for ulcers after 1–3 weeks.^{11,46} The transmission rate per sex act (β) is unknown. In a small study, 70% of 28 women who

were secondary contacts of men with chancroid had genital ulcers,³² suggesting that the upper limit for β is 0.7. For $\beta = 0.7$, the calculated sex partner change rate (c) per year is 18; for $\beta = 0.35$, $c = 36$; and for $\beta = 0.18$, $c = 72$.²⁶ These estimates suggest that chancroid can be perpetuated only in highly sexually active populations such as CSWs, which is consistent with epidemiological data.

Elimination of chancroid from CSW should result in disappearance of the disease from the community.¹ In Thailand, widespread policies for 100% condom use and presumptive treatment of CSWs with quinolones led to a 95% decrease (from 30,000 cases to less than 2000 cases) in chancroid in the 1990s.¹²⁷ As a result of increased condom use and syndromic management, chancroid now accounts for less than 10% of GUD seen in clinics in Nairobi, Kenya.¹ In a South African mining community, monthly presumptive antibiotic treatment of CSWs with a 1 g dose of azithromycin, condom promotion, and education directed toward prevention resulted in a 78% decline in GUD prevalence over 9 months.^{1,128}

Many countries with a high seroprevalence of HIV-1 are chancroid endemic areas.¹ Given the dynamics of *H. ducreyi* transmission and the association between chancroid and HIV-1, strong arguments have been made for public health programs to eradicate chancroid.^{1,26}

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Nigel O'Farrell

HISTORY

Donovanosis is a chronic, progressive, and mildly contagious bacterial infection that usually involves the genital region. The causative organism was recognized as a gram-negative bacillus, *Calymmatobacterium granulomatis*, but a proposal that the organism be reclassified as *Klebsiella granulomatis comb nov* has been put forward.¹ The condition has been known under numerous terminologies, including serpiginous ulceration of the groin, lupoid form of groin ulceration, ulcerating granuloma of the pudenda, granuloma genitoinguinale, granuloma venereum genitoinguinale, infective granuloma, granuloma inguinale tropicum, chronic venereal sores, and ulcerating sclerosing granuloma, but is known more commonly as granuloma inguinale or granuloma venereum.² In the past, there has been considerable confusion between granuloma inguinale and lymphogranuloma venereum. Marmell and Santora³ recognized this and recommended *donovanosis* as the most suitable name. Most authorities now accept this view.

The first description of donovanosis is attributed to McLeod, Professor of Surgery at the Medical College of Calcutta, India, in 1882.⁴ He reported cases of serpiginous ulceration and formation of an imperfect cicatrix involving the scrotal and penile tissues in men and long-standing elephantiasis of the clitoris and labia in a woman. Subsequent cases were reported from British Guinea⁵ and the UK.⁶

The causative organism was first described in 1905 by Donovan working in Madras, India.⁷ He identified the characteristic Donovan bodies measuring $1.5 \times 0.7 \mu\text{m}$ in macrophages and epithelial cells of the stratum malpighii. Difficulties in culturing the organism led to considerable debate about the causative agent. Aragao and Vianna⁸ claimed to have cultured a pleomorphic bacterium from ulcer lesions and identified it as *C. granulomatis*.

Cornwall and Peck⁹ cultured an organism that, when injected into rabbits, produced granulomatous lesions simulating donovanosis at the site of injection. Experimental transmission of the organism from one individual to another

was reported by McIntosh in 1926.¹⁰ DeMonbreun and Goodpasture¹¹ grew gram-negative bacilli of the *Aerogenes* group from ulcers and feces of patients with donovanosis in a filtrate of chick membrane in both the capsulated and non-capsulated forms. Greenblatt et al.¹² accomplished transmission of the disease into human volunteers by introducing material from a pseudobubo but were unable to grow the organism on the chorioallantois of chick embryos.¹³

Attempts at culture remained unconvincing until 1943 when Anderson¹⁴ reported the isolation of the causative organism on the yolk sac of chick embryos and proposed a new genus, *Donovania*, and species, *granulomatis*.¹⁵ Further efforts to develop an artificial medium for the culture of *D. granulomatis* met with only limited success. Some growth was achieved using beef heart infusion agar and normal chick embryo yolk sacs with subsequent transfer to tryptose beef heart infusion broth and modified Levinthal's stock broth.¹⁶ Positive skin reactions were demonstrated in human subjects with donovanosis after injection of bacterial antigen prepared from infected yolk sacs.¹⁷ It would now seem that some of the earlier claims of successful cultures may have been due to contamination.

A link between *C. granulomatis* and *Klebsiella* species was suggested on the evidence of antigenic cross-reactivity.¹⁸ Goldberg¹⁹ characterized the organism further and showed that two factors were necessary for growth: (1) a low oxidation-reduction potential, which could be satisfied by the use of a thioglycolate medium, and (2) a factor or factors in eggs, which could be substituted by the enzymatic digests of bovine albumin or soya meal.

Despite these developments, progress in donovanosis research was slow. After 1962,²⁰ there were no reports of successful culture until 1996–97 in Durban,^{21,22} where the causative organism was shown to multiply in a monocyte co-culture system from biopsy specimens after pretreatment with amikacin. In Darwin, growth of the organism was achieved using a modified chlamydia culture system with human epithelial cell lines.²³ Polymerase chain reaction (PCR) tests were developed in Darwin and Durban and further

molecular characterization of the causative organism was undertaken.^{1,24–26} DNA sequencing of the 16S rRNA and *phoE* genes demonstrated that *C. granulomatis* had a greater than 99% similarity with *Klebsiella pneumoniae* and *K. rhinoscleromatis*, and Carter et al. proposed that the causative organism be reclassified as *K. granulomatis comb nov* and set out an amended description of the genus *Klebsiella* to include donovanosis.¹ However, Kharsany et al. performed a phylogenetic analysis of *C. granulomatis* based on 16S rRNA gene sequences and found that strains had similarities of only 95% and 94%, respectively, to the genera *Klebsiella* and *Enterobacter*.²⁶ They concluded that *C. granulomatis* was a unique species distinct from other related organisms belonging to the subclass of *Proteobacteria*. Differences in these results have not been explained, and resolution of the conflict regarding classification has not been achieved.

PATHOGENESIS AND BIOLOGY

The first manifestation of donovanosis is usually a small, firm nodule in the genital region in skin that has been subjected to a degree of trauma. Most established infections are associated with poor standards of personal genital hygiene. Goldzieher and Peck²⁷ were the first to identify Donovan bodies in histologic sections of tissue in 1926 and described a large, swollen mononuclear cell containing the specific organisms. Pund and Greenblatt,²⁸ using Delafield's hematoxylin and eosin and Dieterle silver-impregnation staining methods, also described a large mononuclear cell 25–90 μm in diameter with intracytoplasmic cysts filled with deeply stained bodies that they regarded as pathognomonic of donovanosis. These cysts eventually rupture and release the infective organisms. Sehgal et al.²⁹ described gram-negative intra- and extracellular Donovan bodies with different morphologic features—coccoid, coccobacillary, and bacillary.

Electron microscopic studies have shown organisms with typical gram-negative morphology and a large capsule but no flagella. Filiform or vesicular protrusions may be seen on a corrugated cell wall,^{30,31} but other surface structures such as fimbriae and bacteriophages are not found.³²

EPIDEMIOLOGY

In the preantibiotic era, donovanosis was prevalent in many diverse geographic locations. Rajam and Rangiah² stated that the disease was distributed in both hemispheres and endemic in southern China, the East Indies, northern Australia, some countries of Central, South, and North America and the West Indies. In the United States, Greenblatt³³ estimated a population prevalence of 5000–10,000 cases in 1947. Nowadays, significant numbers are found in only a few developing countries, although sporadic cases may occur in developed countries. A small epidemic of 20 cases was reported in 1984 in the United States.³⁴

The main foci of donovanosis in recent times have been in Papua New Guinea,³⁵ southern Africa, particularly the Durban-KwaZulu-Natal region³⁶ but also eastern Transvaal³⁷ and Zimbabwe,³⁸ parts of India,³⁹ northeast Brazil,⁴⁰ French Guyana,⁴¹ and aboriginal communities in Australia.⁴² Papua New Guinea seems to be the worst affected region; in 1980, donovanosis accounted for 46% of genital ulcers in women.⁴³ In a study at five health centers in 1989–90, donovanosis was the second most common cause of genital ulceration after genital herpes⁴⁴ and the most common sexually transmitted infection (STI) amongst new STI attendees in Porgera Enga province in 1992–93.⁴⁵ However, a more recent WHO consensus report states that donovanosis has now become rare in Papua New Guinea.⁴⁶ The largest epidemic recorded was in Dutch South New Guinea between 1922 and 1952, when 10,000 cases were reported from a population of 15,000.⁴⁷

In the main STI clinic in Durban, following a decrease after a peak in 1969–74,³⁶ the numbers of donovanosis cases recorded in the annual reports of the medical officer of health increased from 312 in 1988 to 3153 in 1997.^{36,48} In a microbiologic study of genital ulcer disease among STI clinic attenders in Durban, donovanosis was diagnosed in 11% of men⁴⁹ and 16% of women in 1988.⁵⁰ Although genital ulcer diagnoses in Durban were recorded by syndrome without mention of likely specific etiologies after 1997, it would appear that donovanosis has now decreased significantly. Recent genital ulcer surveys in men identified donovanosis in 4% in 1999⁵¹ with a further reduction to $\leq 1\%$ in 2001⁵² and 2004.⁵³ Before the 1980s, few cases were present in South Africa and it was suggested that donovanosis had all but disappeared.⁵⁴ A more likely explanation is that the condition attracted little interest and went unrecognized or was diagnosed as lymphogranuloma inguinale or lymphogranuloma venereum.⁵⁵ Elsewhere in Africa, sporadic cases of donovanosis have been reported in recent times from Botswana,⁵⁶ the Central African Republic,⁵⁷ Gabon,⁵⁸ and Zambia.⁵⁹

In India, donovanosis accounted for 14% of genital ulcer cases at a southern STI clinic, 15% of whom were HIV positive between 1993 and 1997,⁶⁰ but in North India the numbers of cases dropped considerably in the 1990s.⁶¹ In Jamaica, the prevalence of donovanosis diagnosed on clinical grounds decreased from 4.1% in 1982–83 to 2.3% in 1990–91.⁶²

In Australia, a donovanosis elimination program was launched in 1998 amongst Aborigines.^{63,64} This involved designated clinical officers who coordinated clinical protocols, performed health promotion activities, validated epidemiological data, ensured laboratory control, and assisted in the follow-up of hard to reach cases. This program has achieved remarkable success and reduced the number of annual cases to a handful throughout Australia.⁶⁵

It has been questioned as to whether donovanosis is a sexually transmitted disease (STD) because of the low incidence of the disease, the differences in the racial and sex

distributions, uncertainty about the incubation period, infrequency of cases of conjugal infection, and the occurrence of primary extragenital lesions.⁶⁶ The condition undoubtedly has several unusual epidemiologic features that warrant close scrutiny.

The majority of cases are in the 20- to 40-year age group, i.e., the most sexually active. Most case series have recorded a preponderance of males, although in some studies with limited numbers of cases, such as in Zambia,⁵⁹ western Australia,⁶⁷ and eastern Transvaal, South Africa,⁶⁸ more women than men have been reported. Rajam and Rangiah² recorded 1350 men and 562 women in their large series and similar male-to-female ratios have been reported in Zimbabwe³⁸ and southeast India.⁶⁹ Higher male-to-female ratios of more than 6:1 have been reported from Papua New Guinea³⁵ and India.⁷⁰ In Durban, HLA studies showed an association between donovanosis and HLA-B57 and a trend toward resistance to disease with HLA-A23.⁷¹

The incubation period is uncertain. Sehgal and Prasad⁷² found the average incubation period to be 17 days, but a range of 1–360 days has been reported.⁷³ Experimental production of typical donovanosis lesions was induced in humans 50 days after inoculation.¹²

Among sexual partners of index cases, wide variations in the rates of infection have been reported. In Papua New Guinea³⁵ and the United States,⁷⁴ the coinfection rate was 1–2%, whereas in India rates of up to 50% were reported among marital partners examined.^{69,75} A more recent study of 255 cases in India in which eight couples were examined found conjugal involvement in one pair only.⁷⁶ In many cases, the disease is mild, particularly in men,² and examination of all regular sexual partners is recommended.

Transmission via fecal contamination of abraded skin was suggested as a possible mode of transmission by Goldberg.²⁰ Although he isolated the causative organism from feces, there are no subsequent reports to support this hypothesis. Cases in children have been attributed to sitting on the laps of infected adults.⁷⁷ Disseminated donovanosis has been reported in a neonate born to a mother with a large granulomatous lesion of the vulva who incurred a third-degree tear during delivery.⁷⁸ Careful cleansing of neonates born to infected mothers is recommended.⁷⁹

CLINICAL MANIFESTATIONS

The first sign of infection is usually a firm papule or subcutaneous nodule that later ulcerates. Four types of donovanosis are described classically: (1) ulcerogranulomatous—the most common variant—nontender, fleshy, exuberant, single or multiple, beefy-red ulcers that bleed readily when touched (Fig. 40-1), (2) hypertrophic or verrucous type, an ulcer or growth with a raised, irregular edge, sometimes completely dry with a walnut like appearance (Fig. 40-2), (3) necrotic, usually a deep, foul-smelling ulcer causing tissue

destruction (Fig. 40-3), and (4) sclerotic or cicatricial, characterized by extensive formation of fibrous and scar tissue.

The genitals are affected in 90% of cases and the inguinal region (Fig. 40-4) in 10%. The usual sites of infection are, in men, the prepuce, coronal sulcus (Fig. 40-5), frenum, and glans penis and, in women, the labia minora and fourchette



FIGURE 40-1. Typical subpreputial ulcerogranulomatous donovanosis lesions.



FIGURE 40-2. Hypertrophic verruciform form of donovanosis in inguinal region.



FIGURE 40-3. Deep necrotic donovanosis ulcer causing tissue destruction.

(Fig. 40-6). A preponderance of cases has long been recognized in uncircumcised men.⁸⁰ Lesions of the cervix may mimic cervical carcinoma. Extragenital lesions occur in 6% of cases but are often missed in nonendemic areas.^{2,81,82} Sites of infection include the lip, gums, cheek, palate, pharynx, neck, nose, larynx, and chest. Extragenital lesions are usually associated with primary genital disease. On the rare occasions when primary extragenital lesions are diagnosed, the possibility of rhinoscleroma should be considered.



FIGURE 40-4. Inguinal lesions of donovanosis.



FIGURE 40-5. Multiple ulcerogranulomatous penile lesions of donovanosis.



FIGURE 40-6. Confluent donovanosis lesions at fourchette.

Lymphadenitis is an uncommon finding.⁸³ Disseminated donovanosis is rare; secondary spread to liver and bone may occur and is usually associated with pregnancy and cervical lesions. Donovanosis has a more aggressive course during pregnancy.^{80,84,85} Polyarthrititis and osteomyelitis are rare complications.⁸⁶ Neonatal cases often present with ear infections.^{79,87}

DIAGNOSIS

Ulcerogranulomatous donovanosis lesions have a characteristic appearance and should be distinguished readily from the other classic STI causes of genital ulcer disease.⁸⁸ However, primary syphilitic chancres, secondary syphilis (condylomata lata), chancroid, and large herpetic ulcers can all be mistaken for donovanosis. Amebiasis and carcinoma of the penis should also be considered if tissue destruction or necrosis is present.

Tissue smears remain the mainstay method of diagnosis. Confirmatory specimens can usually be obtained as long as an adequate smear is prepared and antibiotic treatment has not been started. Most centers with experience with donovanosis have developed their own methods for maximizing the diagnostic yield from clinical specimens. Greenblatt and Barfield⁸⁹ advocated obtaining crush biopsy samples from the edges of lesions and stressed the importance of obtaining clean specimens for the preparation of tissue smears. Rajam and Rangiah² obtained material by means of a curette, forceps, the sharp end of a broken slide, or the edge of a safety razor blade and crushed the specimen between two slides and stained by the Leishman or Giemsa methods. Rapid results have been achieved using material obtained with a chalazion spoon.⁹⁰ Other stains used include Delafield's hematoxylin and eosin,²⁸ Wright's,⁹¹ and pinocyanole.⁹² A 100% success rate was claimed using a slow-Giemsa (overnight) technique.⁹³ A modified Giemsa's stain (RapiDiff) has yielded rapid results in a busy clinic environment⁹⁴ (Fig. 40-7). Donovan bodies also have been identified in Papanicolaou smears.⁹⁵ If multiple swabs are taken from ulcers and donovanosis is

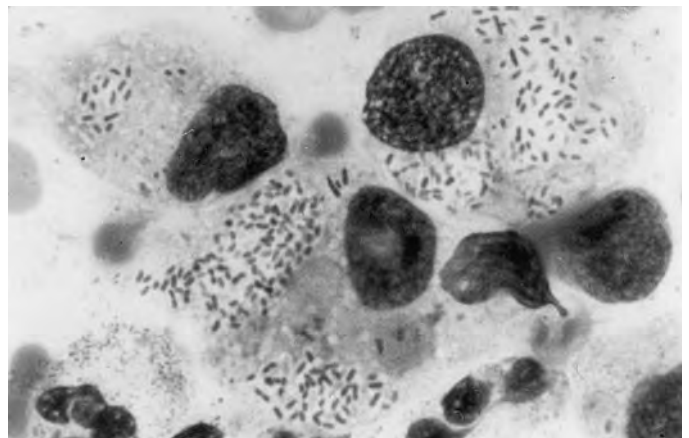


FIGURE 40-7. Tissue smear stained by rapid Giemsa (RapiDiff) technique showing numerous Donovan bodies in monocytes.

considered likely, the smear for Donovan bodies should be taken first so that an adequate amount of material can be obtained from the ulcer.

Biopsy and histologic examination may be required for lesions that are small, dry, sclerotic, or necrotic. Giemsa's or silver stains are the most effective methods for visualizing the organisms in tissue sections. The characteristic histologic picture shows chronic inflammation with infiltration of plasma cells and polymorphonuclear leukocytes²⁷; the dermis shows a dense cellular infiltrate with large numbers of plasma cells. Ulceration and acanthosis with focal collections of polymorphonuclear leukocytes are found in the epidermis; elongation of rete ridges occurs in association with the hypertrophic variant.²⁹

No serologic tests are currently in generalized use. Complement-fixation tests were developed and found to be quite sensitive.^{16,17} An indirect immunofluorescent technique had a high sensitivity for established lesions but was not deemed suitable for early donovanosis ulcers. However, this test could be of use as an epidemiologic tool in population studies.⁹⁶

The organism has been characterized further by the development of molecular-based tests and the similarity of the causative organism to *klebsiella* species confirmed. A diagnostic PCR was developed using the observation that two unique base changes in the *phoE* gene eliminate HaeIII restriction sites enabling clear differentiation from closely related *klebsiella* species.²⁵ This method has been refined further to a diagnostic colorimetric PCR test although further validation with samples from diverse geographic sites is awaited.⁹⁷ A genital ulcer disease multiplex PCR (GUMP) test has recently been developed in Australia using an in-house nucleic acid amplification technique that incorporates *C. granulomatis* primers.⁹⁸ This test will be useful in defining the prevalence of the various causes of genital ulcers in at-risk populations and also in assessing long-term efforts to eliminate donovanosis.

TREATMENT AND MANAGEMENT

Donovanosis is one of the few bacterial infections that could be treated in the preantibiotic era. Antimony compounds were used successfully for primary infections but had limited efficacy for recurrences or reinfections.

The first antibiotic shown to be effective for donovanosis was streptomycin in 1947.⁹⁹ Nowadays, various therapeutic treatments are used and probably reflect local availability of different drugs. Streptomycin has been used extensively in India and is effective for large lesions, although daily injections are required.¹⁰⁰ Chloramphenicol has been used in Papua New Guinea,¹⁰¹ cotrimoxazole in India¹⁰² and South Africa,¹⁰³ and thiamphenicol in Brazil.¹⁰⁴ Healing is usually achieved with tetracycline, although resistance is reported.¹⁰⁵ Norfloxacin,¹⁰⁶ ciprofloxacin,¹⁰⁷ and high-dose ceftriaxone¹⁰⁸ are also effective.

Gentamicin 1 mg/kg 3 times daily intramuscularly or intravenously can be given if there is no response in the first few days with other regimens. Erythromycin is recommended during pregnancy. Encouraging results have been shown with azithromycin which has now become the drug of choice; a course of 500 mg daily for 1 week or 1 gram weekly for 4–6 weeks are both effective¹⁰⁹; WHO recommends 1 gram followed by 500 mg daily¹¹⁰ and the CDC recommends 1 gram weekly for at least 3 weeks until lesions are healed.¹¹¹ Children with donovanosis should receive a short course of azithromycin 20 mg/kg. Children born to mothers with untreated donovanosis should receive prophylaxis with a three-day course of azithromycin 20 mg/kg once daily.⁷⁹

COMPLICATIONS

Rajam and Rangiah² found carcinoma, either as a complication of or a sequel to long-standing donovanosis, to be a rare occurrence seen in 0.25% of 2000 cases. Positive reactivity with *D. granulomatis* antigens was found in 9 of 62 cases of carcinoma of the penis in Jamaica, but this work was not developed further.¹¹²

Nowadays, the most frequent complication is pseudoelephantiasis (Fig. 40-8), which is more common in women and found in up to 5% of cases.¹¹³ Surgical intervention may be indicated for advanced intractable lesions.¹¹⁴ Stenosis of the urethra, vagina, or anus may occur in the sclerotic variant of donovanosis.²

The differential diagnosis between donovanosis and squamous cell carcinoma of the penis may be difficult. A therapeutic trial of antibiotic therapy should always be given, even if donovanosis is only a remote possibility.



FIGURE 40-8. Extensive vulval donovanosis with lymphedema and esthiomene.

Donovanosis ulcers may be coinfecting with other STIs, particularly syphilis.^{43,49} Such cases justify management by the syndromic approach with treatment for both conditions. However, it is important that these patients be followed, even when managed by primary health-care workers, until complete healing is achieved. The presence of donovanosis ulcers does not preclude sexual intercourse,¹¹⁵ and the risks of reinfection should be stressed at the initial consultation.

DONOVANOSIS AND HIV INFECTION

The classic STIs, and genital ulcer diseases in particular, are significant risk factors for HIV in developing countries. In Durban, in a population where HIV infection had been introduced only recently, the proportion of men with donovanosis and HIV infection increased significantly as the duration of lesions increased, thereby suggesting that HIV was acquired via sexual intercourse in the presence of ulcers.¹¹⁶

The treatment of donovanosis may need to be modified in HIV-infected patients with significant immunosuppression. In Mumbai, India, the mean healing time in HIV-positive patients with donovanosis was 25.7 days compared to 16.8 days in HIV-negative subjects.³⁹ In Brazil, two AIDS patients with donovanosis failed to respond to conventional treatment with combinations of cotrimoxazole, tetracycline, and thiamphenicol.¹¹⁷ Interestingly, two HIV-positive patients with oropharyngeal infections with *K. rhinoscleromatis* required prolonged courses of antibiotics before clinical cure.¹¹⁸ However, among HIV-positive pregnant women without significant documented immunosuppression, the clinical presentation and response to treatment in donovanosis appeared to be unaltered by HIV.¹¹⁹ Further clarification of the role of oral azithromycin in the management of donovanosis in HIV-positive patients is awaited.

■ PREVENTION AND CONTROL

Donovanosis is one of the most easily recognizable causes of genital ulcer disease clinically in endemic areas.⁸⁸ Because it is limited to a few specific geographic locations, local elimination and even global eradication are realistic objectives^{65,120} that are justified if the high proportion of HIV transmissions attributable to genital ulcers is taken into consideration.¹²¹ Such programs would need to appreciate the diverse nature of the communities affected and include careful appraisal of local customs and beliefs. Although communities in the donovanosis-endemic countries of Papua New Guinea, India, South Africa, Brazil, and Australia differ markedly, they all have similarities that may be relevant to donovanosis control. Most individuals with donovanosis in these communities are subject to social deprivation, low socioeconomic status, and poor standards of personal genital hygiene.

Donovanosis should remain high on the list of differential diagnoses of genital ulceration in female sex workers in donovanosis-endemic countries. In India,² the United States,³⁴ and Papua New Guinea,³⁵ prostitutes have been identified as source contacts of index cases and usually have clinically detectable lesions. In Papua New Guinea, local sexual practices and beliefs may play a significant role in the spread of donovanosis: It is not unknown for many men to have sexual intercourse with a single woman during festival occasions¹²²; furthermore, some men believe that impurities in their blood cause donovanosis ulcers and resort to self-mutilation in an attempt to “release” the cause of the problem.¹²³ It should also be noted that Papua New Guinea now has the highest prevalence of HIV in the Oceania region.¹²⁴

Since the overall prevalence of donovanosis in most endemic areas is low, mass surveys to identify cases or mass treatment campaigns are probably not justified. However, mass treatment of cases identified in house-to-house visits in Goilala, Papua New Guinea, was successful in controlling a localized epidemic in the 1950s.⁷⁷ This strategy merits further consideration as an HIV prevention measure in that country if donovanosis is found to be still prevalent there.

Poor understanding has in the past led patients with severe donovanosis to become shunned like lepers.² Many sufferers express profound feelings of shame, guilt, and embarrassment. Some have resorted to suicide. Greenblatt³³ has painted an emotive picture of the disease—“poorly understood and poorly handled, the disease becomes so loathsome that few clinics and fewer physicians are willing to treat those afflicted with it.” Even now, extreme rejection is not unusual.¹²⁵

In many developing countries, donovanosis patients are seen at STI clinics after attending primary health-care centers where various treatment approaches have failed. Patients with donovanosis may need prolonged courses of antibiotics and require careful explanation and reassurance about a condition that they may have had for a long time. Where possible, this is probably best given by staff who have chosen to work with STI patients and can give individual attention coupled with a sympathetic, nonjudgmental approach.¹²⁶ Clearly, there is a need for ongoing education of health-care workers about donovanosis in endemic areas and to raise community awareness of the importance of genital ulcer disease as a proven risk factor for HIV transmission.¹²⁷ Expanded access to azithromycin would be a major step forward and contribute significantly to limiting compliance problems with other therapies currently in use.

Globally, donovanosis has declined considerably over the last ten 10 years. The reasons for this are multifactorial but include syndromic management for genital ulcers at the primary health-care level and a more rational use of antibiotics. However, there is still a need for clinicians to be vigilant for outbreaks in the same way that recent epidemics of syphilis and lymphogranuloma venereum have been identified.

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INTRODUCTION

Research in the past decade has led to many exciting discoveries of the disease associations and pathogenic mechanisms of the genital mycoplasmas. The recognition of *Mycoplasma genitalium* as a cause of idiopathic urethritis in men and a possible cause of cervicitis and upper tract disease in women suggests that this organism may have a significance rivaling that of *Chlamydia trachomatis*. Recognition that *Ureaplasma urealyticum* organisms, previously called T-strain mycoplasmas, represent two distinct species, designated *U. urealyticum* (formerly biovar 2) and *U. parvum* (formerly biovar 1), has led to research evaluating their possible differential disease associations in both men and women. These studies have only recently become possible due to the development of specific PCR assays to identify and easily differentiate these fastidious species. In the following chapter, we focus on the most common genital mycoplasmas—*M. genitalium*, the ureaplasmas (*U. urealyticum* and *U. parvum*), and *Mycoplasma hominis*—their detection, prevalence in various populations, role in human disease, pathogenesis, and treatment, when appropriate.

The genital mycoplasmas, as with other bacteria in the class *Mollicutes* (“soft skin”), are thought to have devolved from ancestral anaerobic bacteria (clostridia) by gene deletion. Indeed, one species, *Mycoplasma genitalium*, holds the distinction of having the smallest genome of any known cellular organism that can be cultured axenically, and thus has been used as a model for the minimal requirements for cellular life.^{1,2} Of the eight genera within the class, five, namely, *Mycoplasma*, *Ureaplasma*, *Acholeplasma*, *Anaeroplasma*, and *Asteroleplasma*, comprise more than 120 species, most of which belong to the genus *Mycoplasma*. The term “mollicutes” is sometimes used trivially to describe any of the organisms in the class, irrespective of genus or species, as is the term “mycoplasmas,” which is used in this chapter. However, the term “ureaplasmas” is often used to refer to organisms that hydrolyze urea and are therefore classified within the genus *Ureaplasma*. Of the approximately

20 mycoplasmas that have been detected in the human species, four are commonly detected in the genitourinary tract, which is their primary site of colonization. Characteristics of these mycoplasmas and their disease associations in comparison with the human respiratory pathogen, *M. pneumoniae*, are listed in [Table 41-1](#). Due to orogenital contact, some of these genital species are found occasionally in the oropharynx and, conversely, some of those mycoplasmas that have the oropharynx as their primary site of colonization are found in the genital tract.

EPIDEMIOLOGY

■ COLONIZATION OF INFANTS AND CHILDREN

Infants may become colonized with genital mycoplasmas during passage through the birth canal; infants who are delivered by cesarean section are colonized less often than those delivered vaginally.^{7,8} Ureaplasmas have been isolated from the genitalia of up to one-third of infant girls, and *M. hominis* from a smaller proportion.^{7,9,10} These genital mycoplasmas are isolated even less frequently from the genitourinary tract of infant boys.¹⁰ Mycoplasmas, mainly ureaplasmas, have also been isolated from the nose and throat of infants of both sexes.⁷ Infant colonization figures for these genital mycoplasmas vary from one population and from one study to another, depending upon the proportion of pregnant women who are colonized. Since *M. genitalium* is frequently detected in the cervix, vagina, and endometrium, the potential for neonatal infection exists, yet neonatal infections with this organism have rarely been reported to date.^{10a}

Neonatal colonization with *M. hominis* and the ureaplasmas tends not to persist, particularly in boys, and the proportion of infants who are colonized decreases quite rapidly as they get older. Thus, these genital mycoplasmas are seldom recovered from urine or genital-tract specimens from prepubertal boys, but 5–22% of prepubertal girls are colonized with ureaplasmas and 8–17% with *M. hominis*.^{11–15}

Table 41-1. Distinguishing Features and Disease Associations of the Most Prevalent Human Mycoplasmas with Possible Pathogenic Significance

Species	Energy Source	Genome Size (kb) ^a	Disease Associations ^b					
			Urethritis (Men)	Cervicitis	Bacterial Vaginosis	Endometritis and/or PID	Preterm Birth	Infertility (Women)
<i>M. hominis</i>	Arginine	ND ^c	—	—	++++	+/-	—	—
<i>M. genitalium</i>	Glucose	580	++++	+++	—	++	+/-	+
<i>M. pneumoniae</i>	Glucose	816	—	—	—	—	—	—
<i>Ureaplasma spp.</i> ^d	Urea	NA	+/-	?	+++	?	+/-	?
<i>U. urealyticum</i> ^d	Urea	840–1140	+	?	?	?	?	?
<i>U. parvum</i> ^d	Urea	750–760	—	?	?	?	?	?

The primary site of colonization for all species listed is the reproductive tract except for *M. pneumoniae* for which the respiratory tract is its primary colonization site.

^aGenome size was determined by whole genome sequencing (*M. genitalium* and *M. pneumoniae*)^{2,3} or RFLP analysis (*U. urealyticum* and *U. parvum*)⁴; whole genome sequencing confirmed the genome size of *U. parvum* as 752 kb.⁵ These genomes are approximately 10-fold smaller than most Firmicutes, for example, *Escherichia coli*.

^b++++, strong association, +, weak association; +/-, association in some, but not other studies; -, no association or negative (inverse) association.

^cND, not determined; NA, not applicable.

^d*U. urealyticum* and *U. parvum*, formerly designated as T960 and Parvo biovars within the sole species *U. urealyticum* (designated as the ureaplasmas or *Ureaplasma spp.* herein) are now considered two different species.⁶ *U. urealyticum* (T960 or biovar 2) consists of serovars 2, 4, 5, and 7–13. *U. parvum* (parvo or biovar 1) consists of serovars 1, 3, 6, and 14.

In sexually abused children, figures of as much as 48% and 34%, respectively, have been recorded.¹³

■ COLONIZATION OF ADULTS

After puberty, colonization with *M. hominis*, *M. genitalium*, and the ureaplasmas occurs primarily as a result of sexual contact.^{11,16–20} Sexually mature individuals without a history of sexual contact are colonized infrequently with these genital mycoplasmas and colonization increases proportional to the number of different sexual partners. Recently, the prevalence of *M. genitalium* in two general population-based studies was reported as 2.3% and 1.1% in 21–23-year-old women and men in Denmark²⁰ and 1.4% and 1.1% in 18–27-year-old women and men in the United States.¹⁹ In the latter study, the prevalence of this organism in this largely asymptomatic population was similar to that of *Neisseria gonorrhoeae* (0.4) and *C. trachomatis* (4.2). In both studies, detection of *M. genitalium* was associated with a history of sexual intercourse. Sexual transmission of this organism is also supported by the concordance of *M. genitalium* detection²¹ and identity of strain types²² among sexual partners.

CLINICAL MANIFESTATIONS AND SEQUELAE

■ ROLE OF GENITAL MYCOPLASMAS IN DISEASES OF THE GENITOURINARY TRACT OF MEN

Nongonococcal urethritis

In the past 10 years, *M. genitalium* has become increasingly recognized as a possible cause of urethritis with a prevalence similar to that of *N. gonorrhoeae* and *C. trachomatis*. This bacterium was originally isolated from urethral specimens from 2 of 13 men with nongonococcal urethritis (NGU),²³ yet the difficulty of culturing this fastidious organism in subsequent studies precluded assessment of its association with reproductive tract disease in men and women. Initially several investigators developed DNA probes to detect this organism in patient specimens,^{24,25} but this approach was superseded by the superior sensitivity of PCR assays developed for this organism.^{26,27} The availability of these assays provided the first opportunity to show that *M. genitalium* is associated with NGU.^{28,29}

To date, more than 10 PCR assays have been used in more than 20 studies showing the association of *M. genitalium*

with NGU.^{30–32} From the earliest studies,^{28,29} *M. genitalium* has been detected more frequently in the urethra of men with NGU than in men without this condition (OR_{unadj} 4.7 [3.5–6.3]), particularly among men with nonchlamydial NGU (OR_{unadj} 7.0 [4.6–10.8] see Fig. 41-1). Studies using multivariate analysis to assess possible confounders confirmed the association of *M. genitalium* with NGU with reported odds ratios of similar magnitudes and statistical significance.^{33,34} Among STD clinic populations, 85–90% of *M. genitalium* infected men have microscopic evidence of urethritis, defined in different studies as ≥ 4 , ≥ 5 , or ≥ 10 PMNs/HPF or urethral “threads” containing ≥ 10 PMNs/HPF,^{21,29,33,35,36} and the majority of *M. genitalium* infected men (65–77%) reported symptoms.^{21,35} The development of quantitative PCR assays for *M. genitalium* allowed the demonstration of a dose/response relationship between signs and symptoms of urethritis and *M. genitalium*-DNA load in urethral and urine specimens,^{37–39} further supporting the causal relationship of *M. genitalium* with urethritis. Finally, animal experiments demonstrated that intraurethral inoculation of male chimpanzees with *M. genitalium* resulted in the development of urethritis in the majority, shedding of the organism for up to 18 weeks after inoculation, and a humoral antibody response, thus fulfilling Koch’s postulates of causation.^{40,41}

Several studies have shown a strong correlation of *M. genitalium* with persistent and recurrent NGU, perhaps due in part to the association between microbiologic treatment failure and persistence of urethritis.^{42–48} In settings where tetracyclines or quinolones are the drugs of choice, *M. genitalium* has been found in a high proportion of patients with recurrent or persistent urethritis. For example, in a follow-up study of 86 men with acute NGU, Horner et al.⁴⁶ found that 7 (13%) of 56 men with chronic NGU were *M. genitalium* positive and all *M. genitalium*-positive men identified during follow-up had chronic NGU. Similarly, Taylor-Robinson et al. reported that 11 (21%) of 52 men with persistent or recurrent NGU were *M. genitalium* positive.⁴⁵ In a study of 78 men who had received standard treatment for urethritis with doxycycline, and who reattended the clinic because of persisting or recurring symptoms, Wikström and Jensen⁴⁷ found that 32 (41%) were *M. genitalium* positive, demonstrating both the lack of efficacy of doxycycline and the strong correlation with symptomatic urethritis. More recently, azithromycin treatment failure was reported among men with *M. genitalium*-positive NGU (28% treatment failure, CI₉₅ 15–45%) and was correlated with a reduced susceptibility of *M. genitalium* to this antibiotic.⁴⁸ Clearly, randomized, controlled, treatment trials are needed to establish the optimal treatment regimen for this emerging pathogen.

In contrast to the consistency of studies linking *M. genitalium* with NGU, the association of ureaplasmas with this syndrome has been controversial. In several studies conducted in the 1970s and 1980s,^{49–53} these bacteria were isolated significantly more often, and in higher quantities, from men with chlamydia-negative NGU, than from men with chlamydia-positive NGU, controls, or both. In contrast, other studies did not reveal this association.^{33,54–56} In one study, this organism was associated with chronic, but not acute, NGU.⁴⁶ Notably, the strongest association of ureaplasmas with NGU (and high quantities [$\geq 10^3$ ccu/mL] of ureaplasmas with NGU) was conducted among Caucasian men with first episode nonchlamydial NGU,⁴⁹ a population that has not been typically analyzed in subsequent studies of STD clinic populations. Finally, a role for ureaplasmas in urethritis is supported by a study in which two investigators from the UK inoculated themselves intraurethrally with a ureaplasma strain previously isolated from patients who had NGU; both subjects developed urethritis and a specific antibody response to this organism.⁵⁷

The association of the ureaplasmas with NGU may be partially resolved by assessing the correlation of the newly recognized species, *U. parvum* and *U. urealyticum*, with disease. These two species, initially recognized as biovar 1 and 2 within the genus *Ureaplasma* based on serotype groupings and manganese susceptibility, now can be differentiated by genome size, whole cell DNA homology, protein antigenicity and polymorphisms, and sequence divergence within selected genes.^{6,58}

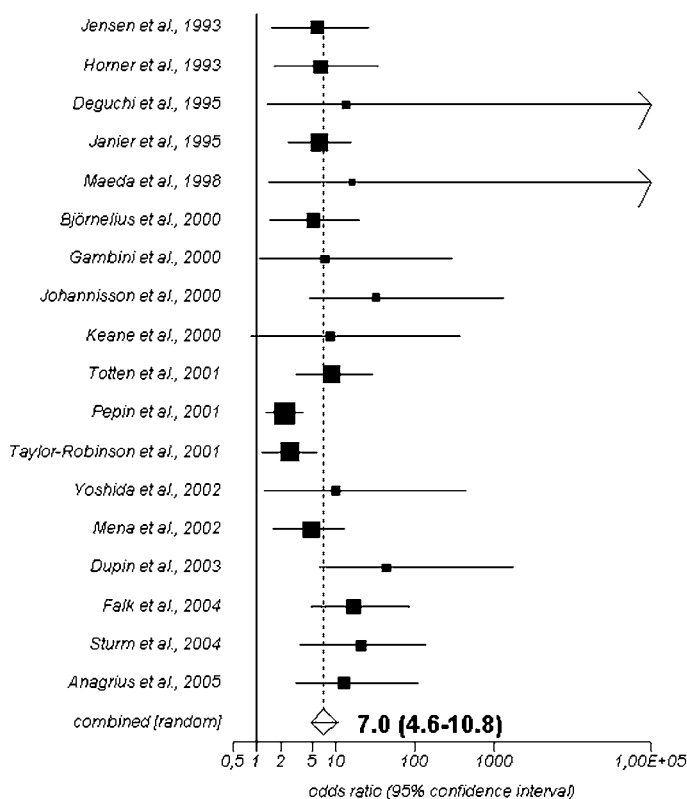


FIGURE 41-1. Forest plot showing the association between *M. genitalium* infection and nonchlamydial NGU expressed as odd ratios with 95% CI as calculated from published studies.

The designation of the two *Ureaplasma* species as *U. urealyticum* and *U. parvum* is a little confusing considering that formerly all urea-hydrolyzing human *Mycoplasma* spp. were also designated as *U. urealyticum*. Thus, in this chapter, we will use the terms “the ureaplasmas” or “*Ureaplasma* spp.” in studies in which the two species were not differentiated.

Three studies to date assessing the association of the newly defined *Ureaplasma* spp. with NGU have yielded conflicting results.^{59–61} In all three studies, *U. parvum* was detected more often in controls, consistent with its role as a commensal at this site. In contrast, the association of *U. urealyticum* with NGU differed among the three studies. In their study of 235 men with, and 205 without, NGU, Povlsen et al.⁵⁹ detected *U. urealyticum* in 18% of cases and 9% of controls ($p = 0.01$, our calculations) in contrast to *U. parvum* which was detected in 14% of cases and 21% of controls. The association of *U. urealyticum* with NGU was further supported in a study by Deguchi et al.⁶⁰ in which 16% of 329 men with NGU and 8% of 141 men without NGU were infected with this organism ($p = 0.025$). However, the results of both the studies were contradicted by the study by Bradshaw et al.⁶¹ in which *U. urealyticum* was not associated with NGU (*U. urealyticum* was detected in 43 [13%] of 329 cases and 54 [18%] of 307 controls), even after controlling for possible confounders by multivariate analysis. Clearly, the association of *U. urealyticum* with NGU requires further study. Differences in the association of *U. urealyticum* with NGU may reflect differences in the population studied, selection of cases and controls, PCR method used, prevalence of more pathogenic strains in different geographic locations, and/or previous infection with, and possible partial immunity to, *Ureaplasma* spp. Further studies, including those in which race, age, number of sexual partners, and past history of NGU are assessed for their effect on this association, are needed to resolve this controversy. In addition, the impending whole genome sequencing of all 14 ureaplasma serovars (John Glass and Ken Waites, personal communication) might reveal the presence of potential virulence factors that could be exploited to assess the differential association of *Ureaplasma* spp., serotypes, or strains with disease.

Treatment trials assessing clinical cure and clearance of *U. urealyticum*, *U. parvum*, and other pathogens may increase our understanding of the role of ureaplasmas in NGU. In one study, men were treated with aminocyclitols, which are active against ureaplasmas but not against chlamydiae, or with sulfisoxazole, which is active against chlamydiae but not against ureaplasmas.⁶² The clinical results suggested that both chlamydiae and ureaplasmas could cause urethritis. In another study, men who had NGU were treated with rifampicin, which is active against chlamydiae but not against ureaplasmas.⁶³ The proportion of patients cured clinically was much smaller than that of another group who were given minocycline, which is active against both kinds of microorganism. Of course, the extent to which the existence of *M. genitalium* in

some of the patients in these studies, not appreciated at the time they were undertaken, may have affected the results and jeopardized the conclusions is unknown. In clinical trials assessing the responses of *Ureaplasma* spp. to the tetracyclines and azithromycin, microbiologic and clinical treatment failures of 22–55% have been reported,^{64–69} consistent with the occurrence of tetracycline resistance mediated by *tetM* among a subpopulation of ureaplasma strains⁷⁰ and the moderate baseline susceptibility of ureaplasmas to macrolides.⁷¹

Studies using either PCR or culture to detect *M. hominis* do not indicate that this organism is a cause of NGU.^{33,50,72}

Prostatitis

Thirty years ago, Mårdh and Colleen⁷³ recovered *M. hominis* from urethral specimens of 8 (10%) of 79 patients with chronic prostatitis (now presumably classified as category III in the current NIH classification of prostatitis, the chronic prostatitis/chronic pelvic pain syndrome) and from none of 20 normal age-matched controls, a difference certainly insufficient to suggest an association with the disease. Likewise, Peeters and associates⁷⁴ isolated this mycoplasma from 10 (12%) of 85 men who had prostatitis of unknown origin and from two (4%) of 51 healthy men ($p = 0.26$) and *Ureaplasma* spp. were isolated from 40 (47%) of the patients and from 13 (26%) of the healthy men ($p = 0.02$). Hofstetter et al.⁷⁵ studied men with what was described as urethroprostatitis and found that mycoplasmas, mainly ureaplasmas, were also isolated significantly more often and in greater numbers from patients with disease than from normal men who served as controls. Later, Brunner and colleagues⁷⁶ associated ureaplasmas with prostatitis in 82 (13%) of 597 patients who had the disease, and Weidner and coworkers⁷⁷ implicated these organisms in 46 (11%) of 412 men who had urethroprostatitis, a claim also made by Ohkawa et al.^{78,79} a decade later, in chronic prostatitis on the basis of isolation and antibiotic investigations. In contrast to these studies in which isolation was successful, this was not always so; Meares⁸⁰ and Vinje et al.⁸¹ failed to recover ureaplasmas from men with chronic nonbacterial prostatitis. On reflection, three important issues are raised by these various studies. First, the accuracy of the diagnosis. It clearly appears that chronic prostatitis has not always been truly chronic but sometimes “acute on chronic prostatitis” or “acute urethritis on chronic prostatitis.” Second, patients with chronic disease have often been subjected to multiple courses of antibiotics before microbiological investigations have been undertaken, diminishing the chance of recovering an etiological agent. Third, whether the organisms that were detected had been derived entirely from the prostate or are “contaminants” that had come partly, or totally, from the urethra as a consequence of the detection procedure is unclear. With the first and third points particularly in mind, biopsies taken under transrectal

ultrasound control from the prostates of 50 men with chronic prostatitis, defined by the Stamey technique, were found to contain chronic inflammatory cells but no microorganisms.⁸² Most recently, *M. genitalium* was detected by specific PCR assays in 5 (4%) of 125 prostatic biopsies from men with chronic idiopathic prostatitis.⁸³ Thus, the available evidence suggests that a causative role for the genital mycoplasmas in the truly chronic condition is at best questionable and can be no more than minimal.

Epididymitis

Most cases of acute epididymitis in heterosexual men less than 35 years of age are due to *N. gonorrhoeae* or *C. trachomatis*, whereas among older men and homosexuals, gram-negative bacilli are usually responsible.^{84–86} The recovery of *M. hominis* from an epididymal aspirate has been recorded once.⁸⁷ Furthermore, although ureaplasmas may be recovered from urethral specimens from some men who have epididymitis, recovery from percutaneous aspirates of the inflamed epididymis has also been recorded only once, in this instance in association with a greater than fourfold serologic antibody response.^{88,89} Thus, the role of genital mycoplasmas seems to be meager, but the influence of ureaplasma biodiversity has not been assessed and thus the ureaplasmas should not be discounted completely as a cause. In addition, the association of *M. genitalium* with epididymitis has not been assessed, but clinical experience suggests that it may play a role in some patients.

■ ROLE OF GENITAL MYCOPLASMAS IN DISEASES OF THE GENITAL TRACT OF WOMEN

Cervicitis

In most, but not all studies, *M. genitalium* has been associated with cervicitis (Table 41-2), an important finding, given the increased risk of upper tract infection associated with other organisms causing this disease. After the initial report of an association of *M. genitalium* with cervicitis in 1997,⁹⁰ in which *M. genitalium* was detected among 5 (7.8%) of 64 cases and none of 80 pregnant controls ($p < 0.05$), several studies have assessed and expanded upon this association. In a cross-sectional study, Manhart et al.⁹² showed that *M. genitalium* was detected in 24 (11%) of 215 women with, and in 26 (5%) of 504 women without mucopurulent cervicitis and that this organism was independently associated with cervical mucus ($p < 0.01$), cervical PMNs ($p < 0.01$), and easily induced cervical bleeding ($p = 0.06$). Further, after controlling for age, phase of the menstrual cycle, and other known cervical pathogens, the strength of this association (3.3 [CI₉₅ 1.7–6.4]) was similar to that for *N. gonorrhoeae* (3.0 [CI₉₅ 1.8–5.2]) and *C. trachomatis* (4.7 [CI₉₅ 2.7–8.2]). Subsequently, in a study of 826 West African women, Pépin et al.⁹³ demonstrated by multivariate analysis that four signs of cervicitis (cervical discharge,

cervical pus, easily induced bleeding, and inflammatory cervix) were associated with *M. genitalium* ($p \leq 0.05$ for each sign) with adjusted OR (between 1.6–1.8 for the four signs) very similar to that for *C. trachomatis* (1.3–4.1). A similar association of *M. genitalium* with signs of cervicitis was detected by Anagrius et al.,²¹ Falk et al.,⁹⁴ and Gaydos et al.⁹⁵ Interestingly, in these latter two studies, *M. genitalium* was also associated with urethritis in women, a not unexpected finding given its strong association with this disease in men. In contrast to the above studies, no association between *M. genitalium* and cervicitis was detected by Casin et al.⁹¹ in a study that differed from those above in its high prevalence of women with mucopurulent cervicitis (85%) and vaginal discharge (100%), analysis of multiple specimen types in some women, and definition of cervicitis as ≥ 10 PMNs/HPF. An etiologic role of *M. genitalium* in cervicitis is consistent with the results of chimpanzee experiments in which increased vaginal PMNs were detected, an antibody response was induced, and *M. genitalium* was persistently cultured (up to 11–14 weeks after inoculation) from the vagina in all four chimpanzees inoculated with this organism.⁴¹

The association of *M. hominis* and the ureaplasmas with cervicitis has been studied infrequently. In the study by Paavonen et al.,¹⁰¹ it was found that mucopurulent cervicitis was associated with isolation of ureaplasmas ($p = 0.02$), although the relative prevalence of *U. urealyticum* and *U. parvum* and the role of *M. genitalium* and bacterial vaginosis as confounders in these analyses were not assessed.

Bartholin's gland abscess

Genital mycoplasmas have been isolated from Bartholin's gland abscesses, but often they had ruptured or been opened surgically before specimen collection; hence it is not clear to what extent the results represent "contamination" of the abscesses by mycoplasmas present in the vagina.⁷² This problem was overcome by Lee et al.¹⁰² who obtained percutaneous aspirates from 34 intact Bartholin's gland abscesses; *M. hominis* was isolated from only one, together with other vaginal organisms, and ureaplasmas from none of the aspirates. Thus, it would appear that genital mycoplasmas are not an important cause of Bartholin's gland abscesses. Whether they might have any role in less severe disease (Bartholinitis) and whether *M. genitalium* is associated with this disease has not been determined.

Bacterial vaginosis

Vaginal specimens from women who have bacterial vaginosis are positive for *M. hominis* more often, and contain larger numbers of the organisms, than specimens from women who do not have this syndrome.^{100,103–107} Although mycoplasmas are resistant in vitro to metronidazole, this drug is often effective in treating bacterial vaginosis and at

Table 41-2. Results of Studies Assessing the Association of *M. genitalium* with Reproductive Tract Disease in Women

Study and Disease Syndrome	Detection of <i>M. genitalium</i>		Association (<i>P</i> values)
	No. Detected/Total No. (%) in Patients with Disease	No. Detected/Total No. (%) in Patients without Disease	
Cervicitis			
Uno et al. (1997) ^a	5/64 (7.8%)	0/80	0.01
Casin et al. (2002) ^b	42/99 (42)	23/71 (32)	0.19
Manhart et al. (2003) ^c	24/215 (11)	26/504 (5)	0.004
Pepin et al. (2005) ^d	34/172 (16.5)	28/363 (7.2)	0.05
Falk et al. (2005) ^e	12/118 (10.2)	13/336 (4.0)	0.019
Anagrus et al. (2005) ^f	4/20 (13.3)	6/227 (2.6)	0.02
Gaydos et al. (2006) ^g	38/133 (28.6)	24/191 (12.7)	<0.001
Acute endometritis			
Cohen et al. (2002) ⁹⁶	9/58 (16)	1/57 (2)	0.02
Pelvic Inflammatory Disease			
Simms et al. (2003) ⁹⁷	6/45 (13)	0/37	0.03
Tubal factor Infertility			
Clausen et al. (2001) ⁹⁸	29/132 (22)	11/176 (6.3)	0.003
Svenstrup et al. (2007) ⁹⁹	5/30 (17)	7/164 (4.2)	<0.01
Bacterial Vaginosis			
Keane et al. (2000) ¹⁰⁰	0/15	2/17 (12)	NS ^h
Manhart et al. (2003) ⁹²	10/232 (4.3)	40/487 (8.2)	0.05 ⁱ

Cervicitis defined by

^aPurulent or mucopurulent cervical discharge or ≥ 20 PMNs/HPF⁹⁰

^b ≥ 10 PMNs/HPF⁹¹

^cMucopurulent cervicitis (visible mucus or > 30 PMNs/HPF in cervical mucus⁹²

^dMany indicators of cervicitis measured; shown is the association of mucopurulent discharge (yellow cervical exudates ("swab test")⁹³

^eMore PMNs than epithelial cells in wet smear of lateral fornix and lateral vaginal wall⁹⁴

^f ≥ 30 PMNs/HPF²¹

^gCervical discharge or friability⁹⁵

^hNS, non significant

ⁱNote that this is an inverse association

the same time eliminating *M. hominis* from many of the subjects,¹⁰⁸ suggesting that *M. hominis* proliferates in the milieu created by the other microorganisms and when the latter are eliminated, so too is *M. hominis*. Thus, although *M. hominis* could conceivably play a role in bacterial vaginosis as

a primary pathogen, it is more likely to behave symbiotically with the other bacteria that are an integral part of this condition. The ureaplasmas have also been associated with bacterial vaginosis in most, but not all studies.^{100,105,107,109,110} The relative association of *U. urealyticum* and *U. parvum* with

bacterial vaginosis has not yet been assessed. Preliminary studies indicate that, unlike the ureaplasmas and *M. hominis*, *M. genitalium* is not associated with bacterial vaginosis¹⁰⁰ and may even be inversely associated with this condition⁹² (Table 41-2).

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is caused by an ascending infection in which organisms present in the vagina and cervix invade the endometrium, fallopian tubes, and surrounding structures. *C. trachomatis* and *N. gonorrhoeae* are the organisms that are most frequently associated with PID. In addition, a mixture of aerobic and anaerobic bacteria, many associated with bacterial vaginosis, has been implicated as a cause of this condition by some investigators¹¹¹⁻¹¹⁴ and it is against this background that the role of the genital mycoplasmas is considered.

M. hominis has been recovered more frequently from vaginal and cervical specimens from women with PID than from normal women.^{112,115-117} However, this organism is often recovered from the lower genital tract of women who have bacterial vaginosis (see the preceding) and, as the aforementioned studies linking *M. hominis* to PID did not include an assessment of bacterial vaginosis, the data are difficult to interpret. Relating the microbial flora of the lower tract to changes in the upper tract is difficult and studies based on laparoscopy are much more relevant. Mårdh and Westrom¹¹⁸ first drew attention to the possibility that genital mycoplasmas might have a role in PID, by showing that *M. hominis* was isolated from the fallopian tubes of four (8%) of 50 women with salpingitis, but not from those women without salpingitis. More recently, in a study in which laparoscopy and endometrial biopsy were undertaken on 36 women with suspected PID, *C. trachomatis* or *N. gonorrhoeae* was identified in 11 of 14 women with both salpingitis and endometritis, in two of nine with salpingitis or endometritis, and in none of 13 patients who had neither condition ($p < 0.0001$), but *M. hominis* organisms were not isolated from any of the patients.¹¹³ On the other hand, in another laparoscopy study, *M. hominis* was isolated directly from the fallopian tubes of 1 (5%) of 21 women with salpingitis and from the endometrium of 7 (33%) of these women.¹¹⁹ However, since it is rare to dissociate *M. hominis* from bacterial vaginosis, one should be cautious before accepting *M. hominis* as an unequivocal cause of PID.

In several studies, antibody to *M. hominis* and fourfold rises in antibody titer to *M. hominis* were found more often among women who had PID than among controls.^{112,116,120} In several such studies, the antibody titer rises were associated with the isolation of *M. hominis* from the lower genital tract or from the inflamed fallopian tubes.^{119,121,122} In one study, an increased level of IgM antibody was found in 34% of patients with acute salpingitis and was associated with the isolation of *M. hominis* and with the presence of indirect hemagglutinating antibody to the mycoplasma.¹²³ High coinfection rates

with other microorganisms¹²⁴ suggest that epithelial damage caused by these organisms allows contact between *M. hominis* and the immune system and thus an immune response.¹²⁵ Damage to fallopian tube epithelium has also been studied in organ cultures. *N. gonorrhoeae* produced profound damage to the epithelium.¹²⁶ In contrast, *M. hominis* multiplied and persisted but did not cause damage.¹²⁷ However, scanning electron microscope examination showed that the organisms induced pathologic changes in the form of ciliary swelling,¹²⁸ possibly due to the effect of ammonia produced by mycoplasma metabolism. Studies in intact animals may be more relevant than studies in organ cultures. Female grivet monkeys infected with *M. hominis* developed a self-limited acute salpingitis and parametritis.¹²⁹ Further studies in grivet monkeys have shown that ascending *M. hominis* infection of the genital tract must be preceded by mechanical injury to the epithelial barrier and that subsequent spread occurs via blood and lymph vessels rather than by the canalicular route.¹³⁰

Ureaplasmas have also been isolated directly from the fallopian tubes of patients with PID, as well as from pelvic fluid obtained by culdocentesis from such patients,^{118,131-134} yet their occurrence at both sites is rare and usually in association with other known pathogens. Since most serological tests and inoculation studies in subhuman primates and in fallopian tube organ cultures have proved negative, ureaplasmas probably do not play a role in salpingitis.^{127,135} In the cluster analysis of bacterial vaginosis-associated bacteria conducted by Ness et al.,¹³⁶ PID was associated with the absence of hydrogen peroxide-producing lactobacilli and the presence of *Gardnerella vaginalis*, *M. hominis*, anaerobic gram-negative rods, and ureaplasmas (p for trend = 0.008), but the role of individual organisms in this disease could not be assessed.

M. genitalium may play a casual role in upper tract infection, including endometritis and PID. In one study, 12 (39%) of 31 women with PID who had not been infected with *N. gonorrhoeae* and had no antibody to *C. trachomatis* or *M. hominis* had a fourfold or greater rise in the titer of antibody to *M. genitalium* as measured by microimmunofluorescence,¹³⁷ although another study failed to confirm these data.¹³⁸ In a case-control study of PID, *M. genitalium* was detected by PCR in cervical specimens in 6 (13%) of 45 women with the disease, but in none of 37 controls ($p < 0.01$), and only one was coinfecting with *C. trachomatis* and none with *N. gonorrhoeae*.⁹⁷ *M. genitalium* has also been associated with endometritis. Using PCR to detect this organism in both cervical and endometrial specimens, Cohen et al.⁹⁶ found an association of *M. genitalium* with endometritis (9 [16%] of 48 with histologically confirmed endometritis were positive vs. 1 [2%] of 57 women without this condition [$p=0.02$]). *M. genitalium* was detected by PCR in 1 of 123¹³⁹ and 1 of 23 (D. Taylor-Robinson and J. Jensen, unpublished data) laparoscopically obtained fallopian tube specimens

from women with salpingitis and has been shown to cause lower genital tract inflammation as well as salpingitis in marmosets, grivet monkeys, and baboons.¹⁴⁰ In addition, this organism is able to attach to spermatozoa, perhaps enhancing its ascension into the upper genital tract.¹⁴¹

In summary, there is some evidence that *M. hominis* may be a cause of PID, but very little evidence that ureaplasmas have a similar role. The possibility that these organisms play a role only within the context of bacterial vaginosis needs to be addressed. *M. genitalium* is not associated with bacterial vaginosis, but evidence is mounting that it may play a causal role in cervicitis and possibly endometritis and PID.

■ ROLE OF GENITAL MYCOPLASMAS IN DISORDERS OF THE URINARY TRACT

Urinary calculi

Infection (struvite) stones, composed of ammonium magnesium phosphate, are thought to be caused by urea-hydrolyzing bacteria including *Proteus* and *Ureaplasma* spp. In several studies, ureaplasmas have been detected in 12–27% of infection stones, often in pure culture,^{142–145} and are more frequently detected in the urine and stones of patients with infection, compared to those with metabolic stones.¹⁴⁶

Several groups have demonstrated the development of struvite stones in rats following inoculation with ureaplasmas (either *U. urealyticum* or *U. parvum*, depending upon the study),^{147–150} and inhibiting the growth of ureaplasmas, either with doxycycline or with the urease inhibitor flurofamide, prevented stone formation.¹⁵⁰ In one study,¹⁴⁷ magnesium ammonium phosphate calculi developed in the bladders of male, but not female, rats after ureaplasmas were inoculated directly into the bladder or renal pelvis. Ureaplasmas have also been shown to induce crystallization of struvite and calcium phosphate in urine in vitro.^{146,151} However, in a recent study, Reyes et al.¹⁴⁹ showed that susceptibility to infection with ureaplasmas and subsequent struvite stone formation was associated with a robust immune response in rats, a response that differentiated rat strains that developed stones from those that did not. Although these findings suggest that ureaplasmas have a role in the development of infection stones and that the inflammatory response plays a key role in stone development, ureaplasmas are less often detected and implicated in stone formation than other urease-positive bacteria.

Pyelonephritis and urinary tract infection

M. hominis does not appear to play a role in acute cystitis, similar isolation rates having been recorded for symptomatic women and controls, and the organism was not found in suprapubic aspirates.¹⁵² In contrast, ureaplasmas

have been associated with chronic urinary symptoms and the acute urethral syndrome (defined by dysuria and frequency in women whose urine contains $<10^5$ /mL of known uropathogens^{153,154}). Stamm et al.¹⁵³ isolated ureaplasmas from 4 (27%) of 15 suprapubic aspirates taken from women with an acute urethral syndrome of unknown etiology and showed an association of relatively larger numbers of ureaplasmas ($\geq 10^3$ ccu/mL) with pyuria. Similarly, in a study by McDonald et al.,¹⁵⁵ ureaplasmas were recovered from suprapubic urine aspirates of one-fifth of patients with urinary tract infections; in one-third of these as the sole isolate. Potts et al.¹⁵⁶ assessed urinary tract infections in women referred to their clinic for chronic voiding symptoms and possible interstitial cystitis and found that 22 (46%) and 1 (2%) of 48 subjects had ureaplasmas and *M. hominis*, respectively, the majority of whom were clinically improved and had negative cultures following treatment. Together, the results of these studies suggest a role for ureaplasmas, but not *M. hominis*, in lower urinary tract infections, but confirmatory studies are needed, such as those controlling for possible vaginal contamination among women with bacterial vaginosis and those in which *U. urealyticum* and *U. parvum* are differentiated.

The association of ureaplasmas and *M. hominis* with pyelonephritis has also been assessed. Thomsen¹⁵⁷ isolated *M. hominis* from the upper urinary tract of 3 (14%) and ureaplasmas from the renal pelvis of 2 (9.5%) of 21 women with chronic pyelonephritis in contrast to none of 40 patients with noninfectious urinary tract diseases. In this study, only one of the three patients who harbored *M. hominis* had an associated bacteriuria, but all three patients had an acute exacerbation of pyelonephritis, two of whom developed antibody to *M. hominis*. In another study of patients with acute pyelonephritis,¹⁵⁸ ureaplasmas and *M. hominis* were isolated from the upper urinary tract of 5 (7%) and 7 (10%) of 67 such patients, respectively, in contrast to none of 50 control women with noninfectious diseases of the urinary tract. Antibodies to *M. hominis*, measured by indirect hemagglutination, were found in serum and in urine from some of these patients.¹⁵⁹ In dogs, ureaplasmas have multiplied and survived for at least 3 weeks after being introduced into experimentally obstructed upper urinary tracts, causing severe interstitial nephritis accompanied by an antibody response.¹⁶⁰ However, there is no evidence that ureaplasmas cause this disease in humans and there is insufficient evidence to indicate that they cause acute pyelonephritis. We conclude that to date, there is no clear evidence that either *M. hominis* or ureaplasmas is a significant cause of pyelonephritis, a concern highlighted by the lack of confirmatory clinical studies in the almost 30 years from the original observations.

■ ROLE OF GENITAL MYCOPLASMAS IN DISORDERS OF REPRODUCTION

Involuntary infertility

Ureaplasmas and *M. hominis* have been isolated more often from genital specimens from infertile than from fertile couples by some investigators but not by others.^{161–165} Similarly, antibodies to these organisms have been linked to infertility in some, but not all, studies.^{166–169} In several studies, ureaplasmas were recovered more often from endometrial specimens from infertile women than from fertile women.^{170–172} However, the role of other organisms has rarely been considered, nor the possibility that ureaplasmas might be involved in only one of the several clinical categories of infertility. In this regard, Cassell and colleagues found ureaplasmas twice as commonly in a subpopulation of women whose infertility was associated with a “male factor” than in other women.¹⁷³

Treating infertile couples with antibiotics is clearly one way of defining the role of microorganisms in infertility. However, the results have been contradictory. As reviewed elsewhere,⁷² conception rates ranging from 23% to 84% have been recorded among ureaplasma-colonized infertile couples who were treated with tetracyclines. Busolo et al.¹⁷⁴ reported that conception had occurred in 5 (26%) of 19 doxycycline-treated patients in whom ureaplasmas were eradicated; there were no conceptions among 29 couples in whom ureaplasmas persisted after treatment with doxycycline. In another study, ureaplasmas were eradicated from 129 infertile couples; the 3-year conception rate was 60% compared to only 5% for 32 infertile couples in whom ureaplasmas could not be eliminated ($p < 0.001$).¹⁷⁵ In contrast, although others were able to eradicate ureaplasmas from 91% of infertile couples, the subsequent pregnancy rates were the same whether or not eradication had occurred.¹⁶¹ Furthermore, in another study, after 1 year the conception rate among untreated ureaplasma-positive infertile women was 28%, similar to that among untreated ureaplasma-negative women (27%).¹⁶² It is obvious that double-blind, placebo-controlled, antibiotic studies of couples with unexplained infertility are likely to provide the best information. In this regard, Harrison et al.¹⁷⁶ gave couples who had primary infertility of unknown cause either doxycycline or a placebo. Although a 28-day course of the antibiotic eradicated *M. hominis* and ureaplasmas, the rate of conception (17%) was no greater in those given the antibiotic than in those given the placebo. The results of three other studies also failed to show an association between administration of tetracycline to ureaplasma-colonized couples and conception.^{171,177,178} However, these results may be confounded by antibiotic resistance of ureaplasmas and *M. hominis*.^{70,179} We conclude that to date, there is no convincing evidence to implicate *M. hominis* or ureaplasmas as important causes of infertility.

The role of *M. genitalium* in involuntary infertility has also been examined. In a seroepidemiologic investigation of 308 infertile women, Clausen et al.⁹⁸ found that 22% (29/132) of women with tubal factor infertility had antibodies to a recombinant antigen specific for *M. genitalium* compared to 6.3% (11/176) of women with normal fallopian tubes ($p = 0.005$). In a subsequent study, this group⁹⁹ determined that antibodies to *M. genitalium* were detected in 17% (5/30) of women with tubal factor infertility compared to 4% (7/164) of women with normal tubes (OR of 4.5 [CI₉₅ 1.2–15.6]) after adjusting for *C. trachomatis* infection and age]. Surprisingly, *C. trachomatis* was not associated with tubal factor infertility, a finding attributed to the recent effective programs for diagnosis and treatment of this pathogen. Others have shown that approximately one-quarter of infertile women have antibody to *M. genitalium*, although there is no correlation with abnormal hysterosalpingograms as there is when antibody to *C. trachomatis* is associated with infertility.¹⁸⁰ A role of possible tubal damage leading to tubal scarring and occlusion was demonstrated by Baczynska et al.,¹⁸¹ who showed that *M. genitalium*, but not *M. hominis*, damaged ciliated cells in a human fallopian tube organ model, although the effect was moderate compared to that of *C. trachomatis*. Clearly, future studies are needed to clarify the role of *M. genitalium* in this important sequela to upper tract infection in women.

Habitual spontaneous abortion, stillbirth, and preterm birth

Ureaplasmas and *M. hominis* have been associated with adverse outcomes of pregnancies in some, but not all, studies. In one study, ureaplasmas were found more often in endocervical specimens from women with a history of spontaneous abortion, especially recurrent spontaneous abortion, than from a control group of women ($p < 0.05$).¹⁸² However, most investigators have not been able to relate lower genital tract colonization with ureaplasmas to fetal loss, although the possibility that a smaller subgroup was at higher risk could not be excluded.^{72,183–186} Ureaplasmas have also been isolated more frequently from spontaneously aborted fetuses, stillborns, or premature infants than from induced abortions or normal full-term infants and isolation was not entirely due to superficial contamination, since the organisms were isolated from the lungs and from the brain, heart, and viscera.^{72,187–191} Others found a significant association between chorioamnionitis and mycoplasmal infection, even when the duration of the rupture of the membranes was taken into account in the analyses.^{189,192–198} Such membrane inflammation might be important in bringing about the poor outcome of pregnancy. Furthermore, there are serologic data to support the concept that ureaplasma infections occur more commonly in women who have poor pregnancy outcomes than in those who have normal

pregnancies.¹⁹⁹ Unfortunately, none of these observations answers the major question of whether abortion of the fetus occurs because mycoplasmas invade it and cause its death, or whether they invade after the fetus dies for some other reason. Furthermore, the question of an etiological association is difficult to resolve, since possible roles of other microorganisms were ignored in most studies. This is of critical importance because ureaplasmas often are part of the complex bacterial flora of bacterial vaginosis, and bacterial vaginosis has been associated with preterm labor and stillbirth.²⁰⁰ However, in one study in which bacterial vaginosis was excluded and women were analyzed who were infected apparently only with ureaplasmas, the T960 biovar (now designated *U. urealyticum*) was dominant in patients who had had a miscarriage and in those who delivered preterm.²⁰¹ Nevertheless, the role of ureaplasmas is difficult to interpret because it is necessary to assume that infection with a single microorganism occurred and the outcome of pregnancy in those without ureaplasmas was not revealed. In another study, Donders et al.²⁰² determined that bacterial vaginosis, or isolation of *G. vaginalis*, *M. hominis*, or ureaplasmas was associated with a six- to sevenfold increased risk of spontaneous abortion ($p < 0.01$).

There are reports of successful pregnancies occurring after antibiotic treatment of women who were colonized by ureaplasmas and who had had frequent abortions previously.^{170,190,203} However, to postulate on the basis of this that mycoplasmal infection is a cause of reproductive failure seems inadvisable as specimens were not examined for other microorganisms and the treatment trials were largely uncontrolled or the numbers of persons studied were too few.

An observation in the early 1960s indicated that rates of low-birth-weight deliveries were unexpectedly low in pregnant women who had received tetracycline.²⁰⁴ This notion was supported by finding that the rates of isolation of genital mycoplasmas from the nose and throat of newborn infants were roughly inversely proportional to birth weight⁷ and occurrence of *M. hominis* and ureaplasmas in cervical specimens taken from women at their first antenatal visit was related to the low birth weight of their infants.⁹ Other workers^{189,195,197} agreed and the results of serological²⁰⁵ and therapeutic²⁰⁶ studies also supported the association of ureaplasmas with low birth weight. In the latter study,²⁰⁶ women given erythromycin for 6 weeks during the third trimester had babies of a significantly greater mean birth weight (3331 g) than did those given a placebo (3187 g) ($p < 0.05$). However, not all investigators have been able to associate ureaplasmas with low birth weight.^{10,207,208} Indeed, the true association may be confounded by the fact that ureaplasmas and *M. hominis* are only two of the flora associated with bacterial vaginosis and this syndrome itself is associated with low birth weight.^{209–211}

In more recent studies, the association of preterm birth with *U. urealyticum*, *U. parvum*, and also *M. genitalium* has been assessed. Kataoka et al.²¹² found an association of vaginal *U. parvum* (3.0, CI₉₅ 1.1, 8.5), but neither *U. urealyticum*, *M. hominis*, nor *M. genitalium* with preterm birth. In contrast, Edwards et al.²¹³ analyzed vaginal fluid specimens from a prospective cohort of 134 women of 23–32 weeks gestation, of which 22% delivered preterm (31–36 weeks gestation), and determined that *U. urealyticum*, but not *U. parvum*, was associated with preterm birth (prevalence 38%, OR 2.27 [1.01–5.08]). In this same study, *M. genitalium*, detected in 20% of the women, was associated with preterm delivery (OR 3.48; CI₉₅ 1.41, 8.57) independently of demographic factors, other mycoplasmas, other genital pathogens, anaerobic bacteria, or bacterial vaginosis-associated bacteria. This finding was consistent with another study in which *M. genitalium* was associated with preterm birth (4% vs. 2%, OR 2.5, CI₉₅ 1.2–4.9),²¹⁴ but not with others.^{212,215}

Perhaps the most convincing data associating adverse outcomes of pregnancy with mycoplasmas were obtained from prospective studies in which the adverse outcome occurred subsequent to detection of ureaplasmas in amniotic fluid, sampled by amniocentesis prior to rupture of membranes.^{198,216–218} Gray et al.²¹⁶ cultured for ureaplasmas from the amniotic fluid obtained from 94 women undergoing second-trimester genetic amniocentesis and determined that all of the 8 ureaplasma-positive women subsequently delivered prematurely or had spontaneous abortions, compared to 9 (10.5%) of 86 ureaplasma-negative women ($p < 0.001$). Similar results were obtained by Horowitz et al.,²¹⁷ who determined that adverse pregnancy outcomes were associated with 3 (50%) of 6 and 15 (12%) of 123 women with ureaplasma-positive and -negative amniotic fluid cultures, respectively, ($p = 0.035$). *M. hominis* was not detected in these studies. In possibly the most comprehensive study of aerobic and anaerobic bacteria detected in amniotic fluid obtained by amniocentesis of women in preterm labor with intact membranes, Watts et al.²¹⁹ reported that ureaplasmas, detected in 7 (35%) of 20 women in preterm labor, were one of the three most common bacteria isolated in this study. These organisms were detected in 5 (8%) of 61 women at 31–35 weeks of gestation, compared to 2 (4.5%) of 44 women at 23–30 weeks of gestation and were detected as the sole isolate in 4 (57%) of the 7 ureaplasma-positive cases. *M. hominis* was detected in only one specimen, which also contained ureaplasmas. These results were expanded by Hitti et al.²²⁰ who used a broad range 16S PCR to detect occult amniotic fluid infections and subsequently identified previously uncultured ureaplasmas in 1 (20%) of the 5 analyzed.²¹⁸ Additional studies of the role of the ureaplasmas and *M. genitalium* in preterm birth are eagerly awaited.

Postpartum and postabortal fever

Endometritis is the most common cause of postpartum fever, whether in the first 24–48 hours, or later. It occurs more often after cesarean section than after vaginal delivery, infections developing after vaginal delivery also tending to be less severe and often remitting spontaneously.

A relation between genital mycoplasmas and fever is least likely to be determined if it is based on vaginal colonization, unless the number of subjects studied is very large. In a study of over 300 women who were delivered consecutively, no association was seen between detection of genital *M. hominis* and postpartum fever.²²¹ However, Harrison et al.¹⁸⁵ evaluated 1365 pregnant women and reported that *M. hominis*, but not the ureaplasmas, was associated with fever and/or endometritis after vaginal delivery (relative risk 7.3). Furthermore, Berman et al.²²² studied more than 1200 Navajo women and found that those undergoing cesarean section had a higher rate of postpartum endometritis if *M. hominis* was present on predelivery endocervical culture. The association between vaginal colonization and postpartum fever is likely to be seen best when there is prolonged labor and prolonged rupture of the membranes.²²³

Employing protected transcervical catheters, Eschenbach et al.²²⁴ found that *G. vaginalis* was the most common endometrial isolate in early febrile postpartum women, but that nearly 20% had ureaplasmas as a sole isolate. From 3 of 18 such patients, ureaplasmas were also isolated from the blood. Jones and Tobin²²⁵ avoided the vagina and cervix by examining the amniotic surface of placentas obtained at cesarean section; they found that patients whose placental cultures were positive for *M. hominis* or ureaplasmas were more likely to be febrile after delivery than those who had negative cultures. Williams and associates²²⁶ studied intraoperative transabdominal specimens from women undergoing cesarean sections and found that ureaplasmas were isolated from the amniotic fluid and lower intestinal segment of 5 (25%) of 20 and 6 (42%) of 15 febrile women, respectively, compared to none of 49 and 4 (10%) of 40 afebrile women cultured at these sites. There was a high degree of co-isolation of virulent bacteria with the ureaplasmas, suggesting that the latter might play a symbiotic role in the pathogenesis of endometritis following cesarean section or could possibly just be a marker of the disease or of other organisms associated with bacterial vaginosis.

Finding genital mycoplasmas in the blood is perhaps the best way of establishing a relationship between the organisms and fever; however, many commercially available blood culture systems do not support mycoplasma growth due to the addition of sodium polyanetholesulphonate (SPS). Genital mycoplasmas as well as other vaginal microorganisms can be found transiently in the bloodstream following vaginal delivery, but this transient invasion has not been associated with

postpartum fever.²²⁷ As detailed elsewhere, there have been many reports describing individual patients with postpartum fever, from whom *M. hominis* or the ureaplasmas were isolated a day or more after delivery.^{72,228} An antibody response was seen in nearly all cases with *M. hominis* infection.^{221,229} In one study,²³⁰ *M. hominis* was isolated from the blood of 9 (7%) of 125 febrile postpartum women, compared to none of 60 afebrile postpartum subjects ($p < 0.005$). Very rarely, *M. hominis* spreads, even in an immunocompetent postpartum woman, to an extragenital site such as the brain and causes a major problem.²³¹ In addition, the association of *M. hominis* with febrile abortions is undoubted. Thus, in one study,²³² *M. hominis* was isolated from the blood of 4 (8%) of 51 women who had febrile abortions but from none of 53 women who had afebrile abortions. Antibody responses to *M. hominis* were detected in 50% of the women who had febrile abortions but in only two (14%) of 14 women who had afebrile abortions. The role of *M. genitalium*, if any, in postpartum and postabortal fever has not been assessed.

From the above studies, we conclude that *M. hominis* is capable of causing postpartum and postabortal fever, and there is some but less evidence for ureaplasmas being involved. This assumes that these organisms have been recovered from the blood and other sites in pure culture, at least in a proportion of cases. Otherwise, it is possible that genital mycoplasmas, particularly *M. hominis*, might be no more than a marker for bacterial vaginosis and not have a role in their own right.

■ OTHER DISEASE ASSOCIATIONS IN MEN AND WOMEN

Sexually acquired reactive arthritis

Sexually acquired reactive arthritis (SARA) or the less common Reiter's disease, in which conjunctivitis also develops, occurs in men who have or have recently had NGU, and less often in women. The disease is seen most often in those who are genetically predisposed, that is, who have the HLA-B27 histocompatibility antigen. When exposed to infectious and, possibly, other stimuli, these individuals develop the disease. There is considerable evidence that *C. trachomatis* is capable of initiating this pathophysiologic process, based principally on the detection of chlamydial elementary bodies and chlamydial DNA in joint material from some patients with SARA.^{233,234} HLA-B27-positive men who have chlamydia-negative NGU are just as likely to develop arthritis as men who are chlamydia positive.²³⁵ This suggests that agents other than *C. trachomatis* associated with NGU may play a role in SARA and Reiter's disease, but the role, if any, of the ureaplasmas or *M. genitalium* in SARA or Reiter's disease is unclear. Serologic studies have been of limited utility,²³⁶ and evidence for the involvement of ureaplasmas, not entirely convincing, is based on a specific response of synovial

mononuclear cells to ureaplasma antigens.^{237,238} Attempts to isolate mycoplasmas by cultural procedures from diseased joints have not been fruitful. However, using a PCR assay, *M. genitalium* was detected in the joints of 2 of 13 patients with arthritis, one with Reiter's disease and one with rheumatoid arthritis,²³⁹ and the results of further attempts to detect this mycoplasma and to seeking ureaplasmas by such technology are awaited.

Association of mycoplasmas with immunodeficiency states and HIV

Patients with primary antibody deficiency disorders, agammaglobulinemia, and hypogammaglobulinemia, are particularly susceptible to extragenital *M. hominis* and ureaplasma infections, and there are reports of several different species being involved in sinusitis, pneumonia, cystitis, cellulitis, osteomyelitis, suppurative arthritis, and subcutaneous abscesses.^{240–242} In some patients, the arthritis responds to antibiotic therapy, whereas in others, the disease persists and so do the organisms in the joints for many months, despite antibiotic and antiinflammatory treatment, and γ -globulin replacement.²⁴³ *M. hominis* and the ureaplasmas have also been implicated in infections of the vascular system, sternal wounds, the central nervous system, joints, and the respiratory tract, particularly after immunosuppressive therapy and after organ transplantation.^{244,245} Thus, suppressed cell-mediated immunity or antibody deficiency, or both, promote mycoplasma infections at extragenital sites. Given the immunologic defects among subjects with AIDS, it is not surprising that genital mycoplasmas would be more often detected among HIV-infected versus noninfected individuals. Indeed, Cohen et al.²⁴⁶ reported that HIV infection was associated with an increased risk of *M. genitalium* infection (adjusted HR = 2.2, CI₉₅ 1.2–3.5) among a cohort of sex workers in Nairobi, Kenya. *M. genitalium* has also been detected more often in endometrial biopsies from HIV-infected than HIV-uninfected women (19.1% versus 4.6%).²⁴⁶

In the late 1980s, investigators in the United States raised the possibility that a novel *Mycoplasma* spp., originally called *M. incognitus* and subsequently found to be *M. fermentans*, was an important cofactor in the pathogenesis of AIDS.^{247–252} This organism was detected in a significant number of tissues and organs in patients with AIDS in some,²⁵¹ but not other,²⁵³ studies. Supporting the contribution of an antibiotic susceptible agent in AIDS progression was the observation that tetracyclines or a fluoroquinolone inhibited the cytopathic effect induced by HIV-1 or 2 in lymphoblastoid leukemic cells without suppressing virus growth,^{254,255} a finding consistent with the observation that various mycoplasmas in cell cultures enhance HIV replication and are able to bring about cell death.^{256–259} Thus, several

investigators postulated that *M. fermentans* (and other mycoplasmas) could enhance the proliferation of HIV *in vivo* by stimulating immune activation, lymphocyte proliferation, cytokine production, and HIV-LTR-dependent gene expression.^{260–268} However, the hypothesis that *M. fermentans* is an important cofactor in AIDS pathogenesis was muted by the finding that this mycoplasma was detected in only a small subpopulation of HIV-positive patients,^{269,270} its prevalence was similar in HIV-positive and HIV-negative subjects,²⁷¹ there was no significant association between the occurrence of *M. fermentans* and disease severity in the HIV-positive subjects, and there was no association between the presence of this mycoplasma and viral load.²⁷¹ Currently, there is no consistent evidence implicating the role of *M. fermentans* nor *M. penetrans*, another species originally detected in HIV-infected individuals,²⁷² in the development or progression of AIDS. Although the results of *in vitro* studies indicate the ways in which *M. fermentans* and other mycoplasmas could hasten the onset and progression of AIDS, as yet there are few indications from studies *in vivo* that this is a reality. We conclude that these organisms may in fact be opportunists that are able to proliferate among subjects suffering from immunosuppression mediated by HIV.

Other Mycoplasma spp. identified in the human urogenital tract

In addition to *M. fermentans* and *M. penetrans*, other *Mycoplasma* spp. have been detected in genital tract specimens. Some, such as *M. primatum* and *Acholeplasma oculi*, are detected very infrequently and are not known to be associated with disease.²⁷³ *M. pirum*, which was isolated originally only from cell cultures and then from cells that had been cocultivated with peripheral blood lymphocytes of AIDS patients,²⁷⁴ has been detected subsequently using PCR technology, in the rectum of homosexual men,²⁷⁵ but its role in disease, if any, is unknown. Similarly, *M. pneumoniae*^{276,277} and *M. spermatophilum*²⁷⁸ have been detected in human genital tract specimens, but have yet to be associated with disease at these sites. *M. amphoriforme*,²⁷⁹ the most recently isolated mycoplasma of human origin, has been isolated from the respiratory tract, but its recovery from the urogenital tract has not so far been reported.

■ DETECTION AND CULTURE OF GENITAL MYCOPLASMAS

Collection of Specimens

The collection of specimens for culture of *M. hominis* and ureaplasmas in the male genitourinary tract can be successfully accomplished using a urethral swab specimen and/or a first-void urine specimen.²⁸⁰ Vaginal and endocervical swab

specimens are likely to be more satisfactory than urine specimens for recovering these organisms from women,²⁸⁰ and avoiding antiseptics, analgesics, or lubricants is important.²⁸¹ Swabs should be expressed immediately in mycoplasma broth or another suitable transport medium such as 2SP medium without antibiotics. In temperate climates, mycoplasmas survive well for at least 24 hours at room temperature if transported in 2SP or mycoplasma broth. However, because of the rapid growth of ureaplasmas, specimens for quantitative cultures should be transported at 4°C.²⁸⁰ If room temperature transportation is chosen, overgrowth of other bacteria could be a problem, but addition of polymyxin B (50 µg/mL) and penicillin G (100 U/mL) to the transport medium may suppress most of the contaminating flora. Urines should preferably be transported directly to the laboratory or transported at 4°C within 24 hours. Culture of *M. genitalium* is considerably more difficult than culture of the ureaplasmas or *M. hominis*, but can be accomplished from male urethral or urine specimens as outlined below.

For specimens to be examined in nucleic acid amplification tests (NAATs, ex. PCR), viability is not important, and thus these specimens can be transported in phosphate-buffered saline (pH 7.2), 2SP, SP4, or other media found to be compatible with the subsequent detection assay. If transport medium is not available, or if vaginal specimens are analyzed, the swab may be transported “dry” to the laboratory, preferably within 24 hours, then frozen dry or in transport medium until analysis. The relative performance of different specimen types (ex. urethra vs. urine for men and cervix, vagina, or urine for women) for detection of *M. genitalium* by NAATs has been assessed (see below), but may depend upon the sample preparation procedure as well as the NAAT assay used.

Culture

The isolation of mycoplasmas has traditionally depended on a medium comprising beef-heart infusion broth, available commercially as PPLO broth, which supplies amino acids, supplemented with fresh yeast extract supplying nucleic acid precursors, horse serum providing the essential cholesterol, and phenol red as a pH indicator to monitor growth.²⁸⁰ This medium is supplemented either with arginine or urea for the growth of *M. hominis* or ureaplasmas, respectively. Other sera, such as fetal calf serum, may improve growth, and media of quite different formulations have been used satisfactorily for the isolation of both mycoplasmas and ureaplasmas.²⁸³ In particular, SP4 medium, developed originally to cultivate spiroplasmas, has improved the isolation of not only the more fastidious mycoplasmas,²⁸⁴ but also those more easily isolated, such as *M. hominis*.²⁸⁵ Alternatively, H broth, a simple medium composed of soy peptone, yeast extract, and horse serum, has been used successfully by other researchers.²⁸⁶ It is important to note, however, that the mere

fulfillment of a particular medium formulation is unlikely to be successful without systematic work on improvement of the quality; different manufacturers and even lot numbers of undefined components may drastically influence the ability to culture these organisms. Therefore, pretesting of medium components for their ability to support growth and maintaining rigorous quality control, using a fastidious isolate, are important features of successful isolation.

Inoculation of specimens into liquid medium, which is diluted serially, followed by subculture to liquid or agar media, provides the most sensitive method for isolation of ureaplasmas.²⁸⁷ Thus, the specimen is inoculated in liquid medium to make a 10-fold dilution, further serial 10-fold dilutions are made to at least 10³, and the vials are incubated at 37°C. As ureaplasmas possess a urease that hydrolyzes urea to CO₂ and ammonia, their growth results in a color change in the medium, set initially at pH 6.0, from yellow to pink. We have recently used a soy peptone-based broth for this purpose,³³ the formula for which is described in detail elsewhere.⁵⁴

To detect *M. hominis* in broth, the specimen is diluted in broth similar to that used for ureaplasmas except containing arginine, rather than urea. *M. hominis* metabolizes arginine with the resulting release of ammonia, also resulting in an increase in pH, initially set at 7.0, and a color change from yellow to pink. Ureaplasmas usually produce a change within 24–48 hours or less and rarely thereafter, *M. hominis* less rapidly, but usually well within a week. Serial dilution of specimens is valuable for various reasons, most notably for diluting antibiotics and other inhibitors of growth in the original specimen, for reducing the number of contaminating bacteria, and for providing an estimate of the number of organisms in the original specimen; thus, the highest dilution at which a color change is seen may be regarded as containing one color-changing unit (ccu).²⁸⁷ As an example, a change up to the 10⁵ dilution suggests that the original specimen that was inoculated contained 10⁵ ccu (or 10⁵ organisms).

To confirm the identity of the cultured mycoplasma, aliquots (0.1 or 0.2 mL), taken from liquid cultures that are just changing color, are introduced into fresh broth medium and onto agar medium. On the latter, colonies of the genital mycoplasmas may develop in ambient air, in CO₂ or in N₂ plus 5% CO₂. Those of *M. hominis* have the classical “fried egg” appearance and are up to 200–400 µm in diameter (Fig. 41-2). Ureaplasmas produce much smaller colonies, 10–30 µm in diameter, which usually do not have a “fried egg” morphology because they lack the peripheral surface growth. On agar medium containing urea, HEPES buffer, and a sensitive indicator of ammonia, that is manganous sulphate or better still calcium chloride, ureaplasmas produce colonies that are slightly larger and dark brown so that they are easier to detect (Fig. 41-2).^{288,289} However, because these colonies are so tiny, scanning the agar medium with a dissecting

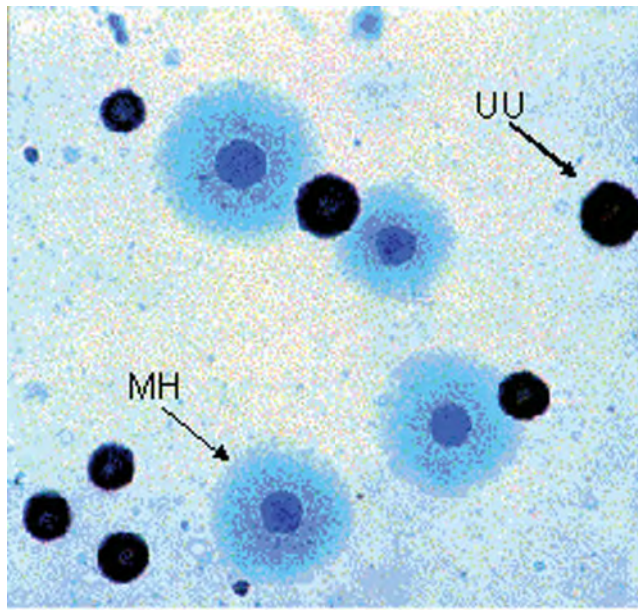


FIGURE 41-2. Differentiation of colonies of *Ureaplasma* spp from those of *M. hominis* resulting from inoculation of a clinical specimen from a patient with NGU. The colonies have developed on A7 agar medium (containing urea, ampicillin, and manganous sulfate). The brown/black colonies of the ureaplasmas can be easily distinguished from those of *M. hominis*, which have a typical mycoplasmal “fried egg” appearance and appear blue after the addition of Dienes strain. (Figure courtesy of *Trends in Microbiology and JD Pollack*.⁴⁰⁷)

microscope is required for detection, a labor-intensive exercise. We recommend A8B plates for growth of ureaplasmas and *M. hominis* as we have described previously.³³ On these plates, which contain 1.0 mM rather than 1.5 mM calcium chloride as an indicator, dark brown ureaplasma colonies can be detected more easily.

Commercial kits designed for the isolation, quantitation, identification, and antimicrobial susceptibility testing of *M. hominis* and ureaplasmas are available in several European countries and sold, for example, by bioMérieux, Marcy l’Etoile, France, but are unavailable in the United States. Specialist laboratories are likely to have media of superior quality, but successful use of the kits has been reported and they may be of particular value where the need to detect these microorganisms arises infrequently.^{290,291} No commercially available kits or media are available for the growth of *M. genitalium*.

Cultured organisms require specific identification, and certain nonspecific features that are determined routinely during the course of isolation may give a lead. Thus, a specimen from the genitourinary tract that produces an alkaline color change without turbidity in medium containing arginine is most likely to contain *M. hominis*, and one that produces a similar change in medium containing urea is almost certain to contain ureaplasmas. Such clues narrow the range of specific antisera required to make a definitive identification. Incorporation of such antisera in filter-paper discs on agar to inhibit colony development (agar growth inhibition)²⁹² is

widely used, but more than one antiserum to a species may be required to identify various strains of that species. Epiimmunofluorescence or immunoperoxidase techniques used to stain colonies are advantageous in enabling different ureaplasma serovars or, indeed, mycoplasmal species to be distinguished in mixtures.²⁹³ Alternatively, and perhaps more easily, depending upon the laboratory, PCR assays for *M. hominis*, *U. urealyticum*, and *U. parvum* can be used to identify the cultured mycoplasmas.

Contrary to the experience with *Ureaplasma* spp. and *M. hominis*, culture of *M. genitalium* by primary inoculation of conventional mycoplasma media has rarely been successful. A method of inoculating the clinical specimens into Vero cell cultures²⁹⁴ and monitoring the growth by PCR allowed the successful isolation of more than 20 *M. genitalium* strains shown to be genotypically distinct.^{22,37,294} The method has been optimized by the use of quantitative PCR³⁷ which allows a closer monitoring of the growth. In brief, the swab or freshly obtained urine specimen is washed by resuspending the cell pellet in mycoplasma broth after centrifugation and in cell culture medium after a subsequent centrifugation step. The washed specimen is inoculated into Vero cells grown in Eagle’s MEM with 2% Ultrosor G and incubated at 37°C with daily inspection for bacterial contamination. When, after 2–3 weeks, approximately 50% of the cells detach from the surface, the remaining cells are scraped off, and 1 mL of the cell suspension is added to 2 mL of fresh cells and the incubation is repeated. When the *M. genitalium* titer, determined by quantitative PCR, is >100,000 copies/mL, Friis’ broth medium without antibiotics²⁹⁴ is inoculated with the cell culture to provide a 10-fold dilution of the latter. When good growth in broth medium is observed, passage onto solid medium may be attempted, but usually, several passages in broth are needed before colonies will form on agar. It is not recommended to use the G37 strain as a positive control during the isolation attempts, since this strain is very fast growing and may contaminate the new isolates.²⁸ DNA typing of the new isolate in comparison to the DNA type in the inoculum is highly advisable in order to document the absence of cross-contamination between strains. There have been reports of the isolation of *M. genitalium* directly in SP4 medium, notably from the respiratory tract, from a joint fluid in a mixed culture with *M. pneumoniae*, and from vaginal and cervical specimens.^{295–297} However, based on the ability of these strains to grow after only 14–20 days incubation and their genotypic similarity to G37, concerns have been raised about the validity of these presumptive novel isolates.^{37,298,299} For validation we recommend the system developed by Jensen et al.³⁷ because it is easily performed by sequencing the amplicons generated by the standard PCR assay used to detect this organism and is conserved between sexual partners and between specimens obtained months apart from the same patient.²² A detailed description of

methods to isolate clinical strains of *M. genitalium* has been published recently.³⁰⁰

Noncultural methods of detection

Noncultural procedures have enhanced the appreciation of the disease associations of genital mycoplasmas, particularly by those, such as *M. genitalium*, that are almost impossible to culture directly from patient specimens. While such tests are sometimes essential for detection of these fastidious organisms, culture still remains a worthy goal since it allows the assessment of antibiotic sensitivity or other biological features of the infecting strain. NAATs are the most widely used and will be described below.

Use of the two PCR tests for *M. genitalium* developed in 1991^{26,27} resulted in the association of this organism with NGU.^{28,29,301} Subsequently, many different PCR tests have been developed to detect this emerging pathogen.³¹ Most target the MgPa adhesin gene,^{26,27,34,36,302,303} undoubtedly because it was the first to be sequenced, or the rDNA gene,³⁰⁴ of which there is only one copy in the limited *M. genitalium* genome. Several of these PCR assays^{302,304} contain internal controls to assess PCR inhibition. More recently, a research-only transcription-mediated amplification assay specific for *M. genitalium* has been developed by Gen-Probe, Inc.,^{305,306} but this test is not yet commercially available. Finally, quantitative PCR assays, targeting the *gap* gene in the glycolysis pathway,³⁸ the MgPa adhesin gene,³⁰⁷ or the 16S rDNA gene³⁷ have been developed and have been used to assess growth in vitro as well as the organism load in patient specimens relative to treatment efficacy and to signs and symptoms of disease.

The relative performance of the different NAATs depends not only on the sample preparation method, the target sequences, and the detection methods, but also on the sample type used for analysis. Among men, urine was more sensitive than urethral specimens for detection of *M. genitalium* in one study,³⁰⁸ but these specimen types were comparable to each other in another (Totten, unpublished). A comparison of vaginal, cervical, and urine specimens from women, all analyzed by both PCR and TMA, served to validate both assays and establish that self-obtained vaginal specimens were the most sensitive specimen type for detection of this organism in this study,³⁰⁶ a finding that would facilitate specimen collection in nonclinic settings. Indeed, self-obtained vaginal swabs are well accepted by women and have been successfully used for home-based self-collection, with subsequent testing for *C. trachomatis* after the swab was placed in the provided container and mailed to a reference laboratory.³⁰⁹ Undoubtedly, a similar strategy could be used to enhance detection of *M. genitalium* in future studies.

PCR methods for *Ureaplasma* spp. and *M. hominis* have not been as extensively developed, probably because these organisms are much easier to detect in patient specimens by

culture. Importantly, PCR assays targeting the urease or 16S rDNA genes of the ureaplasmas are able to distinguish the newly designated species, *U. urealyticum* and *U. parvum*, in patient specimens and have allowed the assessment of the association of these two species with NGU in men.^{310–312} Yoshida et al.^{310,312} developed a PCR assay designed to amplify a broad range of mollicute species within patient specimens, but its sensitivity relative to species-specific PCR assays has not been assessed.

Serology

Detection of antibodies to individual mycoplasmal species is useful when assessing the prevalence of these organisms within a subpopulation or geographic site, when genital tract specimens are not available for analysis, and when assessing the association of these organisms with sequelae of infection. However, detection of mycoplasma-specific antibodies in a single serum specimen is of less diagnostic value than demonstrating a rise in titer of antibodies associated with symptoms, and cross-reactions with other mycoplasmas need to be ruled out. Many serological tests have been used to measure antibodies to mycoplasmas and differ in the antigen and technique used to detect reactivity, sensitivity, and specificity. The complement fixation, indirect hemagglutination, indirect immunofluorescence, and metabolism-inhibition tests have all been used to detect antibodies to mycoplasmas in human sera but are not currently widely employed, either due to the complexity of the test, specific expertise required, or the lack of sensitivity or specificity.⁷² However, these tests have been used to detect antibodies to ureaplasmas in two-thirds of patients with NGU,³¹³ to *M. hominis* among women with acute salpingitis,¹²¹ and to *M. genitalium* in women with salpingitis.^{287,314} Devising *M. genitalium*-specific serologic tests is particularly challenging, given the cross reactivity between *M. genitalium* and *M. pneumoniae* antibodies.^{98,315–317} Fairly recently, an enzyme immunoassay, based on lipid-associated membrane proteins (LAMPs) to measure antibody to *M. genitalium*, was developed and showed a high sensitivity (15 positive/15 specimens from *M. genitalium*-positive subjects) and specificity (64 negative/64 blood donors tested) relative to genital infections detected by PCR.³¹⁸ Clausen et al.⁹⁸ used a cloned portion of the MgPa adhesin gene of *M. genitalium* and an immunoblot assay to demonstrate a lack of cross-reactivity with *M. pneumoniae* antibodies, and then showed that seropositivity was associated with tubal-factor infertility. This test was further refined by incorporating other *M. genitalium*-specific recombinant peptides, then assessed relative to a LAMP-based ELISA test among *M. genitalium* infected and uninfected men (detected by PCR) with and without urethritis.³¹⁹ This test was 59% sensitive and 81% specific relative to *M. genitalium* infection in men and should prove useful for assessing the association of *M. genitalium* with sequelae of infection. No serological

tests for urogenital mycoplasmas have been standardized and made commercially available.

Strain typing and serotyping

Several methods have been developed to differentiate between strains of *M. genitalium*. This was performed initially by amplified fragment length polymorphisms applied to whole cell DNA from cultured *M. genitalium* strains.²⁹⁸ However, the need for culture was eliminated by detection of sequence polymorphisms within PCR products specific for *M. genitalium* derived directly from PCR amplification of patient specimens.^{37,299} These sequence-based typing systems, one based on polymorphisms within the MgPa adhesin gene (also designated MGpB and MG191), the other based on the number of tandem repeats in the lipoprotein gene MG309, are stable over time in persistently infected individuals, allowing the demonstration of concordance among sexual partners, consistent with sexual transmission of *M. genitalium*.²² A fourth typing system based on polymorphisms within the variable region of MG192,³²⁰ should be used with caution because the portion of this gene analyzed has been shown to be highly variable within isolated strains.³²¹

The ureaplasmas have been traditionally differentiated into 14 serotypes based on reactivity with polyclonal antibodies, with serotypes 1, 3, 6, and 14 now classified as *U. parvum* (formerly biovar 1) and types 2, 4, 5, and 7–13 classified as *U. urealyticum* (formerly biovar 2). This differentiation has allowed the assessment of the disease associations and relative pathogenicity of the cultured serotypes, which remains controversial.^{322–324} Possible variability in different preparations of polyclonal antibodies may be resolved by using serotype-specific monoclonal antibodies,^{325,326} although this has not been extensively analyzed. Hopefully, future studies based on DNA typing,³²⁷ serotyping, or expression of specific virulence factors in different isolates may clarify differences in pathogenicity among ureaplasma strains.

■ PATHOGENESIS

The ability of mycoplasmas to colonize and elicit pathological changes in the human host depends upon a complex set of interactions between the organisms and host. For example, the organisms must be able to adhere to host tissues, to attenuate or escape the innate and adaptive immune response of the host, and, as a special adaptation to the reproductive tract, adjust to changes in host tissue occurring as the result of the cyclical effect of hormones. Although much needs to be learned about bacterial/host interactions, some of the strategies used by *M. genitalium*, *M. hominis*, and the ureaplasmas to survive in this unique anatomical niche will be discussed below.

M. genitalium

The ability of *M. genitalium* to elicit pathological changes and persist in infected subjects is remarkable given its small genome size (580 kb) and limited predicted coding capacity (approx 500 predicted proteins). Even more astonishing is this organism's ability to encode a complex attachment organelle composed of an ordered array of at least seven proteins, required both for adherence to host cells and for cellular locomotion. Although the biogenesis and function of many of the proteins comprising this organelle are not fully understood, two, MgPa (aka MG191 and P140) and P110 (aka MG192), have been the most studied, primarily by Baseman et al.^{328–333} Both MgPa and P110 are highly immunogenic and are required for adherence to host cells. MgPa is the primary adhesin of *M. genitalium* for host cells and is exposed on the bacterial cell surface,^{329,334–337} but the specific function of P110 is currently unknown. However, as demonstrated by using defined mutants in these genes, expression of both MgPa and P110 is required for the typical structure and function of the attachment organelle (Fig. 41-3).³³⁸ Furthermore, the “gliding motility” of *M. genitalium* is also mediated by the structural components of the attachment organelle as well as at least two proteins specific for motility.³³⁸

The attachment organelle of *M. genitalium* is similar to a homologous appendage of *M. pneumoniae* in which the structure and function of its component proteins have been best characterized, including host cell adherence and motility.^{339–344} Presumably, due to the homology of the attachment organelle genes between *M. pneumoniae* and *M. genitalium*,³⁴⁵ a similar mechanism for motility exists in the latter. How motility relates to virulence in *M. genitalium* has not been described, although presumably it contributes to expanded surface colonization and perhaps translocation through cervical or vaginal mucus to the underlying tissue.

Despite the surface exposure and antibody accessibility of MgPa (and possibly P110), single strains of *M. genitalium* are able to persist for months, if not years, in infected individuals.^{22,246} However, the finding that both MGpB and MGpC vary within single strains of this organism cultured in vitro or detected in vivo^{321,346,347} suggests a mechanism for immune evasion and persistence. A mechanism for this variation was first evident in the study by Dallo and Baseman,³²⁸ who determined that specific sections of MGpB were homologous to sequences present at other sites on the *M. genitalium* chromosome. Subsequent studies^{2,321,346,347} revealed that full-length copies of MGpB and MGpC are present at only one site, yet nine incomplete copies, designated MgPar sites that are homologous but not identical to these genes, are distributed throughout the chromosome (Fig. 41-4A). These MgPar sites contain sequences that are homologous, but not identical to sequences within three regions (designated B, EF, and G) of MGpB (see Fig. 41-4B)^{346,347} and to the 5' region of

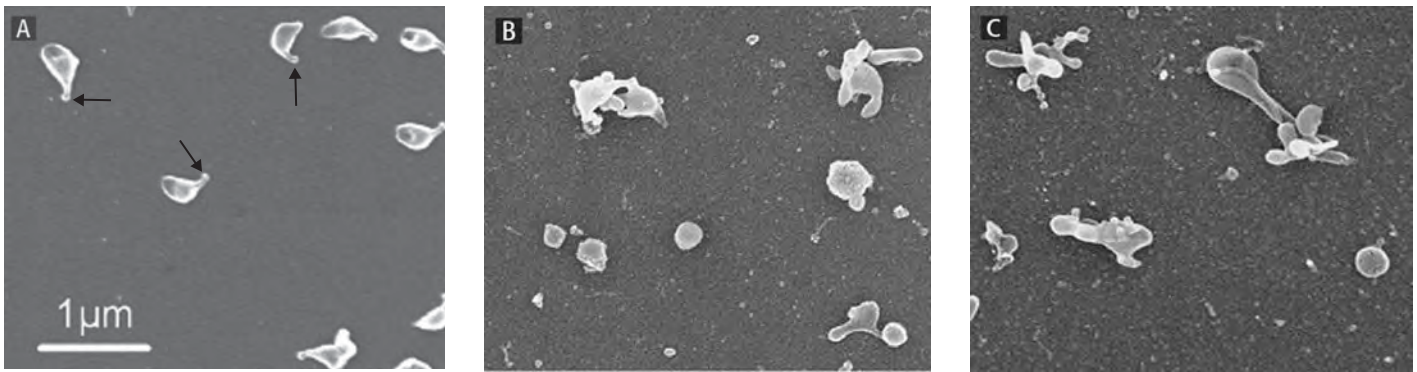


FIGURE 41-3. Scanning electron micrographs of *M. genitalium* type strain G-37 and its derivatives: **A.**, G37; **B.**, a *mgpB* deletion mutant; and **C.**, a *mgpC* deletion mutant, showing that expression of the characteristic structure of the terminal attachment organelle is dependent upon expression of *mgpB* and *mgpC*. Unlike the wild type G-37 strain, the *mgpB* and *mgpC* mutants have a rounded, pleomorphic morphology lacking the typical attachment organelle structure, are deficient in adherence to red blood cells, and have decreased levels of both MgPa (designated as P140 in this study) and P110.³⁵⁵ Arrows point to the attachment organelle in the wildtype G-37 strain. (Figure courtesy of J. Piñol, and further described in the study by Burgos et al.³⁵⁵)

MgPc³²¹ and mediate sequence variation within *mgpB/mgpC* by reciprocal recombination³²¹ possibly contributing to the heterogeneity of these genes, antigenic variation of the resulting proteins, and persistence in vivo.

In addition to the ability of *M. genitalium* to attach to epithelial cells, exhibit gliding motility, and perhaps express antigenic variants, other virulence-associated phenotypes have been characterized. *M. genitalium* is able to attach to mucin,³⁴⁸ and reside intracellularly within epithelial cells.^{329,349–351} An antioxidant repair enzyme, methionine sulfoxide reductase,³⁵² and a surface-localized glyceraldehyde-3-phosphate dehydrogenase³⁴⁸ have been identified, the former enhancing survival in the hamster model and the latter mediating binding to mucin.

Ureaplasma spp.

The requirement for urea as an energy source makes *Ureaplasma* spp. uniquely suited to the urinary tract where this compound is abundant. Although ureaplasmas lack the complex attachment organelle of *M. genitalium*, several cell-surface proteins have been identified and adherence to eukaryotic cells has been demonstrated. However, the specific adhesins that enable these organisms to attach to eukaryotic cells,^{353,354} and presumably withstand the clearing action of urination, have been elusive. The multiple-banded antigens (MBA) are surface-exposed immunodominant proteins that differ in size and sequence among different serovars and are thought to provide the serotype specificity both among and between *U. urealyticum* and *U. parvum* strains.^{327,355–359} Remarkably, the 3' two-thirds of this gene contains 18-nucleotide tandem repeats that are identical in sequence, but variable in repeat number within a single strain,³⁵⁵ suggesting a possible role in differential antigenicity, phase variation, or function. Several potential virulence factors have been identified in the fully sequenced strain of

U. parvum,⁵ but their phenotypic expression, role, and presence in different strains and serotypes of both *U. parvum* and *U. urealyticum* have not been determined. Perhaps the imminent whole genome sequencing of all 14 ureaplasma serovars, including the first whole genome sequence of *U. urealyticum* (John Glass and Ken Waites, personal communication), might reveal species and serotype differences between these, and other as yet unidentified, potential virulence factors that might enhance knowledge of the pathogenesis of this group or organisms.

The pathogenic effect of ureaplasmas on tissue cultures and in animal models has also been studied. Ureaplasmas of bovine origin were reported to cause a loss of ciliary activity in bovine oviduct organ cultures, an effect suggested to be due to a putative toxin-like product.^{360,361} However, such a change was not seen with ureaplasmas in fallopian tube organ cultures.¹²⁷ Nevertheless, several ureaplasma metabolites and extracellular enzymes may have the capacity to damage eukaryotic cells. Several groups have identified a proteolytic activity that is specific for human IgA1, but not human IgA2, nor IgA from mice, pigs, or dogs,^{362–365} presumably enhancing survival by immune evasion in mucosal secretions. However, the possible role of this enzyme in virulence or persistence or in cleaving targets other than IgA (such as has been demonstrated for the gonococcal IgA protease³⁶⁶) has not been examined. In addition, the production of ammonium ions and the local changes in pH as a result of urea hydrolysis may have a role in pathogenicity.^{367,368} The enhanced colonization of ureaplasmas mediated by estrogen treatment in the mouse model,³⁶⁹ possible serotype-specific differences between colonization between strains,³⁷⁰ and the ability of ureaplasmas to recruit inflammatory cells and induce a local cytokine response need further study. Clearly, much needs to be learned about the pathogenicity and apparent differential virulence of ureaplasma species, serotypes, and strains.

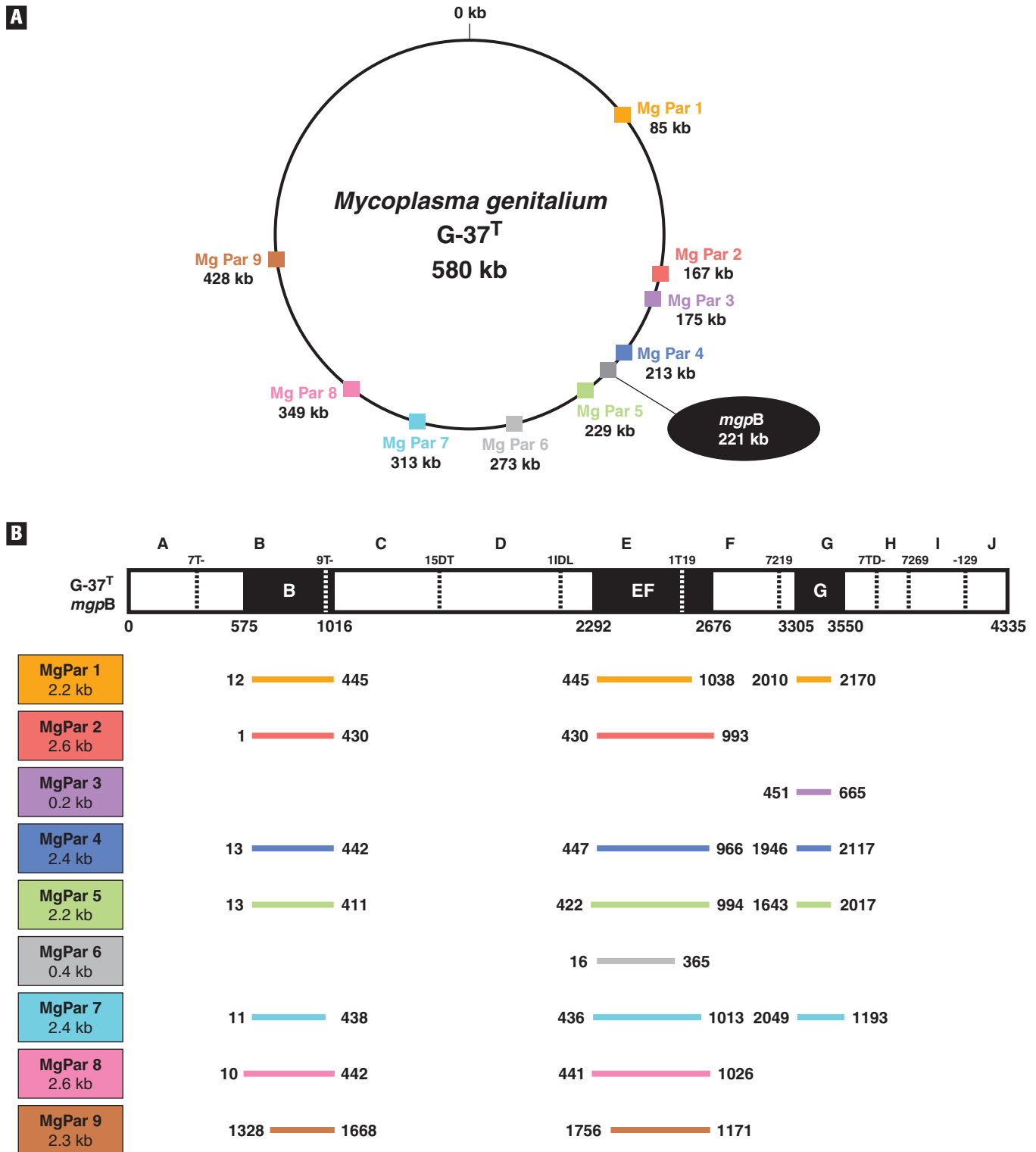


FIGURE 41-4. Schematic drawing of the *mgpB* and the MgPar sites, showing their architecture and the location of these sites on the *M. genitalium* genome. **A.** Location of the nine MgPar sites and the *mgpB* expression site in the completely sequenced G-37^T genome. **B.** Schematic of *mgpB* and the nine MgPar sequences showing that only portions of *mgpB* (regions B, EF, and G, designated in black boxes) are homologous to the MgPar sites, while the remainder of *mgpB* is unique to the expression site. Below the schematic of *mgpB*, each of the nine MgPar sites is listed with their corresponding sizes. Sequences within each MgPar site containing homology to *mgpB* are shown diagrammatically by a colored line, placed relative to the location of the homology with *mgpB*. Note, by the numbering indicating the consecutive order of the sequences within each MgPar site, that these sites contain incomplete copies of *mgpB* and regions homologous to B, EF, and/or G, but not the intervening sequences of *mgpB*. (Figure courtesy of Infection and Immunity³⁴⁷ and Stefanie Iverson-Cabral.)

M. hominis

Several adhesins and possible antigenic variants in surface exposed proteins of *M. hominis* have been characterized.^{371–377} Attachment to eukaryotic cells, demonstrated with a variety of cell lines including HeLa cells, is believed to be due to surface-exposed proteins because treatment of *M. hominis* with trypsin and pronase reduces adherence.³⁷⁸ Two proteins, the P100 and the Vaa antigen (variable adherence-associated antigen, aka P50), have been identified as adhesins based on inhibition experiments with monoclonal antibodies and purified proteins. The Vaa antigen is perhaps the best studied and contains one to four copies of tandem homologous, but not identical, cassettes of 121 amino acids. The number of copies of this cassette varies within a single strain, resulting in size-variant proteins.^{374,376} In addition, the C-terminus of this protein is highly divergent between strains, possibly contributing to evasion of antibody-mediated immunity and differential adherence. Finally, this protein undergoes phase variation mediated by an insertion or deletion within a short tract of homopolymeric sequences in the 5' region of the coding sequence that causes a translational frameshift, the loss of detectable protein, and inability to attach to cultured human cells.³⁷² Two other surface-exposed proteins, P120 and Lmp, are encoded by genes that are variable, contain tandem repeats within their coding sequences, and have homologs at other sites on the chromosome. Undoubtedly, all three surface-exposed proteins contribute to the antigenic variation within this species, differential ability to attach to host cells, and persistence in vivo.

The pathogenic effect of *M. hominis* has been studied in organ cultures and in animal models. Inoculation of *M. hominis* into fallopian tube organ cultures caused a subtle change, namely ciliary clubbing, in one study,¹²⁸ but not others.^{127,181} The effect of hormonal changes in women, occurring during the menstrual cycle and pregnancy, on the natural history of *M. hominis* infection has not been examined, although there is evidence that hormones probably do have an effect based on observations made in animals. Thus, colonization of the genital tract of female mice was shown to be dependent on prior administration of estradiol, which induced the estrous phase of the cycle.³⁷⁹ Progesterone, which induced diestrus, did not render the mice susceptible.³⁸⁰ Indeed, progesterone given to estradiol-treated mice colonized by *M. hominis* converted the cycle to the diestrus phase and eliminated the organisms at least as effectively as tetracycline treatment.³⁸⁰ *M. hominis* in some mice persisted for more than 6 months, with spread to the uterine horns and ovaries in a few.³⁷⁹

In summary, much needs to be learned about the pathogenesis of the genital mycoplasmas. Gene variation, presumably resulting in antigenic variation, phase variation, and possibly differences in adherence, are common themes in

these organisms that are limited to animal hosts, including humans, for survival.³⁸¹ Interestingly, this variation is achieved by different mechanisms and by divergent surface proteins in the different species. The effect of hormone changes on colonization and pathogenesis of infection in humans is unknown. Identification and characterization of potential toxins and their effect on host cells, as well as the extent and effect of immune cell activation on the pathogenesis of infection remain challenges for studies elucidating the pathogenesis of these organisms.

ANTIMICROBIAL SUSCEPTIBILITY AND TREATMENT

SUSCEPTIBILITY PROFILES AND TREATMENT OF MYCOPLASMAL INFECTIONS

Mycoplasmas are resistant to all β -lactams and cephalosporins due to the lack of a cell wall. Rifampicin is also inactive.³⁸² Resistance to macrolides and tetracycline is variable among strains of the *Mycoplasma* and *Ureaplasma* spp. Notwithstanding, there are few outcome data documented in a controlled setting with microbiological information to assess the efficacy of antimicrobial treatment for *M. genitalium* infections. Clearly, such trials are needed.

As indicated earlier in this chapter, current data indicate that *M. genitalium* is a cause of NGU and possibly cervicitis, endometritis, and PID, so that antimicrobial therapy targeting this organism seems warranted. The usual treatment of NGU with macrolides or tetracyclines, appropriate for *C. trachomatis*, is also recommended for the treatment of *M. genitalium* by the U.S. Centers for Disease Control and Prevention.³⁸³ However, microbiologic and/or clinical treatment failures with these two antibiotics have been reported,^{42–44,46,48,384} a finding consistent with the association of this organism with chronic and recurrent urethritis^{44–47,385} as well the detection of strains with decreased susceptibility to the tetracyclines in vitro.^{386,387} Clearly, randomized treatment trials and susceptibility testing of contemporary *M. genitalium* strains are necessary to determine the optimal treatment regimens for this emerging pathogen.

Treatment of ureaplasmas in men with urethritis is controversial, given the variability in the association of this organism with reproductive tract disease between different studies. However, tetracycline-resistant *Ureaplasma* spp. have been detected^{382,388,389} and resistance is mediated by the *tetM* determinant which encodes a protein that binds to the ribosomes, protecting them from the actions of these drugs.^{70,390–392} The extent to which this resistance occurs undoubtedly varies geographically. Tetracycline resistance in *Ureaplasma* spp. has been associated with treatment failure in NGU,⁶⁸ although these studies were performed before the contribution of *M. genitalium* in NGU was appreciated.

Thus, patients with NGU who show no response to treatment with a tetracycline should be treated with an alternative antibiotic active against these organisms, for example, a macrolide (azithromycin or clarithromycin).³⁸²

Extragenital infections, often in immunocompromised hosts, are sometimes caused by multidrug-resistant mycoplasmas and ureaplasmas,³⁹³ making guidance of chemotherapy by in vitro susceptibility tests particularly important. In this situation, eradication of infection may be extremely difficult, requiring prolonged therapy, preferably with at least two antibiotics with different modes of action, even when the organisms show susceptibility. This difficulty highlights the fact that a functioning immune system plays an integral part in mycoplasmal eradication and, as mentioned before, inhibition but not killing occurs with most commonly used antimicrobial agents in concentrations achievable in vivo. Antimicrobial profiles of the genital mycoplasmas are available in several publications.^{71,386,394–397}

■ METHODS OF SUSCEPTIBILITY TESTING

Agar dilution, microbroth dilution, and the Etest have been used for testing the minimal inhibitory concentrations (MICs) for easily cultivable mycoplasmas. Agar dilution has been used extensively as a reference method because it is less sensitive to inoculum size, pH, and incubation time than the microbroth dilution method.^{398,399} In the agar plate method, multiple strains can be tested on each of several plates containing different dilutions of antimicrobials. In contrast, the microbroth dilution is more practical if testing fewer or occasional strains against a wide variety of antimicrobials, because one strain can be tested for susceptibility to several antimicrobials in the same microtiter plate. However, using carefully controlled techniques and standard procedures, the agar dilution and microbroth dilution provide similar results for various antimicrobials tested against *Ureaplasma* spp. and *M. hominis*.⁴⁰⁰ In addition, mycoplasmacidal, as opposed to static, activity can be tested directly by removing the mixture of organisms and antibiotic from the well of a microbroth dilution MIC assay, diluting it to a subinhibitory concentration in fresh medium, and looking for a color change as evidence of growth.⁴⁰¹ Detailed procedures for determining the minimal inhibitory and mycoplasmacidal concentrations for the mycoplasmas are available.⁴⁰² A modification of the microbroth dilution method is provided by commercially produced kits (bioMérieux), available in Europe for several years. These consist of microwells containing dried antimicrobials, generally in two concentrations, to classify a strain as susceptible, intermediate, or resistant.

The Etest (AB BIODISK, Solna, Sweden) agar gradient diffusion technique has produced results comparable to microbroth dilution for testing the susceptibility of the

ureaplasmas and *M. hominis* to various antimicrobials.^{403–405}

The Etest is simple, provides endpoints which do not move over time, and is most cost-effective if only a small number of antimicrobials or a few isolates are to be tested. Irrespective of methodology, lack of universally accepted standards and guidelines for susceptibility testing has led to diverse and often inconsistent susceptibility profiles for mollicutes, especially for the genital mycoplasmas. Furthermore, the correlation between in vitro MICs and in vivo microbiological cure is not completely established. Tetracycline-resistant *M. hominis* and *Ureaplasma* spp. can usually be distinguished by broth or agar-based methods since the resistant strains generally have MIC values of >2 µg/mL. Because tetracycline resistance is often encoded by the *tetM* gene in these organisms, direct detection of *tetM* by PCR provides an alternative method of identifying resistant organisms.⁴⁰⁶ Methods are currently under evaluation by the National Committee for Clinical Laboratory Standards (NCCLS) Subcommittee on Antimicrobial Susceptibility Testing of Human Mycoplasmas (Ken Waites, personal communication) to identify optimal methods for MIC testing of the ureaplasmas and *M. hominis*.

Due to the difficulty of culturing clinical strains of *M. genitalium*, antimicrobial susceptibility testing for this mycoplasma has been performed using the traditional broth dilution method on less than 10 strains.^{382,387,394,396,397} However, the development of improved methods for isolation³⁰⁰ and antimicrobial testing³⁸⁶ of *M. genitalium* should foster a better understanding of the antimicrobial profile of this species.

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Our knowledge of leukorrhea is unsatisfactory and incomplete. The majority of physicians neither appreciate the gross aspects of the condition nor discover the locality from which discharges arise, practically none of us possesses an adequate knowledge of the bacteria involved, and most clinicians admit that their curative efforts yield poor results.

Arthur H. Curtis, M.D. (1913)¹

DEFINITION

Bacterial vaginosis (BV) is the most prevalent cause of vaginal symptoms among women of childbearing age. Many primary care providers perceive BV as a trivial and ill-defined syndrome of uncertain etiology. These perceptions may explain why clinicians still commonly prescribe ineffective treatments for BV.

When it is symptomatic, BV produces slightly increased quantities of malodorous vaginal discharge. Although past conventional practice allowed the diagnosis of BV only after excluding other causes of vaginal discharge, such as trichomoniasis, vulvovaginal candidiasis, or cervicitis, these conditions can undoubtedly coexist with BV. Physical examination and analysis of vaginal fluid among women with BV reveal the following: a thin homogeneous, white, uniformly adherent vaginal discharge; elevation of the pH of vaginal fluid above 4.5; development of a fishy odor after mixing vaginal fluid with 10% (wt/vol) KOH; and “clue cells” on microscopic examination of vaginal fluid. Whereas Gram stain of normal vaginal fluid shows a predominance of lactobacilli, the Gram stain of vaginal fluid from a woman with BV shows a decrease or absence of lactobacilli and a predominance of Gram-variable coccobacilli consistent with *Gardnerella vaginalis* or anaerobic Gram-negative rods species. Culture of vaginal fluid reveals mixed flora that typically includes genital mycoplasmas, *G. vaginalis*, and anaerobic bacteria such as peptostreptococci, *Prevotella* spp., and *Mobiluncus* spp., and cultivation-independent methodologies reveal an even wider array of anaerobic bacteria, as discussed below. Biochemical analysis of vaginal fluid from

women with BV usually shows characteristic changes that are likely due to bacterial metabolism. The vaginal fluid contains an altered pattern of organic acids (e.g., increased succinate and decreased lactate) and abnormal amounts of putrescine, cadaverine, and trimethylamine that probably contribute to malodor. Mucin-degrading enzymes produced by Gram-negative anaerobic bacteria associated with BV are also abundant and are probably responsible for the increase in quantity of vaginal discharge. The pathogenesis of BV remains far from clear. Inflammation of the vaginal epithelium in the form of evident white blood cells is often, but not always, limited, and cytokine profiles characteristically deviate from those seen in the normal vaginal environment. The vaginal microbial ecosystem is clearly disturbed in BV, but whether this represents a true tissue or epithelial infection is unclear. Women with BV are at increased risk of prematurity and chorioamnionitis during pregnancy, pelvic inflammatory disease (PID), and pelvic infection following obstetrical or gynecological surgery, and, possibly, acquisition of genital herpes² and human papillomavirus.³

HISTORY

Nearly a century ago, Doderlein described a nonmotile bacillus, which he considered to be the normal flora of the vagina of pregnant women.⁴ The Doderlein bacillus later became known as *Lactobacillus*. In 1899, Menge and Kronig reported isolation of both facultative and strictly anaerobic microorganisms, as well as the Doderlein bacillus, from the vagina of most women.⁵ These early studies established that normal vaginal flora includes a mixture of microorganisms, with *Lactobacillus* spp. as the predominant species.

“Leukorrhea,” or white discharge from the vagina, became the focus of much research in the first quarter of the century. Some thought that vaginal discharge resulted from infection of the uterus and treated the condition by curettage of the endometrium. In 1913, Curtis demonstrated that the endometria of women with leukorrhea lacked a white discharge, thus suggesting a vaginal, not endometrial, origin. He

confirmed that the vaginal flora of clinically normal, married women consisted of Doderlein's bacilli and that the greater the deviation of vaginal flora from the normal state, the greater the likelihood of vaginal discharge. Curtis linked vaginal discharge with high concentrations of black-pigmented anaerobes, curved anaerobic motile rods, and anaerobic cocci, and with Gram-variable diphtheroidal rods, which probably represented *Gardnerella*. Curtis' 1913 paper established three central themes: (1) the discharge arose from the vagina and not from the uterus, (2) women having white discharge did not have large numbers of Doderlein bacilli, and (3) the presence of anaerobic bacteria in the vagina, especially anaerobic rods, correlated with vaginal discharge.

Research on vaginal flora continued in the early 1920s when Schroder reported three different types of vaginal flora, which corresponded to the "rheinheitsgrad" (grade of cleanliness) of the vagina.⁶ He considered the flora of the first group, dominated by acid-producing rods (Doderlein's bacillus), the least pathogenic. A second group had a mixed flora with Doderlein's bacillus in the minority. The third group, designated as the most pathogenic type of flora, had mixed vaginal flora without lactobacilli.

Despite observations by Curtis and Schroder linking vaginal discharge with a shift in the community of vaginal flora (from predominance of lactobacilli to predominance of anaerobes), other workers attempted to attribute the symptoms of nonspecific vaginitis to a single microorganism. In 1950, Weaver again reported a link between lack of lactobacilli, presence of anaerobes spp., and nonspecific vaginitis.⁷ However, the lack of association of other aerobic and facultative bacteria with abnormal vaginal discharge led him to conclude that no particular organisms caused this syndrome. The recognition of the association of *G. vaginalis* with nonspecific vaginitis by Gardner and Dukes in 1955⁸ (discussed below) provided the first clear evidence that *G. vaginalis* caused nonspecific vaginitis. However, because these investigators failed (erroneously) to find an association between other anaerobic bacteria and BV, workers over the next 25 years tended to ignore the potential role of microorganisms other than *G. vaginalis*.

Confusion surrounding the etiology of this syndrome has prompted the use of various names to describe BV. Prior to 1955, leukorrhea or nonspecific vaginitis was the term most frequently used. Gardner and Dukes first applied the name *Haemophilus vaginalis* vaginitis to this syndrome in 1955, and today some clinicians still use the term *Gardnerella* vaginitis or vaginosis; others have used the term anaerobic vaginosis.⁹ The term bacterial vaginosis is now relatively widely accepted, as BV is associated with vaginal overgrowth not only by anaerobic bacteria, but also by certain facultative bacteria, genital mycoplasmas,^{10,11} and a broad range of other microorganisms.¹² Since vaginal inflammation, as defined by neutrophil predominance in vaginal fluid, is not always seen

as a feature of this infection, the term "vaginosis" replaced the more familiar term "vaginitis."

EPIDEMIOLOGY

■ PREVALENCE OF BV AND ASSOCIATED MICROORGANISMS

Data on prevalence vary widely, because of differing diagnostic criteria and differences in clinical populations sampled as well as actual differences between populations. Relatively few nationally representative surveys have been performed. Recently, BV prevalence measured by the Nugent Gram's stain criteria was reported for women in the National Health and Nutrition Survey (NHANES),¹³ which uses a complex, stratified, multistage probability sample design with unequal probabilities of selection to obtain a nationally representative sample of the U.S. civilian noninstitutionalized population.¹⁴ Of over 12,000 women in the 2001–2004 NHANES who supplied a self-collected swab of vaginal secretions for Gram stain analysis by Nugent score, BV prevalence was 29.2% (95% CI 27.2–31.3, $p = 0.003$); only 15.7% with BV reported symptoms. Prevalence was 51.4% among non-Hispanic blacks, 31.9% among Mexican Americans, and 23.2% among non-Hispanic whites ($p < 0.01$ for each comparison). Detection of BV was also associated with increasing number of lifetime sex partners (chi square p for trend $p < 0.001$), a previous female sex partner ($p = 0.003$), douching frequency (chi square p for trend < 0.001), low educational attainment, poverty, smoking, high body mass index, and having been pregnant. Current use of oral contraceptive pills was inversely associated with BV prevalence. Significant differences by race/ethnicity remained after accounting for other risk factors. Among young women entering the U.S. military, BV prevalence in a large cross-sectional study was 27%.¹⁵ In a population-based sample of nearly 3000 women in Goa, India, BV prevalence was 17.8%.¹⁶

The prevalence of BV among pregnant women varies widely, as might be expected from the NHANES data, above. In one large study in the United States, 13,747 pregnant women at 23–26 weeks' gestation underwent evaluation for BV by standardized vaginal Gram stain criteria.¹⁷ While 16.3% of the women had BV, the prevalence varied widely by ethnicity, from a low of 6.1% of Asians, to 8.8% of white women, 15.9% of Hispanics, and 22.7% of black women. Other studies have found antenatal BV prevalence of 5% among asymptomatic Italian women,¹⁸ 12% in Helsinki,¹⁹ 14% in Denmark,²⁰ 21% in London,²¹ 14% in Japan, 16% in Thailand,²² and 17% in Indonesia.²³

In family planning clinics, BV prevalence was 14% among young Swedish women.²⁴ In Morocco, a three-city study of women with vulvovaginal or lower abdominal complaints showed BV based on clinical criteria in 19% of those attending

family planning clinics, and 24% of those attending primary health-care clinics.²⁵ In Lima, Peru, BV was detected in 25% of asymptomatic women seen in family planning clinics, and in 23% of asymptomatic women and 37% of women with symptoms of vaginal discharge seen in a gynecology clinic.²⁶ In women of 18 rural villages in Peru, BV prevalence was 44%.^{26a}

Women attending sexually transmitted disease clinics have had relatively high BV prevalence—for example 24–37% of women attending STD clinics in Uppsala, Sweden²⁷; Seattle, Washington²⁸; and Halifax, Nova Scotia²⁹; and Madagascar.³⁰ In Thailand, 33% of female sex workers had BV,³¹ compared to the 16% prevalence found among pregnant Thai women. The highest prevalence of BV reported in a large population-based sample of women was 51% among 4718 rural Ugandan women.³² On the other hand, BV was diagnosed in only 18% of women in the United States hospitalized with complications of AIDS.³³ In one longitudinal study, BV was detected among 43% of HIV-infected and 47% of HIV-uninfected high-risk women.³⁴ Over time, BV decreased among both groups of women, suggesting that HIV infection is not a risk factor for BV. Interestingly, treatment of HIV-infected women with HAART was associated with lower rates of BV.³⁴ These and other data, in aggregate, suggest that BV is common in most populations, is more common in STD clinics than in family planning or antenatal clinics, is more common among women with symptoms of vaginal discharge than among those without symptoms, has been related to ethnicity for unknown reasons, and is common in rural sub-Saharan Africans.

Is BV transmitted sexually? Sexually active women have vaginal carriage *G. vaginalis* more often than sexually inexperienced women,³⁵ but nonetheless 10–31% of sexually inexperienced adolescent girls have had positive vaginal cultures for *G. vaginalis*.^{36,37} In one small study, of 20 virginal women, *G. vaginalis* and *Atopobium vaginae* were detected in 45% and 7%, respectively, and *G. vaginalis* detection was associated with history of receptive oral sex and hand–genital contact without penetrative vaginal intercourse.³⁸ While these studies demonstrated that *G. vaginalis* and—in the case of *A. vaginae*—other bacteria more specific for BV—can be detected in sexually inexperienced females, overall, the weight of evidence supports sexual transmission of this organism. Gardner and Dukes⁸ and Pheifer et al.³⁹ detected *G. vaginalis* in the urethras of 79% and 86% of the male sex partners of women with BV, but not in male controls. As discussed below, more recent data on a potentially protective effect afforded by male partner condom use might support a role for unprotected sex in initiating or maintaining BV. Piot et al. developed a biotyping scheme for *G. vaginalis* and observed that isolates of *G. vaginalis* from the vaginas of women with BV and from the urethras of their male sex partners belonged to identical biotypes when the strains were isolated within the same 24-hour period from both partners.^{39a}

Among postpubertal females, those reporting no sexual experience have had significantly lower prevalence of BV than those with sexual experience.³⁵ Some studies⁴⁰ but not others³⁵ found BV associated with younger sexual debut. Among college women, Amsel et al. found BV in zero of 18 virgins versus 69 (24%) of 293 sexually experienced women ($p < 0.03$).³⁵ Data on the relationship between BV and numbers of lifetime or recent sex partners are somewhat inconsistent but generally weigh in favor of a positive association. In heterosexual women, BV generally occurs more frequently among those who report new or higher numbers of male sex partners or more frequent intercourse, consistent with sexual acquisition.^{20,41–45} Other risks consistent across studies include douching^{44,46–48} (which promotes loss of H_2O_2 + lactobacilli), IUD use,^{49,50} and black race⁵¹ (independent of douching).⁵² Hormonal contraception,^{53,54} smoking,^{20,53} menses,⁵⁵ and chronic stress⁵⁶ have also emerged as risks in different studies. One cohort study⁴⁴ of 182 women demonstrated acquisition of BV was associated not only with having a new sex partner, and (as discussed below) with lack of H_2O_2 -producing lactobacilli (hazard ratio 4.0, $p < 0.001$), but also with douching for hygiene (HR 2.1, $p = 0.05$). Both Amsel et al.³⁵ and Holst et al.⁵⁷ found use of an intrauterine device more common among women with BV than among other women (18.8% vs. 5.4%, $p < 0.001$, and 35% vs. 16%, $p < 0.03$, respectively). In a prospective study, Avonts et al. reported a twofold increased incidence of BV among IUD users compared to oral contraceptive users.⁴² A prospective study of female sex workers in Peru also found IUD use associated with more than a two-fold increased risk of acquiring BV (J Sanchez, KK Holmes, unpublished). However, history of abnormal Pap smears, days of menstrual flow, days since last menstrual period, form of menstrual protection, age at menarche, and years since menarche have not been associated with BV.^{35,58}

For reasons that are not understood, BV prevalence is highest among black women, even after controlling for amount and type of sexual activity of the women themselves, and douching habits.^{51,52} Some investigators have examined the hypothesis that chronic stress associated with residing in urban environments may contribute to the link between African American race and BV. In a cross-sectional study of the prevalence of BV among 2304 women at first prenatal visit, stress was measured at the individual and community levels with the use of interviews and administrative records.⁵⁶ Black women had a significantly higher BV prevalence (64%) compared with white women (35%). Almost one-third of black women reported threats to personal safety compared with 13% of white women, and 63% of black women lived in neighborhoods with aggravated assault rates that were above the citywide mean compared with 25% of the white women. After adjustment for sociodemographic, behavioral risk, and perceived stress, the odds of BV associated with the community-level stressor of “homelessness” was significant

(odds ratio [OR], 6.7; 95% CI, 1.6–27.8). Inclusion of both individual and community-level stressors reduced the black/white BV OR by 27%. The authors concluded that measurement of stressors at multiple levels explained a significant proportion of the racial disparity in the rates of occurrence of BV. Stress is known to modulate key cytokines involved in local immune responses, so this hypothesis is of interest.

Condom use may prevent BV and its recurrence.^{50,53,54,59} Women in a large prospective study that evaluated response to treatment had a fivefold reduction in BV persistence and recurrence if their partners consistently used condoms.⁶⁰ In another prospective study, women who reported less frequent use of condoms were less likely to have normal vaginal flora sustained over time.⁴⁵ A relationship between receptive oral sex and BV has been reported,^{61,62} but not confirmed in other studies.^{58,63} Although *G. vaginalis*, *Mobiluncus* species, and *M. hominis* have been isolated from the male genital tract,^{64,65} short-course systemic antibiotic treatment of male partners of women with BV does not reduce BV recurrence.^{64–71} One study of 38 women showed that male partners of 17 women with abnormal vaginal flora were more likely to be colonized with *M. hominis* than partners of women with normal flora, but this was not a significant difference.⁷² Among heterosexual couples in Kenya,⁷³ multivariate analysis of factors specific to male partners of women with or without BV showed that crowded living and fewer bathing facilities were associated with higher odds of BV, while poor genital hygiene was associated with fourfold increase in their female partners' BV risk.⁷³ In later analysis, the male partner's HIV status was also highly associated with his poor genital hygiene.⁷⁴ Because 97% of men in this study were circumcised, an independent contribution of circumcision status to BV could not be assessed. The subprepuceal area may be a suitable environment for some bacteria associated with BV; also of interest, subprepuceal "wetness" (a surrogate for poor hygiene) has been associated with increased risk of HIV infection.⁵⁹

BV is considerably more common among women who report sex with other women than among those who do not.^{53,63,75–83} An important limitation of these studies is that women were self-referred and, thus, may not have been representative. In the NHANES study noted above,¹³ BV prevalence was 45.2% (95% CI 35.5–57.4) among women who reported having had a female sex partner, compared to overall prevalence of 29.2% (95% CI 27.2–31.3, $p = 0.003$). Among STD clinic populations, report of sex with another woman has emerged as a risk for BV in larger, well-controlled studies.^{53,83,84} Moreover, report of sex with another woman was associated with increased risk of BV recurrence in one prospective study.⁸⁴ The reasons that lesbians have a high prevalence of BV are unclear, but sexual practices that transmit vaginal fluid increase BV risk, and a high degree of

concordance for the presence or absence of BV among lesbian couples has been reported.^{63,76} Among 329 women who were sexually active with women,⁶³ risks for BV included higher number of female lifetime partners, shared vaginal use of sex toys, and report of oral–anal sex. Among 73 couples in this study, 95% were concordant for presence or absence of BV. Both partners had BV in 21 couples, and one woman had BV in only six couples; this degree of concordance differed dramatically from the expected distribution ($p < 0.001$). These data confirmed an earlier study that reported that, among 101 lesbians seeking gynecologic care, 29% had BV and pairs of monogamous lesbians had high concordance in having BV.⁷⁶ The likelihood of a female partner having BV was nearly 20 times greater if her partner had BV.⁶³ The authors concluded that this concordance probably reflected sexual transmission of BV. Lesbians' reportedly frequent practice of receptive oral sex⁸⁵ has been suggested as a risk for BV,⁶¹ but few studies have detected this association.^{44,63} Those that have found this association did not control for some important variables⁶¹ or showed association between receptive oral sex and "unstable" vaginal flora,⁵⁸ not BV.

The relatively consistent association between report of anal sexual behaviors and BV in the few studies that have assessed this practice deserves comment.^{63,73} Perineal transfer of rectal bacteria to the vagina is a well-recognized consequence of vaginal intercourse for common bacteria such as *E. coli* and Group B *Streptococcus*,⁸⁶ and it is possible that BV may be precipitated or promoted if unprotected vaginal intercourse encourages the translocation of key bacteria from the rectum to the vagina. Many of the bacteria that have been described using molecular approaches in the setting of BV (discussed below) appear to be strict anaerobes and hypothetically may prefer the rectal environment; whether and how they may play a pathogenic role in initiating BV is under study. Another possibility is that different species of *Lactobacillus* that colonize the rectum may be introduced into the vagina during vaginal intercourse and may somehow disrupt the normal vaginal environment,⁸⁷ although beneficial species of lactobacilli are also harbored in the rectum.

MICROBIOLOGY

■ CULTIVATION-BASED DEFINITION OF VAGINAL FLORA ASSOCIATED WITH BV

Gardnerella vaginalis

Leopold first reported the isolation of a small, nonmotile, nonencapsulated, pleomorphic Gram-negative rod from the genitourinary tract of women with cervicitis in 1953.⁸⁸ Two years later, Gardner and Dukes isolated this organism, which they named *Haemophilus vaginalis*, from 92% of 141 women with "bacterial vaginitis," 20% of women with

Trichomonas vaginalis infection, and 4% of women with clinical “moniliasis,” and from none of 78 controls.⁸ In an attempt to fulfill Koch’s postulates, Gardner inoculated 15 women not infected by *H. vaginalis* with material from the vaginas of infected patients and reproduced the manifestations of this condition in 11 of 15 women. However, inoculation of pure *H. vaginalis* resulted in these manifestations in only one of 13 women, despite isolation of *H. vaginalis* from the vagina of all of these women 1 or more weeks after inoculation. Both Brewer et al.⁸⁹ and Heitai and Taleghany⁹⁰ confirmed the association between nonspecific vaginitis and *H. vaginalis*, but, unlike Gardner and Dukes,⁸ they also isolated other organisms and concluded that *H. vaginalis* was not the sole etiology of nonspecific vaginitis.

The body of literature over the past 30 years has substantiated the association of *G. vaginalis* with VB. However, with use of more sensitive culture media *G. vaginalis* can be isolated, often in high concentrations, from women with no signs of vaginal infection and is estimated to colonize approximately 40% of women whose vaginal fluid is characterized by normal Nugent scores.⁹¹ Many investigators now believe that *G. vaginalis* somehow interacts with anaerobic bacteria to cause VB. When assessed by a specific fluorescent probe, *G. vaginalis*, unlike several other recognized vaginal species, has been detected in large quantities within adherent biofilms among women with BV.⁹²

■ ANAEROBIC BACTERIA

Anaerobic rods and cocci were first isolated from the vagina in 1897⁵ and were found to be associated with vaginal discharge by Curtis in the early part of this century.¹ In 1980, Spiegel analyzed the vaginal fluid from 53 women with BV using quantitative anaerobic cultures and gas–liquid chromatography, to detect the short-chain organic acid metabolites of the vaginal flora.¹⁰ She isolated *Bacteroides* spp. (now *Prevotella* and *Porphyromonas*) from 76% and *Peptococcus* (now called *Peptostreptococcus* [not further speciated]) from 36% of the women with BV and recovered both types of anaerobes significantly less often from normal women. The recovery of anaerobic species correlated directly with a decrease in lactate and an increase in succinate and acetate in the vaginal fluid. Paavonen et al. later confirmed the presence of succinate and other short-chain fatty acids in vaginal fluid from women with BV.⁹³ After metronidazole therapy, the anaerobic Gram-negative rods and cocci decreased, and lactate again became the predominant organic acid in the vaginal fluid. Spiegel concluded that anaerobes interacted with *G. vaginalis* to cause VB.

In our experience with cultivation of bacteria from vaginal fluid of women with BV, the most common anaerobic Gram-negative rods include *Prevotella bivia*, the black-pigmented species belonging to the genera *Prevotella* and

Porphyromonas, *Bacteroides ureolyticus*, and *Fusobacterium nucleatum*.¹¹ Members of the *Bacteroides fragilis* group (*B. fragilis*, *B. ovatus*, *B. vulgatus*, and *B. thetaiotaomicron*), although common in the intestinal tract, are less common in the vagina and not associated with BV.¹¹ The vaginal flora of most normal women also includes anaerobic Gram-positive cocci.

Although researchers “discovered” *Mobiluncus* during the early 1980s, Kronig first observed a curved anaerobic rod by Gram stain of uterine discharge in 1895,⁹⁴ and Curtis first isolated such an organism from the uterine discharge of women with postpartum fever⁹⁵ in 1913. Prevot suggested the name “*Vibrio mulieris*” in 1940.⁹⁶ Most early microbiologic studies failed to detect this nutritionally fastidious and strictly anaerobic microorganism, but in 1980, Durieux and Dublanquet isolated and characterized 18 strains of succinate-producing anaerobic curved rods from women with vaginal discharge.⁹⁷ Spiegel detected this organism by direct Gram stain of the vaginal fluid from 31 (51%) of 62 women with BV and from none of 42 normal controls.⁹⁸ In 1984, Spiegel and Roberts proposed the genus name *Mobiluncus* for this motile rod. Two species were described: *M. curtisii* and *M. mulieris*.⁹⁹ One study employed DNA probe, culture, and/or Gram stain to demonstrate *Mobiluncus* spp. in 68% of women with BV.¹⁰⁰ In the vagina, *Mobiluncus* always occurs together with other organisms associated with BV and has also been associated with gonorrhoea. *Mobiluncus* spp. have most frequently been recovered from black women but are not associated with young age at first intercourse, lifetime number of sexual partners, or having a new partner in the past month.¹⁰¹

Schwebke and colleagues¹⁰² have reported phenotypic variants of *M. mulieris* and *M. curtisii*. The phenotypically and antigenically distinct *M. curtisii* strains are more frequently recovered from women with normal vaginal flora than from those with BV.¹⁰² Recent studies have demonstrated serum antibody to *M. curtisii* very commonly in sexually experienced women (75%) (including many who denied a history of BV) and rarely in pediatric patients (6%) or virgins (0%).¹⁰³ The authors concluded that humoral antibody to *M. curtisii* may provide a useful serological marker for BV and that BV may commonly go unrecognized in sexually experienced women. The genus *Mobiluncus* and the genus *Falcivibrio* are closely related, and it has been proposed that *F. vaginalis* and *F. grandis* be transferred to the genus *Mobiluncus*.^{103a}

■ GENITAL MYCOPLASMAS

In 1970, Mendel reported isolation of mycoplasmas from nearly half of patients with trichomoniasis or *G. vaginalis*, but without any specific disease.¹⁰⁴ Taylor-Robinson and McCormack first suggested in 1980 that *Mycoplasma hominis*

could have a role in nonspecific vaginitis, either in symbiosis with *G. vaginalis* and other organisms or as a sole pathogen.¹⁰⁵ Pfeifer et al. supported this hypothesis, by recovering *M. hominis* from 63% of women with BV and 10% of normal controls.³⁹ In 1982, Paavonen et al. also reported the association of BV with *M. hominis* and *G. vaginalis* in vaginal fluid.⁹³

■ APPLICATION OF MOLECULAR ANALYSIS TO BV-ASSOCIATED FLORA

More recently, cultivation-independent techniques have been employed to define bacteria associated with BV.^{12,106} These include various approaches to analyzing products of broad-range 16S rDNA PCR, including denaturing gradient gel electrophoresis (DGGE) and sequence analysis of all products or products screened for sequence diversity by amplified ribosomal DNA restriction analysis (ARDRA) and restriction fragment length polymorphism analysis (RFLP). On the whole, these studies have confirmed that women without BV typically have *Lactobacillus* species as the overwhelmingly predominant bacteria.^{12,107,108} Women with BV, however, have even greater bacterial diversity than previously appreciated. In addition to confirming the presence of previously described cultivatable BV-associated bacteria, these studies have detected *A. vaginae*, *Lactobacillus iners*, *Eggerthella*, *Megasphaera*, *Leptotrichia*, *Dialister*, *Bifidobacterium*, *Slackia*, and bacteria related to *Arthrobacter*, *Caulobacter*, and *Butyrivibrio*.^{109–114} One of the first studies, reported by Burton and Reid, used both bacterium-specific and broad-range 16S rDNA PCR with DGGE to follow vaginal flora over time in 20 asymptomatic, postmenopausal women.¹⁰⁹ Of seven women with BV, sequencing was consistent with the presence of *Gardnerella*, *Prevotella*, *Peptostreptococcus*, and *Bacteroides* species and of a 16S rDNA sequence that was 89% similar to an uncultivated bacterium found in soil. A small group of premenopausal women studied by this group generally had similar vaginal flora with the addition of unusual bacteria related to *Arthrobacter*, *Caulobacter*, and *Butyrivibrio* and frequent detection of *L. iners*.¹⁰⁹ Of note, the use of DGGE analysis allows for a relatively limited and occasionally less than specific assessment of bacterial diversity, as PCR products present in relatively low quantity may not appear as visible bands on the gel or, if they have similar mobility, may appear as overlapping bands. Using the DGGE approach, Ferris et al. identified *A. vaginae* in 12 of 22 women with BV and in only two of 24 normal women;¹¹⁰ subsequently, this group applied a PCR assay specific for detection of *A. vaginae* to 19 women without BV, who had no *A. vaginae* detected, and to 11 women with BV, four of whom had *A. vaginae* detected. This was the first study to show that *A. vaginae*, while not always present in BV, is relatively specific for BV when it is present. Subsequently, a similar approach used by

Burton et al. showed that approximately half of women with BV were positive for *A. vaginae*.¹¹¹ Of interest, *Atopobium* species have been detected in upper female reproductive tract disease and are resistant to metronidazole^{115–118} and when present in vaginal fluid in higher quantity were associated with recurrent BV in one study.¹¹⁹

Another approach, which allows for detection of greater bacterial diversity than DGGE, has been to use the more labor-intensive technique of sequence analysis of cloned PCR products generated by broad-range 16S rDNA PCR. This was combined with cultivation techniques, for example, in a study by Verhelst et al. in which colonies were characterized using either fingerprint patterns by PCR of spacers between transfer RNA or actual sequencing of 16S rRNA genes.¹¹³ Again, the predominance of *Lactobacillus* species was noted among women with normal flora, *A. vaginae* was present among many women with abnormal flora by Gram stain, and 47% of the species detected were identified only by cloning. Among 20 asymptomatic premenopausal women (not described by standard Amsel or Nugent criteria) studied by Hyman et al., seven women had clone libraries that consisted of more than 50 bacterial 16S rDNA sequence types, again supporting the observation that the diversity of bacterial species associated with BV is profound.¹¹⁴

Fredricks et al. used broad-range PCR to amplify a ~1000 base pair segment of the bacterial 16S rRNA gene from vaginal fluid samples from nine women with BV and eight without BV, defined by Amsel criteria and confirmed by Gram stain; four women were followed serially to assess changes with incident, cured, recurrent, and persistent BV.¹² The PCR products were cloned into *Escherichia coli*, 100 clones were selected, and plasmid inserts were screened for sequence diversity using RFLP analysis with two restriction enzymes (ARDRA). Inserts with unique ARDRA patterns were sequenced to identify bacteria or infer phylogenies. As noted consistently in all of these studies, women without BV had clone libraries dominated by a few *Lactobacillus* species, while those with BV had diverse flora that included several novel species in the *Clostridiales* order, as well as bacteria related to *Megasphaera*, *Leptotrichia*, *Dialister*, *Atopobium*, and *Eggerthella* species. Individual subjects studied longitudinally had parallel changes in vaginal flora with incident, cured, and relapsing BV that mirrored the cross-sectional study. These investigators also developed bacterium-specific PCR assays for the more sensitive detection of vaginal bacteria and applied these assays to a group of 27 subjects with BV and 46 subjects without BV. The uncultivated *Clostridium* species, termed BVAB1, BVAB2, and BVAB3, were highly specific indicators of BV (>95% specificity). The *Atopobium* and *Megasphaera* assays were very sensitive tests for BV (>96%), but detection of *Megasphaera* was more specific for BV (91%) than *Atopobium* (80%). They used fluorescent in situ hybridization with bacterium-specific probes to

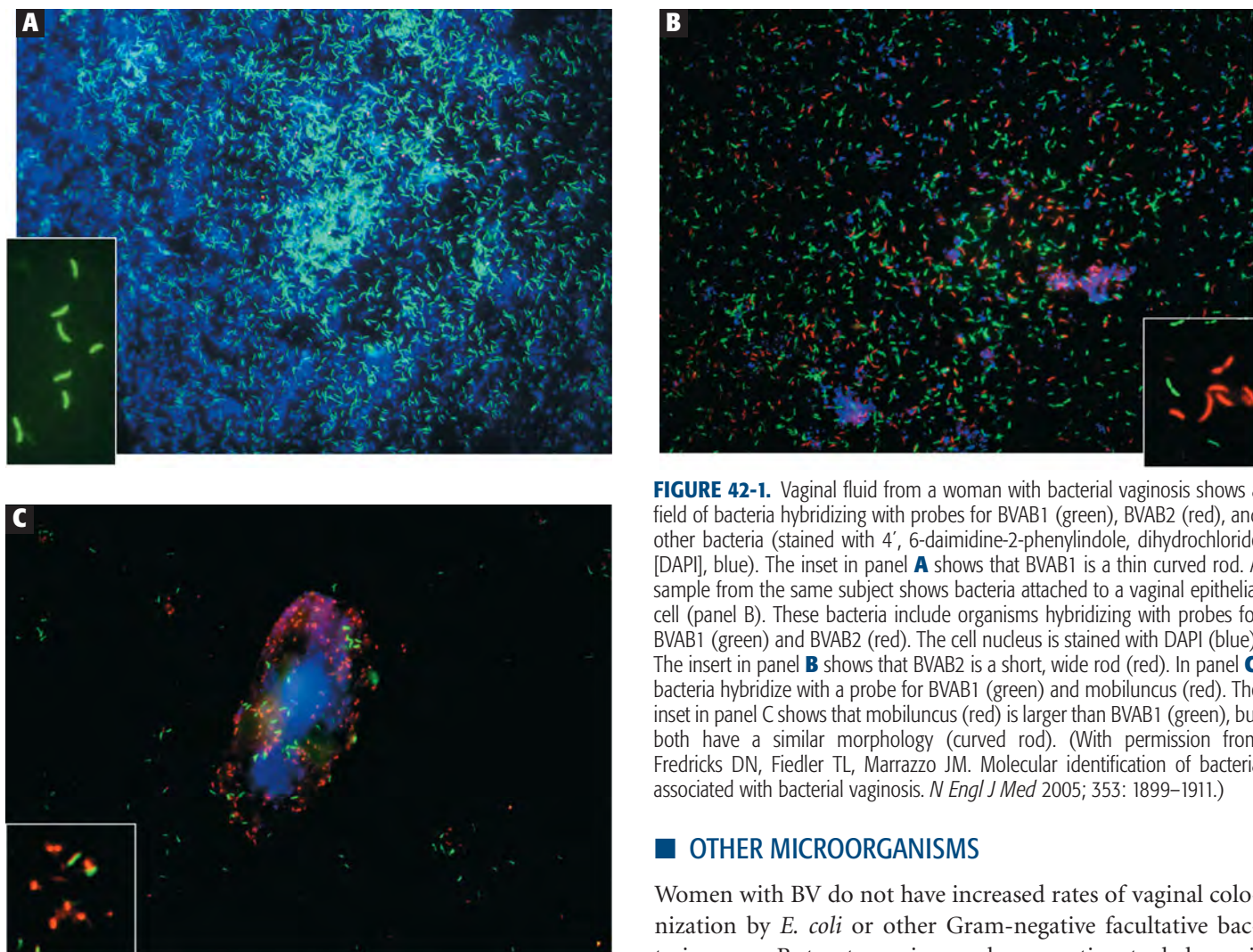


FIGURE 42-1. Vaginal fluid from a woman with bacterial vaginosis shows a field of bacteria hybridizing with probes for BVAB1 (green), BVAB2 (red), and other bacteria (stained with 4', 6-diamidino-2-phenylindole, dihydrochloride [DAPI], blue). The inset in panel **A** shows that BVAB1 is a thin curved rod. A sample from the same subject shows bacteria attached to a vaginal epithelial cell (panel **B**). These bacteria include organisms hybridizing with probes for BVAB1 (green) and BVAB2 (red). The cell nucleus is stained with DAPI (blue). The insert in panel **B** shows that BVAB2 is a short, wide rod (red). In panel **C**, bacteria hybridize with a probe for BVAB1 (green) and mobiluncus (red). The inset in panel **C** shows that mobiluncus (red) is larger than BVAB1 (green), but both have a similar morphology (curved rod). (With permission from Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. *N Engl J Med* 2005; 353: 1899–1911.)

visualize these bacteria and showed that they are morphologically distinct from other vaginal bacteria, including *Mobiluncus* species, and that they apparently adhere to the surface of vaginal epithelial cells (Fig. 42-1).

Two major findings from these studies merit emphasis. First, several newly defined BV-associated bacteria are previously undescribed species that have to date not yet been cultivated, including BVAB1, BVAB2, BVAB3, and members of an entirely uncultivated phylum called TM7. Second, in contrast to *G. vaginalis*, several of these newly described bacteria appear highly specific for BV, including BVAB1, BVAB2, BVAB3, and *A. vaginae*. In one study, none of these bacteria were detected in women with normal flora as defined by Nugent criteria.¹² Because *Atopobium* species have been detected in upper female reproductive tract disease and are resistant to metronidazole and were associated with recurrent BV in one study, these findings have implications for understanding the pathogenesis and optimizing the treatment of BV and upper genital tract infection that involves previously undefined bacteria associated with BV.

OTHER MICROORGANISMS

Women with BV do not have increased rates of vaginal colonization by *E. coli* or other Gram-negative facultative bacteria, group B streptococci, coagulase-negative staphylococci, diphtheroids, or most species of viridans streptococci. However, vaginal colonization by *Enterococcus* occurs more frequently among women with *Lactobacillus*-predominant vaginal flora than among women with BV.¹¹

It is apparent that no single organism causes VB. It is likely that BV is due to a consortium of bacteria, which may be interdependent from a metabolic perspective.

PATHOGENESIS

BV results from the replacement of the normal vaginal flora (*Lactobacillus*) with a mixed flora consisting of *G. vaginalis*, anaerobes, and *M. hominis*. Thus, most studies of the pathogenesis of BV have focused on how the microbial ecosystem of the vagina becomes altered. The epidemiologic data described above are consistent with the notion that introduction of a particular set of organisms via sexual intercourse may initiate the change in vaginal flora characteristic of BV.

Lactobacillus spp. may help normal women to resist vaginal and cervical infection. Vaginal lactobacilli inhibit *G. vaginalis*, *Mobiluncus*, and anaerobic Gram-negative rods in vitro.¹²⁰

Some strains of *Lactobacillus* produce H_2O_2 ,^{87,121,122} and studies have demonstrated that H_2O_2 -producing strains of lactobacilli more frequently colonize the vagina of normal women, compared to women with BV.^{11,22,44,87,122} Further, during a prospective study, women colonized with H_2O_2 -positive lactobacilli less often developed VB than did those colonized with H_2O_2 -negative lactobacilli.⁴⁴ The H_2O_2 produced by the vaginal lactobacilli may inhibit the growth of anaerobic rods, *Gardnerella*, *Mobiluncus*, and *Mycoplasma* in the vagina either directly via the toxic activity of H_2O_2 or by reacting with a halide ion in the presence of cervical peroxidase as part of the H_2O_2 -halide-peroxidase antibacterial system.¹²² Chapter 18 presents more information on the role of lactobacilli in modulating vaginal flora.

So far, no host factor has been identified that increases susceptibility to BV. A possible exception is IUD use, but the mechanisms by which IUD use may increase the risk of BV are not understood and newer types of progestin-releasing IUDs have not been evaluated for their association with BV. The redox potential (Eh) of the vaginal epithelial surface is lower in women with BV than in normal women.¹²³ After the women with BV were treated with metronidazole, the redox potential of the vaginal epithelium returned to the normal range, a result suggesting that the low vaginal Eh was not a persistent underlying host factor.¹²⁴

It is thought that amines produced by the microbial flora, perhaps via the action of microbial decarboxylases, account for the characteristic abnormal fishy odor that is produced when vaginal fluid is mixed with 10% KOH. This so-called “whiff test” is thought to be due to volatilization of aromatic amines including putrescine, cadaverine,^{124,125} and trimethylamine¹²⁵ at alkaline pH. *Mobiluncus* is known to produce trimethylamine,¹²⁵ but the other microbial sources of the amines are still unknown. However, it is still unknown which, if any, organisms produce these amines. Trimethylamine can be detected at relatively high concentrations in the vaginal fluid of VB, with a median concentration of 5 mM.¹²⁶ The presence of trimethylamine in the vaginal fluid is thought to be largely responsible for symptoms of malodor experienced by women with BV.

The vaginal fluid of women with BV has increased levels of endotoxin,¹²⁷ sialidase,^{128,129} and glycosidases, which degrade mucin and decrease its viscosity.¹³⁰ An increased host response to BV has been documented in the form of increased levels of several cytokines and chemokines in the cervical mucus of both pregnant and nonpregnant women^{131,132} with BV (see Chapter 18). In addition, secretory leukocyte protease inhibitor is decreased in the vaginal fluid of women with BV.¹³³ The effects of BV on the vaginal epithelium and on epithelial cell turnover have not yet been well studied. Nonetheless, the increased vaginal concentrations of anaerobic pathogens in BV may increase the risk of ascending upper genital tract infections, including cervicitis and endometritis, as discussed below.

CLINICAL MANIFESTATIONS

In a cross-sectional study of clinic patients, BV by Gram stain criteria was significantly associated with symptoms of vaginal malodor (49% of patients with BV vs. 20% without BV) and vaginal discharge (50% of patients with BV vs. 37% without BV), and with signs of a nonviscous homogeneous, white, uniformly adherent vaginal discharge (69% women with BV vs. 3% without BV) (Table 42-1²⁸). As noted above, the malodor is attributed to the abnormal presence of amines, particularly trimethylamine. The discharge adheres uniformly to the vaginal walls, often visibly on the labia and fourchette before insertion of a vaginal speculum. Although a third of women with BV describe their vaginal discharge as yellow, most studies have found no significant increase in the mean number of polymorphonuclear leukocytes in vaginal discharge in this syndrome. The observation by Rein et al. of an association of BV with a positive test for lactoferrin (a marker for PMN leukocytes) stands apart from other studies in this regard;¹³⁴ in attempting to reconcile this finding with the generally accepted absence of pleocytosis, it was shown that BV-associated fluid was toxic for PMNs. The finding of PMNs in the wet mount should not exclude a diagnosis of BV. This is especially true if cervicitis is detected in the setting of BV. One study showed that leukorrhea (>5–10 white blood cells per high-power field on microscopic examination of vaginal fluid) may be a sensitive indicator of cervical inflammation with a high negative predictive value,¹³⁵ particularly among women with BV.^{136,137}

Nearly all women with BV have a vaginal pH of ≥ 4.5 when measured with pH paper having an appropriate pH range, although this finding is by no means specific for BV. A fishy odor was noted when vaginal fluid was mixed with 10% KOH (the “whiff test”) in 43% of those with BV versus 1% of those without BV. Microscopic evaluation of vaginal fluid at high power (400 \times) revealed clue cells representing $\geq 20\%$ of vaginal epithelial cells in 81% of those with BV versus 6% of those without BV.²⁸ Clue cells are epithelial cells heavily coated with bacteria sufficient to obscure the cell borders. (Fig. 42-2) The bacteria covering the clue cells include *G. vaginalis* as well as anaerobes such as *Mobiluncus*. Newer approaches to visualizing uncultivable bacteria associated with BV indicate that these bacteria may also contribute to the characteristic appearance of clue cells, as depicted in Fig. 42-1.

DIAGNOSIS

Self-diagnosis of vaginitis is frequently incorrect. In a study of 552 women aged 16 years or older, only 3–4% of women could accurately identify the symptoms associated with BV.¹³⁸ Many women believe that vaginal malodor is due to poor hygiene or are embarrassed about the symptoms and do not report this as

Table 42-1. Symptoms and Signs Among 661 Randomly Selected Women Attending a Sexually Transmitted Disease Clinic

	Bacterial Vaginosis (<i>n</i> = 311) (%)	No Bacterial Vaginosis (<i>n</i> = 350) (%)	Univariate Odds Ratio	<i>P</i>	Multivariate ^a Odds Ratio	<i>P</i>
Symptoms						
Chief complaint						
None	47	36	1.5	0.01	2.6	0.2
Abdominal pain	7	3	3.0	0.05	2.6	0.2
Vaginal bleeding	0.6	0.3	2.3	0.5	2.1	0.3
Vaginal discharge	17	7	2.9	<0.0001	2.6	0.01
Vulvar pruritus	8	18	0.4	<0.001	0.9	0.9
Other (dysuria and ulcers)	20	36	0.5	<0.01	0.7	0.3
Odor						
Increased discharge	49	20	3.9	<0.001	3.4	<0.001
Yellow discharge	50	37	1.7	0.001	1.3	0.005
Abdominal pain	24	17	1.6	0.01	1.2	0.08
Increased amount of menstrual bleeding	45	35	1.5	0.01	1.2	0.4
Prolonged menses	14	9	1.6	0.04	1.4	0.2
Intermenstrual bleeding	11	6	2.1	0.01	1.2	0.4
Intermenstrual bleeding	16	13	1.2	0.4	1.2	0.5
Signs						
Homogeneous discharge	69	3	77	<0.001	103	<0.001
Frothy discharge	2	0		0.007		
Increased discharge	9	4	2.3	0.02	1.5	0.001
Yellow vaginal discharge	32	18	2.2	0.001	2.3	0.001
Ectopy (any)	51	52	1.0	0.8	1.1	0.8
Ectopy ($\geq 50\%$)	7	8	0.8	0.4	1.2	0.8
Mucopus	28	21	1.5	0.03	1.2	0.4
Adnexal tenderness ^b	28	21	1.5	0.03	1.2	0.4
Uterine tenderness	4	1	2.5	0.08	1.7	0.4
Cervical motion tenderness	3	0.6	4.6	0.04	2.8	0.2
Clinical diagnosis of PID	3	0		0.003		
Macroscopic warts	7	14	0.5	0.009	0.5	0.004
Amine-like odor of vaginal fluid in potassium hydroxide	43	1	88	<0.001	113	<0.001
pH ≥ 4.7	97	47	30	<0.001	23	<0.001
Mean pH + SD	5.0 \pm 0.3	4.6 \pm 0.3				

(Continued)

Table 42-1. (Continued)

	Bacterial		(n = 350) (%)			
Microscopic result						
Any clue cells	81	6	69	M0.001	75	<0.001
Clue cells \geq 20% of epithelial cells	78	5	72	<0.001	88	<0.001
Cervical Gram stain \geq 30 PMN/HPF	28	22	1.4	0.08	1.1	0.7
Vaginal wet mount \geq 30 WBCs/HPF	40	34	1.3	0.2	1.4	0.1
Vaginal wet mount showing—predominance of lactobacilli	2	59	0.02	<0.001	0.02	<0.001

Univariate and multivariate comparison of patients with and without gram stain criteria for bacterial vaginosis.²⁸

PID, pelvic inflammatory disease; PMNs, polymorphonuclear leukocytes; HPF, high-power field; WBCs, white blood cells.

^aEach finding was adjusted for age, race, parity, education, occupation, current smoking, age at first intercourse, lifetime sexual partners, *C. trachomatis*, *N. gonorrhoeae*, yeast, and herpes simplex virus in the analysis. Women with *T. vaginalis* were excluded from the analysis.

^bAdnexal tenderness scored as moderate to severe.

a symptom to their health-care provider. Thus, symptoms alone are not reliable for the diagnosis of VB. Amsel et al. recommended basing the clinical diagnosis of VB on the presence of at least three of the following four signs:³⁵ (1) characteristic homogeneous white adherent discharge, (2) vaginal fluid pH > 4.5, (3) release of a fishy amine odor from vaginal fluid when mixed with 10% KOH, and (4) presence of clue cells (usually representing at least 20% of vaginal epithelial cells). These simple clinical tests are inexpensive and available in most office settings. Evaluation of wet mounts of vaginal fluid is technically difficult and highly subject to interobserver variation. Therefore, determination of pH and amine odor can significantly enhance the accuracy of diagnosis of BV.

■ DISCHARGE

Douching, recent intercourse, menstruation, and concurrent infection all can alter the appearance of the discharge associated with BV. The white, nonflocular discharge of BV adheres to the walls of the vagina and is only slightly or moderately increased in amount over that normally seen. Absence of a discernable white homogeneous discharge should not rule out BV, if the other manifestations are present.

■ VAGINAL FLUID pH

The vaginal fluid pH determination requires pH paper having appropriate range (pH 4.0–6.0). Commercially available pH paper suitable for this purpose includes a pH range of 3.0–6.5. Vaginal pH is best determined by swabbing the

lateral or posterior fornices of the vagina, and then placing the swab sample directly on the pH paper. Alternatively, the pH paper can be placed on vaginal fluid pooling in the speculum after removal from the vagina. The cervical mucus must be avoided since it has a higher pH (pH 7.0) than the vaginal fluid. Eschenbach et al.²⁸ reported that none of 178 women with pH \leq 4.4 had clue cells, while all of 257 women having \geq 20% clue cells had vaginal pH \geq 4.7. Of these 257 women, 89% had a homogeneous discharge, an amine odor, or both. Vaginal fluid pH has the greatest sensitivity of the four clinical signs, but the lowest specificity.

■ ODOR

Vaginal malodor is the most common symptom of women with BV, and release of the “fishy” amine odor from vaginal fluid after addition of 10% KOH greatly increases the detection of the malodor by the clinician. A drop of vaginal fluid should be placed on a glass slide and a drop of 10% KOH added, immediately releasing an amine odor as the pH of the mixture approaches the pKa of the amines (e.g., putrescine, cadaverine, histamine, and trimethylamine), and amines that are no longer protonated become volatile. The odor then dissipates quickly. A coverslip placed over this preparation permits microscopic exam for the pseudohyphal forms associated with candidiasis. Although the KOH odor test was reportedly the most powerful single predictor for diagnosis of BV,¹³⁹ others have reported this test to be the least sensitive of the four clinical tests for diagnosis of BV. Eschenbach et al.²⁸ reported a positive predictive value of only 76% for this test

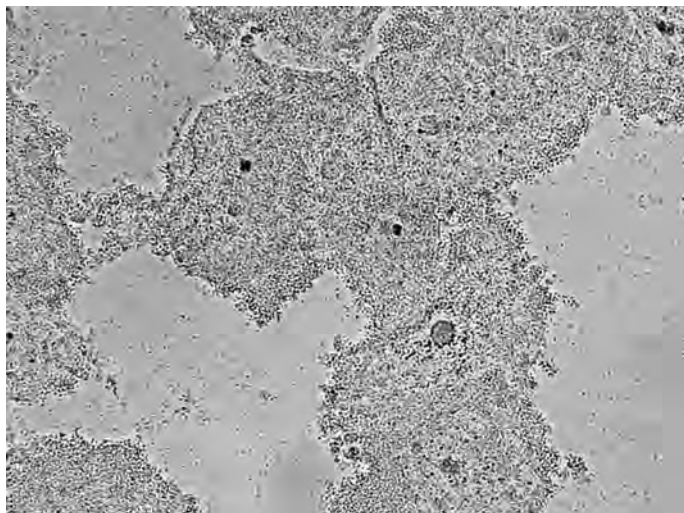


FIGURE 42-2. Wet mount of vaginal fluid showing a typical clue cells from a woman with bacterial vaginosis. Note that the cell margins are obscured ($\times 400$ magnification). (Photograph provided by Lorna K. Rabe.)

compared with Gram stain diagnosis of BV. However, when an objective diamine test was used as a screening test for BV in 229 women, the detection of diamines was found to be 92% sensitive and 83% specific with respect to identification of clue cells.¹⁴⁰ In another study of 164 women attending a genitourinary medicine clinic, the same colorimetric diamine test had an 87% sensitivity and 98% specificity compared to Gram stain criteria.¹⁴¹

■ WET MOUNT EXAM FOR CLUE CELLS

Clue cells are squamous vaginal epithelial cells covered with many vaginal bacteria, giving them a stippled or granular appearance. The borders are obscured or stippled owing to adherence of small rods or cocci (Fig. 42-1), including *Gardnerella*, *Mobiluncus*, and other bacteria. Lactobacilli may also bind to exfoliated vaginal epithelial cells, although seldom in high enough concentrations to mimic clue cells. At least 20% of vaginal epithelial cells resembling clue cells should be present to establish a diagnostic criterion for BV. However, when an experienced microscopist identifies only 1–20% of vaginal epithelial cells as clue cells, this is highly correlated with Gram stain features of BV.¹⁴² A sample of vaginal fluid obtained with a swab and mixed on a glass slide with a drop of normal saline is covered by a coverslip, and 10 fields examined under high power ($\times 400$) for clue cells. An example of a wet mount showing predominant vaginal lactobacilli is shown in Fig. 42-3, and a wet mount with numerous neutrophils is shown in Fig. 42-4.

■ VAGINAL CULTURE

Cultures for *G. vaginalis* or other individual microbes have little utility for the diagnosis of BV. *G. vaginalis* can be recovered from nearly all women with BV, but also from up

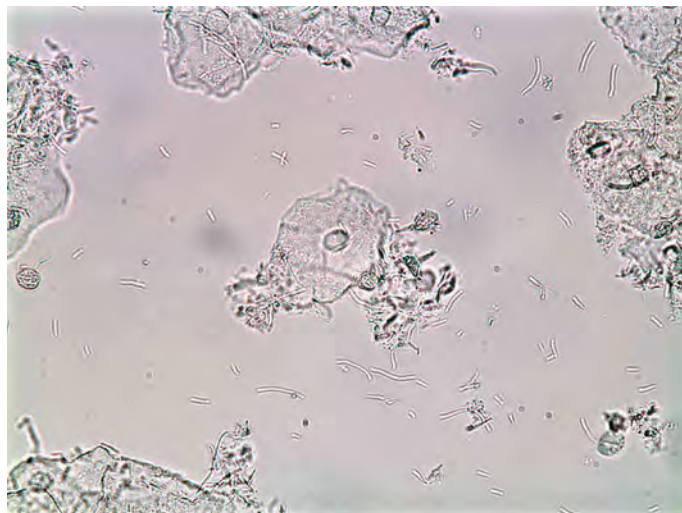


FIGURE 42-3. Wet mount of vaginal fluid showing absence of clue cells and presence of long lactobacilli morphotypes ($\times 400$ magnification). (Photograph provided by Lorna K. Rabe.)



FIGURE 42-4. Wet mount of vaginal fluid showing absence of clue cells and presence of numerous PMNs ($\times 400$ magnification). (Photograph provided by Lorna K. Rabe.)

to 58% of those without BV.²⁸ A positive vaginal culture for *G. vaginalis* in the absence of the clinical signs of BV does not warrant therapy. Likewise, *G. vaginalis* culture does not constitute “test of cure,” since many women without clinical signs of BV have positive cultures for this organism following effective treatment.

■ GRAM-STAINED SMEARS OF VAGINAL FLUID

Dunkelberg first proposed the evaluation of vaginal Gram-stained smears for diagnosis of BV,¹⁴³ and Spiegel et al. later published specific guidelines.¹⁴⁴ A standardized 0–10-point scoring system for evaluation of Gram-stained vaginal smears (Table 42-2) was later developed, based on three morphotypes: large Gram-positive rods (lactobacilli), small

Table 42-2. Standardized Method for Scoring Gram-Stained Smears for Diagnosis of Bacterial Vaginosis (1+, <1/1000× Microscopic Field; 2+, 1-5/1000×; 3+, 6-30/1000×; 4+ >30/1000×)

Bacterial morphotype	None	Points ^a Scored per Morphotype			
		1+	2+	3+	4+
Large Gram-positive rod	4	3	2	1	0
Small Gram-negative/variable rod	0	1	2	3	4
Curved negative/variable rod	0	1	1	2	2

^aScore or 0–3 points, normal; 4–6, intermediate; 7–10, bacterial vaginosis.

Modified from Nugent RP, et al. *J Clin Microbiol* 1991; 29: 297–301, with permission of the American Society for Microbiology.

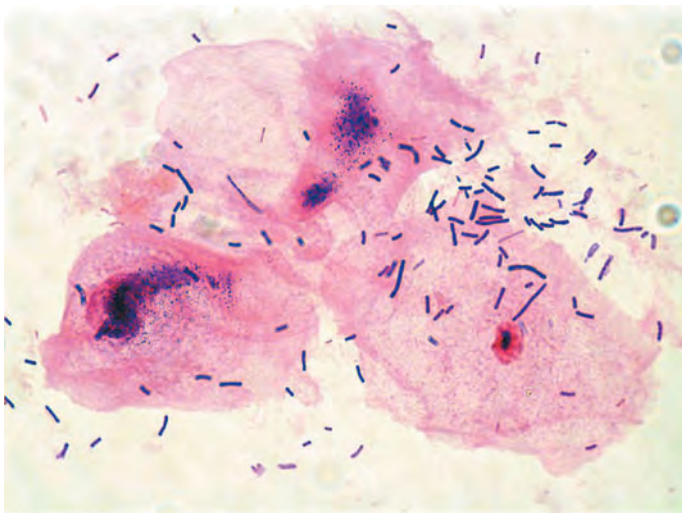


FIGURE 42-5. Gram stain of normal vaginal fluid, showing gram-positive rods with blunt ends consistent with lactobacilli (×1000 magnifications). (Photograph provided by Lorna K. Rabe.)

Gram-negative or variable rods (*Gardnerella* and anaerobic rods), and *Mobiluncus*.¹⁴⁵ This method, based on the shift in bacterial morphotypes from predominance of lactobacilli (Fig. 42-5) to a mixed flora (Fig. 42-6) to predominance of *Gardnerella* and anaerobic bacterial morphotypes, including *Mobiluncus* (Fig. 42-7), has had 89% sensitivity and 83% specificity for diagnosis of BV, in comparison with clinical criteria,¹⁴⁶ and has had excellent intercenter reproducibility.^{145,147} Two studies evaluating the Nugent Gram stain criteria for diagnosis of VB have reported sensitivities of 86–89% and specificities of 94–96%, compared to the Amsel criteria.^{142,148} In one of the studies, the Nugent and Spiegel methods were directly compared.¹⁴⁹ Evaluation of vaginal smears by the Nugent criteria yielded similar sensitivity (86% vs. 83%) and greater specificity (96% vs. 89%), compared to the Spiegel method. The vaginal smear for Gram stain evaluation can be prepared at the same time that the wet mount is

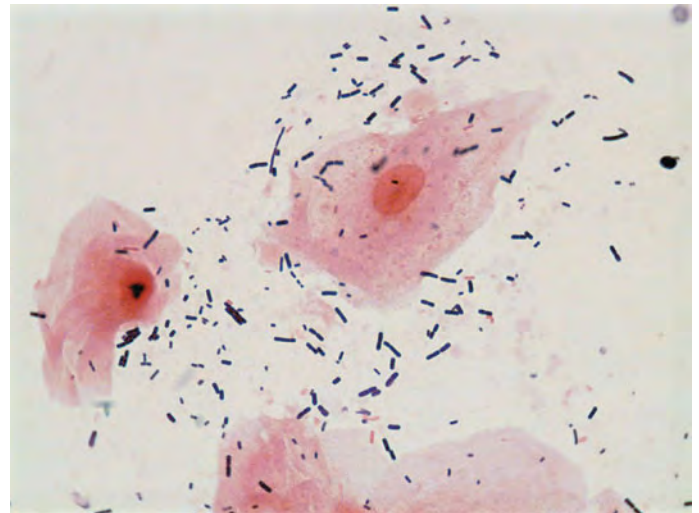


FIGURE 42-6. Gram stain of vaginal fluid from a woman with intermediate vaginal flora (Nugent score 5) (×1000 magnification). (Photograph provided by Lorna K. Rabe.)

prepared by rolling (not streaking) the swab across the surface of a glass slide. After air drying, the slide can be stored for months or years prior to staining with no appreciable loss in quality. Self-obtained swabs have also been proven to be acceptable for preparation of Gram-stained vaginal smears.^{149,150} The slide should be heat fixed and stained as usual in the clinical lab. The advantages of Gram stain for diagnosis include interpretation by standardized objective criteria by a microbiologist, suitability for quick screening, and storage for batch reading or later confirmation if desired.

■ OLIGONUCLEOTIDE PROBES

A specific oligonucleotide probe test adjusted to detect only high concentrations (>10⁷/mL vaginal fluid) of *G. vaginalis* was 95% sensitive and 79% specific for the diagnosis of BV in 113 women (Affirm VP III, Becton-Dickinson,

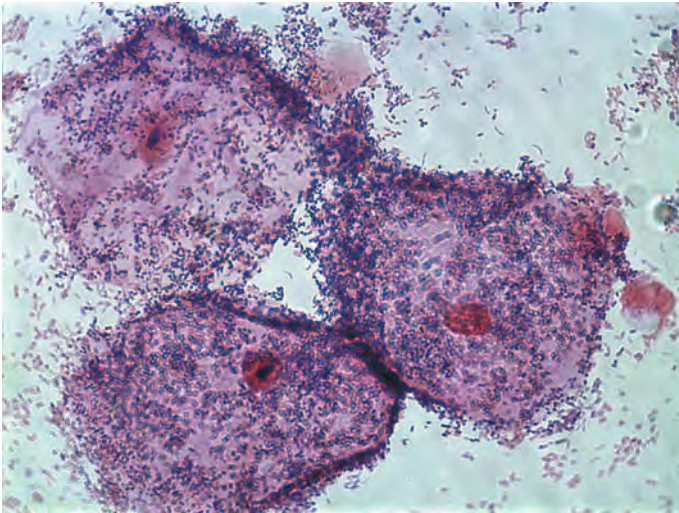


FIGURE 42-7. Gram stain of vaginal fluid from a woman with bacterial vaginosis showing absence of lactobacilli and large numbers of gram-negative or gram-variable coccobacilli. Curved gram-variable rods are consistent with *Mobiluncus* ($\times 1000$ magnification). (Photograph provided by Lorna K. Rabe.)

Cockeysville, MD).¹⁵¹ A commercially available 40-minute version of this test was 94% sensitive and 81% specific for the diagnosis of BV in an STD clinic population.¹⁵² This test simultaneously detects *Candida* species as well as *T. vaginalis* and provides a laboratory-based option for detection of all three vaginal pathogens. The advantage of this system is that it is objective, detects mixed vaginal infections, and can be used in any setting approved for moderately complex laboratory tests. Other researchers have continued to work toward development of a broader array of DNA probes for detection of *p. bivia*, *B. ureolyticus*, and *Mobiluncus curtisii*, in addition to *G. vaginalis*.¹⁵³ In a study of 134 pregnant women, having multiple pathogens present by DNA probe was highly correlated with a Gram stain diagnosis of BV.

■ DETECTION OF METABOLIC PRODUCTS

Several published methods for BV diagnosis involve detection of metabolic products of the microorganisms in the vaginal fluid of women with BV. Some of these tests have been modified for ambulatory clinic use, with commercial availability of tests for detection of sialidase and proline aminopeptidase.

TREATMENT

Gardner first described triple sulfa cream as a treatment for “*H. vaginalis* vaginitis” in 1955.⁸ Subsequently, sulfa creams have been shown to have low efficacy and are inappropriate for treatment of BV. Over the past 25 years, numerous studies of various therapies for BV have repeatedly shown that only those antimicrobial compounds with broad activity against most anaerobic bacteria are highly effective for the treatment of this syndrome.

■ METRONIDAZOLE

Pheifer et al.³⁹ first observed in 1978 that metronidazole used for vaginal trichomoniasis also cleared concurrent nonspecific vaginitis and went on to demonstrate the efficacy of a 7-day metronidazole regimen for this condition.

Most of the carefully conducted clinical trials used the Amsel criteria for diagnosis of BV, and cure or improvement was usually defined as resolution of two or more of Amsel’s criteria³⁵ for diagnosis. Outcome was generally assessed 1 week and/or 1 month after therapy. Several studies found that 10–15% of women who initially respond to therapy relapse by 1 month after treatment. A 1998 draft guidance from the U.S. Food and Drug Administration recommends that clinical cure be defined as the resolution of all four clinical signs of BV and return to a Nugent’s Gram stain score of 0–3. If this definition of “cure” is used, cure rates for metronidazole or clindamycin therapy are usually substantially lower, so an understanding of the criteria used to define cure is needed to interpret clinical trial data.¹⁵⁴

In a meta-analysis of metronidazole therapy treatment of BV, Lugo-Miro et al.¹⁵⁵ reported initial cure in 87% of 280 women receiving oral metronidazole (400–500 mg) two to three times daily for 7 days, and an 86% response in 317 women receiving 5 days of oral therapy. From this analysis of over 1200 women, there was a consistent finding that over 85% of women responded initially to metronidazole therapy. However, these authors reported that the 2 g stat dose was equivalent to 7 days of oral therapy.

Our own analysis of six studies, which compared the single 2-gm dose of metronidazole versus 800–1200 mg per day for 7 days and followed patients for at least 1 month after treatment, shows that five of these six studies showed lower cure rates with the single dose.¹⁵⁶ When results from the six studies are combined, BV persisted at follow-up >4 weeks after completing therapy in 27% of those given a 2-gm single dose of metronidazole and in 18% of those given a 7-day treatment regimen ($p = 0.03$).

Side effects of oral metronidazole include nausea, metallic taste, headaches, and gastrointestinal distress. Oral metronidazole may also lead to a disulfiram-like reaction after alcohol consumption, which may decrease patient compliance.

To reduce systemic absorption of metronidazole and decrease side effects, intravaginal metronidazole therapies have been developed (Table 42-3 summarizes a series of studies of topical metronidazole or clindamycin). In the initial study of intravaginal 0.75% metronidazole gel used twice daily for 5 days, 26 (87%) of 30 women were free of BV 4–16 days after therapy; four (15%) of the women relapsed at the 1-month follow-up,¹⁵⁸ giving a 73% cure rate at 1 month. Livengood and his colleagues evaluated this same formulation of metronidazole gel in 49 women and reported cure rates of 78% and 71% at the first and second follow-up visits, respectively.¹⁵⁹ A study

Table 42-3. Efficacy of Intravaginal Metronidazole or Clindamycin, for the Treatment of BV

Agent	Dosage	Frequency	Duration (d)	No. of Patients	Clinical Efficacy (%) ^a	Reference
Topical metronidazole	5 g 0.75%	bid	5	30	73	158
	5 g 0.75%	bid	5	49	71	159
	5 g 0.75%	bid	5	96	66	160
	500 mg	Once daily	7	19	74	161
	500 mg	Once daily	7	75	71	162
Topical clindamycin	5 g 2%	Once daily	7	16	94	163
	5 g 2%	bid	5	16	90	164
	5 g 2%	Once daily	7	66	77	165
	5 g 2%	Once daily	3	69	65	166
	5 g 2%	Once daily	3	23	82	167
	5 g 2%	Once daily	7	30	85	168
	5 g 2%	Once daily	7	53	87	169
	Ovule	Once daily	3	99	83	170
	Cream	Once daily	1	21	86	
	5 g 2%	Once daily	7	21	86	171

^aEfficacy determined 1 month after therapy, usually defined as absence of BV.

comparing intravaginal metronidazole versus triple sulfa cream showed higher efficacy of vaginal metronidazole.¹⁶⁰ Use of intravaginal metronidazole has resulted in fewer side effects than have been observed after use of oral metronidazole. None of 53 subjects who used the metronidazole gel experienced nausea or headache, or complained of having a metallic taste during this placebo-controlled trial. A direct randomized comparison of metronidazole vaginal gel twice daily for 5 days versus oral metronidazole 500 mg twice daily for 7 days showed that 5 weeks after therapy BV was eliminated in 71% (29/41) of the intravaginal metronidazole group, and in 71% (32/45) of the oral metronidazole group.¹⁷² A once-daily dosage of the 0.75% metronidazole gel, given over 5 days, has been approved for use in the United States. In a randomized trial of 7 days of oral versus 5 daily doses of a topical metronidazole for treatment of BV during pregnancy, efficacy was similar for both groups.¹³¹ Finally, limited data suggest that increasing the dose of vaginal metronidazole may effect higher cure rates for BV. Sanchez et al. compared metronidazole vaginal gel (Metrogel™) to Flagystatin™ (ovules containing 500-mg metronidazole and 100,000-U nystatin) given nightly for 5 nights.⁶⁰ Of 138 women

evaluable for follow-up at a mean of 42 days, BV persisted in 38% in the Metrogel and 17% in the ovule group ($p = 0.01$). While the higher dose of metronidazole was presumed to be the reason for the superior efficacy of the combination product, a potential contribution of the antifungal component could not be ruled out in this study design. Moreover, the study was limited by relatively low rates of follow-up and assessment of cure at variable intervals. Nonetheless, the data are intriguing and support a potential route of investigation toward more effective regimens for BV treatment.

In summary, metronidazole therapy used orally or intravaginally has been evaluated in hundreds of women with BV. These studies have consistently reported resolution of BV in 71–89% or more of women 1 month after therapy. In smaller studies, intravaginal therapies have had efficacy similar to that of oral metronidazole regimens with fewer side effects.

■ CLINDAMYCIN

The effectiveness of oral clindamycin for treatment of BV was first reported by Greaves et al., who randomized 143 women

to receive metronidazole, 500 mg bid for 7 days or clindamycin 300 mg bid for 7 days.¹⁷³ The clinical efficacy at 1 week was 94% for the oral clindamycin group, compared to 96% for the oral metronidazole group. Overall 16% of the clindamycin group and 22% of the metronidazole group reported adverse effects, none of which necessitated discontinuation of therapy. Oral clindamycin appeared as effective as metronidazole for treatment of BV and was of particular interest for the treatment of pregnant women.

Intravaginal clindamycin for the treatment of BV in non-pregnant women has been evaluated in numerous studies.^{163–170,174} Livengood et al.¹⁶⁴ and Hillier et al.¹⁶³ reported two dose-ranging studies of intravaginal clindamycin for BV. In a placebo-controlled, double-blind, randomized trial, women received 5 gm of clindamycin cream at concentrations of 0.1%, 1.0%, or 2.0% to be used each night for 7 nights. The authors concluded that 2.0% topical clindamycin was both clinically and microbiologically effective therapy for treatment of BV, whereas lower concentrations of clindamycin had lower clinical efficacy.

In a placebo-controlled trial of 2% intravaginal clindamycin, 50 (77%) of 66 women with BV given clindamycin and 17 (25%) of 69 women given placebo were free of BV at the first follow-up visit.¹⁶⁵ In a smaller, placebo-controlled trial of 3 days of intravaginal clindamycin therapy for BV, only one had persistent BV at first follow-up, and three additional patients developed recurrent BV at the second follow-up visit.¹⁶⁷

Several double-blinded, placebo-controlled trials have compared 7 days of intravaginal clindamycin cream (and twice-daily oral placebo) to 7 days of oral metronidazole administered twice daily (and once-daily placebo vaginal cream) for treatment of BV.^{166,168,169,171} In all of these trials, intravaginal clindamycin vaginal cream was as efficacious as 7 days of oral metronidazole therapy for the treatment of BV after both 1 week and 1 month of follow-up. Another study compared topical clindamycin, in the form of intravaginal ovules for these days with intravaginal metronidazole gel, applied daily for 5 days. Cure rates were not statistically significantly different for the two groups, although clindamycin-resistant microorganisms were detected more frequently among women in the clindamycin treatment group.¹⁷⁰

In two of these placebo-controlled, double-blind trials directly comparing intravaginal clindamycin to oral metronidazole, side effects were also compared. Only 3% and 5% of women assigned to intravaginal clindamycin and oral metronidazole, respectively, discontinued treatment because of side effects. Metronidazole was associated with a slightly higher incidence of gastrointestinal upset and nausea and metallic taste. Vaginal irritation and yeast vaginitis occurred in similar proportions of the two treatments. In summary, intravaginal therapies with metronidazole gel or clindamycin

cream, as described above, have been considered effective treatments for BV. Intravaginal therapies have been well tolerated. However, the costs of such therapies currently far exceed the cost of one dose or 7 days of oral metronidazole.

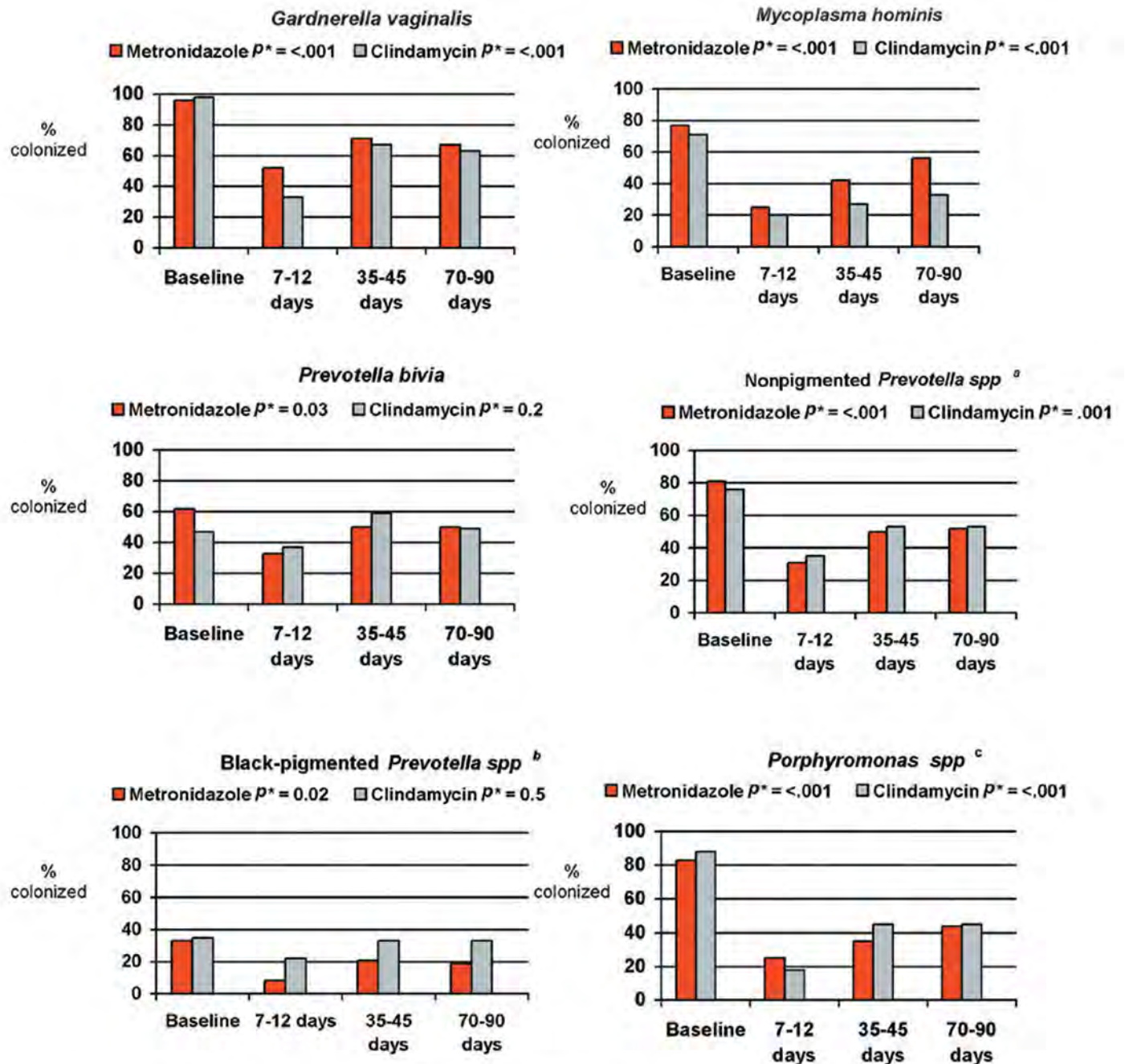
More recently, a sustained-release cream containing 2% clindamycin (Clindesse™) has been approved for the treatment of BV. The single published study on the efficacy of this product found that efficacy for BV was equivalent to that achieved with 7 days of vaginal clindamycin 2% cream (Cleocin™).¹⁷⁴ Overall 112 of 128 women (87.5%) given single-dose sustained release clindamycin cream versus 104 of 125 women given the 7-day intravaginal regimen (83.2%) experienced resolution of at least three of four Amsel criteria.

In many developing country settings,¹⁷⁵ especially in Latin America, topical intravaginal therapies with various mixtures of metronidazole, antifungal, antibacterial, antiseptic, and anti-inflammatory drugs are very commonly used for vaginal discharge and are often dispensed by pharmacies without prescriptions. Apart from the study noted above,⁶⁰ we are not aware of any published data documenting the effectiveness of such peculiar preparations.

■ MICROBIOLOGICAL RESPONSE TO THERAPY WITH METRONIDAZOLE OR CLINDAMYCIN

Although metronidazole is active against Gram-negative anaerobes and *Mobiluncus mulieris*, it is less active against *G. vaginalis*, anaerobic Gram-positive cocci, and *Mobiluncus curtisii*,¹⁷⁷ and inactive against *M. hominis* and *A. vaginae*. *G. vaginalis* is more susceptible to the hydroxymetabolite of metronidazole than to the parent drug, but, nonetheless, about 50% of women clinically cured after treatment with metronidazole remain colonized by *G. vaginalis*. *M. curtisii* is not susceptible to metronidazole in vitro but is usually eradicated following metronidazole therapy. It is possible that inhibition or elimination of metronidazole-susceptible members of the vaginal flora in BV results in a decline in certain nonsusceptible members as well.

A graphical analysis comparing the changes observed among the vaginal microorganisms associated with BV isolated at baseline and 7–12, 35–45, and 70–90 days following therapy with metronidazole or clindamycin is presented in Fig. 42-8.¹⁷⁷ The presence of H₂O₂-producing lactobacilli are considered to be indicators of optimal vaginal ecology, and a significant increase in colonization by H₂O₂-producing *Lactobacillus* species was observed among women following therapy with either metronidazole or clindamycin over 90 days of follow-up ($p < 0.002$). However, the proportion of women colonized by H₂O₂-producing lactobacilli differed at baseline for the two treatment groups. Clindamycin treatment resulted in a larger increase in colonization by *E. coli*, compared with metronidazole-treated women, although these differences did not



*Cochran's Q test performed to determine p value for frequency of microbes between visits.

^a Nonpigmented *Prevotella* spp includes: *P. oralis*, *P. buccalis*, *P. veroralis*, *P. oulorum*, *P. oris*, *P. buccae*, *P. capillosus* and *P. disiens*.

^b Black-pigmented *Prevotella* spp includes: *P. intermedia*, *P. corporis*, *P. denticola*, *P. loeschii*, *P. melaninogenica* and *B. levii*.

^c *Porphyromonas* spp includes *P. assachrolytica*, *P. endodontalis* and *P. gingivalis*.

FIGURE 42-8. Changes in vaginal microbiology from baseline among women with BV after therapy with topical metronidazole or clindamycin.

reach statistical significance (data not shown). A significant decrease in colonization by *G. vaginalis* and *M. hominis* ($p < 0.001$) was observed among women following therapy with either clindamycin or metronidazole.¹⁷⁷ Women treated with metronidazole had a significant decrease in colonization by *U. urealyticum* (from 94% to 79%, $p < 0.001$), whereas clindamycin-treated women did not (from 73% to

65%, $p = 0.3$). Following therapy with metronidazole, there was a significant decrease in colonization by *P. bivia* ($p = 0.03$) and black-pigmented *Prevotella* spp. ($p = 0.02$), two of the anaerobic Gram-negative rods associated with BV, but a significant decrease in these organisms was not observed among women who were treated with clindamycin (Fig. 42-7). Both *Porphyromonas* spp. and nonpigmented

Prevotella spp. decreased significantly following treatment with either regimen.

Antimicrobial susceptibility testing of anaerobic Gram-negative rods recovered from the women before and after treatment revealed a marked and sustained increase in the proportion of clindamycin-resistant anaerobic Gram-negative rods from women following therapy with clindamycin, but not from those treated with metronidazole. The proportion of *P. bivia*, nonpigmented *Prevotella*, black-pigmented *Prevotella*, and *Porphyromonas* isolates resistant to clindamycin before treatment with clindamycin was 8%, 14%, 11%, and 3%, respectively. However, at 7–12 days following therapy with clindamycin the percentage of clindamycin-resistant isolates was 51%, 43%, 68%, and 14%, respectively.¹⁷⁷

In summary, treatment with clindamycin versus metronidazole for BV results in a different microbiological pattern following therapy. While both topical metronidazole and clindamycin yielded similar clinical responses to treatment, metronidazole may be superior to clindamycin, based on the lower level of resistance and its capacity to eradicate anaerobic Gram-negative rods from the vagina.

■ TINIDAZOLE

Tinidazole, like metronidazole, is a nitroimidazole with antiprotozoal and antibacterial activity and is approved in the United States for the treatment of trichomoniasis when given as a single 2.0-g dose orally. Outside of the United States, tinidazole has been used widely for the treatment of BV in various oral dosing regimens, including 2 g as a single dose or daily for 2 days, 500 mg twice daily for 5 days, and 150 mg twice daily for 5 days, and as an intravaginal regimen (given as a tablet) at 500 mg daily for 14 days. Because different standards and timing for assessing cure rates were used in several studies, comparing treatment efficacy is difficult, but in general, efficacy of the single 2-g oral dose ranged from 46% to 71% in placebo-controlled trials and from 75% to 94% when compared to comparable regimens of metronidazole or clindamycin. Efficacy for the 2-g dose given daily for 2 days ranged from 50% to 80%.

A multicenter, placebo-controlled randomized trial of oral tinidazole given as either 2 g daily for 2 days or 1 g for 5 days has recently been completed. Resolution of BV as defined by absence of at least three Amsel criteria was seen in 46% of subjects who received the 2-day regimen and in 64% of those who received the 5-day regimen.¹⁷⁸ In vitro, tinidazole has activity against anaerobes comparable to metronidazole, and somewhat greater activity against *G. vaginalis*.¹⁷⁶ In a study comparing a single dose of tinidazole followed by vaginal acidifier to 7 days of clindamycin cream treatment, the single dose of tinidazole was found to be as effective as 7 days of clindamycin.¹⁷⁹

■ TREATMENT OF SEXUAL PARTNERS

Several placebo-controlled trials have demonstrated that treatment of the male partner(s) does not improve the clinical outcome of treatment of BV or reduce recurrence.^{68,180–183} For example, Moi and his colleagues¹⁸⁰ reported no differences in initial response of BV to therapy or in recurrence at 4–12 weeks after therapy for women whose partners were or were not treated with oral metronidazole. In a double-blind, randomized trial, Vejtorp et al.⁶⁸ observed no effect of treatment of the male partner on symptoms, clinical signs of BV, or isolation of *G. vaginalis* from the vagina 1 and 5 weeks after treatment of BV. Similarly, Vutyavanich et al.¹⁸² reported that tinidazole treatment of male partners in Thailand had no effect on clinical response in the female but was associated with a significant increase in side effects in the male partners who received tinidazole compared to placebo-treated men (22% vs. 7%, $p = 0.006$). In a study in which women were treated for BV with clindamycin vaginal cream, and their male partners were randomly treated with oral clindamycin or placebo, recurrences of BV were unrelated to treatment of partners.¹⁸³

Because all carefully controlled trials of male partners show no benefit of treatment of male partners, the U.S. Centers for Disease Control Guidelines for STD Treatment do not recommend routine treatment of male partners. The discrepancy between data suggesting sexual acquisition of BV and the lack of benefit of treating the male partner remains puzzling. Part of the issue may be that the selection or dosing of the antibiotics used in the trials done to date was not appropriate or adequate for eradicating a potential reservoir for BV-associated bacteria in men. An explanation may await better understanding of the role of sexual exposure and of the male partner in transmission.

■ TREATMENT OF BV WITH OTHER ANTIMICROBIAL AGENTS

The relative efficacies of other antimicrobial therapies for treatment of BV are summarized in (Table 42-4). Although sulfonamide creams have been used to treat BV for over 40 years, numerous studies document an unacceptably low efficacy for this product.^{160,184} Cephalosporins are generally less effective than metronidazole or clindamycin against BV, presumably because of their limited activity against anaerobic bacteria.¹⁸⁵ Although ampicillin has been used as an alternative therapy for BV, especially in pregnancy, and has in vitro activity against *G. vaginalis*, ampicillin has given cure rates as low as 43% in studies with sufficiently long follow-ups.^{186,187} Lack of efficacy may be due to production of beta lactamase by the anaerobic Gram-negative rods in the vagina of women with BV. Like clindamycin, ampicillin is also active against lactobacilli and delays vaginal recolonization by lactobacilli.¹⁸⁷ The poor efficacy of ampicillin does not support its use for BV even during pregnancy.

Table 42-4. Comparative Efficacy of Various Agents and Regimens Other than Metronidazole, Tinidazole, or Clindamycin for the Treatment of BV Omit or Update

Agent	Route ^a	Dosage	Regimen		Clinical Efficacy (%)	Reference
			Frequency	Duration (d)		
Tinidazole	o	500 mg	bid	5	95	184
	o	2 g	Once daily	2	76	178
	o	2 g	Once daily	5	63	178
Cephadroxil	o	500 mg	bid	7	64	185
Ampicillin	o	500 mg	qid	7	43–48	186,187
Tetracycline	o	500 mg	bid	7	50	188
Erythromycin	o	500 mg	qid	7	23	189
Triple sulfonamide	v	500 mg	bid	7	44–77	184,186
Ofloxacin	o	300 mg	bid	7	28	190

^ao, oral; v, intravaginal.

Antimicrobial agents used for the treatment of chlamydial or gonococcal cervicitis, including tetracycline, erythromycin, and ofloxacin, have very limited activity against anaerobic bacteria. Furthermore, erythromycin has limited antibacterial potency at the acid pH of the vagina, even at the slightly less acid intravaginal pH characteristic of BV. These antimicrobial agents cure BV in only one-fourth to one-half of women and are considered poor treatment choices.^{188–190} A recent study showed that addition of azithromycin to metronidazole for treatment of BV did not improve response to therapy.¹⁹¹

■ SYNDROMIC MANAGEMENT OF VAGINAL DISCHARGE IN DEVELOPING COUNTRIES (SYNDROMIC MANAGEMENT OF VAGINAL DISCHARGE IS DISCUSSED IN CHAPTER 55)

A recent study in West Africa involved syndromic management of vaginal discharge in women seen at primary care clinics in Ghana, Guinea, Mali, and Togo. Women were randomized to single-dose treatment with a single dose of tinidazole 2 g po plus a single dose of fluconazole (150 mg po) versus 7 days of metronidazole (500 mg bid for 7 days) plus clotrimazole vaginal cream for 3 days. The two treatment regimens were considered effective with complete resolution in 66% and 64% of participants, respectively, with similar results for women with BV, trichomoniasis, or vulvovaginal candidiasis, and for women with and without HIV infection.^{191a}

■ ALTERNATIVE TREATMENTS FOR BV, INCLUDING RESTORATION OF NORMAL VAGINAL ECOLOGY

Because BV results from an ecological shift in the vaginal microflora, a number of researchers have evaluated therapies that either act as vaginal disinfectants or are aimed at restoring the vaginal ecosystem (Table 42-5).^{192–198} Chlorhexidine pessaries reportedly had 79% efficacy in 34 women with BV, but 48% had recurrence at 1 month post-treatment. Povidone-iodine inserted vaginally twice daily for 2 weeks was completely ineffective in two studies. Studies reporting high success rates with povidone-iodine have usually had a very high incidence of spontaneous resolution of BV in the placebo group, suggesting potential problems with diagnosis, or in applying the data to populations in which the spontaneous resolution is low.

The efficacy of vaginal acidifiers in the form of gels, suppositories, and acid-soaked tampons has varied widely from 18% to 80% in several small studies. However, intermittent use over weeks is usually required. Vaginal acidifiers will suppress, but not kill, vaginal anaerobes, so may suppress without effecting a cure. Hydrogen peroxide douches have been advocated for BV treatment as an alternative to antimicrobial therapy. In one study of 23 women with recurrent BV, a 3-minute vaginal treatment with 3% hydrogen peroxide was reportedly effective in most women. However, the authors noted no recolonization of the vagina with lactobacilli. Concerns with this approach include that it involves

Table 42-5. Lack of Efficacy of Alternative Treatments for BV

Class	Type	Form and Use	No. of Women	Efficacy (%)	Follow-Up (d)	Reference
Disinfectant	Chlorhexidine, 150 mg	Pessary	34	79	7	192
	Povidone-iodine	Pessary bid × 14 d	28	20	7	193
Acidifier	Lactic acid	Suppository	125	20	30	194
	Lactate pH 3.5, 5 g	Gel, daily × 7 d	31	77	7	195
	Lactate pH 3.8, 5 g	Gel, intermittent use × 6 wk				
	Acetate	Gel	17	18	30	196
Yogurt	5% acetic acid	Tampon, bid × 7 d	32	38	30	197
	Commercial	Douche 10–15 mL	32	88	30	197
	pH < 4.5	bid × 14 d				
<i>Lactobacillus</i>	Commercial	Daily	14	7	30	196
	Vivag; Pharmac-Vinci A/S, Denmark	Suppository bid × 6 d	28	43	1–4	198

douching, a procedure most experts feel should be generally discouraged; that simple application of H₂O₂ may produce short-term disinfection but will not sustain resolution of abnormal flora over time; and that even H₂O₂-producing lactobacilli may be killed by high concentrations of H₂O₂.

Lactobacilli appear to be the primary microbiological deterrent to vaginal infection. Therapies employing yogurt probably have little utility. While Fredricsson et al.¹⁹⁶ found that yogurt had only 7% efficacy for treatment of BV, another report claimed 88% efficacy for twice-daily douching with yogurt for 2 weeks.¹⁹⁷

In a placebo-controlled trial of purified *Lactobacillus* spp. in suppositories, about half of the women receiving *Lactobacillus* improved during therapy, but only four of 29 women remained free of BV at the second follow-up visit.¹⁹⁸ Even though certain lactobacilli may play an important role in maintaining the normal vaginal flora, it remains to be determined whether the application of such lactobacilli is sufficient to restore the vaginal microflora. Another study evaluated the effectiveness of Gynoflor®, Medinova Ltd, Zurich, Switzerland, a tablet containing hydrogen peroxide-producing *Lactobacillus acidophilus* in combination with 0.03 mg of estriol.¹⁹⁹ At least one human-derived strain of *Lactobacillus crispatus* is currently under study as treatment for BV but is not yet commercially available.^{200,201} However, a recent study of orally administered lactobacilli reported a high level of effectiveness

among African women.²⁰² Advocates of alternative or nature-based treatments for BV have not proven the efficacy of these therapies in large, well-controlled, randomized, double-blind trials.

■ PREVENTION OF RECURRENT BV

Only one study to date has reported on attempts to suppress BV using ongoing antibiotic therapy.²⁰³ Sobel and colleagues performed a prospective multicenter study in which women with current BV and at least two prior episodes of BV in the previous year were initially treated with 10 days of vaginal metronidazole gel (Metrogel) and then, if cured, randomly assigned to receive twice-weekly metronidazole vaginal gel or placebo for 16 weeks.²⁰³ They were subsequently followed off therapy for 12 weeks. Of 157 eligible women, 112 of 127 returning evaluable women (88.2%) responded clinically and were randomly assigned. During suppressive therapy, recurrent BV occurred in 13 women (25.5%) receiving metronidazole and 26 (59.1%) receiving placebo (modified intent to treat analysis, relative risk [RR] 0.43, CI = 0.25–0.73, *p* = 0.001). During the entire 28-week follow-up, recurrence occurred in 26 (51.0%) on treatment compared with 33 (75%) on placebo (RR 0.68, CI = 0.49–0.93, *p* = 0.02). Probability for remaining cured was 70% for metronidazole compared with 39% on placebo, which declined to 34% and 18%, respectively, by 28 weeks'

follow-up. Adverse effects were uncommon; however, secondary vaginal candidiasis occurred significantly more often in metronidazole-treated women ($p = 0.02$). The authors concluded that suppressive therapy with twice-weekly metronidazole gel achieves a significant reduction in the recurrence rate of BV. No other regimens, including clindamycin-based or oral metronidazole, have been studied for suppression of recurrent BV.

BV IN PREGNANCY

BV during pregnancy has been linked to a significantly increased risk of preterm/low-birth-weight deliveries, intra-amniotic infection, histological chorioamnionitis, and postpartum endometritis. Is treatment necessary among women with symptoms, or does BV resolve spontaneously during pregnancy? Two published studies have reported on the persistence of BV during pregnancy. The first study evaluated 762 pregnant women at 23–26 weeks' gestation and again at 31–36 weeks' gestation.¹⁴⁶ Women who used antibiotics during this interval were specifically excluded. In this study, 69% of women who had BV in the second trimester still had this syndrome in the third trimester. In a second study, VB persisted in almost half of the women who had the condition initially and who went to term, that is in 15 (47%) of 32, while the flora reverted to the intermediate stage in two women (6%) and to normal in 15 women (47%).²⁰⁴ There was, however, a significant association between VB status at visits 1 and 3. Women who had the infection initially were more likely to have it at visit 3 than women who did not (15/32 vs. 4/144, McNemar's test $\chi^2 = 0.05$). These data suggest that spontaneous clearance of BV does not occur in most pregnant women and support the 2006 recommendation from the CDC that all pregnant women who have symptomatic BV require treatment.²⁰⁵

■ PRETERM LABOR, LOW BIRTH WEIGHT AND PROM

In 1984, Minkoff et al. published a prospective study of perinatal morbidity in 233 women enrolled for prenatal care at 14 weeks' gestation and followed through delivery; women underwent vaginal cultures for *Bacteroides* spp. and *M. hominis*, evaluation for BV (then called nonspecific vaginitis) based on clinical manifestations (vaginal pH > 4.5, clue cells, amine odor), and cultures for *T. vaginalis*, yeast, herpes simplex virus, *C. trachomatis*, and facultative bacteria.²⁰⁶ BV was diagnosed in 30% of 218 women. Subsequently, 16% developed preterm labor and received tocolysis; 50% of those who failed tocolysis had BV, compared to 29% of those whose labor stopped with tocolytic agents. In a stepwise logistic regression analysis of risk factors for perinatal morbidity, adjusting for maternal age, parity, previous premature delivery, abortion, and vaginal bacteria, isolation of *Bacteroides* spp. from the vagina was associated with preterm

delivery (RR = 1.4, $p < 0.03$), preterm premature rupture of membranes (PROM) (RR = 1.8, $p < 0.03$) and birth weight less than 2500 g (RR = 1.8, $p < 0.04$). This study was the first to describe the association of vaginal anaerobic bacteria and of BV with perinatal complications. Several subsequent studies supported and extended these findings, although randomized trials have not supported a role for routine treatment of BV for prevention of adverse pregnancy complications.²⁰⁷

From 1984 onward, a larger series of studies linking BV to preterm delivery or low birth weight have been published. Observational studies conducted in the United States, Scandinavia, and Australia, which included women from different ethnic and socioeconomic groups, have consistently reported an increased risk for preterm delivery and/or low birth weight among women colonized by BV-associated pathogens (anaerobic Gram-negative rods and *M. hominis*) and among those with clinical or Gram stain evidence of BV, and some have noted a decrease in prematurity among those vaginally colonized by *Lactobacillus* spp.^{208–212}

■ CHORIOAMNIONITIS AND AMNIOTIC FLUID INFECTION

Several studies link BV with infection of the fetal placental membranes (chorioamnion) and amniotic fluid, suggesting that ascension of vaginal microorganisms into the decidua, chorioamnion, or amniotic fluid, resulting in infection and inflammation at these sites, represents a probable mechanism by which BV can initiate labor and result in preterm delivery. In two studies, BV diagnosed by Gram-stained vaginal smear was related to histological chorioamnionitis and to recovery of microorganisms from the chorioamnion (OR = 3.2, $p < 0.05$).^{213,214}

Amniotic fluid infection results most commonly from invasion of lower genital tract bacteria through the placental membranes. Frequently, most isolates recovered from the amniotic fluid of women with intact membranes are the microorganisms associated with BV,²¹⁵ and women with BV are twice as likely to have invasion of the amniotic fluid as women with *Lactobacillus*-predominant vaginal flora. An increased risk of intra-amniotic infection among women with BV at less than 34 weeks of gestation has been reported by Hitti.²¹⁶ Watts et al. reported a relationship of BV diagnosed at the time of C-section to clinically diagnosed amniotic fluid infection: Amniotic fluid infection occurred among 22% of women with a Gram stain diagnosis of BV compared to 4% of those with a *Lactobacillus*-predominant vaginal smear.²¹⁷ Hitti evaluated 197 afebrile women in preterm labor with intact fetal membranes and found that women having a Gram stain consistent with BV were more likely to have amniotic fluid infection.²¹⁶ High concentration of IL-8 in the vagina and anaerobic flora were both associated with amniotic fluid infection.²¹⁶

In summary, BV during pregnancy has consistently been related to chorioamnion infection, histological chorioamnionitis,

and amniotic fluid infection. These three entities are strongly interrelated and are associated with preterm delivery.

■ TREATMENT OF BV DURING PREGNANCY FOR PREVENTION OF PRETERM BIRTH

Multiple published studies have evaluated whether treatment of BV in pregnancy prevents preterm birth.²⁰⁷ Because of the efficacy of clindamycin applied intravaginally for the treatment of BV, and early concerns with the potential teratogenicity of metronidazole in pregnancy,²¹⁸ initial efforts to reduce preterm birth among women with BV focused on the use of intravaginal clindamycin.^{219,220} However, these and subsequent studies failed to demonstrate that clindamycin-treated women had the same incidence of preterm birth as placebo-treated women and at least some studies showed a trend toward a higher incidence of birth before 32 weeks' gestation and of low birth weight among the clindamycin-treated women.²²⁰ One study did demonstrate a reduced incidence in preterm birth among women treated with topical clindamycin;²²¹ however, most studies did not support use of clindamycin vaginal cream for prevention of preterm birth among women with BV. Because of the increased incidence in adverse birth outcomes in these studies,^{219,220,222} the CDC does not recommend use of topical clindamycin for treatment of BV in the first half of pregnancy.²⁰⁵

Several published trials have evaluated oral metronidazole for treatment of BV during pregnancy. Two studies were conducted among women who were considered at high risk of preterm birth because of a previous preterm delivery or low pregnancy weight.^{223,224} In a study of 80 high-risk women with BV, 18% of those randomized to metronidazole versus 39% of those randomized to placebo delivered preterm, $p < 0.05$.²¹⁶ Hauth et al. evaluated oral metronidazole, 250 mg, tid for 7 days plus erythromycin 333 mg, tid for 14 days versus placebo in a population at high risk for preterm birth due to previous preterm birth or having a prepregnancy weight of <50 kg.²²⁷ Among women with BV and a history of previous preterm delivery, the percent delivering preterm was 39% for those assigned to metronidazole plus erythromycin, versus 59% for those assigned to placebo (RR = 1.6, 95% CI 1.1, 2.1).²²⁷ However, a randomized trial of oral metronidazole in a low-risk population of pregnant women failed to document a reduced incidence of preterm among metronidazole-treated women,²²⁵ although the study lacked sufficient size to allow for statistical power to detect small decreases in incident preterm births. A large NIH-sponsored randomized trial used an unusual dosage regimen of metronidazole, consisting of two single 2-g doses to women with BV who were at 16 to less than 24 weeks of pregnancy. This large trial found no decrease in preterm birth or other adverse perinatal outcomes among women

randomized to receive metronidazole.²²⁶ Since the publication of that study, numerous agencies have evaluated the available data on treatment of BV in pregnancy and concluded that routine treatment of asymptomatic women with BV cannot be justified.^{205,207} A Cochrane review published in 2007 concluded that (1) there was good evidence that antibiotic therapy was effective at eradicating BV, (2) treatment did not reduce the risk of preterm birth before 37 weeks or the risk of preterm PROM, (3) treatment before 20 weeks' gestation may reduce the risk of preterm birth at less than 37 weeks, and (4) treatment of women with a previous preterm birth did not affect the risk of subsequent preterm birth. This analysis is summarized in Table 42-6. Although some authors have asserted that BV may be more of a stimulant for preterm delivery at earlier gestational ages, an analysis of 12,937 deliveries failed to demonstrate that the risk of preterm birth was increased when BV was identified at earlier gestational ages.²²⁷

The mechanisms by which BV may cause prematurity and low birth weight are not completely understood, and some experts argue that BV may be a biomarker for other factors that lead to preterm birth. As discussed above, BV-associated microorganisms ascend to cause infections of the decidua, placenta, and/or amniotic fluid. Although some experts have postulated that BV could lead to initiation of preterm birth through local production of proinflammatory cytokines such as IL-8,²⁰⁶ treatment of BV has been shown to normalize levels of proinflammatory cytokines and chemokines in the cervical fluid of women with BV.¹³¹ It has become clear that the association of infection with preterm birth is complex and likely attributable to numerous interrelated factors. A greater understanding of these complex interrelations between infection, the immune response in pregnancy, and genetic differences in response to infection will be needed in order to develop the insights needed for more effective approaches to prevention of preterm birth.

OTHER COMPLICATIONS OF BV

■ POSTPARTUM ENDOMETRITIS

In a prospective study of risk factors for post-Cesarean endometritis in 462 women,²²⁸ those with BV diagnosed by Gram stain had an increased risk of postpartum endometritis following Cesarean section compared to women with a *Lactobacillus*-dominant flora (OR 5.8, 95% CI 3.0, 10.9) after adjusting for possible confounding factors, including maternal age, length of labor, and duration of membrane rupture. Women with BV also had increased rates of abdominal wound infection, and all of the documented wound infections were related to anaerobic bacteria. The

Table 42-6. Cochrane Review of Impact of Antibiotic Treatment on BV in Pregnancy²⁰⁷; Conclusions

Outcome	OR (95% CI)	Number of Trials	Number of Women
Treatment eradicates BV in pregnancy	0.17 (0.15–0.20)	10	4357
Treatment did NOT reduce preterm birth <37 wk of gestation	0.91 (0.78–1.06)	15	5888
Treatment did NOT reduce preterm premature ruptures of membranes	0.88 (0.61–1.28)	4	2579
Treatment before 20 weeks' may reduce risk of preterm birth <37 wk	0.63 (0.48–0.84)	5	2387
Treatment did not affect risk of subsequent preterm birth among women with previous preterm birth	0.83 (0.59–1.17)	5	622
Treatment may decrease risk of PPROM and LBW	0.31 (0.13–0.75)	2	114
Clindamycin did not reduce risk of preterm birth before <37 wk	0.80 (0.60–1.05)	6	2406

endometrial aspirates from patients with BV who developed postpartum endometritis contained the microorganisms associated with BV.²²⁸

The risk of postpartum endometritis remains high in patients with BV despite routine use of antibiotic prophylaxis. Cephalosporin prophylaxis is presumably inadequate early because of the large number and variety of bacteria contaminating the amniotic fluid of patients with BV and because some of the bacteria present are not highly susceptible to the cephalosporin used. The impact of antibiotic prophylaxis on patients with BV undergoing cesarean section needs further study. While women undergoing cesarean section experience the highest risk for postpartum endometritis, and BV is a strong risk factor among patients who deliver by cesarean section, BV also appears to increase the risk for postpartum endometritis among patients who deliver vaginally, specifically when amniotic fluid becomes contaminated with bacteria associated with BV during labor.²²⁸ Invasion of anaerobes (most commonly *P. bivia*), *G. vaginalis* and *M. hominis* in the amniotic fluid resulted in a twofold increased risk of postpartum endometritis among patients delivered vaginally or by cesarean section.

■ VAGINAL CUFF CELLULITIS

Vaginal cuff cellulitis occurs when vaginal bacteria contaminate the operative field during a hysterectomy. Women with more virulent bacteria in the vaginal flora, present in the increased concentrations characteristic of BV, would be expected to have

increased risk of vaginal cuff cellulitis following hysterectomy. In two separate studies, postabdominal hysterectomy cuff cellulitis occurred four times more commonly among patients with BV than patients with a normal *Lactobacillus*-dominant flora. In one of the studies, presence of *T. vaginalis* also was associated with a threefold increase in cuff cellulitis; however, after adjusting for the BV, the relative risk of cuff cellulitis in those with *T. vaginalis* alone was not significantly increased.²²⁹ A second study evaluated the association between clue cells and cuff cellulitis after abdominal hysterectomy and found a similar increased risk of infection among these with BV.²³⁰

■ POSTABORTION PID

PID is frequently caused by *Neisseria gonorrhoeae* and *C. trachomatis*. Many investigators have found PID following induced abortion related to *C. trachomatis*. Postabortal endometritis following induced first trimester abortion has also been related to BV. Postabortion PID occurred more commonly among patients with BV than among those with a *Lactobacillus*-dominant flora (OR = 2.4, 95% CI 1.1, 5.3).²³¹ *C. trachomatis* was also associated with postabortal PID ($p = 0.06$), but BV was more than twice as common as *C. trachomatis* infection, so that postabortion PID occurred in eight patients who had preoperative BV, two patients with preoperative *C. trachomatis* infection, and 18 patients with neither. In another study, 174 patients with BV underwent double-blind randomization to placebo or metronidazole prior to undergoing induced abortion.²³² Placebo-treated patients had higher rates of postabortal PID (OR = 30, 95% CI, 1, 11.8, suggesting

that prior treatment of BV could significantly decrease infectious morbidity following termination of pregnancy. However, a subsequent randomized trial in the United States of 393 women failed to document any benefit of metronidazole treatment for women having a termination of pregnancy.²³³

■ PELVIC INFLAMMATORY DISEASE

The role of BV in spontaneous PID not associated with abortion or instrumentation of the uterus is less clear, even though anaerobes have long been linked with salpingitis.²³ Among randomly selected STD clinic patients, those with BV had adnexal tenderness significantly more often than patients with a *Lactobacillus*-dominant flora, suggesting that spontaneous PID occurring without instrumentation may also be related to BV.²⁸ In this study, the relationship between BV and adnexal tenderness persisted after adjusting by multifactorial analysis for infection with *N. gonorrhoeae* or *C. trachomatis*. Many of the bacteria recovered from the endometrium and fallopian tubes of patients with PID are those present in the vagina in high numbers among women with BV.²³⁴ However, the proportion of women with BV who develop overt symptoms and signs of PID without instrumentation may be relatively low compared to the proportion of those infected with *N. gonorrhoeae* and *C. trachomatis*. Further, the interactions between *C. trachomatis*, *N. gonorrhoeae*, and facultative bacteria in producing PID is not known, and the relationship between BV or intermediate flora and acquisition of *C. trachomatis* and *N. gonorrhoeae* is probably complex and may depend in part on the microbiologic composition of BV itself. In one study, that prospectively followed more than 1000 women for 3 years, BV at baseline was associated with concurrent chlamydial or gonococcal infection (adjusted OR 2.8, 95% CI 1.81–4.42) but not significantly with subsequent detection of either of these pathogens at follow-up visits (RR 1.52, 95% CI 0.74–3.13). However, among women whose BV at baseline was characterized by dense growth of pigmented, anaerobic Gram-negative rods, risk of subsequent detection of chlamydia or gonorrhea was increased (RR 1.93, 95% CI 0.97–3.83).⁴⁷ Therefore, until recently it has seemed that treatment of asymptomatic nonpregnant women with BV to reduce PID could be viewed as optional and of no proven benefit until further information is available. However, the risk of more subtle manifestations of endometritis attributable to BV may be greater than the risk of overt PID. A small amount of intermenstrual bleeding or increased bleeding with menses is a frequent occurrence in patients with endometritis and salpingitis. A randomized, double-blind trial was conducted among patients with BV who had these symptoms of abnormal bleeding. Abnormal bleeding resolved in all 11 patients treated with metronidazole and considered cured of BV versus only one (5%) of 11 placebo-treated patients not cured ($p = 0.04$).²³⁵

The foundation for our understanding of the connection between BV and upper-tract infections was laid in 1987,

when Paavonen and colleagues published research showing that 29% of 31 patients who had histologic evidence of endometritis also had BV, while none of 14 controls without endometritis had BV.²³⁶ In 1995, Korn and colleagues published the findings of a case–control study in which they performed endometrial biopsies on 41 women who presented to an STD clinic complaining of vaginal discharge or pelvic pain.²³⁷ All of the biopsies were examined for histopathologic evidence of plasma cell endometritis and cultured for *N. gonorrhoeae*, *C. trachomatis*, *U. urealyticum*, *M. hominis*, and facultative and anaerobic bacteria. None of the patients had culture or serologic evidence of *N. gonorrhoeae* or *C. trachomatis* infection. Ten (45%) of the 22 women with BV had plasma cell endometritis, compared with only one of the 19 women who served as controls. Microorganisms associated with BV were cultured from the endometria of nine of the 11 patients who had plasma cell endometritis, as well as from eight of the 30 patients who did not have that histologic diagnosis.²²⁹

In a study of symptomatic women presenting for care, endometrial biopsies were obtained on 178 consecutive women with suspected PID.²³⁸ Endometrial specimens as well as cervical swabs were tested for *N. gonorrhoeae* and *C. trachomatis*. Eighty-five of the patients also underwent laparoscopy to confirm a clinical diagnosis of salpingitis. Sixty-five percent, or 117, of the 178 patients had endometritis as confirmed by the presence of plasma cells and PMNs in the endometrial biopsy specimen. Among the patients with endometritis, 27% had *N. gonorrhoeae* present in the endometrium, while 13% had endometrial samples positive for *C. trachomatis*. Approximately 50% of the patients with endometritis had anaerobic Gram-negative rods in their endometrial samples. A logistic regression analysis on the data showed that endometrial *N. gonorrhoeae* was associated with a fivefold increase in endometritis, which was similar for endometrial *C. trachomatis* (OR = 4.8) and anaerobic Gram-negative rods (OR = 2.6), respectively. BV was not an independent risk factor for endometritis in the absence of endometrial anaerobes. However, it was concluded that when the anaerobic Gram-negative rods ascend and infect the endometrium, they are a cause of endometritis independent of STDs.

In a case–control study in which plasma cell endometritis was evaluated, 111 women with gonorrhea, chlamydia, or BV were compared to 24 women without any of these infections for plasma cell endometritis.²³⁸ For the 5% of women with BV alone (those with coinfection by gonorrhea or chlamydia were excluded), plasma cell endometritis was detected in 42%, while endometritis was detected in only 13% of the controls (OR 6.4, 95% CI 1.7–35.0).²³⁹ These studies suggest that women with BV may have clinically inapparent or “silent” endometritis. However, whether BV-associated endometritis leads to salpingitis and infertility is the focus of ongoing studies.

More recently, Wiesenfeld and colleagues performed endometrial biopsies on women with BV (and other lower genital tract infections, including chlamydia and gonorrhea)²⁴⁰ but without symptoms or signs of acute PID. Among 377 women with BV, 58 (15%) had evidence of subclinical PID (defined as the presence of five neutrophils per 400× field and one plasma cell per 120× field of endometrial tissue), while plasma cell endometritis (defined as the presence of at least one plasma cell per 120 of endometrial tissue) was present in 90 (24%). Subclinical PID, but not plasma cell endometritis, was more common in women with BV than in women without BV. Women with intermediate vaginal flora on Gram stain were at intermediate risk of subclinical PID ($p < 0.05$, test for trend), but not plasma cell endometritis. In a multivariate model that included proliferative phase of the menstrual cycle, previous pregnancy, black race, and current infection with *N. gonorrhoeae*, *C. trachomatis*, VB, or *T. vaginalis*, subclinical PID remained significantly associated with BV (adjusted OR 2.7, 95% CI 1.02–7.2).

■ CERVICITIS

A possible association between BV and cervicitis, independent of concomitant chlamydial and gonococcal infection, has emerged in several studies.^{241–244} Moreover, intravaginal antibiotic therapy for BV in the treatment regimen for women with cervicitis was associated with enhanced resolution rates of cervicitis in two studies.^{245,246} Marrazzo et al. reported that among 424 women with BV, cervicitis was relatively common, occurring in 15%, and the overwhelming majority (87%) was not associated with NAAT-based detection of cervical chlamydia or gonorrhea.²⁴¹ In this study, increasing age, fewer years of formal education, report of a new male sex partner or of a current female sex partner, more recent receptive oral sex, and absence of H₂O₂-producing *Lactobacillus* species were independently associated with an increased likelihood of cervicitis among women with BV. Intriguingly, vaginal colonization with H₂O₂-producing *Lactobacillus* species was associated with a 60% reduction in the likelihood of cervicitis.

The mechanism by which BV might cause cervicitis is not clear, and it could be multifactorial. Cervical shedding of HIV is increased in the setting of BV, suggesting that BV itself may have direct effects at the endocervical mucosa.^{247,248} Factors that help regulate the normal function of mucosal defense systems include SLPI, which helps to maintain healthy vaginal mucosa and is decreased in the presence of several STD;¹³¹ IL-10;²⁴⁹ IL-1β; and TNE,¹³² which may increase susceptibility to HIV-1 infection. IL-1β has been associated with a higher number of vaginal neutrophils among women with BV.²⁵⁰ Even when vaginal flora is normal, the balance of pro- versus anti-inflammatory

cervical cytokines may play a key role in modulating visible signs of cervical inflammation and in permitting ascension of STI pathogens or other potential pathogens to the upper genital tract. Decreased cervical proinflammatory cytokines—IL-1β, IL-6, and IL-8—have been associated with an increased likelihood of clinical manifestations of chorioamnionitis.²⁵¹ The possible role of proinflammatory vaginal cytokines, such as IL-1β, IL-6, and IL-8, in BV-associated cervicitis is also supported by the observation that these cytokines decline after successful treatment of BV.¹³¹ Cervical inflammation may be linked to the degradation of mucins, which protect the cervix as well.¹³⁰

■ BV AND HIV

As discussed in Chapter 18, there is growing body of evidence which suggests that the presence of BV, or absence of vaginal lactobacilli, may increase a women's risk of acquiring HIV via heterosexual intercourse. A direct association between HIV infection and BV has been seen in numerous cross-sectional studies^{32,252–254} and supported by prospective studies.^{62,255–257} Taha et al. followed 1196 pregnant women in Malawi for a median of 3.4 months in the antenatal and 2.5 years in the postnatal periods, with monthly assessment of vaginal flora and HIV serostatus.²⁵⁵ They observed that the risk of HIV acquisition as measured by seroconversion increased proportionally to increasingly abnormal vaginal flora, as measured by clinical criteria ($p = 0.04$), and that, overall, BV conferred more than a twofold increase in risk of HIV acquisition ($p = 0.04$). They estimated that the population-attributable risk of BV was 0.33 for HIV acquisition. Among Kenyan sex workers seen monthly, absence of any vaginal *Lactobacillus* and absence of H₂O₂ + *Lactobacillus* and abnormal vaginal flora were independently associated with increased risk of HIV acquisition in multivariate models.²⁵⁶ Absence of hydrogen peroxide-producing *Lactobacillus* strains conferred the highest risk of HIV acquisition (adjusted hazard ratio 2.8, 95% CI 1.1, 4.7). In a large, prospective, nested case-control study of women participating in a cervical cancer screening trial in Capetown, South Africa, HIV acquisition was significantly associated with interim BV (adjusted OR 2.01, 95% CI 1.12–3.62) after adjustment for sexual behavior and acquisition of other STD.⁶² BV was suggested as a reason for low efficacy of STD control in reducing HIV acquisition in a community-based intervention trial in Rakai, Uganda,²⁵⁸ because it frequently persisted after women received single-dose metronidazole.²⁵⁷ In vitro data support the plausibility of a potentiating effect of BV on HIV. Some anaerobes associated with BV augment HIV expression in T cells in vitro, which could enhance frequency or quantity of HIV genital shedding or activate these T cells to further promote HIV transmission.^{259–263} Among HIV-infected women, the quantity of HIV shed in vaginal secretions from those with

BV is increased nearly sixfold relative to those without BV;²⁴⁸ high vaginal pH (>5.5) is associated with nearly twice the quantity of HIV shed.²⁴⁷

The specific reasons for the association of BV and HIV are not clear. In addition to the known viricidal properties of H₂O₂, and of the H₂O₂-halide-peroxidase system, some anaerobes associated with BV augment expression of HIV in T cells in vitro, which might enhance the likelihood or amount of shedding, or activate these T cells in a way that further supports viral transmission.^{259–261} The relationship between BV and HIV acquisition may be most synergistic—and most alarming—in areas of the world where both are highly prevalent. The prevalence of BV among many women in sub-Saharan Africa has been 50% or greater in many studies; with HIV-1 seroprevalence up to 38% in some of these countries, even if BV confers only a small increase in the relative risk for HIV acquisition, the population-attributable risk could be considerable.³²

UNRESOLVED ISSUES IN PATIENT MANAGEMENT

■ HOW COMMON IS LATE RECURRENCE AND WHY DOES IT HAPPEN?

In 1955, Gardner noted that “before the advent of antibiotics and sulfonamides, the treatment of bacterial vaginitis was discouraging because eradication of the causative organism was difficult and recurrences were common.”⁸ Unfortunately, 50 years after Gardner made his initial observation, the treatment of BV can still be discouraging because of the high rate of recurrent infection. Long-term BV recurrence rates exceed 70%.^{84,264} Of 127 women in a prospective study of metronidazole-suppressive therapy, BV recurred in 84% by 4 months in the placebo group and was associated with black race, older age, and higher Nugent score at enrollment.²⁰³ In a study of 139 women with symptomatic BV followed for a year, 58% had recurrence, which was directly associated with report of prior BV, having a regular sex partner throughout the study, or a female sex partner, and was inversely associated with hormonal contraception.⁸⁴ Possible reasons for high recurrence rates include failure to continually suppress growth of some pathogens due either to complete or partial antibiotic resistance,^{177,265} reinoculation with pathogens from an exogenous source (possibly through sex), persistent host factors such as douching or IUD, failure to recolonize the vagina with H₂O₂ + lactobacilli, or infection with a phage that destroys lactobacilli.^{156,266} None of these has been conclusively shown to explain recurrence or identify women at increased risk of BV. However, as noted above, twice-weekly suppressive vaginal metronidazole (Metrogel 0.75%, 37.5 mg) significantly

reduced recurrence rates relative to placebo over 4 months.²⁰³ Microbiologic studies have established that about half of women lack vaginal lactobacilli, which produce H₂O₂ following therapy with clindamycin or metronidazole.¹⁷⁷ Some investigators have promoted the use of H₂O₂ douches for women with BV recurrences,²⁶⁷ but the utility of this approach is unproven.

■ SHOULD MALE PARTNERS BE TREATED?

While many women believe they have contracted BV from a male partner, no study to date has convincingly shown that treatment of the male partner decreases risk of recurrence. For this reason, the CDC does not recommend routine treatment of the male partner at present but does believe that better data on this approach are needed. Randomized, placebo-controlled trials of new approaches to partner treatment, with long-term follow-up in monogamous couples, would be of interest, with better understanding of how men carry and transmit the organisms responsible for BV necessary to guide such trials. No data are available to guide clinicians in empiric treatment of female partners of women with BV.

■ ARE OVER-THE-COUNTER PREPARATIONS OF LACTOBACILLI USEFUL?

A number of women have used over-the-counter lactobacilli products to attempt to reconstitute the vaginal flora. These include acidophilus milk, yogurt or various *Lactobacillus*-containing capsules, and powders available from health food stores. Some of the earliest treatments for VB involved attempts to restore the vaginal flora by application of *Lactobacillus* preparations.^{268,269} Butler reported cure of 18 of 19 patients given from one to eight applications of pure culture of a human-derived strain of Doderlein bacillus at weekly intervals.²⁶⁸ However, only one of 14 women were cured after applying yogurt intravaginally twice daily for 7 days.¹⁹⁶

Bacteria found in an ecologic niche have uniquely adapted to that particular environment. However, the commercial strains of lactobacilli found in dairy products have adapted to the dairy food industry. Strains of lactobacilli that do not adhere well to vaginal epithelial cells may not successfully colonize the vagina. It is unlikely that currently available vaginal probiotic products are of therapeutic value for the treatment or prevention of BV. Treatment of BV using H₂O₂-producing lactobacilli has been an unsuccessful therapeutic option,¹⁹⁸ suggesting that recolonization of the vagina with exogenous lactobacilli will probably be of benefit as an adjunct to, rather than as a replacement of, antimicrobial therapy. However, even this approach has not been proven to be beneficial with currently available products.²⁷⁰

■ SHOULD WOMEN WITH SIGNS OF BV BE TREATED IF ASYMPTOMATIC?

In our experience, some women with BV are aware of a discharge or odor but discount it because it has been present for months or even years. Thus, many women who do not complain of symptoms will acknowledge symptoms of odor and/or discharge on questioning. Women with BV should be informed of their diagnosis, and treatment should be offered if requested. However, definitive recommendations for routine treatment of asymptomatic, nonpregnant women with BV await further studies defining risks of upper tract infection among women with BV and also await more information on the benefits of treating BV to prevent HIV acquisition, as well as improved strategies to prevent late recurrence.

PREVENTION

Since the microbiologic and host risk factors for acquisition of BV are poorly understood, it is difficult to define useful approaches for the prevention of this condition. Since BV is associated with sexual activity, abstinence may represent the most effective (if least popular) means of prevention. Information on condom use and risk of BV is limited, but more recent data indicate that condoms do protect against BV.^{45,50,53,54,58,60} Since the role of sexual transmission in BV is not well defined, and concurrent treatment of male partners has not yet been shown to prevent recurrent BV, treatment of male sex partners cannot be recommended. Recolonization of the vagina with H₂O₂ lactobacilli may protect against infection by BV-associated organisms, but this has not yet been adequately evaluated. Similarly, treatment of BV has not yet been adequately evaluated as a method for preventing pregnancy and puerperal morbidity or postgynecological surgery morbidity. The role of IUD usage as a risk factor for BV requires further study, to confirm or refute the association, and assess the importance of IUD type to any relationships found. The role of genital hygienic practices in the male in protecting the female partner from BV warrants further study, as does the role of douching in increasing the risk among women.

SUMMARY AND FUTURE ISSUES

Several exciting areas in the field of BV offer the potential to significantly advance our understanding of vaginal microbiology and of ways to prevent BV and other STD, including HIV. First, the spectrum of organisms associated with BV will continue to expand as investigators apply culture-independent molecular methods to detect previously obscure organisms. Some of these organisms may help to provide clues to the epidemiology and natural history of BV. For example, are

they associated with the oral or anorectal environments, and does that explain the intriguing relationship of certain sexual behaviors with BV acquisition? Can they be detected as part of the male genital flora and will there consequently be a role for targeted management of male sex partners in women with recurrent BV? Second, the field of probiotic therapy is in its infancy. Investigators have already engineered vaginal strains of *Lactobacillus jensenii* to express functional two-domain CD4 proteins that recognize a conformation-dependent anti-CD4 antibody and bind HIV-1.²⁷¹ This preparation inhibited HIV-1 entry into target cells in vitro in a dose-dependent manner. If this line of investigation continues to prove fruitful, the development of engineered commensal vaginal lactobacilli might be useful not only to inhibit heterosexual transmission and/or acquisition of HIV, but possibly other STDs. Third, research into vaginal microbicides that support or do not inhibit normal vaginal lactobacilli is likely to intensify as the need for female-controlled methods to protect against STI/HIV continues to intensify. Fourth, suppressive therapy for women with recurrent BV—now in the form of metronidazole, and possibly in future with other agents—may become more widely used, where it is affordable and feasible. Finally, there is a critical need to continue to clarify the complex immune dysregulation apparent in BV, particularly in relation to its role in mucopurulent cervicitis, upper genital tract involvement, and adverse outcomes of pregnancy.

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PART 7

Sexually Transmitted Protozoa, Fungi, and Ectoparasites

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INTRODUCTION

Trichomonas vaginalis is a pathogenic protozoan parasite of the human urogenital tract. Transmitted primarily by sexual intercourse, this organism causes vaginitis in women and urethritis in men, though a considerable proportion of infections are asymptomatic. *T. vaginalis* is also implicated in various other genitourinary syndromes. An association between maternal trichomoniasis and premature rupture of the membranes with concomitant preterm delivery has been reported,^{1–3} and there is mounting evidence of an association with cervical cancer.^{4–9}

The World Health Organization (WHO) estimates that trichomoniasis accounts for more than half of all curable sexually transmitted infections (STI) worldwide.¹⁰ *T. vaginalis* caused an estimated 113 million new infections in Africa and Southeast Asia, and nearly 19 million in Western Europe and North America in 1999.¹⁰ Although accurate surveillance data are not available, there were an estimated 5 million new cases of trichomoniasis per year in the United States in the late 1990s, exceeding similar figures for gonorrhea and chlamydial infections combined.¹¹

Infection with *T. vaginalis* can be a marker for high-risk sexual behavior, and high prevalence rates in many populations indicate the need for counseling and behavioral change to reduce patients' risks for acquiring other STIs, including human immunodeficiency virus (HIV). As with other STIs, genital inflammation associated with trichomoniasis increases sexual transmission of HIV.^{12–15} Epidemiological studies suggest that trichomoniasis is associated with increased HIV transmission. Coinfection with *T. vaginalis* and HIV may result in "epidemiological synergy" with prolonged or augmented infectiousness of both infections.^{12,16} Because the prevalence of trichomoniasis is so high, a large proportion of HIV infections could be attributable to *T. vaginalis* infection in populations where both infections are common.¹⁷

HISTORY

T. vaginalis was first described in 1836 by French physician Alfred Donné who observed the organisms in a preparation of fresh vaginal discharge.¹⁸ The protozoan was long regarded as a harmless inhabitant of the vagina. This opinion was unchanged by subsequent descriptions of *T. vaginalis* in the female and male urinary tracts.^{19,20} During the next 50 years, many case reports were published, and in the 1940s, Koch's postulates were fulfilled establishing *T. vaginalis* as an etiologic agent of vaginitis.^{21,22} *T. vaginalis* began to receive increased attention as a cause of urogenital morbidity in men as well.²³ Numerous reports of high prevalence rates for trichomoniasis in different populations have appeared in the literature in the intervening years. More than 150 years after the initial discovery of *T. vaginalis*, it is clear that trichomoniasis can no longer be considered a minor STI.^{17,24–28} Diagnosis and treatment of trichomoniasis in women and men are assuming a higher priority in STI management.^{29,30} However, active control programs for *T. vaginalis* infection are still lacking, and recognition of the importance of *T. vaginalis* infections, by clinicians, is slow in coming.

EPIDEMIOLOGY AND TRANSMISSION

Compared to other STIs, the epidemiology of *T. vaginalis* infection is not as well recognized due to limited diagnostic techniques, absence of screening programs, and lack of disease reporting, even in the most developed national surveillance programs. Prevalence reports for trichomoniasis vary widely, depending on the techniques employed in diagnosis and the population studied. Until the mid-1990s, studies reporting *T. vaginalis* prevalence relied on wet-mount microscopy and culture. Since then, more sensitive nucleic acid amplification techniques, primarily polymerase chain reaction (PCR), have also been used. Recent studies among female sex workers report *T. vaginalis* prevalence rates ranging

from 14.4% in India,³¹ identified by wet-mount or culture, to 43.2% in China, detected by PCR.¹⁰ In general, prevalence estimates range from 5% to 74% in women and 5–29% in men, with the highest rates in both genders reported among STD clinic attendees and other high-risk populations.^{32,33} A community-based study in sub-Saharan Africa found a significantly higher prevalence of trichomoniasis (29–34%) among women in cities with high HIV prevalence compared to women in cities with low HIV prevalence.¹⁵

■ TRICHOMONIASIS AND HIV

T. vaginalis is epidemiologically associated with HIV, and can facilitate the transmission and acquisition of the virus due to inflammatory responses in the vaginal epithelium and ectocervix in women and the urethra in men. Cross-sectional studies demonstrating an association between trichomoniasis and HIV in women suggested two- to threefold increases in HIV transmission.^{34,35} These findings were supported by a prospective study conducted among HIV-negative female sex workers that also showed a twofold increased rate of HIV seroconversion among women with prior *T. vaginalis* infection.¹³ In men, urethritis associated with *T. vaginalis* has been reported to increase HIV shedding in semen eightfold.³⁶ Assuming that *T. vaginalis* increases the risk of HIV transmission by 90% (less than twofold) in a population with a 25% prevalence of trichomoniasis, one estimate indicates that approximately 20% of prevalent HIV cases could be attributable to *T. vaginalis*.³⁷ Another suggests that 6.2% of incident HIV infections among women in the United States may be attributable to trichomoniasis.³⁸

Concomitant infection with other STIs occurs commonly in persons with trichomoniasis.^{3,39} Mixed infections with *T. vaginalis* and *Neisseria gonorrhoeae* and/or *Chlamydia trachomatis* occurred in 1.4% of 504 East African transport workers, while 61.5% of 91 men with trichomoniasis in West Africa also had a gonococcal infection.⁴⁰

■ PREVALENCE IN WOMEN

In general, *T. vaginalis* is highly prevalent among sexually active women. Community-based studies conducted in various parts of the world indicate prevalence figures for trichomoniasis in women range from 2% to 46%.^{41–47} Clinic-based studies in women have found *T. vaginalis* prevalences of 3–18% in adolescent clinics,^{48–50} 10–14% in gynecology or family planning clinics,^{51,52} and 2–18% in STD clinics.^{5,26,53,54} Commercial sex workers and incarcerated women have been identified with prevalences as high as 22–25% and 37–47%, respectively.^{55–58}

In antenatal or prenatal clinics using culture for *T. vaginalis* detection, reported prevalences range from 10% to 18%.^{59,60} Higher prevalences of 20–28% were reported among pregnant women in studies using PCR for *T. vaginalis* detection.^{61,62}

Trichomoniasis has been identified as the most commonly diagnosed STI among HIV-infected women receiving care. Prevalence rates from 9% to 30% have been reported,^{17,63–66} and trichomoniasis accounted for 89% of incident STIs in HIV-positive women in one U.S. study.⁶⁷ High rates of recurrent *T. vaginalis* infection have also been seen in HIV-infected women; one-third of a population of women attending a public HIV outpatient clinic were noted to be reinfected during the follow-up period.⁶⁸ These findings suggest that unprotected sex among HIV-positive women is not uncommon and raise serious concerns about the potential for increased spread of HIV among coinfecting persons.

Among women presenting with vaginal complaints, the reported prevalence of trichomoniasis is as high as 75%.³³ The high prevalence of disease among women with vaginitis has prompted empiric treatment for *T. vaginalis* in syndromic management algorithms when vaginal symptoms are present.⁶⁹ However, approximately 50% of infections with *T. vaginalis* may be subclinical in presentation,⁷⁰ underscoring the need for identification of other risk factors associated with infection especially when universal screening for this pathogen is not feasible.

Factors associated with trichomoniasis in women

Because of the nonspecific clinical presentation of trichomoniasis in women, and the limited performance of available diagnostic methods for *T. vaginalis* in most clinical settings, studies have focused on identifying predictors of infection in women. In multivariate analyses, factors that have been independently associated with trichomoniasis in women include demographic, behavioral, and clinical characteristics (Table 43-1). In the United States, African American race has been strongly associated with trichomoniasis in women, with adjusted odds ratios (OR) between 5.6 and 13.5.^{37,71,72} The association between African American race and trichomoniasis is likely to be multifactorial, and may reflect differences in sexual behaviors, access to care, and socioeconomic factors rather than variations in genetic or racial-based susceptibility to *T. vaginalis* infection.¹⁷

Behavioral factors associated with an increased risk for trichomoniasis include reported sex with nonsteady partners or older partners, and marijuana use among adolescent females.⁷³ In multivariate analyses, other health behaviors such as smoking, alcohol use, injecting drug use, and crack cocaine use have been associated with *T. vaginalis* infection.^{56,66,74,78}

Clinical predictors of *T. vaginalis* infection include the vaginal pH > 5.0, color of vaginal discharge, cervical erythema, and friability (Table 43-1).^{3,75} Cervical atrophy has been reported to be inversely associated with trichomoniasis, suggesting that reduced estrogen, which may affect cervical atrophy, is protective for *T. vaginalis* infection.⁷⁸ The presence of HIV infection and other genital infections such as bacterial

Table 43-1. Risk Factors Associated with Trichomoniasis in Women, from Multivariate Analyses

Reference	Population	<i>T. vaginalis</i> Prevalence	Factor	OR _{adj} ^a	95% CI ^b
15	Random population sample (Kenya and Cameroon)	18–29%	HIV infection	1.7	1.1, 2.7
			HSV-2 infection	2.2	1.3, 3.7
			Gonorrhea	3.0	1.0, 8.6
73	Adolescent females in primary care clinics (US)	13%	Typical sex partner ≥5 yrs older	2.6	1.3, 5.2
			Sex with nonsteady partners	1.9	1.2, 3.3
			Marijuana use	6.2	2.3, 16.6
			Delinquency	1.3	1.0, 1.6
66	HIV+ and HIV- women recruited from general population (US)	23–29%	Injecting drug use	6.7	4.8, 8.5
			Crack cocaine use	2.1	1.5, 2.6
			Alcohol use	4.4	3.1, 5.7
			BV	5.2	3.8, 6.7
			Vaginal candidiasis	1.4	1.0, 1.8
76	Women attending family planning clinics (Kenya)	5%	Unmarried	2.3	1.5, 3.4
			Current IUD use	1.5	1.0, 2.3
			HIV infection	2.4	1.5, 3.8
77	Incarcerated women (Portugal)	31%	Syphilis	9.3	1.8, 48.5
65	HIV-infected women attending clinic (US)	13%	Age < 22 years	1.3	1.0, 1.8
			African American race	2.4	1.6, 3.7
			Substance use	2.7	2.0, 3.5
			Presence of other STDs	1.8	1.4, 2.2
71	Women attending primary care clinics (US)	24%	African American race	13.5	NR ^c
			Douching >1/month	3.5	NR
3	Women attending prenatal clinics (US)	13%	Yellow/green/bloody vaginal discharge	1.6	1.3, 1.9
			Copious discharge	1.2	1.0, 1.5
			Abnormal consistency	1.2	1.1, 1.4
			Cervical friability	1.3	1.1, 1.5
			Cloudy/opaque cervical mucus	1.1	1.0, 1.3
75	Women attending family planning clinics (South Africa)	18%	No travel outside district	2.8	1.0, 7.7
			Cervical erythema	3.5	1.7, 7.5
			Nonclear, nonwhite vaginal discharge on examination	3.2	1.3, 8.1
56	Pregnant women attending jail clinic (US)	47%	Crack cocaine use	2.3	1.2, 4.5
			Serological evidence of syphilis, past or present infection	2.3	1.0, 5.3
37	HIV-infected women attending HIV outpatient clinic (US)	17%	African American race ^d	5.6	2.3, 13.3

(Continued)

Table 43-1. (Continued)

Reference	Population	<i>T. vaginalis</i> Prevalence	Factor	OR _{adj} ^a	95% CI ^b
72	Women attending STD clinic (US)	18%	African American race	10.3	3.2, 32.8
			Sexual exposure to <i>T. vaginalis</i>	6.6	1.3, 34.3
			Any drug use	2.9	1.8, 4.8
74	Women attending STD clinic (US)	24%	Age	1.03 ^e	NR
			Cocaine or heroin use in the prior week	9.2	NR
			Abnormal vaginal discharge	2.6	NR
7	Women in cervical cancer screening program (China)	11.2/1000 person-years (incidence)	Smoking	1.3	1.1, 1.5
			Alcohol use	1.5	1.2, 2.0
			Number of extramarital partners ^f	1.1	1.0, 1.2
			Number of induced abortions	1.1	1.0, 1.2
			Cervical atrophy	0.5	0.4, 0.6

^aAdjusted odds ratio.^bConfidence interval.^cNot reported.^dNonblack referent group.^eAmong nonblacks only; negative response referent group.^fOR per year of age.

vaginosis (BV), vulvovaginal candidiasis, gonorrhea, genital herpes, and syphilis have also been independently associated with trichomoniasis.^{15,66,76} However, one retrospective study of female patients presenting to an emergency department with STI symptoms reported a strong negative association between *T. vaginalis* detected by wet-mount microscopy and coinfection with *N. gonorrhoeae* and/or *C. trachomatis*.⁷⁹

Among HIV-positive women, young age, African American race, substance abuse, and presence of other STIs have been associated with *T. vaginalis* infection.⁶⁵ Trading sex for drugs or money has been reported to be a strong risk factor (adjusted RR = 25.2) for trichomoniasis in non-African American women coinfecting with HIV.³⁷ Neither immune status defined by CD4 counts nor use of protease inhibitors among HIV-positive women was associated with initial or subsequent trichomoniasis, suggesting that *T. vaginalis* is not an opportunistic pathogen.⁶⁵

■ PREVALENCE IN MEN

The prevalence of trichomoniasis in men is not well described, because most infected men are asymptomatic and may not seek evaluation. Furthermore, *T. vaginalis* diagnostic tests are seldom available or used for evaluation of male

patients presenting for care. In a community-based study of men in Tanzania, *T. vaginalis* was found in 11% by microscopic examination and culture of urine sediment, and was the most common sexually transmitted pathogen identified in this population.⁸⁰ In clinic-based studies using *T. vaginalis* culture of specimens from male patients in the United States and Africa, prevalences of trichomoniasis ranged from 3% to 13%.^{81,82,84} In one study in Malawi, a higher prevalence of 15.7% was noted among men with symptomatic urethritis, compared to 8.7% among asymptomatic men.⁸²

Using more sensitive PCR detection methods with or without culture, other studies conducted in men suggest higher prevalences of *T. vaginalis* infection in STD clinics ranging from 13% to 20%.^{16,28,74} In a U.S. study using PCR detection, the prevalence was significantly higher (51.4%) in asymptomatic men compared to men with urethral symptoms (23.0%).²⁸

Factors associated with trichomoniasis in men

Only a few studies have identified independent risk factors associated with trichomoniasis in men (Table 43-2). Demographic factors associated with *T. vaginalis* infection in men from community- and clinic-based studies include older age and being married.^{16,80} Not surprisingly, never having

Table 43-2. Risk Factors Associated with Trichomoniasis in Sexually Active Men, from Multivariate Analyses

Reference	Population	<i>T. vaginalis</i> Prevalence	Factor	OR _{adj} ^a	95% CI ^b
83	Men attending STD clinic (US)	11%	Sexual contact to <i>T. vaginalis</i>	3.7	1.9, 7.4
			History of prior treatment for trichomoniasis	3.1	1.4, 6.9
81	Men attending STD clinic (US)	3%	Age > 30 AND discharge AND NGU ^c diagnosis	10.9	3.3, 35.7
16	Men attending dermatology clinic (Malawi)	13%	Age 21–25 years ^d	6.6	1.5, 29.7
			Age ≥ 31 years ^d	7.1	1.3, 37.2
			No condom use	3.0	1.6, 5.6
16	Men attending STD clinic (Malawi)	20%	≥ Secondary school education	0.6	0.4, 0.9
			Divorced or widowed ^e	2.7	1.4, 5.2
			Married ^e	1.6	1.0, 2.5
			No condom use	1.8	1.2, 2.6
			Presence of GUD	1.7	1.2, 2.6
80	Men from general population (Tanzania)	11%	Unskilled manual laborer	8.9	1.8, 43.9
			Religion ^f	4.3	1.1, 16.1
			Married, one wife	1.8	1.0, 3.1
			Married, two or more wives	3.2	1.4, 7.4

^a Adjusted odds ratio.^b Confidence interval.^c Nongonococcal urethritis.^d Referent group of 18–20 years of age.^e Referent group of single marital status.^f Non-Muslim, non-Catholic, non-Protestant religion.

used a condom was found to be associated with trichomoniasis.¹⁶ A history of exposure to a woman with trichomoniasis and a history of prior trichomonal infection are clinical factors that have been significantly associated with *T. vaginalis* in men. In a U.S. study of men attending an STD clinic, the combination of symptoms of discharge, diagnosis of NGU, and age ≥ 30 years was highly predictive of *T. vaginalis* infection.⁸¹ Among men with trichomoniasis, the strongest clinical association is with NGU.²⁵ In a study conducted in Malawi, where genital ulcer disease (GUD) is a common presenting complaint in STD clinics, men with GUD were also more likely to have *T. vaginalis* infection.¹⁶

■ TRANSMISSION

T. vaginalis is transmitted almost exclusively by sexual intercourse. In the past, however, there was active debate on the route of transmission for this pathogen.^{85,86} Studies showing

that trichomonads can survive for up to 45 minutes on toilet seats, washcloths, clothing, and in bath water fueled speculation that nonsexual transmission was common.⁸⁵ Although nonsexual transmission by contaminated fomites may explain reports of trichomoniasis in a few patients, such as sexually mature virgins, the data suggest that nonsexual transmission of *T. vaginalis* is rare.^{87,88} Therefore, *T. vaginalis* detection in a prepubertal child should raise the suspicion for sexual abuse, despite the tendency to believe that the mode of transmission may be asexual. In a study of girls under 16 years of age who were referred for evaluation of sexual abuse, trichomoniasis, gonorrhea, and chlamydia were detected in similar proportions.⁸⁹ *T. vaginalis* infection has also been reported in both partners of a lesbian couple who denied use of penetrative sex toys or recent male partners, suggesting transmission may occur through mutual masturbation.⁹⁰

Perinatal transmission can occur in about 5% of female children of infected mothers. Although neonatal genital infections

are usually self-limited, with progressive metabolism of maternal hormones,^{91,92} respiratory *T. vaginalis* infection can occur in newborns of infected mothers and may be accompanied by suppurative nasal discharge and respiratory distress.^{93–96} The detection of *T. vaginalis* by PCR from adult pharyngeal specimens has been recently noted among HIV-positive men with a history of orogenital sexual activity.⁹⁷ The significance of this finding is unclear, and further investigations are required to understand the potential role of orogenital transmission in the current epidemiology of trichomoniasis.

The consensus view that *T. vaginalis* is acquired predominantly by direct genital contact is strongly supported by evidence from (1) human inoculation studies, (2) isolation of the organism from urogenital sites, and (3) epidemiological data. Human challenge studies, conducted in the 1940s–1950s, before the availability of effective therapy, fulfilled Koch's postulates documenting that clinical trichomoniasis can be produced by inoculation of the human vagina or male urethra with pure cultures of *T. vaginalis*.^{21,22,98} Intravaginal inoculation in women led to infection in up to 75%, regardless of the bacterial flora that was initially present (as definable at that time).²² Findings characteristic of vaginal trichomoniasis occurred in experimentally infected women after a 5–28-day incubation period. In a study involving men, all five subjects inoculated intraurethrally with *T. vaginalis* developed urethritis within 24 hours of inoculation.⁹⁸ Two of the men also developed prostatitis, based on microscopic examination of expressed prostatic secretions.

The prevalence of *T. vaginalis* among sexual contacts of infected patients clearly supports the view that trichomoniasis is transmitted primarily by sexual contact. In various studies, *T. vaginalis* was isolated from 14% to 60% of male partners of infected women.^{99–101} In addition, *T. vaginalis* was isolated from 67% to 100% of female partners of infected men.^{86,102}

Factors affecting transmission or concordance of *T. vaginalis* infection between sexual partners are largely unknown. One large study of male sexual partners of women with trichomoniasis investigated demographic, clinical, and behavioral risk factors for concordant infection in couples.¹⁰³ Results from this study suggested that an abnormal vaginal pH > 4.5 in infected women and male partner age < 40 years are independently associated with concordant infection.¹⁰³ Further determination of factors associated with concordant *T. vaginalis* infection will improve our understanding of the dynamics of its sexual transmission.

PARASITE TAXONOMY AND MORPHOLOGY

Trichomonads are flagellated eukaryotic microbes belonging to the protozoan order trichomonadida. There are over 100 species; most are commensal organisms of the intestinal tract of mammals and birds. Three species are found in

humans; *T. vaginalis* is a parasite of the genitourinary tract, while *T. tenax* and *Pentatrichomonas hominis* are nonpathogenic trichomonads found in the oral cavity and large intestine, respectively.

Trichomonads represent one of the most ancient eukaryotic lineages.^{104,105} *T. vaginalis* has been considered a primitive eukaryote since it lacks many features of higher eukaryotes including mitochondria, peroxisomes, and 28S ribosomes. However, *T. vaginalis* ribosomes do have typical, conserved eukaryotic features; their smaller size is due to reduced or absent variable regions.¹⁰⁶ Furthermore, the identification of splicing machinery and intron-containing genes, previously thought to be absent in *T. vaginalis*,¹⁰⁷ suggests that many of the features that distinguish this amitochondriate protist from higher eukaryotes are the result of secondary loss of more typical eukaryotic structures and functions and do not necessarily represent primitive or intermediate development during early eukaryotic evolution.

The size and shape of *T. vaginalis* vary, depending on the vaginal microenvironment or on culture conditions. Typically, the organism has a pyriform shape approximately 7–32 μm long and 5–12 μm wide,¹⁰⁸ roughly the size of a leukocyte (Fig. 43-1A). Upon interaction with epithelial cells, *T. vaginalis* assumes an amoeboid form¹⁰⁹ (Fig. 43-1B), and recent clinical isolates readily attach to plastic. Free-swimming trichomonads demonstrate a characteristic erratic, twitching motility as they are propelled by four anterior flagella that originate in a structure known as the kinetosomal complex. A fifth flagellum originates from the kinetosomal complex and extends halfway down the organism, attached to the undulating membrane supported by a complex array of filaments known as the costa. The parasites contain an anterior nucleus, a parabasal apparatus, a Golgi complex, and an axostyle that runs centrally through the cell and protrudes to form a posterior tail, or projection. Parallel to the axostyle and costa are three rows of large chromatic granules including hydrogenosomes. Hydrogenosomes, characteristic organelles found in *T. vaginalis* and other protists that lack mitochondria, are double membrane-bound structures that generate hydrogen and ATP from metabolism of pyruvate.¹¹⁰ The recent discovery of *T. vaginalis* hydrogenosomal proteins with notable homology to mitochondrial components suggests that these organelles may share a common ancestry with mitochondria.^{111–113}

Trichomonads are generally thought to exist only in the motile, vegetative trophozoite form, and true cysts or resistant stages have not been described. However, *T. vaginalis* pseudocysts, which appear in vitro under unfavorable environmental conditions, have been observed.^{114,115} Pseudocysts have altered structural features, including internalized flagellae and a compact form lacking a true cell wall.¹¹⁶ Whether the pseudocyst form plays a role in trichomoniasis is not yet clear.

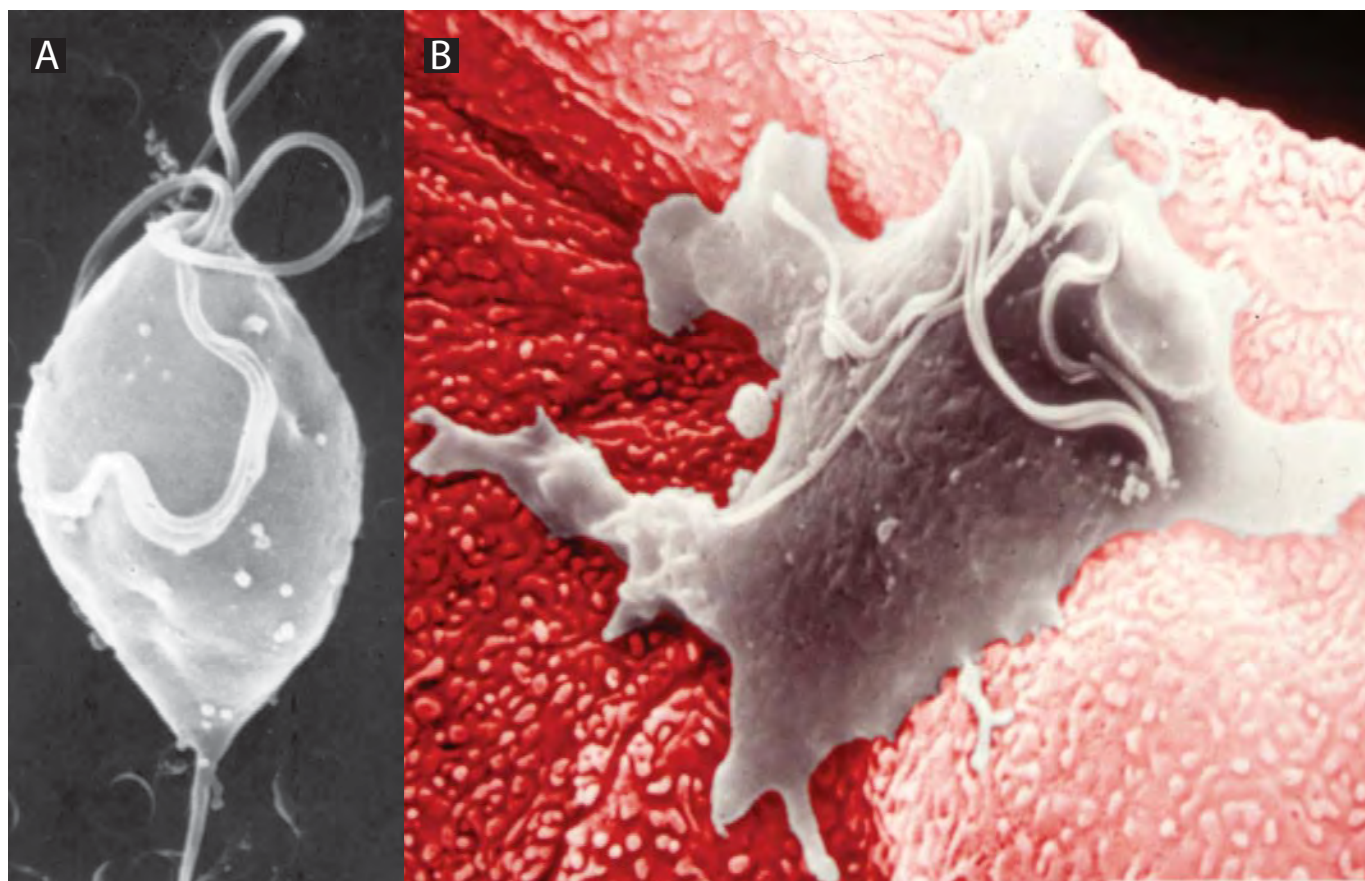


FIGURE 43-1. Scanning electron micrographs of *T. vaginalis*. In panel **A**, three of the four anterior flagella (and the origin of the fourth), the undulating membrane with its trailing flagellum, and the axostyle protruding at the end of the pyriform body are visible. $\times 6000$ magnification. (With permission from Honigberg BM. *Trichomonads Parasitic in Humans*. New York: Springer-Verlag, 1990, Fig. 3.2c, p. 10.) In panel **B**, *T. vaginalis* undergoes amoeboid transformation within 5 minutes after contact with vaginal epithelial cells in vitro; bar, $5\mu\text{m}$. (From Arroyo R, Gonzalez-Robles A, Martinez-Palomo A, et al. Signalling of *Trichomonas vaginalis* for amoeboid transformation and adhesion synthesis follows cytoadherence. *Mol Microbiol* 1993; 7: 299. With permission from Blackwell Publishing.)

T. VAGINALIS GENETICS AND BIOLOGY

■ NUCLEIC ACID CONTENT AND STRUCTURE

Trichomonads reproduce asexually by mitosis followed by longitudinal cell division. In an unusual process known as closed mitosis, the parasite nuclear envelope remains intact, and the mitotic spindle is external to the nucleus. Results of electrophoretic and cytologic analyses suggest that the *T. vaginalis* nucleus contains six haploid chromosomes.^{117–119} However, preliminary data generated by the *T. vaginalis* Genome Sequencing Project (<http://www.tigr.org/tdb/e2k1/tvg/>) suggest a highly repetitive genome of approximately 180 megabases, much larger than anticipated based on earlier studies.¹²⁰ While the exact genome size and chromosome number are uncertain, the haploid nature of *T. vaginalis* is confirmed by the ability to disrupt genes by homologous recombination.¹²¹

Protein-coding genes in *T. vaginalis* are preceded by promoters that have structures similar to those of higher eukaryotes

with a conserved core promoter region and upstream gene-specific regulatory elements.¹²² Although trichomonad promoters lack a typical TATA-box sequence, there is a highly conserved sequence element surrounding the transcription start site of *T. vaginalis* genes.^{122–124} Promoter features identified upstream of *T. vaginalis* genes include positive and negative regulatory sequences, and iron-responsive elements.^{123,125,126}

A potentially functional transposable element in the *mariner* family has been documented in the *T. vaginalis* genome.¹²⁷ Sequence analyses identified several hundred copies of the transposon in strain G3, and Southern blot hybridization of several other strains suggested that the transposable element, named *Tvmar1*, may be widely distributed within the species. Transformation vectors based on transposons like *Tvmar1* are valuable tools for insertional mutagenesis studies in a variety of organisms, and this discovery suggests that similar studies in *T. vaginalis* may be possible.

Some *T. vaginalis* strains contain double-stranded RNA viruses known as *T. vaginalis* virus (TVVs). First described in the mid-1980s,¹²⁸ TVVs are a group of divergent viruses

classified in the *Totiviridae* family.^{129,130} TVV RNAs encode a capsid protein and an RNA-dependent RNA polymerase, and some viral genomes appear to encode two additional proteins in alternate reading frames.¹²⁹ Whether these putative additional proteins are expressed in infected parasites and what their functions might be remain to be determined. Observations of purified virus particles from infected parasites indicate that *T. vaginalis* organisms can harbor different TVVs simultaneously.^{131,132}

In studies of recent clinical *T. vaginalis* isolates, 50–80% contain TVV.^{74,133–135} TVV-harboring *T. vaginalis* undergo phenotypic variation with respect to surface and cytoplasmic expression of the P270 protein.^{136–138} Virus-negative trichomonads also exhibit decreased expression of P270 mRNA; thus, TVV influences trichomonal gene and protein expression. However, a role for TVV in the pathogenesis of trichomoniasis has not been established.

■ GROWTH AND METABOLISM

The growth and multiplication of *T. vaginalis* are optimal in microaerophilic or anaerobic conditions with temperatures between 35°C and 37°C and pH levels between 4.9 and 7.5. The organisms can be cultivated axenically in nutrient media designed to provide optimum redox potential, pH, and antimicrobials to suppress other microorganisms.¹³⁹ More robust, smaller organisms are observed at pH 5.5–5.8, whereas less motile, larger organisms are encountered at pH levels lower or higher than optimum. In batch cultures, parasites typically have generation times of 4–6 hours.¹⁴⁰

T. vaginalis is an aerotolerant anaerobic protist. Growth is inhibited at high oxygen tensions due to deficiency of catalase,¹⁴¹ but some multiplication can be observed in media equilibrated with air. This aerotolerance is attributed to the presence of active superoxide dismutase. Whether oxygen is absent or present, trichomonal metabolism is fermentative. Pyruvate produced by glycolysis in the cytosol is reduced to lactate in the hydrogenosomes. *T. vaginalis* hydrogenosomes can also metabolize malate via decarboxylation to pyruvate. These organelles contain pyruvate-oxidizing enzymes (pyruvate-ferredoxin oxidoreductase) and hydrogenase that are linked by an electron transport protein of low redox potential.

In addition to its role as the metabolic powerhouse, the trichomonad hydrogenosome is important in drug activation. Metronidazole and other nitroimidazoles, used in the treatment of trichomoniasis, enter the cell and subsequently the hydrogenosomes by passive diffusion in an inactive form.¹⁴² Electrons required for drug activation are thought to be provided by 2Fe-2S ferredoxin. Ferredoxin-linked electrons are generated during oxidative decarboxylation of pyruvate catalyzed by pyruvate:ferredoxin oxidoreductase. Additional electrons are released during oxidative decarboxylation of

malate catalyzed by activity of NAD-dependent malic enzyme. Under anaerobic conditions, reduced ferredoxin transfers electrons to hydrogenase.¹⁴³ In the presence of 5-nitroimidazoles, ferredoxin preferentially transfers electrons for the reductive activation of the drug.¹⁴⁴ This process is highly efficient under anaerobiosis; however, under aerobic conditions, oxygen can compete with metronidazole for ferredoxin-transported electrons, thus inhibiting the drug activation. Consequently, the efficiency of the redox system of a particular *T. vaginalis* strain appears to be critical for susceptibility of trichomonads to the drug.¹⁴⁵

Trichomonads, like most other parasitic protozoa, are unable to synthesize purine ring structures or to interconvert purine nucleotides. However, *T. vaginalis* can salvage the purine bases adenine and guanine and their nucleosides. Trichomonad nucleoside phosphorylase and nucleoside kinase activities appear to be responsible for conversion of the purine bases and nucleosides to nucleoside monophosphates. In vitro, *T. vaginalis* disrupts monolayers of human female- and male-derived genital epithelial cells.^{146–150} The parasite can bind to nuclei released from lysed host cells, hydrolyze extracellular nucleotides, and incorporate ³H-thymidine from labeled epithelial cells into its own DNA, suggesting that host cell nuclei may serve as a source of nucleotides for *T. vaginalis* growth in vivo.^{150–152}

T. vaginalis also possesses hemolytic activity.^{153–157} Specific association with erythrocytes (hemagglutination) and subsequent hemolysis are thought to be important for destruction of erythrocytes in menstrual blood, with release of iron, lipids, and fatty acids for parasite membrane biosynthesis.^{158,159}

■ T. VAGINALIS STRAIN CLASSIFICATION

As early as the 1960s, mouse models of *T. vaginalis* infection using subcutaneous chambers or intraperitoneal inoculation were used to classify strains as virulent or avirulent.^{160–162} However, correlation of strain characteristics in mice and clinical disease in patients was inconsistent.^{163,164}

Early characterization of *T. vaginalis* isolates using traditional serotyping methods indicated some heterogeneity among strains.¹⁴¹ Results of studies using polyclonal antisera in assays relying on hemagglutination, gel immunodiffusion, and complement-fixation estimated that there were from two to eight different serotypes in Europe. Isoenzyme patterns (zymodemes) of *T. vaginalis* were also evaluated in early attempts to characterize differences among isolates. Using this technique, isolates could be classified into groups. However, zymodemes were not useful for distinguishing virulence potential or antimicrobial drug sensitivity.^{165,166}

T. vaginalis strain variation has been observed with respect to expression of the phenotypically varying P270 immunogen.^{136,137,167} All *T. vaginalis* isolates can express a P270 protein under certain conditions, and size polymorphisms

have been attributed to different numbers of tandem repeats composing the central portion of the protein.¹⁶⁷ However, P270 expression and surface localization are influenced by iron and parasite infection with the TVV.^{136,137} Microbial strain typing based on protein expression phenotypes is affected by differences in protein expression at the time of analysis that do not necessarily reflect intrinsic strain differences.

In more recent studies employing genetic typing methods, investigators have classified *T. vaginalis* strains using random amplified polymorphic DNA (RAPD) analysis^{135,168,169} and restriction fragment length polymorphisms of specific genomic loci including ribosomal intergenic sequences.^{170,171} While these studies indicate that there is substantial genetic variability among *T. vaginalis* strains, no reproducible, widely accepted strain typing system has yet been established. The availability of *T. vaginalis* genome sequence data should facilitate development and improvement of parasite genotyping tools for use in molecular epidemiological studies of trichomoniasis and its impact on transmission of other STIs including HIV.

PATHOGENESIS

To establish infection in the human urogenital tract, *T. vaginalis* penetrates the mucous layer to gain access to the underlying epithelial cells where parasites can attach, resulting in tissue damage and inflammation. Intensive research efforts have been aimed at elucidating the molecules and mechanisms involved in these processes. Although it is far from complete, an interesting and complex picture of trichomonas pathogenesis is emerging.

■ T. VAGINALIS ENZYMES AND ADHESINS

T. vaginalis produces numerous proteolytic enzymes, many of which have been shown to be involved in cytotoxicity, hemolysis, evasion of immune responses, or adherence. The genes encoding many of these proteinases are iron regulated, and examples exist for both increased^{126,172,173} and decreased¹⁷⁴ proteinase expression under high iron conditions. Several cysteine proteinases have been identified both on the surface of the parasite and secreted during growth in vitro.^{175–177} Trichomonal enzymes are found in vaginal secretions of infected women along with antibodies that recognize these enzymes.^{178–180} Trichomonads bind mucin in vitro, and several secreted proteinases can degrade mucin. Mucinases are active over a pH range of 4.5–7.0,¹⁷⁴ consistent with a role in the vaginal, urethral, or prostatic milieu to facilitate parasite penetration of the mucous barrier.

Once *T. vaginalis* traverses the mucous layer, adherence to epithelial cells is mediated by parasite surface adhesin proteins known collectively as APs. Several APs have significant homology with known metabolic enzymes.^{181–184} The localization of metabolic enzymes on the surfaces of

microbial pathogens is a recently recognized example of functional diversity and molecular mimicry.¹⁸²

T. vaginalis adherence to epithelial cells in vitro is required for parasite-induced cytopathic effects (CPE) with likely contributions to pathogenesis. Both contact-dependent^{149,155,157,185} and -independent mechanisms^{157,186} have been proposed to mediate CPE. *T. vaginalis* contains soluble and membrane-associated enzymes with phospholipase A (PLA) activity.^{153,154,187} *T. vaginalis* PLAs lyse nucleated mammalian cells and red blood cells in vitro and may contribute to tissue damage and inflammation in trichomoniasis. In studies using male- and female-derived urogenital cells, *T. vaginalis* disruption of polarized epithelial monolayers facilitated penetration of HIV to underlying layers.¹⁴⁶

Trichomonads adhere not only to host epithelial cells but also to extracellular matrix components including fibronectin and laminin.^{188–190} *T. vaginalis* encodes a putative surface protein that contains a leucine-rich repeat domain also found in fibronectin-binding proteins from other organisms that colonize mammalian mucosal surfaces.¹⁹¹ *T. vaginalis* binding to the host extracellular matrix may be important for persistence once the vaginal epithelium has been exfoliated, either by parasite-induced CPE or shedding during the menstrual cycle.

■ HOST COMPONENTS ASSOCIATED WITH T. VAGINALIS

Numerous host macromolecules are known to coat the *T. vaginalis* cell surface. These host-derived molecules are important to the survival of the parasite in vivo and contribute to *T. vaginalis* metabolism and pathogenicity, either through biological mimicry or through accumulation of nutrients from the host. These molecules include α_1 -antitrypsin, α_2 -macroglobulin, fibronectin, lactoferrin and other iron-binding and iron-containing proteins, lipoproteins, and lipids.¹⁴⁰ Specific receptor-mediated acquisition of iron-binding proteins is important in the pathogenesis of trichomoniasis. In vitro, *T. vaginalis* can obtain iron from lactoferrin, ferritin, hemoglobin, heme, and cytochrome c, but not transferrin.^{172,192} Iron uptake and increased intracellular enzyme activity follow host lactoferrin binding to parasite surface receptors, and growth in high iron results in increased expression of many virulence genes involved in adherence.^{125,172,173,181,190,193–195}

■ T. VAGINALIS PHAGOCYTOSIS

The capacity of *T. vaginalis* for phagocytosis has long been recognized.^{196–199} Vacuoles, particles, bacteria, viruses, and rarely leukocytes, erythrocytes, and epithelial cell membranes can be found within the parasite cytoplasm.^{155,200–205} Particle recognition and phagocytosis appear to be mediated by both nonimmunological means²⁰⁶ and by specific immunological

cell surface receptors similar to the Fc and complement receptors of polymorphonuclear leukocytes.²⁰⁷

T. vaginalis infection is often clinically associated with detection of bacteria in the urogenital tract including *N. gonorrhoeae*, *C. trachomatis*, and *Mycoplasma hominis*,^{41,78,80,83,208–210} and in vitro studies demonstrated that trichomonads readily take up these bacteria.^{171,196,211–213} Early suggestions that gonococcal or chlamydial transmission or persistence could result from protection of engulfed bacteria inside *T. vaginalis* were contradicted by in vitro studies showing that phagocytized bacteria were efficiently killed by the parasite.¹⁹⁶ However, documentation of survival and replication of *M. hominis* within *T. vaginalis* suggests that the protozoan may play a role in transmission of mycoplasma.^{211,213–215} Whether there are consequences of such a relationship for the pathogenesis of trichomoniasis remains to be determined.

■ HOST IMMUNE RESPONSES

Infection with *T. vaginalis* elicits cellular, humoral, and secretory immune responses. However, these responses do not protect patients against reinfection. Repeated infections in women are commonly encountered in clinical settings, and a history of prior treatment for trichomoniasis is a risk factor for infection in men.⁸³

Inflammatory responses

Vaginal or urethral inflammation, characterized by an influx of polymorphonuclear leukocytes, represents the most obvious host response to infection with *T. vaginalis*. In some cases, inflammation is greater in patients with higher parasite loads.¹⁶³ Recent reports suggest that *T. vaginalis* can stimulate human neutrophil production of IL-8²¹⁶ and TNF- α production by murine splenocytes through activation of toll-like receptor 4 (TLR4).²¹⁷ IL-8 is a potent chemoattractant produced by neutrophils and epithelial cells in response to microbial infection, and its stimulation likely induces further neutrophil recruitment to the site of infection. TLR-4 engagement on host cells, whether through binding of a parasite product or an endogenous ligand produced in response to *T. vaginalis* infection, would also result in stimulation of proinflammatory host responses. Increased proinflammatory cytokine production in trichomoniasis is consistent with increased HIV transmission, providing a plausible mechanism for the observed epidemiological synergy. *T. vaginalis* has been shown to activate HIV-infected leukocytes resulting in TNF- α production and increased viral replication.¹⁴⁶

Antibody and complement

Antibody and complement components, present in serum and genital fluids of some individuals with trichomoniasis, can bind the surface of *T. vaginalis*, lyse trichomonads, and stimulate the

neutrophil respiratory burst facilitating parasite killing via classical and alternative complement pathways.^{140,218,219} *T. vaginalis* antigens recognized by antitrichomonal antibodies include surface and secreted cysteine proteases,^{178,220} heat-shock proteins,²²¹ alpha actinin,²²² and the P270 protein.²²³ However, there is little evidence that development of such antibodies contributes to parasite clearance. Furthermore, persistent trichomonal infections, a hallmark of trichomoniasis, suggest that humoral immune responses are not broadly protective. *T. vaginalis* resistance to humoral immune responses may be due to parasite production of proteinases that can cleave human immunoglobulins and complement components.^{140,224,225} Expression of these proteolytic enzymes is upregulated under conditions likely to be encountered during infection such as high iron levels present during menstruation.

Despite the lack of protection afforded by immune responses to naturally acquired *T. vaginalis* infection, there is evidence to suggest that antibodies that block attachment of the parasite to mucosal surfaces could be protective. Reduced adhesin expression mediated by antisense RNA silencing results in reduced attachment,²²⁶ and antibodies that bind surface adhesins block *T. vaginalis* adherence to host cells in vitro.^{172,176,181,227} Moreover, administration of high doses of monoclonal antibodies against a trichomonad surface proteinase/adhesin protected mice from intraperitoneal challenge with *T. vaginalis*.²²⁷ Whether these observations can be translated into an effective *T. vaginalis* vaccination strategy remains to be seen.

CLINICAL PRESENTATION

■ SITES OF INFECTION

In women, *T. vaginalis* has been isolated from all genitourinary sites. Vaginal infection is most common, followed by infection of the urethra, Bartholin's and Skene's glands, and endocervix. While concomitant infection of the urethra occurs in a majority of women with vaginal trichomoniasis, concordance of infection is not absolute. Among women infected with *T. vaginalis*, almost 10% demonstrated positive cultures only from the urethra.²²⁸

In men, *T. vaginalis* has been isolated from the urethra, urine, semen, external genitalia, epididymis, and prostate.^{29,101,140,229} Marked rates of anatomically discordant sites of infection for men have also been documented. [Figure 43-2](#) shows recovery of trichomonads from different urogenital specimens from men. Nearly one-third of infections in men will be missed when a single specimen is evaluated.²²⁹

■ INFECTIONS IN WOMEN

The spectrum of clinical presentations with *T. vaginalis* infections ranges from asymptomatic disease, to severe vaginitis.

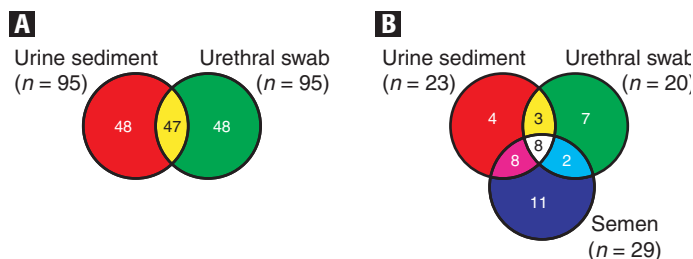


FIGURE 43-2. Detection of *T. vaginalis* in different urogenital specimens from men. **A.** Cases detected by use of urine specimen culture and urethral swab culture. A total of 143 infections were identified from a total of 1701 complete sets of specimens. **B.** Cases detected by use of urine specimen urethral swab and semen specimen culture. A total of 43 infections were identified from a total of 288 complete sets of specimens. (From Kaydos-Daniels SC, Miller WC, Hoffman I, et al. The use of specimens from various genitourinary sites in men, to detect *Trichomonas vaginalis* infection. *J Infect Dis* 2004; 189: 1926. With permission of the University of Chicago Press.)

The degree to which this variability in presentation is influenced by differences in host susceptibility or parasite-specific virulence factors is not known. Furthermore, studies describing clinical manifestations often rely on insensitive diagnostic methods for *T. vaginalis*, and frequent coinfection with other STIs confounds analysis of clinical presentation.⁵⁴

Although many women are asymptomatic, the most common presenting complaint among symptomatic women diagnosed with *T. vaginalis* is vaginal discharge. Vaginal discharge is seen in more than 50% of cases. Other symptoms include pruritus, dysuria, and abdominal pain.^{87,230} Some women remain asymptomatic until after menses, suggesting a role for iron in the pathophysiology of trichomoniasis.¹⁹⁴ Symptomatic patients may also complain of malodorous discharge. Dysuria is a common complaint and has been observed in up to one-third of women diagnosed with *T. vaginalis*.⁷⁵

On genital examination, vulvar erythema and edema may be noted. Upon speculum examination, the vaginal discharge can have any color or characteristic, although a frothy yellow or greenish discharge has classically been associated with trichomoniasis (Fig. 43-3). An inflammatory vaginal discharge as defined by presence of polymorphonuclear cells may be present even in the absence of symptoms.²³¹ The vaginal walls may also be erythematous.

Cervical pathology may be seen with *T. vaginalis* infections. Colpitis macularis, or “strawberry cervix” (Fig. 43-4), is a result of microscopic, punctate hemorrhages on the cervix. Colpitis macularis may be observed in fewer than 5% of women with trichomoniasis; however, a proportion of trichomoniasis cases with colpitis macularis can be identified using colposcopy.^{162,232,233} Although uncommon, this finding is highly specific for trichomoniasis; rarely, there are other etiologies.²³⁴ The resulting cervicitis may lead to postcoital bleeding and cervical friability. Cervical mucopurulence and/or cervical erythema have also been observed in women



FIGURE 43-3. Profuse purulent vaginal discharge due to trichomoniasis. Color is greenish yellow when viewed on a white swab. Appearance is occasionally frothy, as seen here.

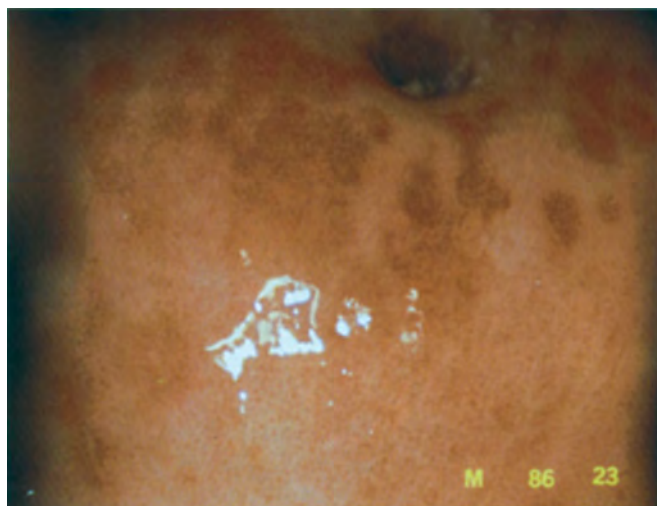


FIGURE 43-4. Colposcopic photograph of “strawberry cervix” showing petechiae on the ectocervix in a patient with trichomonal vaginitis and ectocervicitis.

diagnosed with trichomoniasis, but these findings are neither sensitive nor specific. Although women with trichomoniasis may present with mucopurulent cervicitis, other STIs such as gonorrhea and chlamydial infection should also be considered.

Women with trichomoniasis are more likely to present with an elevated vaginal pH, amine odor, milky discharge, or colonization by *Gardnerella vaginalis*, *Bacteroides* spp., or genital mycoplasmas than women with normal flora characterized by predominant lactobacilli. Specifically, *T. vaginalis* has been associated with intermediate vaginal flora characterized by reduced lactobacilli detected by Gram stain.²³⁵ Because the vaginal environments for trichomoniasis and BV are similar, BV is found concomitantly in 25–60% of women with trichomoniasis.^{74,235–238} One multicenter

study of 7918 pregnant women found that trichomoniasis was associated with reduced concentrations of vaginal lactobacilli.²³⁵ Moreover, *T. vaginalis* growth in vitro is optimal at pH between 4.9 and 7.5; therefore, more trichomonads may be visualized in women with concomitant BV who have a resultant alkaline pH than in women with a normal vaginal pH. However, the debate continues as to whether trichomoniasis induces changes in the vaginal flora consistent with BV, or BV is a risk factor for acquisition of *T. vaginalis*.

Potential complications of trichomoniasis include vaginal cuff cellulitis following hysterectomy and atypical PID.^{239,240} Abdominal pain, described in over 10% of women with trichomoniasis, may be secondary to adenopathy from the infection or concomitant infection with other sexually transmitted pathogens. Other complications associated with trichomoniasis include increased risk of low birth weight infants, premature rupture of membranes, and preterm delivery in pregnant women with trichomoniasis.^{2,59,241}

■ INFECTIONS IN MEN

T. vaginalis infections are recognized as a cause of non-gonococcal nonchlamydial urethritis in men, but are less well characterized than infections in women. This paucity of information is largely due to the fact that men are neither routinely screened for this infection nor commonly treated. The incubation period is thought to range from 3 to 9 days, though it could be much longer. In a study of untreated male partners of women with trichomoniasis, one untreated patient, who denied any ensuing sexual contact, continued to harbor the organism for months. However, more than two-thirds of men had cleared the infection after 2 weeks.¹⁰¹

Asymptomatic infection is common in men diagnosed with trichomoniasis.^{39,80,242} When symptoms of trichomoniasis manifest in men, they include a urethral discharge that may be less profuse and purulent than discharge associated with gonorrhea.^{39,243} Among symptomatic men diagnosed with trichomoniasis, dysuria is a common complaint.²⁴² In one study conducted in an urban STD clinic, men with trichomoniasis alone were more likely to complain of urethral discharge, have urethral discharge on examination or demonstrate inflammation on microscopic examination (≥ 5 PMNs/hpf on Gram stain) than men without *T. vaginalis*, gonorrhea, or chlamydia.²⁵

T. vaginalis prostatitis and epididymitis have also been described. However, it is difficult to rule out contamination via passage through an infected urethra as an explanation for trichomonads in semen and prostatic fluid, and few studies have included histopathological confirmation.^{244–247} *T. vaginalis* was documented by PCR from prostate biopsies from men with chronic prostatitis, despite negative urine and urethral cultures.²⁴⁸ Persistent trichomoniasis has been

associated with anterior urethral strictures, although a causal effect has not been clearly established.¹⁴⁰

■ RECURRENT AND PERSISTENT TRICHOMONIASIS

The most common source of recurrent trichomoniasis is an untreated partner. Trichomoniasis may also recur following treatment if the organisms are resistant to antimicrobial therapy. Resistant trichomoniasis is an increasingly common clinical problem. No clinical signs or symptoms can differentiate between susceptible or resistant infections. A history of potential reexposure or sexual activity with an untreated sexual partner should allow differentiation between reinfection versus persistent infection.

Persistent trichomoniasis is a phenomenon that has been described anecdotally in female nursing home patients who have, reportedly, not been sexually active for years. Whether the organism is harbored silently in immunologically or physiologically “protected” sites is unclear. Given the problems with currently available diagnostic methods, it seems possible that these patients may have escaped detection by virtue of a low organism or symptom burden. The association between trichomoniasis and older age in women has led some to speculate on the role of estrogen in *T. vaginalis* infection.^{249–251}

■ TRICHOMONIASIS AND INFERTILITY

Trichomoniasis in women would appear to be an uncommon cause of infertility, since many studies have documented highly prevalent *T. vaginalis* infection in populations of pregnant women. However, in a recent study of Cuban couples attending an infertility clinic, *T. vaginalis* was cultured from one or both members of 10% of couples.²⁵² Early experiments showed that *T. vaginalis* parasites and proteins, secreted during growth in culture, inhibited sperm motility in vitro.^{253,254} In one study, men with trichomoniasis were more likely than uninfected men to have abnormalities of sperm morphology and motility, along with increased seminal fluid viscosity and particulate debris.²⁵⁵ These abnormalities improved after treatment. In a recent case report of *T. vaginalis* orchitis, severely low sperm count and lack of motility improved following antitrichomonal therapy.²⁵⁶ Thus, *T. vaginalis* infection may contribute to male infertility.

DIAGNOSIS

Diagnosis of trichomoniasis based solely on clinical signs and symptoms is unreliable because the spectrum of infection is broad, and other sexually transmitted pathogens cause similar signs and symptoms.¹⁴⁰ Diagnosis may prove particularly difficult in men, where infections are characterized by fewer organisms than infections in women.^{101,257} High concentrations of

zinc and other substances with antitrichomonal activity in prostatic secretions may help explain the lower concentrations of organisms in infected men.^{207,243}

■ DIRECT MICROSCOPIC EXAMINATION

In clinical practice, diagnosis of trichomoniasis is most often based on examination of a wet-mount preparation of vaginal discharge or of male urinary sediment. In expert hands, wet-mount microscopy can be 50–70% sensitive in women, but the technique is much less reliable in men.¹⁴⁰ Diagnosis by wet-mount requires visualization of viable, motile protozoa; therefore, specimens must be examined immediately. The sensitivity of wet-mount is further reduced as a result of even short delays between specimen collection and microscopic examination.²⁵⁸

Various staining methods for visualization of *T. vaginalis* include Gram, Giemsa, Papanicolaou, periodic acid-Schiff, acridine orange, fluorescein, neutral red, and immunoperoxidase. Papanicolaou-stained smears can detect *T. vaginalis* in asymptomatic women during routine cytologic examinations.^{259–263} However, detection using the Papanicolaou test results in a high percentage of false-negative results with a sensitivity of 60% and a specificity of 95–97%.^{263,264} Confirmation of the finding of trichomonads using another method is recommended; however, most clinicians will only have access to wet-mount evaluation, which lacks adequate sensitivity.

■ CULTURE

Culture, using a variety of liquid and semisolid media, remains the “gold standard” for diagnosis of trichomoniasis in women.^{139,140,265,266} Culture pouches containing modified Diamond’s medium are commercially available and convenient. Once inoculated, cultures are incubated and examined daily using microscopy for 3–5 days. Cultures from women with trichomoniasis are usually positive in the first 3 days. However, cultures inoculated with specimens from men should be incubated and examined daily for the full 5 days, since they often do not become positive before 3–5 days of incubation.²⁶⁷ Vaginal swab specimens transported in Amies gel transport tubes maintain *T. vaginalis* viability for up to 24 hours prior to inoculation into culture media.²⁶⁸ Trichomonads from vaginal swab specimens have been shown to remain viable in a small amount of saline for up to 20 minutes prior to culture inoculation.²⁶⁹ Self-collected vaginal swabs are as sensitive as clinician-obtained specimens for *T. vaginalis* culture.²⁷⁰ A combined approach of microscopy followed by culture if the wet-mount is negative can be useful.⁷²

In research settings, obtaining multiple cultures or evaluating multiple sites increases the rate of laboratory diagnosis. One study of 600 randomly selected women at high risk for trichomoniasis found that duplicate vaginal cultures using Feinberg-Whittington or modified Diamond culture medium resulted in a diagnosis of 82 and 78 cases, respectively, while

the combination of the two cultures identified 88 infected women. In comparison, wet-mount examination detected only 60% of the cases.²⁷¹

Although culture of *T. vaginalis* in men is preferred over wet-mount microscopy for diagnosis, the optimal site or specimen for culture is not clear. Studies indicate that evaluating multiple sites substantially increases the detection of *T. vaginalis*.^{101,83,229} Semen cultures have been shown to be valuable for documentation of infection in men; infections may be diagnosed by positive semen cultures in the face of concomitant negative cultures from urine, urethral swabs, or external genitalia.^{101,229} However, routine collection of semen may be problematic, and in busy clinic settings, thorough microscopic examination of more than one specimen per subject may be prohibitively time consuming. A practical approach is to combine a urethral swab specimen with a first-voided urine sediment in a single culture.¹⁰¹

■ RAPID DIAGNOSTIC TESTS

Other methods for diagnosis of trichomoniasis in women are now commercially available. The Affirm™ VPIII Microbial Identification Test is an office-based oligonucleotide probe test that has a sensitivity of 80–90% and a specificity of 95% compared to wet-mount and culture.^{272,273} The OSOM® Trichomonas Rapid Test²⁷⁴ and XenoStrip™-TV²⁷⁵ are immunochromatographic assays that detect *T. vaginalis* antigens in vaginal swabs and have sensitivities of 78–83% and specificities of 98–99%, which is superior to wet-mount. These tests may be of value in settings where culture and microscopy are not possible. The current rapid Trichomonas tests are only as good as, or somewhat better than, wet-mount microscopy, which is widely recognized as inadequately sensitive, particularly in the diagnosis of infection in men. The tests are certainly better than nothing, and their simplicity and similar performance compared to wet-mount microscopy make them an important addition to the STI testing toolbox. But they are not good enough. The need remains for *T. vaginalis* diagnostic tests that can combine the sensitivity and specificity of nucleic acid amplification tests with the ease-of-use and rapid results of point-of-care tests. To achieve the maximum benefit, such tests should be applicable to noninvasive specimens including urine and self-obtained vaginal swabs or tampons, and validation of test performance in women and men is essential.

■ NUCLEIC ACID AMPLIFICATION TESTS

Several groups of investigators have reported on the development of PCR assays for the diagnosis of trichomoniasis in women. The performance of the various primers in clinical studies differ, with reported sensitivities of 85–100%.^{276–284} Unlike PCR for STIs such as gonorrhea and chlamydia, for which amplification results in greater sensitivity than culture

methods, the currently published amplification techniques for trichomoniasis in women do not appear to offer a similar diagnostic advantage. PCR of vaginal swabs may be advantageous in settings where incubation of cultures is not possible and shipping specimens to a reference laboratory is required.

PCR is superior to culture for the diagnosis of *T. vaginalis* in men. Amplification assays that have been validated in specimens from men have reported sensitivities ranging from 80% to 100%.^{82,257,285} In studies of men attending U.S. STD clinics, culture detected *T. vaginalis* infection in 3–5% of men versus 12–17% detected by PCR.^{285,286} In a study of men attending STD or dermatology clinics in Malawi, the addition of urethral swab PCR to wet-mount microscopy and urethral culture increased *T. vaginalis* detection from 16% to 21% in symptomatic men and from 9% to 12% in asymptomatic men, compared to wet-mount and culture alone.⁸² For diagnosis in men, PCR from urine appears to be more sensitive than from urethral swabs.²⁸⁵ However, for PCR detection of *T. vaginalis* in men, just as for culture, testing multiple specimens will substantially increase the number of cases identified.

Perhaps the biggest obstacles to diagnosis of trichomoniasis are the lack of attention given to *T. vaginalis* infection in patients, particularly men, receiving care in general practice and the lack of access to sensitive nucleic acid amplification tests. In many medical centers and commercial laboratories, no diagnostic test beyond wet-mount microscopy is available. Development and widespread use of sensitive diagnostic tests in conjunction with increased awareness of *T. vaginalis* as an important pathogen in men and women are essential for control of trichomoniasis.

ANTIMICROBIAL SUSCEPTIBILITY AND THERAPY

■ SUSCEPTIBILITY AND RESISTANCE

Metronidazole was the first effective treatment for trichomoniasis and remains the mainstay for therapy.¹⁴⁰ However, the U.S. FDA recently approved tinidazole for treatment of trichomoniasis in women and men. Metronidazole, tinidazole, and other drugs used in treatment of trichomoniasis are derivatives of 5-nitroimidazole. The specific antimicrobial effects of these drugs depend on their activation within *T. vaginalis* hydrogenosomes, resulting in the generation of cytotoxic nitro-radicals. The precise targets of these toxic radicals in *T. vaginalis* are not known, but damage to DNA, proteins, and interference with protein trafficking are likely.²⁸⁷

In most cases, trichomoniasis is easily treated with a single dose of metronidazole. Resistant strains do occur and may be increasing in prevalence.^{135,288–290} The resistance is relative and can often, but not always, be overcome by treatment with higher doses.²⁹⁰ However, side effects from metronidazole,

such as nausea, are common and may limit the dose. The 5-nitroimidazoles share a common mode of action; not surprisingly, cross-resistance between drugs in this class has been reported.^{142,291} However, differences in the pharmacokinetics between the drugs might affect their in vivo efficiencies.²⁹² The plasma elimination half-life of tinidazole is approximately twice that of metronidazole,^{59,293} and in vitro studies suggest that tinidazole minimal lethal concentrations (MLCs) are commonly lower than those of metronidazole.²⁹³

In principle, there are two types of metronidazole resistance (aerobic and anaerobic).²⁸⁷ Aerobic resistance is manifested only if some oxygen is present.^{294,295} The MLCs of metronidazole determined in vitro under aerobic conditions for resistant clinical isolates range between 25 and 1000 µg/mL.^{142,294,295} Although the exact mechanisms are not known, it has been suggested that impaired oxygen scavenging system is responsible for aerobic resistance.^{142,296}

All strains responsible for clinical metronidazole resistance that have been examined so far display anaerobic resistance. Anaerobic metronidazole resistance depends on inactivation of the key components of drug-activating (electron-generating) pathways.²⁹⁷ However, inactivation of a known *T. vaginalis* ferredoxin gene by genetic manipulation does not lead to aerobic or anaerobic resistance in vitro,¹²¹ suggesting there may be additional mechanisms of drug activation. Anaerobically resistant strains developed in vitro display high MLC values in anaerobic assays (metronidazole up to 1425 µg/mL).²⁹⁶

■ CURRENT TREATMENTS

Treatment recommendations

Because *T. vaginalis* often infects the urethra and periurethral glands, systemic chemotherapy is superior to topical treatment.¹⁴⁰ Therapy that treats only vaginal organisms may leave organisms at other sites, resulting in subsequent endogenous reinfection. Metronidazole or tinidazole is the treatment of choice for trichomoniasis in both women and men, with various doses depending on the type of infection and treatment guidelines, summarized in [Table 43-3](#).²⁹⁸ Patients who are coinfecting with HIV can receive the same treatment regimens as HIV-negative persons.

The recommended dose of metronidazole or tinidazole is 2 g orally in a single dose with reported cure rates of up to 97%.³⁰¹ Sexual partners should also be treated; simultaneous therapy for sexual partners increases the cure rates with single-dose treatment.¹⁴⁰ Alternative regimens include metronidazole 500 mg twice daily for 7 days.³⁰ For patients who fail therapy and have not been reinfected, higher doses of metronidazole (2 g oral dose once daily for 3–5 days) or a multiday dosing regimen of tinidazole are options.²⁹² Metronidazole intravaginal gel has limited efficacy against *T. vaginalis* and should not be used to treat trichomoniasis.

Table 43-3. Treatment Recommendations for *Trichomonas vaginalis* Infections

Treatment Regimen	Reference
Vaginal infections	
<i>Recommended regimens</i>	
Metronidazole 2 g orally in a single dose	30, 69
Tinidazole 2 g orally in a single dose	69
Metronidazole 400–500 mg orally twice a day for 5–7 days	297
<i>Alternative regimens</i>	
Metronidazole 500 mg orally twice a day for 7 days	30
Metronidazole 400–500 mg orally twice a day for 7 days	69
Tinidazole 500 mg orally twice daily for 5 days	297
<i>Pregnancy</i>	
Metronidazole 2 g orally in a single dose	30, 69
Urethral infections	
<i>Recommended regimens</i>	
Metronidazole 2 g orally in a single dose	30
Tinidazole 500 mg orally twice daily for 5 days	69
Metronidazole 400–500 mg orally twice a day for 7 days	69
Treatment failures	
<i>Recommended regimens</i>	
Metronidazole 500 mg orally twice daily for 7 days	30
Metronidazole 2 g orally once daily for 3–5 days ^a	30
<i>Alternative regimens^b</i>	
Tinidazole 2 g twice daily for 14 days	298
Tinidazole 500 mg three times daily for 7–10 days	299
Tinidazole 1.5 g three times daily for 14 days	291
Tinidazole 1 g twice daily for 14 days	291
Neonatal infections	
<i>Recommended regimen</i>	
Metronidazole 5 mg/kg orally three times daily for 5 days	297

^a Recommended regimen if treatment failure occurs again after metronidazole 500 mg twice daily for 7 days.³⁰

^b Alternative regimens can include oral and vaginal doses.

Current recommendations focus on epidemiological treatment of sexual partners of infected women, without specific diagnosis.³⁰ In situations where appropriate diagnostic facilities are unavailable, epidemiologic therapy is reasonable to reduce subsequent transmission and limit the potential for reinfection following successful treatment. However, epidemiological therapy is limited by compliance with partner notification and tends to miss partners of asymptomatic women, since such women are less likely to be diagnosed.²⁰⁸

A specific diagnosis of trichomoniasis in men could prompt identification of more infected males and enhance detection of additional infected women through partner notification.⁸³

Estimates suggest that approximately 2.5–5% of all cases of trichomoniasis display some level of resistance to treatment with metronidazole.³⁰² This resistance is relative and can usually be overcome with higher doses of oral metronidazole. For example, treatment of marginal resistance, defined as an aerobic MLC of metronidazole 50 µg/mL requires a total dose of 10 g administered over several days for cure, whereas treatment of high-level resistance (MLC of ≥ 400 µg/mL) requires 40 g. Intravenous formulations offer no advantage over oral medications for trichomoniasis. Some authorities have recommended higher doses of oral regimens in combination with pharmacy-prepared intravaginal preparations. There are limited anecdotal reports of success with paromomycin cream; however, there may also be a high incidence of local side effects associated with this therapy.²⁹⁰

Tinidazole, which was recently licensed in the United States, but has been used in other countries for years, may be particularly useful for treatment of metronidazole-resistant infections. The U.S. Centers for Disease Control and Prevention (CDC) tested 195 metronidazole-resistant *T. vaginalis* clinical isolates with both metronidazole and tinidazole. The mean aerobic MLCs were metronidazole 400 µg/mL, compared to tinidazole 100 µg/mL.³⁰³ Several studies have evaluated different doses of tinidazole for treatment of metronidazole-resistant trichomoniasis.^{292,299,300,304} In the largest study, 20 patients with clinically refractory trichomoniasis (failure to respond to therapy with oral metronidazole, at least 500 mg BID for 7 days) were treated with high doses of oral and vaginal tinidazole (2–3 g orally plus 1–1.5 g intravaginally for 14 days). The cure rate was 92%, and no patient discontinued therapy due to side effects.²⁹²

Relatively few studies have addressed treatment of trichomoniasis in men. In one study, a 7-day multidose metronidazole regimen proved highly effective in curing men.¹⁴⁰ The single-dose regimen has not been evaluated extensively, and existing reports are contradictory. One study indicated a 43% failure rate with single-dose therapy.³⁰⁵ Other investigators found that metronidazole, 2 g as a single oral dose, was highly effective in curing men.^{101,306}

Adverse reactions and toxicity of metronidazole and other 5-nitroimidazoles

Occasionally, patients present with an allergy to metronidazole, and we lack data on cross-reactivity with tinidazole. Since there is no effective alternative, desensitization followed by later treatment is recommended for metronidazole-allergic patients with trichomoniasis.³⁰

Animal data suggest that metronidazole may be both carcinogenic and mutagenic.¹⁴⁰ However, human data suggest that metronidazole has limited carcinogenic or mutagenic

potential. A cohort of 771 women followed for 15–25 years after treatment with metronidazole showed no significant increase of cancer morbidity and mortality over the expected rate.³⁰⁷ Taken together, the data suggest that the risk of short-term, low-dose metronidazole is extremely small. There are no documented cases of fetal malformation attributed to its use in pregnancy, even in the first trimester.³⁰⁸ Based on these considerations, the Centers for Disease Control (CDC) recommends treatment of symptomatic pregnant women with trichomoniasis with a single 2-g oral dose of metronidazole.³⁰ This dose of metronidazole can also be used in breastfeeding women.

Recent controversy has arisen concerning the treatment of trichomoniasis in pregnancy and its relationship to preterm birth. Two studies suggest that treatment of trichomoniasis in pregnancy may actually increase the risk of preterm birth rather than decrease the risk as predicted.^{309,310} However, there are limitations to both of these studies. One of the studies used much higher doses of metronidazole than recommended. In addition, the study was stopped prematurely because of the observed trend toward preterm birth in women who received metronidazole, and thus was not allowed to continue subject enrollment for a definitive analysis.³⁰⁹ The second study was a subanalysis of a larger study investigating STD and HIV risk. The subanalysis was not primarily designed to assess risks of preterm birth associated with treatment of trichomoniasis in pregnancy.³¹⁰ Despite the publication of these reports, the CDC has not revised recommendations for treatment during pregnancy.

PREVENTION AND CONTROL

Primary prevention programs for trichomoniasis are unfortunately lacking, and rely mainly on individual management, counseling, and partner notification. In areas of high prevalence or among high-risk groups, syndromic management or screening for *T. vaginalis* has been applied depending on resources and available laboratory techniques. However, based on a mathematical model of disease transmission dynamics, success in controlling trichomoniasis through these interventions is likely to be transitory without a sustained investment in resources.³¹¹ Given an estimated 50% of asymptomatic disease, high levels of syndromic management are projected to lead only to modest reductions in the endemic prevalence of trichomoniasis. In comparison, modest levels of constant screening (vs serial screening) for *T. vaginalis* can result in significant reductions in its prevalence as predicted by the model.³¹¹

Partner notification, whereby the index patients or the health-care providers notify the sexual partners of the potential exposure and encourage them to seek treatment, is essential for *T. vaginalis* control in light of the high rate of infection noted among partners.²⁰⁸ Several studies have shown that treatment of male sexual partners of infected women improves cure rates and avoids recurrent

infection.^{24,312,313} Partners of patients with trichomoniasis who have had sexual contact with the index patient in the past 60 days should be notified for evaluation and treatment to decrease the reservoir of potentially infectious persons. Sexual abstinence for 7 days should be recommended following treatment of both the index case and the partner(s) for trichomoniasis. Patient-delivered partner medication shows promise as an approach for other STIs, but may not be a widely available option.^{314–317}

The promotion of condom use and other barrier methods is important to decrease the transmission of *T. vaginalis*. A study evaluating condom effectiveness reported a significant reduction in female sex workers' risk of acquiring trichomoniasis.³¹⁸ Repeated behavioral interventions focused on preventive education and provision of testing and treatment for female sex workers has also been shown to successfully reduce the incidence of trichomoniasis and other STIs.³¹⁹

Vaginal microbicides have received renewed interest because they are alternative agents to female condoms that do not require male cooperation. In vitro tests had suggested that spermicides containing nonoxynol-9 (N-9) can kill sexually transmitted pathogens including *T. vaginalis*.³²⁰ However, a meta-analysis of randomized clinical trials to evaluate the effectiveness of N-9 for the prevention of trichomoniasis did not find a statistically significant difference between the microbicide and the no treatment groups.³²¹ A novel peptide antibiotic, D2A21, has been investigated as an intravaginal application and is reported to be efficacious in preventing vaginal *T. vaginalis* infections in mice.³²²

In light of the cost of treating frequent and recurrent trichomoniasis, there has been some research into vaccine development for *T. vaginalis*. A recent review of earlier studies details mechanisms by which protection from infection could potentially be achieved.²⁸⁹ Two *T. vaginalis* vaccine candidates have been tested. In the 1960s, intravaginal inoculation with a heat-killed *T. vaginalis* preparation in a single study was reported to improve clinical symptoms,³²³ but the work was not repeated and has not been pursued. In the late 1970s, a vaccine marketed in Europe under the name SolcoTrichovac was developed from heat-inactivated “abnormal strains of lactobacilli” isolated from the vaginal sections of women with trichomoniasis.³²⁴ Despite initial reports claiming cure of existing *T. vaginalis* infection and protection from reinfection, the vaccine has not been evaluated in well-controlled, double-blind prospective studies, and is not recommended. Murine and bovine models have been developed for the related pathogen, *T. foetus*, and may provide insights for future *T. vaginalis* vaccine efforts.^{325,326}

T. vaginalis warrants greater attention and concern as a highly prevalent sexually transmitted pathogen that has been associated with various adverse health sequelae and increased HIV transmission among sexually active men and women. Moreover, there appears to be an increasing incidence of

resistant infections with *T. vaginalis*,²⁹⁰ and there currently is no safe and effective alternative to nitroimidazoles for treatment. Therefore, consideration of disease prevention and control strategies for *T. vaginalis* along with other STI control efforts is imperative. Future control strategies for *T. vaginalis* should include development of screening programs in populations with high prevalence, improvement and utilization of sensitive, noninvasive diagnostic methods in both men and women, and better surveillance to monitor disease trends which can assist in the development of potential interventions for trichomoniasis.

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Intestinal Protozoa: *Giardia lamblia*, *Entamoeba histolytica*, *Cryptosporidium*, and New and Emerging Protozoal Infections

Circle Alcantara Warren and Richard L. Guerrant

Enteric protozoan pathogens are increasingly recognized causes of diarrhea. This chapter reviews the biology of the major protozoan causes of diarrhea: *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium*. Predominantly considered as low infectious dose pathogens, these protozoa may sometimes be transmitted directly by sexual practices that enable fecal–oral spread. *E. histolytica* and *G. lamblia* are the two most common protozoa isolated in men who have sex with men (MSM). *Cryptosporidium* infections present particularly severe problems in patients with the acquired immunodeficiency syndrome (AIDS). Other intestinal protozoa that may also cause severe diarrhea in HIV-infected patients include *Cyclospora* and microsporidia, which are discussed at the end of this chapter.

GIARDIA LAMBLIA

■ HISTORY, EPIDEMIOLOGY, AND CLINICAL MANIFESTATIONS

History

G. lamblia was probably first discovered by the inventor of the microscope, Anton van Leeuwenhoek, when he examined his own diarrheal stool. In a letter to the Royal Society on November 4, 1681, he described “a number of animalcules approximately the size of a blood cell, with flattish bodies and several legs, moving much like a wood louse running up against a wall.”¹ In 1859, Vilem D. F. Lambl described the parasite and called it *Cercomonas intestinalis*. However, since this organism was found in a number of asymptomatic individuals,² it was not considered to be a pathogen until it was repeatedly observed to be associated with diarrhea,^{3–5} malabsorption,⁶ and occasional tissue invasion.⁷ Even the demonstration of experimental human infection in 36% of volunteers ingesting 10–25 *Giardia* cysts in water, and the presence of moderate to marked diarrheal symptoms in 60% of 15 infected individuals, left some question about the pathogenicity of this flagellated protozoan parasite.⁸ Since then have been

numerous studies of the different strains of *Giardia*, its animal host-species specificities, its morphological and functional characteristics, its in vitro cultivation, and the possible mechanisms by which it may cause enteric disease. As with *E. histolytica*, the in vitro cultivation of *G. lamblia* has enabled the study of different strains at the molecular level.

■ EPIDEMIOLOGY

Several epidemiologic surveys have revealed that 2–9% of the population in many parts of the world excrete *G. lamblia* cysts.^{9,10} Prevalence rates are higher in tropical areas and among travelers; exposed infants and children have the highest rates.^{11,12} This skewed distribution of giardiasis toward children is in distinct contrast to amebiasis, where gain and loss of infections (with a median duration of 2 years) appears to be independent of age.¹³ The geographic and age distribution, as well as increased frequencies of giardiasis in institutions where hygienic standards are difficult to maintain, indicate that spread occurs by the fecal–oral route.^{3,14} The human volunteer studies by Rendtorff⁸ suggest that ingestion of relatively small numbers of cysts in food or water or as a result of person-to-person contact results in infection. A food-borne outbreak was reported in which contamination of canned salmon apparently occurred after careful diaper changing of an infected infant.¹⁵

Venereal transmission of *Giardia* is also known to occur, predominantly, in MSM. Depending on the year and location of the study and the microbiologic techniques employed, the prevalence of giardiasis in MSM, ranged from 3% to 15.7%.^{16–21} In patients with AIDS, the prevalence may be higher (up to 55% in an inner city AIDS clinic).^{22,23} In one of the earlier studies looking at the association of enteric protozoan and helminthic infection and gender, and sexual practices, homosexuality and oral–anal sex were identified as the most important risk factors for infection.²⁴ In this study, 29 of 163 men and none of 17 women had an enteric infection. The prevalence of enteric infections (*E. histolytica*, *Giardia*, or both) was 21.5% in homosexual men, 6.2% in bisexual men, and

0 in heterosexual men. In a similar investigation, *Giardia* was isolated in 13% of MSM versus only 3% of the heterosexual men in the study population.¹⁶ Although homosexual orientation has persistently been associated with giardiasis, specific sexual practices, e.g., oral–anal, orogenital, or penile–anal, and number of sexual partners were less consistently reported as risk factors, probably because of the nature of data extraction employed in the studies.^{16,19,20,22,24–27} High degree of spatial clustering of giardiasis in AIDS patients has also been noted.²³

Waterborne giardiasis has been widely recognized in the last 15 years and is now the commonest reported parasitic infection in England and the United States.²⁸ Although first suggested by an outbreak of amebiasis and giardiasis in 1946 in a Tokyo apartment building where sewage-contaminated water was implicated (*Giardia* cysts were demonstrated in 80% of symptomatic individuals who did not have amebiasis),⁴ attention was drawn to waterborne giardiasis by an outbreak in Aspen, Colorado, in 1965, when 11% of skiers and 5% of residents were infected, and *Giardia* cysts were demonstrated in sewage that had contaminated the drinking water. A total of 23 additional outbreaks of giardiasis involving over 7000 individuals in the United States subsequently implicated water which was inadequately sedimented and filtered, often despite bacteriologically adequate chemical disinfection.^{28–30}

More recently, *G. lamblia* has been reported as one of the most frequently identified agents in outbreaks associated with recreational water in the United States, accounting to 6% of the pathogens. Like cryptosporidiosis, giardiasis was associated with treated water swimming and wading pools.³¹ In an analysis of voluntarily reported cases at the Centers for Disease Control National Electronic Telecommunications System, it was noted that a greater number of reports were received for children aged 1–9 years and adults aged 30–39 years. It was also noted that the seasonal peak in age-specific case reports coincided with the summer recreational water season.³² Similarly, in a case control study in Southwestern England, swallowing water while swimming (odds ratio [OR] 6.2, 95% confidence interval [CI] 2.3–16.6) and recreational fresh water contact (OR 5.5, CI 1.9–15.9) had been identified among risk factors for sporadic infection with *G. lamblia*.³³

Studies of travelers from the United States and other countries to Leningrad and Moscow, summarized in a 1974 journal article,³⁴ noted impressive attack rates of giardiasis, ranging from 22% to 41%. In one of these studies, the mean incubation period was 14 days, and 69% of those infected were symptomatic.

Besides humans, potential reservoirs include small animals such as beavers, which may be found contaminating even the remotest streams. As shown by Rendtorff in 1954,³⁵ *G. lamblia* cysts remain infectious for humans after holding in water for over 2 weeks. Furthermore, chemical disinfection

of contaminated surface water is inadequate, especially when the water is cold, and appropriate flocculation, sedimentation, and filtration are necessary to remove infectious cysts. Cysts may also be killed by 2–5% phenol or Lysol. Transmission may also occur with contaminated, uncooked foods¹⁵ or by person-to-person contact in families, nurseries, institutions, and day-care centers.^{3,9,14} Fecal–oral and rectal–genital spread of *Giardia* have been implicated in homosexual men.^{36–38}

Modern molecular techniques have recently been employed to elucidate further the epidemiology, risk factors, zoonotic potential, and environmental contamination of *Giardia*. Polymerase chain reaction of DNA extracted from fecal specimens from different geographic locations have identified *G. lamblia* assemblages A and B to be associated with human infections. Although helpful in investigating the role of zoonoses in giardiasis, the relationship of the different genotypes to the severity of clinical disease remains unclear.³⁹

Clinical manifestations

In endemic areas, the majority of *G. lamblia* infections are asymptomatic; however, a significant portion of residents and most previously uninfected travelers are symptomatic. The most characteristic symptoms include diarrhea of more than 10 days' duration, cramping upper abdominal pain, bloating, flatulence, and weight loss.^{29,34} Less commonly, nausea, vomiting, and fever may be seen.

Although the incubation period ranges from 1 to 8 weeks, symptoms often precede the first detectable fecal shedding of the parasites; the median prepatency period in one study (14 days) was 6 days longer than the median incubation period (8 days).⁴⁰ Thus, it may be necessary to examine upper small bowel aspirates or repeated fecal specimens to document a diagnosis of giardiasis. While the infection is usually self-limited,⁸ symptoms may intermittently recur or persist for prolonged periods of up to months or even years.²⁴ The illness may last up to 6 or 7 weeks.³⁴

Signs and symptoms of malabsorption, ranging from mild noninflammatory diarrhea, steatorrhea, or weight loss to a more severe celiac syndrome, especially in children,⁶ are well documented, with malabsorption of D-xylose, fat, carotene, vitamin A, folate, and vitamin B₁₂.^{5,41,42} Giardiasis has been associated with childhood malnutrition^{43,44} and may have detrimental effect on cognitive development in late childhood.⁴⁵ Malabsorption may be especially severe in patients with achlorhydria,⁴¹ immunodeficiency,^{41,46} protein–calorie malnutrition,⁴⁷ or bacterial overgrowth⁴⁸ complicating their illnesses. In patients with hypogammaglobulinemia, giardiasis can be associated with mucosal inflammation, with villus flattening, and with lactase, maltase, or sucrase deficiency.^{42,49,50} Likewise, giardiasis may mimic or accentuate the malabsorption seen in chronic pancreatitis.⁵¹

For poorly understood reasons, patients with giardiasis may rarely develop eosinophilia, urticaria, or other symptoms, such

as arthritis,⁵² that are suggestive of an immune response to an antigen exposed during acute diarrhea. These symptoms respond to specific anti-giardial therapy.⁵³

While giardia-induced diarrhea is usually noninflammatory, with only rare tissue invasion,⁷ inflammatory proctitis and vaginitis have been reported.⁵⁴ In MSM, coinfection with other pathogens, including other enteric (such as *E. histolytica*) and sexually transmitted organisms may occur. Sigmoidoscopy in symptomatic MSM to distinguish proctitis (secondary to herpesvirus, gonococcal, chlamydial, or syphilitic infection), colitis (*Campylobacter*, *Shigella*, *Clostridium difficile*, or *Chlamydia*), or noninflammatory diarrhea (due to *Giardia*) is recommended.⁵⁵

■ STRUCTURE AND BIOLOGY OF THE ORGANISM

Named “*Giardia*” by Kunstler, who observed it in tadpole intestinal tracts in 1882, the genus was considered by Alexeieff and Dobell to be the same as the human flagellated protozoan. The genus and the disease are called “*Lamblia*” and lamblia in eastern Europe; however, most authorities agree on the genus name *Giardia*. At least three species are recognized on the basis of morphology and host-species specificity.⁵⁶ Although species specificity is debated and size can be changed with host diet,⁵⁷ *G. lamblia* trophozoites usually measure 12–15 μm long by 5–15 μm wide and 1–4 μm thick. Cysts are usually 8–12 μm long by 7–10 μm wide. Shaped like a horseshoe crab, with a rounded dorsal surface and concave ventral surface, the *G. lamblia* trophozoite has four pairs of flagella directed posteriorly from the lateral and ventral surfaces.

The trophozoite (Fig. 44-1) has a unique anterior ventral adhesive disk, to which are attached a clockwise spiral of microtubules and contractile elements. The disk has a posterior vent where beating ventral flagella appear to expel fluid that may help establish a mechanical suction for adherence of the parasite to mucosal or other surfaces.^{58,59} Alternate suggestions for the disk's functions include contractile or grasping actions. The adhesive disk is divided into two lobes, the medial surfaces of which are the median groove. Two nuclei lie dorsal to the adhesive disk lobes, and the eight flagella appear to arise from basal bodies located anterior to the nuclei.

Endocytic or exocytic vacuoles that have been shown to concentrate ferritin or even bacteria are found adjacent to the disk and elsewhere.⁶⁰ There is evidence that *G. lamblia* have surface receptors for lectins such as wheat germ agglutinin and that these receptors can be blocked by specific carbohydrates.⁶¹ In addition, a 56-kDa protease-activated *Giardia* lectin has been isolated by SDS-PAGE from a lipopolysaccharide (LPS)-sepharose column.⁶²

The median body appears to be a tight packet of microtubules that lies between the posterior poles of the nuclei; it appears to be unique to *Giardia* spp.⁵⁹ The median bodies of

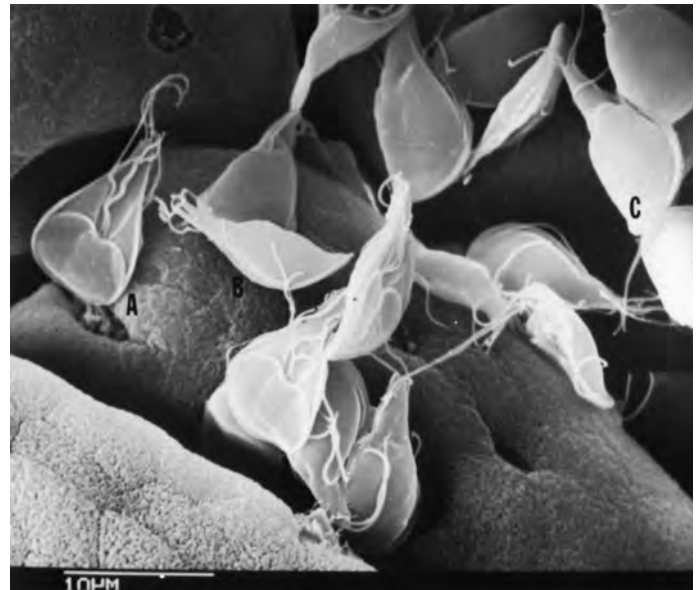


FIGURE 44-1. Scanning electron micrograph of *Giardia lamblia* trophozoites from a jejunal biopsy of a patient with symptomatic giardiasis. **A.** In the ventral view, flagella lead from the adhesive disk to the tapered posterior end. **B.** In the lateral view, anterior flagella can be seen. **C.** The dorsal view. (Courtesy of R. L. Owen.)

G. lamblia that infect humans, dogs, rabbits, and other mammals are characteristically claw shaped and lie transversely across the trophozoite. *G. muris* trophozoites from rodents or birds have small, round central median bodies, and the long, narrow *G. agilia* trophozoites from amphibians have long, tear-shaped median bodies.^{56,57,62}

As with *E. histolytica*, differences among *G. lamblia* strains as to isoenzyme patterns,⁶³ antigens, and surface proteins,^{64,65} and restriction endonuclease patterns⁶⁶ have been described. A double-stranded RNA virus has been described in the Portland I strain of *G. lamblia* that could infect another *G. lamblia* strain (WB).⁶⁷ Recent evidence on the antigenic variation of a cysteine-rich 170-kDa protein expressed on the surface of certain *G. lamblia* suggest frequent rearrangements at the gene locus as well as long tandem repeats in the DNA.^{68,69}

Trophozoites may encyst in response to a reduced pH, detachment, immunologic attack, or other hostile environments in vivo;⁵⁹ encystment has been accomplished in vitro using primary bile salts.⁷⁰ Apparently, after a single division in the cyst and a period of maturation, two daughter trophozoites can be induced to excyst in vitro by special conditions and reduced pH.⁷¹

■ GROWTH, PHYSIOLOGY, AND CULTURE

Although culture has not been successful with other *Giardia* strains, the human strain *G. duodenalis* (*G. lamblia*) has been grown in vitro, first symbiotically with *Candida guilliermondii* and then axenically (without other bacteria

or parasites) by Meyer.⁷² In 1978, Bingham and Meyer successfully cultured trophozoites that were obtained in vitro from cysts shed by humans and monkeys.⁷¹ As shown by Visvesvara, the conditions for culture of *G. lamblia* in vitro are similar to those for culture of *E. histolytica*. *G. lamblia* may be more oxygen tolerant, but both parasites require serum and cysteine.^{73,74} Bile salts have been shown to support growth of *G. lamblia*.^{74,75} Giardia trophozoites can be preserved at low temperatures in glycerol or dimethyl sulfoxide.

The in vitro cultivation of giardia trophozoites has enabled definition of their growth curves, with doubling times of 7–40 hours noted by different investigators.^{73,74} *G. lamblia* appear to facultatively metabolize glucose to ethanol acetate and carbon dioxide via a flavin-mediated electron-transport system rather than a cytochrome-mediated electron-transport system or a Krebs cycle.⁷⁶

■ IMMUNOLOGY AND PATHOGENESIS

Immunology and host response

A substantial number of studies of humoral and cellular immune responses to *Giardia* infection reveal a complexity ranging from partial protection to possible roles in pathogenesis. Evidence for acquired resistance includes the skewed age distribution toward children (in contrast to amebiasis),¹³ the observation that long-term residents of endemic areas appear to have a lower infection rate than short-term residents,⁷⁷ and the tendency for individuals in endemic areas to be infected asymptotically. In addition, prior infection appears to result in acquired resistance to *G. muris* infection in the mouse model.⁷⁸

The nature of acquired resistance appears to be related in part to local antibody production. Although initial humoral responses to *G. lamblia* infection are predominantly IgM, there follows an IgA and IgG response⁷⁹ that correlates with the severity of the histologic jejunal lesion.⁸⁰ Although debated by others,⁸¹ the findings of Zinneman suggested that patients with giardiasis had lower secretory IgA levels.⁴⁶ Of seven patients described by Hermans et al., who had type 2 IgA and IgM deficiency and nodular small bowel lymphoid hyperplasia, six had giardiasis that improved with therapy.⁸² Ament et al. have shown that hypogammaglobulinemic patients who acquire giardiasis develop enteric symptoms and malabsorption.⁸³ However, the frequent occurrence of selective IgA deficiency without recognized problems with giardiasis suggests that other Ig classes or possibly still other factors are also involved in protection against symptomatic giardia infections.

Human serum kills *G. lamblia* trophozoites via activation of the classical complement pathway.⁸⁴ IgM-supported complement-dependent lysis of *G. lamblia* has been demonstrated. Anti-IgM treated mice develop heavy, prolonged infections (without any serum or local antibody responses)

with *G. muris*.⁸⁵ Peyer's patch B cells show an early increase in surface IgM-bearing cells, followed by a switch to surface IgA-bearing cells with *G. muris* infection in mice.⁸⁶ The absence of severe disease with *G. lamblia* infections in AIDS patients (in contrast to cryptosporidial and mycobacterial infections, for example) militates against a major primary role for cellular immunity in preventing symptomatic giardiasis.

In the mouse model, transient protective immunity can be transferred by milk to suckling offspring, possibly at the cost of the nursing mother's effective intestinal immunity.⁸⁷ Whether this transient immunity is related to passive transfer of cellular or documented humoral immunity⁸⁸ or both remains to be determined. Anti-*Giardia* IgA in human breast milk has been reported to protect children against giardiasis early in life.⁸⁹

Murine and human biopsy studies have suggested roles for several types of cells in the pathogenesis and resistance in *G. lamblia* infection: microfolded epithelial (M) cells overlying Peyer's patches that have to do with processing giardia antigens, small lymphocytes that undergo intraluminal migration and directly attack the parasite, and intraepithelial large T lymphocytes or macrophages which are also involved.^{59,62,90} Paneth cells secrete defensins which has been shown to possess anti-giardial activity in vivo.⁹¹ Another recent mouse study implicated the role of bacterial endosymbionts in the trophozoites in the parasitocidal activity of Paneth cells.⁹²

Evidence for a role for cell-mediated immunity in protection against *G. lamblia* infection again comes from the *G. muris* mouse model⁹³ in which athymic mice develop a prolonged *G. muris* infection.⁹⁴ Subsequent study has shown that the helper/inducer T lymphocytes (L3T4+), rather than the cytotoxic/suppressor (Ly-2+) subset, are responsible for clearance of murine *G. muris* infections.⁹⁵ Resistance to giardiasis may also be provided by toxic free fatty acids produced from breast milk by a bile-salt-stimulated lipase.^{96,97}

The resistance to *G. lamblia* infection, however, is far from absolute. Normal human adults are usually susceptible to this widespread parasite; Rendtorff infected all 13 adults challenged with more than 100 cysts.⁸ Despite the evidence for increased susceptibility when specific humoral or cellular responses are impaired or absent, the relative infrequency of giardiasis in most patients with IgA deficiency and the acquisition of incomplete resistance by athymic nude mice⁹³ show that resistance to *G. lamblia* infection is complex and may involve both local humoral and cellular immune responses.

The apparent increased frequency of giardiasis in patients with blood group A⁹⁸ may reflect less recognition of a parasite antigen similar to blood group A antigen,⁹⁹ or it may be related to other traits associated with blood group A, such as achlorhydria or differences in cell surface or mucus glycoproteins.

Pathogenesis

The initial stages in the pathogenesis of *G. lamblia* infection follow ingestion of a relatively small number of cysts (usually in water or by contact). Excystation and release of the short-lived “excystoite” occur in the upper small bowel.¹⁰⁰ Each excystoite generates four trophozoites which divide by binary fission. Larger inocula probably cause more severe infection.⁸ Although gastric acidity may contribute to excystation,⁷¹ several investigators have noted increased symptoms with giardiasis in hypochlorhydric or postgastrectomy patients.

There are several tantalizing hypotheses regarding the mechanism by which *G. lamblia* alters small bowel function or histology to cause disease. Some have suggested that the close adherence of many trophozoites mechanically impedes normal absorptive processes.¹⁰¹ Holberton has shown evidence for a physical suction and some microvillus brush border damage under the ventral disk of giardia trophozoites that resulted in deformation of the gut cell cortex.⁵⁸ Imprints of the ventral disks have also been demonstrated in the microvillus brush border in the mouse model with *G. muris* infection.¹⁰² Jejunal histology of infected mice showed reduction in the height of brush border microvilli.¹⁰³ However, this has not been shown in humans, nor do symptoms correlate with density or intensity of infection.¹⁰⁴ Instead, symptoms have been correlated with lymphocytic infiltration in the jejunal epithelium,¹⁰⁴ suggesting possible immunologic damage. Increased crypt cell production with lymphocytic infiltration has been noted in mice infected with *G. muris*.¹⁰⁵ Furthermore, Roberts-Thomson and Mitchell showed villus injury when T-lymphocytes were added to nude, athymic mice before infection with giardia protozoa.⁹⁴ Inflammatory responses with plasma cell infiltrates are also seen in segmentally damaged mucosa, especially in immunoglobulin deficiency states.¹⁰⁶

Other researchers have described direct invasion of the mucosa by trophozoites in vivo.¹⁰⁷ Whether this tissue damage relates to cytotoxic or enterotoxic products of *G. lamblia* is unclear at present. Malabsorption and specific brush border enzyme deficiencies are well recognized in giardiasis.⁴² These findings might be explained in part by increased epithelial cell turnover with increased villus-tip cell extrusion.^{42,94} Others suggest that the parasite may compete with the host for nutrients.¹⁰¹ Possible strain differences in pathogenicity based on differences in surface antigens, patterns of infection, and homologous immune responses have been suggested by studies in a gerbil model.

Finally, the interaction of *G. lamblia* with other microorganisms appears to be important in certain instances. Whether by host-tissue damage or by actual carriage of other microorganisms by giardia organisms,⁶⁰ severe malabsorption and steatorrhea with giardiasis has been associated with small bowel bacterial overgrowth.^{35,47} Concentrations of

10^3 – 10^7 bacteria (mostly enteric coliforms) have been described with giardiasis and malabsorption or steatorrhea; in some instances the bacteria had to be eradicated before the symptoms resolved. Symptomatic responses to tetracycline without eradication of *G. lamblia* have also been noted.¹⁰⁸

Bile salt deconjugation by bacterial overgrowth or by *Giardia* themselves has been postulated but not proved.⁴⁸ Smith and coworkers failed to confirm direct bile-salt deconjugation by *G. lamblia*;¹⁰⁹ however, direct uptake of bile salts by the parasite may be significant and clearly enhances its growth.¹¹⁰ Development of the in vitro culture techniques and the animal models of *G. muris* in mice offer considerable promise of improved understanding of the pathogenesis of giardiasis, as do recent studies in gerbils, rats, and mice. The recent sequencing of the *G. lamblia* genome and development of gene array technology hold promise in elucidating the yet unclear mechanisms of disease in giardiasis.¹¹¹

■ DIAGNOSIS

Examination of fresh and concentrated stool specimens

The diagnosis of *G. lamblia* infection can often be made by examining fresh or concentrated fecal specimens in cases of diarrhea that persist beyond the prepatency period of 5–7 days. As summarized in Table 44-1, the prompt examination of a fresh diarrheal stool specimen may reveal the striking motile trophozoites of *G. lamblia* on an unstained direct wet-slide preparation or a specimen that has been trichrome stained for cysts or trophozoites before or after concentration (Fig. 44-2).

The diagnosis of giardiasis is usually made by examining one to three stool specimens after concentration, using such methods as flotation in 33% zinc sulfate (after clarification by centrifugation in water) or formalin–ether sedimentation in approximately 10 mL of 10% formalin suspension with 3 mL

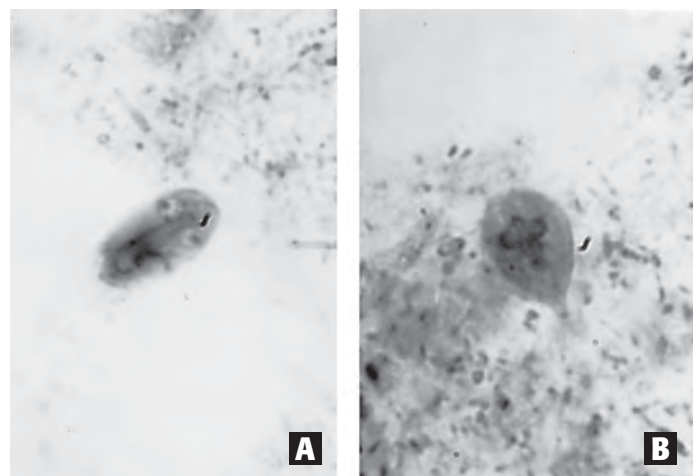


FIGURE 44-2. *Giardia lamblia*, **A.**, cyst and trophozoite, **B.**, from fecal specimens of a patient with active giardiasis. Gomori-Wheatley trichrome stain, oil immersion $\times 640$ magnification. (Courtesy of G. R. Healy.)

Table 44-1. Diagnosis of *Giardia lamblia* Infection

Test	Sensitivity	Specificity
<i>Microscopy</i>		
Fresh fecal exam for motile trophozoites	Better with active diarrhea	Specific in experienced hands, but finding trophozoites does not prove disease causation
Stained, concentrated fecal exam Duodenal aspirate or string test	Approximately 34–98%	May be more sensitive than stool exam early in illness and in children (83–86%)
Jejunal biopsy/imprint Approaches 100%		
<i>Serologic tests:</i>		
IFA using patient's cysts or trophozoites	89% of symptomatic patients	71–100%
Immunodiffusion (with sonicated cysts)	91%	Approaches 100%
IFA (with cultured trophozoites)	97% \geq 1:16	85–100%
ELISA (with cultured trophozoites)	81%	88%

ether. The concentrate is then stained with 1% potassium iodide saturated with iodine. While some report that three concentrated fecal specimens are adequate to diagnose the vast majority of cases, others have shown that as few as 34% of stool specimens from patients with the parasite in the upper small bowel were positive. Barium, kaolin products, oily laxatives, antibiotics, antacids, paregoric, enemas, and cotton swabs will greatly reduce the value of the microscopic examination.

A monoclonal antibody combination reagent for direct fluorescence detection of *Giardia* cysts and *Cryptosporidium* oocysts has proved useful in fecal microscopy.¹¹² In addition, fecal antigen ELISAs (enzyme-linked immunosorbent assays) using polyclonal or monoclonal antibodies range in sensitivity and specificity from 87% to 100%.¹¹³ Finally, DNA-based probes for *G. lamblia* are in development, but they are not yet widely useful.¹¹⁴

■ EXAMINATION OF SMALL BOWEL CONTENTS OR TISSUE

From studies in adult volunteers, several observers have reported an improved yield (although this is debated by some researchers) with examining duodenal aspirates or even small bowel biopsies in patients whose fecal examinations are negative for *G. lamblia*.¹¹⁵ When jejunal biopsy is performed, one should examine a Giemsa-stained sample of the “imprint” of the tissue, as well as the tissue itself, for the purple-stained trophozoites. Effective sampling of small bowel contents can also be accomplished, without intubation or biopsy, using the string test (Enterotest, Hedeco, Palo Alto, CA). This involves swallowing a gelatin capsule with one end of the 140-cm

(or 90-cm for children) nylon line taped to the side of the mouth. Removing the string after 4 to 6 hours and examining the bile-stained mucus has been helpful in demonstrating *G. lamblia* trophozoites, particularly in young children and in adults early in their illness. When jejunal biopsy is performed, one should examine a Giemsa-stained sample of the “imprint” of the tissue as well as the tissue itself for the purple-stained trophozoites.

■ ANTIBODY AND ANTIGEN ASSAYS

Primarily because of limitations on antigen supply prior to in vitro cultivation of *Giardia*, little was known until recently about serologic responses to *G. lamblia* infections. In 1976, Ridley and Ridley, using an indirect fluorescent antibody (IFA) test and patient isolates of cysts and trophozoites as antigen, found that 32–36 cases (89%) of giardiasis with malabsorption gave positive results, whereas neither of two cases of giardiasis without malabsorption and none of 17 controls was positive. There was a crude correlation of severity of jejunal histopathology with antibody titer.⁸⁰ FA titers fell in 11 of 19 cases (58%) 1 month or longer after therapy. Of 34 patients with malabsorption (mostly after travel to tropical areas) but negative stool and biopsy studies for giardia trophozoites, 10 (29%) had significant IFA anti-*G. lamblia* titers, which suggests that available diagnostic tests by direct examination may miss clinically significant giardiasis. These investigators also noted that use of mature cysts gave less reproducible results.

Vinayak et al. used washed, concentrated, sonicated *Giardia* cysts from fecal specimens to develop an immunodiffusion test for giardiasis that was said to be 91% sensitive as

well as negative in all 31 healthy or other-parasite-infected controls.¹¹⁶ Visvesvara and colleagues have developed an IFA test using axenically cultured *G. lamblia* trophozoites as antigen.¹¹⁷ They found antibody titers of 1:16 to 1:1024 among 29 of 30 patients with symptomatic giardiasis and 1:2 to 1:4 in 19 healthy controls. These positive titers could be absorbed with *G. lamblia* trophozoites in vitro. Fifteen patients with other parasitic infections for bacterial overgrowth syndromes had titers of \leq 1:16. Smith et al. reported the use of *G. lamblia* trophozoites cultivated in vitro in development of an ELISA that appeared to be specific and sensitive, with 81% of symptomatically infected patients developing antibody titer rises at 2 weeks to 15 months.¹¹⁸ The sensitivity of an ELISA for detection of giardia antigen in feces has been 92–98% (probably more sensitive than fecal microscopy); the specificity is also high.^{119–121} A rapid antigen detection method that distinguishes *G. lamblia* from *Cryptosporidium parvum* using nonenzymatic solid-phase qualitative immunochromatographic assay

has also recently been developed.¹²² This test has a sensitivity and specificity of 93.5% and 95.5%, respectively. In a comparison of three assays—direct immunofluorescence antibody (DFA), enzyme immunoassay, and nonenzymatic immunochromatographic assay, DFA was found to be the most sensitive.¹²³

■ GENETICS, ANTIMICROBIAL SUSCEPTIBILITY, AND THERAPY

Axenic cultivation of *G. lamblia* has enabled studies of the genetics of strain variation^{66–68} as well as in vitro sensitivity testing to antiparasitic agents.¹²⁴ Because the natural history of giardiasis is usually self-limited but occasionally recurrent over long periods of time, studies of the clinical efficacy of anti-giardial therapy are difficult at best. Table 44-2 summarizes the pertinent features of the drugs used to treat giardiasis. Quinacrine (Atabrine) 100 mg three times a day (t.i.d.)

Table 44-2. Agents Used in the Treatment of Giardiasis

Agent	Dosage	Cure Rate %	Side Effects
<i>Acridine derivative</i>	100 mg t.i.d. for 5–7 days	63–100	Occasional: toxic psychosis; insomnia; headache; yellow sclerae, skin and urine; nausea; vomiting. Rare: exfoliative dermatitis. Contraindicated in patients with psoriasis.
Quinacrine (Atabrine)	Pediatric: 6–8 mg/kg per day (or 2 mg/kg t.i.d.) for 5–7 days	84–93	
<i>Nitroimidazoles^a</i>			Nausea, headache, metallic taste; occasional insomnia, diarrhea, vertigo, paresthesia, rash; rare mild disulfiramlike reaction with alcohol, ataxia, urethral burning, reversible neutropenia. (Single daily dose metronidazole causes more gastrointestinal side effects.)
Metronidazole (Flagyl)	250 mg t.i.d. for 5–10 days	56–70	
	750 mg t.i.d. for 3–10 days	95	
	1.6–2.0 g q.d. for 1–5 days	91	
	Pediatric: 15–25 mg/kg per day (or 5 mg/kg t.i.d.) for 5–7 days	61–90	
<i>Thiazolides</i>			Mild and transient abdominal discomfort, diarrhea, nausea; very rarely anorexia, enlarged salivary glands, fever, infection, malaise, mild jaundice, azotemia, elevated alanine transferase, pruritus, swearing, rhinitis, dizziness, discolored urine.
Nitazoxanide	Pediatric, 12–47 months: 100 mg b.i.d. for 3 days	71–94	
	Pediatric, 4–11 years: 200 mg b.i.d. for 3 days Adults: 500 mg b.i.d. for 3 days		
Tinidazole and others (nimorazole, ornidazole)	2 g po for 1 dose 125 mg b.i.d. for 7 days	93–97	
<i>Nitrofurantoin</i>			Occasional nausea, vomiting. Headache; rare disulfiramlike reaction with alcohol, arthralgia, rash, urticaria, hemolysis, other blood dyscrasias.
Furazolidone (Furoxone)	100 mg t.i.d. for 7 days Pediatric: 1.5 mg/kg suspension q.i.d. for 7 days	72–92	

^aNot approved in the United States for giardiasis.

for 7 days, formerly the drug of choice in the United States, results in 80–100% cure rates,^{9,41,125} but is no longer readily available. Whether the mechanism of action of quinacrine is related to its relative distribution and then intercalation into DNA or to other membrane effects is currently unclear.

Metronidazole (Flagyl) 250–750 mg t.i.d. for 10 days effects 70–95% cure rates, the cure rate varying with the dose.⁴¹ Single daily doses of metronidazole of 1.6–2.0 g for 2 to 3 days also appear to be effective, but may cause more gastrointestinal side effects. Other nitroimidazole derivatives, including tinidazole, nimorazole, and ornidazole (Ro 7-0207), have also been effective, with possibly fewer side effects when given for 1 to 7 days.¹²⁶ The ability of nitroimidazoles to kill giardia protozoa may relate to inhibition of DNA synthesis, competition for reducing equivalents with electron-transport proteins, or other mechanisms that are not understood at present. As metronidazole is not officially approved in the United States for giardiasis and because of concern about its mutagenicity and carcinogenicity in some experimental animals, the potential risks should be weighed before this agent is used.

Nitazoxanide is a new thiazolide antiparasitic that shows in vitro activity against a wide variety of protozoa and helminthes. This has been approved for treatment of giardiasis for children ≥ 1 year of age.¹²⁷ The recommended dosage for children aged 12–47 months is 100 mg b.i.d. for 3 days, and for children aged 4–11 years, the recommended dosage is 200 mg b.i.d. for 3 days. For adults, the dosage is 500 mg b.i.d. for 3 days. In vitro studies have shown that nitazoxanide inhibits pyruvate-ferredoxin oxidoreductase (PFOR), an enzyme essential to anaerobic energy metabolism.¹²⁸ Clinical studies have demonstrated the efficacy of nitazoxanide to be comparable to metronidazole.^{129,130}

Furazolidone, which is available in liquid form for pediatric use, has also been suggested for treatment of giardiasis.¹²⁵ Tartrazine, which is in certain Latin American preparations of furazolidone, may be related to the serum sickness seen with this drug. Paromomycin has been used in pregnant patients with symptomatic giardiasis.¹³¹

Recent in vitro cultivation of *G. lamblia* has enabled studies of anti-giardial activity of these agents.¹²⁴ Although the appropriate methods and standardized criteria remain to be determined, “4-day end point” killing of *Giardia* has been noted with 0.05–0.1 $\mu\text{g}/\text{mL}$ quinacrine and with 0.05–6.4 $\mu\text{g}/\text{mL}$ metronidazole.^{56,72} Immobilization of the parasites by anti-giardial agents in vitro has also been suggested.¹³² Further definition of the in vitro inhibitory concentrations of these and other agents with axenically grown *Giardia* and amebas has recently become feasible and is under further study.

Epidemiologic control measures are needed, including improved hygienic and sanitary conditions as well as water treatment by means of flocculation, sedimentation, and

filtration. In addition, recent developments in in vitro culture technique and animal models are now opening the potential for developing means to control giardiasis. The roles of external and in vivo environments, pH, mucus, specific parasite and intestinal surface receptors, gut motility, and interaction with bacterial or other flora in causing or controlling disease are among the current frontiers in giardiasis research. Despite tantalizing suggestions of a protective role for cellular or humoral immunity, it remains unclear at present whether a vaccine might actually worsen the disease process in giardiasis. The *Giardia* genome project, as well recent advances in molecular techniques are key to understanding the epidemiology and pathogenesis of giardiasis and holds promise in the development of preventive, as well as therapeutic interventions to this disease.

ENTAMOEBIA HISTOLYTICA

HISTORY, EPIDEMIOLOGY, AND CLINICAL MANIFESTATIONS

History

For over a century, amebiasis has been recognized as an invasive enteric illness in humans. The clinical syndrome of amebiasis and effective therapy are well known. In recent years, there has been a renewed interest in the pathogenesis of *E. histolytica* infections.

The early history of amebiasis has been reviewed extensively.¹³³ Although a British surgeon, Timothy Richard Lewis, first described amebas in human stool in 1869, L \ddot{o} esch is credited with the first description of amebic dysentery, in a patient from St. Petersburg, Russia, in 1875. L \ddot{o} esch also reproduced colitis in dogs by introducing the patient’s stool orally or rectally. Koch first noted amebas in tissue specimens in 1887, and in 1893 Quincke and Roos first described amebic cysts. In 1903, Fritz Schaudinn named the parasite *E. histolytica* from its apparent capacity to destroy tissue. In 1912, Bernard Rogers found that emetine extracts from the ipecac root effectively cured amebic dysentery and liver abscesses. *E. histolytica* was definitively shown to be a human pathogen (as distinguished from the commensal *Entamoeba coli*) in human volunteer studies by Walker and Sellards in the Philippines in 1913.¹³⁴

More than a century after the first description of infection with *E. histolytica*, we now have the complete genomic sequence of the protist parasite, providing new insights into the evolution, virulence, metabolic pathways, and potential targets for chemotherapeutic or preventive interventions.¹³⁵

Epidemiology

Entamoeba spp. infect 10% of the world’s population; although the vast majority of those infected are asymptomatic, invasive

amebiasis is the third leading parasitic cause of death worldwide.¹³⁶ A distinct nonpathogenic species, *Entamoeba dispar*, has been identified by studies of isoenzyme patterns, genomic DNA, and ribosomal DNA.^{137–139} *E. dispar*, morphologically indistinguishable from *E. histolytica*, does not invade the host or elicit a systemic immune response during transient intestinal infection. *E. dispar* infection is usually up to tenfold more prevalent than *E. histolytica* infection,¹⁴⁰ although foci of transmission of *E. histolytica* are often observed. Therefore, all invasive amebiasis syndromes result from *E. histolytica* infection. Although approximately 90% of *E. histolytica* intestinal infections are also asymptomatic, they typically induce a systemic antiamebic immune response.^{141,142}

Epidemic outbreaks of amebiasis have been reported with food or water contamination from many areas.⁴ However, endemic amebiasis as currently seen in the United States is acquired by the fecal–oral route, usually by person-to-person spread.¹⁴³ High-risk groups include mentally challenged institutionalized patients (with stool cyst excretion rates of up to 70%),¹⁴⁴ lower socioeconomic groups, recently immigrated Mexican Americans in the southern United States,¹⁴⁴ travelers to highly endemic areas such as Mexico, Southeast Asia, China, India, the Middle East, Africa, and South America,^{17,145} and homosexual men (with cyst excretion rates in San Francisco and New York as high as 20% in the past).^{145–148} In Japan, where only a minority of the cases are imported, the most common group affected by amebiasis are male homosexuals or bisexuals and the mentally handicapped in institutions.¹⁴⁹

Overall, the combined prevalence of *E. histolytica* and *E. dispar* in the United States is approximately 4%,¹³⁶ but reported rates in MSM from the 1970s to early 1990s were higher and ranged from 20% to 37%.^{16–20,26} Keystone et al. has reported the prevalence rate of infection with *E. histolytica* to be 27% in MSM versus only 1% in heterosexual men.¹⁶ Prior history of STD, multiple sexual partners, and oral–anal sex were shown to be risk factors for amebiasis in some earlier studies.^{19,20,24,25} However, the prevalence of *E. histolytica* infection in MSM has declined in the last decade; the decline has accompanied the alteration in sexual practices within this group.¹⁴⁸ A recent study in Taiwan reported a prevalence rate of only 6% in MSM visiting gay bathhouses.¹⁵⁰ Higher rates may be seen in the immunocompromised population as noted in another study in Mexico City where infection was observed to be higher in HIV/AIDS positive patients (5.9% by microscopy and 25.3% by PCR) than in HIV negative patients (2.9% by microscopy and 18.5% by PCR).¹⁵¹

Clinical manifestations

Clinical syndromes with *E. histolytica* infection range from asymptomatic cyst excretion to acute rectocolitis, chronic nondysenteric intestinal disease (which can be confused with inflammatory bowel disease), typhloappendicitis, ameboma, or toxic megacolon. Extraintestinal amebiasis usually results

from hepatic abscesses and may extend to pleuropulmonary disease, pericarditis, or peritonitis. Unusual extraintestinal manifestations include venereal genital lesions, cutaneous lesions, and brain abscess.

Sexual transmission of *E. histolytica* results in enteric infection with possible dissemination or in venereal infection in males and females. Although many infections are asymptomatic or do not correlate with clinical symptoms,^{16–19} sexually transmitted amebic colitis may occur primarily in MSM between 20 and 40 years of age, with anilingus being a significant risk factor for acquisition of *G. lamblia* and *E. histolytica* infections. Some infections may present with anorectal exudates or proctitis.¹⁵² Penile and cervical amebiasis in conjugal partners is rare but reported.¹⁵³ In a review of literature performed by Antony and Lopez-Po, 148 cases of genital amebiasis confirmed by direct smear, cervical cytology, or tissue biopsy were identified between 1924 and 1997.¹⁵⁴ Vaginal discharge, usually bloody and foul smelling, was seen in all of the women ($n = 126$). In addition, infected women also presented with abdominal pain (37%), genital ulcers (8.1%), weight loss (2.8%), cervical squamous cell cancer (5.5%), and labial squamous cell cancer (0.79%). Most men (86%) presented with penile ulcers (86%) and urethritis (14%). Risk factors identified in the review included homosexual and heterosexual contact with infected partners and concomitant intestinal (also rectosigmoid) infection, poor genital hygiene, and vulvovaginitis. Very rare cases of uterine,¹⁵⁵ tubal,¹⁵⁶ testicular,¹⁵⁷ seminal vesicle,¹⁵⁷ and prostatic¹⁵⁸ involvements were also reported elsewhere.

■ STRUCTURE OF THE ORGANISM

E. histolytica and *E. dispar* trophozoites range in size from 10 to 60 μm , with an average size of 25 μm . Trophozoites contain a single 3–5- μm nucleus with fine peripheral chromatin and a central nucleolus (Fig. 44-3). The cytoplasm consists of a clear ectoplasm and a granular endoplasm that contains numerous vacuoles (Fig. 44-4). Cysts of *E. histolytica* average 12 μm in diameter (range 5–20 μm), and depending on their maturity contain one to four nuclei that have the same morphology as trophozoite nuclei. Like other members of the order Amoebida, young *E. histolytica* cysts contain chromatin bodies with smooth, rounded edges. Immature cysts may contain clumps of glycogen which stain with iodine.

Other members of the Entamoebidae family found in humans include *Entamoeba polecki*, *E. coli*, *E. gingivalis*, *Endolimax nana*, *Iodamoeba butschlii*, and *Dientamoeba fragilis*. *E. hartmanni* is recognized as a distinct species,¹⁵⁹ differing from *E. histolytica* in being smaller, having distinct antigenic differences, and being noninvasive.¹⁵⁹ Most experts agree that another nonpathogenic species of *Entamoeba* is the Laredo-like strain, which grows in culture at lower temperatures (25°–30°C) and does not cause clinical disease.¹⁶⁰

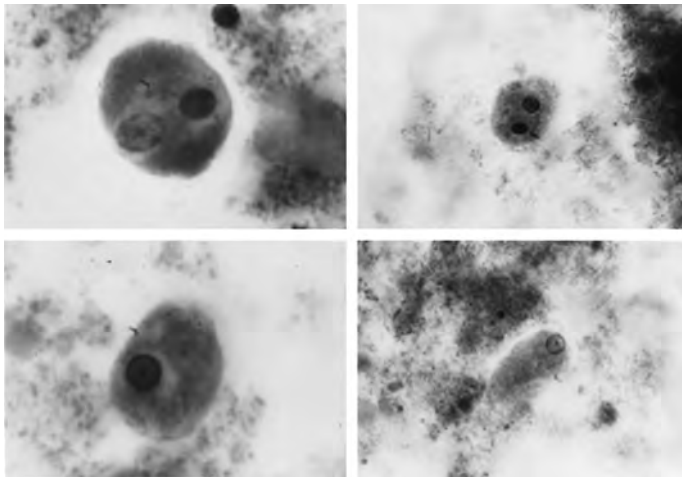


FIGURE 44-3. *Entamoeba histolytica* trophozoites from fecal specimens of a patient with amebic colitis. Gomori-Wheatley trichrome stain, oil immersion. (Right panel) $\times 320$ magnification. (Left panel) $\times 640$ magnification. Note single nuclei with central, punctate karyosome, with delicate peripheral nuclear chromatin. The top two trophozoites also have an ingested red blood cell. (Courtesy of G. R. Healy.)

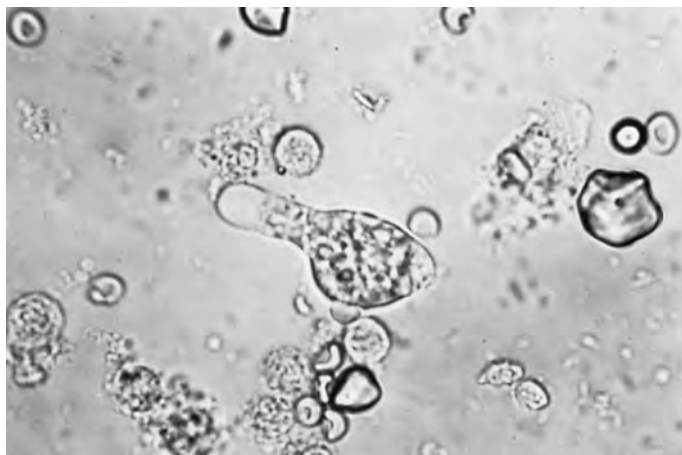


FIGURE 44-4. *Entamoeba histolytica* trophozoites from a saline suspension of a vaginal specimen from a patient whose partner also had amebic colitis. A single typically motile trophozoite is seen.

Extensive electron-microscopic studies of *E. histolytica* reveal no mitochondria; ribonucleoprotein exists in helical arrays in the cytoplasm.^{1612–163} Endoplasmic and ectoplasmic vesicles are bound by a 120-Å double-layered membrane, much like the outer limiting membrane.¹⁶²

Amebas also contain a uroid area where vesicles are noted external to the cell membrane.¹⁶⁴ An external fuzzy glycocalyx measures 20–30 nm on bacteria-associated trophozoites from tissue and 5 nm on axenic amebas.¹⁶⁵ Actin and structures resembling microfilaments have been identified in amebic trophozoites,^{166,167} and the actin gene has been cloned.¹⁶⁸ Microtubules have not been demonstrated. Apparent functions for microfilaments, but not for microtubules, have been described in studies of the cytopathogenic capacity of *E. histolytica*.^{169–171}

The surface membrane of *E. histolytica* has been well characterized biochemically. Amebas are agglutinated by the lectin concanavalin A,¹⁷² which may be a marker for degree of pathogenicity of different strains.^{172,173} Using concanavalin A binding to stiffen the external surface membrane, Aley et al. isolated relatively pure membrane preparations of *E. histolytica*.¹⁷⁴ Petri et al. have isolated the galactose-inhibitable adherence lectin of *E. histolytica*.¹⁷⁵ Microfilament-dependent capping, or aggregation of receptors, for concanavalin A or fluorescent-tagged antiameba antibody has been shown on *E. histolytica*, and the capped membrane material has been characterized biochemically, but the capping capacity does not appear to correlate with virulence.^{176,177} However, capping may help amebas avoid attack by host defenses.

■ GROWTH, PHYSIOLOGY, AND CULTURE

Life cycle

The life cycle of *E. histolytica* has been well characterized.^{178,179} Cysts are the infective form of *E. histolytica* because they can survive outside the host for weeks to months in a moist environment. Infected individuals excrete up to 45 million cysts per day.¹⁷⁸ Ingestion of cysts from fecally contaminated sources is followed by excystation in either the small or the large bowel. The nuclei then divide to form eight nuclei (transient metacystic stage), cytoplasmic division occurs, and eight amebic trophozoites emerge.¹³⁴ The trophozoite population then resides in the large bowel, where tissue invasion may occur. *E. histolytica* cyst walls contain chitin, an oligosaccharide of *N*-acetyl-D-glucosamine, sialic acid, and other cyst-specific antigens.^{180,181} Encystation is an active process: anaerobic glycolytic respiration and DNA synthesis occur.¹⁷² The conditions that induce encystation, excystation, and tissue invasion by amebas remain unclear and are the subject of current investigation.

Culture

Axenic cultivation of *E. histolytica* in medium without other organisms was first reported in 1961 by Diamond.¹⁸² This was accomplished by microisolation of amebic cysts, which were then introduced into a monophasic medium seeded with crithidial trypanosomes. A liquid medium was reported in 1968, and the current medium in use (TYI-S-33: trypticase, yeast extract, iron, serum) was developed in 1978.¹⁸³ These culture techniques have made it possible to grow amebas in large numbers and to maintain cultures for prolonged periods. Clonal growth of *E. histolytica* in semisolid medium allows quantitative cultures for drug susceptibility testing and other laboratory studies.¹⁸⁴ Studies of axenic culture in vitro have clarified nutritional and other requirements for amebic growth. These include requirements for cysteine, riboflavin (B_2), vitamin B_{12} , iron, serum, optimal

pH, and low oxygen tension.¹⁸³ Recently, Clark has succeeded in establishing *E. dispar* in axenic culture.¹⁸⁵

■ IMMUNOLOGY AND PATHOGENESIS

Immunology and host response

There is no evidence that intestinal colonization by *E. histolytica* elicits a protective host-immune response.¹⁸⁶ However, extensive but anecdotal evidence indicates that cure of amebic colitis or liver abscess is followed by resistance to subsequent invasive amebiasis.^{187,188} The mechanisms of immune defense against *E. histolytica* infection have not been fully characterized. Serum from both healthy controls and infected patients (with high antibody titers to *E. histolytica*) are amebicidal to trophozoites through activation of the alternate complement pathway.^{189,190} However, trophozoites that cause invasive disease are resistant to complement-mediated lysis. Complement-resistant amebas can be selected in vitro by culture in normal human serum.^{191,192} Serum antibodies and coproantibodies have been demonstrated to increase during invasive disease.^{191,192}

A protective role for humoral immunity is suggested by the presence of antibody to the parasite's galactose-inhibitable adherence lectin.¹⁹³ Human immune sera can prevent amebic in vitro adherence,^{193,194} despite the parasite's ability to aggregate and shed attached antibodies. The other *E. histolytica* antigens most frequently recognized by human immune sera have also been characterized,¹⁹⁵ which may be useful for development of diagnostic tests and vaccines. Lectin recombinant antigens (such as a 52-kDa fusion protein including the cysteine-rich LC3 section of the 170-kDa subunit),¹⁹⁶ as well as the entire 29-kDa surface antigen,¹⁹⁷ have recently been shown to conserve antigenicity.

Mucosal IgA immune responses have been studied in subjects cured of amebic liver abscess and colitis or with asymptomatic *E. histolytica* intestinal infections. Salivary sIgA to purified native galactose-inhibitable lectin has been found in subjects with amebic liver abscess¹⁹⁸ and colitis.¹⁹⁹ Fecal and salivary anti-LC3 sIgA responses occur in amebic colitis²⁰⁰ and liver abscess; such patterns are absent or diminished in subjects with *E. dispar* infection.²⁰⁰ In a study of Bangladeshi children, fecal antilectin IgA has been associated with protection from intestinal reinfection.²⁰¹ Oral immunization of mice with the recombinant LC3 fusion protein and cholera holotoxin induced intestinal anti-LC3 IgA antibodies that inhibited amebic adherence in vitro.²⁰² Combined intranasal and intraperitoneal application of purified native Gal/GalNac lectin in the C3H mouse model of amebic colitis elicited fecal antilectin IgA response and protected against invasive intestinal disease.²⁰³

Cell-mediated immune (CMI) defense mechanisms appear to have a role in limiting invasive disease and possibly in resistance to recurrent invasion following pharmacologic cure.¹⁸⁶ Following invasive amebiasis, the CMI response consists of antigen-specific lymphocyte blastogenesis, with production of lymphokines (including gamma interferon) that activate monocyte-derived macrophages to kill *E. histolytica* trophozoites in vitro.^{204–206} In addition, cured patients develop effective antigen-specific cytotoxic T-lymphocyte activity for *E. histolytica* trophozoites.²⁰⁵ Purified native 260-kDa galactose-inhibitable lectin induced lymphocyte proliferation, gamma interferon production, and amebicidal activity in cultivated peripheral-blood mononuclear cells from subjects with serum antilectin IgG antibodies (indicating prior *E. histolytica* infection).²⁰⁷ In addition, immunization of gerbils with native 260-kDa lectin induces a protective amebicidal cellular immune response.²⁰⁸ However, in acute disease, CMI to *E. histolytica* is specifically depressed by a serum factor.²⁰⁹ The high prevalence of *E. histolytica* intestinal infection in homosexual men with AIDS or certain other clinical manifestations of HIV infection without an increased incidence of invasive amebiasis¹⁴⁸ suggests that host resistance to the initial amebic invasion of the colonic mucosa does not involve CMI mechanisms.

Nonimmune host defenses may be most important in prevention of parasite attachment to and disruption of the colonic mucosa. In animal models, mucus trapping of *E. histolytica* trophozoites occurs,²¹⁰ and depletion of the colonic mucus blanket is always seen before parasite invasion.²¹¹ *E. histolytica* elaborates a potent mucin secretagogue²¹² that may contribute to depletion of the mucus layer. A family of thiol (cysteine) proteinases (EhCPs) apparently disrupt the polymerization of MUC2, the major component of human colonic mucus.²¹³ Chadee and coworkers demonstrated that purified rat and human colonic mucins, which are rich in galactose residues, are high-affinity receptors for the ameba's lectin, while mucin inhibits amebic adherence to and lysis of colonic epithelial cells in vitro.²¹⁴ Therefore, colonic mucin glycoproteins act as an important host defense by binding to the *E. histolytica* adherence lectin; however, this interaction may facilitate intestinal colonization by amebas and thus promote parasitism by *E. histolytica*.

■ PATHOLOGY

The pathology of human amebiasis provides clues to its pathogenesis. *E. histolytica* appears to exert a tissue lytic effect, for which the organism is named, whether in colon, liver, lung, or brain; this lytic effect leaves an amorphous, granular, eosinophilic material surrounding trophozoites in tissue²¹⁵ and can be studied in vitro. Consistent with the trophozoites' capacity to destroy leukocytes, inflammatory cells are found only at the periphery of amebic lesions and not adjacent to the trophozoites.^{171,173,215,216}

The typical flask-shaped colonic ulcers are usually superficial, reaching only the muscularis mucosa level and separated by normal mucosa. Amebic trophozoites are seen in clusters in the periphery of necrotic areas. Light- and electron-microscopic studies have been alternatively interpreted as showing contact lysis of mucosal cells or diffuse mucosal damage prior to amebic invasion.^{164,217} Current in vitro studies favor direct invasion and contact-dependent cytolysis by amebic trophozoites.

Liver pathology consists of the necrotic abscess and periportal fibrosis; however, the so-called abscess contains acellular, proteinaceous debris rather than white cells and is surrounded by a rim of amebic trophozoites.²¹⁵ Triangular areas of hepatic necrosis have been observed, possibly due to ischemia from amebic obstruction of portal vessels.²¹⁵ Periportal fibrosis alone, without trophozoites present, has been reported in patients with amebic colitis.²¹⁸ Whether this reflects past trophozoite invasion or host reaction to amebic antigens or toxins is currently unclear. “Amebic hepatitis” is a debated entity; liver function abnormalities commonly present with amebiasis are associated with periportal inflammation without demonstrable trophozoites.

■ PATHOGENESIS

The pathogenesis of invasive amebiasis can be divided into four steps: (1) colonization of the intestine with a virulent *E. histolytica* trophozoite, (2) disruption of mucosal barriers with adherence to colonic epithelial cells, (3) lysis of adherent epithelial cells and host inflammatory cells, and (4) resistance to host humoral and cellular defense mechanisms with deep tissue invasion. Recent in vitro studies have markedly increased our understanding of the biochemical and molecular mechanisms of the pathogenesis of invasive amebiasis.

■ VIRULENCE

Current evidence indicates that there exist distinct pathogenic and nonpathogenic strains of *Entamoeba*. Sargeant and coworkers (reviewed in Ref. 200) demonstrated that starch gel electrophoresis of *E. histolytica* clinical isolates reveals patterns for the enzymes hexokinase, phosphoglucosmutase, and glucosephosphate isomerase, which are characteristic for invasive or noninvasive amebic infection at the time the sample was collected. The isoenzyme patterns are referred to as zymodemes. Sargeant²¹⁹ and others²²⁰ proposed in 1986 that zymodeme studies reflect stable strain differences and that there was no need to treat individuals infected with *E. histolytica* expressing a “nonpathogenic” zymodeme.

Many *Entamoeba* strains producing nonpathogenic zymodemes are now thought to be *E. dispar*. Epidemiologic studies of thousands of subjects confirm that *E. dispar* is not invasive, nor does it elicit a serum antibody response.^{141,142} Tannich and coworkers were the first to demonstrate

differences in genomic DNA between *E. histolytica* and *E. dispar*.²²¹ Recent studies by Clark and Diamond further characterized *E. dispar*.¹³⁹ Earlier studies indicating conversion of *E. dispar* to *E. histolytica* appear to be due to incomplete cloning of cultivated isolates.

In vivo experiments have drawn attention to the association of *E. histolytica* with bacteria (reviewed in Ref. 222). Associated bacteria facilitated early culture of *E. histolytica* in vitro, and Phillips et al. showed that bacteria were required for the establishment of invasive disease in germ-free guinea pigs infected with amebas grown with *Trypanosome cruzii*.²²³ They interpreted the role of bacteria to be one of providing an environment which enables amebas to grow in the colon.²²⁴ Wittner and Rosenbaum subsequently demonstrated that amebas required direct association with viable bacteria for virulence and that a soluble virulence factor could not be demonstrated.²²⁵

Recent axenic culture methods have allowed strains of amebas to retain virulence after prolonged periods (up to 9 years) of in vitro culture.²²⁶ However, in vitro destruction of tissue-culture cells by axenic trophozoites is stimulated by parasite ingestion of viable bacteria.²²⁷ Apparently these associated bacteria either accelerate the ameba's electron-transport system or increase its reducing capacity.²²⁷ Viral particles have also been demonstrated in axenic amebas and can result in lysis of the amebas.²²⁸ However, viral passage from amebic strains of higher virulence to less virulent strains does not consistently alter amebic virulence.²²⁹

Host nutritional factors appear to relate to the invasiveness of amebic infections. Weanling rats given protein-deficient diets are more susceptible to amebic infection; those already infected can eliminate the parasite when subsequently given high-protein diets.²²⁹ High-carbohydrate, low-protein diets resulted in higher colonization but reduced tissue invasion compared with rats on a normal diet.²³⁰ Faust and Read have noted an association of a poor nutritional state with more invasive amebic disease in humans.²³¹ Wanke and Butler reported a very high mortality for amebic colitis in malnourished patients in Bangladesh.²³² Although feeding of iron to experimental animals appears to increase the severity of experimental amebiasis, studies in humans do not reveal any correlation of invasive amebiasis with either serum iron or saturation of iron-binding proteins.²³³ Finally, several investigators have noted an interesting association of ameba virulence with exposure of the parasite to cholesterol or with liver passage.^{234,235} The increased virulence apparently persists for weeks after cholesterol exposure and is therefore not a temporary membrane or nutritional effect; it remains to be further elucidated.

■ ADHERENCE MECHANISMS

E. histolytica trophozoites maintained in axenic culture must establish adherence in order to lyse target cells.^{169,170} Ravdin and coworkers have demonstrated that in vitro adherence of

E. histolytica trophozoites to Chinese hamster ovary (CHO) cells and human colonic mucins is exclusively mediated by the parasite's inhibitable surface lectin.^{170,214,236} The galactose lectin also participates in amebic in vitro adherence to human leukocytes,^{189,236} rat and human colonic mucosa and submucosa,¹⁹⁴ human erythrocytes,^{170,237} Chang liver cells,²³⁸ opsonized bacteria or bacteria with galactose-containing LPS,²³⁹ and rat colonic epithelial cells.²¹⁴

Ravdin and coworkers²⁴⁰ produced monoclonal antibodies which inhibited amebic adherence to CHO cells. Using the lectin's carbohydrate-binding activity and lectin-specific monoclonal antibodies, Petri and coworkers isolated the *E. histolytica* adherence lectin.²⁴¹ Using ³⁵S-methionine, they metabolically labeled amebic proteins from a culture filtrate or detergent-solubilized amebas, which were then applied to an ASO affinity column. After washing, a peak of ³⁵S-methionine activity was eluted with galactose; with autoradiography, SDS-PAGE under reducing conditions demonstrated a 170-kDa metabolically labeled amebic protein (Fig. 44-5).

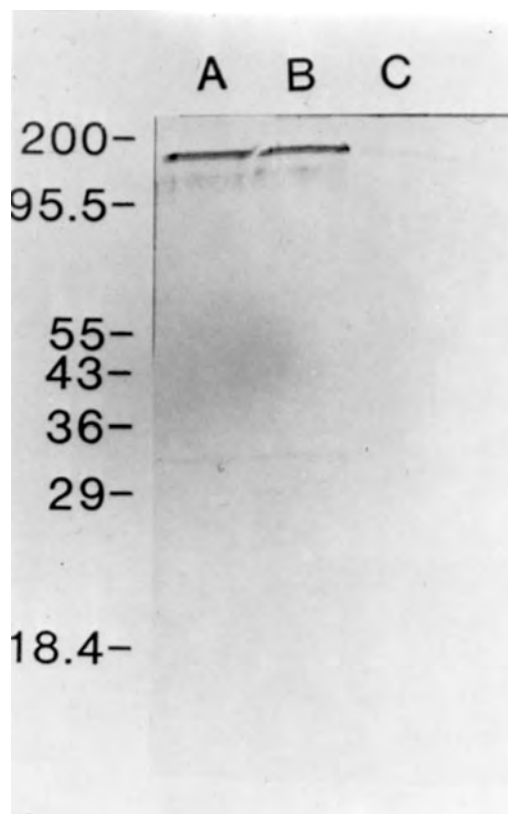


FIGURE 44-5. Galactose inhibition of binding of the amebic adherence lectin to the asialoorosomuroid (ASOR) affinity column. Autoradiograph of SDS-PAGE of [³⁵S]methionine-labeled proteins eluted with galactose from an ASOR column to which conditioned medium, **A**; conditioned medium plus 0.5 M dextrose, **B**; or conditioned medium plus 0.5 M galactose, **C**; has been applied. The columns were extensively washed in 50 mM Tris, 200 mM NaCl, 10 mM CaCl₂, pH 7.35, and then eluted with 0.5 M galactose in the above buffer. Galactose-eluted fractions were electrophoresed on 10% polyacrylamide gels and analyzed by autoradiography. (Adapted from Petri WA, et al. Isolation of the galactose-binding lectin which mediates the in vitro adherence of *Entamoeba histolytica*. J Clin Invest 1987; 80: 1238.)

Petri et al. confirmed that the purified amebic protein is the galactose-inhibitable lectin in three ways: (1) application of [³⁵S]-methionine metabolically labeled amebic proteins to an adherence-inhibitory H8-5 antibody Affigel-10 column resulted in elution of the same protein; (2) on immunoblotting, the most adherence-inhibitory monoclonal antibody, F-14,²¹¹ exclusively recognized the 170-kDa protein purified by ASO affinity chromatography; and (3) the lectin purified by H8-5 immunoaffinity chromatography bound to CHO cells in a galactose-specific manner and competitively inhibited adherence of viable amebas.

Subsequent studies determined that the galactose-inhibitable lectin consists of two subunits with masses of 170 and 35 kDa.²⁴² The lectin has a mass of 260 kDa under nonreducing conditions. The 170-kDa subunit is highly antigenic and immunogenic. It contains the galactose-binding activity, as determined by recognition with adherence-inhibitory monoclonal antibodies and by the in vitro galactose-specific binding of an in vitro expressed PCR product based on 170-kDa subunit DNA.²⁴³ The amebic genes encoding the 170-kDa subunit have been identified and sequenced,^{244,245} as has the gene encoding the 35-kDa subunit.²⁴⁶ The 35-kDa subunit is not antigenic and apparently exhibits fibronectin-binding activity.²⁴⁶ The 170-kDa subunit of the *E. histolytica* adherence lectin is the most prominent antigen immunoprecipitated by a pool of human immune sera (Fig. 44-6); immune sera from such diverse geographic regions as Mexico, India, the United States, South Africa, and Zaire all recognize this adherence protein on immunoblotting.^{175,247,248}

A chitotriose-inhibitable lectin in *E. histolytica* homogenate which agglutinated erythrocytes was described by Kobiler and Mirelman.²⁴⁹ In a high-ionic-strength buffer, amebic adherence to Henle cells was inhibitable by 40% with chitin.²⁵⁰ The chitotriose-inhibitable lectin may have a role in encystation.¹⁸¹ Arroyo and Orozco²⁵¹ produced monoclonal antibodies which inhibit parasite adherence and ingestion of fixed human erythrocytes by up to 60% and on immunoblotting recognized a 112-kDa *E. histolytica* surface protein. Carbohydrate specificity of this putative amebic adhesin is not described; apparently more than one amebic adhesin mediates adherence to erythrocytes.¹⁷⁷

Cytolytic mechanisms

The pathology of invasive human amebiasis has a characteristic appearance: amebas are surrounded by amorphous granular debris, presumably due to tissue lysis.²¹⁵ Axenic *E. histolytica* trophozoites kill target cells only upon direct contact rather than via secreted cytotoxins.^{169,170} Lectin-mediated adherence is required for lysis of target CHO cells, Chang liver cells, rat colonic epithelial cells, and human PMN or mononuclear cells.^{170,233,236–238} Purified lectin is a cytotoxin which induces rapid reversible increases in target-cell [Ca^{++}].²⁵² Amebic cytolytic activity is dependent on parasite

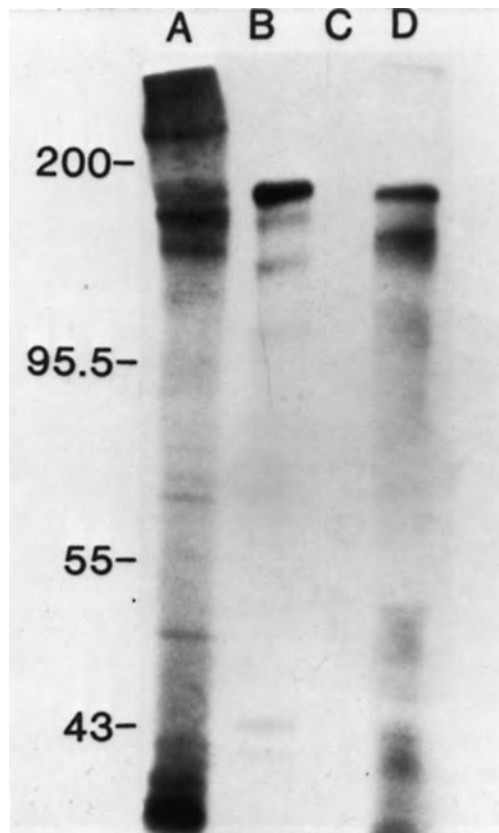


FIGURE 44-6. Immunoprecipitation of [³⁵S]methionine metabolically labeled amebic protein with H8-5 and pooled human immune sera (PHIS). Autoradiograph of SDS-PAGE (10% acrylamide separating gel) of [³⁵S]methionine-labeled amebic proteins, **A**; immunoprecipitated with monoclonal antibody H8-5, **B**; normal human serum, **C**; or PHIS, **D**; A 170-kDa metabolically labeled amebic protein was immunoprecipitated by lectin-specific H8-5 and PHIS and is the most intensively labeled antigen recognized by PHIS. (Adapted from Petri WA, et al. Recognition of the galactose- or *N*-acetyl-galactosamine-binding lectin of *Entamoeba histolytica* by human immune sera. *Infect Immun* 1987; 55: 2327.)

microfilament function,^{169,170} [Ca⁺⁺]_i,^{252,253} Ca⁺⁺-dependent parasite phospholipase A (PLA) activity,^{253,254} and maintenance of an acid pH in amebic endocytic vesicles.²⁵⁵ Establishment of adherence by *E. histolytica* trophozoites is followed by a marked sustained elevation of target-cell [Ca⁺⁺]_i, which contributes to but may not be totally sufficient for target-cell death.²⁵² Phorbol esters specifically augment amebic cytolytic activity.²⁵⁶

An ionophorelike *E. histolytica* protein induces lipid bilayers or vesicles of target cells to leak Na⁺, K⁺, and to a lesser extent Ca⁺⁺.^{257–261} This protein, packaged in dense intracellular aggregates, can depolarize erythrocyte membranes.^{259,260} The amebic ionophore apparently acts as a defense mechanism against ingested bacteria. It has homology to the pore-forming proteins granulysin and NK-lysin produced by cytotoxic T cells and natural killer cells.²⁶² The gene encoding the ionophore has been sequenced.²⁶¹ The *E. histolytica* genome reveals 3 genes encoding for amebapores and additional 16 genes encoding for structurally similar proteins, all belonging to the family of saposin-like proteins.²⁶³

E. histolytica contains numerous proteolytic enzymes, including a cathepsin B protease,²⁶⁴ an acidic protease,²⁶⁵ a collagenase,²⁶⁶ and a major neutral protease.²⁶⁷ Proteases appear to be involved in dissolution of the extracellular matrix-anchoring cells and tissue structure.²⁶⁷ Twenty genes for cysteine proteinases have been identified and expression of these genes had been correlated with pathogenicity.^{268,269} Recent data involve cysteine proteases also in proteolysis of enterocyte villin causing effacement of microvilli.²⁷⁰ Furthermore, they have also been shown to cleave and activate preinterleukin-1B possibly contributing to inflammation during the early colonic invasion.²⁷¹ *E. histolytica* enterotoxigenic activity^{272,273} may induce a secretory diarrheal component.

In vivo models of amebic liver abscess^{274,275} and in vitro studies²³⁸ demonstrate that parasite adherence to and lysis of host polymorphonuclear leukocytes enhances tissue destruction by release of toxic neutrophil oxidative products. A further understanding of the biochemical and molecular basis for the pathogenicity of *E. histolytica* should aid in the development of a vaccine or pharmacologic strategies to combat this disease.

■ DIAGNOSIS

Stool and proctoscopic examination

The key to laboratory diagnosis of colonic amebiasis is the stool examination. Three stool specimens or one purged specimen should be examined for maximum yield prior to use of barium, antacids, enemas, or antimicrobial or antiparasitic agents, which will interfere with the microscopic examination.^{276,277} If fecal specimens cannot be examined immediately, they should be refrigerated or fixed. Trophozoites in stool will rapidly lyse at room temperature or at 37°C. A saline wet-mount should first be examined to establish the presence of amebic trophozoites or cysts. Differentiation of *Entamoeba* spp. requires permanent stains (trichrome or iron-hematoxylin) following fixation in 10% formalin or polyvinyl alcohol to reveal characteristic nuclear morphology, as described above (see Figs. 44-3 and 44-4). The most common error in diagnosis is mistaking fecal leukocytes or macrophages for amebic trophozoites.¹³⁷ Of note, fecal leukocytes are usually pyknotic or absent in patients with amebic colitis, in contrast to patients with bacterial dysentery, possibly because of the direct toxic effect of amebas on leukocytes.^{171,173,215}

The stool examination is positive in approximately 90% of patients with invasive amebic colitis;²⁷⁸ however, if the stool examination is negative in a suspected case of amebic colitis, proctoscopy or colonoscopy is indicated.^{279,280} The margin of a colonic ulcer should be scraped (not swabbed, as amebic trophozoites may adhere to cotton swabs) and appropriate stains made of the scraping material, which often shows the

parasite. If tissue is obtained, a careful search for invading trophozoites should be made on routine hematoxylin and eosin (H&E)- and periodic acid–Schiff (PAS)-stained material.

Genital specimens

Genital amebiasis may be diagnosed by direct smear (or Papanicolaou smear) of vaginal, cervical, or urethral discharge.¹⁵⁴ Ulcerative lesions require biopsy to demonstrate invading trophozoite, in addition to inflammatory infiltrate and necrotic debris.²⁸¹

In vitro cultivation

E. histolytica can be cultured from clinical specimens. Numerous culture media have been used, including liver extract (Cleveland and Collier), egg-infusion medium (Balamuth), and alcohol-egg extract of Nelson.²⁸² However, none is selective for *E. histolytica*. Both cysts and trophozoites can be cultured, a technique which can help differentiate *E. histolytica* from *E. coli*, *E. hartmanni*, and the Laredo strain of *E. histolytica*. Cleveland and Collier's medium can be made more selective by adding rice powder and antibiotics (penicillin and streptomycin).¹⁶⁰ Failure of the culture to grow at low temperatures excludes the Laredo-like strain, which grows well at 23°C.¹⁶⁰ These methods can be used to document amebiasis in patients. Zymodeme determination using starch gel electrophoresis of in vitro cultivates can be used to differentiate *E. dispar* from *E. histolytica*. However, this is a laborious technique that is available only in research laboratories.

Antibody and antigen assays

Numerous techniques have been developed for study of the serologic response to *E. histolytica* infection (Table 44-3). All methods are highly specific; patients without exposure to *E. histolytica* are rarely positive. These tests are usually quite

sensitive for detection of patients with amebic liver abscess or invasive colitis; *E. dispar* infection does not elicit a serum anti-amebic antibody response, whereas asymptomatic *E. histolytica* infections do. Therefore, a negative serology is quite helpful in ruling out *E. histolytica* infection in an endemic area.^{141,142} The indirect hemagglutination test (IHA) is the most widely used method at present in the United States.^{191,283,284} The IHA uses antigen prepared from axenic cultures of *E. histolytica* (usually strain HK9). Serum is heat inactivated and added in serial dilutions to sheep or human red blood cells sensitized with amebic antigens; hemagglutination is evaluated in comparison with known positive and negative controls.²⁸⁵ IHA titers are usually elevated at the time of initial presentation with invasive amebiasis, often to titers of $\geq 1:1024$,²⁸³ and then fall to lower levels 2–11 years after therapy.^{191,283,284}

When repeated exposure or persistent infection renders the IHA less useful,²⁸⁴ the gel diffusion precipitin test, which remains positive for shorter periods following acute illness (6 months), may be helpful.²⁸⁴ Serologic testing for amebiasis should be considered and may be quite helpful in differentiating inflammatory bowel disease from amebic colitis. Fewer than 2% of patients with inflammatory bowel disease and negative stool examinations for amebas have positive IHA titers.^{283–285} Because of the widespread occurrence of amebiasis, patients in whom the diagnosis of inflammatory bowel disease is considered should have sera tested and stools examined for amebic infection, especially before steroid therapy is considered.

Other techniques used for detection of serum antibodies to *E. histolytica* include counterimmunoelectrophoresis, amoebic gel diffusion test, complement fixation, indirect fluorescence assay, latex agglutination, and ELISA.²⁸⁶

Antigen-based ELISA are now commercially available for detection of infection in fecal specimens. These kits use monoclonal antibodies against the Gal/GalNAc-specific lectin of *E. histolytica* (*E. histolytica* test II; Techlab,

Table 44-3. Systems in Use to Evaluate Serologic Response to Infection with *E. histolytica*

Percent positive in Serologic test	Controls	Cyst Passes	Rectocolitis	Liver Abscess
Indirect hemagglutination	0–7	8–15	81–98	83–100
Indirect immunofluorescence			57	57
Countercurrent immunoelectrophoresis		0–1.7	87	95–100
Agar gel diffusion	0–18	1–52	55–95	80–100
Enzyme-linked immunosorbent assay (ELISA)			50	100
Complement fixation	0–16	28	85–90	83–100
Cellulose acetate membrane precipitation		0	100	
Immunolectrophoresis		87	93	
Latex agglutination	0	75	100	
Thin layer immunoassay				79

Blacksburg, VA) or monoclonal antibodies against the serine-rich antigen of *E. histolytica* (Optimum S kit; Merlin Diagnostika, Bornheim-Hersel, Germany). These antigen assays may have good correlation with PCR from stool specimens for detecting infection.²⁸⁷

Nucleic acid amplification techniques are currently for research purposes only, but may become the technique of choice in the future.

■ TREATMENT

At present, drug susceptibility of *E. histolytica* is based on clinical activity and nonquantitative observations. Quantitative, clonal growth of *E. histolytica* provides a method for drug evaluation that can be standardized for static and amebicidal activities.^{288,289} Appropriate drug therapy of amebiasis must take into account drug distribution (absorption, penetration, excretion in the intestinal tract) and sites of amebicidal activity. For example, antibiotics are usually active only in colonic and not in hepatic disease. Drugs that are active in all tissues include metronidazole, tinidazole, dehydroemetine, and emetine hydrochloride.^{278,290–292} Agents which may help eradicate gut luminal infection include diloxanide furoate, paromomycin, bismuth iodide, and diiodohydroxyquin.^{279,292,293} Tetracycline and erythromycin have some activity in colonic disease and chloroquine may be active in hepatic disease.²⁷⁸ Recommended drug regimens, including dosages and possible adverse reactions, are outlined in [Table 44-4](#). Nitazoxanide is a new thiazolide agent with in vitro activity against a wide variety of protozoal and helminthic pathogens including *E. histolytica*. Its clinical efficacy for amebiasis, though, is yet to be proven.

Standard medical regimen should be sufficient for genital amebiasis. However, surgical intervention may be necessary in neglected and progressive lesions.^{294,295}

■ PREVENTION AND BIOLOGICAL CONTROL

At present, prevention of amebiasis rests on interference with fecal–oral transmission by improved hygiene, sanitation, and water treatment; by abstaining from oral–anal–genital contact; and by proper isolation of index cases.²⁹⁶ Numerous tantalizing but unexplored possibilities for biological control also exist. One approach would be to prevent commensal carriage in the human host; another, disregarding carriage, would be aimed at altering the parasite or host to avoid tissue invasion. Systemic and especially local intestinal immunity for alterations in microbial flora might well alter the parasite's carriage and shedding or its invasiveness. A number of ameba proteins had been identified to be potential vaccine candidates. The most promising among these proteins are the 25-kDa serine-rich *E. histolytica* protein called SREHP and the 260-kDa galactose and *N*-acetylgalactosamine-inhibitable ameba lectin,²⁹⁷ showing encouraging results in animal models of intestinal amebiasis.

Certainly giardiasis and amebiasis rank among the widespread, often devastating human diseases for which the current renaissance of immunobiologic research holds great promise of many exciting developments. The groundwork that has been laid has already resulted in improved understanding of the biology of the giardia protozoa and amebas through in vitro culture and animal models. We now stand at the threshold of greatly improved understanding of the pathogenesis and, hopefully, eventual control of these two protozoan enteric parasitic infections.

CRYPTOSPORIDIUM

■ INTRODUCTION AND HISTORY

Organisms of the genus of *Cryptosporidium* are small (2–6 μm) coccidian protozoans that may inhabit the gastrointestinal, respiratory, and biliary tracts of a variety of animals including humans. In 1907, Tyzzer first described this parasite as a cause of asymptomatic infection in the gastric glands of the common laboratory mouse.²⁹⁸ In 1955, Slavin reported the first case of symptomatic diarrheal disease in poultry due to *Cryptosporidium*.²⁹⁹ The parasite was subsequently demonstrated to be a pathogen of many animals and to cause epidemics of diarrheal disease. However, the first instance of symptomatic human disease was recorded in 1976 in a young immunocompetent child.³⁰⁰

Human infection with *Cryptosporidium* was considered rare prior to 1982, the result of opportunistic infection with a pathogen outside its normal host range. With the recognition of AIDS in the early 1980s, an increasing number of cases of severe cryptosporidiosis were reported.³⁰¹ *Cryptosporidium* has been identified to be the most common pathogen associated with chronic diarrhea and AIDS among MSM, accounting to 16% of 49 cases in one U.S. study.³⁰² In another European study of AIDS patients with chronic diarrhea, the overall prevalence of intestinal cryptosporidiosis was 15.6% (43 of 275); the prevalence was noted to be significantly higher in MSM (33.3%) than in intravenous drug users (10.6%).³⁰³ In 1983, an outbreak of symptomatic cryptosporidiosis among animal handlers stimulated clinical interest leading to the recognition of this parasite as an important diarrheal pathogen in the immunocompetent host.³⁰⁴ Numerous waterborne and swimming pool outbreaks have since occurred, culminating in 1993 in the largest waterborne outbreak in US history, involving over 400,000 people in Milwaukee. These outbreaks, along with studies in developing areas, have placed cryptosporidiosis among the leading causes of diarrhea worldwide.^{305–309}

■ PATHOGENESIS

Historically, *Cryptosporidium* was assumed to be host specific, similar to another coccidian parasite, *Eimeria*. Although the exact number of distinct species of *Cryptosporidium* is

Table 44-4. Treatment of *E. histolytic* Infections

Condition and Drug	Dose and Duration	Cure Rate	Adverse Reactions
<i>Cyst passage</i>			
Diloxanide furoate (obtain from CDC)	500 mg tid for 10 days	87–96%	Mild gastrointestinal upset (uncommon).
Diiodohydroxyquin (followed by tetracycline)	650 mg tid for 20 days	95%	Subacute optic neuropathy, dermatitis, diarrhea, headache. Avoid if hepatic disease or iodine intolerance present.
Paromomycin	300 mg/kg per day for 5–10 days	80–90%	Gastrointestinal upset.
<i>Invasive colitis</i>			
Metronidazole ^a	750 mg tid for 10 days	>90%	10–20% Gastrointestinal upset (less with divided dosage), disulfiram effect, bitter taste, seizures, possible carcinogenesis.
	750 mg tid for 5 days ^b	>90%	
	2.4 g qd for 2–3 days ^b	>90%	
Tetracycline	50 mg/kg for 1 dose ^b 250 mg qd for 14 days ^b	>90%	Gastrointestinal upset, hepatotoxicity, fungal suprainfection, teeth discoloration.
Dehydroemetine	1–1.5 mg/kg per day IM for 5 days [†]	80–90%	25–50% Cardiotoxicity (tachycardia, hypotension, angina, electrocardiograph changes), neuromuscular (tremor, muscle tenderness, and weakness), gastrointestinal.
<i>Liver abscess^c</i>			
Metronidazole	750 mg tid for 5–10 days ^b or 2.4 g qd for 1–2 days ^b	99%	See above.
Dehydroemetine (followed by chloroquine)	1–1.5 mg/kg per day for 5 days [†] (600 mg qd for 2 days)	90%	See above.
		(60% Alone)	Gastrointestinal upset, headache, pruritus.

^aAlternate therapies to metronidazole with possibly less toxicity, but which are unavailable in the United States, include the following drugs: tinidazole, 50 mg/kg per day for 3 days (plus luminal agent from the therapy for cyst passage), and tiberol, 15–30 mg/kg per day for 5 days (plus luminal agent from the therapy for cyst passage).

^bPlus luminal agent from the therapy for cyst passage.

^cAspiration of abscess not necessary for cure, but in experienced hands it may decrease symptoms and recovery time. The only absolute indication is a lack of response or worsening while the patient is on medical therapy for 3–5 days.

debated, recent studies indicate a limited number of valid species that can be distinguished by size, life-cycle characteristics, ability to transmit infection between animals (e.g., mammal to mammal vs. mammal to poultry), and chromosome pattern.^{310–315} Recent advances in molecular tools for species differentiation, genotyping, and subtyping have led to identification of 13 accepted species of *Cryptosporidium* and over 30 genotypes. Eight *Cryptosporidium* spp./genotypes have been identified in humans, including *C. hominis*, *C. parvum*, *C. meleagridis*, *C. felis*, *C. canis*, *C. muris*, *C. suis*, and *Cryptosporidium* corvine genotype.^{316,317} The two most common causes of human infections are *C. hominis* and *C. parvum*. The genome sequences of these two species had recently been completed, revealing new insights on the host interactions, pathogenesis, and possible targets for therapeutic and preventive interventions.^{318,319}

Disease among animal hosts includes diarrhea in large mammals such as calves, piglets, lambs, foals, and goats; intestinal and respiratory disease in poultry; and asymptomatic carriage in most rodents. Persistent infection associated with diarrhea has been reported in nude (nu/nu) BALB/c mice infected at 6 days of age; when the mice were inoculated at 42 days of age, only asymptomatic infection developed.³²⁰ These observations and the fact that AIDS patients manifest severe symptomatic disease suggest that T lymphocytes, particularly the T-helper subset, are important in recovery from infection and the development of protective immunity.³²¹ In general, young animals are more susceptible to infection, possibly because innate resistance develops or specific protective immunity is acquired as the animal matures. Experimentally, diarrheal disease develops in gnotobiotic animals monoinfected

with *Cryptosporidium*, indicating that this parasite is a primary enteric pathogen.^{322,323}

The life-cycle of *Cryptosporidium* is similar to that of other coccidia (Fig. 44-7).^{323,324} Infection is initiated when the host accidentally ingests oocysts. Although the infectious dose for many animal species is not clear, inoculation of 100–500 oocysts causes infection in 50% of Swiss-Webster mice.³²⁵ A report of a researcher who acquired infection after a rabbit inoculated with *Cryptosporidium* coughed on him suggests that the infectious dose is also low in humans.³²⁶ Indeed, studies in human volunteers demonstrate that an estimated ID₅₀ is 132 oocysts,³²⁷ and some have estimated from mathematical modeling in the Milwaukee outbreak that the infectious dose may be as low as one oocyst for some individuals.^{305,328}

The asexual cycle of *Cryptosporidium* is initiated when gastric acid and proteolytic enzymes in the upper small bowel cause the oocyst wall to dissolve at its single suture, resulting in a slitlike opening from which the four sporozoites can exit the oocyst.³²⁹ The sporozoites are able to penetrate and parasitize the intestinal epithelial cells and potentially other epithelial surfaces contiguous to the gastrointestinal tract, such as respiratory or biliary tract epithelium. Within the host cells, sporozoites develop into trophozoites and subsequently into type I meronts. The type I meront releases six to eight merozoites capable of reinfesting the host epithelial cell. Some of these merozoites develop into type II meronts

containing four merozoites. The merozoites released by type II meronts initiate the sexual cycle with the development of macrogamonts and microgamonts. Microgamonts are aflagellar but motile and fertilize macrogamonts, resulting in immature oocysts that develop within the intestinal epithelial cell. Oocysts released from the host epithelial cell are either thin- or thick-walled and immediately able to initiate infection (i.e., fully sporulated). Thin-walled oocysts may excyst within the bowel, releasing sporozoites which reinfest the host epithelial cells. Thick-walled oocysts are excreted by the host and are known to be extremely hardy.

Thus, autoinfection of the host can occur due to either type I meronts or thin-walled oocysts. This may account for the ability of *Cryptosporidium* to cause sustained symptomatic infections in the immunocompromised host, potentially lasting for the life of the individual.³²⁴

In general, the pathogenesis of *Cryptosporidium* infections is poorly understood. In humans, detailed studies of intestinal histopathology and function are provided only by case reports of immunocompromised patients, primarily with the AIDS. Ultrastructural studies generally show that the intestinal mucosa are intact and the enterocytes well preserved.^{330,331} Microvilli are displaced at the sites of parasite attachment to the enterocyte surface, and they may be elongated next to the parasite. In addition, “peaking” of the host-cell cytoplasm may occur at the point of attachment of the cryptosporidia.^{330,332}

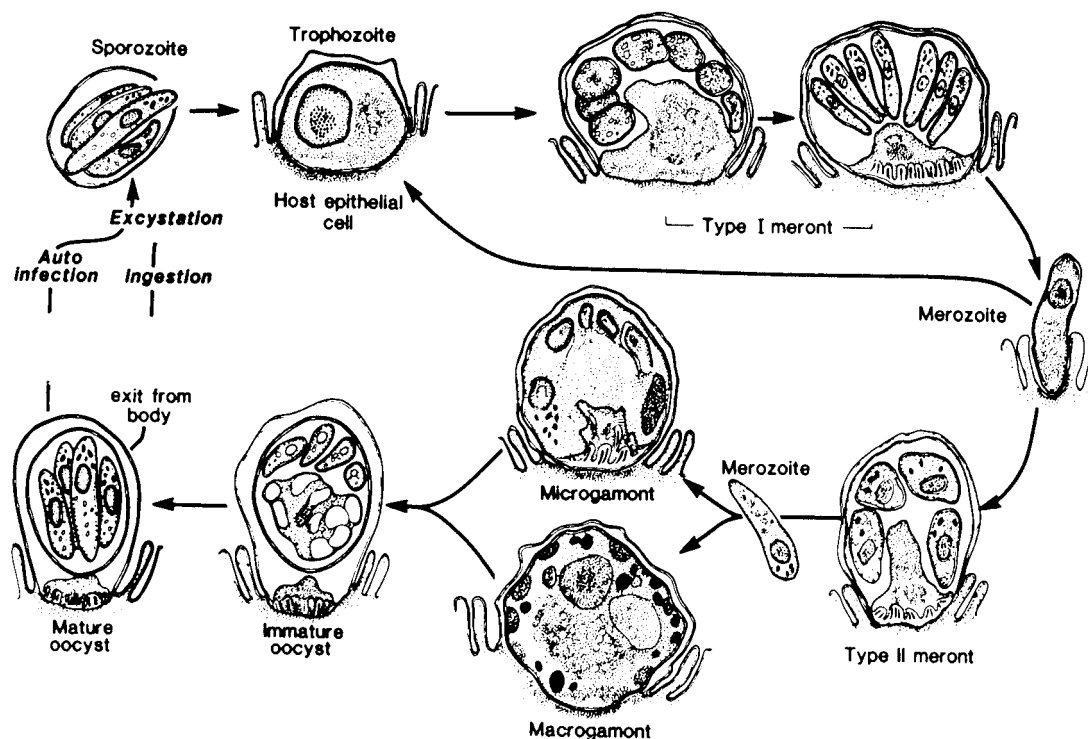


FIGURE 44-7. Diagrammatic representation of the life cycle of *Cryptosporidium*. Sporozoites excyst from an oocyst and enter the microvillus of an epithelial cell, where they differentiate into trophozoites. Trophozoites undergo nuclear proliferation to form type I meronts. A merozoite leaves the type I meront to form either a type I or II meront. A merozoite leaves the type II meront to form microgamonts or a macrogamont. The microgamont fertilizes the macrogamont, which then develops into an oocyst. Oocysts sporulate in situ and either release sporozoites for autoinfection or pass from the body in the feces. (Adapted from Fayer R, Ungar BLP. *Cryptosporidium* spp and cryptosporidiosis. *Microbiol Rev* 1986; 50: 458.)

In some infections, villous architecture by light microscopy is moderately to severely abnormal, revealing crypt elongation and villous atrophy.^{333,334} However, significant diarrhea (≥ 1 L/day) may occur with minimal histopathologic change in the gut.³³¹ The degree and cell content of the inflammatory infiltrate in the lamina propria of gut infected with *Cryptosporidium* in clinically affected patients has ranged from minimal³³⁵ to substantial^{331,333,334} and may include plasma cells, lymphocytes, macrophages, and/or polymorphonuclear leukocytes. One limitation of these human case reports is that it is often not clear how extensively the patients were evaluated for additional enteropathogens.

In animal studies, the degree of pathologic abnormality has tended to correlate with the extent of infection and in some animals, including calves, lambs, and piglets, with the severity of clinical illness.^{321,323,336,337} In rodents such as mice, rats, and guinea pigs, no obvious clinical illness occurs, and pathologic findings range from inapparent to moderate.^{337,338} In studies of spontaneously infested guinea pigs, cryptosporidial organisms have been observed deep in the cytoplasm of M-cells overlying Peyer's patches and associated with macrophages subjacent to the M-cells. These observations suggest antigenic sampling by the intestinal immune system.³³⁹

The mechanisms by which *Cryptosporidium* causes diarrhea in either the immunocompetent or the immunocompromised host have not yet been elucidated. Both secretory (unaffected by fasting) and malabsorptive diarrhea have been reported in AIDS patients infected with *Cryptosporidium*.^{331,340,341} D-xylose and vitamin B₁₂ malabsorption, steatorrhea, and increased fecal α_1 -antitrypsin clearance have been reported.^{331,334,340,341} Radiographic studies have also showed results consistent with malabsorption, such as flocculation of the barium, mucosal thickening, and dilation in the small bowel.³⁴² Animal studies have confirmed lactase deficiency and xylose malabsorption in calves infected with *Cryptosporidium*.^{321,336}

Detailed electron micrograph studies indicate that *Cryptosporidium* develops intracellularly in the host epithelial cell but is extracytoplasmic.^{312,332} A striking electron-dense zone described as a "feeder organelle" forms at the interface between the parasite and the host cell.^{312,332} It may be through this zone that the parasite receives nutrition and delivers products capable of stimulating intestinal secretion. The observation that voluminous, watery diarrhea may occur in the immunocompromised host might suggest production of an enterotoxin or neurohumoral products by the parasite. Experimental results to date are mixed.^{343–345} Reports of enterotoxic effects do not distinguish the source of potential secretory products.^{346,347} Indeed, Argenzio et al. suggest that the cytokines [such as tumor necrosis factor (TNF)] and macrophages seen in cryptosporidiosis may elicit prostaglandin-dependent secretion, possibly via secondary cells such as fibroblasts.^{348,349} Studies in humans with cryptosporidiosis show villus tip damage and malabsorption.³⁵⁰ Analysis of gene expression profiles of a

C. parvum-infected human epithelial cell line revealed upregulation of genes of actin, tubulin, heat shock proteins, and proinflammatory chemokines IL-8, RANTES, and SCYB5.³⁵¹ Host genes associated with cell proliferation and apoptosis were differentially regulated. This study suggested that infection with *C. parvum* alters the host biochemical pathways by affecting gene expression.

■ CLINICAL MANIFESTATIONS

Infection with *Cryptosporidium* has been documented in both immunocompetent and immunocompromised patient populations.^{304,314,335,336,344,352,353} In immunocompetent hosts, the majority of cases are sporadic and may involve either children or adults, in both the developed and developing world.³⁵² Infection has also been reported in animal handlers,^{304,314} homosexual men,³³⁴ travelers,^{354,355} and contacts of infected individuals (e.g., household contacts or hospital personnel).^{314,353,356,357}

The clinical manifestations of cryptosporidiosis depend on the immune status of the host. In the immunocompetent host, infection results in a flulike, noninflammatory gastrointestinal illness characterized by malaise, anorexia, vomiting, abdominal pain and cramps, and sometimes fever. Blood and pus are not present in the stool and the fecal leukocyte examination is negative. Diarrhea lasts on average 6–14 days, although some patients will have a more prolonged illness, with diarrhea lasting a month or even, rarely, as long as 4 months.^{335,353,358–360}

Diarrhea may occasionally be much more severe (e.g., 17 L of daily stool output) in immunocompromised hosts with defects in either humoral or cell-mediated immunity.^{301,314,361} In these hosts, infection is frequently persistent and the resulting morbidity—for instance, in AIDS patients—may contribute to earlier mortality.³⁶² AIDS patients have been reported to develop extraintestinal infection involving the respiratory or biliary epithelium.^{335,363–368} Although the contribution of respiratory cryptosporidiosis to clinical disease is unclear, individuals with biliary infection may present with the clinical picture of cholecystitis and may also be coinfecting with cytomegalovirus.^{335,368}

The incubation period of the infection is usually between 3 and 14 days.³¹⁴ Experimental data show that the parasite can complete its developmental cycle in 3 days.³²⁴ Until recently, asymptomatic carriage of the oocysts in clinically unaffected populations has been thought to be infrequent. For instance, in three studies examining predominantly asymptomatic homosexual men attending sexually transmitted diseases clinics during the early 1980s, none of 375 individuals were found to have *Cryptosporidium* oocysts in their stools. In contrast, *G. lamblia* was found in 3.3–6.5% and *E. dispar* in 5.5–23.5% of the men.^{369–371} In studies examining the prevalence of infection with *Cryptosporidium* in developed countries such as the United States, Australia, or Europe, rates of infection in

situations other than outbreaks average 2.1% in symptomatic individuals (range = 0.26–22%).³⁰⁸ Among controls, only 0.2% of stools were positive.^{308,309} In contrast, infection rates have been highest in developing countries, with rates of 6.1% in individuals with symptoms (range = 1.4–40.9%) and 1.5% in controls.^{308,309,372–374} Persistent asymptomatic oocyst excretion may extend beyond clinical illness.^{358,359,375–377} Oocyst excretion lasts an average of 7 days beyond illness but may, on occasion, extend for several weeks.^{358,359}

Several potential modes of transmission for *Cryptosporidium* have been identified. Earlier studies documented the potential for animal-to-human spread, and *Cryptosporidium* is clearly a zoonotic infection.^{304,314,335,352,361} Both domestic animals such as calves and companion animals such as puppies and kittens serve as potential sources of human infection. Increasing evidence indicates that person-to-person spread of this infection is important and is probably a major mode of transmission.^{314,335,352,353,357} Since large numbers of *Cryptosporidium* oocysts can be present in feces and the infectious dose is quite small, it is very likely that fecal–oral contamination through sexual contact could play an important role in transmission.

Human-to-human transmission is particularly well illustrated by the reports of outbreaks of diarrhea associated with *Cryptosporidium* infection in day-care centers,^{359,378,379} and by reports of intrafamilial spread of infection in households showing that they are among the highest for any enteric pathogen.³⁰⁶ In addition, waterborne outbreaks traced to surface water³⁸⁰ or to sewage contamination of both chlorinated well water and fully treated municipal water have been reported.^{305,381,382} *Cryptosporidium* oocysts have been identified in treated sewage effluents and surface waters, and several outbreaks have occurred with public swimming or wading pool exposure.^{383,384} Unpasteurized apple cider has also been a source of *Cryptosporidium* infection.

Because the clinical syndrome associated with cryptosporidiosis is not unique, the differential diagnosis includes the extensive list of enteric pathogens which cause noninflammatory diarrhea. Rotaviruses and enterotoxigenic *Escherichia coli* are the leading causes of acute noninflammatory diarrhea worldwide, especially among young children; Norwalk-like viruses must also be considered. In immunocompromised individuals such as AIDS and bone marrow transplant patients, adenoviruses and coxsackieviruses may cause diarrhea.³⁸⁵ The diagnosis of *Cryptosporidium* infection is especially important in patients with AIDS, as is the diagnosis of even more treatable causes of diarrhea in this setting. These causes include microsporidiosis and *Cyclospora* infection (see section “New and Emerging Protozoal Infections”), as well as *G. lamblia*, *Strongyloides stercoralis*, and *Isospora belli*, all potential parasitic causes of noninflammatory diarrhea. Epidemiologic data such as travel history, food ingestion

(e.g., raw seafood), and recent antibiotic use may be helpful in prioritizing the diagnostic possibilities.³⁸⁶ Cryptosporidiosis causes a substantial mortality (>30%) in HIV-infected patients with low CD4 counts, especially when the biliary tract is involved.^{382,387}

■ DIAGNOSIS

The diagnosis of cryptosporidiosis is established by staining the stool with a modified acid-fast or immunofluorescence technique specific for the oocyst stage of *Cryptosporidium* and observing the characteristic oocyst morphology (Fig. 44-8). Examination of at least two fecal smears may be necessary for diagnosis,^{358,388} and concentrating the stool may improve detection of the parasite, particularly in nonacute illness or in evaluation of contacts of infected individuals. Oocyst excretion may be intermittent; positive and negative smears from the same patient on the same day have been reported. In addition, a minority of the oocysts may not readily take up the acid-fast stain and may appear as empty holes in a fecal smear.³⁸⁹ This variability in the staining characteristics of the oocysts does not hinder diagnosis in experienced hands.

A direct immunofluorescent antibody stain is sensitive and specific and may require less technician time.^{388,390,391} Several ELISA methods are available for detection of fecal cryptosporidial antigen; these are 83–95% sensitive in diarrheal specimens but may miss lighter infections or asymptomatic carriage.^{388,392} ELISAs for detection of serum IgM and IgG antibodies to *Cryptosporidium* have been developed;³⁹³ when both these tests were used, over 90% of the patients with cryptosporidiosis, including patients with AIDS, had detectable antibodies at the time of medical presentation. These ELISAs for detection of immunoglobulins should prove to be particularly helpful in epidemiologic studies of cryptosporidiosis.

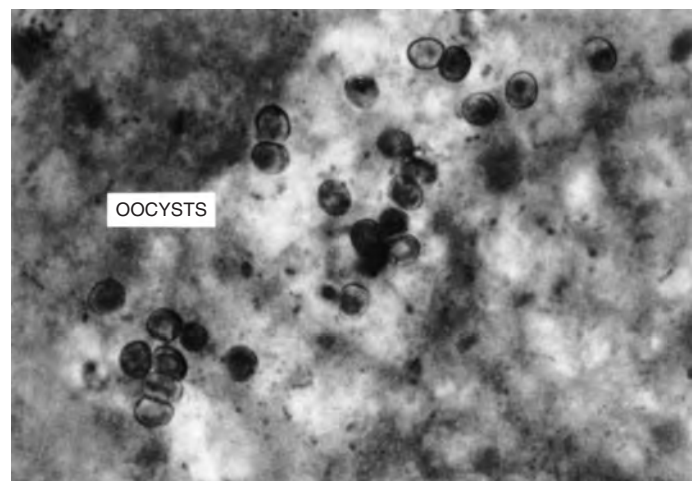


FIGURE 44-8. *Cryptosporidium* oocysts stained with a modified acid-fast stain. Oocysts are approximately 4–6 μm in diameter.

There is growing interest in the use of PCR assays for diagnosis of cryptosporidiosis; however, cost remains an issue for clinical laboratories.³⁹⁴ The development of multiplex rt-PCR assay, which allows for diagnosis of multiple pathogens such as *E. histolytica*, *Giardia*, and *Cryptosporidium* spp. and genotypes, is on the horizon. Solid evidence for the clinical significance of PCR positive fecal samples is still lacking.

■ PREVENTION OF INFECTION AND THERAPY

The primary therapy for all forms of diarrheal illness, including cryptosporidiosis, is fluid and electrolyte replacement. Rehydration may be oral or intravenous, depending on the clinical status and age of the patient. In studies to date, from 0% to 30% of immunocompetent patients have required hospital admission for intravenous rehydration during *Cryptosporidium* infections.^{314,353,395–397} Although many drugs have been evaluated in animals or humans, no clearly effective pharmacologic therapy for cryptosporidiosis has emerged.^{314,335,361,398–401} Paromomycin has shown modest benefit in a controlled study, but it fails to eradicate the parasite in immunocompromised patients.⁴⁰² Development of an effective specific therapy for cryptosporidiosis has been hindered by the lack of a simple model for testing of drug sensitivity. Although nonspecific antidiarrheal therapies such as kaolin plus pectin (Kaopectate), antimotility agents (loperamide, paregoric), or bismuth subsalicylate (Pepto-Bismol) may be helpful in controlling symptoms, their efficacy and safety in cryptosporidiosis have not been evaluated.

Nitazoxanide has also been shown to have activity against *Cryptosporidium*.¹²⁷ However, it has only been proven to be effective in resolving symptoms and eradicating parasites in HIV-negative children so far.^{403,404} The results of clinical trials in adults and HIV-positive patients had been varied, and thus nitazoxanide is only FDA-approved for use in otherwise healthy children. The recommended dosage for children aged 12–47 months is 100 mg b.i.d. for 3 days, and for children aged 4–11 years, the recommended dosage is 200 mg b.i.d. for 3 days. Higher dose and prolonged treatment may be required for clinical and parasitological response in the immunocompromised host.⁴⁰⁵

The thick-walled oocysts of *Cryptosporidium* are known to be very hardy and resistant to chlorine and numerous tested disinfectants. Only heat (boiling for 1 minute, at sea level), freezing, and prolonged treatment (18 hours) with 10% formalin or 5% ammonia, have been shown experimentally to reduce the infectivity of the oocysts.^{336,406,407} Therefore, careful hand washing and enteric precautions in the hospital setting are important to interrupt person-to-person spread of infection. Current USPHS/IDSA guidelines for prevention of opportunistic infections in HIV infected

persons include avoidance of fecal exposure during sexual contact; careful hygiene, including hand washing in handling pets and avoidance of new pets under 6 months of age; precaution concerning exposure during travel; and possible boiling or filtering of drinking water.⁴⁰⁸ Future research to better understand the ecologic niches of this parasite will be important in the development of measures to control the spread of infection.

NEW AND EMERGING PROTOZOAL INFECTIONS

In addition to *G. lamblia*, *E. histolytica*, and *C. parvum*, additional intestinal protozoan infections are increasingly recognized. *Cyclospora cayetenensis* appears to be spread in contaminated water and is a potentially treatable cause of diarrhea in both normal hosts and in patients with AIDS.^{409,410} *Cyclospora* infections are diagnosed with acid-fast stain of fecal specimens and are treated with sulfamethoxazole-trimethoprim.^{411–415}

Microsporidial infections with *Enterocytozoon bienusi* or *Encephalitozoon* (formerly *Septata*) *intestinalis* are found predominantly in patients with AIDS and diarrhea, and can be diagnosed with a special trichrome stain of fecal specimens.^{416,417} However, their epidemiology and routes of transmission remain largely unknown. Importantly, these infections, especially *Encephalitozoon* (*Septata*) *intestinalis*, appear to respond to albendazole therapy.^{418–420}

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Jack D. Sobel

Previously, symptomatic infections of the vagina due to *Candida* spp were termed *Candida* vaginitis; however, since symptoms and signs almost invariably involve the vulva, vulvovaginitis better reflects the disease process. The term vulvovaginal candidiasis (VVC) was introduced to be more inclusive and includes not only symptomatic *Candida* vulvovaginitis, but less frequent asymptomatic *Candida* vaginal infection with positive microscopy and culture. VVC does not refer to the very common carrier state, in which asymptomatic women without signs of disease and with negative routine microscopy are found to have positive vaginal yeast cultures.

The earliest reports of VVC appear in the writings of Hippocrates and Galen. Frank is purported to have written the first clinical description in 1792.¹ A report by Wilkinson in 1894 is the earliest clinical description that also linked clinical manifestation with fungal etiology.²

EPIDEMIOLOGY

Information on the incidence of VVC is incomplete, since VVC is not a reportable entity. Collecting data on VVC is hampered by inaccuracies of diagnosis and using nonrepresentative study populations. Most studies suggest a VVC prevalence of 5–15%, depending on the population studied.¹

VVC affects most females at least once during their lives, most frequently in the childbearing age, at an estimated rate of 70–75%,^{3–5} of whom 40–50% will experience a recurrence.^{5,6} A small subpopulation of probably fewer than 5% of all adult women has recurrent episodes of VVC defined as ≥ 4 episodes per annum. Among women with symptoms of vulvovaginitis, 29.8% had yeast isolated, confirming the diagnosis of VVC.⁷ Most studies indicate that VVC is a frequent diagnosis among young women, affecting as many as 15–30% of symptomatic women visiting a clinician. Regrettably, the recent availability of over-the-counter antimycotics will further limit the ability to measure asymptomatic *Candida* carriage and VVC in women populations. Diagnosis and therapy of VVC, together with lost productivity, result in an

estimated cost of 1 billion dollars annually in the United States.³ Statistical data in the UK derived from the patients whose conditions were diagnosed at genitourinary medicine centers show a sharp increase in the annual incidence of VVC from 118 per 100,000 to 200 per 100,000 women during the last decade.⁸ In the United States, VVC is the second most common cause of vaginal infections following bacterial vaginosis (BV).^{9,10} The number of prescriptions written to treat yeast infections between 1980 and 1990 indicates that the incidence of VVC almost doubled during that time; approximately 13 million prescriptions were written in 1990.

Point-prevalence studies indicate that *Candida* spp may be isolated from the lower genital tract of approximately 20% (range 10–80%) of asymptomatic healthy women without abnormal vaginal discharge.^{11–13} Higher cumulative incidence of *Candida* colonization is reported.¹⁴

MICROBIOLOGY

Between 85% and 95% of yeast strains isolated from the vagina belong to the species *Candida albicans*.^{15,16} The remainder are non-*albicans* species, the commonest of which is *Candida glabrata* (*Torulopsis glabrata*). Non-*albicans* species can also induce vaginitis, which is clinically indistinguishable from that caused by *C. albicans*; moreover, they are often more resistant to therapy.^{13,17,18} In many parts of the world, non-*albicans* isolates, notably *C. glabrata*, affect 10–20% of women.^{19,20}

It has been claimed, but not proved, that VVC caused by non-*albicans* strains is rising dramatically.^{21,22} The use of single-dose oral and topical regimens, together with low-dosage azole maintenance regimens and the availability of over-the-counter antimycotics, have been blamed for this increase. Two large multicenter studies failed to confirm any increase in the prevalence of VVC caused by non-*albicans* species.^{23,24} Diabetes mellitus is a risk factor for *C. glabrata* vaginitis. Infrequent causes of fungal vaginitis include *C. parapsilosis*, *C. tropicalis*, and *C. krusei*, although virtually every species of *Candida* has been associated with vaginitis.^{25,26}

Typing of vaginal *C. albicans* isolates has failed to demonstrate strains of tropism for the vagina. Similarly, no evidence emerged of vaginopathic strains demonstrating greater or lesser virulence to explain why some women remain entirely asymptomatic despite being heavily colonized with *Candida* spp, whereas other women develop severe symptomatic vaginitis. The concept of yeast vaginopathogenicity is not entirely without merit and may be the result of switching phenotypic and virulence properties, but upon gene activation.²⁷ Yeast adaptation would facilitate persistence and survival in the vagina.

In general, yeast blastospores (blastoconidia) represent the phenotypic form responsible for transmission and spread, including the bloodstream phase, as well as the form associated with asymptomatic colonization of the vagina. Germinated yeast with production of mycelia (hyphae) most commonly (but not exclusively) is found in symptomatic vaginitis.

CANDIDA VIRULENCE FACTORS

Colonization of the vagina requires yeast adherence to vaginal epithelial cells. *C. albicans* adheres in significantly higher numbers to such cells than do *C. tropicalis*, *C. krusei*, and *C. kefyer*.²⁸ All *C. albicans* strains appear to adhere equally well to both exfoliated vaginal and buccal epithelial cells. In contrast, there is considerable person-to-person variation in in vitro vaginal epithelial cell receptivity to *Candida* organisms in adherence assays.²⁹ However, no increased receptivity has been revealed in women with recurrent infections.³⁰ No epithelial cell receptor for *Candida* has yet been identified, and the yeast adhesin appears to reside with the surface mannoprotein.

Germination of *Candida* cells enhances colonization³¹ and facilitates tissue invasion. Using a mutant strain of *C. albicans*, which failed to germinate at 37°C, Sobel and coworkers demonstrated in vivo that nongerminating mutants were incapable of inducing experimental VVC.³¹ Accordingly, factors that enhance or facilitate germination might promote symptomatic vaginitis, whereas inhibit and germination may prevent vaginitis in asymptomatic carriers of yeast.³²

Little is known regarding the role of candidal proteolytic enzymes, toxins, and phospholipase in determining the virulence of the organisms. Secreted aspartyl proteinases elaborated by pathogenic *Candida* spp has been identified in vaginal secretions and are detected in women with symptomatic vaginitis, but not in those with asymptomatic colonization.^{33,34} These proteolytic enzymes, which have broad substrate specificity, destroy free and cell-bound proteins that impair fungal colonization and invasion.³⁵ Several genes governing proteinase production (SAP1, SAP2, and SAP3) have been cloned, and a strong correlation exists both in vitro and in experimental vaginitis between gene expression, aspartyl proteinase secretion, and ability to cause the disease.^{36,37} Mycotoxin, including a vaginal identified gliotoxin, may act to inhibit phagocytic activity

or suppress the local immune system. High-frequency heritable switching occurs in colony morphology of most *Candida* spp grown on amino acid-rich agar in vitro at 24°C.³⁸ The variant phenotypes represent a varying capacity to form mycelia spontaneously and to express other virulence factors, including drug resistance, adherence, etc. There is insufficient evidence that phenotypic switching occurs in vivo at 37°C; however, this is an attractive hypothesis to explain spontaneous in vivo transformation from asymptomatic colonization to symptomatic vaginitis. Fresh clinical vaginal isolates obtained during acute vaginitis have been found to be in a high-frequency mode of switching. These multiple phenotypes are derived from the same or related genetic strains.^{27,39,40}

In one patient with recurrent VVC (RVVC), who was sampled during three episodes of vaginitis, Soll observed colony phenotype switch with each recurrence of infection, even though DNA fingerprinting (genotype) remained identical.²⁷ Schroppel, using DNA analysis demonstrated that even though the same strain may persist long-term in the vagina, a certain degree of yeast genetic instability exists associated with repeated courses of antifungal therapy.⁴¹

Iron binding by *Candida* organisms facilitates yeast virulence.⁴² Availability of erythrocytes and hemoglobin in the vagina creates an ideal niche for yeast possessing erythrocyte-binding surface receptors.

PATHOGENESIS

Candida organisms gain access to the vaginal lumen and secretions predominantly from the adjacent perianal area.^{43,44} Two questions are critical in understanding the pathogenesis of VVC. First, the mechanism whereby asymptomatic colonization of the vagina transforms to symptomatic VVC. The second is the mechanism whereby some women suffer from repeated and chronic VVC. (Fig. 45-1)

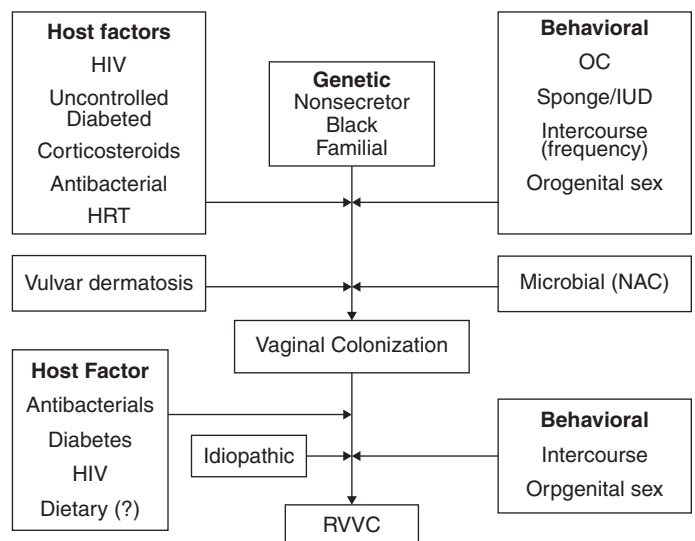


FIGURE 45-1. Pathogenesis of vulvovaginal candidiasis.

Hurley et al. fostered the view that *C. albicans* is never a commensal in the vagina, maintaining that clinicians can almost always detect vaginal pathology even in asymptomatic patients from whom such strains have been isolated.^{5,6} Subsequent investigators have disagreed observing that many if not all women carry *C. albicans* in the vagina at sometime, yet without symptoms or signs of vaginitis, usually with low concentration of yeast organisms.^{11,14} Accordingly, *Candida* may be either a commensal or a pathogen in the vagina and that changes in the host vaginal environment are usually necessary before the organism induces pathologic effects.

PREDISPOSING FACTORS

■ PREGNANCY

During pregnancy, a higher prevalence of vaginal colonization and symptomatic vaginitis occurs.^{23,45} The latter is maximally increased in the third trimester, symptomatic recurrences are also more common, and therapeutic response is reduced.^{18,45} High levels of reproductive hormones, by providing a higher glycogen content in the vaginal tissue, provide an excellent carbon source for *Candida* organisms.⁴⁶ A more complex mechanism seems likely in that estrogen enhances adherence of yeast cells to the vaginal mucosa. A cytosol receptor, or binding system, for female reproductive hormones has been documented in *C. albicans* resulting in enhanced mycelial formation.⁴⁷

■ CONTRACEPTIVES

Many small, poorly controlled studies have produced conflicting data. Several studies have shown increased vaginal colonization with species of *Candida* following high estrogen-content oral contraceptive use.^{1,48} Studies of women using low estrogen-content oral contraceptives have not found an increase in VVC.^{49–52} Nevertheless, most investigators continue to incriminate oral contraceptives as predisposing to RVVC.⁴⁸ Increased carriage of such yeasts is reported in IUD users,^{53,54} in diaphragm and condom users, with or without use of spermicide.^{52,55,56} Other risk factors may include the contraceptive sponge. Foxman, in an extensive study of risk factors in college students, failed to identify increased risk in users of oral contraceptives, diaphragms, condoms, and spermicides.⁵¹

■ DIABETES MELLITUS

Vaginal colonization with *Candida* is more frequent in diabetic women. Women with NIDDM are more prone to colonization with *C. glabrata*.⁵⁷ Although uncontrolled diabetes undoubtedly predisposes to symptomatic vaginitis, well-controlled diabetics do not suffer from an increased prevalence of VVC.^{1,58} It has become traditional to perform glucose

tolerance tests (GTTs) in all women with RVVC. The yield of these expensive studies is extremely low; testing, therefore, is not justified in premenopausal women. Occasionally women with RVVC describe an association between “candy binges” and exacerbation of symptomatic vaginitis. Donders et al. performed GTTs in women with RVVC.⁵⁹ Although an increased frequency of abnormal GTTs compatible with diabetes or prediabetes was not found, plasma glucose levels were still significantly higher than in control subjects suggesting that a diet high in refined sugars may contribute to the risk of VVC.⁵⁹

■ ANTIBIOTICS

Onset of symptomatic VVC is frequently following vaginal or systemic antibiotics.^{60–63} All antimicrobials appear responsible. Estimates of postantibiotic VVC include a range of 28–33%.^{64,65} Vaginal colonization rates increase from approximately 10% to 30%.^{66,67} Antibiotics are thought to act by eliminating the protective vaginal bacterial flora allowing *Candida* overgrowth in gastrointestinal tract, vagina, or both.⁶⁷ Vaginal, particularly *Lactobacillus* spp, flora are thought to provide colonization resistance and prevent germination, maintaining low numbers of yeast, and preventing superficial mucosal invasion. Auger and Joly found low numbers of lactobacilli in vaginal cultures obtained from women with symptomatic VVC.⁶⁸ Studying adult mice, Pultz et al. reported that antibiotics that inhibit intestinal anaerobes promote *C. glabrata* gut colonization.⁶⁹ Lactobacillus–yeast cell interactions include competition for nutrients as well as steric interference by lactobacilli with *Candida* adherence, elaboration of inhibitory bacteriocins by lactobacilli, as well as a direct antibiotic-induced stimulatory effect on growth of *Candida* spp.⁶⁸

In contrast, Agnew and Hillier failed to demonstrate a reduction in vaginal lactobacilli following several antibiotic regimens.⁷⁰ In spite of the evidence indicating a role for antibiotics, most women who receive antibiotics do not develop symptomatic VVC.⁷¹ Moreover, the majority of women with acute VVC have not been recent recipients of antibiotics. Hence, only a subpopulation of women, already colonized by potentially virulent species of *Candida*, are at risk of vaginitis following antimicrobial therapy.

■ BEHAVIORAL FACTORS

The incidence of VVC increases dramatically in the second decade, corresponding to the onset of sexual activity. It peaks in the third and fourth decade, declining in females older than 40 years, until the permissive effect of hormone replacement therapy becomes apparent. Several studies have shown that sexual transmission of *Candida* organisms occurs during vaginal intercourse, although the role of nonsexual practices

in introducing *Candida* organisms into the lower genital tract has not been appraised.^{44,72–75} There exists conflicting evidence as to the role of sexual behavior in causing symptomatic VVC.^{3,51,52} Some authors suggest that recent sexual intercourse frequency is correlated with acute vaginitis,^{51,75,76} and others have identified receptive orogenital sex.^{76–78} In spite of anecdotal evidence, Foxman found no epidemiologic evidence incriminating female hygiene habits as risk factors for VVC.⁵¹

The use of well-ventilated clothing and cotton underwear may be of value in preventing infection.⁷⁹ On the other hand, Foxman found no increased risk for VVC among wearers of tight clothing or noncotton underwear.⁵¹ There is no evidence confirming that iron deficiency predisposes to infection.⁸⁰ Chemical contact, local allergy, or hypersensitivity reactions may alter the vaginal milieu and permit the transformation from asymptomatic colonization to symptomatic vaginitis.

SOURCE OF INFECTION

■ INTESTINAL RESERVOIR (REINFECTION)

Although the gastrointestinal tract may well be the initial source of colonization of the vagina by *Candida* organisms, controversy continues regarding the role of the intestinal tract as a source of reinfection in women with RVVC.⁸¹

Candida isolates were recovered on rectal culture from 100% of women with RVVC and found identical on typing,⁸² supporting the concept of a persistent intestinal yeast reservoir. Reinoculation of the vagina might occur from the persistent rectal focus following apparent eradication of vaginal yeast by topical therapy. Several authors, however, have found much lower concordance between rectal and vaginal cultures in patients with RVVC.^{44,45} The high rate of anorectal cultures in some studies likely reflects perineal and perianal contamination from the vaginal discharge. Moreover, VVC recurred frequently in women in the absence of simultaneously positive rectal cultures. Two controlled studies using oral nystatin treatment, which reduces intestinal yeast carriage, failed to prevent symptomatic recurrence of vaginal candidiasis.^{83,84}

■ SEXUAL TRANSMISSION

Asymptomatic male genital colonization with species of *Candida* is four times more common in male sexual partners of infected women.⁷³ Penile *Candida* organisms are present in approximately 20% of partners of women with RVVC.^{73,74} *Candida* organisms are most commonly found in uncircumcised, usually asymptomatic males. Infected partners usually carry identical strains⁴⁴; however, the contribution of sexual transmission to the pathogenesis of infection remains

unknown. From the prevalence of positive penile and urethral cultures, it appears that the role of sexual spread is limited. Limited evidence is available that anogenital and particularly orogenital contacts transmit infection.⁷⁸

■ VAGINAL RELAPSE

After clinically effective antimycotic therapy of VVC, negative vaginal *Candida* cultures once more turn positive within 30 days in 20–25% of women, strongly supporting the concept of vaginal persistence of some strains of yeast and hence a vaginal as opposed to intestinal reservoir. Strains isolated before and after therapy are of the identical type in more than two-thirds of recurrences.⁴⁴ Small numbers of the microorganisms persist within the vaginal lumen, generally in numbers too small to be detected by conventional vaginal cultures. It is also conceivable that small numbers of *Candida* organisms might sojourn temporarily within superficial cervical or vaginal epithelial cells only to reemerge some weeks or months later.⁸⁵

VAGINAL DEFENSE MECHANISMS

■ HUMORAL SYSTEM

Patients with profound immunoglobulin deficiencies are not susceptible to VVC. Following acute VVC, systemic (IgM and IgG) and local (S-IgA) responses are elicited.^{86,87} The protective role of vaginal antibodies is unknown. Lower antibody titers have been described during active vaginal infections, which may reflect an adsorption effect. Polonelli and coworkers, using an experimental animal model of vaginitis, reported suggestive evidence for a protective role of specific antibodies induced by immunization.⁸⁸ Experimental studies in mice have provided some evidence for protection using *Candida*-specific antibodies.⁸⁹ Patients with recurrent vaginitis, however, do not lack antibody, in fact high serum immunoglobulin titers are typically found.⁹⁰ Elevated serum and vaginal IgE antibodies to *Candida* organisms were detected in some women with RVVC, even though the total IgE levels were normal.^{91–93} In summary, the protective role of vaginal anti-*Candida* antibodies is controversial. Certainly, women with recurrent disease do not lack antibody. It is also feasible that antibody-based anti-*Candida* hypersensitivity reactions (IgE) may contribute to symptoms.

■ PHAGOCYtic SYSTEM

Although both polymorphonuclear leukocytes (PMNs) and monocytes play an important role in limiting systemic candidal infection and deep-tissue invasion,⁹⁴ these phagocytic cells are characteristically absent from vaginal fluid during acute VVC.⁹⁵ Accordingly, phagocytic cells have not been thought to play a role in influencing mucosal colonization or

prevent superficial invasion by *Candida* organisms. In the rat model of experimental VVC, as in humans, histology of the vagina fails to demonstrate leukocytes in the vaginal fluid or stratified squamous epithelium. Polymorphonuclear cells can be seen concentrating within the underlying lamina propria, but appear not to be presented with a chemotactic signal to induce migration into more superficial layers or vaginal fluid. Recently, Fidel et al. have challenged this view and suggested that mucosal and luminal PMNs play a prominent early protective role against *Candida* organisms.⁹⁶ This view is based upon experimental mice VVC and human *Candida* vaginal challenge studies.^{97–99}

■ CELL-MEDIATED IMMUNITY

Oral thrush, which correlates well with depressed cell-mediated immunity (CMI), is frequently seen in debilitated or immunosuppressed patients. This is particularly evident in patients with chronic mucocutaneous candidiasis or with AIDS. Accordingly, one might anticipate that lymphocytes similarly contribute to normal vaginal defense mechanisms, possibly preventing yeast mucosal invasion by the elaboration of cytokines such as gamma-interferon, which inhibits germ-tube formation.

Most healthy adult women have positive cutaneous delayed hypersensitivity reactions, as well as in vitro lymphoblast proliferation response to *Candida* antigens. Earlier studies reported cutaneous anergy and depressed lymphoblastic response to *Candida* antigens in women with RVVC.^{94,100–103} The existence of a subpopulation of suppressor lymphocytes or serum factors inducing suppression of local vaginal CMI in women with RVVC.¹⁰⁴ In conflict with these observations, more recent studies using a variety of *Candida* antigens and measurement of cytokine elaboration demonstrated a normal systemic CMI response in women with idiopathic RVVC.¹⁰⁵ Observations showed that the previously reported cutaneous anergy was transient only—the consequence and not the cause of RVVC—and that impaired systemic CMI was not involved in the pathogenesis of RVVC. This conclusion was compatible with the observation that women prone to RVVC are not prone to oral, esophageal, or cutaneous candidiasis. Several additional studies by Fidel et al., using the mouse vaginitis model, determined that systemic CMI has a minor role only in providing a defense function at the level of the vaginal mucosa.^{98,99,106,107} These studies also demonstrated that local and systemic immunity to infection by *Candida* organisms could be induced by vaginal sensitization and that the immunity provided is partially protective in the vagina.¹⁰⁷

The studies by Fidel et al. did not exclude the possibility of an acquired local vaginal defect in CMI predisposing to RVVC.^{98,99,105,107} In this regard, Witkin et al. reported in vitro studies supporting impaired CMI in women with RVVC.^{102,108} They postulated that local elaboration of prostaglandin E2 by

the patient's macrophages blocked local protective lymphocyte function (Th-1), possibly inhibiting interleukin-2 production.¹⁰⁹ According to this hypothesis, abnormal macrophage function could be the result either of local IgE antibodies to *C. albicans* in the vagina of women with RVVC or of inhibitory serum factors.¹¹⁰ The protective mechanism of vaginal T lymphocytes was postulated to conform to a Th-1 profile and disease state, i.e., RVVC with Th-2 state.⁹⁹ Additional studies indicate unique subpopulations of vagina-specific lymphocytes.⁹⁷

Accordingly, an aberrant Th-2 dominant profile is postulated to be operative in women with RVVC. Nitric oxide (NO), another component of the innate immune defense against *Candida*, is produced by macrophages.¹¹¹ The *anti-Candida* activity of NO is strongly inhibited by IL-4,¹¹² a cytokine product of the Th-2 subset of cytokines. IL-4 inhibits production of proinflammatory cytokines by Th-1 T cells and blocks macrophage activation. Babula et al. recently reported elevated vaginal concentrations of IL-4 in women with RVVC, providing a possible hypothesis and explanation for an impaired *Candida* control mechanism.¹¹³ In the same study, increased IL-4 levels appear to correlate with reduced NO concentrations. Most importantly, a single nucleotide polymorphism consisting of a C → T transition at position –589 in the promoter region of the IL-4 gene has been reported. Possession of the T variant is associated with increased IL-4 production. In the study by Babula et al., the frequency of IL-4 was 76.2% in patients with RVVC and 23.3% in control subjects. In the same study, vaginal mannose-binding lectin (MBL) levels were similarly measured. MBL, a component of the innate immune systems, binds to mannan residues on *C. albicans* and promotes complement activation and killing. Women with RVVC had significantly reduced MBL levels.¹¹³

The T cell or CMI role in health or disease (VVC) is anything but clear. Based upon mice and human challenge studies, Fidel et al. found no evidence of Th-2 activity in vaginal secretions.¹¹⁴ He concluded that natural protection to *Candida* organisms in the vagina is provided by PMNs and vaginal epithelial cells (innate immunity) only and that VVC supervened when yeast numbers increase and exceed natural defenses.

■ VAGINAL FLORA

Probably the most important defense against both candidal colonization and symptomatic inflammation is the normal vaginal bacterial flora. Any newly arrived *Candida* organisms, in order to survive and persist, must initially adhere to epithelial cells and then grow, proliferate, and germinate in order to colonize the vaginal mucosa successfully. Although microbial competition for nutrients has long been considered the most important source of competition, animal studies suggest that lactobacilli as the most prevalent bacteria and *Candida* organisms frequently survive side by side.¹¹⁵ The

role of bacteriocins in inhibiting yeast growth and germination requires additional investigation.⁶⁸ Although antibiotic-induced VVC suggests a critical role of lactobacillus deficiency in causation of VVC, virtually all studies of vaginal flora in non-antibiotic-related situations have failed to confirm that lactobacillus deficiency both qualitatively and quantitatively predisposes to VVC or RVVC.

■ MISCELLANEOUS DEFENSE MECHANISMS

Although not studied in the vagina, various natural secretions have been shown to possess considerable antifungal activity. Pollock et al. reported fungistatic and fungicidal activity against *C. albicans* of human parotid salivary histidine-rich polypeptides.¹¹⁶

■ VAGINAL EPITHELIAL CELLS

Investigators reported that vaginal epithelial cells from mice and nonhuman primates as well as human oral epithelial cells inhibited the growth of *Candida* in vitro.^{117,118} Epithelial cell-mediated anti-*Candida* actually involves cell contact between a carbohydrate moiety or the epithelial cell and *Candida* with no role for soluble factors, phagocytosis, or oxidative killing.¹¹⁸ No differences in activity at various stages of the menstrual cycle was observed.¹¹⁹ Women diagnosed with RVVC under similar study conditions had reduced epithelial cell anti-*Candida* activity. These results suggest a possible protective role for epithelial cells in providing an innate host-resistance mechanism against *Candida* and that reduced activity may contribute to RVVC.¹²⁰ MBL has been suggested as an innate defense against *Candida*, enhancing complement activation.¹²¹ To date, no such lectin has been reported for vaginal epithelial cells.

TRANSFORMATION TO SYMPTOMATIC VAGINITIS

The mechanism whereby *Candida* organisms induce inflammation is not yet established. Yeast cells are capable of producing several extracellular proteases as well as phospholipase. The paucity of phagocytic cells in the inflammatory exudate possibly reflects the lack of chemotactic substances elaborated. Both blastoconidia and pseudohyphae are capable of destroying superficial cells by direct invasion.

During the symptomatic episode, there is a conspicuous appearance of the germinated or filamentous forms of *Candida* cells. Hyphal elements not only enhance colonization but also represent the dominant invasive phase capable of penetrating intact epithelial cells and invading the vaginal epithelium, although only very superficial layers are involved.¹²² Although symptoms are not strictly related to the yeast load, VVC does tend to be associated with greater numbers of *Candida* organisms and with hyphal elements.¹²² Approximately 10^3 – 10^4

Candida cells per milliliter of vaginal fluid may be recovered in both symptomatic and asymptomatic states.¹

The clinical spectrum varies from an acute florid exudative form with thick white vaginal discharge and large numbers of germinated yeast cells, to the other extreme of absent or minimal discharge, fewer organisms, and yet severe pruritus. Based on this, it is suggested that more than one pathogenic mechanism may exist. In the presence of pruritus alone, host hypersensitivity or immune mechanisms are likely to be involved.^{123–125} Although clinical signs and symptoms are indistinguishable in infections caused by different *Candida* spp, *C. glabrata* and *C. parapsilosis* tend to be associated with milder and often absent symptoms.^{19,25} Not infrequently, male partners of asymptomatic female carriers of *Candida* develop postcoital penile erythema and pruritus, which usually last several hours only.

CLINICAL MANIFESTATIONS

Acute pruritus and vaginal discharge are the usual presenting complaints, but neither symptoms is specific to VVC. Vaginal discharge is not invariably present and is frequently minimal. Although described as typically cottage-cheese-like in character, the discharge may vary from watery to homogeneously thick. Vaginal soreness, irritation, vulvar burning, dyspareunia, and external dysuria are commonly present. Odor, if present, is minimal and inoffensive. Examination reveals erythema and swelling of the labia and vulva, often with discrete pustulopapular peripheral lesions (Fig. 45-2). The cervix is normal, and vaginal epithelial erythema is present together with adherent whitish discharge. Characteristically, symptoms are exacerbated in the week preceding the onset of menstrual flow.

Several surveys indicate the unreliability of patient diagnosis.

Although *Candida* spp occasionally cause extensive balanoposthitis in male partners of women with vaginal candidiasis, a more frequent event is a transient rash, erythema,



FIGURE 45-2. Clinical appearance of acute vulvovaginal candidiasis.

and pruritus or a burning sensation of the penis which develops minutes or hours after unprotected intercourse. The symptoms are self-limiting and frequently disappear after showering.

DIAGNOSIS

The lack of specificity of symptoms and signs precludes a diagnosis that is based on history and physical examination only.^{126,127} A positive culture alone of *Candida* should be regarded as a satisfactory basis for diagnosis of VVC.¹²⁸ The most specific symptom in genital candidiasis is pruritus without discharge, and even this criterion correctly predicted VVC in only 38% of patients.¹²⁷

Most patients with symptomatic vaginitis may be readily diagnosed on the basis of microscopic examination of vaginal secretions. Accordingly, a wet mount or saline preparation should routinely be done, not only to identify the presence of yeast cells and mycelia but also to exclude the presence of “clue cells” and motile trichomonads. A 10% potassium hydroxide (KOH) preparation is more sensitive in identifying germinated yeast (65–85%) sensitivity (Fig. 45-3). Large numbers of white cells are invariably absent in VVC and when present should suggest a mixed infection. Similarly, vaginal pH estimations reveal a normal pH (4.0–4.5) in VVC, and the finding of a vaginal pH in excess of 5.0 usually indicates BV, trichomoniasis, or a mixed infection.

Unfortunately, up to 50% of patients with culture-positive symptomatic VVC will have negative microscopy.⁴³ Thus, although routine cultures are unnecessary if the wet-mount of KOH preparations shows yeast and mycelia, vaginal culture should be performed in symptomatic women in the presence of negative microscopy, if VVC is suspected on the basis of symptoms or signs and a normal pH estimate (Fig. 45-4). The PAP smear is unreliable as a diagnostic modality, being positive in only about 25% of patients with culture-positive symptomatic VVC.¹²⁹

Although vaginal culture is the most sensitive and specific method currently available for detecting *Candida* cells, a positive culture alone does not necessarily indicate that the yeast is responsible for the vaginal symptoms since 10–15% of normal asymptomatic women are colonized with *Candida* and hence culture positive.¹³⁰ Positive microscopy usually correlates with relatively high yeast concentrations in vaginal secretions as confirmed by quantitative vaginal cultures, and in most women the yeast cell numbers correlate with severity of clinical signs and symptoms,¹²⁷ and that commensal yeast vaginal carriage tends to be associated with lower numbers of vaginal yeast. Diagnosis of VVC requires a correlation of clinical findings, microscopic examination, and vaginal culture. Although some prefer to use a selective medium, there is no difference in using Sabouraud agar, Nickerson's or Microstix-*Candida* media, or in adding antibiotics such as chloramphenicol to the



FIGURE 45-3. Wet-mount examination of vaginal discharge from a woman with vulvovaginal candidiasis, showing mycelia. 1000× magnification.

isolation medium. There is no reliable serologic or antigen detection technique available for the diagnosis of VVC.

Since the majority are unable or unwilling to measure vaginal pH and perform microscopy, current diagnosis worldwide is empiric and extremely inaccurate. The majority of women with vulvovaginal symptoms remain incorrectly diagnosed.

PCR detection of *Candida* spp in vaginal samples is possible but not an available diagnostic test.¹³¹

DIFFERENTIAL DIAGNOSIS

Most clinicians consider only trichomoniasis and BV in the differential diagnosis of VVC. Given the profound differences in pH, PMN count, and wet-mount appearances, these three common clinical infectious entities are easy to differentiate. More consideration is needed in the symptomatic patient in whom these three conditions have been excluded. The differential

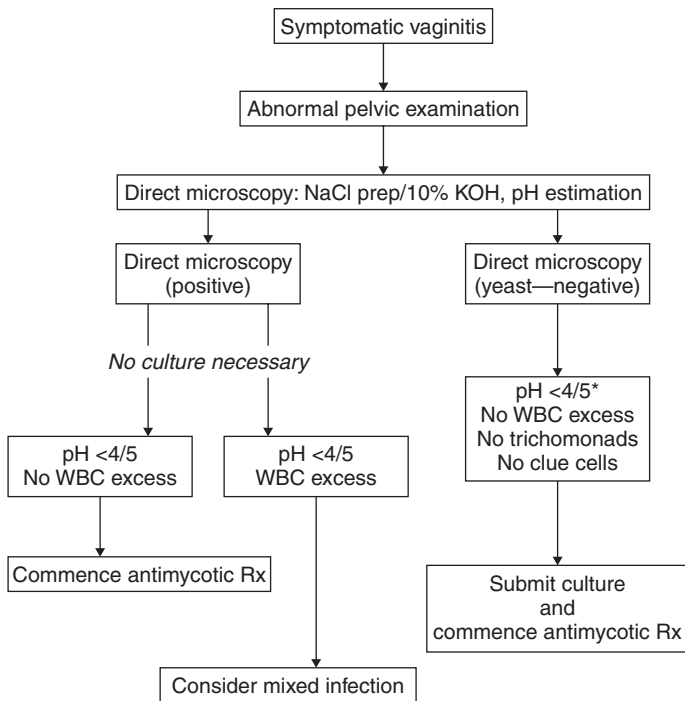


FIGURE 45-4. Algorithm for diagnosis and treatment of vulvovaginal candidiasis.

diagnosis of vulvovaginitis in the presence of normal pH, PMN count, and negative yeast cultures includes unrecognized genital herpes and numerous noninfectious causes, including hypersensitivity, irritant and allergic vulvovaginitis, idiopathic focal vulvovestibulitis, and physiologic leukorrhea.

TREATMENT

■ ACUTE SYMPTOMATIC VAGINITIS

A classification of VVC is available which determines the selection and duration of antifungal therapy. The majority of women with VVC suffer from uncomplicated vaginitis (Table 45-1)

characterized by sporadic, infrequent attacks of mild-to-moderate severity due to *C. albicans* and these attacks occur in healthy adult women without unique host-predisposing factors. In contrast, 10–20% of women suffer from complicated VVC in which attacks are either more severe, occur on a recurrent basis, or are due to non *C. albicans* spp. Patients with complicated VVC more frequently have underlying host factors in the form of uncontrolled diabetes or immunosuppressed conditions.

According to this classification, women with severe vulvovaginal symptoms and signs do not respond well to the single dose and short-course antifungal therapy.²⁴ This approach was verified in a randomized study in which single and sequential doses of fluconazole were compared.¹³² The study confirmed the premise that treatment of VVC requires individualization and more prolonged duration, i.e., 5–7 days, is essential.

A variety of highly effective topical azole agents are now available in a variety of formulations (Table 45-2).^{133,134} No strong evidence exists that any one formulation results in superior cure rates, nor is there convincing evidence of the superiority of any specific azole over another azole in the treatment of VVC.^{133,134} Overall cure rates for topical azole agents, defined as eradication of symptoms and mycologic-negative cultures, are of the order of 80–90%. Oral systemic azole agents achieve comparable or questionably marginally higher therapeutic cure rates, although most patients prefer the convenience of oral administration, which eliminates local side effects and messiness.¹³⁵ Oral azoles suffer the drawback of potential systemic toxicity, which has dramatically limited the use of ketoconazole, although not a consideration for itraconazole and fluconazole. In a meta-analysis, performed by Watson et al.,¹³⁶ of 17 trials published between 1989 and 1995 involving 2919 antifungal treatments for uncomplicated VVC, azoles were similarly effective when administered by either the oral or vaginal route.

Use of topical vaginal antimycotics has been remarkably safe and free of untoward side effects, although high-dose regimens of terconazole were associated with fever and flu-like

Table 45-1. Classification for Vulvovaginal Candidiasis

	Uncomplicated	Complicated
Severity	Mild to moderate and	Moderate to severe or
Frequency	<4 episodes per year and	≥ 4 episodes per year or
Microscopy	Pseudohyphae/hyphae and	Budding yeast only or
Host	Healthy, nongravid	Adverse factors (pregnancy, diabetes, immunocompromise)
Treatment	Any short-course antimycotic therapy	Intensive regimens (avoid short-course)

Table 45-2. Azole Therapy of Vaginal Candidiasis

Drug	Formulation	Dosage
Fluconazole (Femstat)	2% cream	5 g × 3 days
Gynezone	2% cream	Single dose
Clotrimazole (Gynelotromin, Mycelex)	1% cream	5 g × 7–14 days
	10% cream	5 g single application
	100 mg vaginal tab	1 tab × 7 days
	100 mg vaginal tab	2 tab × 3 days
Miconazole (Monistat)	500 mg vaginal tab	1 tab once
	2% cream	5 gm × 7 days
	100 mg vaginal supp	1 supp × 7 days
	200 mg vaginal supp	1 supp × 3 days
Econazole (Gyno-Pevaryl)	1200 mg vaginal supp	1 supp once
	150 mg vaginal tab	1 tab × 3 days
	150 mg vaginal supp	Single dose
Fenticonazole	2% cream	5 g × 7 days
Sertaconazole (Monazol)	300 mg supp	Single dose
Ticonazole (Vagistat)	2% cream	5 g × 3 days
	6.5% cream	5 g single application
Teraconazole (Terazol)	0.4% cream	5 g × 7 days
	0.8% cream	5 g × 3 days
	80 mg vaginal supp	1 supp × 3 days
Fluconazole (Diflucan)	150 mg tab	Single dose
Ketoconazole (Nizoral)	200 mg tab	2 tab × 5 days
Itraconazole (Sporonox)	100 mg tab	2 tab × 3 days

symptoms, which resulted in the withdrawal of this topical agent in high concentrations.¹³⁷ Among the shortcomings of the azole class is their relatively poor efficacy in vaginitis caused by non-*albicans* species of *Candida*.

There has been a growing tendency to use shorter and shorter courses of both topical and oral agents.^{133,138} Single-dose therapy by any route is effective in mild to moderate disease. Many of the single-dose drugs such as vaginal clotrimazole (500-mg suppository) and fluconazole (150-mg oral tablet) possess pharmacokinetic properties such that concentrations

of the antimycotic persist in the vagina for up to 5 days following the single administration of these agents.^{139,140} Hence, single-dose therapy may be more than “single-day” therapy. Asymptomatic vaginal colonization is not considered an indication for treatment.

At the same time, patient expectations should be reasonable with regard to resolution of symptoms. While pruritus usually resolves in a few days, soreness, tenderness, discomfort, and dyspareunia may take several more days to completely resolve following a severe attack.

■ ACUTE VAGINITIS IN PREGNANCY

Management of VVC during pregnancy is more difficult, since clinical response tends to be slower and recurrences more frequent.^{141–144} In general, most topical antifungal agents are effective, especially when prescribed for longer periods (1–2 weeks).¹⁴⁵ Longer duration of therapy may be necessary to eradicate yeast infection. However, single-application, high-dose topical therapy with clotrimazole has been shown to be effective in pregnancy and may be considered for the initial therapeutic attempt.^{145,146} In the past, nystatin was considered the drug of choice in the first trimester of pregnancy; however, all topical imidazole agents can be used throughout pregnancy. Oral azoles are contraindicated.¹⁴⁷

■ MANAGEMENT OF RECURRENT VULVOVAGINAL CANDIDIASIS

Prior to initiation of treatment, diagnosis must be confirmed by culture. Thousands of women carry the label of “RVVC” when their symptoms are in fact due to noninfectious etiologies such as allergic and hypersensitivity vulvitis. Following confirmation of VVC, every effort should be made to eliminate factors predisposing to VVC. However, in the majority of women no reversible or correctable causal factors are present.

Initial antimycotic therapy requires an induction course of either oral or vaginal antimycotic therapy, which must be continued daily until the patient is completely asymptomatic and a culture-negative status has been achieved. In RVVC, failure to initiate a maintenance regimen will result in a clinical relapse of VVC in 50% of patients within 3 months.^{148,149} Maintenance-suppressive regimens include ketoconazole 100 mg daily and once-weekly regimens of either 500 mg clotrimazole suppositories or 100 mg fluconazole orally. All three maintenance regimens are effective in preventing breakthrough vaginitis.^{148,150,151} In a recent multicenter prospective randomized control trial, following induction therapy, patients with RVVC were assigned to receive fluconazole 150 mg or placebo weekly for 6 months and followed up for a further 6 months off therapy. The proportion of women who remained attack free at 6, 9, and 12 months were 90.8%, 73.2%, and 43.9% as compared with 35.9%, 27.8%, and 21.9%, respectively, in the placebo group.¹⁴⁹ The median time to clinical recurrence in the fluconazole group was 10.2 months, as compared with 4.0 months in the placebo group ($P < 0.001$). No evidence of fluconazole resistance in isolates of *C. albicans* or of superinfection with *C. glabrata* emerged. The superior safety profiles of fluconazole and clotrimazole have resulted in the latter two agents replacing ketoconazole suppressive prophylaxis. Whatever the maintenance regimen, cessation of therapy is accompanied by symptomatic relapse in half the women within a short time of stopping therapy.^{148–152} Relapse following cessation of fluconazole suppressive prophylaxis is invariably caused by the

original strain of *Candida* responsible for preprophylaxis vaginitis, and the organism remains susceptible to fluconazole. Most experts recommend reinstatement of maintenance fluconazole prophylaxis.

The role of treatment of male sexual partners was reviewed by Sobel, and no benefit was demonstrated in several large studies.¹³³ Similarly, Fong evaluated systemic ketoconazole treatment of male partners and failed to reduce the recurrence rate in women with RVVC,¹⁵³ although Spinillo et al. did report decreased RVVC in women when attempts were made to eradicate *Candida* organisms in both partners.⁷⁵ Dennerstein reported a reduced rate of recurrence in RVVC in 15 patients during a 3-month period of depomedroxyprogesterone acetate therapy.¹⁵⁴ In a small study using patients as their own controls, Hilton et al. reported fewer episodes of VVC in women placed on oral yogurt.¹⁵⁵ Given the small numbers and lack of controls in this unblinded study, the role of yogurt in preventing *Candida* vaginitis remains unproved.

An alternative approach to long-term maintenance antifungal therapy is the use of hyposensitization with *Candida* antigen preparation. Two small studies achieved encouraging results, but this is rarely used.^{125,156}

■ RESISTANT AND NON-ALBICANS CANDIDA VAGINITIS

In contrast to oral candidiasis, vaginitis caused by azole-resistant strains of *C. albicans* is extremely rare.^{157,158} Only a single case in a HIV-negative woman is reported.¹⁵⁹ Although clinically resistant VVC due to in vitro resistant *C. albicans* is rare, the isolation of *C. albicans* strains with higher MICs to fluconazole is not infrequent.¹⁶⁰ In general, peak vaginal concentrations of fluconazole do not exceed 4–8 µg/mL; therefore, only isolates with a fluconazole MIC > 8 µg/mL should be clinically resistant to conventional doses of fluconazole. However, both clinical and research experience do not support this prediction, i.e., in vitro susceptibility testing is not validated or reliable in predicting clinical response. This is in sharp contrast to systemic candidiasis, as well as oral candidiasis, where a good correlation exists between in vitro susceptibility tests and clinical outcome. A partial explanation for this lack of correlation and to explain why isolates with higher MICs still respond may relate to proven in vitro synergy between fluconazole and organic acids, e.g., acetic acid normally found in the vagina.¹⁶¹ Adding acetic to the yeast–fluconazole mixture converts fungistatic fluconazole to fungicidal and dramatically enhances its antiyeast activity potentially enhancing its in vivo effect. It should be emphasized that azole-resistant strains of *C. albicans* are similarly rarely the cause of RVVC.¹⁴⁹

On the other hand, RVVC is not infrequently due to non-*albicans* species, the majority of which show reduced susceptibility to all azoles. *C. glabrata* is particularly common, and

approximately half the strains show reduced sensitivity to available azoles.^{162,163} Boric acid 600 mg administered vaginally once daily in a gelatin capsule has been shown to be moderately effective in this clinically resistant infection.^{163–165} Therapy should be continued until cultures are negative (usually 10–14 days), and when a history suggests RVVC, a maintenance regimen of alternate day and then twice-weekly boric acid should be prescribed. Unfortunately, there is still little experience published on the efficacy of this maintenance regimen, and the long-term safety of intravaginal boric acid has not been confirmed. *C. krusei* vaginitis is resistant to fluconazole therapy, but usually responds to boric acid or other azole therapy.²⁶

Sobel et al. reported their experience with boric acid and 17% flucytosine topical therapy in women with azole-resistant vaginitis due to *C. glabrata*.¹⁶⁴ Boric acid was successful in approximately 70% of symptomatic patients, and if this failing, a success rate of >90% was achieved with a 2-week course of topical flucytosine. Flucytosine for vaginal use should be limited because of the potential for the acquisition of resistance. *C. krusei* isolates are resistant to flucytosine.

■ OVER-THE-COUNTER ANTIFUNGAL THERAPY OF PATIENT-DIAGNOSED VVC

In most industrialized countries, topical imidazoles and nystatins are available over the counter without the need for physician prescriptions.¹⁶⁶ The topical agents, in their own right, are undoubtedly effective and identical to other topical prescription antifungals. With rare exceptions, oral azoles are not available at present without prescriptions, although most are now generic and hence dramatically less expensive. The critical issue is the use of these readily available topical antifungal agents for self-diagnosed VVC. Multiple studies have consistently demonstrated the inability of many women to correctly self-diagnose VVC in the presence of vulvovaginal symptoms.¹⁶⁷ In the most recent study, Ferris et al. found that only 34% of women acquiring over-the-counter antifungals for presumed VVC actually had VVC. A history of previous clinically based diagnosis of VVC and reading the package label did not help women self-diagnose VVC properly. Unfortunately, ready access to these products is associated with wasted financial expenditures, unfulfilled expectations, and a delay in correct diagnosis for a substantial number of women. This entire problem could resolve overnight with future availability of a simple inexpensive *Candida* detection diagnostic tests.

VULVOVAGINAL CANDIDIASIS IN HIV-POSITIVE WOMEN

From the onset of the AIDS epidemic, both the prevalence and the significance of oral and esophageal candidiasis were recognized.¹⁶⁸ As the percentage and numbers of women with

HIV grew in the 1980s, vaginal candidiasis was increasingly reported.^{169,170} Without supporting data, RVVC was regrettably incorporated as an AIDS-defining illness.¹⁷¹

The increased prevalence of oral candidiasis occurred on the basis of the loss of oral mucosal CMI defense mechanisms, and the deficiency was thought also to apply to the vagina.¹⁷² Furthermore, given the enormous quantities of broad-spectrum antibiotics administered for prophylactic and therapeutic purposes to women with HIV, together with the women's progressive debilitation, one might similarly predict the frequent occurrence of symptomatic *Candida* vaginitis, especially with severe immunodeficiency.

A 1987 report indicated that 24 HIV-infected women followed at the Walter Reed Army Medical Center had a history of unexplained chronic vaginal candidiasis for at least 1 year.¹⁶⁹ All the patients described had oral thrush and severe T-helper cell depletion and most were anergic. Within a 30-month follow-up, 80% of the patients developed other severe opportunistic infections. The authors emphasized that RVVC was the presenting complaint, pre-dating the recognition of oral thrush, and was frequently the only clinical indication of severe underlying immunodeficiency. HIV-associated RVVC was considered unique in having only temporary symptomatic improvement following the use of intravaginal antifungal agents and in requiring constant therapy for control of symptoms. The authors concluded that HIV-positive women with RVVC were at serious risk for rapid progression to AIDS, as are males with recurrent oral thrush.¹⁶⁸ Rhoads et al. concluded that women with "chronic refractory" vaginal candidiasis should be tested for HIV, but did not define either word.¹⁶⁹

A subsequent report described *Candida* vaginitis in 70% of an HIV-positive female cohort from Rhode Island.¹⁷⁰ In this study, VVC responded well to appropriate therapy, but had a tendency to recur. The authors also reported increased severity and duration of episodes of VVC.¹⁷³ More than half the women with new onset of increased frequency or severity of *Candida* vaginitis described their symptoms as originating 6 months to 3 years before the diagnosis of HIV infection had been considered. Over 90% of the women presenting with oral candidiasis had experienced new onset of increased frequency of vaginal candidiasis. The location and severity of *Candida* infections in these HIV-positive women were closely related to degree of immunosuppression at the time the infection developed as measured by CD4 counts. Thirty percent of HIV-positive women with only vaginal candidiasis and no oral disease had CD4 counts identical to those of HIV-positive women without evidence of mucosal candidiasis. The authors concluded that mucosal infections by *Candida* organisms occur in a hierarchical pattern (first VVC, then oral, and finally esophageal candidiasis) in women with HIV infection, and that recurrent, often severe, vaginal candidiasis was common with little or no suppression of CD4 cells.¹⁷³

A major limitation of the above studies is the lack of information concerning diagnosis of *Candida* vaginitis. Any epidemiologic information based on the history only or on physical examination without KOH or culture confirmation is unreliable. In the absence of an HIV-negative control group, it is possible that RVVC in HIV-positive women with high CD4 counts, as described by Imam et al.,¹⁷³ reflects background VVC prevalence in a sexually active group of women still possessing a sense of well-being. Moreover, if progressive loss in mucosal immunity accompanies the decline in CD4 cells, one would anticipate a further increase in frequency of RVVC accompanying advanced AIDS, but none of the published reports have described this occurrence. Duerr et al. observed that the rate of vaginal carriage of *Candida* organisms did not increase until the CD4 count dropped below 200 cells/ μ L.¹⁷¹

Most of the data that accrued in the second decade of the HIV epidemic regarding VVC in HIV-infected women originated from cross-sectional studies, and even those based upon longitudinal cohort studies failed to measure the true attack rate of symptomatic VVC in both HIV-ART treated and untreated women.¹⁷⁴ Based upon epidemiologic definitions of asymptomatic VVC, but including women with both *Candida* microscopy positive and culture positive women, results indicate a small moderate increase in VVC in HIV-positive women not receiving ART.¹⁷⁵ Including positive microscopy in the epidemiologic definition of VVC was an attempt to differentiate VVC from vaginal colonization. Overall, the increased incidence of VVC in HIV-positive women was modest compared to the increased occurrence of oropharyngeal candidiasis.¹⁷⁶ Certainly, vaginal colonization is significantly more common in HIV-positive women, as is duration of colonization, both in contrast to *Candida* vaginitis. Higher HIV loads were significantly associated with increased odds of incident or persistent vaginal colonization and candidiasis.¹⁷⁶ CMI, as reflected by CD4 counts while significantly associated with increased odds of oral colonization and candidiasis, was not associated with vaginal colonization or candidiasis.¹⁷⁶ In contrast, Duerr et al., using a different definition for VVC, did find an association between lower CD4 count and VVC. Notably, regardless of the definitions used to characterize VVC, none of the studies have indicated that VVC is more severe or less likely to respond to therapy than in HIV-infected women.^{175,177}

The microbiology of VVC in HIV-positive women appears identical to that of matched high risk HIV-negative women, although longitudinal studies indicate that with time and possible, but unmeasured, azole exposure, there is a gradual tendency to observe an increased frequency of isolation of non *albicans* *Candida* spp, notably *C. glabrata*.¹⁷⁸ Moreover, with time, a mild increase in isolation of fluconazole-reduced sensitivity *Candida* isolates of all species were found.¹⁷⁹ To date, these changes have not translated into altered treatment response.

As with other forms of lower genital ulceration and inflammation, *Candida* vaginitis has been associated with enhanced vaginal HIV shedding with increased genital-tract HIV RNA level.^{180,181} Hence, VVC may facilitate HIC transmission, although its contributory role is unknown.

The issue of HIV testing in the presence of VVC was previously controversial.¹⁸² Most women experiencing a single episode of VVC today are obviously not HIV infected and clearly do not require testing. Even in the case of women with RVVC, the issue is anything but clear, since the overwhelming majority of women with RVVC are HIV-negative. Only women with RVVC who have risk factors for HIV infection should be tested, but high-risk women should be tested anyway, regardless of the presence of *Candida* vaginitis.

Treatment of symptomatic *Candida* vaginitis in HIV-positive women is identical to that of HIV-negative women, i.e., uncomplicated VVC should be treated with short course of fluconazole (150 mg single dose) or topical azoles for short duration. In contrast, complicated vaginitis should be treated with longer duration oral systemic or topical regimens and maintenance weekly fluconazole should be used for RVVC.¹⁷⁷ Regardless of HIV serostatus, occasional failures occur due to fluconazole-resistant *C. glabrata* infection.

Treatment of asymptomatic VVC remains controversial. In HIV-negative women, antifungal therapy is generally not advised. In HIV-positive women with *Candida*-positive microscopy, because of associated enhanced HIV virus vaginal shedding,¹⁸¹ an argument can be made for treating asymptomatic VVC so as to theoretically reduce the risk of HIV transmission, although little data of its utility are available.¹⁸³

■ PREVENTION OF VULVOVAGINAL CANDIDIASIS

No measures are routinely required for all women undergoing or exposed to factors that may precipitate VVC, unless they reveal a history of RVVC. Even then, given the complex etiology of VVC, there are no universal steps that protect against all pathogenic mechanisms. Moreover, there are few studies evaluating widely used methods of prophylaxis.

The most obvious scenario is the receipt of antibiotics (systemic or local vaginal) in those women known to be susceptible to antibiotic-induced VVC. Postantibiotic VVC is certainly a common problem in general practice and women frequently resort to use of probiotic *Lactobacillus* spp to prevent and treat this. A recent study conducted in Australia by Pirotta et al.¹⁸⁴ used a four-arm study of oral lactobacillus, oral placebo, vaginal lactobacillus, and vaginal placebo in an attempt to prevent postantibiotic VVC. Unfortunately, both routes of lactobacillus administration failed to prevent postantibiotic prophylaxis. Many practitioners recommend prophylactic oral fluconazole 150 mg

not daily, but with the onset and combination of antibiotics, and possibly additional fluconazole dosing if duration of antibiotics is prolonged. No data has been published in support of this approach; moreover, given the expense involved, treatment should be highly selective, aimed at susceptible women only.

Fluconazole prophylaxis has already been discussed in relation to idiopathic RVVC.¹⁴⁹ However, other categories of secondary RVVC may benefit from fluconazole prophylaxis, often long term, for example, presence of underlying dermatosis lichen sclerosus or coexistent vaginitis, DIV, or BV. Frequently, multiple predisposing factors accumulate to result in secondary RVVC, e.g., underlying dermatosis in a postmenopausal women prescribed topical steroids as well as topical estrogen dramatically enhancing risk of opportunistic VVC (three risk factors) after a single supervening episode of VVC, it is reasonable to prescribe long-term suppressive fluconazole.

Preventable measures also depend upon the predisposing cause. Accordingly, poorly controlled diabetics can prevent exacerbations of symptomatic disease by controlling hyperglycemia. Likewise, when identified in individual women, avoidance of individual-specific dietary factors such as a candy binge, alcohol consumption, or diet high in refined sugars may be useful. As mentioned above, treatment of male partners with local or systemic antifungals is of no value. Finally, sexual behavioral factors have been suggested in some but not in the majority of women as contributing factors for RVVC. Occasionally, women report cessation of episodes of RVVC following major changes in sexual activity, e.g., cessation of receptive oral sex.

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Peter A. Leone

PUBIC LICE

The order Anaplura includes over 400 species of sucking lice, which are ectoparasites of mammals. Sucking lice are dorsoventrally compressed, wingless, and small, with retractable piercing-sucking mouthparts. One species is the cause of a common sexually transmitted disease (STD): pubic lice, or “crabs.”

Three species of lice infest human beings: *Phthirus pubis*, the crab louse; *Pediculus humanus humanus*, the body louse; and *Pediculus humanus capitis*, the head louse. This chapter focuses principally on pubic lice, but head and body lice will be considered briefly for purposes of comparison.

■ HISTORY

Lice have been constant companions of human beings since antiquity. DNA analysis of lice suggests that lice specific to humans and lice specific to chimpanzees appeared 5.6 million years ago¹. Israeli scientists confirmed that the warriors in Bar Kochba’s Jewish revolt against Rome 18 centuries ago were afflicted with lice. These lice were morphologically identical to *P. capitis* (Anaplura: Pediculidae) that continue to afflict human populations today. The lice were discovered in the hair and clothes of archeological remains from caves in the Sudan desert.

LIFE CYCLE AND REPRODUCTION

Lice have five stages in their life cycle: egg (or nit), three nymphal stages, and the adult stage. All stages occur on the host. Sucking lice undergo a simple metamorphosis in which immature lice are morphologic miniatures of adults but have no reproductive ability.

The egg of the crab louse is smaller than the eggs of either the head or body louse, which measure approximately 0.8 mm long and 0.3 mm wide.² The nit is oval in shape and opalescent in color; it contains a cap (operculum) that comes off intact when the egg hatches (Fig. 46-1). An egg will hatch

within 5–10 days after being incubated in the heat of the host’s body. Interestingly, the young nymph emerges through the cap by sucking air into its body and expelling it from its anus until a cushion of compressed air is formed, which then pops the cap open and allows the nymph to escape.³ Over a period of 8–9 days, the nymph produces three molts. The louse remains on the body and requires frequent blood meals after having hatched. When lice reach adulthood, mating occurs after approximately 10 hours and continues until the lice die. The female louse lays approximately four eggs per day.

In the case of the body louse, the egg case is attached to hair or clothing by a cement like material secreted by the female louse. After hatching, the empty shell may stick to hair or clothing for some time. It is often difficult to remove by washing or shampooing or by vinegar or organic solvents. If all else fails, the empty egg cases are eventually moved away either by growth of the hair, by the use of a fine-tooth comb, or by cutting the hair.

Little is known about the actual life span of the adult louse. Under artificial conditions, lice have survived for about 1 month. Ambient temperature, humidity, and availability of human blood are thought to influence the life span of all types of human lice. Off the host, all stages of the louse can be expected to die within 30 days, regardless of temperature. Unfed adult head and body lice can survive for up to 10 days, whereas adult pubic lice rarely survive more than 24 hours off the host.⁴ Lice leave the host voluntarily only when the host has died or becomes febrile or when there is close personal contact with another host.

The life of the louse is dependent on human blood. When ready to feed, the louse anchors its mouth to the skin, stabs an opening through the skin, pours saliva into the wound to prevent clotting, and pumps blood from the wound into its digestive system. During feeding, dark-red feces may be deposited on the skin.

The pubic louse has greatly enlarged middle and hind legs and claws; the abdomen is wider than it is long, giving it the appearance of a crab (Fig. 46-2). Pubic lice are about 1 mm in length. Adult head and body lice have a longer body

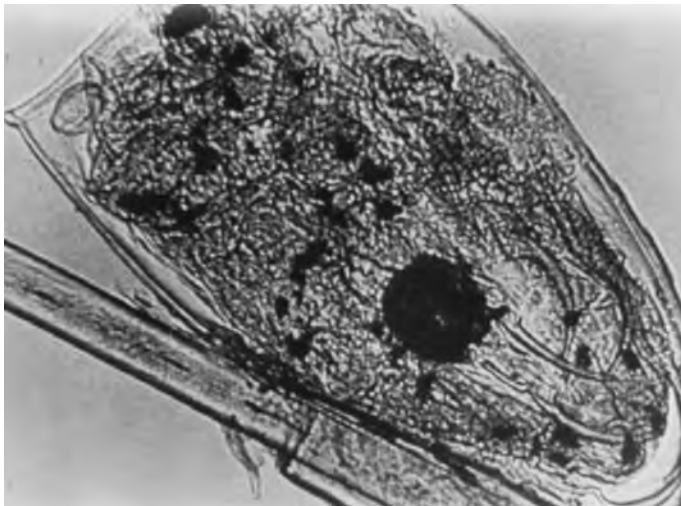


FIGURE 46-1. Close-up micrograph of a louse nit (egg).



FIGURE 46-4. Pubic louse and nits on a hair shaft. (Courtesy of V. D. Newcomer.)



FIGURE 46-2. Pubic louse after a recent blood meal. (Courtesy of V. D. Newcomer.)

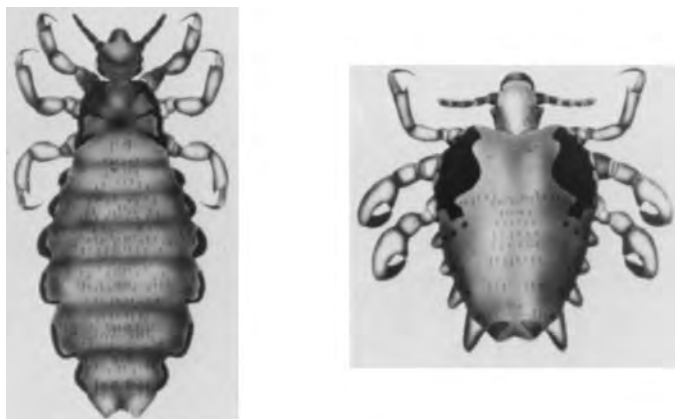


FIGURE 46-3. Comparison of gross structure of (left) the head louse and (right) the pubic louse.

(approximately 3 mm in females and 2 mm in males) and relatively shorter middle and hind legs (Fig. 46-3). The pubic louse has three parts: a head (with a pair of eyes), a thorax (with three pairs of legs), and a segregated abdomen. At the



FIGURE 46-5. Adult pubic lice and nits.

end of each leg, there is a hook-like claw and opposing thumb, that enable the louse to maintain its hold on hair (Fig. 46-4).

A difference between body and head lice and the pubic louse involves their grasping ability. The grasp of the pubic louse's claw matches the diameter of pubic and auxiliary hairs; hence, pubic lice may be found not only in the pubic area (Fig. 46-5) but also have been recovered from the axillae, beard areas of the face, eyelashes (Fig. 46-6), and eyebrows.^{5,6} It is rare in these other areas and is probably mechanically moved to these areas via the fingers. The diameter of the head louse's grasp seems to be uniquely adapted to the diameter of the scalp hair. Therefore, it is very difficult to transplant head lice to other areas of the body.

Another difference between the species is that of egg laying. Adult female pubic lice and head lice glue their eggs to hairs, while the female body louse usually oviposits on the fiber or in the seams of clothing.



FIGURE 46-6. Adult pubic lice and nits on eyelashes.

The third difference is the rate of movement. Pubic lice seem to be the most sedentary. Nuttal and Payot⁷ recorded pubic lice moving at a maximum of 10 cm in a day. Body lice can wander as much as 35 mm in a 2-hour period. Temperature, ambient humidity, and availability of a blood meal also influence the rate of movement. Lice do not like light and will move frantically to escape light.

■ EPIDEMIOLOGY AND TRANSMISSION

It is estimated by sales figures on pediculicides that more than 3 million cases of pediculosis are treated each year in the United States.⁸ Most cases are due to head and pubic lice infestations. Infestation by body lice seems to be less common in this country. Infestations with pubic lice are more common in people of low socioeconomic status.⁹ Epidemics of louse-borne relapsing fever and epidemic typhus are now rare since the body louse is the only species implicated as their vector. Mass epidemics of these diseases have resulted when large populations have lived in unsanitary conditions as in times of famine, disaster, and war.

“Vagabond’s disease” is a diagnosis made in persons who continually harbor these lice and whose skin becomes hardened and darkly pigmented as a result of frequent louse bites and patient response.

P. pubis infestation is frequently associated with the presence of other sexually transmitted infections, and patients presenting with pubic lice should be examined for such infections.¹⁰

Human lice are transmitted from one person to another primarily by intimate contact. Although all types of human lice are relatively host-specific, crab lice occasionally have been reported to infest dogs. Both head and body lice are transmitted by sharing personal articles such as hairbrushes, combs, towels, or clothing. Pubic lice do not seem to spread

as rapidly as other human lice when off the host. They have a shorter life span (24 hours compared with several days for other lice) and their movements are more lethargic. Sexual transmission is considered the most important means of pubic lice transmission. However, there are documented cases of transmission from toilet seats, beds, and egg-infested loose hairs dropped by infested persons on shared objects.

The population with the highest incidence of pubic lice is similar to that of gonorrhea and syphilis: single persons, ages 15–25 years. Prevalence of pubic lice infestation declines gradually to age 35 and is rare in persons older than age 35. Head lice are most common in children up to 6 years of age.

■ CLINICAL MANIFESTATIONS

Sensitivity to the effect of louse bites varies with the individual. When previously unexposed persons are bitten, there may either be no signs or symptoms or a slight sting with little or no itching or redness. At least 5 days must pass before allergic sensitization can occur. At that point, the main symptom is itching, which leads to scratching, erythema, irritation, and inflammation. An individual who has been bitten by a large number of lice over a short period may have mild fever, malaise, and increased irritability.

Ectoparasites produce a variety of immunologic responses in the host.¹¹ Apparently, many persons eventually develop some degree of immunity to the bite of the louse. Persons infested for a long time may even become oblivious to the lice on their bodies. The opposite may also occur. Excessive scratching may lead to superinfection. Characteristic small “blue spots” may appear in the skin as a result of the crab louse bites; these persist for several days. A tubo-ovarian inflammatory mass attributed to *P. pubis* has been reported.

■ DIAGNOSIS

Diagnosis of lice infestation is made by (1) taking a careful history from the patient, (2) considering lice infestation as a possible or probable cause of the patient’s signs and symptoms, and (3) careful examination of the patient. Both adult lice and their eggs (nits) are easily seen by the naked eye (see Figs. 46-5 and 46-6).

Head lice characteristically are found on the scalp surface with the nits attached to the hair. Since scalp hair grows at a rate of about 0.4 mm per day and nits of the head louse usually hatch within 9 days, most of the unhatched nits are within 5 mm of the scalp surface. Nits on scalp hair are usually cemented at an oblique angle, which helps to distinguish them from foreign material that slides up and down and frequently surrounds the hair.

Upon examination of the groin or pudendal area, pubic lice may be perceived as scabs over what first were thought to be “scratch papules.” When taking a closer look, if nits appear

on the hairs, the proper diagnosis becomes obvious. When no adult lice are available, the demonstration of nits under the microscope will also confirm the diagnosis.

When one sees with the naked eye white flakes on the hair, other possible considerations are seborrheic dermatitis (dandruff flakes), hair casts, solidified globules of hair spray, and certain accretions on hair shafts.

■ MANAGEMENT

Treatment and disinfection regimens should be individualized. Ideally the regimen should employ a pediculicide that will effectively kill both the adults and the egg.¹² Patients should be instructed to avoid intimate contact with their sexual partner until they have been treated and both individuals have been seen in follow-up. Examination of other household contacts of the patient should also be made so that both source and spread cases can be treated.

Recommended treatment regimens are listed in Table 46-1. In addition, all bedding, towels, and clothing should be washed. Some patients may require a second application of topical therapy in 3–7 days after the initial treatment.¹³ Infestation of eyelashes should be treated by application of an occlusive ointment such as petroleum jelly twice a day for 10 days. Other agents that may be effective in treatment of *Pthirus pubis* are 0.5% malathion, 0.5–1% carbaryl, and 0.2% phenothrin.¹³

Since 2000, to our knowledge, there have been no new treatment trials published concerning the treatment of *Pthirus pubis*. However, there were three randomized clinical treatment trials assessing the treatment of head lice. In one comparative trial conducted in Florida, 0.5% malathion compared to 1% permethrin demonstrated a clearance rate of 98% with malathion compared to 55% with permethrin.¹⁴ Permethrin coupled with oral TMP/SMX enhanced the efficacy of therapy with permethrin.¹⁵ Combing did not improve clearance in response to therapy with permethrin.¹⁶ One study assessed both in vitro susceptibility of lice and in vivo response to topical lice treatment in children in Bath and Bristol, England. Both cohorts of children had lice that demonstrated a decreased mortality rate in response to permethrin and malathion.¹⁷ Children in Bath were treated with malathion with a 36% cure at 48–72 hours. Children in Bristol were treated with permethrin and had a 13% cure at 48–72 hours. The sample size of this study was only 30 children, but it suggests the presence of dual resistance to permethrin and malathion in these cohorts.

Additional in vitro evaluations were performed by Pollack et al.¹⁸ who sampled head lice from children in Massachusetts, Idaho, and Malaysian Borneo. They found that among lice in the United States, the mortality was ~50% in response to treatment with permethrin. The mortality rate was unaltered by

Table 46-1. Treatment Regimens from *Pediculosis pubis*

	Average Wholesale Price in U.S. \$	Instructions for Use
Permethrin 1% crème rinse (2 oz)	7.67 ^a	Apply to affected areas and wash off after 10 min
Lindane 1% shampoo	3.00–14.72 ^b	No longer recommended as first-line therapy due to toxicity. Should only be used as alternative due to inability to tolerate other therapies.
		Apply to affected areas and wash off thoroughly after 4 min
Pyrethrins with piperonyl butoxide		Apply to affected area and wash off after 10 min
(2 oz) shampoo	1.67 ^c	
(5.5 oz) mousse	9.20 ^c	

^a Warner Lambert product information.
^b Data from 1999 Drug Topics Red Book.
^c Bayer product information

increasing concentrations of drug. Conversely, the lice from Malaysia had a 37% mortality rate at the lowest concentrations of permethrin. Their fatality increased linearly with increasing permethrin concentrations to a maximum mortality rate of about 95%. This study used different evaluation times for the U.S. and Malaysian lice because of baseline differences in survival times. Regardless, this study suggests possible emergence of drug resistance in U.S. head lice. The concern raised by these results is amplified by another in vitro analysis demonstrating that lice with permethrin resistance also have resistance to sumithrin and a newer agent for treatment, deltamethrin.¹⁹ The emergence of drug resistance in head lice throughout the world is concerning but the implications for the treatment of *Pthirus pubis* are unclear. A case of pubic lice resistant to pyrethrins in vitro was reported but the patient demonstrated clinical clearance with 5% permethrin.²⁰ The current recommendations for treatment of *Pthirus pubis* are listed in Table 46-1. Since 1996, there have not been any studies in the English language documenting significant treatment failure in the management of *Pthirus pubis*.

The use of 1% gamma benzene hexachloride (lindane) has several disadvantages and is no longer recommended as a first or second line of therapy. It can be absorbed percutaneously when applied to severely excoriated skin. Case reports have alluded to mild signs and symptoms of neurotoxicity when it has been ingested, applied too frequently, not washed off as directed, or used on massively excoriated skin. In one study, 9% of a single dose was found in the urine in a badly excoriated patient in 5 days following the treatment. No other studies, however, have shown blood, tissue, and urine levels.^{21,22} Nonetheless, blood dyscrasias such as aplastic anemia and leukopenia have been described after use of lindane in agriculture and against ectoparasites in animals and humans, and lindane is reportedly cytotoxic in vitro for human hematopoietic progenitor cells.²³ In particular, lindane use should be avoided in small children, pregnant women, and individuals with massive excoriations or multiple lesions over the scrotum.

Itching is an important feature of all lice infestations. The initial treatment with a pediculicide may be effective for killing both the adult lice and the eggs, but the itching may continue because of an allergic reaction and/or irritation. The possibility of posttreatment pruritus should be discussed with the patient; a mild topical antipruritic/anti-inflammatory cream or ointment may need to be prescribed. The patient should be reevaluated 4–7 days after initial treatment. Attention to these considerations is crucial, since it often prevents excessive pediculicide use and may prevent parasitophobia and feelings of “being unclean.”

■ CONTROL ASPECTS

In discussion of control of epidemic lice infestations with administrators of schools or institutions or control measures with and for an individual, the set of guidelines that can be recommended are as follows:

1. Document that lice are truly the cause of the problem.
2. Diagnose, which louse species is involved.
3. Establish an effective therapeutic regimen, including
 - a. treatment of the individual with a pediculicide that kills adult lice and the nits;
 - b. environmental disinfection;
 - c. treatment of household and intimate contacts;
 - d. reassurance to the infested persons that they are not “unclean” and that they will get better.

Ectoparasites continue to be a common cause of skin disease throughout the world. Topical agents are generally effective in management but are accompanied by sometimes-serious side effects and resistance has been documented to several agents. *Pthirus pubis* is usually effectively treated with topical agents, but rising rates of resistance in head lice warrant

concern regarding future efficacy of current topical agents in the treatment of pediculosis pubis.

SCABIES

Scabies is one of the great epidemic diseases of humankind.^{24,25} The risk of outbreaks or epidemics of scabies have been associated with wars or other events that lead to the disruption of social order. Scabies have been linked to the death of King Herod the Great (73–4 BC) and the “spider” who “sat down beside her and frightened Miss Muffet away.”^{26,27} It is caused by the scabies mite or “itch mite” *Sarcoptes scabiei* (Fig. 46-7). Transmission of the mite can occasionally occur by touching an infected subject, but most commonly infection requires prolonged physical contact, i.e., sharing a bed or sexual contacts. The mite was first discovered by Bonomo in 1687, but this knowledge was not generally accepted until the details were worked out by Von Hebra in the nineteenth century. The pathophysiology of infection was most clearly demonstrated by Mellanby²⁹ in his elegant studies using conscientious objectors during World War II. Mellanby watched asymptomatic burrowing of the mites for 3–6 weeks, followed by the development of local and systemic pruritus and increased inflammation around the burrow. He also demonstrated that experimental reinfestation would produce itching within hours. These experiments provided very strong evidence that the patients had made an immune response. The timing of the response following reinfection and the associated itching implied that the mites had induced immediate hypersensitivity. Mellanby suggested that this immune response could be important in controlling infestation and that scratching was an effective method of dislodging the mites from the skin.

Adult scabies mites have a body structure and short legs that facilitate entry into the skin. Like all acarids, they have four pairs of legs and lay eggs. They are a member of the class that includes spiders, ticks, and chiggers, but they are most closely related to dust mites of the genus *Dermatophagoides*. The adult female is approximately 400 μm in length and is best seen with a hand lens. Mites can move at a rate of ~ 2.5 cm/min on warm skin when choosing a site to burrow. They penetrate down to the stratum granulosum and then extend their burrows by half inch or less over the next month. Mite burrows concentrate on the hands and wrists but they can also be found on axillary folds, breasts, the periumbilical area, and the penis. Arlian and Vyszenski-Moher²⁹ have demonstrated that scabies mites, especially the adult females, are selectively attracted to several lipids that are found in human skin. The lipids include odd-chain-length saturated (e.g., pentanoic and lauric) and unsaturated (e.g., oleic and linoleic) fatty acids as well as cholesterol and tripalmitin. The results suggest that lipids present on the skin of humans and other mammals may influence both the incidence of infection

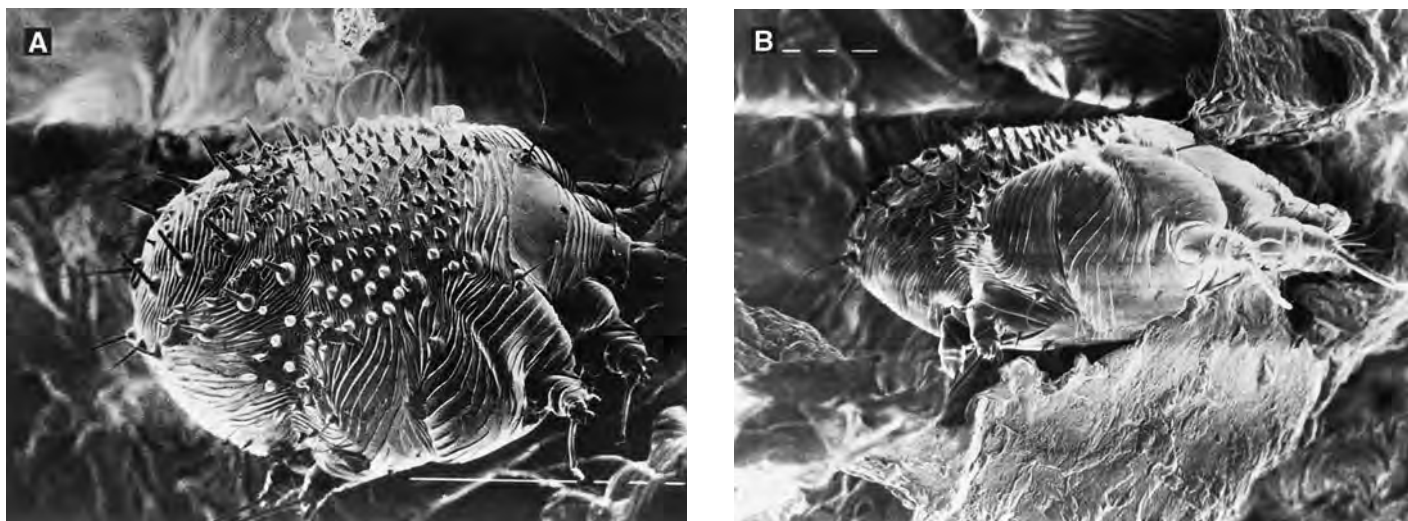


FIGURE 46-7. (A. & B.) Scanning electron micrographs of *Sarcoptes scabiei*. (Courtesy of L. Arlian, Wayne State University.)

and also the distribution of mite burrows on the body. Once established in a burrow, the mites can lay eggs daily. The eggs are approximately 100 μm in length and can progress to the adult stage in about 10 days. The adult male is short-lived but the females can live up to 6 weeks. Although the potential for multiplication is enormous, the average number of adult females on an infected normal host is less than 20. Adult mites deposit both eggs and fecal pellets in the burrows, and by analogy with dust mites, it is likely that digestive enzymes in the fecal pellets are important antigens for the immune response to scabies mites.^{30,31}

■ IMMUNOLOGY AND PATHOGENESIS

Investigation of the immunopathology before 1980 demonstrated a cellular infiltrate and immunoglobulin deposits around lesions as well as circulating immune complexes. It had also been reported that the lesions contained IgE deposits. In 1980, Falk and Bolle³² reported that patients with scabies had elevated total serum IgE and IgE antibodies to *D. pteronyssinus*. This result could have meant that scabies was common in atopic individuals or that infestation with *S. scabiei* produced an immune response including IgE antibodies that cross-react with dust mites. The latter view has been supported by studies showing extensive cross-reactivity between scabies mites and dust mites involving several different proteins.³³ Furthermore, in rabbits it has been demonstrated that immunization with *D. pteronyssinus* extract can protect the animals against infestation with scabies.³⁴

Although it is now clearly established that the scabies mite induces IgE antibodies and immediate hypersensitivity, it is not certain that this response and the associated pruritus play a role in controlling infestation. The lesions around a mite burrow are infiltrated with inflammatory cells.^{35,36} From experimental work with ticks, it is likely that the cellular immune

response to scabies is comparable with cutaneous basophil hypersensitivity in experimental animals and that eosinophils and basophils could play a direct role in killing mites.³⁷ Although the immune response to scabies mites includes IgE antibodies, the relationship to atopy is not clear. Thus, there are no reports that atopic individuals are significantly more likely to become infected. Equally, there is no clear evidence that becoming allergic to dust mites is protective against scabies in humans, as would be predicted from the results in rabbits.³⁴ The lesions are often eczematous or urticarial; in addition to the intense pruritus, all of these are in keeping with a pathogenesis related to immediate hypersensitivity.³⁸

Applying dust mite fecal antigens to the skin of patients with atopic dermatitis will induce a patch of eczema and a characteristic dermal infiltrate of eosinophils, basophils, and T cells.³⁹ A relation between atopic dermatitis and scabies has been reported. On the other hand, almost all adults with atopic dermatitis have high-titer IgE antibodies to dust mites that would be expected to cross-react with scabies mites and make serologic investigation difficult. In other cases of scabies, the lesions include urticaria or nodules as well as papular lesions. All of these could be related to a complex immune response including mast cells sensitized with IgE antibodies and a cellular response induced by cytokines released from Th2 cells and/or mast cells.

■ EPIDEMIOLOGY

Epidemics of scabies appear to cycle at approximately 10- to 30-year intervals.^{24,25} The causes of epidemics are not clear but poverty, sexual promiscuity, waning immunity, travel, and other factors may all contribute. Scabies can occur in any population but is reported to be less common among African Americans. The infestation appears to require prolonged contact for transmission and is thus more likely when partners spend the night together. Among young

adults, sexual transmission is the most likely method of infection; however, tracing routes of infection is made difficult by the long, asymptomatic “incubation” periods. If multiple members of a family develop itching, the diagnosis is usually straightforward, and unlike most other venereal diseases, scabies can be transmitted by nonsexual contact within a family. Casual contact outside families is unlikely to transfer mites except from crusted scabies. For example, although scabies is frequent in school-age children, transmission in school is uncommon. Transmission to hospital staff is also rare but some cases have been reported. Crusted scabies can give rise to cases among hospital staff. When this happens, the infestation in these individuals is usually localized and not severe. However, occasional case reports have been made of severe scabies contacted from a patient with crusted scabies.⁴⁰ In another case where the scabies was lindane resistant, 12 people were infected before the patient was cured with permethrin.⁴¹ Fertile adult female mites generally transmit infection, and the heavier the infestation, the more likely transmission is to occur.

Transmission can occur to humans from mange in animals. In the dog, mange is caused by *S. scabiei* var. *canis*. This mite is very similar to the human scabies mite morphologically, but infection of humans is generally short-lived, lasting some 3–6 weeks (compared with the “seven-year itch” attributed to *S. scabiei* var. *hominis*). The fact that infestation with mites derived from an animal does not give rise to typical burrows and is relatively short-lived may reflect differences in the mites. Thus, they may be attracted by different fatty acids and may be more susceptible to killing by a basophilic or eosinophilic response in the skin. However, detailed studies of the killing of animal mites or the more severe variants of human scabies have not been carried out. Infection of several members of a family from a newly acquired animal can occur, but human-to-human transfer of the dog mite is thought to be rare. Thus, animal-acquired scabies will only produce a few cases and does not usually require treatment of other members of the family.

■ CLINICAL MANIFESTATIONS

The most common manifestation of scabies is pruritic, papular, eczematous lesions on the sides of the fingers and in the interdigital webs (Figs. 46-8 and 46-9). The burrows are often diagnostic and sufficient to recommend specific treatment. Burrows may also be clearly visible on the wrists and elbows. By contrast, lesions elsewhere on the body are papular, nodular, crusted, or lichenified (Fig. 46-10 and Fig. 46-11). In all situations, the lesions are inflamed and extremely pruritic; the pruritus may initially be restricted to the lesions but often becomes generalized. Diagnosis depends on thinking of scabies, demonstrating the mites by scraping or biopsy, and/or observing a response to specific therapy. Itching does



FIGURE 46-8. Papules in the interdigital area, highly suggestive of scabies. (Courtesy of E. Stolz.)



FIGURE 46-9. Multiple scabietic burrows and papules are present on the finger webs. (Courtesy of A. Hoke.)

not begin for 3–4 weeks after initial infestation, but reexposure may produce itching within hours.

■ SPECIAL FORMS OF SCABIES

Scabies can be difficult to diagnose both because of the wide range of skin lesions and because of atypical distribution. Some special forms are worth describing, but scabies needs to be in the differential diagnosis of all pruritic skin diseases.

Nodular scabies

Although unusual, nodular scabies is important to consider because the mildly pigmented, pruritic nodules can persist for months. Clinically, biopsy of the lesions may be necessary to exclude lymphomas of the skin. Diagnosis of scabies may become obvious from biopsy, but sometimes it will not. It is interesting that some cases of chronic atopic dermatitis develop similar nodules. In cases where the diagnosis is not clear from inspection, scrapes, or biopsy, it has to come from a history of scabies in a contact or a trial of specific treatment.



FIGURE 46-10. Grouped excoriations due to scabies on the lower buttocks. Simulating dermatitis herpetiformis.



FIGURE 46-11. Scabies of the penis. Pyoderma of the penis is highly suggestive of scabies.

Scabies incognita

Like all forms of inflammatory dermatitis, scabies responds to steroids either topically or systemically. In most cases, this response is so poor that the diagnosis becomes obvious. However, in some cases steroid treatment may obscure the diagnosis, leading to a more chronic and widespread form that is easily confused with other generalized forms of eczema. These patients remain infectious, so they may come to light because of infection in other members of the family.

Scabies in infants

In infants infection with scabies can give rise to failure to thrive or to generalized eczema. In young children widespread vesicles with an impetiginous appearance or secondary infection with *Staphylococcus aureus* is common.^{42,43}

Crusted or Norwegian scabies

Crusted scabies is characterized by exuberant scaling lesions that are heavily infested with mites. The term *Norwegian scabies* refers to the country of original description of the syndrome and should be replaced by the more descriptive term *crusted scabies*.⁴⁴ The diagnosis is easily made once the possibility is considered. Unlike those with classic scabies, these patients can infect through casual contact. Whether this simply results from the large number of mites present or reflects a different strain of mites is not clear. However, most individuals who become infected because of contact with a case of crusted scabies develop typical scabies, suggesting that it is the host response that is abnormal. Detailed studies on the immunology of the response to crusted scabies have not been reported and would be interesting. The disease is seen commonly in patients who are physically or mentally disabled but also in patients with a defined immunologic defect or who are on immunosuppressive treatment. Therapy may require supportive treatment and antibiotics as well as repeated courses of specific treatment with acaricides.

SCABIES IN PATIENTS WITH HIV/AIDS

The immune response to *S. scabiei* is responsible for much of the symptomatology of the infestation as well as for its control. Thus, it is hardly surprising that the clinical spectrum of scabies is different in patients with AIDS than it is in those with normal immune systems. Although firm data are lacking, it is likely that a disproportionately large number of AIDS patients develop crusted scabies.^{45–51} Although scabetic involvement of the face and scalp is relatively rare in normal adult hosts, AIDS patients often present with lesions in these areas. Likewise, the nails are involved with greater frequency than they are in normal hosts.^{46,48} Unusual presentations of scabies in immunocompromised hosts may invite confusion with Darier–White disease (keratosis follicularis),^{46,48} in which scaly papular lesions develop on the seborrheic areas of the body, including the trunk, face, scalp, and groin.⁵² On the other end of the spectrum, patients may present with generalized pruritus and few lesions.⁴⁸ Scabies should also be considered in the differential diagnosis of AIDS patients with psoriasiform lesions, and some cases have been diagnosed initially as eczema.⁴⁹

Pruritus is a hallmark of scabies in normal hosts, and even in patients with AIDS, pruritus may be quite marked. In other patients, however, perhaps as a consequence of a blunted immune response, pruritus may be markedly decreased, and this phenomenon seems to be associated with the conversion to crusted lesions.⁴⁶

In AIDS patients as well as others, lesions of crusted scabies contain large numbers of mites, and the condition is highly contagious. Several cases of nosocomial transmission to other patients and to health-care workers have been reported.⁴⁶ Transmission has occurred even in settings

wherein the disease was quickly recognized and treated.⁴⁰ Crusted scabies results in a dramatic breakdown of integumentary defenses. When combined with the systemic immunodeficiencies of AIDS, it is hardly surprising that bacteremias have resulted. In addition to the usual bacterial pathogens associated with scabies, *S. aureus* and group A streptococci,⁴³ other streptococci, and gram-negative rods including *Enterobacter cloacae* and *Pseudomonas aeruginosa* have been recovered from the blood of septic AIDS patients with scabies. Although some authors have recommended prophylactic antibiotic treatment of scabetic AIDS patients,⁴⁹ it would seem that careful surveillance and a high level of suspicion are more appropriate in this group.

Treatment of crusted scabies in AIDS patients often requires prolonged application of scabecides. Weekly applications of lindane over 6 weeks have been successful in individual cases^{48,49,51} as have two or three applications at intervals of 48–72 hours.^{48,52} Permethrin has been used in a smaller number of cases.⁵⁵ Concomitant use of a keratinolytic agent such as 6% salicylic acid is recommended.⁴⁸

Difficulty is often encountered in treating crusted scabies in AIDS patients because of the high mite load and because of the difficulty in obtaining adequate penetration of topical scabecides through the crusts. Thus, considerable interest has been generated in the oral treatment of scabies with ivermectin. Ivermectin is a derivative of one of the avermectins, a group of macrolide lactones with broad antiparasitic activity. It is widely used in the treatment of human onchocerciasis. In small series, the drug has been administered as a single oral dose of 200 µg/kg with excellent results, even in cases recalcitrant to topical therapy.^{40,45,47} Multiple administrations of the same dose have been used in some patients as well.⁵⁵

■ SCABIES AS A SEXUALLY TRANSMITTED DISEASE

That scabies is reliably transmitted during sexual intercourse is not questioned.⁵⁶ Although not all cases of adult scabies are so acquired, the disease is recognized as sexually transmitted.^{56–58} As a consequence of this epidemiology, one can make certain clinical assumptions about the disease. First, because the sexually transmitted infections are diseases of lifestyle, individuals with one STD are at significantly higher risk of others to be infected. Thus, patients diagnosed with scabies should be evaluated for other STDs (e.g., chlamydial infection, HIV infection) that may be clinically silent but have greater eventual clinical significance.^{56,57} Second, close household contacts and, particularly, sexual partners within the past month should be examined and treated if necessary.⁵⁷

■ DIAGNOSIS

Typical scabies occurring within a family and presenting with burrows visible on the hands may be obvious by the

time the patient has finished describing the symptoms. Furthermore, many atypical cases can be diagnosed because of an associated typical case that responds to specific treatment. In the isolated atypical case, the differential diagnosis includes many different pruritic dermatoses. Since the lesions of scabies can be eczematous, urticarial, or nodular, the list includes contact dermatitis, atopic dermatitis, infected atopic dermatitis, multiple insect bites, chiggers, dermatitis herpetiformis, papular urticaria, chronic urticaria, and mastocytosis.

■ TECHNIQUES FOR IDENTIFYING MITES IN LESIONS

Using a hand lens to examine burrows is a standard practice. Burrows can be made more easily visible by allowing them to take up ink. After rubbing ink from a fountain pen on the area, the ink should be wiped off with alcohol, and ink in the burrows becomes visible⁵⁹ (Fig. 46-12).

Scraping of the skin with a no. 15 scalpel blade should be sufficiently vigorous to disrupt the top of burrows or papules.⁶⁰ The scrapings are transferred to a slide, covered with mineral or immersion oil and a coverslip, and examined for mites, eggs, and fecal pellets under a microscope (×20 or ×100) (Fig. 46-13). Samples can also be obtained from lesions using a needle or a curette.

Biopsy of atypical lesions may be helpful to identify mites or their eggs. However, it is important to remember that the typical adult case has only 12 live mites, so biopsies are only likely to be helpful if they are of the inflamed lesions. In general, punch biopsies are used, but an epidermal shave biopsy may be simpler and can often be carried out without local anesthetic on even a relatively uncooperative patient.⁶¹



FIGURE 46-12. Intradermal burrow of scabies demonstrated by coating the skin with ink, then wiping away surface ink, leaving the intradermal burrow filled with ink.

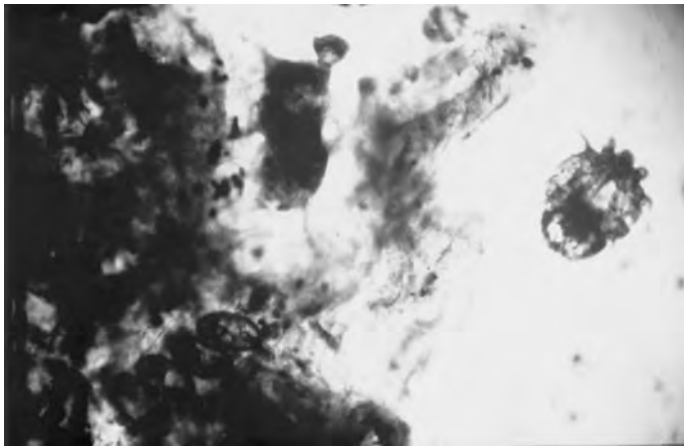


FIGURE 46-13. Skin scrapings of unexcoriated papules fortuitously disclose adults, larva, eggs, and fecal pellets, any of which would be diagnostic.

■ THERAPY

Regimens for the treatment of scabies are presented in [Table 46-2](#). Although not studied in randomized controlled trials, treatment of all close contacts and housemates of persons with scabies and washing bedding, towels, and clothing in warm to hot water are generally recommended. Items that cannot be washed should be isolated from use for 3 days. Since 1996, five randomized, controlled clinical trials of scabies treatment have been reported in the English-language literature.^{62–65} Usha et al.²⁶ performed an important study addressing the relative efficacy of topical permethrin and oral ivermectin. They found that a single topical dose of permethrin produced a clinical cure rate for scabies (97.8%) that was superior to that produced by a single dose of ivermectin (70%). However, two doses of ivermectin administered at a 2-week interval were as effective as a single dose of topical permethrin.

In a comparison of topical lindane and oral ivermectin, 53 patients were enrolled in the study and were randomized to follow a blinded treatment regimen.²⁷ Only 43 patients completed the study, and final results were determined by as-treated analysis. This study suggested treatment equivalency between these medications after administration of two courses of therapy separated by 2 weeks. On clinical evaluation, the rate of cure of signs and symptoms of scabies was 95% for ivermectin and 96% for lindane. This study was limited by low statistical power. Madan et al.⁶² compared ivermectin (200 mg/kg as a single dose) with 1% lindane lotion, with 180% of patients who were given ivermectin demonstrating a marked clinical improvement at 4 weeks of therapy, compared with 44% of patients given lindane lotion. Their study suggests that ivermectin may be a better treatment choice than lindane because of the good clinical response, lower toxicity, and improved adherence associated with ivermectin. A study conducted in Vanuatu compared benzyl benzoate with a single dose of oral ivermectin (200 mg/kg).⁶⁶ There was no

Table 46-2. Treatment of Scabies with 5% Permethrin Cream

- Massage cream in the skin from head to feet (30 gm is sufficient for an adult).
- Remove cream by washing after 12 hours.^a Family and sexual partners should be treated simultaneously.
- Patients may experience burning of the skin and increased itching after application. In addition, patients should be warned that itching may persist for days or weeks after successful treatment.

^aOrkin M and Maibach HI, *Semin Dermatol* 12: 22, 1993.

statistically significant difference between the findings in the two arms in the study. The reported cure rate was low, with a cure rate slightly better than 50% noted 3 weeks after treatment initiation. The study was limited by a 27% rate of failure to return for follow-up by the single dose of ivermectin administered and by the short-term follow-up. Several other clinical studies have been conducted. One retrospective comparative study analyzed the outcomes of 39 HIV-infected inpatients with 60 episodes of scabies treated with benzyl benzoate, ivermectin, or a combination of benzyl benzoate and ivermectin.⁶⁷ Benzyl benzoate achieved a cure in 9 (47.4%) of 19 patients; ivermectin, in 10 (62.5%) of 16 patients; and combination treatment, in 4 (100%) of 4 patients.

Of interest, a cure was not achieved for any of the four patients with crusted scabies who received either treatment alone. All the patients who received combination treatment had been given a diagnosis of crusted scabies, and, for all these patients, a cure was achieved using a combination of topical benzyl benzoate and oral ivermectin. This study provides some preliminary evidence for the use of combination treatment for severe scabies in HIV-infected patients. Several open-label studies of ivermectin for the treatment of patients with uncomplicated scabies have been published since 1996.^{68–71} The studies evaluated 1–2 doses of ivermectin (200 mg/kg separated by 7 days). In the largest study, which included 120 patients, the clinical response rate, as determined by as-treated analysis, was 88% after administration of 1 dose of ivermectin. After 4 weeks and administration of 2 doses of ivermectin, the cure rate increased to 100%.⁶⁸ There have been reports of several other open-label studies that involved smaller patient cohorts treated with ivermectin (200 mg/kg) given in 1–2 doses, with cure rates of 76–100% noted.^{66,67,69} These studies included few cases of crusted scabies. In a cohort study, 20 patients with crusted scabies were treated with 1–3 doses of ivermectin (200 mg/kg) combined with a topical scabicide and a keratolytic agent. Eight of

20 patients had an initial complete response, and 8 of 10 patients had a response to three doses of ivermectin.⁷²

Finally, in a study of 10 patients with uncomplicated scabies, a complete response was seen in all 10 patients after receipt of 3–4 treatments with topical 1.8% ivermectin cream.⁷³ In vitro testing of six different scabicides (neem, permethrin, benzyl benzoate, ivermectin, lindane, and tea tree oil) showed that all reduced mite survival, with the exception of neem.⁷⁴ However, of the five treatments that reduced mite survival, the duration of survival was found to be longest with permethrin exposure.

A clear challenge facing scabies treatment in the future is the optimal management of populations with high rates of endemic scabies. In one recent study, community-wide permethrin treatment was followed by treatment of patients with newly diagnosed scabies at all follow-up visits.⁷⁵ At 25 months of follow-up, the prevalence of scabies had decreased from ~28% to 7% ($P = 0.002$). In Papua New Guinea, inhabitants of two villages were evaluated for filariasis and scabies.⁷⁶ The inhabitants of one village were selected to receive ivermectin (400 mg/kg) as a single dose. The inhabitants of the treated village experienced a decrease in the prevalence of scabies (from 87% to 26%) at 5 months of follow-up. These studies suggest a role for community-wide treatment in controlling disease in communities where scabies is endemic; however, additional studies will be needed to clarify the long-term influence of these treatments and their economic feasibility.

Scabies epidemics in long-term care facilities were the focus of several additional cohort studies that demonstrated good control of the epidemic with the use of 1–2 doses of ivermectin.^{77,78} One of these studies reported that ivermectin treatment was successful after treatment with several different topical scabicides failed.⁷⁶

■ TREATMENT TOXICITY

Topical agents have been the most extensively used type of scabies treatment, and, therefore, their toxicity profiles are fairly well defined. Both permethrin and benzyl benzoate have been reported to cause rash and diarrhea.⁷⁹ More worrisome are the reports of convulsions and aplastic anemia occurring in association with benzyl benzoate and lindane.^{80,81} According to the World Health Organization (WHO) 1998 Collaborating Centre for International Drug Monitoring, convulsions have been associated with the use of benzyl benzoate, crotamiton, lindane, malathion, and permethrin. Deaths were reported to occur in association with crotamiton, lindane, and permethrin treatment.⁷⁹ In 2003, the U.S. Food and Drug Administration issued a health advisory that lindane should be used only as an alternative therapy if other treatments are not tolerated or if other approved therapies have failed. It is thought that warm baths and extensive

dermatitis may increase systemic absorption of lindane. Lindane is not recommended for pregnant or lactating women, for children 2 years of age, or for patients with extensive dermatitis. Given the warnings and concerns about toxicities, lindane is not recommended as a first-line or alternative therapy for scabies. The use of lindane would best be reserved for patients for whom the inability to tolerate other therapies leaves this as a last option.

In a randomized controlled trial of lindane versus ivermectin treatment, all reported adverse effects were mild and transient.²⁷ Patients treated with lindane more frequently complained of headache, but some patients treated with ivermectin noted abdominal pain and vomiting. One patient developed transient hypotension. Ivermectin has been well tolerated in all but one study. This study described an outbreak of scabies in a long-term care facility for elderly individuals; in the study, patients received multiple applications of topical scabicides before finally receiving treatment with a single dose of ivermectin.⁸² Over the following 6 months, there was an increased incidence of death among these 47 patients, compared with age- and sexmatched control subjects. These patients experienced lethargy and anorexia before death. Other investigators argue with the outcomes of the study, pointing out that patients were not matched for comorbidities, such as severity of dementia.⁸³ No other studies have demonstrated increased mortality occurring in association with a history of ivermectin therapy. In another study, involving ~220 patients in a psychogeriatric nursing home who were treated with ivermectin for a scabies outbreak, the mortality rate in the 6 months after treatment was compared with that occurring in the 30 months before treatment; no significant difference was found.⁷⁶ Of note, a rash and a transient increase in pruritus have been reported in the first 3 days after scabietic patients receive ivermectin.⁶⁷

■ PERSISTENT SYMPTOMS

All patients should be informed that the rash and pruritus associated with scabies may persist for up to 2 weeks after treatment.⁶⁵ When symptoms and signs persist for 12 weeks, there are several possible explanations, including treatment resistance, treatment failure, reinfection from family members or fomites, drug allergy, or worsening rash due to cross-reactivity with antigens from other household mites.^{84,85}

Poor response and presumed resistance to lindane have been reported elsewhere.^{78,86–90} Treatment failure not related to resistance can be due to faulty application of topical scabicides. Patients with crusted scabies may have poor penetration of scabicides into thick scaly skin and may harbor mites in these difficult-to-penetrate layers. Particular attention must be given to the hyperkeratotic fingernails of such infested patients. Certainly, to avoid reinfection, it is recommended that all close contacts of patients with scabies be empirically

treated. All linens, bedding, and clothing should be washed, if possible, during the time of application of the topical scabicide. Even when treatment is successful and reinfection is avoided, symptoms may worsen secondary to allergic dermatitis. This complication has been seen with several of the topical scabicides.

Finally, ordinary household mites may drive persistent symptoms resulting from cross-reactivity between antigens. In a study of 25 patients, scabietic patients had higher skin-prick test results and higher levels of IgE to house dust mite and storage mite antigen than did control subjects.⁸³

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PART 8

Overview of STD Care Management

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Caroline A. Ryan, Mary Kamb, and King K. Holmes

Medicine is a science of uncertainty and an art of probability.

Sir William Osler

INTRODUCTION

Rapid advances in biomedical knowledge and technology provide clinicians with a continuously expanding armamentarium of potential diagnostic and therapeutic options. In addition, an increasing number of rigorous biomedical and behavioral research studies—particularly in the form of randomized controlled prevention trials—are providing efficacy data on preventive interventions in specific settings.^{1–7} Unfortunately, randomized trials have not been set up to grapple with all the specific questions needed to pragmatically translate research findings into practice for local programs or individual practitioners. Outside of effective use of vaccines,^{8–10} positive trial results have not always been replicable in other settings.¹¹ For example, enhanced syndromic STI care management appeared to be fairly effective in reducing HIV as well as curable STIs in paired rural communities with high prevalence of curable STIs and low and rising HIV incidence.¹ However, a subsequent trial of mass treatment for STIs in another rural community setting reduced the prevalence of vaginal trichomoniasis in the general population but did not prevent new HIV infections.⁵ Furthermore, a second trial of syndromic STI care management plus enhanced education conducted in a nearby rural setting was effective in reducing new gonorrhea and syphilis infections but did not prevent HIV infection.⁶ Reanalyses of data from these three studies using mathematical models suggested that lower prevalence of STIs and fewer sexual-risk behaviors during the latter two studies may have partly explained the failure of the STI interventions in these two studies to prevent HIV infection.¹² Additionally, the phase of the HIV epidemic and population dynamics affecting STI and HIV transmission may have been important (most HIV transmission in the negative trials occurred within established partnerships). Although the studies of STD syndromic management have helped foster consensus that STI care management can reduce curable STIs in a community, the varying results in terms of HIV prevention

have led to considerable discussion about the best ways, and even the need to approach STI control for HIV prevention. Although a 2006 WHO consultation group¹³ concluded that STI interventions remain important for HIV prevention—especially in concentrated HIV epidemics and among population subgroups with high STI prevalence and high rates of partner change—important questions are still unanswered. Will syndromic STI management programs prevent HIV infections in communities with longer-standing, higher-prevalence HIV epidemics? What about settings with lower population prevalence of curable genital ulcer disease or inflammatory STDs?

Ambiguity about benefit outside research settings also exists for other STI prevention interventions. For example, brief, client-centered counseling approaches have been found to reduce new STIs in primarily young, heterosexual STD clinic patients in the United States. However, these results have not been widely replicated, and insufficient information is available on whether these counseling approaches are effective for other populations (e.g., homosexual men with multiple risks, injection drug users, or heterosexual men and women in developing world settings).^{14,15} Recently, results from three separate randomized trials found that adult male circumcision reduced new HIV infections substantially in heterosexual men in Africa.^{7,16,17} Even with such consistency of results, experts worry that these trials cannot answer whether beneficial results will translate equally to other settings where circumcision rates are higher or where heterosexual transmission is less common, or address whether subsequent behavioral disinhibition (risk compensation) in newly circumcised men may lead to riskier behaviors and thus attenuate or reverse any benefits.^{18,19} It is increasingly clear that although rigorously conducted experimental studies help answer some important questions, they often introduce new ones.

Despite this ambiguity about what may be effective for HIV prevention at the population level, or STI control in the community, the public is concerned about efficacy of STI care management at the individual level and expects diagnostic certainty and effective medical care. Clinicians in developed countries themselves grow increasingly dependent on advanced

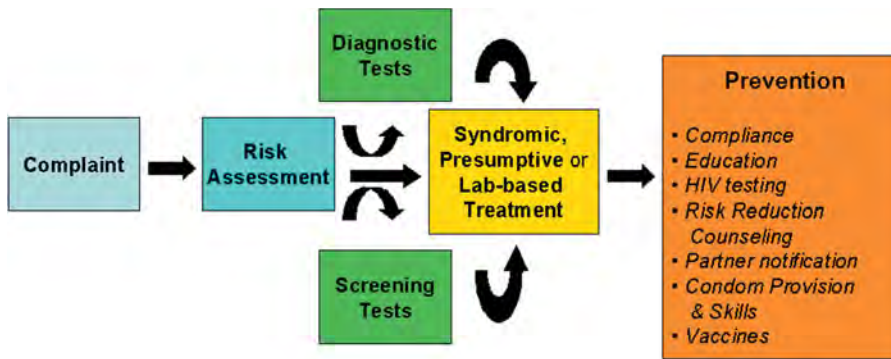


FIGURE 47-1. Essential components of STI care management.

technology in diagnostic and therapeutic decision making. As resources for clinical care management become more constrained even in the best of circumstances, and new epidemiologic models call for greater outreach to resource-poor settings to achieve STI control, clinicians need guidance.²⁰ Clinicians are increasingly asked to do more with fewer resources and forced to practice under conditions of great uncertainty. The desire to help and not harm prompts several questions: What is the true diagnosis? Which laboratory tests will help? What treatment will alleviate symptoms and cure infection? What evidence warrants treatment of sex partners? And increasingly, which preventive interventions work and should be promoted?

The most appropriate answers to these questions depend on a number of factors: the clinical setting, the probability of various infections, the resources available, the expectations of patients, cultural constraints, the overarching programmatic goals of the clinical service (e.g., primary patient care, public health STD clinic, family planning, or prenatal clinic), and the available evidence. Even in developed countries, continuing crises in health-care financing have made clinicians all too aware of the economic implications of their decision making. Diagnostic evaluation and disease treatment concern not only health benefits but also economic costs.^{21–24} A society lacking infinite resources to spend on health care can no longer focus only on the percentage of infections a new screening or treatment program detects, cures, or prevents; we now must examine the balance between costs and proven benefits. But unfortunately, even health economic evaluations are unable to answer all our questions. Many of the proven-effective interventions have been shown to be highly cost effective and even cost savings in their research settings,^{25–28} but whether cost–benefit data from rigorous research settings can be generalized to the “real world” is also unknown.²⁹ Further, relatively few “decision-tree” cost–benefit analyses have gone beyond the benefits received by the individual patient to examine in dynamic models the population-level benefits.^{30,31}

In this section of the book, Chapters 48–54, as well as Chapter 69, deal with risk assessment and patient-centered counseling, the importance of a nonjudgmental, patient-friendly approach to providing care for STIs, including HIV infection in detail. This chapter provides an overview of STI clinical management, examining the various approaches

that are commonly used in the diagnosis and treatment of STIs in a variety of clinical settings, and focusing on strategies clinicians can use to increase their effectiveness. We think (with due respect to William Osler) that medicine is a science of probability and an art of managing uncertainty.

DEFINITION AND GOALS OF STD CARE MANAGEMENT

STI care management requires managing asymptomatic as well as symptomatic individuals. The major steps in effective STI care management include risk assessment and clinical evaluation; identification of persons with STIs (whether symptomatic or asymptomatic) who are unlikely to seek diagnostic and treatment services; appropriate diagnosis and treatment of infected persons; prevention education, counseling, and other strategies around avoiding reinfection and new infections; and effective evaluation, treatment, and counseling of sex partners of STI-infected persons. Additionally, in most parts of the world, HIV infection is also linked to sexual behaviors, and an STI clinical encounter is an opportunity to encourage HIV testing and counseling. Furthermore, pre-exposure vaccination of persons at risk of vaccine-preventable STIs is likely to play an increasing role in STI clinical management²⁹ (Fig. 47-1).

Several factors external to the clinical setting affect STI management. For example, the most effective programs will be driven by prevalence of specific pathogens or STI sequelae and will be responsive to the factors driving infection in the community. Additionally, the presence of a clearly defined national plan, coupled with practical guidelines and supportive laws and policies, will ensure more effective programs. Another systems-level factor critical to STI management is availability of effective drugs, made increasingly important with emerging antimicrobial resistance. Factors affecting access, acceptability, and cost of the clinical services also affect how they are used by the clients to whom the STI services are targeted.^{32,33}

There are several goals of STI care management; the most obvious are to cure or ameliorate the infection and prevent complications and sequelae of the infection (including complications related to pregnancy or family planning). Additional goals are to prevent transmission of the infection

to others, reduce risk for HIV transmission and acquisition, provide counseling on avoiding future infections and (if necessary) on coping with chronic STI, and provide outreach for care management to exposed sex partners or unborn children. In general, the earlier the diagnosis, treatment, and counseling, the greater the impact on preventing further transmission of STIs and their complications.^{1,34}

POTENTIAL STEPS REQUIRED TO TREAT AND PREVENT STIs

Clinic-based STI care management has been, and remains, a cornerstone for STI control and prevention. However, the limitations to clinical care are graphically illustrated in Fig. 47-2 by the Piot–Fransen model for sexually transmitted management that was developed using data collected from rural women in several African nations. Improving clinical care does not address the issue of subclinical (i.e., asymptomatic) STIs, or problems of poor access to services or treatment-seeking behavior by individuals with STI symptoms. Fig. 47-3 shows (1) the potential effects of (1) well-conducted clinic-based STI care management, which requires symptomatic persons seek and obtain appropriate diagnosis, treatment, and preventive services; (2) the potential additional benefits of targeted and other community-based programs that are able to identify and effectively treat most symptomatic STIs in the community; and (3) the additional benefit of screening asymptomatic persons.^{35–37} In the future, provision of preven-

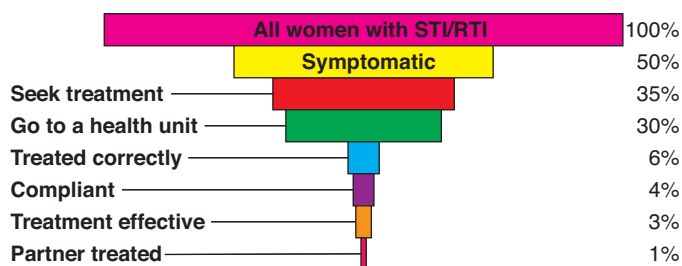


FIGURE 47-2. The Piot–Fransen model of STI prevalence and effects of STI care management.

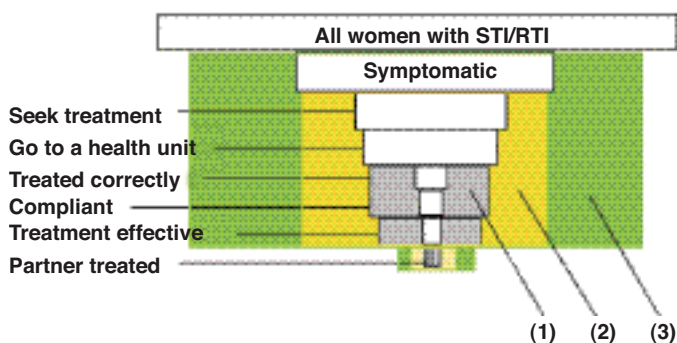


FIGURE 47-3. Piot–Fransen model: Potential effects of additional STI control/prevention strategies in concert with STI care management.

tive vaccinations may go even further, addressing individuals at risk of specific STIs before they are exposed to infection.

It is important that clinicians recognize that when STI care management is focused only on diagnosis and treatment of patients seeking care for STI symptoms, this may have only modest benefits for the population as a whole. The Piot–Fransen model illustrates the importance of additional STI control measures such as partner notification; education of patients and communities on STI symptom recognition, ensuring access to care for those who need it; and screening for subclinical infection³⁶—all too often overlooked or beyond the control of busy clinicians.

A COMPREHENSIVE APPROACH TO STI CARE MANAGEMENT

“From inability to let alone; from too much zeal for the new and contempt for what is old; from putting knowledge before wisdom, and science before art and cleverness before common sense; from treating patients as cases; and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us.”

—Sir Robert Hutchinson

A comprehensive approach to STI care management combines essential services into a practical delivery package. Such an approach begins with a basic knowledge of community disease prevalence and includes an individualized risk assessment (of sexual behaviors, specific exposures, and sociodemographic and other markers of high risk), a history of reproductive health and past STIs, and a clinical assessment (elicitation of specific symptoms and detection of signs of STIs) (Fig. 47-1). Depending on available resources for testing, the results of these assessments may lead to confirmatory diagnostic tests (for symptomatic patients) or screening tests (for asymptomatic individuals judged to be at sufficiently high risk to warrant testing). In some situations, routine screening for specific STIs is recommended. For example, syphilis screening to prevent congenital syphilis is routinely recommended for pregnant women in most of the world, as is routine “opt-out” antenatal HIV screening (especially in communities with generalized HIV epidemics).^{38,39} For other situations or syndromes, rapid tests may be used to narrow the spectrum of initial therapy (e.g., wet mount for women with vaginal discharge, Gram stain for men with urethral discharge and women with cervical mucopus, and darkfield examination and rapid serologic test for syphilis for genital ulcer disease).⁴⁰

STI care management concludes with a series of prevention approaches to reduce the risk of reinfection and help the patient prevent new infections, sometimes referred to as “the six Cs.” These include information about curative (or in the case of herpes, palliative) therapies along with assurance of compliance with medication instructions (“compliance”);

sex partner (“contact”) notification and (if appropriate) treatment; sufficient information and advice about STIs and how they are transmitted, in order to reduce new infections (“counseling”); and provision of condoms along with information on how to use them (“condoms”). A fifth “C” that is sometimes overlooked, but is an integral part of good STI management, is assurance of confidentiality.³³ A sixth “C” that is consistent with provision of integrated primary health-care services is contraception, if appropriate. Two additional prevention strategies that are important parts of comprehensive STI care management are routine provision of voluntary HIV counseling and testing and, if appropriate, prophylactic STI vaccinations.^{32,33} Although this approach specifically applies to care management for STIs, essentially the same steps apply to care management of most if not all infectious diseases—with the preventive steps represented by these approaches differing for different diseases.

In most settings, in both developed and developing countries, treatment of patients with symptoms highly suggestive of an STI is often started on a syndromic presumptive basis (i.e., treatment is selected to cover the most likely causes of the symptoms and signs); in developed countries, treatment often begins while results of confirmatory laboratory tests are pending.

COMMUNITY DISEASE PREVALENCE

In some communities, STI prevalence in the general population is high while, in other communities STIs are largely confined to specific population groups.³² Some wealthier countries have almost eliminated certain bacterial STIs such as chancroid, LGV, and syphilis, while these same STIs are still common in many developing world settings. However, as is the case with all infectious diseases, STI rates are dependent on a number of factors such as changing demographics, stage of the HIV epidemic, social and economic structure, population mobility, and existing STI control measures.⁴¹ STI prevalence rates in a community can change rapidly.⁴¹ In addition, an increasing number of communities are finding that certain STI pathogens such as *N. gonorrhoeae* are no longer susceptible to commonly used antibiotic therapies.⁴² An understanding of community STI and HIV trends, including antimicrobial resistance patterns, is important to providing effective STI care management.⁴³

RISK ASSESSMENT AND CLINICAL EVALUATION

Patients may consult a clinician with a set of symptoms (manifestations of the disease perceived by the patient and either volunteered or brought forth during the history taking) and signs (manifestations of the disease identified during the physical examination). Other individuals with STIs may lack symptoms or fail to perceive symptoms that occur, or may

perceive symptoms of infection but feel that they are too trivial or too embarrassing to prompt them to seek care or to tell the clinician.^{40,44,45} Routine risk assessment can serve as a guide to selective clinical evaluation and selective laboratory testing for STIs in patients who do not report typical symptoms and can also aid in the interpretation of any symptoms or signs that are presented.^{46–51} Thus, clinical evaluation and risk assessment for STIs actually proceed concurrently: Positive risk assessment prompts and guides the clinical evaluation for STIs, and conversely, clinical findings compatible with STIs should prompt risk assessment, since a positive risk assessment increases the probability that suspicious findings actually represent an infection. Chapter 48 reviews risk assessment for STI/HIV, and Chapters 49 and 50 describe the approach to the physical examination of the male and female genitalia as part of the clinical evaluation for STIs.

As discussed earlier, clinicians will best understand which patients need specific clinical evaluation and testing for STIs, and education and prevention counseling services and so forth, when they understand the risk factors driving the spread of infection(s) in their community and ask about those factors. Adolescents in particular may be willing to discuss their sexual behaviors and concerns but will often not bring up the subject unless asked.^{52,53} A U.S. national survey showed that primary care physicians assessed sexual behavior for less than one-half of their patients,⁵⁴ and another survey of U.S. adults who had a routine medical checkup during the previous year found that only 28% were asked about STIs during their evaluation.⁵⁵ Examples of risk assessment tools are available (see Chapter 48).^{33,56} Communities will benefit from collaboration between clinical and health education staff of STI, HIV, and family planning programs, and other community-based organizations to promote sharing or adaptation of existing materials that support counseling of high-risk patients on recognizing and reducing risk. Clinical and public health systems should collaborate to provide clinicians with a comprehensive list of agencies available within the community to refer patients as needed for services that are identified during the risk assessment and examination.

LABORATORY TESTING

Chapters 52, 70, and 104 present different aspects of STI/HIV laboratory testing. Testing of symptomatic patients (diagnostic testing) to establish the microbial etiology of STI-related symptoms is distinguished from testing of asymptomatic individuals who are brought to care as contacts of an infected person or are seeking care for reasons other than symptoms or signs of STDs (case-finding tests), and from testing of individuals identified through outreach to populations outside the clinic (asymptomatic screening). In this chapter, the term “screening” encompasses both case-finding and asymptomatic screening, as defined in the preceding text. As

potential cost benefits of screening (or of any intervention) are directly related to disease prevalence, risk assessment guides selective, cost-effective allocation of resources for each of these types of laboratory testing.^{22,44,48,49} Screening of asymptomatic individuals is most justifiable when disease sequelae are severe. For example, syphilis screening is routinely recommended for pregnant women because of the potential for fetal loss or neonatal morbidity and mortality associated with untreated maternal infections.³² Similarly, cervical screening using Papanicolaou (Pap) smears or, where resources are limited, other techniques such as direct visual inspection of the cervix are a means of detecting precursor lesions of cervical cancer, which is the second leading cause of cancer mortality among women globally and the leading cancer cause among women in many developing nations.³² Because of the association between chlamydial infection and infertility, annual screening for *C. trachomatis* is currently recommended in the United States for all sexually active women 24 years of age or younger.³³ Besides cost, screening asymptomatic individuals is more acceptable to patients and providers when screening tests are simple and noninvasive, which is increasingly the case with STI laboratory testing.

Laboratory testing for specific potentially causative infectious agents can provide the strongest evidence for infection and justification for treatment, and for preventive interventions such as partner treatment. For *N. gonorrhoeae* and *H. ducreyi*, and to some extent for viral pathogens, isolation of the pathogen also permits testing for sensitivity or resistance to antimicrobial agents. Increasingly, for some pathogens, HIV resistance to antiviral or other antimicrobial agents can be identified by detecting resistance mutations even without isolation of the pathogen. For syphilis, quantitative reagin antibody tests allow monitoring the response to therapy.⁵⁷ For cervicovaginal HPV infection, identification of oncogenic HPV types is a potential guide to prognosis and for further diagnostic and therapeutic interventions (see Chapters 28, 57, and 58). Similarly, typing of genital HSV helps predict the likelihood of recurrence.^{58–60} In addition, positive laboratory tests provide the most specific evidence of infection for surveillance purposes.

However, many laboratory tests obviously are not available at all clinic sites, and even when tests are available, test results are often not available soon enough to guide therapy or partner management decisions during the initial patient visit. Further disadvantages of some laboratory tests include high cost and variable test performance. When intrinsic test characteristics or inadequate laboratory quality assurance lead to less than 100% sensitivity, or when patients do not reliably return for test results and treatment, then treatment of symptomatic patients, based only on positive test results rather than on syndromic diagnosis (see below), can lead to undertreatment. Similarly, mathematical modeling suggests that the required sensitivity of a point-of-care test, in terms of STI transmissions averted, can be quite low,

relative to a gold standard test if there is substantial transmission during the delay in treatment while waiting for results of the gold standard test, or many persons do not return for treatment, or both.^{61,62} Likewise, low specificity of a test can lead to overdiagnosis of STI and attendant unwarranted problems with partners (e.g., conflict, perhaps leading to violence), stigmatization for the patient, drug reactions, and drug resistance. The diagnostic tests with best performance characteristics currently available for the more important STIs often cannot be used where the test is too expensive or limited in availability.^{60,32} Specimen collection procedures, such as pelvic examination for cervical samples, urethral swabbing, or venopuncture for obtaining blood, may also discourage patients from seeking testing or providers from performing the test.⁶³ Increasingly, less invasive sampling techniques, such as self-collected vulvovaginal swabs or urine for DNA amplification tests or saliva collection for detection of antibody, help to overcome these problems. Nonetheless, clinical, epidemiologic, technical, and especially resource considerations dictate the extent to which laboratory tests are useful in STI care management.

Even when resources do permit rapid laboratory tests on specimens collected noninvasively, an additional practical concern is that rapid tests used to guide initial therapy of symptomatic patients often must be performed in an office or clinic without nearby laboratory support. This requires the clinician or office staff to perform the tests needed to guide treatment of acute disease syndromes. For example, an office- or clinic-based laboratory analysis of a vaginal specimen is often used to guide management of vaginal infections. A microscopic examination allows recognition of fungal hyphae indicative of vulvovaginal candidiasis, “clue cells” suggestive of bacterial vaginosis, and motile trichomonads indicative of trichomoniasis.⁶⁴ Since 1988, in the United States, these microscopic tests for vaginal infection have been classified as “physician-performed microscopy” tests under the U.S. Clinical Laboratory Improvement Amendment, placing a diagnostic burden on U.S. clinicians in small offices choosing to maintain a laboratory.⁶⁵ Primary care clinicians have demonstrated high specificity but low sensitivity when identifying vaginal trichomoniasis and vulvovaginal candidiasis by microscopic techniques.⁶⁶ Correct microscopic diagnosis of bacterial vaginosis was even more difficult for clinicians. Not surprisingly, clinicians were less accurate than DNA oligonucleotide probe tests in diagnosing vaginal infections.⁶⁶ Thus, in general, a need remains for more reliable, but inexpensive, and rapid clinic-based tests for the acute symptomatic STIs to guide prompt therapy.

Since the early 1990s, a number of new initiatives have promoted diagnostic test development for STI control, particularly for use in the developing world.^{67,68} Perhaps the most notable of these is the STI Diagnostics Initiative (SDI) located in the UNICEF/United Nations Development Programme/World Bank/WHO Special Programme for

Research and Training in Tropical Diseases (TDR). Lack of a substantial array of appealing tests had been the most pressing issue in the past. A 2001 inventory carried out by the SDI identified more than 40 rapid tests for syphilis, *C. trachomatis* and *N. gonorrhoeae* on the market, but found that few had had performance evaluations adequate to meet the needs of clinicians or STI control programs in low-income settings.⁶⁸ Since that time, progress in science and technology and funding from major international donors have stimulated rapid test development. A joint consultation held in 2001 by the SDI and Wellcome Trust concluded that rapid point-of-care tests for *N. gonorrhoeae* and *C. trachomatis* remained the highest priority to reduce overtreatment among women presenting with vaginal discharge.⁶⁸ The consultation also noted an urgent need for a rapid point-of-care test for syphilis, to aid in screening antenatal women at risk of congenital syphilis. The SDI has focused on evaluating existing and new tests as they emerge, with researchers noting that their biggest current challenge is ensuring that adequate-quality, rapid tests are accessible to the developing country populations that need them most.⁶⁸

APPROACHES TO STI DIAGNOSIS AND TREATMENT

Health-care providers have generally used either laboratory tests or clinical findings to establish or infer the likely etiology of symptoms and signs of STIs. Previously, treatment guidelines focused on treatment of specific, laboratory-defined STIs, albeit sometimes with guidelines for management of a few syndromes as well (e.g., NGU, pelvic inflammatory disease [PID], and epididymitis). However, in resource-poor settings, where laboratory tests are not available, the low validity of clinical impression alone for inferring a specific microbial etiology of specific STI syndromes has led to emphasis on guidelines for syndromic management of STIs using antimicrobial regimens likely to have activity against all of the major causes of particular syndromes.

■ LABORATORY-BASED ETIOLOGIC DIAGNOSIS

Sometimes referred to as “test-based management,” this approach involves identifying the organism causing symptoms using microscopy or other laboratory tests, and using test results to support antimicrobial treatment choices. Even when testing is available, treatment is often initiated on the basis of syndromic diagnosis while test results are pending. In practice, rapid testing (if available) can guide initial choice of therapy. Laboratory test results can also strengthen the case for partner evaluation and/or treatment; however, testing is not essential to prompt partner services when certain STI syndromes (e.g., for urethral discharge or genital ulcer) are sufficiently specific. The potential for sequelae with most STI, together with problems of increasing antimicrobial resistance, risk of coinfections, and the limitations of test performance all generally warrant patient

follow-up and the assessment of clinical response, regardless of initial testing and choice of antimicrobials.

■ PRESUMPTIVE ETIOLOGIC DIAGNOSIS BASED ON CLINICAL FINDINGS

This approach, also referred to as “therapeutic trial,” involves making a best guess as to the microbial etiology of symptoms and signs, and providing antimicrobial treatment based on clinical experience without the aid of laboratory tests. This approach is often used in developing countries as an alternative to nonavailable, unreliable, or unaffordable diagnostic tests, in an effort to infer the etiology of symptoms and signs, and in developed countries while awaiting results of laboratory tests. Typically, initial therapy is chosen to cover the most likely diagnosis, or the condition most likely to progress rapidly to serious illness if not treated, or to use the least expensive antimicrobial—all in hopes of avoiding or deferring use of expensive tests or antimicrobials.

A drawback of presumptive etiologic diagnosis is that even experienced STI service providers are often unable to accurately infer the microbial etiology of STI syndromes, based on symptoms and signs. For example, studies from a number of settings, including Africa, the United States, and Jamaica, have consistently demonstrated the inaccuracy of clinical impressions as to the microbial etiology of genital ulceration.^{69–76} In a South African study of 100 men and 100 women with genital ulcers, clinicians correctly identified only about one-third of the cases of chancroid or syphilis in the men, about one-half of the cases in the women, and less than 10% of mixed infections.⁷³ Reasons cited for this low accuracy of clinical diagnosis include (1) similarities in clinical appearance of various types of infection, (2) simultaneous infections with more than one organism, and (3) atypical appearance owing to long-standing disease, prior self-treatment with ineffective therapy, or concomitant HIV infection.^{69–77} Not infrequently, a presumptive etiologic diagnosis approach to STI care management can lead to a series of therapeutic trials with different antimicrobial regimens until definitive testing is performed; this can be costly for patients. Therapeutic trials of less expensive but suboptimal antimicrobials should be discouraged, as this approach can lead to inadequate treatment, and thus chronic sequelae, as well as promote antimicrobial resistance.

■ SYNDROMIC DIAGNOSIS

In resource-poor settings, the most practical approach often is syndromic diagnosis and treatment, or “syndromic management,” ideally with a risk assessment. For treatment of genital ulcers and urethral discharge, this approach has been demonstrated to be cost effective and feasible for health settings with limited resources and laboratory capacity, as it is less technically demanding than laboratory-based or presumptive diagnosis of microbial etiology based on clinical

findings.^{78,79} The WHO has encouraged use of syndromic case management since 1990⁷⁸ and has developed a series of flow charts or clinical algorithms for the standardized management of STIs, recommending that national STD control programs in developing countries incorporate diagnostic and therapeutic flowcharts in their STI management guidelines and adapt them for local conditions.^{78,79}

The basis of the syndromic approach is the identification of a syndrome, that is, a set of easily elicited symptoms and easily recognized signs associated with a limited number of well-defined microbial etiologies. The advantages of syndromic management include expedited care, with treatment at the first visit and thus less opportunity for patients to be lost to treatment if they do not return for test results or comply with referrals; cost savings by not using expensive laboratory tests; and increased patient compliance and satisfaction.^{78,80} The use of flowcharts in STI management also standardizes diagnosis, treatment, referral, and reporting, thus allowing for improved surveillance and program management.

Significant limitations of the syndromic approach include lack of utility for asymptomatic people with STIs, particularly for asymptomatic women with cervical infections. In addition to low sensitivity, the relatively low specificity of the syndromic approach relative to laboratory testing for some infections (especially for cervical infections) leads to many false-positive diagnoses, and thus to unnecessary use of drugs and to potential social problems attending a false-positive diagnosis.⁸⁰ Further, the quandary remains about when to attempt treatment of sex partners of individuals treated on the basis of syndromic diagnosis alone. In clinical settings where acquisition of infection by the patient from a steady sex partner is probable—for example, among women in family planning clinic settings—reinfection of the patient would be very likely without treatment of the steady partner. However, in the absence of specific confirmatory laboratory diagnosis, sex partners may not be offered treatment. The thinking too often appears to be that the treatment should work, and, in the absence of a specific diagnosis, partner treatment may be too challenging to directly address.

In resource-poor nations, promotion of syndromic case management since 1990 has likely contributed to substantial declines in incidence and prevalence of certain bacterial STIs, particularly chancroid, syphilis, and gonorrhea^{32,81} (see Chapter 5). Chancroid was considered the most common cause of genital ulcer syndrome seen by clinicians in 1993, but had become a rare disease in many countries by 2002; syphilis has also rapidly declined as a cause of genital ulcers in many developing world settings.⁷⁷ Unfortunately, genital ulcer syndrome is not disappearing, as genital herpes has emerged as the most common cause of genital ulcers worldwide, particularly in settings with high HIV prevalence.^{13,32,43,82} For example, a study comparing 1993 and 2002 cross-sectional evaluations of genital ulcer etiology in Botswana

suggested some reduction in overall prevalence of genital ulcer syndrome over the period but demonstrated that, as the proportion of ulcer cases due to chancroid declined from 25% to 1%, the proportion due to herpes simplex virus rose from 23% to at least 58%.⁴³

Design of flowcharts for syndromic diagnosis

As described in Chapter 101 and in a compilation of articles on syndromic management of STDs, a clinical flowchart (also referred to as an “algorithm” or “decision tree”) depicts a path of diagnostic reasoning.^{80,83–94} The structure of a flowchart can be hierarchical or nonhierarchical.⁸³ In hierarchical algorithms, the presence of a single symptom is the limiting factor for entry, and one diagnosis excludes another. A nonhierarchical algorithm allows the consideration of several risk markers, signs, or symptoms at once and allows consideration of different diagnoses at the same time. To ensure efficient use for STI care management, WHO recommends that flowcharts be adapted to the level of development of the health-care system and the particular health-care facilities for which they are intended.⁷⁸ Culture-specific perceptions about STIs, patterns of health-seeking behavior, and expectations about health care, to a large extent, determine the usefulness of certain flowcharts.

Common STI syndromes

The major STI syndromes include genital ulcer disease, urethral discharge in men, intrascrotal pain and swelling, lower abdominal pain (LAP) in women, and abnormal vaginal discharge. A growing body of data provides information on how well the major syndromes and various adaptations of flowcharts or algorithms have performed in different clinical settings throughout the world.^{80,83–94}

Genital ulcer syndrome in men and women is most commonly attributable to chancroid, syphilis, or genital herpes, and less commonly to LGV or granuloma inguinale (donovanosis). A 2000 review of studies evaluating syndromic management found five reporting on adapted versions of the WHO algorithm for genital ulcer syndrome, demonstrating 72–100% cure rates for syphilis and chancroid regardless of facility type, but poorer performance for herpes.⁸⁰

Urethral discharge syndrome in men is often attributable to gonococcal or chlamydial infection, or to nongonococcal nonchlamydial urethritis. The latter has numerous other potential etiologies, including *Mycoplasma genitalium*, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, and HSV and probably some still undefined pathogens. The 2000 report reviewed five studies implementing algorithms for urethral discharge, four in primary care settings and one in an STD clinic. Sensitivity of syndromic diagnosis with respect to presence of gonorrhea or chlamydial infection (87–99%) or cure rate (92–99%) was high even without microscopy. but specificity of syndromic diagnosis with

respect to these two infections ranged widely (7–90%), indicating that treatment of patients without gonorrhea or chlamydia for urethritis was common.⁸⁰ Addition of a Gram stain improved specificity of syndromic diagnosis of urethritis with respect to these two infections in one study but not another, reflecting varying prevalence of gonorrhea and chlamydial infection. Note that the role of *M. genitalium*, *U. urealyticum*, *T. vaginalis*, and herpes simplex virus as other causes of urethritis means that a substantial proportion of cases of urethritis in men would not be expected to be attributed to gonorrhea or chlamydial infection (i.e., specificity of syndromic diagnosis with respect to these two infections would not be expected to be high). No doubt in the future, a more relevant use of the terms “positive predictive value” and “specificity” would not be in terms of gonorrhea and chlamydial infection alone, but rather in terms of the presence of any infection likely to respond to the antimicrobial regimen recommended for management of the syndrome.

The syndrome of *acute, unilateral intrascrotal pain and swelling* in heterosexually active men under the age of 35 years most commonly reflects acute epididymitis due to the sexually transmitted pathogens *N. gonorrhoeae* or *C. trachomatis*. In heterosexual men over 35 years of age, particularly those with underlying genitourinary disease, coliform bacteria or *Pseudomonas* are more likely etiologies. Similarly, coliforms are the likely cause of epididymitis in homosexual men who practice anal-insertive sex. WHO guidelines remain unchanged and recommend first exclusion of testicular torsion and trauma, and then treatment with antimicrobials that cover *N. gonorrhoeae* and *C. trachomatis*. In those who fail to respond to treatment, clinicians must consider alternative diagnoses, including testicular neoplasia or other chronic infections, such as tuberculosis and other chronic granulomatous diseases.

LAP syndrome in women has many potential causes, including PID caused by cervical pathogens (*N. gonorrhoeae*, *C. trachomatis*, perhaps *M. genitalium*) and by less pathogenic vaginal bacteria (including vaginal anaerobes) (see Chapters 42 and 56). In general, algorithms for LAP do not perform well in detecting cervical gonococcal or chlamydial infection in most clinical settings, in large part due to the insensitivity and the nonspecificity of the elicited symptom of LAP with respect to objective evidence of salpingitis or endometritis (unless coupled with signs of PID elicited by trained gynecologists).^{84,85,87}

The term *lower genital tract infection* (LGTI) syndrome in women, as discussed in Chapter 55, has had a broader connotation, including mucopurulent cervicitis; ectocervicitis; vaginal discharge that is abnormal in amount, color, or odor; as well as vulvar and urethral inflammation. This definition encompasses disparate cervical, vulvovaginal, and urinary tract infections with overlapping clinical manifestations. The term LGTI is not sufficiently specific to guide

treatment for cervical or vaginal infection but is still useful in calling attention to the need for further evaluation for such infections, and perhaps as an entry point to a flowchart that branches with different syndromes. Below, we consider two such syndromes.

Mucopurulent endocervicitis may be caused by gonorrhea or chlamydia infections, both are also associated with PID and infertility. It is also commonly associated with trichomoniasis and may be caused by other infections as well. Signs of yellow endocervical discharge, edema of the zone of cervical ectopy, and easily induced endocervical bleeding with or without symptoms of abnormally yellow vaginal discharge have been useful predictors of cervical infection in settings with high prevalence (prior probability) of gonococcal and chlamydial infection, particularly in women with positive risk assessment for these cervical infections.^{80,83–94} In such settings or patients, this syndrome remains potentially useful in supporting the diagnosis of PID and as a guide to syndromic management of cervical infection and/or to selective screening for cervical infection. However, in settings with low prevalence of gonococcal or chlamydial infection, mucopurulent cervicitis has a lower predictive value for such infections, remaining useful as a criterion for selective diagnostic testing but not necessarily for treatment of these infections. Note that, as with urethritis in men, mucopurulent cervicitis has also been associated with *M. genitalium* infection in multiple studies and that HSV and *T. vaginalis* also cause distinctive types of inflammation of the cervix (see Chapter 55). The addition of risk assessment to identify women with risk factors *plus* signs of mucopurulent cervicitis or PID has relatively lower sensitivity, but relatively higher specificity and positive predictive value for cervical infection, with gonococcal, chlamydial, and *M. genitalium* infection.^{83,84,95} Critical factors in development and use of such algorithms include development of locally defined, culturally acceptable risk assessment algorithms and the training, experience, and skill of the clinician in detecting manifestations of mucopurulent cervicitis or PID.^{80,84,85}

Vaginal discharge syndrome is usually caused by bacterial vaginosis or trichomoniasis. The symptom of increased amount of vaginal discharge per se has not proven very useful for diagnosis of cervical infection either with *N. gonorrhoeae* or with *C. trachomatis*, or of vulvovaginal candidiasis. In general, symptoms and signs of abnormal vaginal discharge have shown strong correlation with detection of bacterial vaginosis and trichomoniasis, and symptoms of vulvar pruritis and signs of vulvar inflammation have shown strong correlation with vulvovaginal candidiasis.^{80,83,85,87,96} The true utility of algorithms dealing with vulvovaginal symptoms in many clinical settings lies in the management of vaginal infections. This conclusion from several studies of syndromic management of vaginal discharge actually represents an important practical advance in women's health-care practice in developing countries, as

many women suffer substantial symptoms related to bacterial vaginosis, trichomoniasis, or vaginal yeast infection that can be relieved with simple treatment regimens.

Of the three major categories of abnormal vaginal discharge symptoms (abnormally increased amount, abnormal odor, or abnormally yellow color), only the last (abnormally yellow color) has been associated with cervical infection in most studies published to date, after adjusting for the presence or absence of trichomoniasis or bacterial vaginosis.^{77,84,97} In developing countries, classical hierarchical algorithms and risk score-based algorithms for “vaginal discharge” have been tested and compared in a few countries and mainly in family planning or antenatal clinic attendees or in female sex workers.^{80,84,87,88,90–94,98,99} Unfortunately, relatively few studies have been conducted in STD clinics or primary care or gynecology clinics that serve symptomatic women for whom the algorithms are intended.^{83,85–89,97} The 2000 review found that the success of various vaginal discharge algorithms for detecting endocervical gonococcal or chlamydial infection in women ranged from 29% among low-risk women attending antenatal clinics to as high as 93% in symptomatic women attending primary care clinics, but generally demonstrating the futility of using the vaginal discharge algorithms as screening tools for cervical gonococcal or chlamydial infection in most settings.⁸⁰ The addition of speculum evaluation was useful in some studies but not in others; however, the use of risk scores (as noted above for mucopurulent cervicitis) tended to improve sensitivity and specificity.

In summary, in most developing countries, syndromic algorithms calling for treatment for gonococcal and chlamydial infection in men with urethral discharge and for treatment for syphilis and chancroid in men or women with genital ulcers have been found sensitive, specific, and preferable to presumptive etiologic diagnosis based on clinical findings. However, in settings where genital herpes is common, chancroid uncommon, and serologic testing for syphilis feasible, other modified algorithms can defer antibacterial therapy for chancroid and provide antih herpes treatment when herpetic vesicles are seen. Syphilis serologic testing is always indicated, and results can guide partner notification. In many settings, for patients who may not return or may expose others, initiating syphilis therapy at the first visit for genital ulcer is often best, even when a rapid syphilis serologic test is initially negative, since about one-third of patients with primary syphilis still have negative rapid plasma reagin or VDRL tests at the first clinic visit. Prompt treatment of primary syphilis deserves high priority.

TREATMENT FOR STIs

Principles of STI treatment are discussed in Chapter 51. The diagnosis of a curable STI, regardless of the means on which diagnosis has been arrived, should lead to curative treatment.

Curative antimicrobial therapy is available for all bacterial STIs, as well as for those caused by protozoa and ectoparasites.^{32,33} For viral STIs, available drugs are suppressive but not curative; nonetheless, they can alleviate symptoms and prevent or delay complications. For genital herpes, suppressive therapy can reduce transmission of HSV from the patient who adheres to therapy without abandoning other protective measures. For HIV infection, the effect of suppressive therapy in preventing HIV transmission to an uninfected partner is being examined in at least one randomized trial.

■ DIRECTLY OBSERVED THERAPY, SHORT COURSE

WHO guidelines recommend that the most appropriate drugs for STI treatment are those that are highly efficacious, have acceptably low toxicity, are unlikely to select for antimicrobial resistance, can be administered orally (preferably in a single dose), and are not contraindicated for pregnant or lactating women.³³ Although one significant barrier to curative treatment is the patient's failure to comply with a full course of medication, a less well-recognized but perhaps more important barrier is failure of clinicians to provide or prescribe effective therapies that are available and affordable and for which compliance is easy. Effective single-dose curative therapies have been developed for all the major curable STDs (including early syphilis, chancroid, gonorrhea, trichomoniasis, and chlamydia infections), and this should help address this problem.

■ AVAILABILITY OF EFFECTIVE DRUGS

Ongoing problems for many developing nations are that the most desirable drugs (described above) are often not included on a nation's essential drug formulary or drug logistics are underdeveloped. This can lead to a “two-tiered” system of drug availability, in which the most effective—and often most expensive—drugs are only available at referral levels, while only less effective drugs are available at more peripheral health-care levels.¹⁰⁰ This, in turn, can result in an unacceptable rate of treatment failures and unnecessary referrals and is also likely to erode confidence in health-care systems and promote development of antimicrobial resistance.³²

Additionally, although antiviral agents against chronic, recurrent HSV-2 infections exist, they are often underutilized, especially in the very settings most likely to benefit. Underutilization may occur because antiviral agents against HSV-2 are not yet included on the national essential drug lists of many countries, or not included as part of the syndromic algorithm for genital ulcer syndrome. Since less costly and often off-patent (e.g., acyclovir) drug formulations effective against HSV-2 exist, many experts believe these should be made available to clinicians providing STI care management everywhere.¹³

A recent development in STI treatment involves monitoring therapy and providing assistance in self-management. Drugs are now available not only for treatment of HSV infection, HIV infection, and chronic hepatitis B or C. Over time, cumbersome treatment regimens for chronic viral STIs (including HIV and HSV) have been replaced with twice or even once per day drug dosing.

■ ANTIMICROBIAL RESISTANCE

Antimicrobial resistance has complicated STI treatment in many settings, because the most available or convenient (e.g., single dose) drugs may no longer be effective. This is particularly the case for *N. gonorrhoeae*, as globally many strains are now resistant to former first-line therapies such as the penicillins and tetracyclines, and increasingly more strains (particularly in Asia, but rapidly throughout the world) are no longer susceptible to fluoroquinolone antibiotics. This situation has limited the potential to use oral antibiotics against gonorrhea in many settings; affected communities must resort to more expensive and less available drugs (e.g., cefixime) or drugs that require an injection (e.g., ceftriaxone). In some developing settings, newer formulations against resistant organisms are not available on essential drug formularies or, if they are, are too expensive or require such specialized procurement processes that they are unavailable to most patients. The resulting situation is that even when gonorrhea is correctly diagnosed, it is not cured, leading to further selective spread of resistant strains.

■ NATIONAL STI TREATMENT GUIDELINES

Development and promotion of STI treatment guidelines at national and local levels can help greatly with effective STI management. In addition, adoption of locally validated, syndromic management approaches by many low-income nations has helped ensure that the drugs recommended or provided are effective against the STIs (or syndromes) for which they are being used and has increased the likelihood that they are available on national essential drug lists.

PREVENTION APPROACHES

As noted earlier, many of the goals of effective STI management involve prevention: prevention of complications and sequelae of the STI—including complications related to pregnancy or family planning—through effective treatment; prevention of transmission of the STI to others, thus breaking the “chain of transmission” in the community through partner notification or repeated STI screening; prevention of reinfections through partner notification and treatment¹⁰¹; preventing new HIV cases that may arise from the enhanced risk of HIV transmission and acquisition

risk associated with certain STIs, through prompt cure (bacterial STI) or suppression of recurrent genital herpes; and prevention of future infections through sufficient education, risk-reduction counseling, and skills training provided along with condoms.

Partner notification is an important prevention area that can be overlooked or simply ignored if specific etiologic diagnoses cannot be made. However, as pointed out earlier, unless sex partners are treated, individual patients run the risk of reinfection. Several promising new strategies have been evaluated recently, mainly in the United States, but some of these may have application widely. These are discussed in more detail in Chapter 54.

Substantial efforts have been directed toward development and rigorous evaluation of practical behavior change interventions to reduce new STIs and HIV, especially among patients who have been diagnosed with an STI. Several brief interventions suitable for clinical settings have been developed (e.g., individual or group counseling focusing on personal risk reduction, waiting room demonstrations focusing on building skills around correct condom use, and skills building videos).^{4,11,102–108} Many of these have had moderate effects, resulting in up to 40% reductions in new STIs and even larger reductions among adolescents, supporting the notion that an STI diagnosis provides a “teachable moment” in which behavior change interventions may be more successful. Primary interventions have been particularly beneficial for adolescents or other groups who may lack knowledge or skills around safe sex. Less success has been met with interventions geared toward certain populations (e.g., homosexual men), who may already be highly informed, have repeated higher risk exposures, or both.

It is hoped that STI vaccines will be an increasingly important part of STI prevention and care management in the future. Since 1988, safe and effective vaccines against hepatitis B have been available, and substantially less expensive recombinant vaccines have been widely marketed (see Chapter 29).^{8,9} In many countries, the hepatitis B vaccine series is recommended as part of routine infant vaccination, but this has not yet occurred in some of the nations most affected by the sequelae of chronic hepatitis B, the most severe of which include cirrhosis, end-stage liver disease, and hepatocellular carcinoma. As nations are increasingly able to vaccinate infants, an STI clinical encounter offers an opportunity to protect susceptible adults or adolescents who are at most risk of acquiring hepatitis B sexually (and who may not otherwise be easily accessed). New recommendations of the U.S. Advisory Committee on Immunization Practices (ACIP) for adolescent and adult hepatitis B virus immunization now support a more comprehensive immunization strategy to eliminate HBV infection.^{109,110} Recently, vaccines against the HPV subtypes associated with most cervical cancers—HPV 16 and 18—have been found highly effective in preventing acquisition of infection with these

oncogenic HPV types and the associated precursor lesions. The U.S. ACIP now recommends routine vaccination for females 11–12 years of age and catch up vaccination for young women age 13–26 years who have not been vaccinated previously. The HPV vaccine currently costs more than US \$300 for the series; however, even this expense may be very cost effective in nations with high rates of cervical cancer. (See Chapter 57.)

In summary, the importance of viewing the STI clinical care encounter as a prevention opportunity, and STI care management as a package of treatment and prevention services, should not be overlooked by providers. The STI clinical encounter may be the easiest or only way to access highly stigmatized or vulnerable populations who have high prevalence (or risk) for HIV and other STIs. Prevention research suggests an STI diagnosis is a time of heightened perception of personal susceptibility, when patients may be most amenable to trying behavior changes. In addition to on-site prevention messages, the clinical visit provides an opportunity for referrals for more extensive prevention services in the community. Furthermore, at least some experts postulate that the beneficial effects of STI control identified in the Mwanza community trial could be at least partly attributable to providers' instructions to their symptomatic STI patients who had pri-

mary HIV infection (and may have had high HIV viremia) about taking medicines properly and avoiding sex until symptoms resolved.³⁷

ENSURING QUALITY OF SERVICES

Routine, periodic quality assurance for established programs has long been recognized as an essential component of ensuring that medical and public health programs are conducted as they were intended. Six general aims for quality improvement highlighted in 2001 by the U.S. Institute of Medicine address safety, effectiveness, patient centeredness, timeliness, efficiency, and equity (see *Informing the Future. Critical Issues in Health*, 3rd edn. National Academy of Sciences, 2005, pp. 7–10). A variety of specific strategies have been employed to ensure that comprehensive STI clinical management is provided as expected, and in a manner acceptable to patients. Several of these are described in [Table 47-1](#). Provider training is important for the appropriate use of any STI management approach but is particularly critical for provision of syndromic algorithms.¹⁰⁰ Training providers on the overall rationale and utility of the syndromic management approach is important,

Table 47-1. Strategies That Have Been Used to Ensure High Quality of STI Clinical Management

- Development of national STI management guidelines for availability at the clinical setting—as possible with provider aids (e.g., posters with algorithms and laminated cards).
- Training courses on national STI guidelines that cover a “package” of services (e.g., STI diagnosis and treatment, locally supported prevention strategies, maintaining confidentiality of services, and promotion of user-friendly services).
- Development of procedure manuals for STI care management consistent with local policies and availability of commodities (e.g., laboratory tests, condoms, and drugs).
 - Focus should be on critical issues (e.g., confidentiality/privacy of information, nonjudgmental and helpful providers, accurate assessments, appropriate drugs, provision of condoms, routine provision of condom demonstrations by provider or patient, routine recommendation of HIV testing and appropriate education/counseling).
- Timely evaluation of locally collected data with feedback down to local programs and up to policy makers.
- Routine active supervision that focuses on critical issues that involves direct observation and immediate, constructive (not punitive) feedback to providers.
- “Secret shoppers” (i.e., simulated patients) who evaluate service and provide feedback.
- Peer observation and constructive feedback.
- Refresher courses and continuing professional education.
- Case conferences and formal and informal in-service trainings.
- Consultations and communication between health centers and referral centers through visits and radio or telephone links.
- Periodic client satisfaction surveys asking clients about what happened during their visit.

as many health professionals (and particularly physicians) are trained in laboratory-based or presumptive etiologic diagnosis and are hesitant to adopt other approaches that may be viewed as “less scientific.” Some experts have pointed out that the behavior change needed for providers to adopt syndromic management may be even more difficult than what is asked of patients to avoid future STIs.¹⁰⁰ Regardless of the STI care management approach used, training for health providers should include a comprehensive package of services (i.e., all of the elements of Fig. 47-1 ought to be addressed in the training). Specialized training courses offer an opportunity to reinforce elements that may be overlooked, such as the utility and means of providing routine partner treatment, providing condoms and demonstrating (or asking patients to demonstrate) their correct use, and reasons to specifically recommend HIV testing.

INTEGRATING STI CARE MANAGEMENT INTO HEALTH-CARE SYSTEMS

Although vertical STI programs were the norm until recently in much of the world, in most countries today the majority of clinical services, including STI management, occur at the primary health-care level. This approach appears to have led to better delivery of services for women, an important consideration, given the fact that women and infants bear most of the long-term burden of STI-related morbidity, including infertility, reproductive morbidity, adverse pregnancy outcomes, and cervical cancer.³² On the other hand, municipal STI clinics were able to serve large numbers of symptomatic men, who may be important in driving STI prevalence in their communities. Men, especially in developing countries, seem disinclined to seek care in primary-care clinics, at least initially. For many men, the informal health sector and pharmacies often represent the point of first encounter for STI care management. In nations with high STI prevalence, one essential issue for STI control that must be addressed is how to effectively access, diagnose, and treat infected men. In developed countries, declining rates of STIs may warrant a stronger emphasis on STI care management in the public health sector, as STI control relies increasingly on targeted outreach to marginalized (often uninsured) populations with high STI prevalence who are not easily reached.

In light of increasingly integrated services, it is useful to recognize how the different approaches used for STI care management are related to the primary mission and goals pursued by different types of service. Rather than dwelling on the limitations of each service type, it seems more productive to recognize the different primary missions of each service and to consider what each can contribute to STI

care management and to STI/HIV prevention within the framework of its mission. Table 47-2 summarizes the relationships between various services’ primary goals and the resulting emphasis on STI care management.

INTEGRATING STI MANAGEMENT INTO REPRODUCTIVE HEALTH SERVICES

Throughout the world, sexually active women access medical care through antenatal and family planning clinics; these facilities offer important opportunities for delivering STI care and prevention services to a population at risk of long-term STI-associated sequelae.

■ FAMILY PLANNING CLINICS

The International Conference on Population and Development held in Cairo in 1994 stressed that broadening the scope of family planning services could enhance their acceptability and effectiveness.¹¹¹ However, family planning clinics have been less likely to reach adolescents, single, sexually active women, including sex workers, and women who have completed their childbearing. STI rates found in women attending family planning clinics tend to reflect the rates among the general population of low-risk women, with wide ranges in prevalence depending on the specific infection and geographic region.⁸⁰ Incidences and prevalences of STIs, including HIV, are generally higher in urban than in rural areas, related to a combination of factors such as population density, migration, sex ratio imbalances, availability of commercial or transactional sex, loosening of family ties and traditional norms, and economic opportunity.^{32,100} Consequently, STI prevalence in rural family planning clinics is generally considerably lower than in urban clinics. Syndromic approaches for STIs in asymptomatic women in family planning clinics—especially rural clinics—have generally not provided effective STI care management, as most symptoms are related to causes other than STIs. However, syndromic approaches may be reasonable management strategies for other reproductive tract infections (RTIs) (described below).

The integration of STI/HIV services with family planning services, while justified for a number of reasons, requires integration of somewhat differing approaches and objectives.¹¹² Family planning clinics provide a commodity (contraceptives) to consumers and tend to promote the methods most effective in preventing pregnancy, including long-acting contraceptive methods such as the IUD, sterilization, and injectable or implantable hormones, rather than reversible methods such as condoms that are less effective in preventing pregnancy but effective in preventing STIs. STI services, on the other hand, follow the model common to the control of communicable disease. As noted, this model ideally involves case identification, treatment, follow-up of contacts, provision

Table 47-2. Interrelationships Between Type of Health-Care Delivery System, STI Prevalence and the Relative Utility of the Syndromic Diagnosis, Presumptive Diagnosis, and Laboratory-Based Etiologic Diagnosis

<i>Comparison of STD Delivery Systems</i>						
Type of Health-care delivery system	STI Prevalence	Goal(s)	Utility of Syndromic Approach	Utility of Presumptive Diagnosis	Utility of Lab-Based Etiologic Diagnosis ^a	Utility of Asymptomatic Screening ^b
Family planning clinic	Low	Protect reproductive health of client, couple and ensure safe and effective contraceptive use	Poor	Poor	Fair/good, especially CT, GC, HIV ^b	Good for cervical cancer, If no cervicitis present. Poor for syphilis.
Antenatal care clinic	Low	Prevent adverse pregnancy outcomes, maternal morbidity, and neonatal infections	Poor	Poor	Good, syphilis, GC, CT, HIV	Good for syphilis, HIV, GC, CT, and possibly TV and BV.? HSV
Primary health-care clinic	Varies	Relief of symptoms	Good	Fair	Good, but costly	Targeted approaches best. If targeted, good for syphilis, HIV, BV, and TV. May be poor for cervical cancer (Pap) if cervicitis present. HPV screening may be helpful.
STD specialty clinic	High	Prevent STI transmission, relief of symptoms, and HIV transmission/acquisition	Very good	Fair/good	Good, but costly	Good for syphilis, HIV, GC, and CT. May be poor for cervical cancer (Pap) if cervicitis present. HPV screening may be helpful.
Female sex worker clinic	High	Prevent STI transmission and HIV transmission/Acquisition	Good	Fair	Good, but costly	Good for syphilis, HIV, BV, GC, CT, and TV. May be poor for cervical cancer (Pap) if cervicitis present.
Adolescent/teen clinic	High	Prevent STI/HIV acquisition via education and counseling, relief of symptoms	Good	Fair	Good, but costly	Good for CT and HIV.
Men's health clinic	High	Provide safe circumcision, STI clinical management, HIV testing, and prevention services	Good	Fair/good	Good, but costly	Good for syphilis and HIV.

^aDependent on types of tests available and whether rapid tests are available.

^bDependent on STI prevalence in the community.

of condoms, and promotion of other STI prevention services. Reasons for integrating STI care management into family planning services include the opportunity for educating women about STIs and how they can be prevented, need for symptomatic women to know whether they have an STI or are at risk of STI/HIV, and, ideally, to tailor contraceptive options and safer sex counseling to their needs. Family planners are particularly interested in ensuring safety of IUD insertion and of abortion and, therefore, have particular interest in detecting and treating infections before performing these procedures. They are also concerned that women who begin contraception, especially those who then begin sexual activity, may acquire an STI that causes symptoms that could be erroneously attributed by the individual client, and eventually by all women, to the contraceptive method. This could lead to discontinuation of the contraceptive by the client and, eventually, to decreased uptake of the method.

Promotion of dual contraceptive methods (e.g., hormonal plus barrier) is increasingly justified not only because certain clients who are not in stable or mutually monogamous relationships are at risk of pregnancy as well as STIs including HIV, but also because of data suggesting that hormonal contraception may increase the risk of acquiring certain STIs.^{113,114} Although data are less compelling that hormonal contraception increases HIV susceptibility for HIV-uninfected women, for HIV-infected women who are coinfecting with HSV-2, hormonal contraceptives may increase cervical shedding of HIV, perhaps rendering them more infectious to partners.¹¹⁵

The term reproductive tract infections (RTI) is increasingly used by women's health-care workers to encompass cervical, uterine, and vaginal infections. Bacterial vaginosis in particular is referred to by some as an STI and by others as an RTI. In the family planning clinics—a setting where the diagnosis of STI is often unexpected—the term RTI has the advantage of not provoking marital discord for management of diseases that do not currently warrant partner notification, such as BV or HPV infection, but also the disadvantage of potentially not emphasizing the need for partner treatment when this is essential (e.g., gonococcal or chlamydial infection).

■ ANTENATAL CLINICS

The primary mission of antenatal clinics is to maintain the health of the mother throughout pregnancy, ensuring uncomplicated pregnancy and a healthy newborn. Chapters 78–88 outline the relationships of various STIs to reproductive health, pregnancy, the newborn, and pediatrics and the importance of STI care management in pregnancy in preventing congenital and peripartum infections of the newborn, preterm rupture of membranes, amniotic fluid infection, premature delivery, and puerperal infection of the mother. The footnote to [Table 47-2](#) summarizes precautions about treatment of trichomoniasis during pregnancy. Among the

most cost-effective preventive health measures is antepartum screening for syphilis and neonatal ophthalmia prophylaxis.³² Despite this, WHO experts estimate that 1000–4000 neonates still become blind each year because of untreated maternal gonorrhea and chlamydia infections.³² Furthermore, these experts note that untreated syphilis will result in a stillbirth rate of 25% and will account for an additional 14% of all neonatal deaths—resulting in an estimated overall perinatal mortality of 40% among mothers with syphilis.³² Antenatal detection of several STIs, including *C. trachomatis*, *N. gonorrhoeae*, bacterial vaginosis, hepatitis B, and HIV, should lead to curative treatments, preventive treatments, vaccination, or avoidance of breastfeeding, in order to prevent the above-mentioned complications.

Antenatal clinics serve women seeking obstetric care, rather than women with symptoms of STIs, and thus syndromic approaches tend to perform poorly, and detection of STIs requires asymptomatic screening involving laboratory testing. Although most nations today have national policies recommending universal STI screening for pregnant women early in pregnancy, in practice this does not always occur.³² Many women do not access antenatal care at all, or not until late in pregnancy when adverse outcomes have already occurred. For women who access antenatal care early, tests may be unavailable, or when available may be unreliable without the hands of trained staff in controlled settings (e.g., nontreponemal card tests). When tests are sent out, women may be lost to follow-up by the time test results return. On-site, rapid serologic testing for syphilis in antenatal clinic settings in developing countries would help ensure that infected women are detected and receive effective treatment, and these tests are increasingly available at low cost; however, they can lead to substantial overtreatment in the settings that need them most.^{67,68} The expectation in the near future of an affordable, rapid, dual-antigen test for point-of-care detection of syphilis seroreactivity is expected to greatly improve the likelihood of early detection and treatment of maternal syphilis among pregnant women attending antenatal clinics. Similarly, reliable rapid tests for chlamydia and gonorrhea would greatly assist in identifying infections in women attending antenatal and family planning clinics and could prevent substantial unnecessary sequelae.^{67,68}

INTEGRATING STI MANAGEMENT INTO PRIMARY HEALTH CARE

Increasingly, all over the world, primary care providers now diagnose the majority of STIs and will likely assume an even greater role in STI prevention and control because of the declining emphasis on vertical public health programs.¹⁰⁶ Integrating STI services into existing primary care systems has potential benefits; perhaps most important (as is the case for reproductive health services) is the expanded access of STI services for women, who are most affected by STI sequelae but also most affected by stigmatization around STIs.

■ PRIMARY HEALTH-CARE CLINICS

Health care in the primary care setting tends to emphasize relief of symptoms, and preventing complications in individual patients served, rather than protecting the public health. Consequently, services tend to be client centered, directed toward the patient's perceived needs, and treatment is frequently based on management of the patient's symptoms. Advantages of STI care in the primary care setting include the ongoing relationships between the clinician and the individual, which can increase the likelihood of early STI detection and effective preventive interventions, such as regular clinician counseling. In addition, incorporating STI-related services into primary care may improve access to services, since primary care providers are much more numerous than public STI clinics, especially as public funding for public health programs decreases.¹¹¹ Because STI-related services provided in primary care clinics are not provided in isolation, but rather in the context of other medical problems, primary care clinics do not carry the stigma associated with dedicated STD clinics. Primary care providers may have more opportunity and success in coordinating the variety of health and social services available in the community, which are especially needed by those persons at highest risk of STIs and other infectious diseases that often require multiple services. In addition, certain prevention interventions, such as provision of STI vaccines and referrals, may be easier to accomplish.

Although development of STI care management services at the primary care level has advantages, disadvantages for effective STI care management may also be numerous. At the primary health-care level, STI services tend to be less efficient and more rudimentary. Training in clinical evaluation and risk reduction counseling may be lacking in some primary care settings, especially in developing countries where the quality and effectiveness of services designed for STI care management (e.g., use of syndromic management flowcharts) have not been extensively documented. The interaction between health systems may be inefficient. A study of sexual and reproductive health services in Ghana found that, some years after decentralization of services, many systems-level challenges remained, particularly clarity on how different agencies related to each other and to regional and district health authorities.¹¹⁶ Such challenges are not restricted to the developing world. A 2003 study of genitourinary medicine (GUM) clinic attendees in England found that 40% of those diagnosed with an STI had already visited a primary health-care clinic for their problem but had been referred to (or preferred) the GUM clinic for specialized services.¹¹⁷ In the United States, private health insurance plans often cover STI services but may be inconsistent in their coverage, sometimes restricting or excluding some basic types of services related to reproductive and sexual health concerns.¹¹⁸ Around the world, regardless of the health systems in place, public

health agencies will be most effective if they can develop partnerships that support delivery of locally tailored, comprehensive STI care management and prevention services to the entire community.

■ COMMUNITY-BASED CLINICS

Community-based health providers at urban community health centers, school-based health clinics, and adolescent clinics, serving teens and young adults, represent a particular type of primary health care that has potential to ensure effective STI care management for younger, otherwise hard-to-reach patient populations with high prevalence of STIs. Although many community-based health programs provide STI-related clinical services, most have not made STI management a priority, even when STI prevalence in their patient population is high. This may occur if community-based practitioners lack knowledge about local STI prevalence (or prevalence among their patients), expertise about management, or the essential technical resources needed to provide such effective STI care management services. Enhanced training opportunities (e.g., when standardized national guidelines are developed) and collaboration with local public health agencies or health-care training institutions could improve the quality of services offered.

■ PRIVATE SECTOR

As is the case for primary health-care management, the goal of STI care management in the private sector is predominantly treatment and relief of symptoms presented by clients. In many settings, patients with STI symptoms who can afford to do so seek evaluation with private providers rather than at public clinics, even when they perceive public clinics to provide better care technically.¹⁰⁰ This seems to be related to concerns about privacy and confidentiality of information, judgmental attitudes of providers or prior experiences of "scolding" by public providers, or long waits or inconvenient or limited hours of operation at public clinics.¹⁰⁰ Symptomatic individuals may seek treatment with private practitioners who are part of the official private sector or may seek treatment directly from pharmacies or in the unofficial private sector (e.g., with traditional healers or alternative providers), and while this occurs all over the world, it is particularly common in certain developing country settings.^{100,119} Given the public trust and use of the private sector, strategies aimed at improving STI care management in a community are likely to be more effective if private provider training and management can also be addressed.

Private practitioners

Throughout the world, private providers, often general practitioners, see most patients with STI symptoms who seek

health care from clinicians. Although private providers clearly have the potential to play important roles in disease management (and surveillance), they are often neglected in national STI control strategies. Nonetheless, a number of factors, including development of national guidelines, inclusion of STI care management in the training curricula at professional schools, and provision of incentives (e.g., accreditation, licensure, and continuing education credits) for completing STI training courses, all have been shown to aid in improving STI care management by private providers.^{32,100} In settings where syndromic management approaches are the standard of care, inclusion of private practitioners as part of expanded training courses may improve overall STI management and will at least ensure that all providers understand the rationale behind the approach and thus limit negative perceptions that public STI care management is somehow inferior to that provided in the private sector.

Treatment by pharmacists

In much, if not most of the world, a large proportion of patients—particularly men, but also many women—receive initial care from pharmacies or the informal medical sector, rather than from trained clinicians.^{120–126} As is the case for other private providers, the goal of STI care management in pharmacies is predominantly treatment and relief of symptoms presented by clients, together with sales of pharmaceutical products.¹²³ Pharmacy workers tend to recognize STI syndromes in men better than STI syndromes in women as being attributable to sexual transmission but without training may do a poor job with both.^{120,122,123} For example, a study in Peru that used standardized simulated patients with scripted scenarios who presented to pharmacies found most of the simulated patients were offered medication.¹²² However, effective, recommended medication was rarely, if ever, offered to patients presenting with PID, genital ulcer syndromes, or vaginal discharge syndrome and was offered to only 30% of men complaining of urethral discharge symptoms.¹²² Similar results have been reported elsewhere.^{120,122,123} Additional problems have been observed: In some settings, most people working in pharmacies are actually clerks, with trained pharmacists often not being available on the premises.¹²⁰ Conformance to published guidelines for STD treatment in pharmacies has been recognized as very poor, and pharmacists uncommonly recommend preventive practices such as partner management, condom use, or risk reduction.^{122,123}

Nonetheless, the perceived accessibility, confidentiality, and lack of judgmental remarks of pharmacists make them very attractive to patients with STIs.^{119,123} Adoption of validated, national syndromic algorithms has helped some countries justify standardized training courses for professionals providing STI care, including pharmacists and physicians and nurses in the private as well as public sectors.^{32,100}

Research suggests that pharmacists are willing to participate in expanded training on STI care management, and several communities have proposed or already experimented with training alternative providers, including pharmacists and traditional healers, on understanding and appropriate referral for STI syndromes.^{100,119,120,122–126} Additionally, there is some evidence that prepackaged kits containing the appropriate antimicrobials for urethral discharge sold at pharmacies can lead to high cure rates and condom use (although these has not been found to improve partner notification).^{125,126} The use of incentives and other measures discussed above for private providers may be helpful in encouraging and supporting pharmacists to provide effective STI care management.¹⁰⁰ Again, in Lima, Peru, a district-randomized trial was carried out in which 14 districts were paired and randomly assigned to receive training and support for management and prevention of STIs or a control intervention concerning management of diarrhea. The multicomponent and sustained STI intervention addressed recognition and management of four STI syndromes (urethral discharge, vaginal discharge, genital ulcers, and PID) and included STI/HIV prevention counseling; “prevention salespersons” subsequently distributed materials to pharmacies that included STI/HIV prevention packets containing information, condoms, and cards given to patients for referral of their sex partners. Standardized simulated patients visited pharmacies in intervention and control districts at 1, 3, and 6 months after training to assist outcomes. By “intention-to-train” analyses intervention district pharmacies performed significantly better in syndromic recognition and correct antimicrobial management for all four syndromes and more frequently recommended future condom use and treatment of partners ($p < 0.05$ for 47/48 outcome comparisons).¹²⁷

INTEGRATION OF STI CARE MANAGEMENT INTO SPECIALTY CLINICS

Specialty clinics seek to provide STI/HIV interventions including STI care management to populations with high STI prevalence or risk or who are highly vulnerable to STIs (e.g., sex workers and migrant men). In addition to preventing important STI-related sequelae, the prevention interventions (including STI care management) provided at specialty clinics may reduce STI prevalence in a community if the populations targeted have high rates of sex partner change.

■ SEX WORKER CLINICS

Sex workers are obviously at high risk of contracting STIs, including HIV, and can also promote spread of STIs in the community. Most urban centers and port cities throughout the world have clinics providing STI care management, and several models from industrialized and developing countries

have demonstrated that rates of STIs can be lowered among sex workers in these communities.^{84,128–131,135} Rather limited attention was given to the quality of care or efficacy of the STI care management provided in such clinics in the past. However, more recently, over the past several years, several studies have addressed the quality, client satisfaction, and cost effectiveness of services provided.^{132–134} Additionally, some STI care management models for sex workers have been found effective in preventing new cases of gonorrhea, chlamydia, and trichomoniasis, although thus far not HIV infection.^{128–131,135} Clinical services with regular STI screening, with provision of condoms, has led to increases in condom use and reductions in STI and HIV prevalence.^{135–137} Another model, employing periodic presumptive therapy (routine provision of directly observed antimicrobial drugs, even without symptoms) has been found to rapidly reduce STI rates in some settings; however, once prevalence rates are brought down, other longer-term strategies may be required.^{135,136} Additionally, STI rates have been observed to drop dramatically among sex workers enrolled in HIV prevention trials when they are provided access to free condoms, risk-reduction counseling, and STI therapy, suggesting that such trials may provide the needed commodities, information, or empowerment to support reductions in sexual risk taking.^{137,138} Overall, evidence is strong that clinical services for sex workers offer an opportunity to access a high-risk, often hidden population (particularly true for non-brothel-based sex workers) and allow provision of important prevention services such as HIV testing, empowerment programs promoting consistent condom use and negotiation of condom use with partners, and even alternative physical barrier methods such as female condoms.^{128–138} In some places, sex worker clinics are offered HIV clinical services (e.g., provision of highly active antiretroviral therapies) (Marie Laga, personal communication). However, where sex workers are required to register with municipal authorities and to attend clinics for regular periodic examinations, the threat of withholding health cards needed to work, if STI is detected, can provide a disincentive to attend clinics.

■ HIV CLINICS

HIV-infected persons may be at particular risk of STIs, both behaviorally through sexual risk taking and biologically through enhanced expression of certain STIs (e.g., HSV and HPV). Additionally, HIV-infected persons who are coinfecting with HSV or with some curable STIs have genital inflammatory lesions and higher levels of HIV viremia, providing more opportunity to transmit HIV to partners, and treatment of certain curable STIs has been found to reduce HIV plasma viral load.¹³⁹ Current randomized trials are examining the impact of suppression of genital HSV recurrences on transmission or acquisition. The HIV clinical care system offers an opportunity to identify persons coinfecting with STIs whose

higher HIV viral load may lead to enhanced transmission to others. Strategies addressing prevention of HIV transmission for HIV-infected persons have addressed the potential utility of initial, and possibly periodic, STI testing among HIV-infected persons in clinical care, particularly in communities or subpopulations with high STI prevalence.^{32,140,141} Routine testing for certain STIs among HIV-infected persons may also help access sex partners who require STI therapy and, importantly, HIV testing. This strategy can ensure more prompt identification of HIV infection in sex partners, and referral into HIV clinical care, as well as specialized prevention strategies for negative (i.e., HIV discordant) partners, such as specialized couples counseling to reduce HIV transmission. Discordant couples counseling has been shown to be associated with reduced HIV seroconversion rates in several settings but is a strategy which still requires rapid scale up in many places.^{142,143}

■ ADOLESCENT CLINICS

Adolescents, particularly women are at high risk of STIs for a variety of biological, behavioral, social, and economic reasons discussed in more detail in Chapter 11. In fact, globally it has been estimated that one in every 20 adolescents will develop a new STI.¹⁰⁰ In most developing countries, more than half of the population is under 15 years of age; thus, adolescents represent a group that not only is susceptible to STIs, but may also drive STI (and HIV) transmission and prevalence in a community. Adolescents are often unwilling or unable to access typical health-care services for a variety of reasons, and many experts recommend development of specialized clinical and prevention services for them, perhaps incorporated into other programs of interest to adolescents.³² While specialized services offer an opportunity to access this important population, specialized training on how to provide services in ways that are acceptable (and encourage participation by other adolescents who hear through word of mouth) will likely be important.¹⁰⁰

■ MALE HEALTH-CARE CLINICS

As discussed, many high-risk men do not utilize public sector primary care systems, preferring to access STI care through the private sector or with alternative providers (e.g., traditional healers and pharmacists) who may be utilizing inadequate STI management strategies. In 2005 and 2006, results from a series of randomized controlled trials evaluating adult male circumcision in preventing HIV and other STIs consistently found circumcision to result in approximately 50–60% reductions in new HIV infections.^{7,144,145} Several communities with high HIV prevalence have already begun considering the best ways to implement and scale up circumcision interventions for men, one of which may be to develop model clinics targeting men's

health. Such male health clinics would offer an opportunity to provide a variety of services, including comprehensive STI care management, HIV testing and counseling, risk reduction counseling around high-risk sexual behaviors and partners, and skills building around correct and consistent condom use. These are likely to be particularly used in developing world settings with high HIV prevalence where many men are not circumcised. The 2006 WHO Strategy for STI Prevention and Control includes “male involvement, male motivation and services for men” as one of five new technologies for strengthening a response to STI/HIV control.³²

CONCLUSION

The dynamic advances in medical technology and public expectations drive clinicians to use more and more services that are increasingly sophisticated and costly. This trend must be balanced by streamlined systems of STI care management that use common sense to apply available resources most efficiently in a patient-oriented manner. In addition, comprehensive systems must address each of the potential levels for intervention shown in Fig. 47-1. Clinicians are increasingly called upon to discard old paradigms and consider new ways to package services or referrals within existing systems. Effective STI care management requires providers to consider which systems-wide actions will help solve the major sources of STI-related sequelae facing a population. For example, is active screening for young, sexually active women (e.g., in family planning settings) a more effective approach to prevent infertility than more passive screening approaches? For resource-poor settings, would training alternative providers (e.g., pharmacists) in effective syndromic approaches help reduce STI burden in some communities¹²⁷ or should such training be focused on aiding alternative providers to make prompt referrals to clinicians? Could better training on use of the algorithms and rationale behind various STI management approaches in professional school curricula help health providers in developing country settings better support and utilize syndromic approaches, and would this lead to reductions in the curable bacterial STIs most associated with HIV risk? Can practical partner notification approaches substantially prevent reinfections and further STI spread into the community? Could provision of comprehensive STI care management, together with condom promotion, STI risk reduction and contraception counseling, and provision of male circumcision in specialized men’s health clinics, reduce the prevalence of curable STIs (and possibly HIV) in developing world settings hard-hit by HIV/AIDS? Clinicians must continue to focus on the care they provide to their clients. However, providing clinicians a better understanding of the epidemiology and transmission dynamics of HIV and other STIs, the magnitude of their

social and economic complications, and the potential benefits of a comprehensive STI care management package may help them undertake new and effective actions for reproductive health and prevention of STIs, including HIV.

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Individual-Level Risk Assessment for Sexually Transmitted Infections, Including HIV

Ann E. Kurth and Freya Spielberg

The taking of a thorough history is the foundation of excellent clinical care. This is especially the case for sexual health issues, which some patients may be hesitant to introduce without elicitation. Individual risk assessment conducted in the form of a sexual history focuses sexually transmitted infection (STI) testing, enhances individualized counseling and appropriate referrals, and provides patients the opportunity to address issues of concern.¹ Clinicians, counselors, public health professionals, and community health workers can play central roles in preventing STIs including HIV infection, and in limiting the morbidity and mortality of STIs by identifying and treating these infections as early as possible; by providing risk-reduction counseling to prevent further transmission; and by instituting prophylactic measures for at-risk individuals not yet infected.^{2,3}

There is growing interest in methodologies for ecological or population-level risk assessment for STI/HIV (see Chapters 3 and 5).^{4,5} This chapter concerns individual-level risk assessment for STI/HIV infection, primarily in clinical settings.

Primary care, urgent care, emergency department (ED) settings,⁶ private physician offices,⁷ chemical dependency treatment centers,⁸ prison discharge facilities⁹ and outreach sites,¹⁰ prenatal and family planning clinics, and clinics serving adolescents¹¹ represent important settings for identifying individuals at moderate and high risk for HIV and STIs, and often provide the first opportunity for health-care professionals to identify those with mild and sometimes protean symptoms of early infection. In resource-constrained countries, pharmacists are often a first point of contact for individuals seeking care for infections manifesting as sexually transmitted disease (STD), and such providers can be trained to do syndromic management.^{12,13}

Other important settings for risk assessment include STD or genitourinary medicine clinics^{14,15} and HIV testing sites including mobile outreach units.¹⁶ These settings generally conduct STI/HIV risk assessment as a part of their primary function. However, a national survey of sexual history forms in use at STD clinics in the United States found great

This chapter was based on Curtis JR, Holmes KK. Individual-level risk assessment for STD/HIV infections, Holmes et al., *STD*, 3rd edn, 1999, with permission.

variability in risk behavior items and periods that are routinely assessed. Few (19%) of the history forms in use incorporated questions for men who have sex with men (MSM), and condom use problems were rarely explored (6%). Most forms documented STI/HIV counseling, though few (23%) delineated specific risk reduction plans.¹⁷

In STI/HIV care management, individual-level risk assessment has been most extensively used as a guide to selective screening for gonococcal, chlamydial, and HIV infections.^{18–22} STI/HIV risk assessment can also initiate and personalize counseling on behavioral risk reduction, as well as assess the need for prophylactic measures, such as hepatitis vaccines, and also (in conjunction with elicitation of symptoms and signs) for presumptive diagnosis of STDs and for management of certain STD syndromes (see Chapter 47).²³ **Table 48-1** summarizes the overall goals of risk assessment as an initial component of STI/HIV management.

Although a number of guidelines address STI/HIV risk assessment, they often lack details on how to carry this out, and the literature still contains relatively few formal validations of the reliability and utility of STI/HIV risk assessment in various settings.²⁴ We will review the requirements and potential elements of STI/HIV risk assessment and close with recommendations for improving the consistency with which such assessments are conducted by health-care providers.

EFFECTIVE RISK ASSESSMENT AS A PUBLIC HEALTH STRATEGY

Risk-based screening followed by treatment can prevent secondary and tertiary complications for STI-positive individuals and primary disease transmission to others.⁵ In general, risk assessment must have high sensitivity, specificity, and predictive value in discriminating between those at high and low risk. For a risk-based, selective intervention to be effective, those affected must have a risk profile different from those unaffected; and an intervention must exist that will alter favorably the natural history of the condition.²⁵ Referrals should be made for those

Table 48-1. Sexually Transmitted Infection (STI)/HIV Risk Assessment Goals by Patient Status

Patient Status	Objectives of Risk Assessment
Symptomatic patient	Use risk assessment to determine the prior probability that an STI causes the symptoms; guide testing, syndromic management, and partner treatment
Asymptomatic patient, infection status unknown	Decision on whether to not to screen (cost-effective use of resources) or to use postexposure prophylaxis or preventive treatment
Known uninfected	Individualized counseling to decrease risky behavior to protect oneself from STI/HIV acquisition; assess need for prophylaxis (e.g., hepatitis B vaccine)
Known infected	Individualized counseling to decrease risky behaviors: To protect others To protect oneself against potential reinfection To protect oneself against other STIs or, if HIV-positive, other strains of HIV
All patients	Address sexual concerns

identified to be in need of services, and ethically, such services should be available in order to justify screening in the first place. The US Preventive Services Task Force (USPTF) has emphasized the desirability of delivering preventive services to people with limited access to medical care.²⁰ While it may often be the case that those at highest risk are the least likely to have access to health-care services, this concern must be countered by the public health perspective that for communicable STIs including HIV, intervention in those at highest risk, particularly those most likely to transmit infection, can benefit the entire population. STI transmission dynamics are increasingly understood to be a complex system involving individuals with a multiplicity of risks, often linked through sexual networks, resulting in population level patterns of transmission.²⁶

■ MODEL OF STI/HIV RISK

This leads to asking what should be measured for STI/HIV risk assessment. Disease transmission probabilities are affected by individual-level factors such as host immunity and biologic pathogenicity. Understanding specific sexual partnership patterns is also important. The risk of acquiring

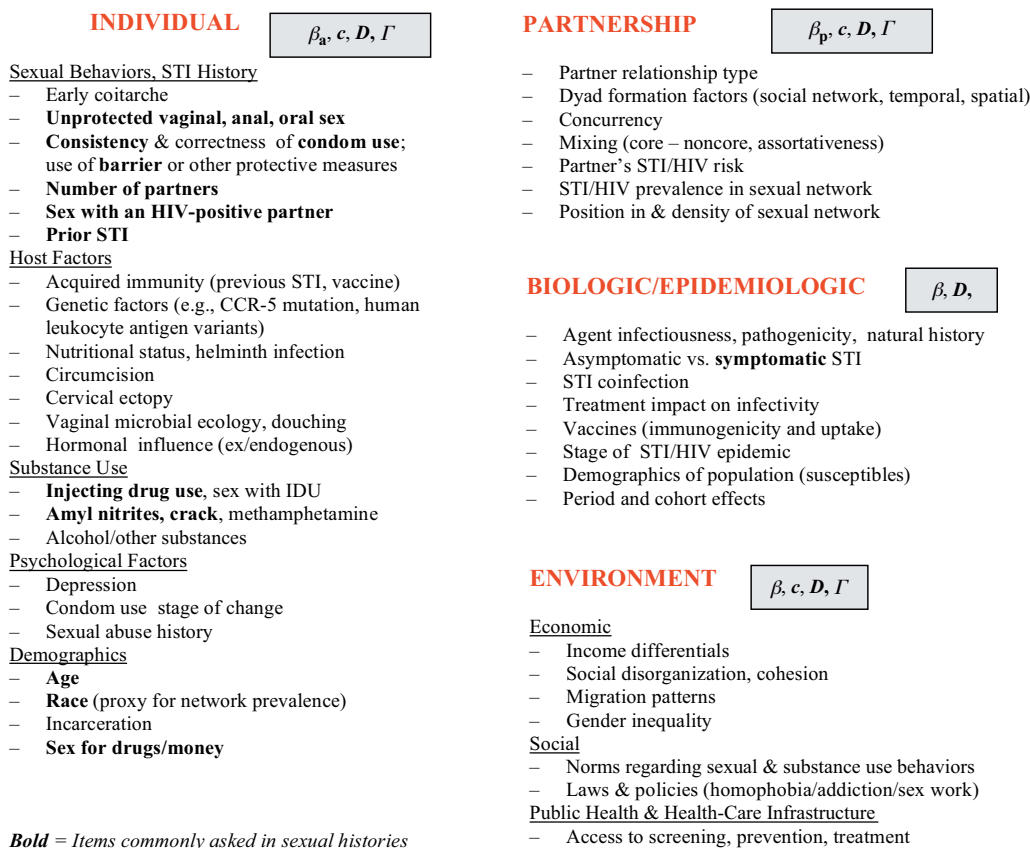
STI/HIV is related to infection status of the chosen partner(s), specific sex acts, and condom and possibly other barrier method use,²⁷ all of which have been shown to vary by sexual partner type (e.g., main vs. casual partners, or partners perceived to be risky vs. those perceived to be low-risk).²⁸ One large behavioral intervention trial found that STD clinic attendees tended to have safe (condom-protected) sex with partners thought to be risky and had risky (unprotected) sex with partner perceived to be safe from STIs/HIV.²⁹ While much epidemiologic focus has been on the individual characteristics that are associated with risk of STI acquisition, recent work points out the limitations of such an approach to explaining incident STIs.³⁰

As outlined in other chapters of this book, it is increasingly clear that sexual behaviors and STI transmission dynamics can be predicated on factors beyond those controlled by the individual or the sexual dyad or couple.³¹ These may include sexual and social³² network characteristics, socioeconomic factors,³³ community social cohesion and trust measures,³⁴ and sex-ratio disruptions in minority communities due to higher rates of incarceration,³⁵ inter alia. The epidemiologist Meryvn Susser has declared that with these supraindividual “contexts unmeasured, neither patterns of mortality and morbidity, nor epidemic spread, nor sexual transmission may be explained.”³⁶ The interdependence of STI risk behaviors necessitates an ecologic approach,^{37,38} since infectious diseases and social behaviors are not statistically independent: the outcome in one person influences the outcome and alters risk factor effects in other people.³⁹

While simulation modeling and some empiric evidence now demonstrate the importance of understanding sexual network-level factors, most STI risk assessment questions have focused on individual-level factors such as “number of sexual partners,” since the individual patient tends to be the primary unit of focus in clinical settings. Sexual histories that focus only on individual level variables may be epidemiologically incomplete, but in practical terms, clinicians are not able to factor in sexual partner risks and other structural-level data in real time during an examination. Of necessity, clinicians will continue to rely on risk assessment questions that reliably target the individual. Some of these standard items are highlighted in bold in [Figure 48-1](#), which also includes the variety of other supraindividual factors that may influence both individual and population-level STI acquisition and transmission.⁴⁰ The figure also classifies the ways in which these factors relate to the classic formula of the basic reproductive rate for STI transmission.^{41,42}

■ INTERVIEW MODALITY AND THE RELIABILITY OF PATIENT SELF-REPORT

Along with the question of what should be measured for STI risk is the question of how to best capture accurate risk



Reproductive number (R_0) for transmission to new and existing partners (Anderson et al., 1999:32):

$$R_0 = \beta c D + \beta c \Gamma$$

β (attack rate) = transmission probability per sexual contact
 c = rate of sex partner change → average # contacts per unit time
 D = mean duration of infectiousness
 Γ = average partnership duration

Transmission probability per partnership (β_p) = transmission probability per act (β_a) & number of unprotected acts (N_a):
 $(\beta_p) = 1 - (1 - \beta_a)^{N_a}$

From Kurth A. Audio computer-assisted self interviewing for sexually transmitted infection prediction. Doctoral dissertation, epidemiology. University of Washington, 2003.

FIGURE 48-1. A model of STI/HIV risk.

exposure information. Social desirability,⁴³ self-presentation, recall, and other biases such as item nonresponse can lead to serious measurement error in sexual behavior surveys.^{44,45} The lack of a gold standard limits interview modality comparisons, since there are few biochemical measures to document actual sexual practice or STI exposure and thus, to validate behavioral self-reports.⁴⁶ Attempts have been made to measure semen,⁴⁷ prostate-specific antigen,⁴⁸ and Y-chromosome deposition in vaginal fluids⁴⁹ as a way to validate reports of unprotected penile-vaginal intercourse, but this cannot distinguish frequency, multiple partners, or nonvaginal intercourse sexual behaviors. Another difficulty is that there is not a linear relationship between a specific behavior

(such as unprotected sex with an infected person) and STI acquisition.^{29,50}

Sex partner concordance has also been assessed as a way to validate self-reported behaviors. Some studies have found reasonably high concordance in partners' reports of recent joint behaviors (83–96%),⁵¹ but recall of all recent partners tends to be lower, with 15–72% of partners from the last 1–3 months forgotten.⁵² However, a National Institutes of Health working group concluded that self-reports of sexual behavior can be useful even if subject to some inaccuracy.⁴² Likewise, a National Academy of Sciences review of the research literature has pointed out that people can consistently report STI-risk-related information.⁵³

Computer-assisted self-interviewing (CASI), sometimes with audio, video, or telephone enhancements, has been used to assess patient histories^{54–56} in a variety of clinical settings including STD clinics.^{57,58} STI/HIV risks have been surveyed using CASI among blood donors,⁵⁹ university students,⁶⁰ adolescents in resource-rich and -poor settings^{61–64} and injecting drug users (IDUs).^{65–68} Test-retest reliability of a complex audio CASI survey administered in English and Spanish to recently-diagnosed HIV patients was good ($\kappa = 0.77$, $r = 0.73$).⁶⁹ CASI formats have been found acceptable among low-income, minority, and low computer-literate populations^{70–73} and among patients in clinical exam settings.⁷⁴ Older persons, those with hearing difficulties and those with low technology-exposure⁷⁵ may be less suitable for CASI interviews. Higher levels of sensitive behaviors such as drug use, same-sex behavior, and anal intercourse have been reported in CASI compared with face-to-face and self-administered paper interview modes in some settings.^{76–78} A video-CASI study in a New Orleans STD clinic found that 30% of women with chlamydia reported discordant responses in a face-to-face interview versus a V-CASI instrument.⁷⁹ Another study comparing clinical sexual histories with audio CASI self-report by 609 STD clinic attendees found that men's behavioral reports were equivalent between interview modalities, while women's were not, with a tendency to report socially sensitive behaviors more often on the computer.⁵⁷ Patients seeking care for STIs may be more motivated than general population samples to report risk behaviors truthfully. Nonetheless, even in that setting, computer interviewing may still provide advantages of data quality and completeness⁸⁰ and may enhance the efficiency of the provider-patient interaction rather than resulting in differential risk reporting per se.⁸¹

■ THE ROLE OF RISK ASSESSMENT FOR DECISION ANALYSIS AND SYNDROMIC MANAGEMENT

By using data from the patient history, physical examination, or simple diagnostic tests to categorize heterogeneous populations into subgroups of risk, clinical prediction rules help clinicians identify which patients require further diagnostic tests.⁸² In clinical decision analysis, identifying risk factors for STDs in patients with various sets of symptoms and signs increases the prior probability that a particular STI causes those signs and symptoms; this might lead to selective testing for that STI, to initiation of treatment while results of tests obtained are pending, or to initiation of empiric treatment without testing—especially if the prior probability of an STI becomes so high that confirmatory tests are not deemed cost-effective.

In the United States, selective screening criteria have been developed for chlamydia in particular.^{83–86} In part because

validation of screening rules is not always carried out among populations different from the ones on which they were developed, these rules may not always be reproducible and may leave out predictors found to be important in other populations.⁸⁷ No screening algorithm or rules can replace clinical judgment. But if soundly developed and validated, they can minimize reliance on subjective assumptions or untested heuristics⁸⁸ regarding the STI-risk likelihood of patients based on perceptions of social class, relationship status, and other nonsensitive markers of STI risk. The predictive value of clinical judgment may also be affected by disease probabilities.⁸⁹ When a particular STI is ubiquitous, e.g., human papillomavirus or herpes simplex virus type 2, it is harder to intuit which persons are at highest risk.

Like any other test, a clinical prediction rule's diagnostic value is affected by prevalence.⁹⁰ Likelihood ratios build on the clinician's judgment and estimated pretest probability of the underlying clinic prevalence and are more stable across different populations.⁹¹ Clinics can use likelihood ratios to set thresholds for the point at which the test result would change clinical action.⁹² An example of this can be seen in one STD clinic that used sexual history-derived risk assessment criteria to find that as chlamydia prevalence increased, the risk score necessary to justify chlamydia laboratory testing decreased.⁹³

Figure 48-2 illustrates how risk assessment influences the potential for under-, over-, and correct diagnosis of an STI in a patient with a hypothetical STI-related syndrome, in a population where the prevalence of that STI is 10%, and the sensitivity and specificity of the symptoms and signs that make up the syndrome are 90% and 85%, respectively, for that STI. For a risk factor or combination of risk factors that carries an odds ratio for the STI of 10.0, the prevalence of STI among those with that risk factor would be 36%, and if treatment were offered, the probability of correct treatment of an STI, relative to the probability of overtreatment, is greatly increased among those who have both the syndrome and the risk factor.

Risk assessment is routinely used by clinicians as an adjunct to diagnosis and management of most diseases, including several STD syndromes, including unilateral intrascrotal pain and swelling (epididymitis); lower abdominal and pelvic pain in women (PID); vaginal discharge; proctitis; acute hepatitis; various STD-associated neurologic and rheumatologic syndromes; and HIV-related clinical syndromes, including the primary infection syndrome, the generalized lymphadenopathy syndrome, various neurologic and hematologic syndromes, and other syndromes related to acquired immunodeficiency. Risk assessment is also potentially useful in managing mucopurulent endocervical discharge, genital lesions, rashes, etc.

For some syndromes, simply age and sexual experience are sufficient to rule in or out the likelihood of an STI in the

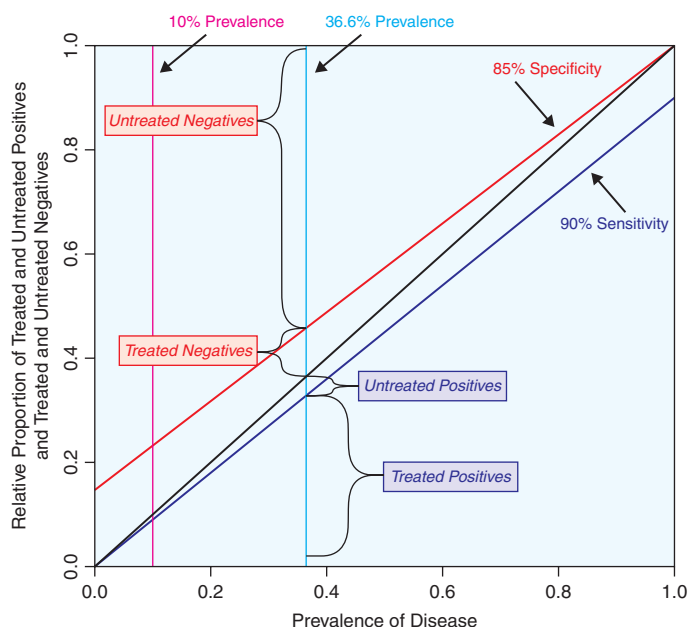


FIGURE 48-2. The plot shows the impact of screening only those who are risk assessment (RA) positive in a population with 10% infection prevalence. In this example, the odds ratio for infection of RA positives against RA negatives was taken to be 10; this means that RA positives have a posterior probability of infection (i.e., prevalence) of 36.6%. The sensitivity and specificity of the diagnostic test was taken to be 90% and 85%, respectively. In this plot, the top line represents the stated specificity of 85%, the middle line the performance of a perfect test, and the bottom line represents the stated sensitivity of 90%. The left-hand vertical line in the plot represents the prevalence of infection in the entire population; the right-hand vertical line in the plot represents the prevalence of infection in the risk assessment-positive subset of the population. The division of the vertical, prevalence lines into four segments represents the performance of the diagnostic test. From top to bottom, the segments represent the relative proportion of patients in the following groups: untreated-negatives, treated-negatives, untreated-positives, or treated-positives. The relative size of the four segments is determined by the prevalence of infection in the group tested and the sensitivity and specificity of the diagnostic test. This plot is one way to examine the performance of a test across different levels of disease prevalence. Note that at 10% prevalence, the ratio of treated negatives/treated positives is 3/2; whereas at 36.6% prevalence that ratio is 2/7. (Figure courtesy of Barry N. Courtois.)

differential diagnosis. For example, in evaluating testicular pain and swelling in an adolescent who has not been sexually active, the likely diagnoses are testicular torsion or trauma; in a sexually active young man the likely diagnoses are acute epididymitis owing to gonococcal or chlamydial infection; and in an older man in a mutually monogamous relationship the likely diagnoses are acute epididymitis caused by urinary pathogens. For other syndromes, more information on risky practices or partners is also useful.

Risk assessment has been most extensively studied recently as an adjunct to syndromic management of vaginal discharge, for which it appears to be less successful than for other syndromes such as genital ulcer disease or urethral discharge.^{94–96}

It was hoped that risk assessment of women with symptoms or signs of vaginal discharge could help identify women with cervical gonococcal or chlamydial infection and that those with vaginal discharge and positive risk assessment could be treated for cervical infection. Unfortunately, because abnormal vaginal discharge (especially increased amount or abnormal odor of the discharge) does not predict cervical infection, and because risk factors for certain vaginal infections may be similar to those for cervical infection, this approach has been generally disappointing for identification of cervical infection or for differentiating cervical from vaginal infection. Although risk factors for cervical infection can usually be identified, in most clinical settings even those with positive risk assessment have a prevalence of cervical infection too low to warrant routine treatment solely on the basis of positive risk assessment. A review of the literature by Pettifor and colleagues found that sensitivities for vaginal discharge algorithms ranged from 73% to 93% among women presenting with vaginal discharge symptoms and from 29% to 86% among asymptomatic women. Vaginal discharge was not seen to be an independently effective screening tool to detect women with cervical infection, especially in low-risk or asymptomatic populations, though the authors stress that incorporating risk scores tailored to local community risks can improve the accuracy of algorithms to detect cervical infection.⁹⁷

■ RISK ASSESSMENT AS A GUIDE TO SELECTIVE SCREENING FOR ASYMPTOMATIC INFECTION

Because many STIs are asymptomatic, particularly in women, risk screening based on presenting symptoms alone is insufficient. Even when symptoms occur, not all patients will recognize them as such. A national study involving five STD clinics whose populations have high STD knowledge and known access to care found that even with clinician questioning, 50% of new STIs were unrecognized by patients.⁹⁸ Behavior changes in response to STI symptoms (such as forgoing sex in the presence of vaginal or urethral discharge) may vary by gender and other patient characteristics and cannot in any case be presumed to occur universally.⁹⁹

In industrialized countries, STI/HIV risk assessment is probably used most extensively to guide selective screening for chlamydial infections and HIV infection, and to a lesser extent, to guide selective screening for gonorrhea and syphilis. The Centers for Disease Control and Prevention (CDC), the USPSTF, the Canadian Task Force on the Periodic Health Examination, and national clinical organizations recommended risk-based routine screening for chlamydial infection, with risk criteria generally focused on age and sexual activity (asymptomatic women aged <26 years with sexual activity or risk, or women over

age 25 who have risk factors such as new or multiple sex partners).¹⁰⁰ The CDC has created software that clinics can use to determine resource allocations based on chlamydia test and treatment costs, protocols, and prevalence.¹⁰¹ Since 2000, such screening has been included as a Health Plan Employer Data and Information Set (HEDIS) quality of care indicator in the United States.¹⁰²

Screening for *Chlamydia trachomatis* evaluated in one health maintenance organization resulted in a 56% decline in PID rates among women 14–55 years of age, for a relative risk (RR) of 0.44, 95% confidence interval (CI) 0.20–0.90.¹⁰³ Despite this apparent benefit, screening levels nationally remain low: 26% of female enrollees aged 16–26 years in commercial plans and 38% of those in Medicaid plans, in 2001.¹⁰⁴ This occurred even though payment for such screening is provided, highlighting some of the challenges to integrating STI screening even when such screening is recommended as a quality assurance measure and is a reimbursed procedure.

As the prevalence of gonorrhea has declined in the United States, the indications for cost-effective risk-based screening for gonorrhea have become less clear. Because syphilis in the United States tends to be geographically clustered, routine syphilis screening of asymptomatic persons is not recommended, though the USPSTF recommends screening all pregnant women and all persons at increased risk based on local incidence, including MSM who engage in high-risk sex, sex workers, persons who exchange sex for drugs, and adults in correctional facilities.¹⁰⁵ Syphilis outbreaks among MSM—many of whom were also HIV-positive, and often related to internet sex-seeking¹⁰⁶—in the early 2000s in some U.S. cities and western European countries did lead to an increased emphasis on bacterial STI screening in MSM.^{107,108} Screening for gonorrhea and syphilis in other populations has focused less on individual risk assessment and more on population and venue characteristics by screening in juvenile detention centers, jails and prisons, or in particular census tracts with relatively high rates of these two infections.^{109–112}

■ RISK ASSESSMENT IN HIV POSTEXPOSURE PROPHYLAXIS OR STD PREVENTIVE TREATMENT

Prophylactic or preventive treatment (to prevent occurrence of infection or disease manifestations, respectively) is commonly provided to patients with known or suspected exposure to an STI. Administration of antiretroviral therapy following occupational exposure to HIV via needle stick or mucosal contamination is an example of the importance of risk assessment in guiding therapy. Updated CDC guidelines regarding PEP in the occupational setting for HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) exposure recommend using a combination of risk assessments related to exposure inoculum and source patient risk to guide HIV

postexposure prophylaxis (PEP) therapy initiation and regimen selection.¹¹³ In most cases, a 4-week two-drug regimen is advised, with a third drug added for deep percutaneous or visibly contaminated exposures associated with higher risk of transmission.¹¹⁴ Consultation is available via the National Clinicians' Post-Exposure Prophylaxis Hotline ([PEPline] 1-888-448-4911).

Guidelines promulgated by the CDC first in 1998 and then in 2005 address the issue of using PEP in nonoccupational exposure situations (nPEP), i.e., involving sexual or IDU exposure. The earlier guideline factored in transmission risk related to the inoculum, the risk of the source, and also the likelihood of whether this nonoccupational exposure was likely to be sporadic or ongoing, to determine whether PEP administration was appropriate.¹¹⁵ The 2005 guidelines stratified risk, recommending a 28-day course of highly active antiretroviral therapy (HAART) for persons seeking care within 72 hours after nonoccupational exposure to blood, genital secretions, or other potentially infectious body fluids of a person known to be HIV infected, when that exposure represents a substantial risk for transmission. For persons seeking care within 72 hours after nonoccupational exposure to body fluids of a person of unknown HIV status, no recommendations are made for the use of nPEP. Clinicians are encouraged to evaluate risks and benefits of nPEP on a case-by-case basis.¹¹⁶

A review of European countries found that 23 of 27 had national guidelines regarding occupational exposure PEP, whereas only 6 out of 27 had policies for nonoccupational PEP.¹¹⁷ Emergency care clinicians are often on the front lines of determining both occupational and nonoccupational PEP utilization.^{118,119}

Prophylactic or preventive treatment may be offered to individuals following known exposure to an STI, while test results from the exposed individual are pending (e.g., for *C. trachomatis* or *Neisseria gonorrhoeae*); or even if initial screening test results are negative (e.g., for syphilis); or in the case of sexual assault. In these cases, the risk assessment consists of defining whether the time of exposure of the individual to the person with a known STI fell within the period when that person was potentially infectious (e.g., within 2 weeks or less before recognition of symptoms of gonococcal urethritis); or was sufficiently recent that the exposed individual might still be in the incubation phase prior to seroconversion to a reactive serologic test for syphilis. In the case of sexual assault, the CDC recommends STI evaluation and prophylaxis, with consideration of HIV exposure likelihood for nPEP.^{120,121} Despite these guidelines, analysis of the National Hospital Ambulatory Medical Care Survey has noted that a large proportion of patients are neither screened nor receive STD medications in EDs following forcible rape.¹²²

BROADENING ACCESS TO STI SCREENING AND PREVENTION

Efforts to modify sexual and drug use risk behaviors to decrease the transmission of HIV infection and other STIs have been effective in selected populations. However, STI incidence is increasing in some populations such as MSM,¹²³ and HIV seroprevalence continues to increase among large groups such as minorities and women. In addition, moderate- or high-risk sexual behaviors remain common in many populations. The dynamic epidemiology of STI/HIV infection necessitates a broad approach to assessing risk behaviors. It is not adequate to concentrate HIV risk assessment solely on MSM or IDUs in high-prevalence regions. Risk assessment should become a part of routine clinical care throughout the United States and in most parts of the world. As heterosexual HIV transmission increases, it becomes important not simply to address an individual's personal sexual and drug use history but also the risk of the individual's sexual partners and social and sexual networks.

Although changing epidemiology makes risk assessment increasingly challenging, the changing patterns of health-care delivery in the United States and elsewhere may provide opportunities that will facilitate systematic risk assessment. The increase in managed care and large systems of health-care delivery offer the opportunity to define effective risk assessment practices in different communities and implement standardized and effective risk assessment strategies. The ability of managed care organizations to promulgate and monitor practice guidelines provides unique opportunities to enhance STI/HIV risk assessment and risk reduction counseling. This may be accomplished through relatively low-cost means, as in one study that used key providers as opinion leaders to reinforce STD screening practices. This intervention was associated with increased patient recall of providers asking about sexual risk factors (OR 1.7; 95% CI, 1.2–2.6) and discussing personal risk reduction (OR 2.6; 95% CI, 1.6–4.3). Overall, 52% of patients with self-reported high-risk behaviors recalled discussing these topics with their provider, an absolute improvement of 13% from preintervention levels, though short of the 75% counseling level recommended by the USPSTF.

A review of STD guidelines has emphasized elements that make guideline incorporation more likely in managed care organizations. These include focusing on primary prevention, addressing health systems practice integration issues, and promulgating the guidelines in the form of pocket handbooks or online versions,¹²⁴ which may be downloaded to personal digital assistants (PDAs) increasingly used by providers. Encouragingly, a seven-city review of STD guideline compliance among Medicaid managed

care organizations found that most organizations and primary care providers interviewed provided recommended preventive counseling while taking a sexual history (though higher-cost services such as partner notification were less often provided).¹²⁵

Partnerships between managed care organizations, which can provide primary and secondary STD/HIV prevention, and categorical public STD clinics, which will likely continue to see high-risk “core group” attendees, may be facilitated by collaborative agreements.¹²⁶

STI/HIV RISK ASSESSMENT IN CLINICAL SETTINGS: CURRENT RECOMMENDATIONS AND CURRENT PRACTICE

Many agencies and professional organizations recommend that clinicians routinely perform STI/HIV risk assessment, and/or offer voluntary screening and counseling to individuals seen in clinical settings, including HIV clinics. Such organizations include the USPSTF, the CDC, the American Medical Association, the Infectious Disease Society of America, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the American Academy of Family Physicians, the Canadian Task Force on the Periodic Health Examination,¹²⁷ and the World Health Organization.^{128–134}

Despite these recommendations, clinicians do not consistently or adequately screen for sexual and substance use-related STI/HIV risk among their patients. A national survey of 4,226 randomly-sampled U.S. physicians found that fewer than one in three routinely performed STI screening of men or women (pregnant or nonpregnant).¹³⁵ In a representative survey of 3390 adults aged 18–64 (the 1994 U.S. National Health Interview Survey), only about one-quarter of U.S. adults reported being asked about STDs during routine checkups; being under age 45, male, and with income below federal poverty level was associated with increased likelihood of discussion. An indicator of provider discomfort may be surmised by noting proportions of patient who said their provider asked about the patient's smoking (58.7%) and exercise (52.3%), versus about illegal substance use (31.3%) and sexual activity (27.9%).¹³⁶

Adherence with STI screening recommendations is often low even in settings serving at-risk populations, such as in EDs¹³⁷ and among obstetrician-gynecologists.¹³⁸ The infrequent provision of preventive STI/HIV services to adolescents in a variety of health-care settings is especially troubling.¹³⁹ One study of a California health maintenance organization found that pediatricians, on average, screened 92% of their adolescent patients for immunization status but only 34% for sexual intercourse.¹⁴⁰ Physicians' self-reported practice of preventive health measures and counseling may overestimate actual practice patterns.^{97,98} One study of

primary care physician screening found that even among standardized patients with classic presentations for HIV and STDs, risk assessment was highly variable.¹⁴¹

Fewer data are available on the performance in STI/HIV risk assessment and risk behavior counseling of clinicians other than physicians. A survey of 1265 randomly selected clinicians in Colorado found that obstetrician-gynecologists, nurse practitioners, and pediatricians were most likely to report regularly taking a sexual history (90.1%, 88.6%, and 76.0%, respectively), while internal medicine specialists were the least likely (43.9%).¹⁴² Another study using unannounced standardized patients found that only 18% of physicians and 27% of nurse-practitioners asked about history of STDs, while 18% and 63%, respectively, inquired about condoms and IDU.¹⁴³ Some studies suggest that female and younger clinicians are most likely to assess and follow up on STI risk with their patients.¹⁴⁴

■ PROVIDER–PATIENT COMMUNICATION

This dearth of routine STI/HIV risk assessment may occur because some clinicians lack the tools and training; experience discomfort and embarrassment;^{145,146} or are constrained by time demands, financial disincentives,¹⁴⁷ or confidentiality concerns that prevent them from performing extensive risk screening and counseling. Regardless of the reasons, and despite widespread recommendations, clinician-initiated risk assessment is not being performed in most primary care settings. Thus, in clinical settings there are many missed opportunities both for STI/HIV control as well as for holistic care, given that many patients have sexual lives and concerns.

Patients want to discuss sexual health with their providers, even when they think their doctor may be dismissive of their concerns, according to one poll,¹⁴⁸ and are willing to disclose sensitive sex and drug use behaviors to their clinicians when asked.¹⁴⁹ It has been noted, however, that while adolescents want to talk about sexual issues,¹⁵⁰ few will initiate the conversation.^{151,152} Stigma (i.e., a societal response seen to set someone apart) has been identified as a significant potential barrier both to disclosure of sexual behaviors to health providers and to STD care-seeking services among females in a Baltimore household sampled-study population.¹⁵³ If patients perceive that providers are uncomfortable with discussions of sexual and drug-use risk behaviors, they are less likely to disclose important information. A UK study of gay men, for example, found that fewer than one in three (30%) had discussed safer sex with their general practitioner, compared with 87–92% who had talked about it with lovers and friends, respectively ($p < 0.001$).¹⁵⁴ Creating a clinical practice climate where STI/HIV risk assessment and counseling are routine can be an effective way to ameliorate patient concerns and reduce STI/HIV-related stigma.

■ BENEFITS OF RISK ASSESSMENT IN PREVENTION AND MANAGEMENT OF STIs/HIV AND THE COSTS OF MISSED OPPORTUNITIES

The benefits of appropriate risk assessment for HIV and STIs can be divided into two categories. First, the benefits to those with unidentified infection include preventing complications, limiting progression, and, where possible, curing infection. Second, the benefits to those at risk for infection but still uninfected include preventing acquisition of infection through appropriate treating of any infection and stimulating risk reduction.

In addition, risk assessment in the context of family planning and prenatal care¹⁵⁵ can help reduce maternal and neonatal morbidity and mortality. This involves tailoring risk reduction counseling, STI/HIV tests or referrals, and contraceptives, including dual method use¹⁵⁶ and/or access to emergency contraception,¹⁵⁷ to the patient's needs. For example, those at increased risk for STDs would be poor candidates for IUDs but may be good candidates for barrier or dual methods.

Benefits to those with unidentified HIV infection

HIV risk assessment leading to voluntary HIV testing represents the first step in the provision of direct health benefits to individuals with undiagnosed HIV infection. Such health benefits include vaccinations, prophylactic therapies, and antiretroviral therapy that, together, can greatly improve both the quantity and quality of life for these individuals. HAART regimens have improved the survival and quality of life for persons with HIV infection, including in resource-poor settings¹⁵⁸ where they have become more available in recent years. Timely initiation of HAART optimizes survival and cost-effectiveness;¹⁵⁹ thus, risk assessment can identify individuals early enough to realize maximum benefit from these therapies. In addition, the myriad of prophylactic measures that can be instituted for primary prevention of opportunistic infections in persons with HIV infection make it critically important that individuals with early HIV infection be identified and offered the appropriate prophylactic measures.¹⁶⁰ Many of these interventions, such as pneumococcal and other types of vaccinations and skin testing for identification of tuberculosis infection, will be most effective if performed as early as possible in HIV infection.

In the United States, up to an estimated 30–40% of HIV infections have been diagnosed late in the course of disease. One study of a managed care organization's membership found that 26% of patients diagnosed with HIV had risks documented in their charts at least 1 year prior to diagnosis, and that this was an underestimate of actual risk. The authors concluded that in their population, effective risk assessment of demographics and behavioral factors would have been more effective than eight HIV-associated clinical indicators

(such as unexplained cachexia or lymphadenopathy) to identify HIV infection in individuals who could benefit from HIV treatment.¹⁶¹ Given these HIV treatment advantages, and to reduce late diagnoses, as early as 2000, some called for expanded routine HIV screening in health-care settings.^{162,163} Screening based on risk factors does identify persons at substantially higher risk but could miss a substantial proportion of those infected. Therefore, the CDC and others have concluded that routine offering of HIV testing to sexually active adults is warranted.

Another potential benefit of identifying individuals with HIV or STIs is the possibility of notifying previous sexual partners of their risk for these infections. Partner notification is an underutilized public health measure, particularly for HIV. One U.S. survey of jurisdictions with 500,000 or greater population or that reported 200 or more AIDS cases in 2001, found that health departments interviewed fewer than one in three people with newly reported HIV (32% of 20,353 persons).¹⁶⁴ Partner counseling and referral services can take the form of information sharing conducted by the index patient alone (patient referral), provider or health department alone (provider referral), or through a combination of these strategies (Chapter 54).¹⁶⁵

Providers often express a preference for patient referral;¹⁶⁶ however, not all patients are able or willing to disclose STI/HIV exposure information to sex partners¹⁶⁷ and should be able to receive health system assistance to do so. Provider/health department notification can, on the whole, be more effective. One early randomized controlled trial of partner notification for HIV infection found that when individuals had full responsibility for notifying their partners, only 7% of the partners were notified. If, however, counselors were available to assist in partner notification, 50% of partners were successfully notified and, of the partners notified, 94% were unaware that they had been exposed to HIV; 23% of those notified and tested were HIV-positive.¹⁶⁸ Voluntary partner notification programs have been found to be acceptable to HIV-positive individuals and have been successful at notifying individuals of their risk for HIV infection.¹⁶⁹ Ongoing evaluation of the need for sex partner counseling and referral services is important, as not all individuals living with HIV will necessarily disclose their status to all new sex partners over time.¹⁷⁰ Despite the current inadequacy of recommending and producing partner notification, risk assessment and selected STI/HIV screening can lead to the identification of previous partners who would benefit from testing, early intervention, risk-reduction counseling, screening for STIs, and secondary HIV prevention, among persons living with HIV.

Many individuals do reduce sexual and other transmission risk behaviors once they learn that they are HIV-positive.^{171,172} Several meta-analyses of studies from the United States, Europe, and Africa have shown that the majority of individuals

found to be HIV-positive reduce their risk behaviors.^{173–175} However, studies show that clinicians often fail to address the critically important issue of HIV transmission risk reduction with their HIV-positive patients.¹⁷⁶ Guidelines for doing so have been published.¹³¹ In one study of 618 HIV-positive patients as they exited from their health providers' office, only 6% said that they had experienced a detailed risk assessment of specific behaviors such as partner gender, type of sex, and condom use, from their provider that day.¹⁷⁷ Infectious disease specialists, who often provide excellent HIV clinical care, were found in several studies to be significantly less likely to provide counseling around condom and substance use.^{178,179}

Clinical HIV care providers have limited time that is often focused on medication management and lab monitoring.¹⁸⁰ The importance of long-term supportive relationships often established by HIV providers with their patients may accentuate providers' fears that bringing up sexual and substance use risk behaviors that can transmit HIV could undermine that relationship. Nonetheless, relatively high incident STI rates demonstrate the missed opportunities for STI detection among HIV-positive individuals.^{181–183}

Encouragingly, brief, clinician-delivered counseling can reduce sexual risk behaviors among persons living with HIV. Two meta-analyses have shown that interventions, including those delivered in HIV care settings, can reduce unprotected sex and incident STIs among persons with HIV.^{184,185}

Richardson and colleagues have shown that “loss” or consequence framing of prevention messages may be more effective than “gain framing” in promoting safer behaviors among HIV-positive persons engaged in risky sex. The loss-frame counseling approach emphasizes consequences—“Unsafe sex may expose you and others to other STDs and strains of HIV”—rather than advantages of safer sex. Individuals presented with these messages in a randomized trial had significantly less unprotected sex at follow-up compared with those presented with gain framing messages emphasizing the benefits of condom use (OR 0.42, 95% CI 0.19–0.91).¹⁸⁶

Another promising intervention uses a scaling algorithm to have patients assess their self-confidence and importance of risk behavior change and provides “prevention prescriptions.”¹⁸⁷ Similar prevention counseling risk reduction “contracts” have been found effective in reducing sexual risk behaviors among persons living with HIV in Uganda.¹⁸⁸

Benefits to those with other unidentified STIs

The individual patient benefits of risk assessment and selective screening for chlamydial infection have been demonstrated by Scholes and colleagues, who showed more than a 50% reduction in the risk of PID among women randomly assigned to selective risk-based screening for *C. trachomatis* infection.¹⁰³ Similarly, risk assessment prior to IUD insertion to exclude those at risk of STIs is the standard of care to

prevent IUD-related PID.¹⁸⁹ For any of the curable STIs, risk-based screening followed by treatment can lead to secondary prevention of complications at the individual level and primary prevention of transmission at the population level.⁵

Benefits to those at risk but without STI or HIV infection

Risk assessment plays an important role in the prevention of further transmission of HIV and other STIs. For those with HIV infection, risk behavior screening and HIV testing can be the first step to behavioral interventions that can limit the transmission of HIV to those who are uninfected. Addiction treatment, needle exchange programs, and primary care for substance users also decreased reported high-risk behaviors among IDUs.^{190,191} Similarly, HIV-related risk reduction efforts, when added to the improving early diagnosis and treatment of curable STD, have undoubtedly contributed to the declining incidence of these other STDs.

For individuals with STI/HIV risk behaviors who screen negative for infection, provision of risk reduction counseling is optimal since behavior change among those testing HIV negative may be more difficult. Several randomized clinical trials of behavioral interventions in individuals at increased risk of STI have achieved significant reduction in STI incidence and in reported risk behaviors.¹⁹² HIV risk reduction interventions may also be successful among HIV-negative IDUs,¹⁹³ although such interventions may require more complex approaches than the standard individual counseling approach that is routinely offered with HIV and STI testing.¹⁹⁴

■ THE COSTS OF MISSED OPPORTUNITIES FOR RISK ASSESSMENT

“Missed opportunity” has been defined as an encounter with a health-care provider, by a patient who is engaging in risk behavior, where testing¹⁹⁵ and risk reduction counseling was not performed. The overall population-level costs of missed opportunities for STI/HIV risk assessment could ultimately exceed several billion dollars in direct medical costs in the United States to the extent that risk assessment leads to selective early detection and treatment, to effective risk reduction counseling and education, and ultimately to the secondary prevention of complications and to primary prevention of transmission.¹⁹⁶ Widespread risk assessment for HIV (and STIs) and appropriate selected screening could potentially lead to the prevention of a substantial proportion of these illnesses.

METHODS FOR ASSESSING HIV AND STI RISK

Screening for HIV infection or STIs can be implemented in a variety of different ways: screening can be routine or selective, voluntary or mandatory, and confidential or anonymous.

Screening is routine when HIV serology or STI screening cultures or serologies are offered to every individual regardless of risk profile. Selective screening involves testing following risk assessment; screening is recommended to those individuals for whom a certain level of risk is identified. Both routine and selected screening can be mandatory or voluntary and both can be anonymous or confidential. Routine voluntary HIV or STI screening is cost-effective and indicated when the prevalence of infection exceeds a certain level and when effective interventions are available. In this circumstance, the virtues of routine screening outweigh the potential harm of false-positive tests because of the large number of infected individuals identified. The cost-benefits of screening for STIs depend on the cost of the various tests available, the prevalence of infection, and the costs of the specific STI and its complications and sequelae.

In many health-care settings throughout the world routine testing for HIV infection or other STI is neither indicated nor feasible, since if the population is low-risk a substantial proportion of those with positive screening tests would represent false-positive tests, with potentially substantial financial and emotional costs. Consequently, in many health-care settings, selective voluntary screening based on risk assessment to identify individuals at increased risk for HIV or STI will remain the most effective method of targeting those individuals who should be offered HIV and STI screening, unless HIV seroprevalence is 1% or greater, where HIV testing should be routinely offered. In settings offering routine testing, risk assessment is still important in order to identify those uninfected with STIs/HIV but at high risk of acquiring infection.

■ STRATEGIES FOR CONDUCTING STI/HIV RISK ASSESSMENT

Ideally, STI/HIV risk assessment should be part of routine screening for all patients in most clinical settings. STI/HIV risk assessment could be accomplished in all patients if it were made part of a routine history and physical on a new patient and during an annual checkup for a patient in ongoing care. There are a number of additional circumstances under which STI/HIV risk assessment is especially important, for example, when a patient presents with the symptoms or signs of an STD- or HIV-related problem; when a patient is pregnant or wants to become pregnant; when a woman initiates contraceptive care; when a patient asks a question about an STI, or HIV or about sex; and when men initiate drug therapy for erectile dysfunction, given a possible association between use these drugs and STI/HIV acquisition, at least among MSM.^{197,198}

Systematic methods to provide uniform STI/HIV risk assessment are an important component of identifying those at risk for infection. Systematic methods can include

approaches targeting clients, clinicians, or clinics. Approaches targeting clients can include routine written screening instruments given to all new clients; computer-based screening programs designed to identify risk and educate; and written educational materials available to those interested. Providing statements regarding confidentiality,¹⁹⁹ STI/HIV posters, and safer sex supplies in visible locations throughout the care setting demonstrates through visual clues that sexual health matters are an open and important part of the clinic climate. Approaches targeting clinicians include education in risk assessment methods, checklists or computer prompts to remind clinicians to assess risk, and the institutional expectation that risk assessment is a part of each new patient visit. System approaches can include all of the preceding methods when a clinic or health-care system formalizes these methods. Also important are dissemination of evidence-based practice guidelines for clinicians.

Given the importance of risk assessment and the difficulties that clinicians have in routinely providing this screening, one solution is to develop a screening instrument that could be administered to all individuals seen in a health-care setting. Such an instrument could be completed in a waiting room and used to signal clinicians that follow-up questions and voluntary HIV or other STI testing may be indicated. Many clinicians have a medical history intake form to which HIV or other STI risk assessment questions could be added. Some countries such as the UK and Australia have defined sexual health minimum data sets that will encourage standardization of data elements collected in settings that see people at risk for STI/HIV. In the United States, a set of standardized items for HIV behavioral surveillance (though not clinical risk assessment per se) has been developed.²⁰⁰

Several sample HIV risk behavior questionnaires have been published, but none with systematic input from the target population, and few have been formally validated. A 10-item HIV screening instrument for use in primary care settings was shown to have an internal consistency coefficient of 0.73; however, its predictive power was not tested for identification of actual HIV and it did not focus on screening for other STIs besides HIV.²⁰¹ An individual “potential risk index for STI” based on the reproductive rate formula (Fig. 48-1) has been developed but again, not validated for screening discrimination performance using STI biomarker outcomes.²⁰² A clinical prediction rule for HIV seroconversion among MSM developed in one STD clinic population and validated against a second, national sample found that five factors accurately predicted 65% of incident HIV acquisitions (area under the receiver operating characteristics curve 95% CI: 0.63–0.67).²⁰³

Risk assessment in the individual clinician–patient encounter requires that clinicians ask culturally sensitive, understandable risk questions and provide an environment that allows patients to reveal potentially embarrassing or

even illegal information. It is important to be aware of culture-specific stigma issues, such as prohibition against same-sex behavior in the African American population, or concerns about family shame in some Asian populations.²⁰⁴

Ideally, assessing STI/HIV risk involves not just checking off a list of defined chart form elements but exploring with patients their sexual lives in the overall social and current life priorities context. Avoiding the tendency to focus on biomedical and pharmacologic approaches to sexual health necessitates understanding patient behaviors in regard to relational, psychosocial, cultural, and economic influences.²⁰⁵ This “new view” approach to sexuality²⁰⁶ is not the paradigm in which many clinicians were trained but is one that likely resonates with patients themselves, since it treats them as whole people rather than reducing them to a matrix of risk factors and specimen collection sites.

Figure 48-3 shows one suggested approach to a brief STI/HIV risk assessment involving a limited number of initial questions to be asked of all patients and follow-up questions when the initial questions suggest that risk is present.²⁰⁷ There may be local or regional differences in language concerning sexual and drug use activity, and it behooves clinicians to know these variations in language to maximize the effectiveness and cultural relevance of their risk assessment.

■ FRAMING THE QUESTION IN RISK ASSESSMENT

Respondents who do engage in sexual risk-taking and who may even perceive this as risky may nonetheless not report risk-taking. Reasons for this at a clinical encounter may include fears that admitting risk could endanger employment or lead to other discrimination, in addition to the usual concerns about embarrassment and loss of face. It is helpful to use language, tone, and body language that suggests that the clinician is respectful, concerned about their patient’s health, and will not be judgmental. Being empathetic, repairing problematic language by asking for clarification or by reframing one’s questions, and being able to negotiate awkward moments while still persevering to elicit the patient’s sexual health issues have been found to substantially improve patient-provider STI/HIV discussions.²⁰⁸

The sexual history should be conducted sitting at eye level, while the patient is still clothed. It is helpful to start by providing a rationale for the risk assessment. One approach is to tell the patients that risk assessment for HIV and STI is an important part of health-care delivery and that the clinician performs this type of risk assessment with all patients. For example, the California Chlamydia Action Coalition²⁰⁹ recommends introductory statements tailored for teens and one for adults as follows:

- *For teens:* “Now I am going to take a few minutes to ask you some sensitive questions that are important for me to help you be healthy. Anything we discuss will be completely

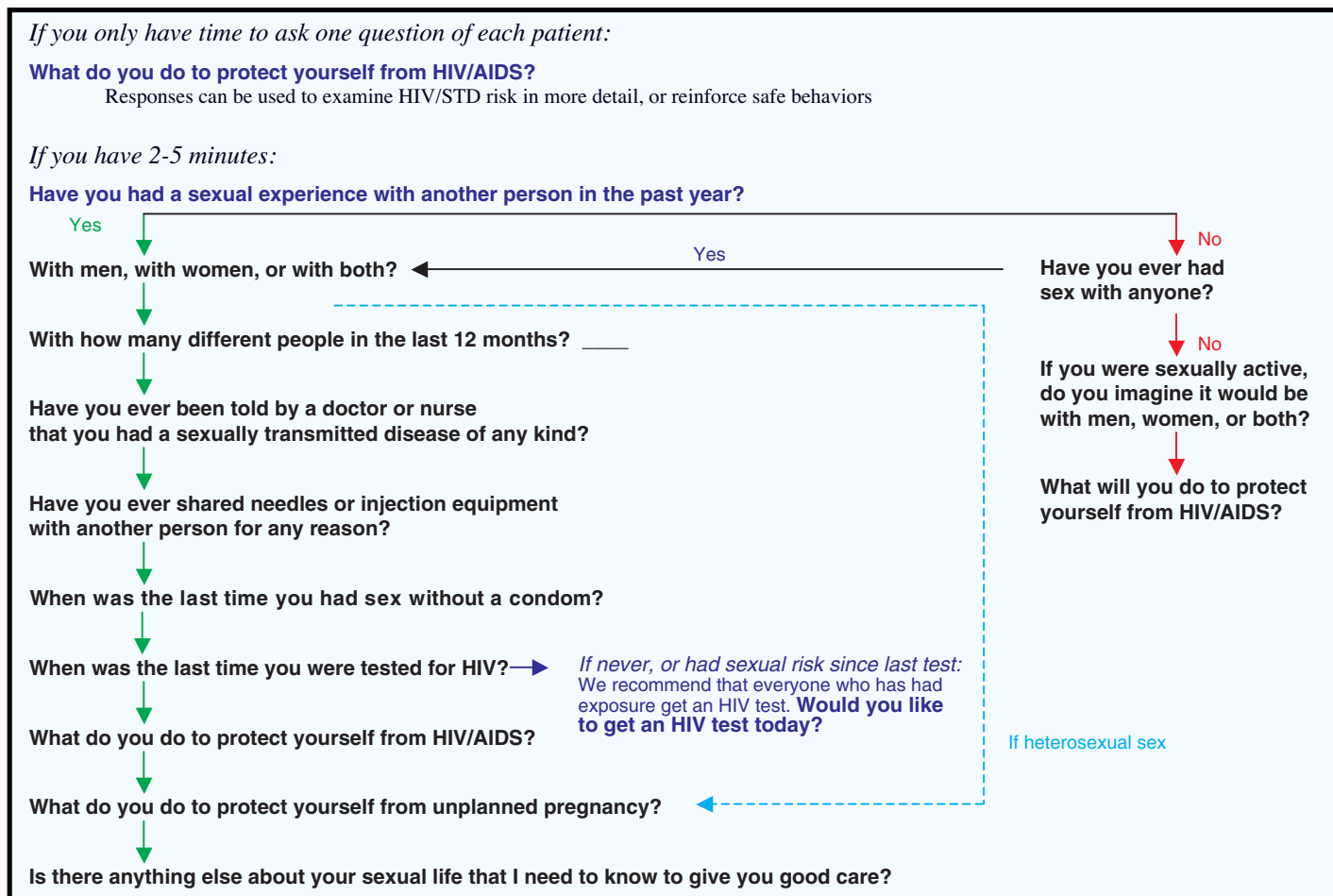


FIGURE 48-3. An abbreviated sexual history. (Adapted from Hatcher R, Trussel G, Stewart F, et al. *Contraceptive Technology*, 18th rev. edn. New York: Irvington Publishers, 2004; Nusbaum MR, Hamilton CD. The proactive sexual health history. *Am Fam Physician*. 2002; 66(9): 1705–1712.)

confidential. I will not discuss this with anyone, not even your parents, without your permission.”

- *For adults:* “Now I am going to take a few minutes to ask you some direct questions about your sexual health. These questions are very personal, but it is important for me to know so I can help you be healthy. I ask these questions to all of my patients regardless of age or relationship status and they are just as important as other questions about your physical and mental health. Like the rest of this visit, this information is strictly confidential.”

The goal of this introduction is to assure the patient that he or she was not singled out for risk assessment because of mannerisms, appearance, race, ethnicity, or some other factor.

Individual questions can be framed in a normalizing way to increase an individual’s willingness to answer certain questions. For example, a clinician may say, “Many people have experimented with drugs such as cocaine or methamphetamine” before asking an individual about past amphetamine use. This type of framing is not necessary in all circumstances but may be helpful in some situations

when a clinician believes that a patient may be reluctant to reveal risk behaviors. Kassler and colleagues offer a series of additional framing statements giving “permission” to discuss taboo topics and to introduce specific questions.²¹⁰ For example, “Many women find it difficult to get their men to use condoms; has this been a problem for you?” “Many men have sex with other men. Have you ever had sex with another man?”

It is useful to ask direct questions about specific behaviors.²¹¹ Use of open-ended questions (e.g., “what are you doing to protect yourself from HIV and other STIs?”) can yield substantive information regarding patient’s risk perceptions and behaviors and may stimulate insights for both the patient and the provider.²¹² In general, “how,” “what,” “where,” types of question can be better used to explore behavior than asking “why” did you or “have you ever” [done this socially stigmatized behavior] sorts of questions.²¹³ Most clinicians are trained, however, and most clinical data forms are designed, to utilize closed-ended questions (“Did you use a condom?”). Both question types have their place when used to elicit specific information as well as to assess risk context and the need for personalized counseling.

The range and depth of questions asked in a risk assessment may vary depending on the venue and setting. For example, in outreach settings a brief but focused set of questions may be appropriate, whereas in primary care settings a more patient-centered focus on risk screening may be effective.²¹⁴

■ SPECIFIC CATEGORIES OF INFORMATION NEEDED IN A COMPREHENSIVE STI/HIV RISK ASSESSMENT

Many sets of practice guidelines, including the evidence-based and influential Guide to Clinical Preventive Services, recommend STI/HIV preventive interventions that depend on risk assessment. The lack of specificity and validation of instruments for this purpose continues to represent the “Achilles heel” of such recommendations. Nonetheless, there are some common assessment domains that are reflected across many of these guidelines. Taken as a whole, and considering the epidemiological evidence related to STI/HIV risk, these may include assessment of the following:

- STI symptoms
- Sexual activity
 - Sex with men, women, or both.
 - Types of sex (vaginal, anal, oral).
 - Use of protective methods, especially condom consistency and correctness (assess user errors).
 - Number and type of recent sex partners (e.g., new, main, anonymous).
- Sex partners’ risk, including HIV status, history of STDs, or IDU
- History of STDs
- Exchange of sex for money or drugs
- History of parenteral exposure (needle-sharing) and other substance use (such as amyl nitrites or crack cocaine)
- HIV testing and hepatitis vaccination history
- Among women, contraception usage including emergency contraception access; menstrual, obstetrical, and gynecologic history; cervical screening (Pap smear or HPV, any cervical dysplasia)

We now discuss elements that may be incorporated into an STI/HIV risk assessment, as conducted in a clinical sexual history. Assessment of risk may take into account consideration of the local epidemiology of STIs. Specific risk factors differ from one country or population to another, and providers and STI/HIV control programs should try to establish what demographic characteristics, behavioral risk factors, and clinical symptoms and signs are associated with the various STIs seen in their own settings.

Demographics

Key demographic data that may serve as potential markers for STI risk in some settings and are available on any clinical intake form include gender (male, female, transgender), area of residence, age, date of birth, and relationship status. Educational level and race/ethnicity (as a proxy measure) may also be helpful in some settings. All could be used to provide standard prompts to clinicians as to STI/HIV risk, and these alone could be sufficient in some settings to prompt screening or more comprehensive risk assessment for certain STIs.

Age

Young age (e.g., ≤ 25 years) is a risk factor in nearly all societies (especially true in females) both for physiologic reasons (cervical ectopy in the young female,²¹⁵ less immunity) and behavioral reasons (more partners, rapid partner change, less condom use negotiation power²¹⁶ or skills). Of note, age of the partner discrepant from that of the patient, has been found in some studies to be a risk factor for HSV-2²¹⁷ and for HIV infection.²¹⁸

Race/ethnicity

There are no empiric data to suggest innate or biological reasons for the higher rates of STI/HIV seen among certain subpopulations in many settings such as in the United States. Reasons for this “racial” differential may include reporting bias,²¹⁹ reduced knowledge of and access to screening and treatment services,²²⁰ high rates of incarceration²²¹ (and resultant disruption of the sex ratio²²² and social disorganization²²³), higher STI/HIV community or sexual network prevalence,²²⁴ and assortative sexual mixing by race,²²⁵ in some populations (Chapter 7). The fact that in many settings minority populations have higher rates of STI/HIV, may support the need for improved screening and treatment services in these populations.

Relationship status

Partnership status (single vs. married or living with a regular partner) may or may not be a risk marker, depending on the local context. In many resource-poor settings, marriage is a significant HIV risk factor for women.²²⁶ A meta-analysis of studies from non-Northern African countries found that the impact of socioeconomic status on HIV risk varies depending on whether the woman is married or unmarried.²²⁷

Sexual history: risk and satisfaction

Two main objectives of sexual history taking are assessment of STI/HIV risk and assessment of sexual function and satisfaction. The latter purpose may at times be overshadowed by an overly vigilant focus on the former.

The basic types of information sought include risk of exposure to STIs/HIV (whether or not the individual has ever had sex; the number and “riskiness” of sex partners; types of sex practices and “riskiness” of these practices) and the risks of acquiring STIs if exposed (methods and consistency of methods used to prevent STIs/HIV). Ascertaining both consistency and correctness of condom use is important, as user errors such as delayed application of a condom after sex starts, taking it off before sex ends, or putting it on backwards, occur even among regular condom users.²²⁸ Incorrect condom use, including delayed application, has been associated with HIV seroconversion among MSM.²²⁹

The prevalence of sexual dysfunctions has been estimated from a review of 52 community sample studies at 0–5% for erectile dysfunction, 4–5% for premature ejaculation, and 7–10% for female orgasmic disorder.²³⁰ Assessing individuals’ satisfaction with their sexual lives and functioning is, therefore, an important component of a complete sexual history.²³¹ Furthermore, an overemphasis on STI and HIV risk can “pathologize” sexual behavior, neglecting the reality that people engage in volitional sex, even when it is high-risk, in order to feel pleasure and connection to others. A number of sexual function assessments have been developed though none of these are brief enough to be particularly useful in limited clinical encounters.²³² Simply asking a single question about sexual functioning²³³ can be a starting point to elicit specific concerns.

Context of risk taking

A given sexual history may reflect high or low risk, depending on the ecological setting where sexual encounters occur (high or low STI prevalence in sexual network characteristics). Assessing the social context in which high-risk exposures occur (e.g., in substance-using situations, bar venues,²³⁴ or bathhouses²³⁵) can provide the information needed to develop an individualized risk reduction plan.

STD history

The question, “Have you ever been told by a health-care provider that you had an STD of any kind?” identifies those who by definition have had high-risk exposure and should lead to probing to identify specific infections that can be reacquired by reexposure within the originally infected sexual network, as well as those who can be chronic or recurrent or carry a risk of late sequelae. A formal checklist of the major STDs for self-administered questionnaires may elicit positive responses not elicited by a more general question.

Partner risks, including HIV status

The question, “Have you ever felt that a sex partner put you at risk for any reason?” may uncover rape or abuse, as well as

a history of a partner’s high-risk behaviors (e.g., IDU, commercial sex, concurrent sex with others, multiple sex partners) or a history of an STD diagnosis or STD syndrome in a partner that should prompt STI screening.

It is crucial to ask the HIV status of sex partner(s) with whom there has been unprotected vaginal or anal sex, to ascertain whether or not that sex is seroconcordant and what might be the risks for primary or secondary HIV transmission.²³⁶ Seroconcordant sex, sometimes called serosorting,²³⁷ occurs when HIV-positive individuals choose to have unprotected sex with other HIV-positive people and HIV-negative individuals choose to have sex with other HIV-negative individuals. Another behavioral variant is negotiated safety, or strategic positioning,²³⁸ wherein some HIV-positive MSM choose to be only the “bottom” or receptive partner in a sexual encounter,²³⁹ on the assumption that HIV acquisition is less likely for the insertive partner, and transmission is less likely from the anal-receptive partner. Because this establishes a dead-end for viral transmission and limits HIV spread to susceptibles, HIV serosorting, if practiced exclusively, theoretically could potentially have population-level beneficial impact. However, this behavior still facilitates transmission of other STIs and may harm the individual(s) by putting them at risk of HIV superinfection²⁴⁰ with other strains including drug resistant variants, thus complicating clinical management.

One critical presupposition of serosorting is that actual and truthful conversation about respective HIV status takes place prior to sexual exposure, two conditions that may not always be met. A South African study of recently HIV-diagnosed heterosexuals found that 78% had not disclosed their HIV serostatus to their sexual partners and 46% had no knowledge of their sexual partner’s serostatus; nondisclosers were more likely to be male and to not use condoms.²⁴¹ Another study in the United States comparing the accuracy of HIV-infected persons’ reported knowledge of their sexual partners’ HIV status and the true infection status of partners found agreement of only 46% ($\kappa = -0.06$), less than that expected by chance.²⁴² Those who have had negative HIV tests in the past are susceptible to new, acute HIV infection, and it is these persons who are most infectious. This probably helps explain why a substantial proportion of those with incident HIV infection report only having had sex with persons who reported being seronegative.

The universal challenges underlying HIV disclosure can be seen in studies that have shown in a variety of settings and populations that HIV disclosure may not always take place,¹⁸³ may be delayed until after sex has occurred,²⁴³ or that unexamined assumptions regarding perceived HIV status still occur without any clear disclosure discussion or negotiation. Willingness to disclose may depend on the type of sexual partnership involved. Less willingness to disclose if the partner is anonymous or casual has been noted in some

studies of MSM,^{244,245} whereas fear of violent partner reaction may be an impediment to HIV disclosure for others, particularly women. Thus, unprotected sex between people of discordant or unknown status obviously still occurs, accounting for an unknown proportion of incident HIV infections.²⁴⁶ While the evidence on whether HIV disclosure results in more condom-protected sex is mixed,²⁴⁷ a harm reduction approach for counseling with HIV-positive patients might follow this hierarchy:

- “If you are HIV positive, it is best to discuss your status with all sex partners, *and* to always use condoms correctly, to protect against passing HIV to others and to avoid getting STIs or other strains of HIV yourself.” [disclose and use condoms]
- “If you are not going to discuss your HIV status with your sex partners, then always use condoms correctly in every sexual encounter.” [if not disclose, then use condoms]
- “If you are not going to use condoms correctly in every sexual encounter, then at a minimum discuss each others’ HIV status so that you can both choose what level of HIV transmission risk you and your partner(s) are willing to take.” [if not use condoms, then disclose/negotiate]

Clinicians can assist their patients in this difficult area by encouraging strategies and skills for discussion of STI/HIV risk and sexual communication between partners.²⁴⁸ Simply focusing attention on this issue may be effective; one randomized trial of 387 HIV-positive individuals who reported engaging in unprotected sex with HIV-negative or partners of unknown serostatus found that several counseling strategies (including a control condition) were equally effective in reducing the median number of unprotected sex acts from 14 to 4 at 12-month follow-up.²⁴⁹

STD symptom review

The routine review of symptoms should include questions about dysuria; past or current genital sores or lesions; abnormal vaginal discharge (i.e., increased amount, abnormally yellow color, or abnormal odor); vulvar pruritus or burning; low abdominal or pelvic pain in the female; testicular pain or swelling; and skin rash. In general, such symptoms, when presented spontaneously or in response to an open-ended question as the chief complaint or reason for visit, have a higher predictive value for STIs than when elicited in response to a specific query or checklist.²⁵⁰

STD history

A history of STDs or PID or of syndromic treatment for a reproductive tract infection predicts increased risk of current STDs, particularly if the partner was not treated or the underlying risk behaviors persist.^{251,252} Even with partner treatment, the persistence and rediffusion of an STD within wider sexual networks may not be adequately addressed.

When the patient is aware that the partner has had recent symptoms of an STD, such as urethral discharge, genital sores, or pain when urinating, several studies document increased risk in the patient. The prevalence of STIs is also increased in association with several symptoms or signs of STDs in the patient her- or himself, particularly those symptoms presented as a chief complaint or a response to a general open-ended question such as, “Do you have any new symptoms that make you think you might have a genital infection?,” particularly those elicited by an experienced clinician who has had the opportunity for the educational feedback provided by repeatedly comparing examination findings with laboratory test results.^{253–255}

Sexual behavior of the patient or patient’s partner(s)

Having a new partner or more than one partner within the past 2 months, especially without correct and consistent condom use, has been associated with increased risk of STDs and HIV in many studies.²⁵⁶ If patients perceive that their sex partner(s) are engaged in concurrency (i.e., sexual partnerships overlapping in time), this can be a risk factor for STI *acquisition* in the patient.²⁵⁷ By the same token, if the index patient is him- or herself engaged in concurrent relationships, and has an STI, this is a risk factor for *transmission* to others that should be addressed with counseling.^{258,259}

Psychological factors

A history of sexual abuse has been associated with STI/HIV risk behaviors in both women^{260–262} and men.^{263,264} Likewise, depression has been found to be associated with high-risk behaviors,²⁶⁵ and for adolescent boys, may be a predictor of future STI incidence.²⁶⁶ Depression is highly prevalent in some at-risk populations (39% in one study in the Baltimore public STD clinic²⁶⁷) and may complicate the ability to engage in behavior change or to adhere to antiretroviral medications.²⁶⁸ If these items are assessed, resources or referrals should be made available to provide appropriate support for any sequelae and needed treatment.

Substance use

Injection drug use has directly and indirectly accounted for more than one-third (36%) of AIDS cases in the United States.²⁶⁹ Not only is sharing syringes and other equipment for drug injection a well-known route of HIV transmission, but people who have sex with an IDU and their children are also at risk for infection. IDUs who do not enter treatment are up to six times more likely to become infected with HIV than are IDUs in treatment.²⁷⁰ Racial and ethnic minority populations in the United States are most heavily affected by IDU-associated AIDS. In 2000, IDU-associated HIV

infection accounted for 26% of all AIDS cases among African Americans and 31% among Hispanic adults and adolescents, compared with 19% of all cases among white adults/adolescents.²⁶⁹ Since the epidemic began, 57% of all AIDS cases among women have been attributed to injection drug use or sex with partners who inject drugs, compared with 31% of cases among men.²⁷¹ Those who inject methamphetamines are at highest risk for HIV, especially if they are also MSM.

Noninjection drugs (such as “crack” cocaine) also contribute to the spread of the epidemic. Some users trade sex for drugs or money to buy drugs. High-risk drug practices and sexual behaviors often are linked because drugs can make users feel less inhibited. One U.S. multisite study found that crack smokers were three times more likely to be infected with HIV than nonsmokers. When assessing STI/HIV risks it is necessary to understand and address the interconnectedness and impact of substance use behaviors and sexual risk-taking.

EXAMPLE OF A COMPREHENSIVE STI/HIV RISK ASSESSMENT

The foregoing discussion illustrates the range of topics that could be addressed in an STI/HIV risk assessment, recapitulating how various agencies, professional groups, or experts suggest conducting STI/HIV risk assessment. Many of these recommendations have not yet been extensively evaluated in terms of objective prediction of STI/HIV infection. [Figure 48-4](#) presents an example of a relatively comprehensive approach to individual-level STI/HIV risk assessment. The figure summarizes many of the key topics, offers ways they might be presented in a comprehensive face-to-face interview, and represents a point of departure for further work in this area. Although excessive for many clinical encounters, the more comprehensive approach may be appropriate for the patient who is positive for any of the risk factors elicited by the screening questions or by the selected priority questions highlighted in bold type in the table.

■ SELF-ADMINISTERED VERSUS FACE-TO-FACE

Few clinical settings other than STD clinics, which already know their patients are at potential risk of STI/HIV, could allow the time needed for a clinician to carry out such a comprehensive risk assessment during a face-to-face interview. Therefore, self-administered STI/HIV risk assessment questionnaires might be used to collect initial, or more comprehensive, information from patients. Particularly in primary care settings, an initial STI/HIV risk assessment could be integrated into an overall risk assessment that addresses risk for a variety of other medical and social problems.

Computer-assisted self-interviews in clinical settings, using tablet, laptop, or handheld computers, may elicit more accurate or at least more complete information on sensitive topics than can face-to-face interviews.

Self-administered risk assessment need not be limited to clinical settings but can be included in confidential settings in schools or on websites or chat rooms on the Internet that are appealing to specific at risk-audiences.^{272,273} Such sites encourage risk-takers to perceive the consequences of risk taking and to motivate behavior change or further health-care consultation.^{274,275} Despite the challenges of conducting research on the Internet,²⁷⁶ such approaches do appear to hold promise.

Whatever the method of administering questionnaires, important barriers to reporting sensitive risk behaviors exist. First, individuals who report high-risk sexual activities often do not perceive themselves at risk.²⁷⁷ The magnitude of any STI/HIV risk perceived may be small relative to the hierarchy of other serious risks encountered by a homeless urban adolescent, for example. Thus, specific questions about specific behaviors are essential in conjunction with questions about subjective perception of risk. Identification of gaps between perceived risk and actual risk highlights the need to change risk perception as one potential outcome of risk assessment. In this regard, it is important to distinguish perceived risk from perceived susceptibility. Kowalewski and colleagues have critiqued current thinking on perceived risk and health behavior.²⁷⁸

Questions clinicians can use to identify the context of any risk-taking reported can encourage further patient insight and identify key avenues for counseling concerning skills, norms, misconceptions, and client-centered strategies for reducing risk. For example, the clinician or counselor can ask, “What happened the last time you had sex without using condoms?” “Were there any avoidable circumstances that put you at risk during that encounter (e.g., not using a condom with a casual partner)? Is there anything you can think of that would make it easier/harder for you to avoid taking that risk again?”

FUTURE RESEARCH AND TRAINING NEEDS

Ongoing research needs include local definition of risk factors for STIs/HIV and evaluation of optional questions and methods (face-to-face interview, self-administered questionnaire, audio-computer-assisted questionnaire) for eliciting information about these risk factors in clinical as well as in nonclinical settings. There is a need for particular emphasis on adolescents and young adults and sexual histories that include a focus on MSM—for development of instruments for risk assessment that not only integrate STI and HIV risk assessment but also integrate STI/HIV risk assessment with practical comprehensive social and medical risk assessment

DEMOGRAPHIC DATA: Date of birth/age, gender, race/ethnicity, relationship status, residential zip code

Framing Statement:

I am going to ask you some questions about your sexual health. I ask them of all my patients to help me provide the best possible care. What we discuss is confidential.

Screening Questions:

STD SYMPTOMS

Are you currently having symptoms that might be caused by a sexually transmitted disease, like a discharge from your [penis/vagina], pain, swollen glands, itching, rash, or sores on your [penis/vagina] or rectum? Yes No

STD HISTORY

Have you ever been told that you had any sexually transmitted diseases or any genital infections? Yes No

If yes, which:

- Gonorrhea
- Chlamydia; NGU; urethritis; cervicitis or cervical infection
- PID (pelvic inflammatory disease, infection of the uterus)
- Syphilis
- Genital herpes / Herpes simplex virus HSV-I/II
- Genital warts/human papillomavirus HPV
- Trichomonas
- Bacterial vaginosis (non-specific vaginitis)

Have any of your sex partners been treated for an STD? If yes, which one? _____

SEXUAL HISTORY

Do you have sex with men, women, or both? Men Women Both I haven't had vaginal, oral, or anal sex

How many sex partners have you had... in the past 2 months? # ___ Men # ___ Women
... in the past 12 months? # ___ Men # ___ Women

How long ago was the last time you had sex with your regular partner? # ___ days Not applicable
 o Types of sex: Vaginal Anal Oral
 o What was the HIV status of that partner? HIV+ HIV Negative Don't know

How long ago was the last time you had sex with any other partner? # ___ days Not applicable
 o Types of sex: Vaginal Anal Oral
 o What was the HIV status of that partner? HIV+ HIV Negative Don't know

How long ago was the last time you had sex without using a condom? # ___ days/months/years Never used
 When using a condom, have you ever had it slip/break; put it on after sex started, took it off before sex ended, put it on backwards, or other problem? No Yes *If yes,* Discussed correct & consistent condom use

We now recommend that all sexually active people in the US get a voluntary HIV test. When was the last time you had an HIV test? ___/___/___ Date of last test/ Result: Positive Negative Indeterminate Did not get result
 ___ Never tested

If never, or last exposure risk occurred after last test: Accepted offer of HIV test today
 Declined / Reason _____

Many people use a variety of substances to change their mood.

Have you ever used crack cocaine? Yes No

Have you ever used methamphetamine ("crystal")? Yes No

Have you ever shared needles to inject drugs, hormones, other? Yes No

Have you ever had sex with some one who injected drugs? Yes No

Have you ever had sex with a known HIV+ person? Yes No

Have you ever exchanged sex for money or drugs? Yes No

(Continued)

Hepatitis vaccination history:

- A only B only Both A & B Neither A nor B If no B vaccination, offered or made referral

Are you trying to get pregnant/get your partner pregnant? Yes No

If no, what method(s) are you and/or your partner using to avoid pregnancy & reduce STD risk? _____

- None Condom Oral contraceptive Ring Patch Injectable IUD Diaphragm/Cap
 Tubal/Hysterectomy Vasectomy Other _____

For women:

Do you have access to emergency contraception? Yes No

Cervical screening (Pap smear or HPV, any cervical dysplasia) history:

HPV vaccination history:

For men who have sex with men:*

In the last 12 months...

Have you had receptive anal sex? Yes No

Exposure Status			Condom Use			
Partner Status	Yes	No	Never	Sometimes	Usually	Always
HIV+						
HIV -						
HIV Unknown						

Have you had insertive anal sex? Yes No

Exposure Status			Condom Use			
Partner Status	Yes	No	Never	Sometimes	Usually	Always
HIV+						
HIV -						
HIV Unknown						

Have you had any unprotected anal sex with a sex partner whose HIV status was different than yours, or was unknown to you, in the last 2 months? Yes No

If HIV+: How often do you tell anal sex partners your HIV status? Never Some Usually Always

For all:**RISK REDUCTION COUNSELING**

What step do you think you could take to reduce your risk? This might include not having sex (abstinence), being only with one person (monogamy), using condoms correctly & consistently, getting HIV/STD testing, reducing alcohol or substance use, or some other plan. Your plan is: _____

- Counseling/Plan not done

SEXUAL FUNCTION/SATISFACTION

Have you noticed any problems in your ability to have and enjoy sex? _____

Is there anything else about your sexual health that you'd like to discuss today? _____

*Questions from Public Health Seattle-King County STD Clinic chart form, courtesy of Matthew Golden, MD, MPH. See Golden et al., *JAIDS* 2004; 36(2): 734-74

FIGURE 48-4. A comprehensive approach to individual-level STI/HIV risk assessment.

for general clinical use. Finally, the instruments and methods of administration should have demonstrated reliability and validity for predicting presence or absence of STI/HIV in a variety of clinical settings.

There remains a clear and ongoing need for improved performance of clinicians in assessing risk for STI/HIV infection. A starting point for this is to include STI/HIV and patient-centered communication skill content in medical, nursing, physician's assistant, pharmacist, and allied health professional school curricula.²⁷⁹ The American Medical Women's Association has developed a reproductive health curriculum, for example, that covers sexual history-taking.²⁸⁰

Clinical workplaces can help improve the sexual health of their patients by identifying enabling and reinforcing factors in their systems, providing training, and making sexual history-taking elements part of their quality-improvement measurement (e.g., "percent of patients whose correct and consistent condom use was assessed"). One managed care organization that incorporated some of these approaches found that patient recall of provider discussion of STI/HIV risk assessment (OR 1.7, 95% CI 1.2–2.6) and personal risk reduction (OR 2.6, 95% CI 1.6–4.3) improved following this intervention.²⁸¹

Information technology tools (guideline distribution by web²⁸² or PDAs, reminder prompts on electronic health record systems²⁸³) may help practicing clinicians in this fundamental task. Clinician–patient communication patterns have been evaluated using video trigger tapes to demonstrate assessment styles.²⁸⁴ Epstein and colleagues have outlined ways to help clinicians learn to provide the rationale for STI/HIV discussions, to take a patient-centered approach, and to handle awkward moments and patient anxieties with empathy.²⁸⁵ Available STI/HIV training resources include the AIDS Education and Training Centers, the STD Prevention Training Centers, and the International Training and Education Center on HIV.²⁸⁶

Helping clinicians and patients to communicate routinely about sexual health concerns and STI/HIV risk reduction will improve the health of individuals, their sexual partners, and communities.

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Anatomy and Physical Examination of the Female Genital Tract

Daniel O. Graney and Claire C. Yang

INTRODUCTION

Any area of the body may be involved in STD syndromes or in the differential diagnosis of these conditions. Clearly there is no single, optimal method for conducting the history and physical examination. The critical areas of interest are determined by the history, other physical findings, and conditions considered in the differential diagnosis. Many critical anatomical points may be important in some contexts but irrelevant in others. Thus, this chapter is an attempt to present succinctly one approach to “the routine examination.” This approach is selective but is based on clinical experience in developing an efficient method for evaluating a large number of patients in a timely manner. Accurate physical examination of the female genital tract can also be used as an integral part of developing and using syndromic management plans for care of STDs when laboratory support is either unavailable or prohibitively expensive.¹⁻³

WHAT SHOULD BE INCLUDED IN THE ROUTINE EXAMINATION OF NONPREGNANT WOMEN FOR REPRODUCTIVE HEALTH CARE?

Several guidelines have been developed for the physical examination of women for routine preventive care, family planning, and STDs. These include the U.S. Preventive Services Task Force *Guide to Clinical Preventive Services*; the two-volume *Recommendations for Updating Selected Practices in Contraceptive Use*, produced jointly by the WHO, USAID, INTRAH (Program for International Training in Health, School of Medicine, University of North Carolina), and Pathfinder International; the *Guidelines for Adolescent Preventive Services*; the unpublished *Program Guidelines for Project Grants for Family Planning Services*, for recipients of the so-called Title X funding in the United States; and the pending *Reproductive Health Guidelines* being coordinated in the United States by the Centers for Disease Control and Prevention, the Office for Population Affairs, and certain professional societies.⁴⁻⁷

The U.S. Preventive Services Task Force recommends that screening examination of adult females includes periodic screening for hypertension every 2 years (for women aged 21 or older); measurement of height and weight and assessment for obesity; and screening of sexually experienced women for cervical cancer by Pap smear every 3 years.⁴ The task force found insufficient medical evidence to support routine clinical breast examination in women younger than 50 years of age. Neither did they find medical evidence to support routine thyroid examination. No medical evidence was found to support routine pelvic examination to screen for ovarian cancer, or to recommend for or against breast self-examination.

Until recently, recipients of federal Title X funding for family planning in the United States were not allowed to defer pelvic examination longer than 3 months for women receiving hormonal contraception. More recently, because of concerns that some women were avoiding contraception to avoid pelvic examination, some agencies have decided to “delink” provision of hormonal contraception from the pelvic examination. For example, Planned Parenthood of America informed its affiliates in 1998 that they could defer pelvic examination for 3 months, 6 months, 1 year, or even longer—in order to remove the requirement for pelvic examination as a possible disincentive to the use of hormonal contraception. Women electing other forms of contraception, such as tubal ligation, diaphragm, or IUD obviously would need a pelvic examination for evaluation of uterine anatomy or properly fitting a diaphragm. Some adolescent medicine specialists have been outspoken about the lack of evidence for benefit of routine pelvic examination for adolescents receiving hormonal contraceptives. There are few data on this issue, except for one nonrandomized study that found no adverse effect from delaying pelvic examination of adolescents seeking hormonal contraception for up to 6 months.⁸

It should be noted that such guidelines have so far arisen from the family planning field, not the STD/HIV field, and efforts are underway to develop interdisciplinary reproductive health guidelines, which should have considerable

impact on what services are included in health-care services purchased for women, funded through insurance programs, and provided by managed care organizations.

Clearly, for women found to be at high risk for STD, based on risk assessment, and for those with symptoms or signs suggestive of an STD, the minimal physical examination should include the following:

Skin and hair (as indicated by symptoms or other findings), throat and mouth (as indicated by symptoms).

Inguinal examination for adenopathy.

External genitalia, including labia majora and minora, clitoris, introitus, perineum, anus, and perianal area.

Urethral meatus and Skene's glands.

Bartholin's glands.

Speculum examination, including vaginal walls and cervix (including Pap smear and tests for cervical and vaginal infection, as indicated).

Bimanual examination (with rectovaginal examination, as indicated).

Further, even for asymptomatic women without risk factors for STDs, medical visits for reproductive health care may be the only source of medical care. For such women, a comprehensive initial physical examination, including pelvic examination, should be strongly encouraged, and the patient should be counseled on the desirability for such examination, and on any risks of deferring the examination, with documentation of counseling and referral in the patients' medical record.

■ GENERAL CONSIDERATIONS IN EXAMINATION OF THE FEMALE GENITAL TRACT

For the female patient who presents to an STD clinic, few portions of the physical examination will yield as much information as the pelvic examination. In the female, the genital and urinary tracts, as well as the anus and rectum, can and should be examined together during the pelvic examination. Symptomatic pathology abounds and unsuspected pathology is found in a significant proportion of relatively asymptomatic women.

Rapport with the patient is always important in the physical examination but is especially critical with the female pelvic examination. Evidence of concern for a woman's problems at the initial interview will help provide needed rapport. The woman worried about STD expects to have a pelvic examination and is understandably concerned about the findings. She will usually be very cooperative. A little effort on the part of the examiner in regard to her well-being and comfort during the pelvic examination will maintain that cooperation and enhance the diagnostic yield.

Some specific suggestions to establish and maintain rapport are as follows. Prior to the examination always wash your hands where the patient can see you. Unless you are checking for incontinence, have the patient void before the examination, as a full bladder is uncomfortable and inhibits the examination. Obtain urine for analysis, culture, or nucleic acid amplification testing as indicated.⁹⁻¹² Recognize that the dorsal lithotomy position is one of vulnerability. The patient's comfort may be improved by elevating the backrest, suggesting that the patient wear her shoes so that the stirrups do not cause discomfort, and providing a drape if desired but not draping if that is the desire of the patient. The speculum should be kept warm in a warming drawer or warmed with water just before the examination. All the equipment necessary for the examination should be present in the examination room, which should be private and quiet.

You should tell the patient what you are doing at each step. It will help the patient's anxiety if she is told of normal structures and normal findings during the examination. A mirror should be available to demonstrate specific findings to the patient, as the more involved the patient becomes in her own care the more apt she is to return for subsequent visits and necessary treatments. The pelvic examination is an opportunity to teach the patient about her anatomy and about the transmission of infectious disease.

The comfort of the examiner should not be overlooked. Equipment should be readily available, lighting should be good, and the examination table and stool should be at the right height. Most often, the standard examination proceeds according to an orderly sequence. This has two advantages. First, the sequence of the examination limits the opportunity for errors of omission in a busy clinical situation. Second, there is minimal need for the patient to move. During the examination any needed specimens should be obtained, and following the examination the findings should be recorded and correlated with the patient's history and complaints. This chapter is further organized to follow this suggested pattern of evaluation. The relevant considerations in routine examination of the female will be presented for each section of the physical examination, and critical anatomical principles will be considered for that area. We will present the examination and anatomical descriptions according to our own opinions, recognizing that some of these opinions are controversial and that other anatomists and clinicians may hold alternative, equally valid viewpoints.

THE EXTERNAL GENITALIA AND PERINEUM

■ PHYSICAL EXAMINATION

Ordinarily, the examination is initiated by having the patient sit on the examining table. If indicated, head and neck examination, inspection, palpation, percussion, and auscultation

of the chest and examination of the breasts may be done in this position. Next, the patient is asked to lie supine. Skin, extremity, breast, cardiovascular, and abdominal examination may be conducted in this position, if indicated. Attention is then directed to the pelvic examination.

With the patient in the lithotomy position, the genital examination begins with palpation of the inguinal nodes and inspection of the mons pubis and the external genitalia. The quantity and location of pubic hair is noted. The amount of pubic hair varies greatly in different racial groups. Normal hair growth for a southern European would imply hirsutism from androgen excess in an Asian woman. Nits on the shaft of the pubic hair are indicative of lice infestation. Freckles that move are probably lice.

The labia are separated and the vaginal introitus is inspected. Redness or erythema signifies an irritation that may be owing to infection with *Candida*, *Trichomonas vaginalis*, herpes simplex virus (HSV), or certain bacteria (e.g., toxic shock syndrome, streptococcal cellulitis). A uniformly adherent homogeneous white or gray discharge at the introitus is suggestive of bacterial vaginosis. Small tender fissures in the mucous membrane should arouse suspicion of vulvovaginal candidiasis and genital herpes; many genital herpes occurrences do not form classic ulcerations. Pigmented or nodular areas on the vulva may be owing to human papilloma virus infection or carcinoma in situ. Use of a magnifying glass or colposcope may help delineate small lesions that would be difficult to detect without magnification. Multifocal carcinoma in situ (i.e., involving more than one site on the cervix, vagina, and vulva) is being found more frequently in young women, and biopsies of suspicious areas of the vulva are important to rule out this disease. Pigmented areas may also be benign nevi or malignant melanomas (see Chapter 62). A suspicious area that is darkly pigmented with irregular borders should be removed by excisional biopsy for histologic inspection. The inspection for such lesions should include the frenulum and clitoris.

While the vulva are held apart, the woman should be asked to strain, cough, or otherwise perform a Valsalva maneuver. This will allow observation of any vaginal relaxation or stress incontinence. At this time the urethra with its associated periurethral (Skene's) glands should be palpated and milked by gentle finger pressure from above downward. If infection or a urethral diverticulum is present, a small amount of discharge may be evident at the urethral meatus or at the orifices of Skene's glands.

The greater vestibular glands (of Bartholin) are located at approximately 5 and 7 o'clock on the face of the posterior fourchette (Fig. 49-1). When these regions are explored with gentle pressure between the thumb and forefinger, the normal gland cannot be palpated and the region is not tender. However, an infected gland is extremely tender. Occasionally a small asymptomatic Bartholin's duct cyst can be seen as a

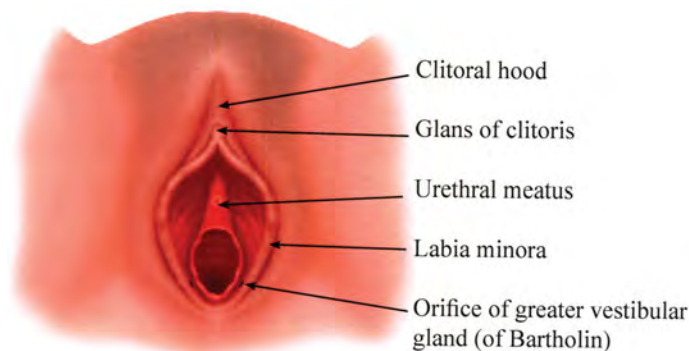


FIGURE 49-1. External genitalia. (Artistic graphics by Robert Holmberg, Seattle, WA.)

convexity of the posterior fourchette and felt as a discrete cystic nodule in the position of the Bartholin's gland. If any palpable mass is discovered in this area in a perimenopausal or menopausal woman, it should be removed for histologic examination, as the incidence of carcinoma increases with age.

■ ANATOMY OF THE PERINEUM AND EXTERNAL GENITALIA

The strict anatomical definition of the perineum is a diamond-shaped region bounded by the symphysis pubis anteriorly, coccyx posteriorly, and ischial tuberosities laterally. Projecting a line between the ischial tuberosities divides the diamond space into two triangles, the urogenital triangle anteriorly and the anal triangle posteriorly. Thus, both triangles share a common base with the apex of the urogenital triangle pointing anterosuperiorly and the anal triangle pointing posterosuperiorly. In lateral profile the floor of the perineum is shaped like a shallow V rather than appearing flat as implied by a two-dimensional drawing. The plane of the anal triangle is open and is filled only with fatty tissue. The plane of the urogenital triangle is closed or occupied by a thick triangular membrane, the perineal membrane that closes the anterior floor of the perineum and defines the anterior wall of the ischioanal fossa.^{13,14}

The region of the urogenital triangle contains two spaces, the superficial and deep perineal spaces (Figs. 49-2 to 49-5). The superficial space can be imagined as a pair of spaces lying between the perineal membrane and the skin of the labia majora. In fact, the two spaces are connected above the clitoris so that the space resembles an inverted U. It is bounded by the perineal fascia of the urogenital diaphragm that continues from the base of the diaphragm and reflects superiorly under the labial skin to join the membranous layer of superficial fascia of the abdomen above the symphysis pubis (see Figs. 49-2 to 49-4). Because of these fascial attachments, a hematoma in the labia majora, that is, superficial pouch, expands superiorly into the abdominal wall but neither laterally to the thigh nor posteriorly to the ischioanal fossa.

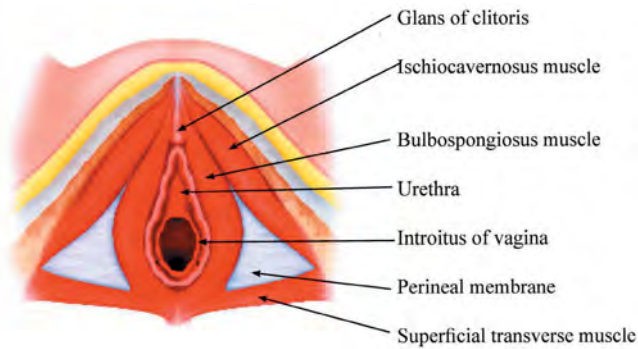


FIGURE 49-2. Muscles of the superficial perineal pouch. (Artistic graphics by Robert Holmberg, Seattle, WA.)

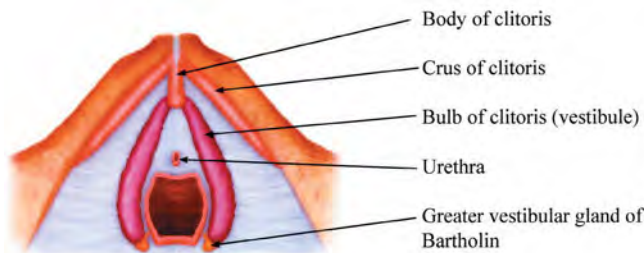


FIGURE 49-3. Erectile tissues of the superficial pouch. (Artistic graphics by Robert Holmberg, Seattle, WA.)

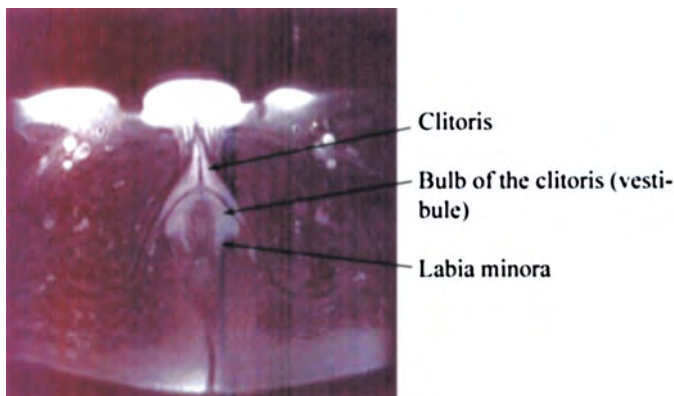


FIGURE 49-4. Magnetic resonance image of a female during sexual arousal illustrating increased blood flow in the erectile tissues of the clitoris and bulb.

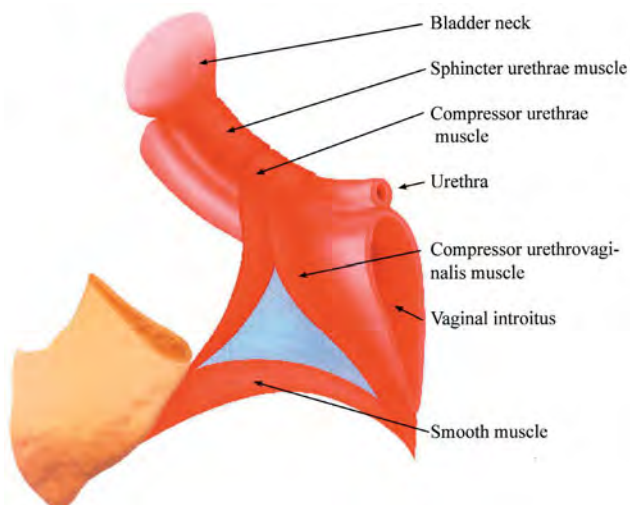


FIGURE 49-5. Contents of the deep perineal space. (From Oelrich TM. The striated urogenital sphincter muscle in the female. *Anat Rec* 1983; 205: 223–232.) (Artistic graphics by Robert Holmberg, Seattle, WA.)

The contents of the superficial perineal pouch include the greater vestibular glands (Bartholin's), crura of the clitoris, bulbs of the vestibule, which are composed of elongated erectile tissue, and the overlying superficial perineal muscles. There have been several changes in the concepts and terminology of the perineal floor in both male and female which have been described in recent years^{15,16}

Clitoris

The clitoris comprises two cavernous (erectile) bodies, arising from beneath the inferior rami of the pelvic bones. The lateral extensions of the erectile bodies, or the crura, meet in the midline and fuse to form the body of the clitoris. The body angles anteriorly away from the plane of the pubis. The distal-most aspect of the clitoris is the glans clitoris, which is the only visible portion of the clitoris. The glans is oftentimes covered by the clitoral hood, or prepuce. The labia minora arise from the ventral midline of the glans and extend laterally to outline the introitus.

Beneath the surface of the vulva, the clitoris has an inverted wish-bone shape, tilted to the plane of the pubic rami. The tips of the crura are covered in skeletal muscle, the ischioavernosus muscle. The cavernous bodies are covered with a fibrous lining and filled with erectile tissue. This tissue fills with blood during sexual arousal.

Directly related to the clitoris are the bulbs of the clitoris, formerly known as the vestibular bulbs.¹⁷ These mounds of erectile tissue are situated in the superficial perineal pouch, bounded by the crus of the clitoris dorsally and posteriorly; the lateral vaginal wall medially; the labia minora ventrally; and the bulbocavernosus muscle laterally. The bulbs are comprised of erectile tissue very similar to that of the clitoris, and also fill with blood during sexual arousal. There have been new studies in recent years detailing more specifically the anatomy and histology of the erectile tissues of the female perineum as well as imaging blood flow during sexual arousal with MRI^{18–21} (Fig. 49-4).

The deep perineal space is a potential space limited inferiorly by the perineal membrane but incompletely closed by the pelvic fascia superiorly. In the female, the contents of the deep perineal space include striated muscles, the external urethral sphincter surrounding the urethra, the compressor urethrae, the urethrovaginal sphincter, and some smooth muscle fibers termed the *deep transverse perineal muscle* (see Fig. 49-5).²²

Urethra

The female urethra measures 3–4 cm in length from the bladder neck to the meatus in the anterior vestibule of the vagina. Proximally, the mucosa is composed of transitional epithelium gradually becoming stratified squamous as it courses distally. The lumen appears stellate in cross section because of extensive longitudinal folding of the mucosa. Beneath the

mucosa is the lamina propria, rich in vascular and neural plexuses. The muscular coat, similar to other body tubes, is composed of a double layer of smooth muscle, with the inner fibers circularly arranged and the outer layer disposed longitudinally. As the urethra traverses the urogenital diaphragm, circularly arranged striated muscle fibers form an external sphincter of the urethra. These fibers are innervated by the internal pudendal nerve (somatic) in contrast to the internal urethral sphincter at the bladder neck, which is innervated by the pelvic splanchnic nerve (parasympathetic).

In essence, the entire length of the female urethra is paralleled by paraurethral glands that are tubuloalveolar outgrowths of the mucosa. Located in the lamina propria, these glands have their openings on the posterior and posterolateral wall of the urethra (see Fig. 49-6). At the distal end of the urethra there are usually two larger glands, commonly identified as Skene's glands, whose ducts are visible on the posterior wall. Both Skene's glands and the paraurethral glands are vulnerable to infection.

More extensive review of female pelvic anatomy and histology may be found in recent texts.^{15,16,23,24}

VAGINA, CERVIX, UTERUS, AND ADNEXAL STRUCTURES

■ PHYSICAL EXAMINATION

Speculum examination and collection of specimens for microscopy and culture

A warm speculum should be inserted into the vagina and opened to reveal the cervix. It should be inserted at an angle

directed toward the hollow of the sacrum (Fig. 49-7). Care should be taken not to apply pressure against the urethra and anterior bony arch of the pubis. With the speculum in place, specimens may be obtained for pH determination and wet mount examination of vaginal fluid; vaginal fluid Gram stain and selected cultures, if indicated; and endocervical Gram stain and cultures and Pap smear. If there are no symptoms or signs of abnormal vaginal discharge or of vaginal inflammation, no tests of vaginal fluid are usually done. If such symptoms or signs exist, a specimen of the vaginal discharge should be tested on pH paper to ascertain the vaginal pH, which is normally 4.5 or below. If the vaginal pH is above 4.5, it is suggestive of bacterial vaginosis or of trichomoniasis. Care should be taken to avoid mixing vaginal discharge with cervical mucus for determination of vaginal fluid pH, since cervical mucus has a pH of about 7. Vaginal discharge should also be mixed with saline for microscopic examination for motile trichomonads and clue cells; and with 10% potassium hydroxide for detection of a fishy, amine-like odor, characteristic of bacterial vaginosis, and for microscopic detection of fungal elements (see Chapter 55). A Gram stain of a thinly smeared slide of vaginal discharge is useful for confirming the diagnosis of bacterial vaginosis. With rare exceptions (e.g., toxic shock syndrome), bacterial cultures of vaginal fluid are not useful. However, for detection of *Candida* or *Trichomonas vaginalis*, vaginal cultures are more sensitive than microscopic examination of vaginal fluid, especially in the absence of abnormal vaginal discharge.

For Pap smear, separate samples should be obtained from the ectocervix, including the transformation zone, using an Ayre's spatula; and from the endocervix, using a cytobrush

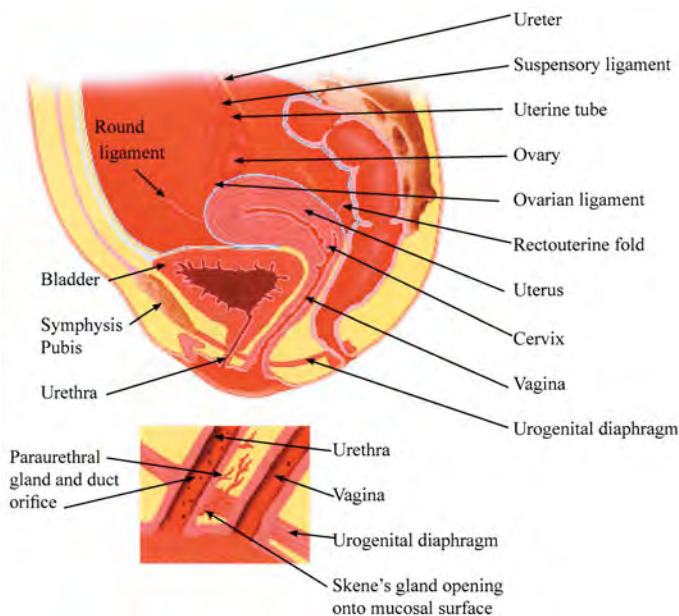


FIGURE 49-6. Sagittal section of female pelvis. Inset shows magnification of urethra and urethral glands. (Artistic graphics by Robert Holmberg, Seattle, WA.)

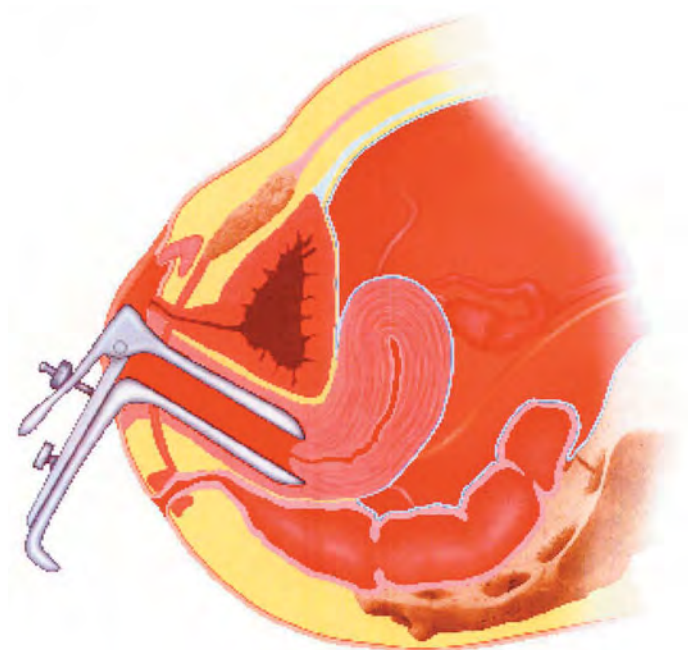


FIGURE 49-7. Position of vaginal speculum. (Artistic graphics by Robert Holmberg, Seattle, WA.)

(see Chapter 47). According to the U.S. Preventive Services Task Force, cervical cytologic screening should be performed at least every 3 years in sexually active women with a cervix.⁵

Specimens for culture for gonorrhea and diagnosis of *Chlamydia* by culture or antigen detection test can be taken from the endocervix. Nucleic acid amplification assays of urine or urogenital swabs may also be used to detect gonorrhea and chlamydial infection. A specimen of the endocervical mucus can also be obtained at this time, inspected for color (yellow color indicates increased numbers of PMN leukocytes), and used to prepare a Gram-stained smear for microscopic enumeration of PMN leukocytes in cervical mucus and for detection of gonococci. Nabothian cysts are a normal finding on the cervix (Fig. 49-8). They develop when squamous epithelium covers mucus-secreting columnar epithelium and the secretions cause the formation of a small cyst. These cysts rupture and reform throughout the reproductive years. While the speculum is still in place, colposcopy can be performed before and after applying dilute (3%) acetic acid or dilute Lugol solution to the cervix. Colposcopy enables one to better visualize cervical, vaginal, and vulvar abnormalities such as dysplasia or infection with human papilloma virus, as well as cervical ulcers caused by HSV, or “strawberry cervix” caused by *T. vaginalis*. Colposcopy is clearly helpful to select lesions or areas for biopsy when evaluating a cervix after Pap smears has shown dysplasia. The role of colposcopy as an initial screening procedure is debated.

Bimanual examination

After removal of the speculum, the first two fingers of the vaginal examining hand are lubricated and inserted into the vagina. The bladder should be compressed. This should cause no discomfort other than the sensation of needing to void. The cervix should be palpated and moved. Both the cervix and the attached uterine body should be freely mobile without pain. The body of the uterus is next located by

providing suprapubic pressure with the abdominal hand to keep the uterus in the pelvic cavity. The two fingers of the examining vaginal hand should outline the uterus in its entirety. This is usually easy if the uterus is anterior. If it is in a mid or posterior retroflexed position, it will be more difficult to locate and may be best palpated on rectovaginal examination (Fig. 49-9). After noting the size, shape, position, mobility, consistency, and contour of the uterus, it is moved to the one side and the fingers of the examining hand are inserted into the right lateral vaginal fornix as far as possible (Fig. 49-10). The abdominal hand produces pressure on the right lower abdomen and the fingers of the vaginal hand are swept to the side to evaluate the adnexal structures consisting of the tube, ovary, round and cardinal ligaments, and the pelvic sidewall (Fig. 49-11). The same procedure is followed on the opposite side. (Some people prefer to change hands, using the left hand to examine the left side of the pelvis.) Only the ovaries should be palpable in the normal examination. Often they are not felt, especially if the patient is on birth control pills, which suppress the ovaries and decrease their size. A normal ovary in a menstruating non-suppressed woman measures approximately $3 \times 3 \times 2$ cm³. Any enlargement above 5–6 cm is an abnormal finding. Both pelvic sidewalls should be evaluated for enlargements of the lymph nodes. Tenderness of any of the pelvic structures is noted. The examination is concluded with a rectovaginal examination.

Rectovaginal examination

After the patient is informed of the procedure, a well-lubricated middle finger is placed in the rectum and the index finger is simultaneously placed in the vaginal vault. The patient can

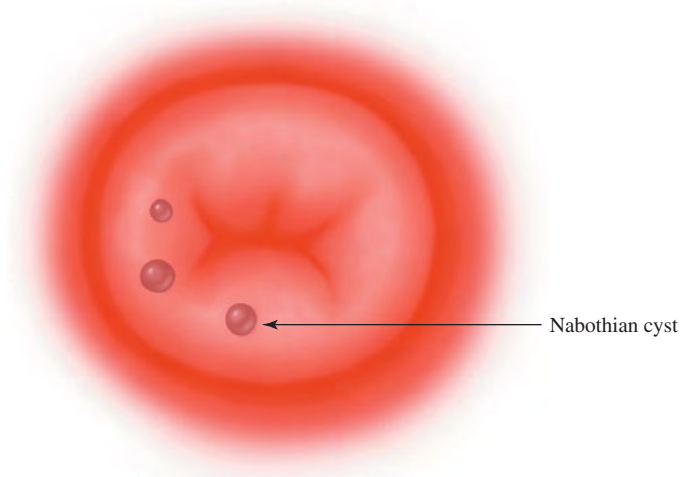


FIGURE 49-8. Cervix, illustrating Nabothian cysts. (Artistic graphics by Robert Holmberg, Seattle, WA.)

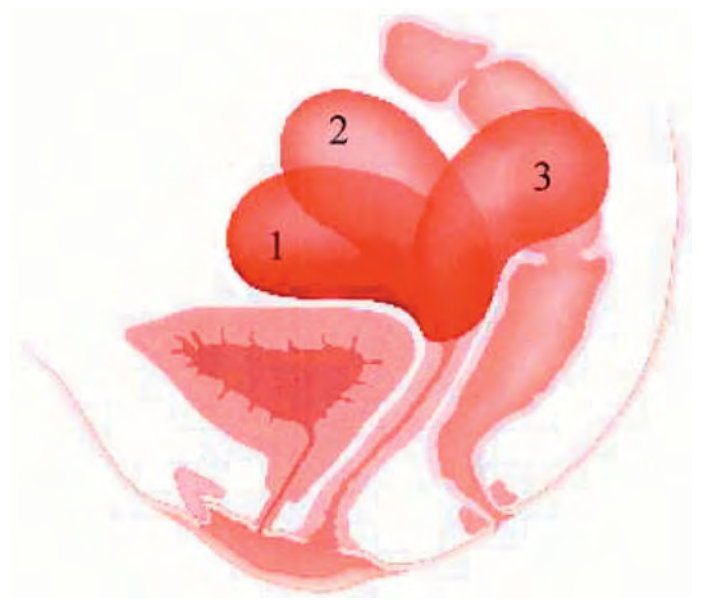


FIGURE 49-9. Positions of the uterus: (1) anteverted, (2) midposition, and (3) retroflexed. (Artistic graphics by Robert Holmberg, Seattle, WA.)



FIGURE 49-10. Preparation for bimanual pelvic examination: placement of vaginal fingers (shaded). (Artistic graphics by Robert Holmberg, Seattle, WA.)

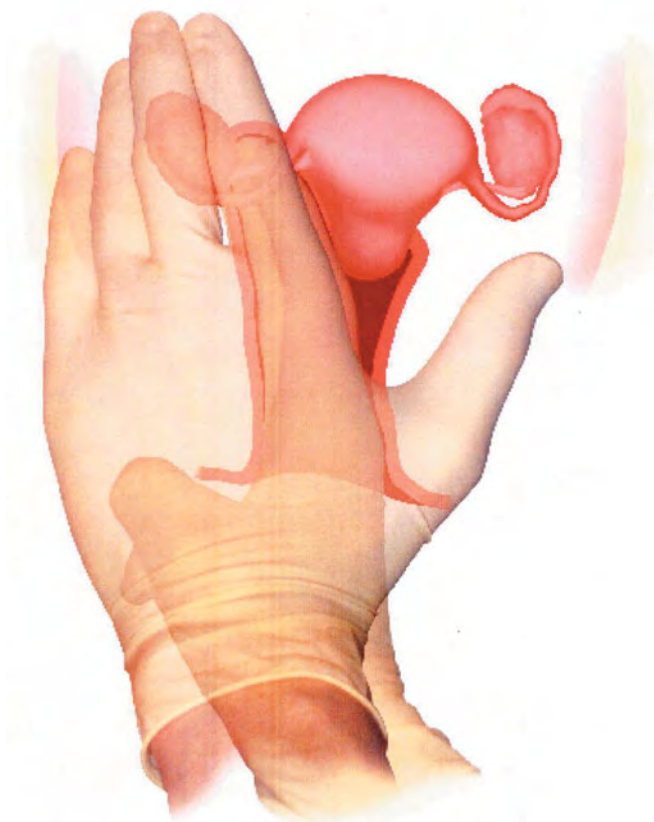


FIGURE 49-11. Bimanual examination: comparing position of vaginal fingers (shaded) and abdominal hand. (Artistic graphics by Robert Holmberg, Seattle, WA.)

often facilitate the rectal examination by relaxing the pelvic muscles during insertion of the fingers. The rectal finger carefully evaluates the entire rectal wall for nodularity or polyps. It is then placed against the cervix, which is felt through the rectal and vaginal wall. Pressure from the abdominal hand brings the uterus down so that its entire posterior surface can be palpated with the rectal finger. This is the best method to examine the posterior wall of the uterus if it is in the mid or posterior position in the pelvis. The uterosacral and cardinal ligaments can be put on tension by elevating the cervix and palpated for nodularity such as may be found with endometriosis. The posterolateral sidewalls of the pelvis should be swept with the rectal finger, and a stool specimen can be obtained if indicated for evaluation of occult bleeding. The American Cancer Society recommends annual testing for gastrointestinal bleeding beginning at age 50.

Throughout the pelvic examination a mental image of the pelvic organs should be formed, noting size, shape, consistency, mobility, contour, and tenderness. Practitioners often confirm or supplement their findings in physical examination with a transabdominal or transvaginal ultrasound. Ultrasound may be especially helpful in patients who are difficult to examine because of pain, fear, or obesity, and in patients who have physical findings of uncertain etiology. It is not as accurate as laparoscopy for the diagnosis of pelvic inflammatory disease. Ultrasound is specifically beneficial in evaluating suspected ectopic pregnancy and differentiating ovarian from uterine tumors and can be used to evaluate other symptoms also.²⁵⁻²⁷ All observations made should be accurately documented in the record. Correlation of the patient's complaints or historical data with the physical findings and the laboratory evaluation will often resolve the concerns of the patient and the questions of the examining physician.

■ ANATOMY

Vagina

The vagina is a fibromuscular tube whose anterior and posterior walls are normally in contact with one another. A longitudinal ridge is present along the mucosal surface of both the anterior and posterior walls; from these ridges, secondary elevations called rugae extend laterally. The vaginal wall consists of three layers: (1) the mucous membrane, composed of stratified squamous nonkeratinized epithelium and an underlying lamina propria of connective tissue; (2) the muscular layer, composed of smooth muscle fibers disposed both longitudinally and circularly; and (3) the adventitia, a dense connective tissue that blends with the surrounding fascia.

There are no glands in the vaginal wall. During sexual stimulation the marked increase in fluid production in the vagina is believed to be caused by transudation across the vaginal wall.

The stratified squamous epithelium of the adult vagina is several layers thick. The basal layer is a single layer of cylindrical cells with oval nuclei. Above this area are several layers of polyhedral cells that appear to be connected together much like those of the stratum spinosum of the epidermis. Above these are several more layers of cells that are more flattened in appearance and accumulate glycogen in their cytoplasm, the significance of which is discussed in the following. They also exhibit keratohyalin granules intracellularly. This tendency toward keratinization, however, is not normally completed in the vaginal epithelium, and the surface cells always retain their nuclei.

The most superficial cells are desquamated into the vaginal lumen where their intracellular glycogen is converted into lactic acid, probably by the bacteria normally resident in the vagina. The resulting acidity is believed to be important in protecting the female reproductive system from infection by most pathogenic bacteria (see Chapter 17).

Estrogen stimulates the production of glycogen and maintains the thickness of the entire epithelium. Before puberty and after menopause, when estrogen levels are relatively low, the epithelium is thin and the pH is higher than in the reproductive years (neutral before puberty and 6.0 or higher after the menopause). The thinness of the epithelium and the relatively high pH of the vaginal milieu are among the factors that are thought to render females in these age groups more susceptible to vaginal infections.

Uterus

The uterus has two major components: (1) the expanded upper two-thirds of the organ, the body of the uterus and (2) the cylindrical lower one-third, the cervix (Figs. 49-12 and 49-13). The fundus is the rounded upper part of the body, superior to the points of entry of the uterine tubes. The isthmus is the short, slightly constricted zone between the body and the cervix.

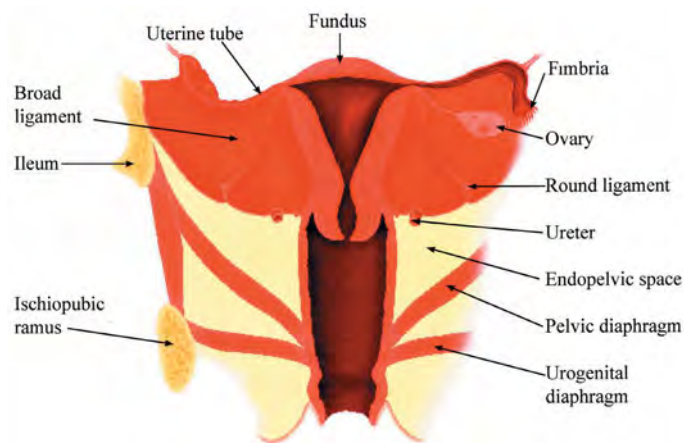


FIGURE 49-12. Coronal section of pelvis viewed from anterior surface illustrating broad ligament, endopelvic space, pelvic diaphragm, and urogenital diaphragm. (Artistic graphics by Robert Holmberg, Seattle, WA.)

The two main components of the uterus are rather different from one another in their structure and function.

Cervix. The cervix consists primarily of dense collagenous connective tissue. Only about 15% of its substance is smooth muscle. In the isthmus, the uterine lumen narrows down to form the internal os. Below this point the lumen widens slightly to form the cervical canal (or endocervical canal). Finally, a constricted opening, the external os, at the lower end of the cervix provides communication between the lumen of the cervix and that of the vagina.

Inside the cervix, the endocervical mucosa is arranged in a series of folds and ridges. A longitudinal ridge runs down the anterior wall and another down the posterior wall; from each of these, small folds (the *plicae palmatae*) run laterally. The resemblance of this arrangement to a tree trunk with upward-spreading branches has given rise to the term *arbor vitae uterina* to describe the endocervical mucosa.

The part of the cervix that projects into the vagina (the *portio vaginalis*, or ectocervix) is covered by stratified squamous, nonkeratinizing epithelium. Usually, in older women, this type of epithelium extends for a very short distance into the cervical canal, where it forms a rather abrupt junction with the simple columnar epithelium lining the rest of the canal. The site of the squamocolumnar junction varies, however. It may occur higher up in the cervical canal, or the columnar epithelium may actually extend out beyond the external os where it forms small patches known as physiologic eversion, or ectopy, on the vaginal surface of the cervix. Ectopy is usually present in adolescents and decreases during the third and fourth decades of life.

The mucosa contains large branched endocervical glands. In reality, they are not true glands but are merely deep grooves or clefts (sometimes called crypts) that serve to increase the surface area of the mucosa tremendously. The epithelium of both the mucosal surface and the “glands” is of the simple columnar type in which almost all the cells are mucus secreting. A few ciliated cells are present. If the ducts of the glands become blocked, mucous secretion accumulates inside them to form small lumps just under the surface.

Unlike the mucous membrane of the body of the uterus, the endocervical mucosa does not slough off at menstruation. It does, however, respond to cyclic changes in the levels

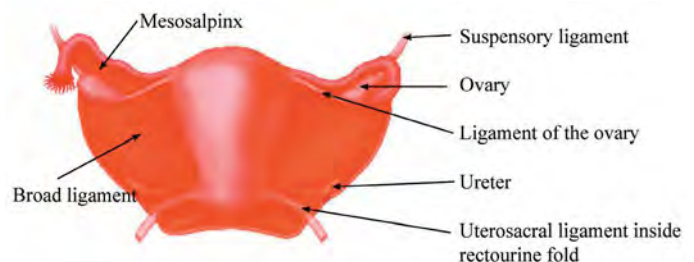


FIGURE 49-13. Posterior view of broad ligament and female reproductive organs. (Artistic graphics by Robert Holmberg, Seattle, WA.)

of the ovarian hormones, estrogen and progesterone. It secretes up to 60 mg of mucus a day throughout much of the cycle, but near the time of ovulation (midcycle), when estrogen secretion reaches a peak, the secretion rate increases 10-fold and the abundant, clear mucus fills the cervical canal. It is less viscous than at other times during the cycle and is easily penetrated by spermatozoa.

The production of progesterone by the corpus luteum after ovulation (or during pregnancy) changes the quantity and properties of mucus produced. It becomes more viscous, less abundant, and much less penetrable by spermatozoa. It acts as a plug to seal off the uterine cavity.

The body of the uterus. The wall of the body of the uterus is composed of three layers: (1) the endometrium, a glandular mucous membrane; (2) the myometrium or smooth muscle layer; and (3) the serosa.

Endometrium. The function of the endometrium is to provide a suitable environment for the implantation and subsequent growth of the developing embryo. As such, it is a luxuriant mucosa with a large population of glycogen-secreting glands and a rich vascular network. However, if there is no developing embryo, most of the endometrium is sloughed off (causing the menstrual flow) and is regenerated again in the next menstrual cycle. This cyclic shedding and regeneration of the endometrium is under the control of the ovarian hormones, estrogen and progesterone. The rise and fall in ovarian hormone levels determine the rise and fall of the growth and shedding of the endometrium.

The endometrium varies from 0.5 mm to approximately 5 mm in thickness, depending on the stage of the menstrual cycle. It is at its greatest height a few days after ovulation, at about the time of expected implantation. It consists of a simple columnar epithelium and a highly cellular lamina propria (the endometrial stroma) in which there are large numbers of tubular uterine glands. The epithelium contains both ciliated and secretory cells.

The endometrium can be subdivided into a rather narrow, deeper layer next to the myometrium, the basalis, and a much thicker, more superficial layer, the functionalis. The latter receives its name because it is the portion that is shed during menstruation.

The arteries that supply the endometrium play an important role in the onset of menstruation. Circumferentially oriented arteries in the myometrium give off numerous branches toward the endometrium. As they enter this region, small basal arteries branch off to supply the basalis. The arteries then become highly contorted as they enter the functionalis and are known as coiled or spiral arteries. These arteries spasmodically contract late in the menstrual cycle that induces ischemia, necrosis, and eventually sloughing of the functionalis.

During the menstrual cycle, the endometrium passes through a number of phases. In the menstrual phase (approximately days 1 to 4 of a typical 28-day cycle) the functionalis is sloughed off; cellular debris and blood are discharged into the vagina. From day 5 until the time of ovulation (approximately day 14) the endometrium is in its proliferative phase. Epithelium in the persisting portions of uterine glands in the basalis grows out and covers the denuded surface. Estrogen from the growing follicles in the ovary promotes rapid proliferation of the epithelium, glands, and stroma. The endometrium may thicken by 2–3 mm at this time. Progesterone and estrogen from the corpus luteum stimulate the secretory phase (days 15–28), in which the epithelial cells begin to secrete. Accumulation of secretory products in the lumina of the glands, together with some edema of the stroma, causes the endometrium to increase further in height.

Late in the secretory phase, ovarian hormone levels drop and the changes that herald menstruation occur. Intermittent constrictions in the spiral arteries cause stasis of blood and ischemia of vessels and tissues in the area of supply. During the intervening periods of relaxation, blood escapes from the weakened vessels, promoting menstrual hemorrhage.

Myometrium. The myometrium consists of bundles of smooth muscle fibers separated by strands of connective tissue. Four layers of smooth muscle have been distinguished, but their boundaries are poorly defined owing to overlap between adjacent layers. In the innermost and outermost layers, most of the muscle fibers are disposed longitudinally, whereas in the middle layers there are rather more circular fibers.

Estrogen is essential for the maintenance of normal size and function in myometrial smooth muscle cells.

Serosa. The serosa is the peritoneal covering of the uterus; hence, only the pelvic portion of uterus has a serosa. The cervix has no serosa. The peritoneal reflections are discussed later in the chapter in the section on the broad ligament.

Uterine tubes

Fertilization and the earliest steps in development occur within the uterine tube. Therefore, these tubes must perform a number of tasks. As well as providing a suitable milieu for the gametes and transporting them to the site of fertilization in the midsection of the duct, they must also provide the nutritional support necessary for the embryo during segmentation and morula formation. In addition, transport mechanisms in the proximal portion of the oviduct must be such that the embryo arrives in the uterus at the appropriate time, both in terms of its own development and in terms of uterine receptivity.

General structure. The uterine tubes lie in the upper margins of the broad ligament. Each is composed of four parts. Beginning at the distal end these are (1) the infundibulum—the funnel-shaped end of the uterine tube that bears numerous delicate processes, the fimbriae, around the abdominal ostium; (2) the ampulla, or longest portion—it accounts for slightly more than half of the total length; (3) the isthmus—a narrow portion leading to the uterus; and (4) the intramural (or interstitial) portion—that part of the duct that extends through the wall of the uterus. At its end there is a minute ostium that connects the cavities of the uterus and uterine tube.

Three layers form the wall of the uterine tube: (1) the mucous membrane, characteristically composed of epithelium and lamina propria. The epithelium is of the simple columnar variety and contains two types of cells, ciliated and secretory. The lamina propria is loose connective tissue. (2) The muscular layer consists typically of two layers of smooth muscle, an inner circular and an outer longitudinal, but the boundary between the two is not distinct. In the intramural portion another longitudinal layer has been described, internal to the circular layer. (3) The serosa, which is typical of serosa elsewhere.

The mucous membrane and the muscular layer vary from one region of the duct to another. The structure and function of the various regions will now be discussed in more detail.

Infundibulum. When the oocyte leaves the ruptured follicle at ovulation, it is still surrounded by a mass of follicular cells that made up the bulk of the cumulus oophorus. The oocyte and its surrounding cells are now called the cumulus mass. The fimbriae of the infundibulum have the task of removing the cumulus mass from the site of follicular rupture on the ovary and transporting it into the ostium. Once contact is made, the cumulus mass begins to be transported over the fimbrial surface by ciliary action. The surface is richly ciliated and all the cilia beat toward the ostium. Since oocytes freed of cumulus cells are easily dislodged and are transported rather poorly, it is believed that the cumulus cells are essential for normal “pickup” and transport.

The epithelium of the fimbriae (and indeed, of the entire uterine tube) is sensitive to ovarian hormones. As estrogen concentration rises during the follicular phase of the cycle, the epithelium increases in height and reaches a maximum at midcycle. During the late luteal phase, cell height decreases. There is little evidence for deciliation and reciliation during the menstrual cycle in the human, but there is no doubt that withdrawal of estrogen will result in deciliation. The fimbriae of postmenopausal uterine tubes are largely devoid of cilia, whereas these from postmenopausal women who are on estrogen therapy are richly ciliated.

Ampulla. The mucous membrane of the ampulla is thrown up into an elaborate system of longitudinal folds. Most of the lumen is thus reduced to a system of fine channels between the folds. Less than half of the epithelial cells are ciliated and they beat toward the isthmus (Fig. 49-14).

Fertilization occurs in the proximal portion of the ampulla. There are potentially two mechanisms for transporting the cumulus mass to this site: ciliary activity and smooth muscle contraction. Although the role of the ciliated cells in the ampulla is fairly clear, the function of the secretory cells is less certain. Loss of cilia may be caused by infection, leading to poor gamete transport with resultant infertility or ectopic pregnancy. Infection may also occlude the tube and persisting secretion may result in hydrosalpinx.

Isthmus. The elaborate mucosal folds of the ampulla give way rather abruptly to simpler, lower folds in the isthmus. Concomitant with a decrease in complexity of the mucosal folds is a marked increase in the thickness of the muscle layer. The ciliated cells of the mucosa beat toward the uterus.

The isthmus is perhaps the least understood portion of the uterine tube. It has the capacity of transporting spermatozoa distally toward the site of fertilization and later, conducting the developing embryo proximally. It is not



FIGURE 49-14. Ampulla of the uterine tube from a 29-year-old woman in midcycle. Scanning electron micrograph illustrates distribution of ciliated and nonciliated cells. (Courtesy Dr. Penny Gaddum-Rosse.)

known how the isthmus (or perhaps the intramural portion) controls the passage of cleaving eggs into the uterus.

Intramural portion. The lumen of the uterine tube becomes extremely narrow in the proximal isthmus and intramural portions. The mucosal folds are reduced to low ridges. The muscular layer, on the other hand, becomes thicker than in any other part of the tube. The large amount of muscle in this region might suggest that a sphincter exists that could close off the uterine tube and help to prevent the spread of infection. However, there are no reported observations documenting the existence of an anatomical sphincter.

Broad ligament

The broad ligament represents a transverse double fold of peritoneum containing the uterus and the uterine adnexa (uterine tube and ligaments) as well as nerves, vessels, and lymphatics (see Figs. 49-12 and 49-13). Inferior to the sacral promontory, the peritoneum covers the anterior surface of the sigmoid colon and dips to its lowest point overlying the posterior vaginal fornix. From this position it reflects superiorly over the fundus and body of the uterus and then anteriorly to cover the dome of the bladder. At the level of the pubic symphysis it reflects superiorly again onto the anterior abdominal wall. From either side of the body of the uterus the folded peritoneum is carried laterally to the wall of the pelvis, forming a transverse vertical partition, the broad ligament. This divides the inferior peritoneal cavity into an anterior vesicouterine (pouch of Douglas) and posterior rectouterine space.

Suspensory ligament of the ovary

The suspensory ligament (infundibulopelvic ligament) is an extension of the most superior and lateral part of the broad ligament. It is misnamed, as it provides no support for the ovary or uterus. In reality, it is merely a fold of peritoneum raised by the underlying ovarian vessels, nerves, and lymphatics as they course between the ovary and the retroperitoneum. It provides a potential route for the spread of infection from adnexal structures to the retroperitoneum and para-aortic nodes.

Ovary. The ovaries have two major functions: to nurture and release the female gametes and to produce the female sex hormones, estrogen and progesterone. These functions entail considerable changes in ovarian structure, both cyclic changes during the reproductive years and long-term changes over the individual's lifetime.

The ovary is covered by a single layer of cells known as the germinal epithelium. This is actually a misnomer, since it does not give rise to germ cells, as was originally believed. The cells are cuboidal in the young individual but tend to become squamous with age. This epithelium is the source of most ovarian neoplasms. These masses may be detected on bimanual examination and can be confused with hydrosalpinx or

more acute infectious processes, especially if the neoplasm undergoes torsion.

The substance of the ovary may be divided into an outer cortex and an inner medulla. The connective tissue stroma of the cortex contains many spindle-shaped cells that resemble fibroblasts and intercellular substance. In the outermost zone of the cortex, just under the epithelium, the ratio of intercellular material to cells is higher than elsewhere. The fibrous nature and relatively poor vascularity of this zone give it a whitish appearance that accounts for its name, the tunica albuginea. The stroma of the medulla is a loose connective tissue containing some smooth muscle cells, many elastic fibers, and large, tortuous blood vessels. The presence of elastic fibers and the convoluted nature of the blood vessels permits the ovary to adapt fairly readily to the large structural changes that occur in the organ during each menstrual cycle.

BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION OF THE PERINEUM AND EXTERNAL GENITALIA

■ BLOOD SUPPLY

The internal pudendal artery (Fig. 49-15) is an arterial trunk providing blood to all the perineal structures inferior to the pelvic diaphragm (see Figs. 49-12 and 49-16). It begins as a branch of the internal iliac artery located subperitoneally in the lateral pelvis. It exits the bony pelvis, crosses the sacrospinous ligament, and enters the ischiorectal fossa. At this point the artery along with the internal pudendal vein and nerve becomes enclosed by the obturator fascia forming the pudendal canal (of Alcock). As the artery enters the

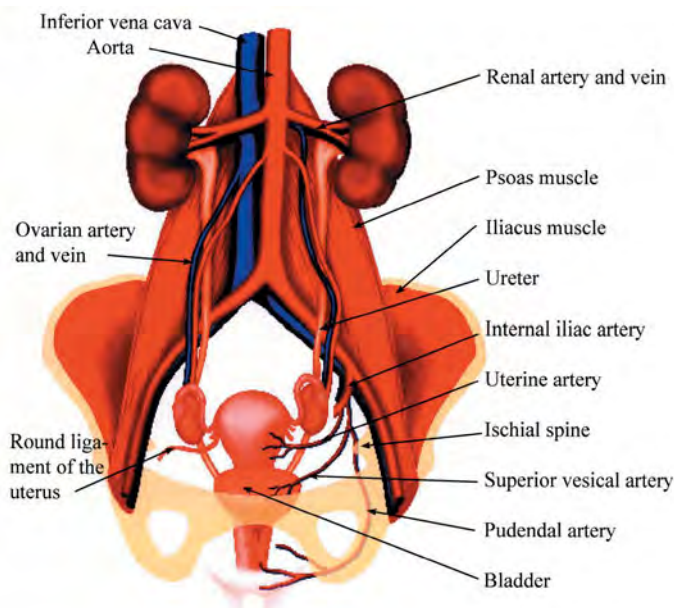


FIGURE 49-15. Blood supply of female reproductive tract. (Artistic graphics by Robert Holmberg, Seattle, WA.)

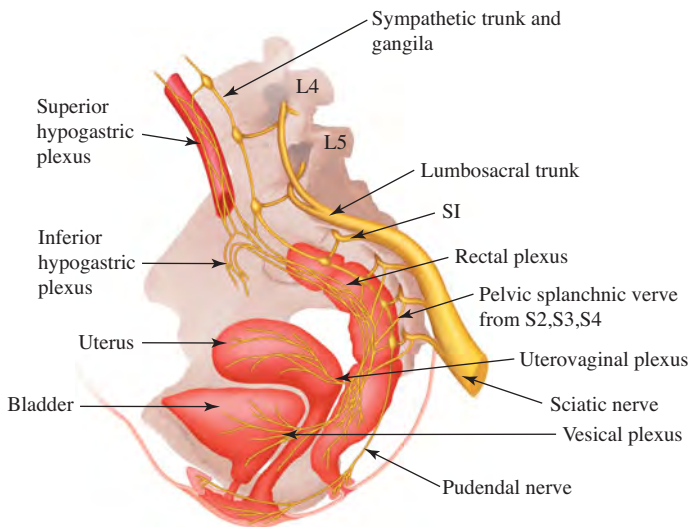


FIGURE 49-16. Innervation of female reproductive tract and pelvic plexuses. (Artistic graphics by Robert Holmberg, Seattle, WA.)

pudendal canal it gives off an inferior rectal artery that supplies the anorectal junction. The remaining portion of the internal pudendal artery reaches the base of the urogenital diaphragm and gives off a series of perineal branches. These supply the contents of both superficial and deep perineal spaces, including the vagina and urethra and clitoris.

The venous drainage of both perineal triangles parallels the arterial supply. There is also a rich submucosal venous plexus in the distal vagina. Distension of these submucosal veins can produce vaginal or vulvar varices. The inferior rectal veins join the internal pudendal vein just as it leaves the ischioanal fossa at the lesser sciatic foramen. Both the rectal and vaginal submucosal plexuses penetrate the pelvic diaphragm to communicate with the endopelvic space. Here, vaginal veins may anastomose with uterine veins and inferior rectal veins with middle rectal veins.

■ LYMPHATIC DRAINAGE

As a general rule, lymphatic drainage follows the blood supply of a region. The lymphatic drainage of the perineum differs in this respect because there is a dual pathway. Deep lymphatics course upward following the pudendal veins, draining the deep parts of both urogenital and anal triangles. However, superficial lymphatics from the skin overlying the vulvar and anal areas course to the medial thigh where they communicate with superficial inguinal lymph nodes. Adenopathy of superficial inguinal nodes is well known in many vulvar and anal infections as well as in carcinoma of these regions.

■ INNERVATION

The motor and sensory innervation of the perineum is via fibers from sacral roots S2, S3, and S4 forming the pudendal nerve (Fig. 49-16). Originating from the sacral plexus in the presacral region, the pudendal nerve exits the pelvis via the

greater sciatic notch, crosses the sacrospinous ligament, enters the pudendal canal, and accompanies the pudendal vessels. The branches of the internal pudendal nerve are the inferior rectal, perineal, and dorsal clitoral nerves, supplying these respective areas.

BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION OF UTERUS AND VAGINA

■ BLOOD SUPPLY

The uterus and upper vagina lie within the endopelvic space, that is, between the pelvic peritoneum and the pelvic diaphragm. These structures as well as the adjacent rectum, bladder, and so on are all supplied by a single arterial trunk, the internal iliac artery (see Fig. 49-13). It arises by division of the common iliac artery at the junction of the sacrum and the ilium. Descending in the lateral pelvis subperitoneally it gives off a series of visceral branches, including rectal, uterine, and vesical. These course medially to enter the endopelvic space, at the base of the broad ligament. Before reaching the isthmus of the uterus the uterine artery crosses superior to the ureter and gives branches to the vaginal fornix and cervix. Turning superiorly in the parametrial space of the broad ligament, a series of arterial branches is given to the body of the uterus until the artery anastomoses with the ovarian artery at the uterotubal junction.

The uterine vein is usually plexiform, coursing laterally in the base of the broad ligament before reaching the lateral pelvic wall. Here the plexus of veins forms a series of tributaries entering the internal iliac vein, which in turn empties into the inferior vena cava. Other veins in the endopelvic space include middle rectal veins draining the rectum.

The normal route of rectal venous flow is into the internal iliac vein. During pregnancy, the fetus may partially occlude the inferior vena cava when the woman is recumbent, increasing venous resistance and diminishing pelvic venous flow into the inferior vena cava. Because the middle rectal veins also communicate with the superior rectal branches of the inferior mesenteric vein, there is the potential that pelvic blood can ascend via the portal circulation. None of the pelvic veins contains valves, allowing blood to take the pathway of least resistance. Middle rectal veins also communicate with inferior rectal veins; these veins are tributaries of the internal pudendal vein that drains into the iliac veins before entering the inferior vena cava. Increased blood flow in these vessels, particularly in the last trimester of pregnancy, is a well-known cause of hemorrhoids.

■ LYMPHATIC DRAINAGE

A plexus of uterine lymphatics parallels the course of uterine veins, entering regional lymph nodes along the internal iliac artery. From these nodes lymph trunks ascend to para-aortic nodes in the retroperitoneum.

■ INNERVATION

The endopelvic space is the primary pathway for both motor and sensory nerve fibers supplying the uterus (see Fig. 49-12). Sensory fibers from the uterine body descend in the parametrial space of the broad ligament to join other fibers from the cervix. These form a large plexus in the paracervical region termed the uterovaginal plexus or Frankenhauser's ganglion. In the endopelvic space these fibers commingle with visceral afferents from other pelvic viscera, before entering the inferior hypogastric plexus. Ascending the sacral promontory the fibers join the superior hypogastric plexus and enter the sympathetic trunk via lumbar splanchnic nerves.

From sympathetic ganglia white rami communicans conduct fibers to the dorsal roots of spinal nerves T10 to T12. The uterovaginal plexus also includes parasympathetic motor fibers from sacral roots that enter the endopelvic space directly, as well as sympathetic motor fibers that enter from the sympathetic trunk. Concentration of uterine sensory fibers in the uterovaginal plexus is the anatomical basis for a regional anesthetic procedure, paracervical block. It is accomplished by inserting the needle of a syringe into each lateral vaginal fornix and infiltrating the paracervical area with a local anesthetic. This will often provide adequate anesthesia for instrumentation of the cervix and uterus.

BLOOD SUPPLY, LYMPHATIC DRAINAGE, AND INNERVATION OF THE OVARY AND UTERINE TUBE

■ BLOOD SUPPLY

The ovarian arteries arise as lateral branches from the abdominal aorta, descend in the retroperitoneal space, cross the ala of the sacrum, and enter the suspensory ligament of the ovary (see Fig. 49-15). As the ovarian artery enters the lateral edge of the broad ligament it courses medially between the two layers of the ligament, giving branches to the ovary and uterine tube.

The venous drainage of the structures in the superior part of the broad ligament is via the ovarian vein, which parallels the ovarian artery as the vein ascends in the retroperitoneal space. On the right side the ovarian vein is a tributary of the inferior vena cava, whereas on the left side it drains into the left renal vein.

■ LYMPHATIC DRAINAGE

Afferent lymphatics from the ovarian and uterine tube accompany ovarian vessels to para-aortic lymph nodes in the retroperitoneum. The fundus of the uterus is drained in part by this same route but also sends lymphatic vessels anteriorly paralleling the course of the round ligaments of the uterus.

This bilateral course carries afferent lymphatics to inguinal lymph nodes on both sides of the pelvis.

■ INNERVATION

The suspensory ligament of the ovary also contains the afferent neural pathway for the ovary and uterine tube (see Fig. 49-13). After reaching the retroperitoneum, these fibers join the superior hypogastric plexus, ascend briefly, and then enter a lumbar splanchnic to reach the sympathetic trunk. Ascending fibers leave the sympathetic trunk via rami communicans to enter spinal sensory roots T10 to T12.

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Clinical Anatomy and Physical Examination of the Male Genital Tract

John N. Krieger and Daniel O. Graney

INTRODUCTION

Any area of the body may be involved in sexually transmitted disease syndromes or in the differential diagnosis of these conditions. Clearly there is no single, optimal method for conducting the history and physical examination. The critical areas of interest are determined by the history, other physical findings, and conditions considered in the differential diagnosis. There are as many correct ways of eliciting historical data and physical findings as there are clinicians. Similarly, there are many critical anatomical points that may be important in some contexts yet irrelevant in others. Thus, this chapter reflects our bias and represents an attempt to succinctly present one approach to “the routine examination.” Pertinent genitourinary tract anatomy will be presented in the context of this examination. This approach is selective but based on our own clinical experience in developing an efficient method for evaluating a large number of patients in a timely manner.

Most often, the standard examination of a patient in our clinic proceeds according to an orderly sequence. The pertinent portions of the examination usually follow the outline in [Table 50-1](#). Proceeding in this fashion has two advantages. First, there is an orderly sequence to the examination that limits the opportunity for errors of omission in a busy clinical situation. Second, there is a minimal need for the patient to move. Ordinarily, we initiate the examination by having the patient sit on the examining table. If necessary, head and neck examination and percussion and auscultation of the chest may be done in this position. Next, the patient is asked to lie supine. Cardiovascular examination may be conducted in this position, if indicated, and attention is directed to the abdominal examination. The patient is then asked to stand for examination of the groin and genitalia. Finally, the patient is asked to turn and bend over, placing his elbows on the examining table, for the rectal and prostate examination. In sum, there is minimal need for the patient to move from position to position if the examination is done in this order.

This chapter is organized to follow the suggested pattern of evaluation. The relevant considerations in routine examination of the male are presented for each section of the physical examination, then critical anatomical principles are considered for that area. Throughout, we emphasize a practical approach and minimize use of Latin terms. This means that we present the anatomy according to our own opinions, recognizing that some of these opinions are controversial and that other anatomists and/or clinicians may hold alternative, equally valid, viewpoints.

There are two major differences in anatomy and examination between male and female patients. First, in the male we are talking about genitourinary tract examination. In the female, there is a urinary tract and a separate genital tract. These two functions are combined in the male lower genitourinary tract in which the urethra serves as a common conduit for the excretory functions of the urinary tract and for the reproductive functions of delivery of semen. The second major difference is that the critical reproductive organs in the male are all easily palpable. In contrast, the reproductive organs in the female are located in the pelvis and, therefore, may be examined less readily than the comparable structures in the male. The clinical implication is that examination of the male lower urinary tract and the entire male genital tract is readily accomplished and is straightforward in most patients.

EXAMINATION OF THE ABDOMEN AND GROIN

■ ABDOMEN

Complete details of the abdominal examination are beyond the scope of this chapter. However, brief mention is necessary of the pelvic organs, specifically the urinary bladder. This may be distended in patients with bladder outflow obstruction caused by an enlarged prostate or urethral stricture, and occasionally in patients with neurological dysfunction, as may occur with herpetic infections. The normal bladder is not palpable or percussible when empty or nearly empty

Table 50-1. Routine STD Examination of the Male

General Appearance
Skin
Abdominal examination
Tone
Tenderness
Mass
Organomegaly
Groin
Hernia
Adenopathy
Genitalia
Penis
Circumcised or uncircumcised
Prepuce retractile if uncircumcised
Balanitis, phimosis, or paraphimosis
Appearance of glans and urethral meatus, spontaneous discharge
Shaft: tenderness or mass, discharge on “stripping” the urethral from posterior to anterior
Scrotum
Testes: position, size, tenderness, masses
Vasa
Epididymides: tenderness, masses
Presence of hydrocele, spermatocele, or other masses
Rectal examination
Tone
Fissure, hemorrhoids, or mass lesions
Prostate examination
Size, tenderness, masses
Laboratory studies
Stool guaiac
Urethral smear or first-void urine examination
Urinalysis
Other

because of its location in the pelvis. As the volume increases to approximately 125–150 mL, the dome of the bladder rises out of the pelvis into the lower abdomen and may project above the symphysis pubis. As it continues to fill, the bladder rises progressively toward the umbilicus. When the bladder contains 400 mL or more, it may be identifiable by observation as a bulge in the lower abdomen. Percussion over a distended bladder may cause the patient to experience a desire to void and may result in a change of the normal resonance

of the lower abdomen on percussion to a dull note. The distended bladder may be palpated as a firm, round, and tender mass in the lower abdomen.

■ GROIN

The groin, or inguinal region, should be examined for the presence of adenopathy while the patient is lying supine on the examining table. The patient is then asked to stand and the inguinal area is again examined for the presence of hernia by direct palpation of the area and again by insertion of the index finger through the neck of the scrotum following the spermatic cord. Both examinations are done with the patient standing quietly and again while he is coughing or straining.

GENITALIA

■ PENIS

Examination

It is critical that the clinic staff instruct patients to refrain from voiding, if possible, prior to examination because signs of urethritis may not be apparent if the patient has recently voided. In fact, in symptomatic patients who do not have objective evidence of urethritis on examination or on the urethral smear, it is our practice to repeat the examination before the first urination of the day. Initially, attention is directed to examination of the skin. Use of a good light source and a hand lens are strongly recommended for evaluating possible lesions.

Attention is then directed to examination of the penis. In uncircumcised patients, the foreskin should be retracted to rule out phimosis with an obstructing small opening. This maneuver may reveal balanitis, condylomata, ulcers, and, occasionally, tumor, as the cause of a foul discharge. The glans and inner surface of the foreskin should be inspected to rule out presence of ulcers, vesicles, or warts. The location of the meatus is determined and the urethra is examined for presence of spontaneous discharge. If the location of the urethral meatus is abnormal, it can usually be found by following the midline along the undersurface of the penis. This is the most common location for an abnormal orifice and is termed *hypospadias*. Hypospadias is associated with a prepuce that does not completely encircle the glans but is incomplete on the lower surface. This is commonly termed a “hooded prepuce.” Patients with more severe degrees of hypospadias, in which the urethral opening is located at the base of the penis or on the perineum, often have bifid, or split, scrotums. Rarely, the location of the urethral meatus may be on the upper surface of the phallus, a condition termed *epispadias*. In either hypospadias or epispadias, there is likely to be

chordee, or an abnormal curvature of the phallus. Partial or complete duplication of the urethra may be noted. Commonly, patients with urethral duplications who present with urethritis have involvement of the accessory urethral meatus. The urethral meatus is examined by pinching the glans between the thumb and the forefinger at the 6 and 12 o'clock positions. This is important to exclude presence of meatal stenosis (or narrowing) and intraurethral lesions, such as condylomata.

The shaft of the penis is palpated, looking for firm fibrotic plaques (characteristic of Peyronie's disease that may result in discomfort and (or penile bending), and the urethra is palpated for evidence of induration. Induration is often secondary to infection, stricture (or scarring), or, rarely, tumor, abscess, or foreign body inserted by the patient. At this point, the urethra should be "milked" or stripped, beginning at the bulbous urethra (located at the perineal body, behind the scrotum in the midline) and proceeding to the meatus. This is necessary for evaluation for urethritis and may result in an expression of discharge at the meatus.

Anatomy

Major divisions. There are two parts of the penis: the base, which is attached to the pubis, and the pendular portion. Underlying the penile skin there are three cavernous erectile bodies, the paired corpora cavernosa that are primarily concerned with erection, and the corpus spongiosum that contains the urethra. These erectile bodies are separate structures at the base of the penis but become bound by fascia along the shaft of the penis (Fig. 50-1). Each corpus spongiosum is surrounded by a tough layer of white fascia. During erection, blood fills the muscular structure of the corpus spongiosum, causing it to expand while the outer covering expands minimally. The result is a rigid expansion of the penis. The corpora cavernosa are cylindrical bodies in the shaft region but taper markedly at the base where they attach to the pubic ramus and

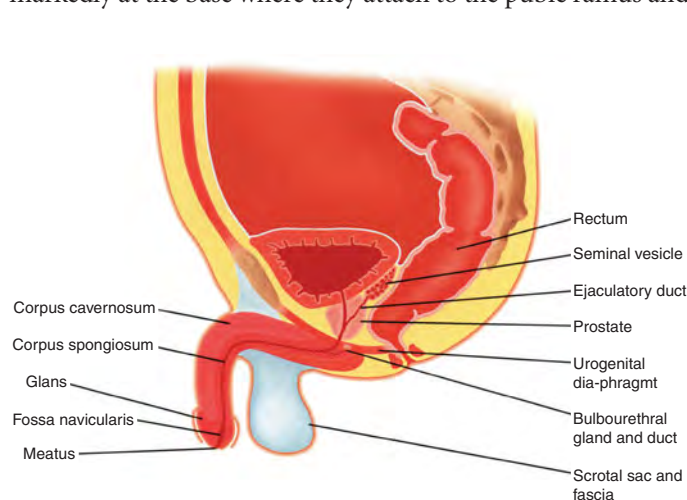


FIGURE 50-1. Sagittal section of pelvis and male reproductive system. (Artistic graphics by Robert Holmberg, Seattle, WA.)

perineal membrane. The corpus spongiosum has three parts; beginning at the perineum, these are the bulb of the penis, the spongy portion, and the glans at the tip of the penis. The base and proximal portion of the penile shaft are covered by thin muscles (Fig. 50-1). The paired ischiocavernosus muscles overlie the crura and corpora cavernosa. Another pair of muscles, the bulbospongiosus, overlies the corpus spongiosum.

Urethra and glans. The urethra is named according to the part of the penis that it is traversing. Thus, in the penis the urethra is divided into bulbous, spongy, and glandular portions. The bulbous and spongy parts of the urethra are lined by a pseudostratified columnar epithelium, except at the tip of the penis, termed *the fossa navicularis*, which is lined by stratified squamous epithelium. The epithelium contains small acini of mucous cells (glands of Littre) as well as mucosal and submucosal glands, termed *urethral or periurethral glands* (Figs. 50-2, 50-3 and 50-4). These glands can become infected and form abscesses.

On the superior surface of the corona of the glans penis, as well as on the undersurface near the frenulum, there are sebaceous glands, the glands of Tyson. These glands secrete a white cheesy type of material, which with desquamating epithelial cells forms the smegma, a substance that accumulates between the prepuce and glans of uncircumcised men.

MALE CIRCUMCISION AND HIV AND STI

Presence of a foreskin has been related to an increased risk of HIV infection, chancroid, and perhaps other STIs.¹ This may be related to the relative lack of keratinization of the mucosal surface of the prepuce, to increased rates of inflammation and trauma, and to relatively poor hygiene of the prepuce. Increased risk of HIV infections may also be related to the density and positions of HIV target cells (CD4 lymphocytes,

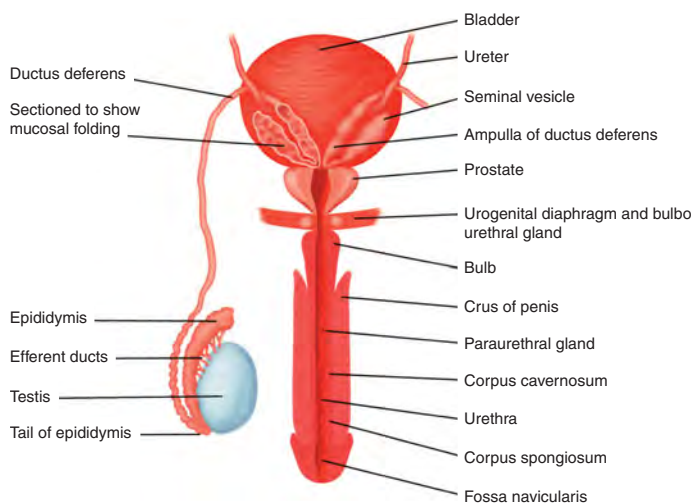


FIGURE 50-2. Coronal section of male pelvis and urethra viewed posteriorly. (Artistic graphics by Robert Holmberg, Seattle, WA.)

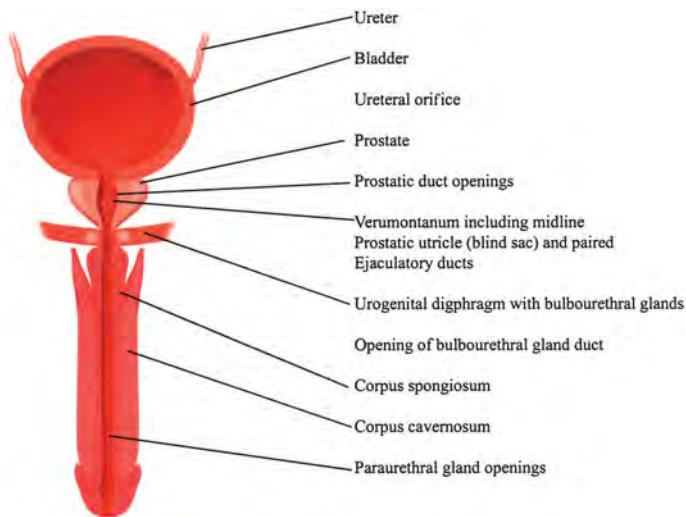


FIGURE 50-3. Coronal section of male pelvis and urethra viewed anteriorly. (Artistic graphics by Robert Holmberg, Seattle, WA.)

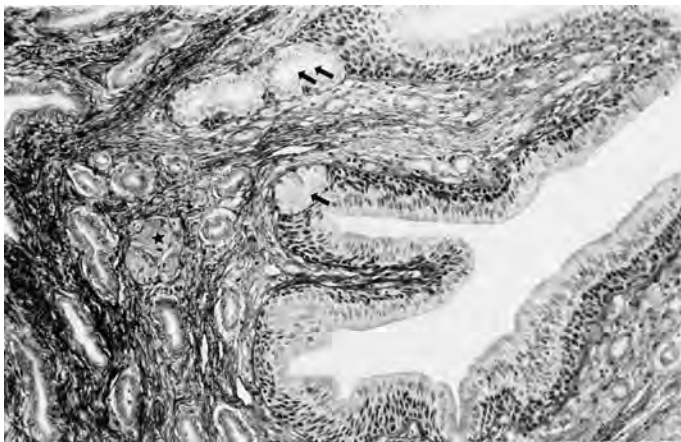


FIGURE 50-4. Photomicrograph of the spongy portion of the penile urethra. Single arrow indicates intraepithelial gland of Littre. Double arrow indicates a crypt or lacuna formed by epithelial evagination. Star indicates periurethral submucosal glands. Human, iron hematoxylin aniline blue stain, $\times 135$ in the original magnification.

macrophages, and Langerhan's cells) in the inner mucosal surface of the human foreskin² (Fig. 50-5). It is also possible that presence of a foreskin increases the duration and amount of retention and exposure to secretions containing HIV and other STI pathogens.

Circumcised men have more keratinized penile skin that may be more resistant to infection. The association between lack of male circumcision and an increased risk of HIV infection has led to three randomized clinical trials of adult male circumcision to prevent HIV infection. The first trial to be completed (from South Africa) found that male circumcision afforded about 60% protection against HIV infection.³ In anticipation of potential widespread implementation of male circumcision, pending results of trials in Kenya and Uganda, the WHO is preparing a manual of male circumcision techniques appropriate for developing countries.⁴

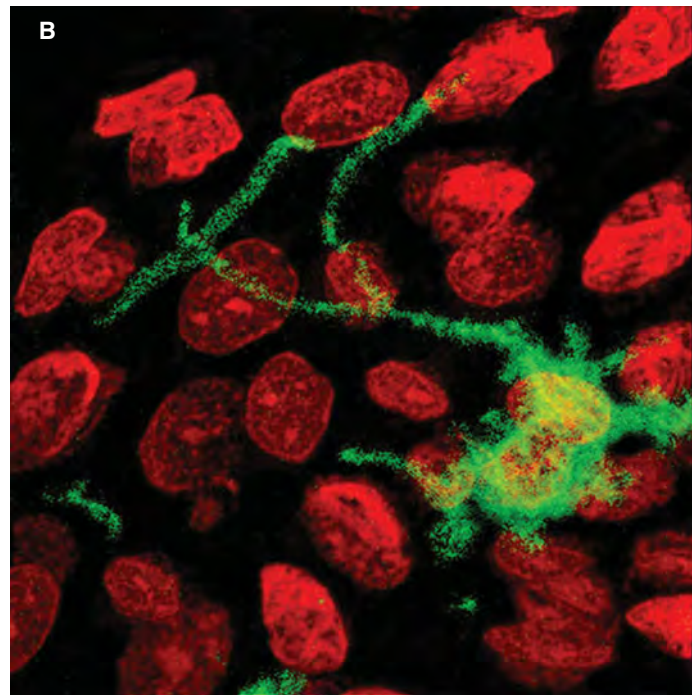
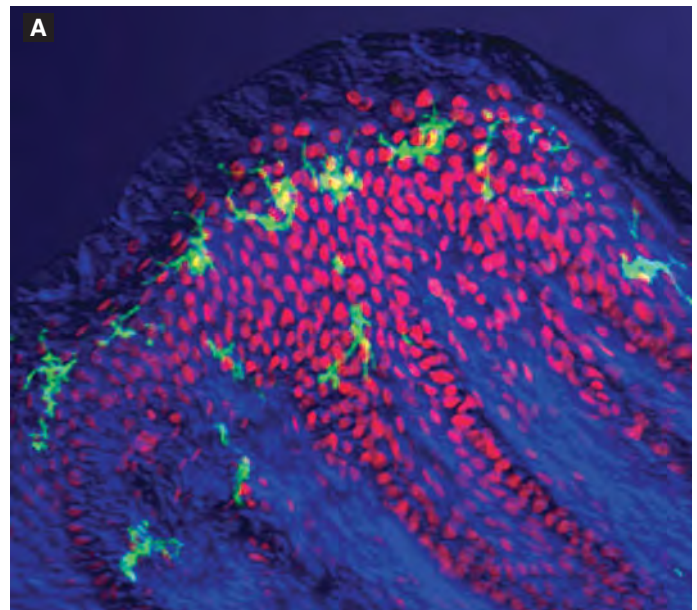


FIGURE 50-5. A. Distribution of Langerhans' cells (green) in the outer foreskin, well beneath the keratinized epithelium ($200\times$ magnification). **B.** A single Langerhans' cell (green) in the outer foreskin with dendritic processes extending towards the epithelial surface ($630\times$ magnification). (Source: McCoombe SG, Short RV. *AIDS* 2006; 20: 1493)

■ SCROTUM

Examination

Skin. The scrotum and its contents are examined next. Palpation of the scrotal skin may reveal small sebaceous cysts. These structures may be multiple and, on occasion, become quite large or develop infections. Malignant tumors of the

scrotum are rare. In contrast, scrotal hemangiomas, bluish, vascular malformations are common and they may bleed spontaneously or following sexual activity. After the skin and subcutaneous tissues of the scrotum and perineum have been palpated, attention is directed to the intrascrotal contents.

Scrotal compartments. The scrotum has two compartments that are divided in the midline. Each side is the mirror image of the other, and an identical examination is carried out for each scrotal compartment. The testis is the most anterior intrascrotal structure and must be examined carefully. The second most important structure in the scrotum is the epididymis that lies immediately posterior to the testis.

Testis. Each testis should be palpated using two hands. Hard areas within the testicular parenchyma must be regarded as potentially malignant until proved otherwise. Testicular tumors are the most common genital urinary tract malignancy in men 20–40 years old. Transillumination of all scrotal masses should be routine. The patient is placed in a dark room and a strong light is applied to the back of the scrotum. Light is transmitted well through benign cystic structures, such as hydroceles or spermatoceles, but not through solid mass lesions, such as testicular tumors. Tumors may be nodular in consistency but are often smooth. The testis that has been replaced by tumor or damaged by a gumma is often insensitive to pressure, and the usual sick sensation produced by firm pressure on the testis is absent. The testis may be absent from the scrotum as a result of maldescent during development, a condition known as *cryptorchidism*, or as the result of abnormal mobility within the scrotal sac and inguinal ring, a condition known as *retractile testis*. An atrophic testis is small and flabby in consistency and may be hypersensitive. This may be congenital; following treatment of an undescended testes; the result of previous infection, such as mumps orchitis; or may follow torsion or previous surgery, such as hernia repair. Although sperm production may not occur in these organs, hormone production may continue. Very small ($1.5 \times 1 \times 1$ cm), abnormally firm testes in a young adult usually are attributable to Klinefelter's syndrome, a relatively common condition present in 0.2% of men and is usually associated with infertility. Klinefelter's syndrome is associated with one Y and two X chromosomes. On occasion, especially in adolescents and young men, the testis may twist within the scrotum, compromising its blood supply. This is termed *testicular torsion* and is one cause of acute scrotal pain and swelling requiring surgical intervention to prevent ischemic necrosis of the testis.

Epididymis. The epididymis is a comma-shaped organ that is usually applied closely to the posterior aspect of the testis. On occasion, however, the epididymis may be loosely applied to the testis. The epididymis should be carefully palpated for size, tenderness, and induration. Induration of the epididymis usually results from infection, as primary epididymal tumors are rare. It

is often possible to feel the groove between the testis and the epididymis everywhere except superiorly, where the two structures are joined. During acute infections, the testis and epididymis are often indistinguishable, as both structures are involved in the inflammatory process. Tenderness is exquisite; swelling may be impressive and accompanied by an acute inflammatory hydrocele. In many men, a small, ovoid mass representing the appendix testis, a vestigial embryological structure, may be located near the groove between the upper pole of the testis and the epididymis. Occasionally, the appendix testis may twist, producing acute tenderness and swelling of the scrotum.

Spermatic cord. At the neck of the scrotum the cord structures should be palpated between the thumb and index finger. The solid, rope-like vas is usually identified easily and may be followed to its junction with the tail of the epididymis. Other soft, stringy structures in the spermatic cord may be palpable but are usually not clearly defined. Swellings in the cord are usually cystic in nature (e.g., hydrocele or hernia) and are rarely solid (e.g., connective tissue tumor). Varicoceles represent collections of dilated veins, are usually present on the left side of the scrotum, are best demonstrated with the patient standing, and feel “like a bag of worms.”

Anatomy

Testis. The testis fulfills two main functions: it produces sperm and it secretes male hormones. Production of sperm takes place in the seminiferous tubules, whereas the production of testosterone, the major male hormone, takes place in the tissue located between the tubules. Each testis contains approximately 400–600 seminiferous tubules. Individual tubules are up to 70 cm in length and are coiled along most of their length in order to be accommodated in a fascial compartment of the testis. These compartments are extensions of the outer fibrous capsule of the testis, termed the tunica albuginea. The seminiferous tubules join to form the rete testis, which is the connection to the excretory duct system.^{1,2} The lining of the seminiferous tubules contains two main types of cells, the developing sperm cells and the Sertoli cells, which support and presumably “nurse” the sperm cells during their development process. Sperm are continuously produced in the testis from puberty to senility following an orderly sequence of events. In the testis this process takes about 64 days.^{2,3} However, when they leave the testis, the sperm cells are immature and are unable to fertilize an egg. The capability of fertilizing an egg is developed during transport of the immature sperm cells through the excretory duct system.

Excretory ducts. The excretory ducts transport sperm from the testis to the end of the male reproductive tract. The excretory ducts are composed of five elements, beginning from the testis: the efferent ducts, epididymis, vas, ejaculatory duct, and urethra.

Efferent ducts. There are approximately 12 efferent ducts, which are convoluted tubules connecting the rete testis to the

epididymis. The epithelium lining the ductules contains both ciliated and nonciliated cells. Ciliary movement helps propel sperm toward the epididymis. On electron microscopy, the nonciliated cells are found to be lined by tall microvilli. Surrounding the epithelium is a thin basal lamina, lamina propria, and smooth muscle fibers oriented circularly.

Epididymis. The epididymis receives the sperm and seminal fluid from each of the efferent ducts. The epididymis has three parts: the head, the body, and the tail. The initial segment of the epididymis is the head, which fuses with the efferent ductules. The epididymis continues inferiorly along the posterior surface of the testis as the body of the epididymis (Fig. 50-2). At the inferior pole of the testis, the epididymis thickens to form the tail. This convoluted tubule, if stretched, will be 6 meters in length.¹ It increases in diameter and thickness as it approaches the tail of the epididymis, where it becomes the vas.

Throughout its course, the epididymis is lined by tall, thin columnar cells with nonmotile stereocilia (Fig. 50-6). In electron micrographs the stereocilia are found to be exceptionally long filamentous microvilli. In addition, the fine structure of these cells is typical of a cell that is both secretory (abundant rough endoplasmic reticulum and Golgi cisternae) and absorptive (apical vesicles and tubules).^{1,2}

Within the epididymis, sperm undergo progressive maturation during their movement from the head to the tail. As sperm emerge from the testis, they are infertile and relatively nonmotile. By the time they reach the tail of the epididymis, they are both motile and fertile.^{1,2} The average time of sperm transit through the epididymis is 12 days.⁴ Together, the sperm and epididymal fluid contribute about 10% of the ejaculate.

Vas. The vas is the continuation of the epididymal duct, with only slight modification of the epithelial surface but substantial thickening of the outer muscle coat. The thickness of the

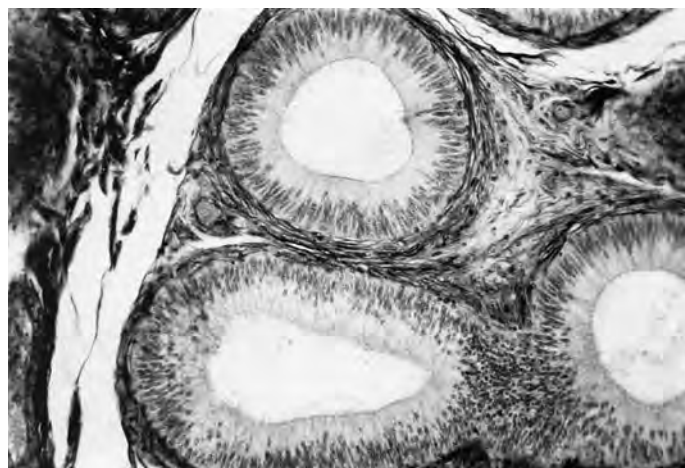


FIGURE 50-6. Light micrograph of the ductus epididymis. Epithelium is composed of pseudostratified columnar cells with stereocilia. Human, Mallory azan stain, $\times 135$ in the original magnification.

muscle coat produces the “whipcord” sensation when the vas is rolled between the thumb and forefinger during physical examination of the spermatic cord. The vas is 2–3 mm in diameter and about 18 inches long.¹

From the inferior pole of the testis, the vas ascends in the spermatic cord within the scrotum, until it reaches the superficial inguinal ring. After traversing the inguinal canal, the vas enters the preperitoneal space at the internal inguinal ring, where it courses inferiorly into the pelvis lying between the pelvic fascia and peritoneum. The terminal portion, or ampulla, of the vas is more dilated and fuses with the seminal vesicle to form the ejaculatory duct.

Ejaculatory duct. The ejaculatory duct represents the short (about 2 cm), slender termination of the vas after it joins the duct of the seminal vesicle. Traversing the substance of the posterior wall of the prostate, the ejaculatory duct opens into the prostatic urethra at the verumontanum, an oval-shaped mucosal excrescence.

LOWER GENITOURINARY TRACT SOURCES OF SEMINAL HIV

Coombs et al.⁵ have studied 23 HIV seropositive men without urethritis or prostatitis in investigating genital tract sources of HIV by quantitative measures of HIV RNA in blood plasma, urethral fluid, preprostate massage urine, expressed prostatic secretions, and postprostate massage urine and by quantitation of HIV RNA and DNA in transrectal ultrasound biopsies from multiple prostate areas. Seminal HIV RNA levels are correlated with HIV RNA levels in urethral fluid and postmassage urine and with prostate biopsy DNA levels. However, distal genitourinary sources other than the prostate appeared to be the major source of HIV RNA in these men. The authors noted that, “Further localization of the source of HIV in semen could be pursued by analysis of split ejaculates, cannulation of the ejaculatory ducts, or in situ detection methods.” Similar systematic studies for localization of many other STI pathogens in the male genitourinary tract are largely lacking. HIV RNA levels did not reliably predict seminal plasma HIV RNA levels, suggesting the importance of the male genital tract as a distinct compartment for HIV replication.

RECTUM AND PELVIC ORGANS

Examination

Inspection may reveal presence of external hemorrhoids, rectal fissures, or fistulas. Internal examination is then carried out by inserting a well-lubricated, gloved index finger into the anal canal. The sphincter tone is evaluated and the canal is examined for undue tenderness or induration. Presence of induration, rectal stenosis, or mass lesions may indicate the need for additional studies, such as anoscopy or proctoscopy.

With the patient bent over the examining table, the prostate and seminal vesicles are palpated through the anterior rectal wall. The size of the normal prostate increases with age, and by palpation is about 4 cm in length and in width, about the size of the terminal segment of the thumb. The prostate is widest superiorly at the bladder neck. Two distinct “lobes” of the prostate are palpable, separated by a median sulcus, or indentation. Normally, the prostate gland is smooth, somewhat mobile, and nontender. The consistency is rubbery and resembles the tip of the nose.

One major problem in the prostate examination lies in differentiating firm areas. Differential diagnosis of a firm area in the prostate includes: cancer, calculi, infarction, granulomatous prostatitis, and nodular, benign hyperplasia. Even the most experienced examiner may have difficulty distinguishing among these possibilities on digital rectal examination.

Above the prostate it may be possible to feel soft, tubular seminal vesicles extending obliquely beneath the base of the bladder (Fig. 50-2). Usually, clear presence of seminal vesicles on rectal examination indicates a pathological process. Most commonly, these patients have pelvic tumors such as prostate cancer or acute infectious processes.

Determination of the prostate specific antigen (PSA) level can prove helpful in evaluating patients with an abnormal prostate examination. Findings such as nodules, asymmetry, or loss of distinct sulci, suggest the possibility of prostate cancer. An elevated PSA provides further support for the possibility of cancer. Prostate biopsy is necessary for diagnosis. Elevation of the PSA and firm areas in the prostate may also occur following acute lower urogenital tract infections, such as prostatitis. In this setting, reevaluation following antimicrobial therapy is appropriate.⁵⁻⁷

Some authorities recommend annual PSA determination and rectal examination for all men over 50 years old.⁸⁻¹⁰ These evaluations are also suggested for men over 40 if they have a family history of prostate cancer. Other investigators suggest that there is little evidence that routine PSA screening, with biopsies and aggressive treatment has improved the overall outcome for patients with prostate cancer.¹¹ Lead-time and length-time biases may explain the results of many clinical series. Because aggressive diagnosis and treatment may be associated with considerable costs and morbidity, these authorities do not recommend routine screening.⁸⁻¹⁰ Thus, the value of routine screening is debatable, but PSA testing is helpful for evaluating men with abnormal prostate glands on digital rectal examination.

Anatomy

Rectum. In the rectum, there are two to four permanent semicircular transverse folds of the mucosa, which are termed rectal valves. They neither serve as valves nor support the feces, as suggested by some investigators. These valves are

readily observed during endoscopy and may be lacerated during blind instrumentation of the rectum.

Microscopically, the mucosa of the rectum is composed of columnar absorptive cells, although goblet-type mucous cells are interspersed among the absorptive cells. Invaginations of the epithelial surface form straight, tubular colonic glands equivalent to the glands of Lieberkühn seen in the small intestine.

Rectoanal junction. The rectoanal junction is not a discrete point but a longitudinal mucosal fold extending superiorly from mucosa that is paler and flatter (Fig. 50-7). This gives the appearance of a horizontal band with teeth, hence the term *pectinate line* (Latin *pecten*, “comb”). The mucosal ridges forming the tooth-like character of the line are termed *anal folds or columns* (of Morgagni). At the pectinate line between the base of the anal columns, the mucosa is redundant with outpockets to form the anal crypts. The epithelium of the anus, i.e., distal to the pectinate line, is characterized by stratified squamous cells of the nonkeratinizing type.

Accessory sex glands. The male accessory sex glands include the seminal vesicles, prostate, and bulbourethral glands (Cowper’s glands).

Seminal vesicles. The seminal vesicles are paired, saccular glands with multiple foldings of their mucous membrane (Figs. 50-1 and 50-2). Embryologically, they begin as tubular buds from the vas. Hence, the seminal vesicles join with the vas, forming a common ejaculatory duct.

The seminal vesicles are lined by multiple foldings of columnar epithelial cells (Fig. 50-8) with abundant Golgi, rough endoplasmic reticulum, and secretory granules in the apical cytoplasm. The mucosal folds of the seminal vesicles are supported by a moderate lamina propria, containing collagen and elastic fibers. There is also a substantial muscular coat, which is important in the emission of secretions.

The seminal vesicles secrete an alkaline, slightly yellowish viscid fluid which constitutes 60–70% of the ejaculate volume.³

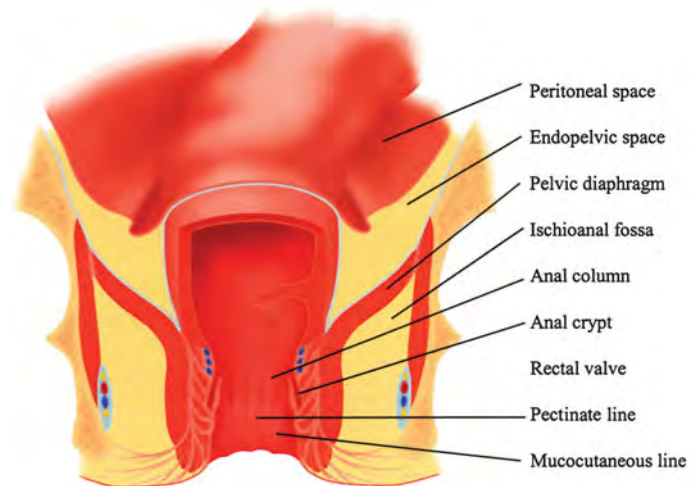


FIGURE 50-7. Coronal section of male pelvis and rectoanal junction. (Artistic graphics by Robert Holmberg, Seattle, WA.)

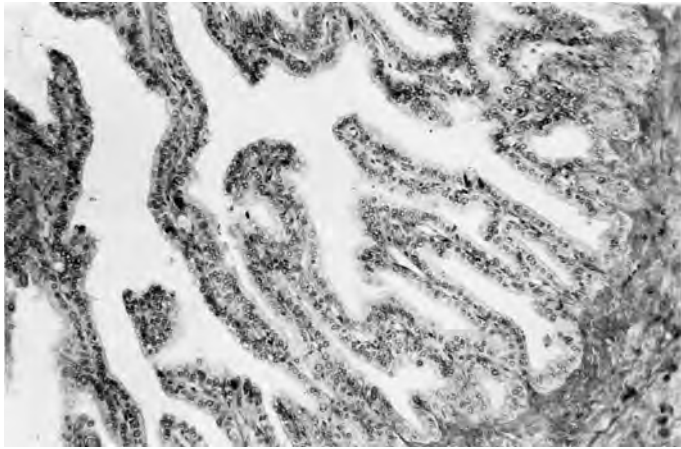


FIGURE 50-8. Light micrograph of the seminal vesicle, illustrating multiple compound foldings of glands. Human, Mallory azan stain, $\times 135$ in the original magnification.

Fractionation by “split-ejaculate” techniques shows that the semen consists of a presperm prostatic fraction, a sperm-rich fraction, and a postsperm vesicular fraction.² Fructose and a variety of prostaglandins appear to be formed specifically by the seminal vesicle.^{2,3} Fructose is the principal energy source for sperm motility, but the role of prostaglandins in male fertility is uncertain.

Prostate. The prostate gland is located between the bladder neck and the urogenital diaphragm (Figs. 50-1, 50-2, and 50-3). The prostate completely encircles the urethra. The prostate measures about 3.5 cm transversely at its base and about 2.5 cm in its vertical and anterior posterior dimensions. Its normal weight is about 18 gm.¹

Zones. The prostate gland is composed of three zones of tissue: a periurethral zone, surrounding the urethra; a wedge-shaped central zone, bounded by the ejaculatory duct, urethra, and base of the bladder; and a peripheral zone, composed of all remaining glandular tissue.¹²⁻¹⁸

The periurethral zone is composed of mucosal and submucosal glands penetrating the smooth muscle of the proximal urethra.¹⁵⁻²⁰ Benign hyperplasia originates in this region^{15,21} and may lead to obstruction of urinary outflow from the bladder.

The central zone of the prostate is located between the urethra and ejaculatory duct.^{12,16,22,23} This area appears to be least susceptible to development of inflammatory, hyperplastic, or neoplastic disease.

The peripheral, or outer, zone is the portion of the prostate that is palpable on rectal examination.^{16,17,19,24} It is lined by multiple ducts (Fig. 50-9). The peripheral zone is also the region of the prostate that is most frequently involved in carcinoma and inflammation.^{16,25}

Prostatic secretions. The prostate contributes approximately 30% of the ejaculate volume,^{2,3} in the form of a thin, slightly

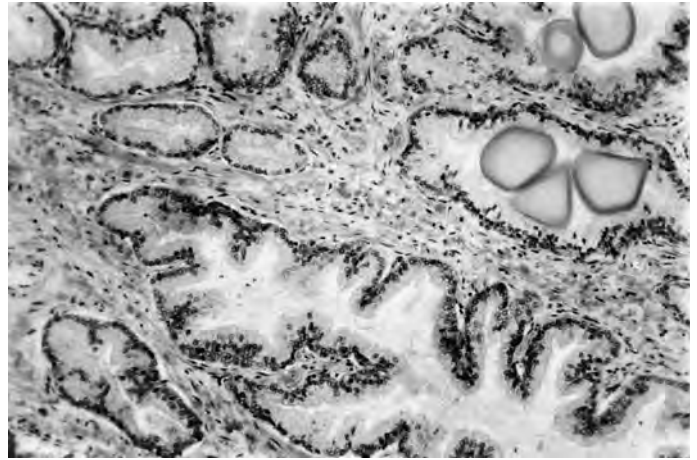


FIGURE 50-9. Prostate gland of older man showing prostatic concretions and columnar epithelium. Human, H & E stain $\times 135$ in the original magnification.

opaque fluid. The prostate gland appears to be important in protecting the male lower urogenital tract against infection, in providing enzymes for “liquefying” the semen after ejaculation, and in providing other components of the seminal fluid. Normally the pH of prostatic fluid is around 7.^{2,3,26} However, in men with well-documented bacterial prostatitis, the secretions alkalinize and may reach or exceed pH 8.25. Zinc, magnesium, citric acid, and acid phosphatase in the ejaculate appear to originate in the prostatic secretions.^{2,26,27}

Bulbourethral glands (Cowper’s glands). These paired, pea-sized glands are located in the urogenital diaphragm (Fig. 50-2). Their excretory ducts drain into the posterior urethra. The bulbourethral glands secrete a thin, mucoid material during the excitatory stage of sexual response, but the bulbourethral glands contribute only a minimal amount to the ejaculate. These glands are relatively immune to hyperplastic and neoplastic disease, although they can be involved in infections.²⁸

BLOOD SUPPLY

■ ARTERIAL PATHWAYS (INTERNAL ILIAC ARTERY)

The pelvic organs in the male receive their blood supply from the internal iliac artery. The internal iliac artery arises at the pelvic brim from the common iliac artery and immediately divides into an anterior and posterior division.

Posterior division

The posterior division of the internal iliac artery provides small branches to the pelvic sidewall and has three branches that leave the pelvis, including the pudendal arteries.

The internal pudendal artery supplies the perineum (Fig. 50-10). This includes all structures located in the ischioanal fossa and superficial and deep pouches. As it leaves the pelvis via the greater sciatic notch, the pudendal

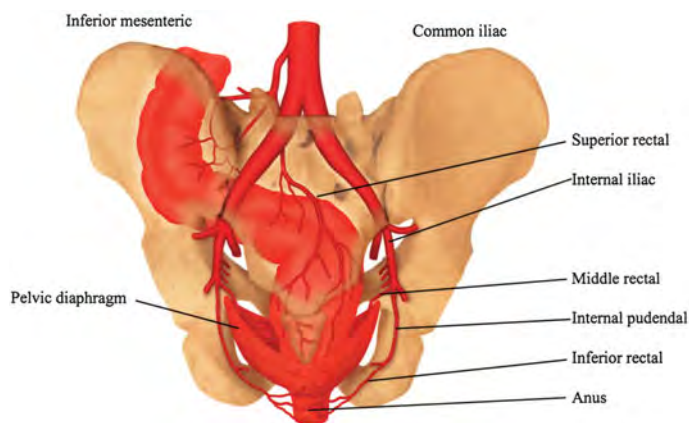


FIGURE 50-10. Branches of the internal iliac artery and the distribution of the internal pudendal artery. (Artistic graphics by Robert Holmberg, Seattle, WA.)

artery gives off the inferior rectal artery and then enters the pudendal canal. The pudendal arteries have three areas of distribution: the anal canal, the perineum, and the phallus.

Anterior division

The anterior division of the internal iliac artery courses on the sidewall of the pelvis until it reaches the symphysis pubis, where it ascends the anterior abdominal wall. As it turns superiorly, the lumen of the vessel disappears and the vessel becomes a fibrous cord, the medial umbilical ligament. The internal iliac artery branches to form the middle rectal, superior, and inferior vesical arteries. The middle rectal artery supplies the rectum and has anastomosing branches with the superior rectal artery from the sigmoid. The superior vesicle artery supplies the fundus of the bladder whereas the inferior vesicle artery supplies the bladder neck, seminal vesicle, vas deferens, and prostate. All these vessels anastomose with their members from the opposite side.

VENOUS AND LYMPHATIC PATHWAYS

■ PELVIC ORGANS

Venous drainage

The pelvic organs have abundant venous plexuses which give rise to larger veins that parallel the arterial pattern. These veins return blood from the pelvic organs to the internal iliac vein that merges with the external iliac vessel to form the common iliac vein. This pathway joins the caval system of veins. Some blood in the perirectal region enters anastomotic channels in the mucosal plexus and ascends via the superior rectal vein to enter the portal drainage system.

Lymphatic drainage

The lymphatic pathways from the pelvic organs follow the venous pattern. The first series of regional node is along the

proximal parts of the internal iliac artery. From these nodes, lymphatic channels ascend to the aorta and the para-aortic lymphatic chain before entering the thoracic duct.

The sigmoid lymphatics follow the superior rectal veins to inferior mesenteric lymph nodes near the aorta.

■ PERINEAL STRUCTURES

Venous drainage

Most structures supplied by the pudendal artery are drained by veins that enter the internal pudendal vein. This vessel returns along a similar route to enter the internal iliac vein. There are two exceptions to this pattern: the anorectal region and the dorsum of the penis.

In the anorectal region, blood may return via veins in the endopelvic space and eventually reach the vena cava through internal iliac tributaries or may continue superiorly to reach the superior rectal tributaries of the portal system. Increased venous pressure in this region, due to increased venous resistance in either the portal system or the caval system, can result in anorectal hemorrhoids. The anorectal submucosal venous plexus is also a pathway for the spread of infection from the perianal and rectal areas to the endopelvic space.

The second nonpudendal venous pathway from the perineum is via the dorsal vein of the penis to the prostatic venous plexus at the neck of the bladder. These veins cross the urogenital diaphragm from the perineum to enter the endopelvic space. The prostatic veins are tributaries of the internal iliac system.

Lymphatic drainage

The lymphatic drainage of the perineum differs from its venous drainage. In essence, all the skin and superficial structures of the perineum have lymphatics which course via the medial aspect of the thigh to the superficial inguinal nodes. Thus, anal and perianal ulcers caused by syphilis, chancroid, herpes simplex virus, or lymphogranuloma venereum cause inguinal lymphadenopathy. Channels from these nodes penetrate the fascia of the thigh at the saphenous opening to join the lymphatics from the leg. These lymphatic vessels course superiorly along the external iliac vein, then merge with para-aortic lymphatics.

An important exception is the lymphatic drainage of the testis, which does not follow the pattern described above. The testicular lymphatics course superiorly in the spermatic cord, traverse the inguinal canal, and then ascend in the retroperitoneum with the testicular vein. In this manner, the lymphatics reach the para-aortic lymph chain at the level of the renal vessels. This point is important clinically because metastases from testicular tumors do not cause inguinal adenopathy unless the usual lymphatic channels have been disrupted by infection or previous surgical procedures.

NERVE SUPPLY OF THE PERINEUM AND PELVIC ORGANS

The three neural components that must reach the perineal and pelvic structures are the somatic, parasympathetic, and sympathetic nerves.

Only the perineum is supplied by somatic fibers. These arise in spinal cord segments S-2, -3, and -4 and travel via the pudendal nerve to all the skins and structures of the anal and urogenital triangles (Fig. 50-11). The pudendal nerve leaves the pelvis along with the pudendal vessels, entering the pudendal canal after giving off the inferior rectal nerves. These supply the perineal skin, external anal sphincter, and the skin of the anal canal. The pudendal nerve then divides into a perineal branch, supplying the deep and superficial pouch structures, and the dorsal nerve of the penis, supplying the skin of the penis. Branches of the perineal division supply the urogenital diaphragm, superficial perineal muscle, and skin of the scrotum.

■ PARASYMPATHETIC NERVE SUPPLY

The parasympathetic innervation of the pelvic organs is also derived from spinal segments S-2, -3, and -4. However, these fibers originate from neurons in the intermediolateral gray rather than the ventral gray, which is the origin for fibers in the pudendal nerve. After these fibers leave the anterior sacral foramina, they join to form the pelvic splanchnic nerve (nervi erigentes), which contributes these fibers to the plexus surrounding the viscera. This is termed the pelvic plexus. These fibers traverse the plexus without synapsing and then

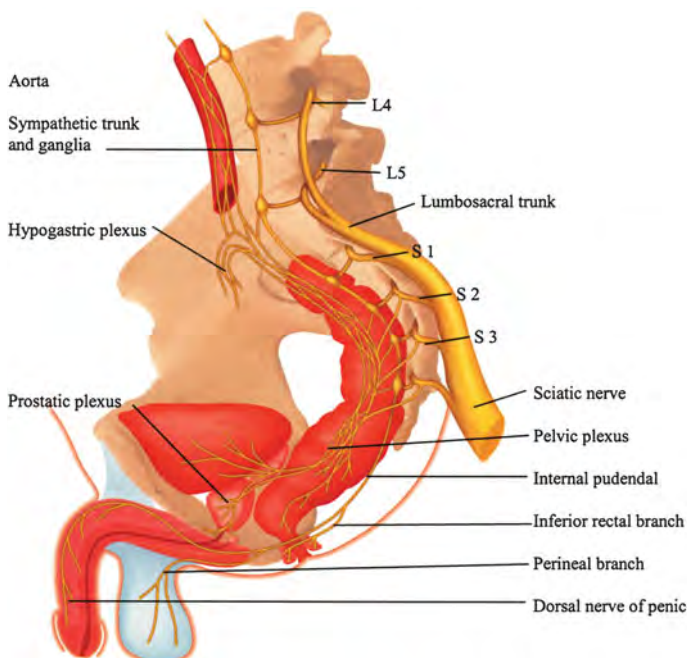


FIGURE 50-11. Innervation of the pelvic viscera. (Artistic graphics by Robert Holmberg, Seattle, WA.)

enter the walls of the pelvic organs, rectum, bladder, and prostate, where they synapse in intramural ganglia. Short postganglionic fibers are then relayed to the muscle fibers.

■ SYMPATHETIC NERVE SUPPLY

Sympathetic fibers to the pelvic viscera are believed to originate in the intermediolateral gray of the spinal segments T-12–L-2.

After joining a spinal nerve, they enter a sympathetic ganglion for that segment but do not synapse in the ganglion. The fibers descend briefly in the sympathetic chain and then course medially to enter the superior hypogastric plexus anterior to the aorta. The preganglionic fibers descend in the plexus to the inferior hypogastric plexus, which divides around the lateral sides of the pelvic organs and becomes the pelvic plexus (rectal, vesical, or prostatic). Synapses occur in the plexus or in the capsule of the organ innervated.

The pelvic plexus, therefore, is a mixture of parasympathetic and sympathetic fibers. At the lower aorta, much of the sympathetic input to the urogenital organs travels through the superior hypogastric plexus that lies anterior to the aortic bifurcation. Disruption of the nerve fibers during retroperitoneal dissection can cause loss of seminal vesicle emission and/or failure of the bladder neck closure, resulting in retrograde (“dry”) ejaculation.^{29–32} From the pelvic plexus, vesical branches emerge to proceed along the lateral sides of the bladder. A separate segment of the vesical plexus innervates the prostate, then forms the cavernous nerves to supply the penile erectile tissue.^{33,34} These fibers contain both parasympathetic and sympathetic components. Detailed understanding of the precise anatomic relationships of these prostatic neurovascular bundles allows surgeons to routinely preserve potency during pelvic operations such as radical prostatectomy or radical cystectomy for pelvic cancers.^{31,35–38}

ERECTION, EMISSION, AND EJACULATION

From many individuals’ perspective, the most important physiological functions are the “three Es” related to reproduction: erection, emission, and ejaculation. Erection is the process of developing a phallus that is sufficiently rigid to allow intromission. Emission is deposition of the semen into the posterior urethra. Ejaculation is the process by which the semen is expelled from the urethral meatus. Intact anatomy is critical for each of these functions. The anatomy and physiology of erection have received intense research scrutiny over the past 2 decades. This massive effort has led to a much clearer understanding of the macroscopic aspects of erection and identification of many prominent causes of erectile dysfunction.

From the standpoint of neuroanatomy, there are three types of erections: psychogenic, reflexogenic, and nocturnal.^{34,39}

(1) Reflexogenic erections occur in response to genital stimulation. Impulses reach the spinal erection center (S2–4 and T10–L2). Some impulses then follow the ascending tract, resulting in sensory perception, other impulses activate the autonomic nuclei to send messages via the cavernous nerves to the penis. This type of erection is preserved in patients with upper spinal cord injury. (2) Psychogenic erections occur after audiovisual stimuli or fantasies. Signals descend from the brain to the spinal erection center to activate the erectile process. This type of erection is preserved in only a small percentage of patients with complete sacral cord lesions, suggesting that the sacral erection center is the main locus of erectile nuclei. (3) Nocturnal erections occur during rapid-eye-movement sleep. Through an unknown mechanism, stimuli descend from the brain to the spinal cord to induce penile erections.

The corpora cavernosa may be considered vascular spaces. In essence, the process of erection involves increased arterial inflow into the corpora accompanied by decreased venous outflow. Because the relatively rigid outer covering of the corpora does not expand in proportion to the increased blood volume, the phallus becomes rigid. This complex erectile process requires an appropriate hormonal milieu, appropriate levels of enzymes such as phosphodiesterase-5, an intact nervous system, arterial inflow, and appropriate venous outflow. Problems with any of these factors result in erectile dysfunction.

The penile arteries arise from the paired internal pudendal arteries described above. The penile artery branches to form the cavernous arteries, which then provide helicine arteries supplying the erectile tissue of the corpora cavernosa. These helicine arteries are contracted and tortuous in the flaccid state but become dilated and straight during erection. The penile arteries and nerves penetrate the tunica albuginea surrounded by a sheath of loose, areolar tissue that protects them from compression during erection. In contrast, the emissary veins, however, are in direct contact with the tunica albuginea and are occluded easily by the shearing action of the tunical layers during erection.^{34,39–41}

The key to the erectile process is the smooth musculature of the corpora cavernosa and penile arterial walls.^{34,39,41} In the flaccid state, the intrinsic smooth muscle tone and the sympathetic discharge exert high resistance to incoming blood flow. The flaccid penis is in a moderate state of contraction. The critical event during erection is relaxation of these smooth muscles from neurotransmitters. This leads to decreased resistance to blood inflow to a minimum, trapping of the incoming blood by the expanding sinusoids, and expansion of the corpora cavernosa, resulting in increased intracavernous pressure. Thus, erection involves sinusoidal relaxation, arterial dilation, and venous compression. Contraction of the ischiocavernosus muscles produces the rigid erection phase by compressing the engorged corpora cavernosa, increasing the intracavernous pressure to several hundred millimeters of mercury. Rhythmic

contraction of the bulbocavernosus muscle expels the semen down the narrowed urethral lumen resulting in external ejaculation from the meatus.

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Most treatment decisions for sexually transmitted diseases (STDs) seem straightforward, made on the basis of the clinician's past experience and general knowledge, often with reference to standardized guidelines such as those of the Centers for Disease Control and Prevention (CDC)¹ (see Appendix B), the Public Health Agency of Canada,² and the World Health Organization (WHO).³ However, the benefits of treatment are maximized at both the patient and community level by understanding of principles that help place authoritative recommendations in context. This chapter reviews the theoretical underpinnings of the antimicrobial therapy of STDs.

APPROACHES TO TREATMENT

The approaches to treatment of persons with or at risk for STD may be conceptualized as *therapeutic goals*, *strategies*, and *practices* (Table 51-1).

■ THERAPEUTIC GOALS

From the perspective of the infected patient, the ultimate goal is *biological cure* or eradication of the causative pathogen. Biological cure is the norm for treatment of gonorrhea, chlamydial infection, trichomoniasis and chancroid, and the intent, often difficult to document, for treatment of syphilis, but it remains elusive for the viral STDs. Whether or not biological cure is attainable or practical, the *amelioration of clinical manifestations* and the *prevention of sequelae* are always desired goals and are often achievable even for the incurable viral STDs such as genital herpes, genital warts and human papillomavirus (HPV) infections, hepatitis B, and HIV infection. However, while biological cure usually results in resolution of all manifestations of disease, it cannot reverse anatomic complications, such as fallopian tube scarring or organ damage by syphilis.

A fourth goal is *prevention of transmission*. This goal may be independent of biological cure. For example, benzathine penicillin treatment for syphilis almost always promptly aborts infectivity but perhaps without biological cure;

suppressive antiviral therapy helps prevent transmission of herpes simplex virus type 2 (HSV-2); and antiretroviral therapy may reduce the infectiousness of persons with HIV infection. Ablating genital warts and HPV-infected cervical or anal tissues infection probably reduces the likelihood of HPV transmission to infected persons' sex partners, but this effect might be related more to reducing viral load than to biological cure. Finally, preventing transmission is central to the fifth goal of therapy, *community-based prevention*. In the paradigm represented by the reproductive rate of infection in the community ($R_0 = (\beta cD)$ (Chapter 3), curative treatment shortens the mean duration of infection in the population (D), and suppressive antiviral therapy reduces the efficiency of transmission (β), either of which reduces the reproductive rate (R_0). In this context, biomedical approaches to diagnosis and treatment that are generally classified as secondary prevention at the individual level (i.e., resolution of infection and prevention of complications) represent primary prevention at the population level.

■ TREATMENT STRATEGIES

Strategies for STD treatment can be viewed as a continuum according to the timing of treatment in relation to exposure and acquisition of infection and the specificity of the diagnosis (see Table 51-1). *Prophylaxis* encompasses three overlapping strategies. *Preexposure prophylaxis* (PrEP), or true preventive therapy administered before exposure, is theoretically feasible and perhaps commonly used for the traditional STDs but little-studied. Informal reports suggest that PrEP usage may be frequent among persons expecting to have high-risk sexual encounters, perhaps especially among military personnel and commercial sex workers and occasionally among persons seeking to prevent genital herpes or HIV infection. PrEP with antiretroviral drugs may have promise as an HIV prevention strategy, although documenting efficacy and translation to routine use are challenging problems.⁴ *Postexposure prophylaxis* (PEP) is treatment of an exposed or potentially exposed person to prevent infection, clinical disease, and secondary

Table 51-1. Approaches to Treatment of Persons with Sexually Transmitted Diseases**Therapeutic goals**

- Biological cure
- Amelioration of clinical manifestations
- Prevention of sequelae
- Prevention of transmission
- Community-based prevention

Treatment strategies

- Prophylaxis
 - Preexposure prophylaxis (PrEP)
 - Postexposure prophylaxis (PEP)
 - Periodic presumptive therapy (PPT)
- Etiology-based treatment
- Syndromic management
- Mass treatment
 - Universal
 - Selective

Treatment practices

- Directly observed treatment
- Prescriptive treatment
- Pharmacy-based treatment
- Expedited partner therapy
 - Patient-delivered partner therapy
 - Other expedited practices

transmission to new sex partners. Depending on the interval following exposure, most such use probably does not entail true prophylaxis but rather cures early subclinical infection. PEP with antiretroviral drugs following documented or suspected exposure to HIV infection is frequently employed following nosocomial exposure of health-care personnel and increasingly following sexual exposure. For the bacterial STDs, PEP is most commonly used in the guise of “epidemiologic” treatment of exposed sex partners.⁵ Objective evidence of efficacy is scanty, but PEP is clearly effective in preventing urethral gonorrhea when administered within several hours of exposure to infected commercial sex workers.⁶ *Periodic presumptive therapy* (PPT) is treatment at specified routine intervals, usually with long-acting antimicrobials such as azithromycin but sometimes using daily treatment with short-acting drugs. PPT can be considered a variation on both PrEP and PEP, since active infections are treated (PEP),

and antimicrobial activity persists for varying periods while exposure to new infections may continue (PrEP). PPT has been shown to reduce the incidence of bacterial STDs in female sex workers.^{7,8}

Etiology-based treatment of infected persons, directed toward a specific pathogen, is the modern historical norm in settings where etiologic diagnosis is practical, especially in industrialized countries. An etiologic diagnosis can be based upon laboratory tests, most of which have imperfect performance depending on the stage of infection and test characteristics; or upon clinical impression of probable etiology, conditioned on the specific infection, the clinical presentation, and the skill of the diagnostician. *Syndromic management*, of special interest in developing countries and other resource-poor settings, requires only determination of broad clinical manifestations together with risk assessment, followed by treatment of the main causes of the syndrome without attempting to identify the specific pathogen.^{3,9–11} Examples include treating women with signs of mucopurulent cervicitis or men with urethral discharge for both gonorrhea and chlamydial infection; treating women with increased amount of vaginal discharge (without cervicitis) for trichomoniasis and bacterial vaginosis; and treating persons with genital ulcer disease for syphilis, chancroid, and, increasingly, genital herpes.¹¹ Some therapeutic strategies amount to a hybrid of etiologic and syndromic management, as when men with urethritis undergo Gram stain of urethral discharge as a diagnostic test for gonorrhea but regardless of the results of Gram stain may also receive treatment for non-gonococcal urethritis (NGU) designed to eradicate chlamydial and *Mycoplasma genitalium* infection without attempting to identify these or other potential pathogens. Successful syndromic treatment requires knowledge of the etiologies of the syndromes treated and their local or regional epidemiology, as well as the susceptibility of the most common etiologic pathogens to locally available antimicrobial drugs. Although distinctly inferior to etiology based treatment,¹⁰ syndromic management is a reasonable accommodation to the limited resources available in low and middle income countries and probably has contributed to improved STD control in such countries.⁹ Syndromic management, including therapeutic recommendations for several syndromes, is addressed in chapters 47 and 48.

Mass treatment is the provision of therapy to entire populations known to have substantial prevalences of infection, without attempting to diagnose infection in individuals. Mass treatment can be *universal*, if applied to all persons in a population, or it may be selective. Selective mass treatment is the treatment of population subgroups with high prevalences of infection or with defined behavioral risks, such as sex workers. There have been few reported studies of mass treatment in STD control.¹² However, in the 1950s and 1960s, selective mass treatment was instrumental in almost eliminating yaws,

pinta, and endemic syphilis in several developing countries. More than 50 million persons in 46 countries were treated with various forms of long-acting penicillin and in some regions (e.g., Bosnia) one or more of these diseases were entirely eliminated.¹³ Selective mass treatment, coupled with widespread serologic screening, also contributed to the near-elimination of syphilis in China in the 1950s and 1960s¹⁴ and it might have helped curtail an outbreak of syphilis in sex workers and seasonal farm workers in California in the 1970s.¹⁵ By contrast, in the Philippines a trial of selective mass treatment for gonorrhea in female sex workers resulted in only a modest, transient reduction in the prevalence of the infection in the treated women and had no significant effect on the rate of gonorrhea among U.S. military personnel who accounted for most of their partners.¹² In Greenland, selective mass treatment in communities with high rates of gonorrhea resulted in only transient benefits in the least populated areas and no measurable benefit elsewhere, and the program was abandoned.¹⁶ More recently, selective mass treatment with azithromycin had a marginal and transient effect, if any, when tried as a measure to curtail the spread of syphilis in a high-risk population in Vancouver, Canada.¹⁷

As suggested by these examples, mass treatment usually has been directed toward a single STD or a few biologically similar infections, such as syphilis and other treponematoses.¹³ However, the Rakai, Uganda trial of STD treatment as an HIV prevention strategy employed periodic selective mass treatment against a broader range of STDs.¹⁸ In the intervention villages, all persons 15–49 years old were treated simultaneously for gonorrhea, chancroid, chlamydial infection, trichomoniasis, and bacterial vaginosis. In addition, periodic mass screening for syphilis was offered both in intervention and control villages, and penicillin therapy was given for those found to be seropositive. Only the prevalence of trichomoniasis was reduced to a significantly greater amount in the intervention villages than in control villages, and STD treatment was not associated with reduced transmission of HIV.¹⁸

On balance, the collective experience suggests that mass treatment has more potential against chronic, prolonged STDs like syphilis than against other bacterial STDs. Presumably, a prerequisite for greater success as a population-based control strategy probably is very widespread implementation in settings with limited population mobility and low potential for repeated reintroduction of infection. Mass treatment is unlikely to be effective in either the short or long term for any STD in open, mobile populations.

■ TREATMENT PRACTICES

STD treatment practices (Table 51-1) refer to the procedural aspects of therapy. *Directly observed treatment* (DOT) has been a central theme of STD management since the beginning of the antimicrobial era and preceded by several decades the

adoption of DOT as a mainstay of treatment for tuberculosis. Multiple-dose, self-administered treatment for STD initially was problematical because only parenterally administered penicillin was available. Further, many clinicians and public health authorities considered patients with STDs to be inherently unreliable and unlikely to comply with unsupervised, multiple-dose regimens. This belief remained common even after orally administered antibiotics became available and access to health care improved. In reality, it is likely that persons with STDs are no less likely to comply with therapy than demographically similar people who have other medical conditions of similar severity or symptomatology. However, compliance with treatment is poor in most population groups, especially so among young persons with subclinical or mildly symptomatic infections. The need to promptly curtail transmission adds a strong public health rationale for DOT, which remains a high priority for the curable bacterial STDs. Accordingly, DOT is considered to be the standard of care in all clinical settings for gonorrhea, chancroid, chlamydial infection, NGU, and trichomoniasis, whether treatment is based upon a specific etiologic diagnosis or upon syndromic management in resource-poor clinical settings^{1–3} (see Appendix B).

Prescriptive therapy, the normative practice for outpatient drug treatment for most indications, is the only practical approach when multiple dose regimens are required for STDs, such as treatment of chlamydial infection or NGU with doxycycline, and for all regimens employed against pelvic inflammatory disease (PID), genital warts using patient-applied therapies, genital herpes, and HIV/AIDS. Ideally, even multiple-dose therapy for STD should be dispensed in the clinical setting, with the health-care provider observing the patient ingesting or applying the first dose. In a study of women with PID diagnosed in a hospital emergency department, 28% of patients later acknowledged that they had not filled their prescriptions for doxycycline and only 31% completed the prescribed 10-day course.¹⁹ Similarly, 223 patients given a 7-day course of doxycycline for chlamydial infection in two STD clinics were studied using a computerized system to monitor the timing and frequency with which their medication containers were opened. Even though the drug was given directly to patients in the clinic, 24% apparently took little or no doxycycline, only 25% completed treatment, and 51% had intermediate levels of compliance.²⁰

Pharmacy-based treatment (PBT) refers to direct treatment of persons with self-diagnosed or suspected STD following recommendations by pharmacists or other pharmacy personnel, without clinical assessment by a personal health-care provider. PBT has evolved opportunistically in resource-poor settings, especially in developing countries, where infrastructural limitations are barriers to traditional clinical assessment and where local regulations or pragmatic policies permit anti-infective therapy without prescription. PBT can be

viewed as a variety of syndromic management based on the patient's self-assessment of symptoms that suggest STD, supplemented by assessment of symptoms by the pharmacy worker. For example, a person with urethral discharge or genital ulcer disease may describe his or her symptoms to a pharmacist, who then recommends and sells the patient a treatment regimen.

Although probably employed in some settings for many decades, PBT for STD has only recently come under systematic evaluation.^{21,22} Not surprisingly, without specific training, pharmacy personnel in developing countries often fail to recognize or counsel customers that typical syndromes are sexually transmitted, and when STDs are recognized, they frequently offer inappropriate therapy. However, when STD syndromes are recognized as such, pharmacy personnel frequently suggest the use of condoms, and with systematic training PBT may have promise as an element of STD prevention in resource-poor settings.^{21–24} In such settings, pharmacy workers may be linked with physician preceptors to learn about choice of antimicrobials. A large randomized trial in Peru evaluated training of pharmacy workers in STD recognition, treatment or referral, and on counseling patients about partner treatment and future condom use. The intervention resulted in dramatic and significant improvements in all aspects of management of simulated patients when they presented to pharmacies with scripted scenarios of urethral discharge, vaginal discharge, genital ulcers, or pelvic inflammatory disease.²³

Expedited partner therapy (EPT) is the practice of treating the sex partners of persons with selected STDs without direct clinical assessment or professional counseling of the partners (Chapter 54). For the curable bacterial STDs, it has traditionally been recommended that patients' sex partners be examined, counseled, and treated, ideally by the provider or clinic that treats the index case. However, the success of this traditional approach in assuring partner treatment is limited by structural impediments (e.g., transportation barriers, insurance coverage), attitudes of exposed persons, such as disbelief that they might be infected when asymptomatic, and privacy concerns by both index patients and partners.²⁵ In the United States, local and state health authorities attempt to identify and treat the partners of fewer than 20% of persons with gonorrhea or chlamydial infection,²⁶ and although stronger efforts are made to assure evaluation and treatment of the partners of persons with infectious syphilis,²⁶ the effort usually is fruitless.^{27,28} From a combination of spontaneous and assisted attempts by patients to notify their own partners, and occasional success through direct contact of partners by providers or public health authorities, it is likely that no more than half the partners of persons with gonorrhea or chlamydial infection are successfully treated through the traditional approach^{27,29} (see Chapter 54).

EPT has evolved, first through spontaneous use by savvy practitioners and increasingly as a systematic approach to partner management, as one strategy to address the poor performance of the traditional approaches. EPT primarily employs patient-delivered therapy to his or her recent partner(s), but other strategies, less dependent on cooperation of the index patient, are also in evolution, such as postal delivery of medication and retrieval of drug at a health-care provider's office or public health clinic. Both randomized controlled trials and observational studies^{27,29} (reviewed in Chapter 54) have documented the effectiveness of EPT as a partner management strategy for chlamydial infection and gonorrhea in heterosexual men and women. Effectiveness has been documented not only in significantly reduced rates of reinfection in index patients but also in process indicators, such as numbers of partners brought to treatment, reduced frequency of sex between index patients and untreated partners, and increased frequency of condom use in the weeks following treatment.^{29,32} Somewhat surprisingly, a single trial did not document any benefit of EPT for reducing rates of recurrent trichomoniasis in index women,³⁰ perhaps because single-dose treatment with metronidazole is only about 90% effective against trichomonal vaginitis and perhaps still less effective among infected men.³³

Thus, EPT has rapidly become a routinely recommended option to assure treatment of the partners of heterosexual men and women for chlamydial infection and gonorrhea, but the practice should be used with caution in the management of trichomoniasis (pending further data).^{1,27,29,32,34} Clinical complexity and reliance on injection therapy or on multiple dose treatment regimens are challenges to the use of EPT for syphilis or the viral STDs. Studies are indicated to evaluate EPT in the syndromic management of genital discharge syndromes. Further research is also indicated for the use of EPT for trichomoniasis and on the utility of EPT for both syndromically and etiologically defined STDs in special populations, such as men who have sex with men (MSM) and pregnant women.^{1,27,29,32,34}

CONCURRENT INFECTIONS

Concurrent STDs are common, and treatment guidelines for certain STDs have often recommended concurrent therapy for undiagnosed STDs likely to coexist with the primary infection. Treatment of gonorrhea with regimens that would eradicate undiagnosed or incubating syphilis was once considered a high priority, based on the belief that both infections were often acquired simultaneously. However, a controlled study in Miami, Florida, from 1985 to 1992, when gonorrhea was epidemic and syphilis resurgent, analyzed 98,441 cases of gonorrhea treated either with drugs effective against syphilis (various regimens that included ceftriaxone, doxycycline, or erythromycin) or with spectinomycin, which is not active against *Treponema pallidum*. New cases of syphilis were rare

in the several weeks following treatment and were not significantly different according to the treatment given.³¹ Thus, in recent years the activity of the selected antibiotic against *T. pallidum* and its efficacy against incubating syphilis have not been major determinants of the recommended treatments for patients with gonorrhea in the United States. Conversely, rates of treatable STDs other than gonorrhea, such as chlamydial infection, have not been assessed in persons with syphilis. Resurgence of syphilis among MSM in industrialized countries since 2000 has been accompanied by equally dramatic increases in gonorrhea and chlamydia morbidity in MSM.³⁵ Few pertinent data are available for developing countries. For the moment, the primary treatment strategy in persons with syphilis should be to routinely undertake screening laboratory tests for other common STDs, including HIV infection, but not to sacrifice the assurance of curing syphilis in order to treat other presumptive infections.

For 3 decades, recommendations for treatment of concurrent STDs have been influenced by the high prevalence of chlamydial infection in patients with gonorrhea. About 10–20% of men and 20–40% of women with gonorrhea in industrialized countries in the 1980s and 1990s were infected with *Chlamydia Trachomatis*.^{36,37} According to the nationally representative, population-based National Health and Nutrition Survey, from 1999 to 2002 the prevalence of *C. trachomatis* was almost 50% among persons with gonorrhea.³⁸ Thus, it is universally recommended that all patients with gonorrhea be treated with regimens effective against *C. trachomatis* unless chlamydial infection has been excluded prior to treatment^{1–3} (see Appendix B). The reverse is not the case: because of the differing population characteristics associated with the two infections, the prevalence of *Neisseria gonorrhoeae* in persons with chlamydial infection is typically below 5%, and treatment for chlamydial infection need not be routinely accompanied by treatment for gonorrhea. In any case, the recommended regimens against *C. trachomatis* usually will eradicate undiagnosed gonococcal infection. However, specific antigonococcal therapy should be considered in persons with chlamydial infection if local epidemiologic assessment suggests a high likelihood of dual infection.

Other combinations of simultaneous infections with treatable STDs are common but few if any systematic studies are available and no standard guidelines recommend routine treatment for other disease combinations. Among some women and men with trichomoniasis, 10–15% have gonorrhea, chlamydial infection, or both.³⁰ Infection with multiple pathogens, including HSV, *Haemophilus ducreyi*, and *T. pallidum*, has been reported in patients with genital ulcer disease in the United States and in developing countries.³⁹ Few data are available on the prevalences of gonorrhea or chlamydial infection among patients with genital herpes, genital warts, or other STDs. In the absence of definitive data, clinicians should screen patients with any of these

infections for locally prevalent curable STDs. In some instances, presumptive therapy based on local epidemiologic data may be indicated for selected patients, such as those who are unlikely to return for follow-up.

POSTTREATMENT FOLLOW-UP

■ TEST OF CURE

Clinical follow-up and retesting to assess both the clinical and the microbiologic responses to therapy have been common practices in settings where funding and infrastructures permit. Syphilis in particular requires clinical and serological follow-up often for several months or years, when practical, in order to document cure^{1–3} (see Appendix B). Clinical follow-up is generally recommended following treatment of chancroid, but prompt resolution of symptoms and signs are reliable indicators of cure so that retesting for *H. ducreyi* is rarely indicated. Likewise, the clinical response of gonococcal or chlamydial urethritis in men is usually a reliable indicator of bacteriologic cure, although subclinical persistence after initial clinical improvement sometimes occurs.^{29,40} On the other hand, cervical, rectal, or pharyngeal infections with *N. gonorrhoeae* or *C. trachomatis* are commonly asymptomatic or have nonspecific manifestations, sometimes necessitating follow-up test of cure to assure eradication of the organism.

Nevertheless, in most industrialized countries the currently recommended treatment regimens for gonorrhea and chlamydial infection^{1–3} are sufficiently reliable that routine test of cure soon after treatment is not cost-effective. Test of cure continues to be indicated when the treatment used has uncertain efficacy or if the potential consequences of persistent infection are especially severe, such as chlamydial infection in pregnant women. Test of cure is also recommended when the susceptibility of the pathogen, especially *N. gonorrhoeae*, is in doubt, or when compliance with therapy cannot be reasonably assured¹ (see Appendix B). In developing countries, where test of cure is most problematic both for financial and logistic reasons, it is especially important that highly effective DOT be used wherever possible.

When test of cure is employed following treatment of uncomplicated gonorrhea, retesting by culture 5–10 days after completion of treatment is probably reliable for detecting treatment failures. However, test of cure for either *C. trachomatis* or *N. gonorrhoeae* by nucleic acid amplification testing should be delayed until at least 3 weeks after completion of therapy because *C. trachomatis* DNA may persist for 2 weeks or occasionally longer after successful treatment.^{1,29,40,41} In addition, some generally effective regimens, especially single-dose azithromycin, may transiently suppress but not eradicate *C. trachomatis*, resulting in falsely negative test results in the first few weeks after treatment.²⁹

■ RESCREENING

Delayed posttreatment testing, or rescreening, is designed to detect both reinfection and, to a lesser extent, delayed treatment failure. Studies in the 1960s and 1970s showed that *N. gonorrhoeae* was reisolated from approximately 10% of women treated for gonorrhea several weeks earlier, primarily owing to reinfection. Accordingly, some authorities recommended routine rescreening of women with gonorrhea 1–2 months after treatment, and mathematical modeling suggested that rescreening women at high risk might contribute to control of gonorrhea. However, compliance was poor so that the use-effectiveness and cost-effectiveness of rescreening were low,⁴² and this strategy was largely ignored and the recommendation was deleted from later treatment guidelines. Several recent studies, however, indicate that 10–20% of men or women treated for either gonorrhea or chlamydial infection have persistent or recurrent infection within the next year, with most cases detected within 4 months.^{27,29,32} These results are consistent with the hypothesis that most reinfections are acquired from untreated sex partners or from reentry into partner networks with high infection prevalence. Rescreening also detects persistent infection resulting from treatment failure.^{29,40} For these reasons, rescreening 3–4 months after treatment is now recommended routinely for all women with chlamydial infection¹ (see Appendix B), and many experts recommend its routine use for men with chlamydial infection and both men and women with gonorrhea.^{29,43}

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INTRODUCTION

Laboratory diagnosis of sexually transmitted infections (STIs) involves the examination of material obtained from a patient to determine current or past infection with a sexually transmitted microorganism. This is accomplished by demonstrating either the presence of the organism or a marker of infection such as antigens, antibodies, nucleic acids, or metabolic products. Valid laboratory assays are necessary for accurate diagnosis of STIs because clinical signs and symptoms are frequently not reliable diagnostic parameters, and diagnoses based on the syndromic approach lead to both under and over treatment of STIs.¹⁻³ When patients present with similar manifestations for infections caused by dissimilar microorganisms, laboratory tests can provide a specific diagnosis and etiology. Laboratory testing plays a role in patient management to confirm diagnoses in symptomatic patients and to monitor antimicrobial susceptibility and the effectiveness of treatment. Accurate diagnoses will prevent unnecessary antimicrobial treatment and development of resistant organisms. Laboratory testing is perhaps most useful for detection of asymptomatic STIs to prevent transmission and complications, and for public health surveillance and interventions.

Laboratory diagnosis has undergone many changes in recent years due especially to the introduction of new technologies and to a lesser extent shifts in disease prevalence. For many STIs, improved methods for laboratory diagnosis have been developed and laboratory directors must evaluate these techniques with the view of adapting new equipment, reagents, and personnel training to their own settings. However, in some cases, older, conventional assays remain valid and should still be used. Deciding which tests to perform depends on factors unique to each individual laboratory environment. The most important attributes of a laboratory test are its ability to produce accurate and precise results consistently over extended periods with a turnaround time that is clinically useful. The characteristics of an ideal laboratory test are described in [Table 52-1](#). Unfortunately, few tests meet this ideal.

This chapter will discuss the general established rules for the laboratory diagnosis of STIs, including gonorrhea, chlamydial infection, trichomoniasis, syphilis, chancroid, bacterial vaginosis (BV), and genital herpes simplex virus (HSV) infections. Testing strategies and approaches, methodology, and performance guidelines are presented. This information will help in making important decisions about laboratory testing of STIs, including when to test, whom to test, and which methodology to use.

TESTING STRATEGIES AND APPROACHES

The goal of laboratory testing is to provide information to the health-care provider regarding the etiologic agent responsible for the patient's symptoms and its antimicrobial profile. This information is then used to guide treatment and other management decisions. Current approaches to STI diagnosis rely upon a number of different but often complementary approaches.

■ ETIOLOGICAL APPROACH

Laboratory tests are used in this approach to identify the causative agent. This is the most accurate and, generally, the most costly approach to diagnosis. The complexity and scale of laboratory testing can be adapted appropriately for use at different levels of a health-care system, but even the most basic laboratory-based testing and diagnostic procedures (such as Gram stain or wet mount) depend upon the availability of trained personnel, infrastructure such as electricity to run microscopes and centrifuges, and reliable, ongoing supply sources of reagents. The more sensitive and accurate tests require a high level of technical expertise, expensive equipment, and testing is often batched to save cost of processing. The results of these tests are often not available the same day, so patients typically must return for their test results and treatment.

■ SYNDROMIC APPROACH

In the absence of laboratory services, the World Health Organization (WHO) has developed algorithms to allow

Table 52-1. Characteristics of an Ideal Laboratory Test

<i>Specimen collection, transport, processing</i>	<ul style="list-style-type: none"> Specimens easily obtained Noninvasive procedure Stable at ambient temperatures No complex handling or processing
<i>Testing</i>	<ul style="list-style-type: none"> Sensitive Specific Technically simple to perform Reproducible Inexpensive Rapid results Reagents easily obtained and stored Little or no equipment required
<i>Interpretation</i>	<ul style="list-style-type: none"> Objective Differentiates past from current infection

health-care providers to identify and treat clinical syndromes caused by STIs.⁴ Syndromic management aims to provide treatment for the most common infections linked to a particular cluster of symptoms. A man presenting with urethral discharge will be treated for the most common causes of genital discharge—chlamydial infection and gonorrhea. A person presenting with genital ulcers would be treated for syphilis, and chancroid, and perhaps for genital herpes. Syndromic management is relatively simple to use, and can be incorporated into all levels of public and private health-care systems. This approach has varying sensitivity and low specificity. To increase specificity, risk scores, generally based on sexual behavior, have been added but at the expense of lowering sensitivity.^{5,6}

In settings where laboratory services are available, the two approaches may be combined. Thus, a patient with a suspected STI is presumptively treated for a clinical syndrome and appropriate specimens are collected for laboratory testing. Confirmation of infection by a diagnostic test for STI serves to reinforce the caregiver's clinical diagnosis and case management and allow partner notification to be initiated. An evaluation of treatment practice in Canada showed that 74% of all STI treatment provided in 1997 was for presumptive treatment of urethral and cervical infection or pelvic inflammatory disease (PID), of which 14.4% were confirmed by a positive test for chlamydia or gonorrhea.⁷

However, presumptive treatment for chlamydia and gonorrhea in women presenting with vaginal discharge, the most common symptom in women, can be problematic outside of high-risk populations. Women with vaginal discharge are often over-diagnosed and over-treated for cervical infection when they are in fact suffering from trichomoniasis or endogenous infections such as candidiasis or BV, or no infection at all. A study in rural Bangladesh showed that the syndromic approach to management of vaginal discharge led to as much as 98% overtreatment for chlamydia and gonorrhea.⁸ Overtreatment carries not only financial implications, promotion of antimicrobial resistance, and needless risk of adverse drug reactions, but is also associated with social implications. Women diagnosed erroneously with an STI may be at risk of violence if they have to inform their sexual partners about their diagnosis and the need for partner treatment. Sensitive and specific rapid tests for chlamydia and gonorrhea are needed so that women with symptoms suggesting these infections can be treated appropriately at the first clinic visit. Although current point-of-care (POC) tests for chlamydia are less sensitive and specific than laboratory-based tests such as nucleic acid amplification tests (NAAT), a study at an sexually transmitted disease (STD) clinic showed that POCs led to more infected patients being treated than did NAATs when the population return rates for test results and treatment were low.⁹

■ SCREENING ASYMPTOMATIC INFECTIONS

A second, and perhaps more serious limitation of the syndromic approach is the fact it fails to identify individuals with STIs who have no overt or specific symptoms. Identification of asymptotically infected individuals is important for the control of STIs to eliminate the reservoir of infection in the population and for the prevention of long-term complications in the infected individual. Screening is especially important in women, who bear a disproportionate share of the disease burden and may transmit the infection to their offspring.

Approaches to screening

Universal screening for STIs is not cost-effective as high concentrations of STI cases tend to be strongly correlated with a number of economic and social conditions, including poverty, inadequate and dysfunctional health systems, high rates of urbanization that create markets for sex work in cities, a demographic profile with a high proportion of young people, gender inequalities that result in a lower status for girls and women, and cultural and economic barriers to diagnostics and treatment access. For example, the economic and social upheavals caused by the break up of the Soviet Union have resulted in a significant increase in syphilis prevalence among adults in the new independent republics.¹⁰ In China, the

change from socialism to a capitalist style market economy has led to changes in access to health services and rapid and uneven economic development that resulted in huge migration of the rural population into urban centers to seek employment. A sex industry has sprung up around booming areas. Migrants and sex workers are often stigmatized and marginalized from the health-care system. Syphilis incidence has increased approximately 20-fold from 1990 to 1998.¹¹

Which STIs should screening programs target?

Priorities for STI screening should be made based on several considerations. They should include STIs likely to be transmitted to partners and newborns, those that enhance transmission of HIV and that are curable, ideally with single dose oral regimens deliverable on site. Affordable curative single dose oral treatments exist for chlamydial infection and gonorrhea, while syphilis requires one or more intramuscular injections of penicillin. STIs that can cause serious consequences if left untreated are especially important targets for screening. Such STIs of course include HIV infection (not the subject of this chapter), and others that can result in problems in pregnancy such as ectopic pregnancy, stillbirths, and prematurity; problems in neonates and infants, including blindness, pneumonia, congenital syphilis, and herpes encephalitis; and long term complications in infected sexually active men and women that include chronic pelvic pain, PID, infertility, and neoplasia (genital cancers including cervical cancer, and hepatocellular carcinoma).

Taking all the above factors into consideration, the highest priorities for STI screening remain the curable bacterial infections of syphilis, gonorrhea, and chlamydia. Most syphilis seroreactive individuals lack any clinical symptoms. Syphilis continues to be a serious public health problem where screening programs are not carried out. Infants born to infected mothers are at risk of acquiring the infection in utero. Primary and secondary syphilis during pregnancy will lead to fetal infection in virtually all cases with approximately 30–50% of pregnancies resulting in fetal death in utero, stillbirth, or death shortly after delivery.¹² These complications can be prevented if syphilis is detected and treated early in pregnancy.

We believe there is currently no widely accepted indication for screening asymptomatic women for vaginal infections such as *Trichomonas vaginalis*, *Candida* species, and BV; although one or more of these conditions have been associated in clinical epidemiologic studies with certain complications in pregnant and in nonpregnant women and with increased susceptibility to or vaginal shedding of HIV, (see Chapter 18) they are not usually treated unless patients are symptomatic. However, one review concluded that screening and treatment for BV before termination of pregnancy and hysterectomy significantly reduced the rate of complications.¹³

There is limited evidence to suggest that screening for viral infections other than HIV is cost-effective^{14–16} (However, see Appendix A and Chapters 23, 24, 57, and 84 for further views on this topic).

The tests of choice for STI diagnosis of symptomatic patients, criteria and test choice for screening asymptomatic individuals, and the appropriate specimens to be collected are briefly summarized in [Table 52-2](#).

Who should be targeted and how?

The serious morbidity and mortality associated with adverse outcomes of pregnancy in women infected with syphilis have led to policies for universal screening of all pregnant women in most countries. To prevent congenital syphilis, the U.S. Centers for Disease Control and Prevention (CDC) and European guidelines recommend prenatal screening in the first and third trimester and at delivery,^{17,18} Appendix A.

For chlamydia and gonorrhea, a targeted screening approach focused on high-risk populations is recommended. Studies of risk factors for infection have been translated into criteria for targeted screening. A number of guidelines have been developed to provide screening criteria for these three STIs.^{19–21} For example, criteria for chlamydia screening vary but most include young age (<25 years of age), a change of sexual partner in the last 6 months, 2 or more sexual partners in the last year, unprotected sex, history of STDs, and diagnosis of another STD in the patient or diagnosis of an STD in a sexual partner. Screening following treatment for chlamydial infection, gonorrhea, or syphilis is also recommended to detect treatment failure or reinfection.

Previous screening approaches have suffered from a number of barriers including lack of access to populations at high risk of infection. Advances in diagnostic technology have resulted in a new generation of STD tests, NAATs, that not only have high sensitivity and specificity but also allow the use of noninvasive or minimally invasive specimens such as urine or self-collected vaginal swabs. These tests do not require the specimens to be viable and can thus be stored or transported at ambient temperatures. This has opened up a variety of screening options not previously thought possible. As shown in [Table 52-3](#), in addition to traditional venues for screening at STD, prenatal, and obstetric and gynecological clinics, opportunistic screening is now possible at a variety of clinic settings where specimens for testing are obtained from women even if pelvic examination is not performed. Opportunities include screening for gonorrhea in emergency rooms and screening for chlamydia prior to termination of pregnancy (TOP).^{22,23} Although it is a common practice to administer doxycycline to women undergoing TOP, concurrent testing for *Chlamydia trachomatis* can be recommended to guide partner treatment, if necessary.

Instead of waiting for individuals at risk to come to a clinic, a more proactive approach to screening is to take the testing to those at risk. This type of outreach program can be

Table 52-2. Testing Options for Diagnosis of Symptomatic Cases and Screening of Asymptomatic Individuals at Risk for STIs

Pathogen	Diagnostic Testing		Target Population	Screening	
	Test of Choice	Specimen		Test of Choice	Specimen
<i>C. trachomatis</i>	NAAT ^a EIA ^a	Urethral/ Cervical/ Vaginal swab Urine	Age < 25 High risk ^b Repeat screening after 3–6 months	NAAT EIA	Vaginal swab Urine
<i>N. gonorrhoeae</i>	Culture NAAT	Urethral/ Cervical/ Vaginal swab Urine	High risk	NAAT	Vaginal swab Urine
<i>T. pallidum</i>	Serology Darkfield DFA ^a PCR ^a	Blood Swab of lesion	Prenatal High risk	Serology	Blood
<i>H. ducreyi</i>	Culture	Swab of lesion ^c	Screening of asymptomatic individuals not recommended for these infections		
Bacterial vaginosis	Nugent Gram stain score	Vaginal swab			
<i>T. vaginalis</i>	Wet mount microscopy Culture	Vaginal swab			
HSV 1 and 2	Culture Antigen detection	Swab of lesion			

^aNAAT-nucleic acid amplification test; EIA-enzyme immunoassay; DFA-direct fluorescent antigen; PCR-polymerase chain reaction.

^bDefinitions of high risk vary but generally include those individuals who exchange sex for money or drugs, have multiple sex partners, or have unprotected sex with an STI case.

^cExcept in high risk populations and during outbreak investigations.

conducted by collecting specimens at venues such as schools, youth centers, remand centers, prisons, or military units.^{24–29} The specimens can be sent to laboratories for testing, or on-site testing can be offered if POC tests of sufficient sensitivity and specificity are available.

There have been other interesting developments in increasing access to STI services outside of clinic settings. In one scenario, pharmacists were trained to provide syndromic management of STIs, while in another, women aged

15–29 years, who bought contraceptives at a pharmacy, were offered a chlamydia screening kit for mailing a home-collected urine specimen to a laboratory.^{30,31} Postal screening for *C. trachomatis* in asymptomatic men and women aged 20–24 randomly sampled from a population registry showed that this approach is cost-effective if prevalence exceeds 5.1% in women and 12.3% in men.³²

In an increasing number of countries, STI services are being advertised on web sites where dating and anonymous sexual

Table 52-3. Screening Options: Traditional Venues and Novel Opportunities

Venues	STI Tests ^a	Comments
<i>Traditional settings</i>		
STD clinics	STI tests ^b HIV offered	
Family planning clinics	Ct ^c , Ng ^d	
Prenatal clinics	Ct, Ng, syphilis	
OB/Gyn clinics	Ct, Ng	
Termination of pregnancy	Ct	POC preferred
Emergency rooms	Ct, Ng	POC needed
VCT/PMTCT ^e	Ct, Ng, syphilis	
Physicians offices	Ct, Ng	
<i>Pharmacies</i>		
Sample collection sites	Ct, Ng	
Testing on site	Ct, Ng	
<i>Outreach settings</i>		
Schools	Ct, Ng	
Youth centers	Ct, Ng	
Detention centers	Ct, Ng	
Street kids	Ct, Ng, syphilis, HIV	
Prisons	Ct, Ng, syphilis, HIV	
Armed forces	Ct	
<i>Home-based</i>		
Mail-in samples	Ct, Ng	Urine Vaginal swabs
Internet services	Ct, Ng, syphilis	Urine Vaginal swabs Dried blood spot
Self-testing	BV	Glove test for vaginal pH

^aHIV testing is also now encouraged and offered increasingly on an “opt-out” or clinician-initiated counseling and testing basis in most of the clinical settings listed and for home-based-mail-in samples.

^bCost-effectiveness of screening is dependent on the prevalence of infection in the target population.

^c*C. trachomatis*.

^d*N. gonorrhoeae*.

^eVoluntary counseling and testing/prevention of mother to child transmission.

Which tests should be used?

Ideally, the screening test should have high sensitivity, and if possible, high specificity. For screening performed outside of clinic settings, the use of non-invasive specimens with tests that can be performed simply and efficiently at point of screening is ideal. This would allow test results and appropriate treatment to be given on site, as in settings where it may not be an option for patients to return.

Performance characteristics. The screening tests of choice for *C. trachomatis* and *Neisseria gonorrhoeae* are the NAATs. These tests are highly sensitive and specific and can be used with non-invasive specimens. Urine specimens can be used for screening chlamydial and gonococcal infections in men. Minimally invasive specimens such as self-obtained vaginal swabs are acceptable for detection of chlamydial and gonococcal infections in women. (Note, however that not all currently available NAATs are equally specific for *N. gonorrhoeae*, so that use of certain tests on specimens that contain other *Neisseria* sp., such as vaginal swab or throat specimens, is not recommended.) Vaginal swab specimens have a higher sensitivity than urine for the detection of chlamydia, gonorrhea, and *T. vaginalis* in women. These swabs can also be mailed to a testing center or deposited at a testing depot at a pharmacy without compromising specimen quality.

The screening test of choice for syphilis has traditionally been nontreponemal tests such as the Rapid Plasma Reagin (RPR) or Venereal Disease Research Laboratory (VDRL) tests. These tests usually require confirmation with a treponemal test such as the *Treponema pallidum* hemagglutination assay. Simple, rapid POC treponemal-specific tests that can use whole blood, require minimal training, no equipment, and cost U.S. \$ 0.45–1.00 are now commercially available.³⁵ Several tests with sensitivities and specificities of 85–98% and 92–98%, respectively, compared to standard treponemal assays, are now available through the WHO Bulk Procurement Scheme (www.who.int/std_diagnostics). The affordability and portability of rapid tests will allow the design of innovative control programs outside of clinic-based settings. A disadvantage of these treponemal tests is that they cannot be used to distinguish between active infection and past treated infection as treponemal antibodies tend to persist for years.

Operational characteristics. A number of operational characteristics of tests are critical to the success of screening programs. Screening at venues where there is no electricity means the tests must be stable at ambient temperatures. Tests that are simple to perform in a few steps and give a visual result in less than 30 minutes allow treatment to be given and partner notification to be initiated on the same day. This is especially important in settings where the target population is unlikely to return for test results and treatment.

encounters are arranged. A number of studies also show that sending specimens such as self-collected vaginal swabs and urines from home to laboratories for STI testing are also viable options (e.g., www.stdtest.org, www.iwantthekit.org).^{33,34}

Cost-effectiveness

Syphilis. In settings with medium to low prevalence of infection, universal screening of STIs can be costly. For syphilis, the consequence of the disease is so serious that antenatal screening for syphilis is cost-effective even at very low prevalence. A recent analysis in the UK showed that universal prenatal screening was cost-effective even at 0.05% prevalence.³⁶ However, a recent 10-year retrospective analysis of universal antenatal screening for syphilis in Sweden showed that at a seroprevalence of 2.8 per 1000 live births (0.028%), this approach was no longer warranted. The screening focus should be shifted to regions of higher prevalence.³⁷

Screening of pregnant women to prevent congenital syphilis can also be carried out within an essential antenatal care package. In areas where there is high HIV prevalence, integrating syphilis screening into Prevention of Mother to Child Transmission programs would not only be cost-effective but would also prevent the tragedy of babies avoiding HIV infection and dying of syphilis.^{38,39}

C. trachomatis and N. gonorrhoeae. Screening of genital chlamydial infections has been found cost-effective, even when expensive NAATs are used, when the prevalence of infection is between 3.1% and 10%.⁴⁰ However, with decreasing rates of genital chlamydial infections in recent years, the cost-effectiveness of screening using broad criteria such as screening asymptomatic sexually-active women aged <25 years needs further study. A recent review of cost-effectiveness showed that it continues to be cost-effective in the United States to offer annual screening of 15–25-year-old sexually-active females.⁴¹ The frequency of reinfection in women has led to the recommendation to rescreen 4–6 months after the initial infection. More frequent screening should be considered in individuals with recent infection and among women <20-years old.⁴²

The cost-effectiveness of using NAATs to screen young men at risk of genital chlamydial infection has not been as well studied as for women. At a prevalence of 5%, the use of a leukocyte esterase strip as a screening test, followed by a NAAT, was a cost-effective means of screening.⁴³

Universal screening for chlamydia and gonorrhea in U.S. jails and detention centers was cost-effective,^{24,25} as was a school-based screening program for genital chlamydial and gonococcal infection.²⁶ NAAT screening of women aged 15–29 presenting to urban emergency departments was found cost-effective and prevented substantial reproductive morbidity.²²

Patients infected with *N. gonorrhoeae* are frequently co-infected with chlamydia. The U.S. CDC had previously recommended presumptive treatment for chlamydia in patients identified with gonorrhea. With declining chlamydia prevalence, this may no longer be cost-effective in some settings, where testing for both infections has become more cost-effective than routine presumptive treatment for chlamydia.^{44,45}

Other means of improving the cost-effectiveness of screening include pooling of specimens to decrease test and reagent costs.^{46–48} At a prevalence of approximately 5%, the savings can be as much as 39–56% of original costs. Batching so that multiple tests are processed in a single run decreases personnel costs.

METHODOLOGY

The type of diagnostic test ordered for each type of STI will vary with the individual infection in question as well as the type, experience, and capability of the laboratory performing the assay. If there is no laboratory and the clinician is performing the test, there are also specific considerations and constraints. This section will cover general principles for different diagnostic methods available for various STIs.

■ TYPES OF TESTS

Microscopy

Direct light microscopy can be a valuable and rapid method for the diagnosis of several STIs. Regular light microscopy can be used for wet preparations for *T. vaginalis* from vaginal swabs or urine pellets of male urine, but with lower sensitivity (~50%) than other methods.^{49,50} Microscopy is useful for reading Gram stains of slides for *N. gonorrhoeae*, especially from symptomatic male urethral smears (sensitivity ~90–95%), but with less sensitivity for asymptomatic males and females (sensitivity ~50–70%).⁵¹ Some serovars of *N. gonorrhoeae* have been noted to have reduced or negative Gram stain microscopy results.⁵² Gram stain is not recommended for diagnosis of trichomonas. Older Giemsa's and iodine stains are no longer recommended for the diagnosis of chlamydial infection. Gram stains of female vaginal swabs can be used efficiently for the diagnosis of BV, a syndrome that can be transmitted sexually, using the standardized Nugent scoring system from 0 to 10, which is based on the number of lactobacilli, gram-negative to gram-variable bacilli, and gram-negative curved bacilli. Scores ≥ 7 indicate BV.⁵³

Darkfield microscopy, although technically challenging, is most useful for visualizing motile treponemes for the diagnosis of primary syphilis from wet preparations of genital ulcer smears, but is not recommended for the diagnosis of oral or rectal lesions because of the presence of nonpathogenic treponemes.⁵⁴ Darkfield examinations must be done immediately after the specimen is taken (at least within 20 minutes) in order to maintain motility and morphology.

Fluorescent microscopy, which requires an epifluorescent microscope, can be used for the direct fluorescent antibody (DFA) staining of genital or ocular smears for several STIs. DFA for *C. trachomatis* has a sensitivity of approximately

80–85% with an experienced microscopist but is technically demanding and, although it provides rapid results, is no longer often used since the advent of molecular methods.⁵⁵ The DFA-*T. pallidum* is commonly used to detect organisms in primary or secondary lesion exudates.⁵⁴ The older Tzanck smear for multinucleated giant cells, stained by Wright or Giemsa's stain, is not widely used as the sensitivity is only ~40% for diagnosis of genital herpes when applied to ulcers.

Several commercial DFA and indirect FA stains are available for the detection and typing of HSV 1 and 2 viruses in cells from lesions. Staining patterns require an experienced microscopist to interpret. DFA is 10–87% sensitive compared to culture, with higher sensitivity for samples from vesicular lesions and poorer sensitivity for specimens from healing ulcers.⁵⁶

Culture

Microbiologic culture is the oldest and original gold standard for the detection of several STI pathogens: *N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*, HSV 1 and 2, and *Haemophilus ducreyi*. Among the organisms associated with STIs that are nonculturable for practical purposes are *T. pallidum*, hepatitis B virus, HPV, and certain agents implicated in BV. Since *H. ducreyi* is rare in the United States and culture is technically difficult and not widely available, it is not usually routinely offered. Only research laboratories can perform culture for *T. pallidum* in rabbits (rabbit infectivity test), but it is the gold standard method to which other methods are compared.⁵⁴

Culture of *N. gonorrhoeae* using modified Thayer-Martin medium is still the gold standard for the identification of the gonococci in genital and oral specimens with a sensitivity of ~90%,⁵⁷ although molecular testing methods are rapidly becoming more widely used since they can be used with urine samples and vaginal swabs.⁵⁵ Culture is especially desirable to obtain the isolate for susceptibility testing, since continued surveillance is necessary in light of the increasing antibiotic resistance of *N. gonorrhoeae* in the world and now in the United States.^{58–61}

Culture for *C. trachomatis* was originally performed in embryonated chicken eggs. Growth and detection of chlamydia are now accomplished by staining chlamydial inclusions grown in tissue culture cells.^{62,63} *C. trachomatis* is a biosafety level 2 agent and should be handled appropriately.⁶³ The cell line most commonly used is McCoy cells, but other cell lines, such as monkey kidney, HeLa, and HEp-2, have been employed. As culture is technically difficult and not as sensitive as molecular assays, it is rarely used except for sexual abuse cases, medicolegal matters, and samples from non-genital sites such as pharyngeal and rectal samples.^{64,65} Recent studies have indicated that culture sensitivity compared to molecular techniques can range from 50% to 100% and is usually considered to average 85%, while specificity is considered to be 100%.⁶⁶ Antimicrobial susceptibility testing is not ordinarily

performed for *C. trachomatis* isolates as they are uniformly sensitive to macrolides, but there have been rare reports of increasing heterotypic resistance.

Culture for *T. vaginalis* can be accomplished in Diamond's medium or using a culture pouch on a microscopic slide (InPouch TV test, Biomed Diagnostics), which has a reported sensitivity of ~70–78% compared to polymerase chain reaction (PCR) for females,^{49,50,67} and of ~28% for urine from males.⁶⁸ There are some reports of metronidazole-resistant trichomonas isolates and antimicrobial susceptibility testing for this drug can be performed using special InPouch kits.

HSV cultures can easily be performed from genital and oral samples when cell cultures are available. Cell lines available commercially, in which typical cytopathic effects can be observed usually within 5 days, include human diploid fibroblasts such as WI-38, human foreskin fibroblasts, and MRC-5; human epidermoid carcinoma cell lines such as HEp-2 and A549; rhabdomyosarcoma cells; and mink lung cells.⁶⁹ Acyclovir resistant strains have been reported, but resistance testing is performed only by research laboratories.

Antigen detection

Nonculture antigen detection tests for agents of STIs became more widely used with the advent of the enzyme linked immunoassay (EIA) tests about 1990, especially for chlamydia. More recently, several EIAs have become available for HSV.

Chlamydia. For chlamydia, antigen detection using EIA was widely used before the advent of molecular tests, and the EIA is still one of the most prevalent nonculture detection tests.^{70–74} There are several EIAs commercially available. The tests use either polyclonal or monoclonal antibodies to detect chlamydia lipopolysaccharide, providing theoretical detection of all species of chlamydia. However, they have been most extensively validated for urogenital *C. trachomatis*. The sensitivity of the EIAs ranges from approximately 53% to 76%, with specificities of about 95%, compared to newer molecular assays. Because these EIAs were originally compared to culture as a gold standard, the sensitivities reported in the older literature are inaccurate. A meta-analysis, adjusting the sensitivities of such assays based on a sensitivity of culture of 85% has been performed.⁷⁵ EIA tests are no longer the recommended method for chlamydia testing due to their poor sensitivity, although they continue to be widely used.⁵⁷

HSV. An antigen detection test for HSV is available but is only 47–89% as sensitive as culture and is not in wide use clinically.⁷⁶

Rapid tests. Rapid antigen detection assays employing antibody coated latex particles or immunochromatographic strip (ICS) tests have been marketed for several STIs. Older latex agglutination tests suffered from low sensitivity (52–85%). However, recent studies of a latex agglutination test for *T. vaginalis* (Kalon Biologicals) and an ICS test for

N. gonorrhoeae (NOW, Binax, Inc.) reported sensitivities of 98.8% compared to wet mount and culture in African women⁷⁷ and 94.1% compared to culture in male urine specimens,⁷⁸ respectively.

Microbial by-product detection

Recently, several commercial products have become available for the identification of microbial byproducts. These are mainly for the diagnosis of BV, a syndrome associated with adverse pregnancy outcomes, which is not exclusively considered an STD, but which has been demonstrated to be transmitted sexually.⁷⁹

The BVBlue test (Gryphus Diagnostics, L.L.C.) is a chromogenic test based on the detection of elevated sialidase enzyme in vaginal fluid samples.^{80–82} It is especially useful in venues where microscopic capabilities are unavailable for using either Nugent⁵³ or Amsel⁸³ criteria for the diagnosis of BV.⁸¹ This assay had a reported sensitivity and specificity of 91.7% and 97.8%, respectively, compared to Nugent Gram stain criteria and 50% and 100%, respectively, compared to Amsel criteria by investigators in Canada.⁸¹ Investigators in Australia reported sensitivities and specificities of 88% and 95%, respectively, compared to Nugent Gram stain criteria and 88% and 91%, respectively, compared to Amsel criteria.⁸⁰

The FemExam test kit (Litmus Concepts) contains two small plastic cards; one card measures pH (4.7 or greater) and trimethylamine and the other measures activity of proline iminopeptidase from *Gardnerella vaginalis*.⁸⁴ Reported sensitivity and specificity compared to Nugent score were 91% and 61.5%, respectively.⁸⁴ Another recent study reported sensitivities of 88%, 41%, 89%, and 40% for a positive pH test, a positive amine test, a positive pH *or* amine test, and both pH *and* amine positive tests, respectively, while the corresponding specificities were 64%, 91%, 61%, and 95%, respectively, compared to Nugent Gram stain criteria.⁸⁵ In a resource poor setting, the pH test result was the most sensitive (94%) but not very specific (57%), while the combined result for both pH and amine was only 59% sensitive, but 92% specific.⁸⁶

The Microbial analyzer (Osmetech, PLC) uses a vaginal swab placed in a sealed vial; the headspace is passed over an application-specific array of conducting polymer sensors, each of which has specific interactions to different volatile organic species based on their size, shape, and functional groups.⁸⁷ Reported sensitivity and specificity were 81.5% and 76.1%, respectively, compared to Amsel criteria and 82.9% and 77.3%, respectively, compared to Nugent Gram stain criteria.⁸⁷

Antibody detection (serology)

Detection of antibodies to STIs is one of the main testing procedures for the diagnosis of syphilis and HSV infection. Many types of antibody tests are available: agglutination

tests, neutralizing or complement-fixing antibody detection, microimmunofluorescence (MIF), indirect immunofluorescence, hemagglutination inhibition tests, EIA, Western blot, and rapid membrane-based immunoassay. Some tests can determine the type of the antibody, e.g., IgG, IgM, or IgA.

Syphilis. For syphilis, antibody tests become positive in response to infection with *T. pallidum*, and serological tests are used for diagnosis and to follow the clinical course of treatment. Tests can be divided into two types: non-treponemal and treponemal.

The nontreponemal screening tests, such as VDRL, RPR, automated reagin test (ART), toluidine red unheated serologic test (TRUST), and Spirotek EIA, which are inexpensive and widely available, measure reaginic antibodies that react with lipoidal particles containing the phospholipid cardiolipin.^{54,88} These tests can be insensitive in the very early phase of primary syphilis and in very late syphilis cases. False positive reactions can occur due to cross-reacting antibodies in persons with autoimmune or collagen vascular diseases, acute viral illness, pregnancy, and intravenous drug use. The possibility of prozone reactions can occur if the titer is very high, with significant antibody excess in relation to the antigen, producing false negative reactions. Despite these limitations, these screening tests are in universal use. The titer of the serum that is reactive in the nontreponemal tests is the most useful assay for following the response to treatment, both in sera and cerebral spinal fluid in the case of neurosyphilis.⁵⁴ The nontreponemal tests can only be considered diagnostic when the clinical syndrome is highly suggestive of syphilis and are usually confirmed by a treponemal test. In the diagnosis of latent syphilis, a reactive nontreponemal test with a negative treponemal test is considered a false positive.⁸⁸ Results are usually reported as nonreactive or as reactive with the highest twofold dilution of serum giving a reactive result being reported.

The treponemal tests use *T. pallidum* as an antigen and are used to confirm a positive screening test. Types consist of FTA-ABS (fluorescent treponemal antibody absorption test), which is the most sensitive; the MHA-TP (microhemagglutination), which uses *T. pallidum* adsorbed to erythrocytes; and the TP-PA (particle agglutination), which uses particulate gelatin or latex. These tests are about 97% specific.⁸⁸ Recently, several rapid tests for *T. pallidum* antibody detection have become clinically available including INNO-LIA Syphilis (Innogenetics NV), RST (Quorum Diagnostics), and Determine Rapid Syphilis TP (Abbott). These ICS tests, utilizing *T. pallidum* antigens immobilized on membranes, have been 75–97% sensitive and 95–98.8% specific when compared to other treponemal tests.^{89–91} Treponemal tests can be falsely reactive in nonvenereal diseases like yaws or pinta and in some cases of Lyme disease.⁵⁴ A persistently reactive treponemal test is common and does not indicate inadequate treatment, relapse, or reinfection.

HSV. Herpes simplex virus EIA tests are available for detection of antibody to the virus; however, the older tests do not reliably distinguish between types 1 and 2 because nearly all HSV structural proteins have antigenic cross-reactivity.⁵⁶ EIA tests must be based on glycoprotein G (gG) to differentiate between the types.⁹² For the diagnosis of antibody to HSV-2, the only FDA cleared EIA test meeting this requirement in the United States is the HerpeSelect 2 ELISA IgG test (Focus Diagnostics) with published sensitivities of 96–100% and specificities of 96–97%.^{56,93} The HerpeSelect 1 ELISA can reliably detect antibody to HSV-1 with a sensitivity of 91–96% and a specificity of 92–95%.^{56,93} These comparisons are with the gold standard of the Western blot assay at the University of Washington. It is important to note that genital herpes infections may be caused by HSV-1 in up to 30–50% of infections depending on the population.⁸⁸

Recombinant-based gG HSV-2 serology tests have provided enhanced specificity over the older HSV crude antigen-based assays. However, even recombinant-based gG2 assays are not 100% specific. The HerpeSelect 2 assay had a low positive predictive value among a population with a relatively low prevalence of HSV-2.⁹⁴ Clinicians using the test in low prevalence populations should consider selectively using a higher index value to define positivity based either on HSV-1 serostatus or on the presence or absence of clinical findings suggestive of genital herpes. Recently, a small protein segment at the distal end of the carboxyl terminal of gG2 has been discovered that contains at least two epitopes that are responsible for binding antibodies from sera that are negative for the presence of HSV-2 antibodies. Inhibiting the binding to these epitopes decreased the number of false positive HSV-2 antibodies by over 50% depending on the patient population being evaluated.⁹⁵ The blocking of antibody to the segment mentioned above does not appear to help in some populations (personal communication Dr. Wayne Hogrefe, Focus Technology).

A rapid POC test for detection of HSV-2 antibody from serum or capillary blood, originally known as the POCkit HSV-2 (Diagnology), is no longer available, but had high sensitivity of 93–100%.⁵⁶ It has since been bought and is now called BiokitHSV-2 (Biokit USA, Inc). Sensitivity and specificity compared to Western blot are listed in the package insert as 86–100% and 59–96.8%, respectively, depending on the population tested.

HSV type 2 EIA tests that perform well in industrialized countries may not perform well in other populations. When 13 commercial EIA kits were tested using sera from men and women in 4 African countries, the HSV Type 2 IgG ELISA kit (kalon Biologicals), though not FDA approved, had the best performance characteristics (sensitivity and specificity greater than 92%).⁹⁶

Chlamydia. The MIF test for chlamydial antibody has been used in large population studies for determining the association of *C. trachomatis* with adverse outcomes of chlamydial

disease such as PID or infertility but is not useful for the diagnosis of chlamydia urogenital disease.^{97,98} MIF is, however, used for the diagnosis of respiratory infections with *Chlamydia pneumoniae*.⁹⁹

Nucleic acid detection

Amplified and nonamplified tests are two types of assays that employ molecular methods for the detection of nucleic acids from organisms causing STIs. Nonamplified tests are simple hybridization assays using a DNA probe of short oligonucleotide sequences that will bind with the organism sequences of interest. Detection can be by colorimetric assay for probes having enzyme moieties, radioisotope detection for radiolabeled probes, or by chemiluminescence. Gen-Probe is a widely used commercially available assay for *C. trachomatis* and *N. gonorrhoeae*.¹⁰⁰ Also available are the Digene assays for HPV and *C. trachomatis* and *N. gonorrhoeae*, which are hybridization assays with amplification of the probe signal.^{101–103}

The Affirm VP III test (Becton Dickinson) for the detection of *G. vaginalis*, *T. vaginalis*, and *Candida spp.*, etiologic agents in vaginal infections, uses synthetic nucleic acid capture probes and color development detection probes complementary to unique genetic sequences of the target organisms.¹⁰⁴ The capture probes are immobilized on a separate bead for each organism on an analysis card. The reported sensitivity and specificity for the diagnosis of BV were 73.2% and 97.1%, respectively, compared to modified Nugent criteria.¹⁰⁴ The Affirm test, originally designed for only *G. vaginalis* and *T. vaginalis*, was 90% sensitive for *G. vaginalis* compared to clue cells on wet mount and 95% sensitive for the detection of *G. vaginalis* in women with more than 5×10^5 colony forming units/mL by culture; 100% sensitive for trichomonas diagnosed by wet mount and 80% sensitive for trichomonas recovered by culture.¹⁰⁵ These nonamplified assays are of much lower sensitivity than amplified assays.^{100,106,107}

Amplified assays are those which amplify the nucleic acid target itself up to a billion fold, so theoretically even a single target copy can be detected from a clinical specimen. Most commercially available assays amplify DNA but some convert RNA from a sample to cDNA, which is then amplified.⁵⁵

Chlamydia and gonorrhea. The first STD for which there was a commercially available PCR assay was *C. trachomatis*.¹⁰⁸ Currently, several different types of NAAT technologies are commercially available for *C. trachomatis* as well as for *N. gonorrhoeae*.^{66,109–111} These NAATs include PCR (Amplicor, Roche Molecular Diagnostics), transcription mediated amplification (Aptima Combo2, Gen-Probe), and strand displacement amplification (ProbTec, Becton Dickinson). These methods offer excellent sensitivity, usually well above 90%, while maintaining very high specificity.^{51,112} However, studies have demonstrated that the specificity of the Amplicor PCR

assay for identification of *N. gonorrhoeae* is less than listed in the package insert.^{113,114} One study showed that more than 40% of 122 genital specimens from Australian women positive for *N. gonorrhoeae* by Amplicor PCR were not confirmed as positive by a consensus of other molecular assays.¹¹⁴ This high false positive rate for the Amplicor PCR emphasizes the importance of confirming all positive tests using a different, but equally sensitive, assay.

HSV. A PCR assay (Cepheid) that detects both HSV 1 and 2 is available as an analyte-specific reagent, which means it is not U.S. FDA cleared but can be validated by an individual laboratory for its own use. The manufacturer also markets a similar assay that can type the HSV as HSV-1 or HSV-2.

Other STIs. NAATs for other STIs for which commercially available amplified tests may soon be available include HPV and *T. vaginalis*. Presently only research assays are available.^{49,115–119} Research PCR assays are also available for agents of genital ulcer disease (syphilis, chancroid, and HSV) but are not available commercially.^{120,121} Several PCRs for syphilis have been published and used, especially for the diagnosis of early syphilis,^{122,123} but currently are only available in research laboratories or from the U.S. CDC.⁵⁴

Real-time PCR amplification and detection methods have the capability to be quantitative and are becoming widely available as research assays but are not yet commercially available. Real-time PCRs are designed so that the amplification product is detected in “real time” by a probe(s) while the PCR product is generated. Cycle threshold values are generated so that the assays can be quantified according to target input by comparison to standard curves resulting from controls of known target copy number or organism number. Several types of probes conjugated to various fluorescent reporter dyes are available, and the assays require a specialized PCR instrument like the LightCycler (Roche) or the ABI Prism sequence detection system (Applied Biosystems).

Confirmation of positive results generated by NAATs had not been recommended until recently. The CDC now recommends that in populations with low prevalence of disease and positive predictive values (PPV) less than 90%, confirmation of positive chlamydia and gonorrhea NAAT results should be performed.⁵⁷ Suggested ways include testing a second specimen with a different test using a different target, testing the original specimen with a different test using a different target or format, repeating the original test on the original specimen with a blocking antibody or competitive probe, or repeating the original test on the original specimen.⁵⁷ Confirmatory testing for NAATs in low prevalence populations where low PPV is a concern is presently controversial and deserves further study.^{124,125} A less sensitive NAAT should not be used to confirm a more sensitive assay,¹²⁶ nor should a less sensitive type of assay such as an EIA be used to confirm an amplified test.¹²⁷ Recently, Gen-Probe has made available

individual amplification tests for chlamydia and gonorrhea that can be used to confirm positive results from their Combo2 test or other amplification tests.¹²⁸

■ SPECIMEN COLLECTION

Nothing is more important than the appropriate choice, collection, and handling of a diagnostic specimen for the diagnosis of an STI with regards to the accuracy of the laboratory test.¹²⁹ Many factors affect the choice of sample type. These include but are not limited to type of STI, location of collection venue, site of active disease, choice of serological diagnosis versus direct detection of disease agent, type of assays and equipment available in the laboratory, and even whether to perform a rapid, bed-side test such as a wet preparation for trichomonas or darkfield examination for primary syphilis.

Invasive vs. noninvasive specimen type

Specimens can be classified as either invasive, for which a clinician will collect a diagnostic sample by an invasive technique, such as a biopsy, a lesion or genital tract swab, etc.; or they can be classified arbitrarily as noninvasive, which generally includes those such as blood or serum, urine, self-collected vaginal or rectal sample, etc. Choice will be dictated by the disease, the patient population, the setting, and laboratory test availability. NAAT assays, with increased sensitivity, have opened the way for diagnostic samples that are less invasive, can often be collected by the patient,^{51,55} and can be used for multiple analyses. For example, liquid cytology specimens routinely collected for preparing Pap smears have been used successfully to test for STIs.¹³⁰ Many of these noninvasive specimens are being used for the diagnosis of chlamydial infection and gonorrhea.

Transport and storage

Clinicians should pay particular attention to the collection, handling, and transport requirements for specimens on which they order a diagnostic test, as accurate results will depend on the quality of the diagnostic sample and the environmental transport of the specimen. Transport containers for clinical specimens and instructions for collection, handling, and transport of diagnostic samples are usually available from the laboratory. The etiologic agent(s) suspected usually dictate the collection method and conditions of transport.¹²⁹ There is a wide range of conditions for transport of samples for the diagnosis of STDs (Table 52-4). These range from transport of blood for serological diagnosis, which does not require special handling, to the necessity to provide rapid transport for wet preparations for trichomonas and darkfield for the examination of primary syphilis and to the need to provide environmental CO₂ for the culture of gonococci and a cold chain for the culture of chlamydia. Requirements for special handling for special environmental

Table 52-4. Collection and Transport Guidelines for Commonly Collected Specimens for Commercially Available Assays

Pathogen	Test Type	Transport Conditions ^a by Specimen Type						
		Blood	Genital Slide	Cervix	Vagina	Urethra	Urine	Lesion
Syphilis	Serology Darkfield	Routine						Immed
<i>C. trachomatis</i>	EIA ^b			RT 4 d STM				
	DFA ^b DNA probe		Routine	RT 4 d STM		RT 4 d STM		
	Culture			CC STM		CC STM		
	NAAT ^b			RT or CC ^c STM	RT ^d STM	RT or CC ^c STM	RT or CC ^c	CC ^c
<i>N. gonorrhoeae</i>	Antigen detection			Routine STM				
	Gram stain DNA probe		Routine	RT 4 d STM				
	Culture NAAT			CO ₂ RT or CC ^c STM	RT ^d STM	CO ₂ RT or CC ^c STM	RT or CC ^c	
<i>T. vaginalis</i>	Wet prep Culture		Rapid		Rapid STM	Rapid STM		
HSV 1 and 2	Serology Culture	Routine		Immed	Immed	Immed		Immed
HPV	DNA probe			Routine STM		Routine STM		
Chancroid	Culture							Rapid STM

^aTransport conditions listed as: routine, rapid, immediate (Immed); maximum days for transit; room temperature (RT), cold chain (CC) required; environmental CO₂ required (CO₂); commercial specimen transport media. (STM).

^bEIA-enzyme immunoassay; DFA-direct fluorescent antibody; NAAT-nucleic acid amplification test.

^cDepends on manufacturer.

^dOnly US FDA cleared for Gen-Probe APTIMA test.

transport again are best obtained from the laboratory performing the assay.¹²⁹ The particular swab or tool for collection of the diagnostic sample often depends on the manufacturer of the particular assay, and the sample is not acceptable unless the required swab or collection kit is used.

Specialized environmental handling, time limitations, and temperature conditions are required for samples that must be mailed to a testing site.¹²⁹ Clinicians should follow guidance from the testing laboratory for the type of STD and the type of diagnostic test ordered.

■ INTERPRETATION OF RESULTS

Interpretation of the results of a laboratory test by a clinician depends on several parameters. Clinicians must understand how well the test performs with regard to sensitivity, specificity, PPV, and negative predictive (see next section). Often the laboratory, the package insert, or the medical literature can provide estimates of these statistics. In clinical practice, the predictive values of the test are probably the most useful parameters, providing guidance for the questions “if the patient has a positive test, how likely is he/she to have the disease” and conversely, “if the patient has a negative test, how likely is he/she not to have the disease.”

Current vs. past infection

Whether the test being used measures current or past infection is an important consideration when interpreting the results of a diagnostic test. Often, a positive serological test result can indicate previous infection and not the presence of “active disease,” as for the example, with syphilis and herpes virus infections.^{54,56} In the case of NAATs, a positive test result can remain positive for a period, even up to 2 weeks after therapy is given and infectiousness is negative, and clinicians should be aware of this tendency, especially if they perform a “test-of-cure” assay.^{131,132}

Confirmatory tests

Confirmatory tests are supplemental tests performed after a positive diagnostic or screening test result. Many screening or diagnostic tests (highly sensitive but of lower specificity) for STIs are considered presumptive positive results, which must be confirmed by another more specific test (very high specificity), as is the case with the RPR or VDRL tests for syphilis, which need to be confirmed by a specific treponemal test such as the TP-PA. Confirmatory tests are also required for *N. gonorrhoeae*. Tests for gonorrhea are considered “presumptive positive” if a Gram stain is performed on a genital exudate or a Gram stain and oxidase test are done on the culture isolate, while “confirmatory” tests such as carbohydrate utilization, nucleic acid amplification, rapid enzyme substrates, serological coagglutination, or fluorescent antibody tests are used to characterize the isolate as “definitive” and are more accurate in identifying the isolate as truly *N. gonorrhoeae*.^{133,134}

Patient history

Patient history can profoundly influence the clinician’s interpretation of a test result. The diagnosis of an STD has emotional and social implications for patients. Consideration of a false positive for an STI such as chlamydial infections in a woman who is not sexually active may lead the clinician to repeat the test, while consideration of a false negative result in a sexually active adolescent with a history of multiple partners and with signs of mucopurulent cervicitis (MPC) may lead to a decision to select an antimicrobial regimen effective for chlamydial infection as well as for other possible courses of MPC, when treating the adolescent, even if the test result for *C. trachomatis* is negative. Multiple reasons exist for erroneous test results: products used by patients such as douching agents, spermicides, or antibiotics result in culture-negative samples, and connective tissue diseases produce false positive results in syphilis screening. Ultimately the decision of how to interpret the STI test result is based on sound clinical judgment, the patient’s history, knowledge of which particular assay is being used by the laboratory, the statistical parameters of the test itself, and the signs and symptoms of disease manifestations in the patient.

■ CHOICE OF DIAGNOSTIC TEST

The choice of which diagnostic test to use in various clinical settings will be determined by many characteristics, including but not limited to the geographical location of the laboratory, the level of capability of the laboratory, the cost of the assay, how much training is required for the person performing the test, and the availability of specific equipment required. [Table 52-5](#) lists the types of tests used to diagnose the most common STIs and summarizes the important characteristics of each method. The assay complexity dictates whether a laboratory can offer a certain test, as well as the cost of reagents, and the availability and cost of the equipment. Sometimes the choice for a clinician is beyond his decision and will be dictated by the laboratory he or she is using. In a large facility, there may be many diagnostic options ranging from a simple Gram stain for the presumptive diagnosis of gonorrhea to a real time research PCR test for chlamydia. In a developing country, choice of laboratory test may be limited by the assay complexity, which may be ranked as easy, moderately complex, or highly complex. If equipment required for a particular test, such as a thermocycler for amplification assays for chlamydia, is not available or is cost-prohibitive, a clinician may have no choice but to use a less sensitive assay.

PERFORMANCE GUIDELINES

Laboratory testing at every level, whether simple or complex, must meet certain performance guidelines. Verification of the performance parameters of new tests before implementation

Table 52-5. Characteristics of Laboratory Methods of STI Diagnosis

Type of Test	Advantages	Disadvantages	Test of Choice for	Ease of Performance	Training	Equipment
Microscopy	Immediate result	Low sensitivity	Gram stain, darkfield DFA ^a	Easy	Extensive	Microscope
Culture	Highly specific	Low sensitivity	<i>N. gonorrhoeae</i> <i>T. vaginalis</i>	Moderate	Extensive	Incubators
Antigen detection	Inexpensive	Low sensitivity	<i>C. trachomatis</i> (if NAAT ^a unavailable)	Moderate	Moderate	Incubators, Plate washers O.D. readers
Microbial biproduct detection	Immediate result	Low sensitivity	BV	Moderate	Moderate	Reader
Antibody detection	Inexpensive	Detects previous infection	Syphilis, HSV	Moderate	Moderate	Rotator
Nucleic acid hybridization	Moderately sensitive	Low sensitivity	<i>C. trachomatis</i> <i>N. gonorrhoeae</i>	Moderate	Moderate	Luminometer
Nucleic acid amplification	Highly sensitive	Expensive	<i>C. trachomatis</i> <i>N. gonorrhoeae</i>	Complex	Extensive	Thermocycling equipment

^aDFA-direct fluorescent antibody; NAAT-nucleic acid amplification.

and ongoing validation of established procedures must be performed. Calculation of test characteristics requires the use of a reference standard for determination of true positive and negative results. This section describes the important test performance parameters, considerations for the choice of a reference standard, guidelines for conducting or assessing a test evaluation, and recommended quality assurance procedures.

■ PERFORMANCE PARAMETERS

The characteristics that are important for evaluating the performance of a test are defined in [Table 52-6](#).

Sensitivity and specificity

Sensitivity is the measure of a test's efficiency in detecting a specific infection and specificity is the measure of a test's efficiency in ruling out an infection. Together they determine a test's accuracy. No test has both 100% sensitivity and specificity when used to test a large number of unknown specimens. Sensitivity can refer to either analytical or clinical sensitivity. Analytical sensitivity, also called the limit of detection (LOD), is applied to tests that detect a quantifiable target. Analytical sensitivity is best expressed as the proportion of positive results among multiple replicate samples containing a known amount of target. For example, the number of target

DNA molecules that can be detected in 15 of 16 replicate specimens by a PCR assay is the 95% LOD.

The sensitivity and specificity of tests that require the conversion of a continuously measured variable into a definitive positive or negative result can be manipulated by the choice of the test cutoff value. Relative operating characteristics (ROC) curves are used to determine the best cutoff value that will optimize assay performance in a particular population. ROC curves are generated by calculating the sensitivity and specificity of a test when different cutoff levels are used to define a positive value, using specimens with known results that were tested by a reference assay ([Fig. 52-1](#)). As the cutoff is varied, the sensitivity and specificity will move in opposite directions. The cutoff value that is chosen should reflect the way in which the test will be used, whether false negative or false positive results are more acceptable, and the population being tested. A cutoff value with 100% sensitivity can be used to rule out disease in patients with a negative test result (100% negative predictive value), while a cutoff value with 100% specificity can be used to rule in disease (100% PPV) ([Fig. 52-2](#)).¹³⁵

Predictive values

The highest predictive values are desired when inappropriate treatment due to false positive or false negative results has serious clinical, emotional, epidemiological, public health, or economic consequences. Predictive values are

Table 52-6. Important Parameters for Test Evaluation**Binary Table Used to Calculate Parameters**

New test results	Reference (“gold standard”) test results		
	Positive	Negative	Total
Positive	True positive <i>A</i>	False positive <i>B</i>	Total positive new test <i>A + B</i>
Negative	False negative <i>C</i>	True negative <i>D</i>	Total negative new test <i>C + D</i>
Total	Total positive reference test <i>A + C</i>	Total negative reference test <i>B + D</i>	Total specimens tested <i>A + B + C + D</i>

Definitions and Formulas for Parameters

Parameter	Formula	Definition
Sensitivity	$A/(A + C)$	Ability of new test to identify people who are truly positive
Specificity	$D/(D + B)$	Ability of new test to identify people who are truly negative
Positive predictive value	$A/(A + B)$	Probability of a positive test being a true positive
Negative predictive value	$D/(C + D)$	Probability of a negative test being a true negative
False positive	<i>B</i>	True negative specimens that test positive
False negative	<i>C</i>	True positive specimens that test negative
Accuracy (agreement)	$(A + D)/(A + B + C + D) \times 100$	Percentage of correct results obtained by the new test compared to the results of the reference standard
Prevalence	$(A + C)/(A + B + C + D) \times 100$	Frequency of a disease in the population of interest at a given point in time
Precision (reproducibility)	Number of repeated results in agreement/number of specimens repeated $\times 100$	Percentage of times the same results are obtained when the test is used to test the same specimens again

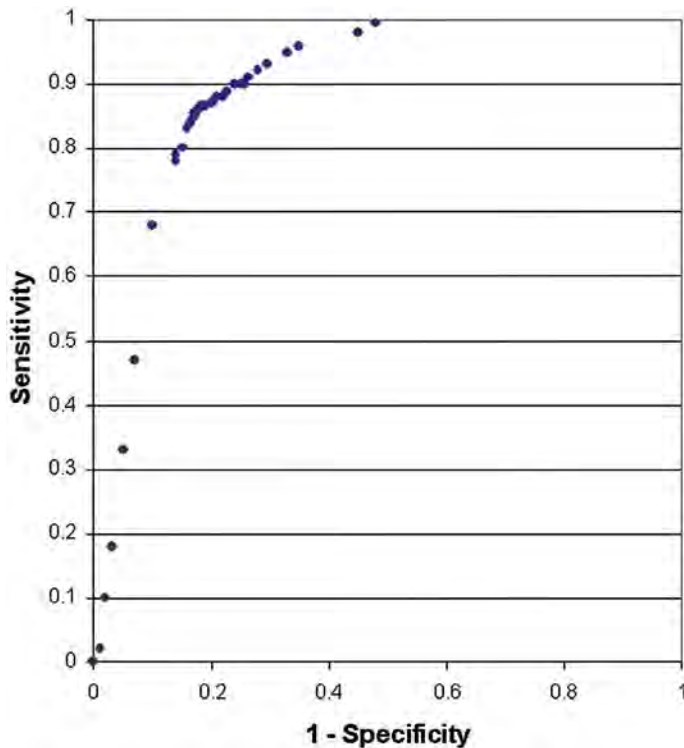


FIGURE 52-1. A hypothetical relative operating characteristics curve for samples tested by an ELISA. Each point represents the sensitivity and 1-specificity of the assay obtained at different optical density cutoff levels, using known positive and negative specimens.

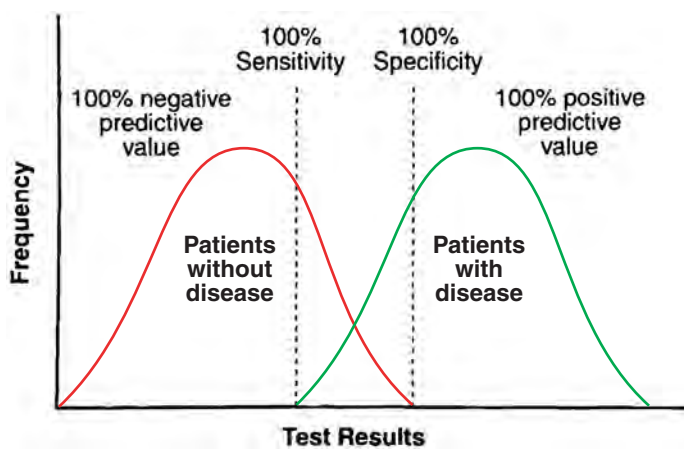


FIGURE 52-2. Relationship of choice of cutoff value to selected test parameters for converting a continuous valued test into a dichotomous test result. (With permission from Albritton WL, Vittinghof E, Padian NE. Human immunodeficiency virus testing for patient-based and population-based diagnosis. *J Infect Dis* 1996; 174(suppl 2): S176–S181.)

most meaningful in evaluating a test's performance in specific risk population groups because predictive values vary significantly with the prevalence of the disease or infectious agent unless the test is 100% sensitive (for negative predictive value, NPV) or specific (for PPV). As the prevalence of the disease in the population decreases, the PPV (the proportion of persons with a positive test having disease)

Table 52-7. Effect of Decreasing Prevalence on Positive and Negative Predictive Values for a Test with Sensitivity and Specificity of 95%

Disease Prevalence (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
1	16.1	99.9
2	27.9	99.9
5	50.0	99.7
10	67.9	99.4
20	82.6	98.7
50	95.0	95.0
75	98.3	83.7
100	100	NA

decreases (Table 52-7), creating more false positives for the test in question. At low disease prevalence (<10%), small decreases in test specificity will result in a large decrease in the PPV, while changes in sensitivity have less effect on NPV. Even a test with a specificity of 99.5% will theoretically have a PPV of only 50% in a population of patients with a prevalence of 1%.

Reproducibility

Reproducibility, also called precision, is a measure of the extent to which replicate analyses agree with each other. Reproducibility can be measured between operators or within the same operator. The reproducibility of an assay that provides a quantitative result can be expressed as the percent coefficient of variation, which is standard deviation/mean \times 100. Automated processes are usually more reproducible than manual processes.

SELECTION OF A REFERENCE METHOD

A reference method or gold standard is used for assessing the performance characteristics of another test method. The test that is chosen to be the reference method should be the best available approximation of the truth; a test method currently accepted as reasonable but not necessarily 100% accurate. However, when the gold standard is imperfect, the results of the comparator test will be skewed. To improve the accuracy of the gold standard, the composite results of two or more assays or the results of more than one specimen collected from each subject can be used. In these situations, a specified

combination of positive results is defined as a true positive, and the reference method is referred to as an expanded reference or an infected-patient standard.

When using an expanded reference, how the reference is defined will alter the performance of the comparator test. The prevalence of *T. vaginalis* infection in men was underestimated when one specimen was used compared to an infected-patient standard using specimens from three sites.¹³⁶ When *C. trachomatis* infection was defined by using results from multiple tests performed on specimens from different sources, the sensitivity of any one test from a single specimen source was substantially lower than previously reported.¹³⁷ For the detection of *C. trachomatis* and *N. gonorrhoeae* by NAATs, the infected-patient standard reduced the sensitivity of the endocervical evaluation because some infected patients were positive only in a urine specimen, while specificities for single specimens improved because patients negative by the reference method for one specimen were positive by another.¹³⁸ Expanded reference or infected-patient standards are especially useful for evaluating the extremely sensitive NAATs. Martin et al. investigated how many test results run by different NAATs and what combinations of specimens comprised the best infected-patient gold standard. They recommended the following approach to evaluation of new diagnostic tests for *C. trachomatis* in women: a swab specimen compared to one urine and two swabs analyzed by two different U.S. FDA approved NAATs, or a urine compared to one swab and two urines. For men, the most efficient combination of infected-patient standard was a swab and urine analyzed by one FDA approved NAAT and a urine by a second NAAT. Any two positive of the three was defined as true positive.¹³⁹

■ CONDUCTING A TEST EVALUATION

Many factors influence the performance of laboratory tests, including the characteristics of the target population, the resources of the testing laboratory or clinic, and the test method. A rigorous evaluation process is required to determine which type of test is most appropriate for a given setting. Laboratories that lack the resources to perform adequate evaluations of diagnostic tests on site should know how to assess evaluations performed by others. The Standards for Reporting of Diagnostic Accuracy (STARD) Initiative has developed a checklist for test evaluators to use that will improve the accuracy and completeness of reporting of studies of diagnostic accuracy. The information reported should allow readers to assess the potential for bias in the study and to evaluate its generalizability.¹⁴⁰

The elements that are essential for evaluating a test's performance concern the objectives and design of the evaluation, the trial site, the selection of subjects, and specimen analysis. The objectives should be stated clearly and the study should be designed to meet them. An adequate number of subjects should be selected and tested in an unbiased manner

from an appropriate population. A recognized, well-validated reference standard should be used and all specimens should be tested by both the test under evaluation and the reference method. Specimens should be tested by well-trained personnel, who are blinded to the results of all other tests. The performance parameters should be calculated accurately.

Discrepant analysis

In some test performance evaluations, when the new test is more sensitive than the reference test, a large number of specimens from infected persons may be classified as false positive (reference test negative, new test positive), producing a falsely low measure of the new test's specificity. In an effort to better estimate the performance of very sensitive new tests such as NAATs, test evaluators have used discrepant analysis to resolve areas of disagreement between the gold standard test and the comparator test. Discrepant analysis involves performing additional tests on the nonconcordant, usually false positive, specimens and acceptance of the comparator test results that are confirmed by the additional tests. Discrepant analysis is a controversial approach that introduces bias into the analysis, even when a perfect test is used to resolve the discrepant results,^{141,142} because any test used to resolve the discrepant results can only improve or leave unchanged the original sensitivity and specificity. Any changes in the results can only favor the new test.¹⁴³ If performed, discrepant analysis should be done with a second, independent comparator test having sensitivity equal to the first but measuring a different target, and the data must be analyzed carefully. A better approach is to expand the gold standard to include the results of other tests or clinical information and use the same standard for all specimens. Alternatively, a random sample of concordant and all discordant samples can be tested by the resolving assay.

Operational characteristics

When evaluating currently performed techniques or considering the implementation of new procedures, laboratory directors must consider many factors as they apply to the population they are testing. Diagnostic tests must be evaluated in a clinically relevant population, because test performance varies across population subgroups (spectrum bias),¹⁴⁴ and performance can be affected by patient characteristics.¹⁴⁵ Although accuracy and precision are the main characteristics used for evaluating assay performance, other considerations include clinical relevance, cost, instrumentation, ease of performance, turnaround time, reagent stability, and specimen requirements.

■ QUALITY ASSURANCE

CQI (Continuous Quality Improvement) is an organizational philosophy and a process that promotes the improvement of

Table 52-8. Quality Assurance Measures in Clinical Laboratories: Each Practice Must Be Documented or Its Value Is Lost

Prior to test introduction

- Method validation
- Analyst training and qualification
- Quality control assessment and plan

Following test implementation

- Periodic analyst competency reassessment
- Reagent qualification when lots change
- Equipment calibration and maintenance
- Proficiency surveys or other blinded external quality assessment
- Troubleshooting when problems arise or are suspected
- System monitoring using patient data or other measurables
- Routine quality control and monitoring

With permission from Garrett PE. Quality control for nucleic acid tests: Common ground and special issues. *J Clin Virol* 2001; 20: 15–21.

patient care.¹⁴⁶ To minimize reporting of inaccurate results and to report results with a high degree of confidence, a system for continuously monitoring and improving the reliability, efficiency, and clinical utilization of laboratory tests must be followed. The concept of the quality assurance program is designed to monitor the elements of specimen quality, the transport of the sample, the correlation of the test methods with clinical data, the test performance, personnel, media and reagents, instrumentation, and result reporting methods.¹⁴⁶ Quality assurance measures encompass quality control and quality improvement practices, proficiency surveys, periodic validation of established tests, and verification of and training for new tests (Table 52-8).¹⁴⁷ Standardized protocols, continuing training, and accurate record keeping contribute to consistency of results and competent personnel. Laboratories in the United States are now bound by CLIA 88 (Clinical Laboratory Improvement Act) requirements and must follow guidelines for determining requirements for competency of laboratory personnel. Although a description of these programs in detail is beyond the scope of this chapter, programs such as these seek to improve the overall quality of test results for the clinician.

Quality control

Quality control in the laboratory is the process of monitoring and evaluating the analytical process. Procedures should be in place for reagent qualification, calibration and maintenance of equipment, and trouble shooting. Adequate control specimens should be analyzed including positive and negative controls for qualitative tests and controls to monitor test linearity for quantitative tests.

A necessary tool for assessing the performance of a laboratory, including personnel performance, is proficiency testing. Both internal and external programs are used. Repeat testing of in-house specimens ensures that a test is performing as expected over time. External programs, in which panels of samples that can be tested with all existing commercial and in-house methods and that resemble clinical samples are analyzed, ensure that the laboratory is reporting accurate results.

False positive and false negative results

Laboratory-caused false positive results are usually the result of specimen contamination due to improper sterilization, handling of contaminated material, and preparation of media and reagents. NAATs are at high risk for false positive results because of their high sensitivity. In a limited number of multicenter quality control studies of NAATs, the false-positive rate ranged from 9% to 57%.¹⁴⁸ The accuracy of these tests depends on use of specific procedures to prevent contamination (reviewed in 148).

Analytical false negative results are caused by interfering substances or inhibitors in the specimen or by improper specimen collection or processing. Some test systems include controls to detect inhibitors or sample degradation. Addition of control material directly to patient specimens can identify problems with sample storage and processing. However, this practice is controversial.¹⁴⁹ Biological false negative results may occur due to recent antibiotic use or incorrect timing of specimen collection.

FUTURE DIRECTIONS

The laboratory diagnosis of STIs has improved greatly in the past decade with the introduction of technologies that perform very sensitive detection of multiple organisms from single noninvasive specimen types. However, many challenges lie ahead for STI diagnostic testing. Unfortunately, the newer technologies and even many conventional laboratory procedures are beyond the reach of many health-care providers in resource-poor settings. As a consequence, syndromic management is practiced in many locations. Even when resources permit testing, the laboratory diagnosis of STIs is compromised when older technologies of limited sensitivity and specificity and often-substandard quality assurance practices are employed.

The availability of rapid, accurate, and inexpensive screening and diagnostic tests, especially for cervical infections in women, is sorely needed to improve patient management. Future directions for STI diagnostic tests should allow not only multiplex screening for all the causes of STI syndromes but also detection of mutations responsible for antibiotic resistance. The WHO and others who see this as a priority are working to develop and assess rapid and low cost diagnostics. Although home-based specimen collection, in which self-obtained specimens are

mailed to a laboratory, has been evaluated in some settings,^{150,151} home-based testing is not yet widely available. Home testing could provide STI diagnostic capabilities to some currently inaccessible populations.

The promise of better rapid tests lies in the rapidly evolving areas of nanotechnology and rapid detection technology. Complex nucleic acid amplification steps can be miniaturized on a nanoscale using microfluidic cartridges of the size of a credit card. This, combined with improved detection technology, will yield molecular rapid tests that can combine reasonable test performance with the operational characteristics of POC tests. Some tests are already in trials, but much work and innovation remains to be done before laboratory diagnosis of STIs is readily available to all those who need it.

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Individual, Couple, and Small-Group Interventions to Reduce HIV and STI Acquisition

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The NIH Consensus Statement on “Interventions to Prevent HIV Risk Behaviors” concluded:¹ “When we consider the available knowledge from the entire body of literature, we can reach a clear conclusion: Prevention programs significantly reduce HIV risk behaviors. This is true across a variety of risk behaviors and in a variety of populations at risk.” The report went on to cite efficacy for individual and group-level interventions in terms of risk behavior reduction for men who have sex with men, men and women, and male and female heterosexuals. The Centers for Disease Control and Prevention (CDC) has formulated its own compendium of efficacious interventions^{2,3} and has found individual and group intervention programs effective in reducing HIV risk behaviors among all the same populations as well. Because sexual transmission of HIV occurs through the same behaviors as sexual transmission of sexually transmitted infections (STIs), it is likely to assume that strategies for reducing sexual risk behaviors will affect both HIV as well as other STIs.

Many hundreds of studies have led to the NIH and CDC conclusions. Most of these studies, funded by the NIH and the CDC, use reported risk behavior as the outcome. This outcome might be regarded as a kind of a “surrogate” endpoint, as it is related to disease acquisition, but reductions in reported risk behaviors do not necessarily guarantee prevention of transmission for several reasons: because people forget or report erroneously, because behaviors were reduced but not sufficiently or consistently enough to prevent disease, or because the behaviors that were reduced were not those of greatest importance for disease prevention.⁴ Thus, one can draw the conclusion that the data from these hundreds of studies using self-reported behavioral endpoints are interesting and promising, but that the results do not necessarily guarantee that such programs will prevent disease, and that individual and group interventions may not be sufficient to recommend changes in public health or clinical practice. In a very real sense, they can be regarded as Phase II studies.

Phase III studies are now needed. Changes in public health practice may require another level of evidence, namely, the

demonstration that social and behavioral interventions to reduce risk behaviors result in clinically meaningful and sustained reductions in acquisition of new HIV or other STIs.

Manhart and Holmes⁵ presented a review of randomized controlled trials of individual, population, and multilevel interventions to prevent STIs, with a focus on analysis of impact on disease endpoints. They found few individual-, couple-, or group-level behavioral interventions efficacious in reducing HIV or STI acquisition. In this chapter, we focus on those, as well as a few studies failing to demonstrate efficacy, in order to understand the benefits and limitations of these kinds of interventions, make suggestions about replications of extensions of these results into further research, and make recommendations regarding integration of these kinds of interventions into public health practice.

INDIVIDUAL LEVEL INTERVENTIONS

Project RESPECT was one of the most important studies examining an individual-level intervention with biological endpoints.⁶ The study was completed in five sexually transmitted disease (STD) clinics (Baltimore, Denver, Long Beach, Newark, and San Francisco) between 1993 and 1996. A total of 5758 heterosexual HIV-negative patients presenting with symptoms at STD clinics were enrolled and randomized to one of four conditions: enhanced counseling consisting of four sessions, brief counseling consisting of two sessions, and the remaining two arms received two brief didactic messages. At the 12-month follow-up, participants in each counseling intervention had 20% fewer new STIs than those in the didactic message arms and this was consistent across study sites. Reduction of STIs was similar for men and women and greater for persons diagnosed with STIs at enrollment. The investigators concluded that short counseling interventions using risk reduction plans can prevent new STIs and can be incorporated into busy public clinics. A total of 82% of the participants completed all assigned intervention sessions but this was markedly lower in the four-session condition where only 72% completed all

sessions. People said that the sessions were “informative,” “good,” and “helpful.”

Project EXPLORE⁷⁻⁹ was similar to Project RESPECT in that it used an individual intervention. But in the case of EXPLORE, the intervention was far more intensive consisting of 10 one-to-one counseling sessions wherein assessments were made of the circumstances and other occasions in which an individual might engage in risk behavior, followed by tailored risk reduction plans to assist the individual in avoiding HIV acquisition. A total of 4295 men who have sex with men in six sites (Seattle, San Francisco, Denver, Chicago, Boston, and New York) were randomized to receive this intervention or semiannual voluntary counseling and testing delivered according to the CDC Project RESPECT model. Thus, Project RESPECT became the control for Project EXPLORE and this is consistent with ethical principles of randomized controlled trials. Thus, the evaluation of Project EXPLORE must take into account that it had to do substantially better than an intervention already proven efficacious. The individuals receiving the experimental intensive intervention also received quarterly maintenance sessions following the conclusion of the treatment sessions. Risk behaviors and HIV incidence were assessed but another important innovation was introduced. Average follow-up was 3.25 years, longer than has occurred in any other behavioral study.

The rate of acquisition of HIV was 18.2% lower in the intervention group than in the comparison group, but this effect was not significant (95% CI = -4.7-36%). Adjustment for baseline variables attenuated the effect further to 15.7% (95% CI = -8.4-34.4%).

Three other important findings emerged from this study. First, the intervention was effective in reducing overall risk behavior defined as unprotected anal intercourse with partners who were HIV-positive or unknown HIV status (20.5% reduction, 95% CI = 10.9-29%). Second, the effects of the intervention on HIV incidence appeared to be substantial in the first 12 months, with a 33% reduction in the first 6 months and a 39% reduction in the first 12 months. Had the study stopped at the time that other studies usually stop (i.e., 12 months), the intervention would most likely have appeared to be effective. Third, the intervention was effective in reducing certain risk factors for HIV (e.g., safer sexual norms, communication skills, self-efficacy) but not others (e.g., methamphetamine and other drug use, heavy alcohol use, depression) and these factors also predicted seroconversion among the entire cohort.

It is always a bit hazardous to generalize from an N of 2, but that is the sample we have at hand. Thus, we might conclude that it is possible, using individualized interventions, to reduce acquisition of new STIs and perhaps even HIV in the short run (e.g., up to 1 year postintervention). Nonetheless, the effect is likely to be modest and will not likely last beyond 12 months, at least given the evidence we have.

COUPLE-LEVEL INTERVENTIONS

The results for individuals inevitably give rise to the notion that it might make sense to involve others in the transmission chain, especially the partner giving the infection in the first place and perhaps giving it after an infection has been cured (in the case of bacterial STIs). Further, investigations in the United States and other places have demonstrated that men are more likely to give HIV to women than vice versa,¹⁰ but equal transmission has been observed in sub-Saharan Africa and is probably dependent on the viral load of the partner as well as other factors.

The potential of couple-level interventions to reduce HIV transmission was inspired by the early work of Allen et al. working in central Africa early in the HIV epidemic.¹¹ She and her colleagues demonstrated the potential of couples counseling and testing for HIV. They counseled and followed 60 serodiscordant couples. Condom use was reported by 3% of the couples at baseline and by 57% at 12 months follow-up. They reported an HIV seroconversion rate of 4 per 100 man-years of follow-up and 9 per 100 woman-years of follow-up. They determined that the absence of their program would have resulted in 22 new infections among serodiscordant couples. They also demonstrated a 50% reduction in incident gonorrhea when couples were tested together.¹²

Padian et al.¹³ followed 175 serodiscordant couples in California. Among these couples, 32% reported consistent condom use at entry into the study and 75% reported consistent condom use as much as 9 years later. Again, this study was uncontrolled, but no new seroconversions were observed during 3000 couple-months of follow-up. Because these studies were observational, they were always subject to concerns of selection bias. The Voluntary Counseling and Testing Efficacy Study Group^{14,15} tested the concept further in a randomized controlled trial and demonstrated that couples randomized to receive VCT, as compared to couples randomized to receive health education, reduced risk behaviors significantly more. This effect was especially pronounced in serodiscordant couples and was the most cost-effective of the interventions.¹⁵ Unfortunately, we have no controlled data to demonstrate the efficacy of these counseling strategies in reducing disease acquisition when couples are counseled together.

SMALL GROUP INTERVENTIONS

Providing instruction, motivation, and skills training in small groups is a strategy employed widely, at least in studies of HIV and STI prevention. The National Institute of Mental Health of the NIH sponsored one of the largest trials using this kind of intervention strategy.¹⁶ Entitled PROJECT LIGHT, the project was implemented in 37 inner-city, community-based clinics in five metropolitan areas: New York,

Baltimore, Atlanta, Milwaukee, and Los Angeles/Orange County, California. The sample was 74% African American, 25% Hispanic, and 58% female. A total of 3706 participants were randomized to a small-group, seven-session HIV risk reduction program, while the others were assigned to a control intervention consisting of health education. Those assigned to the intervention reported fewer unprotected sexual acts and higher levels of condom use than the control group.¹⁷ They also reported fewer STD symptoms over the follow-up period, but there were also no overall differences in STD rates. However, among men recruited from STD clinics, those assigned to the intervention condition had a gonorrhea incidence rate one-half than that of those in the control condition.

Shain et al.¹⁸ did find an effect on STI incidence. They recruited African American and Hispanic women from public health clinics in Texas and randomized them to receive either the control intervention (standard counseling about STIs) or a three-session sex- and culture-specific behavioral intervention. The intervention itself consisted of three small-group sessions of 3–4 hours each designed to help the women to recognize personal susceptibility, commit to changing their behavior, and acquire necessary skills. Rates of subsequent infection were significantly lower in the intervention group than in the control group in the first 6 months (11.3% vs. 17.2%, $p = 0.05$), the second 6 months (9.1% vs. 17.7%, $p = 0.008$), and over the entire 12-month study period (16.8% vs. 26.9%, $p = 0.004$).

Baker et al.¹⁹ compared the effectiveness of two different 16-session group interventions for reducing new STD infections among heterosexual women. A total of 229 at-risk heterosexual women were randomly assigned to skills training based on the relapse prevention model or to health education. Participants in the skills training intervention were significantly less likely to be diagnosed with an STD in the year following intervention and demonstrated superior risk reduction skills at the 12-month follow-up.

Finally, Wingood et al.²⁰ evaluated the efficacy of the WILLOW Program, an intervention to reduce HIV transmission behaviors and STIs among women living with HIV. This is the first study to demonstrate reductions in incident bacterial STIs and reductions in risky sexual behavior among HIV-infected minority women. The intervention emphasized gender pride, maintaining current and identifying new network members, HIV transmission knowledge, communication and condom use skills, and healthy relationships. Over the 12-month follow-up period, women in the WILLOW intervention, relative to the control had a lower incidence of chlamydial infection and gonorrhea (OR = 0.19, $p = 0.006$). They also reported greater HIV knowledge and condom use self-efficacy, more network members, fewer beliefs that condoms interfere with sex, and fewer partner-related barriers to condom use. They also demonstrated greater skill in using condoms.

WHAT DO SUCCESSFUL INTERVENTIONS HAVE IN COMMON?

1. *Working with people recently diagnosed with HIV or an STI may increase the efficacy of social and behavioral approaches.* It may be the case that the surprise of a diagnosis of HIV or an STI may lead people to change behavior and reduce infection. There has been an emphasis recently within public health to identify people with very recent HIV infection, and the public health implications of such an approach could be enormous because of the heightened infectiousness associated with that period of the disease.^{21,22} Such moments may also be teachable moments, as occurs when people seek nonoccupational postexposure prophylaxis,^{23–25} that provide the opportunity to use both biological and social/behavioral strategies to enhance motivation and encourage behavioral change.
2. *Working with couples or sexual networks may increase the efficacy of social and behavioral approaches.* Working with couples or with entire sexual networks^{26–30} may provide the opportunity both to intervene in and interrupt transmission chains and also build up social support systems to reinforce and support behavioral change.
3. *Interventions focusing on gender, racial/ethnic, or cultural issues might have promise.* Several of the successful interventions cited in this chapter^{11,12,14,18–20} focused on issues of importance and relevance to the target populations, including those relating to gender, race/ethnicity, and culture. While we have no evidence that these elements were crucial in the success noted (and while other interventions might have focused on these issues and failed to find intervention effects on disease acquisition), nonetheless this feature is interesting and should be explored further as a potential ingredient of success. There is no specific science to determine which elements of gender or culture or race/ethnicity matter for a specific population, or how specifically to include those elements into an intervention. But the success of these interventions should be noted and, as others attempt to replicate and extend those findings, attempts should be made to use this strategy to the benefit of the participants.

RECOMMENDATIONS FOR RESEARCH

1. *We do not need a further abundance of Phase II types of individual, couples, or small group interventions that use self-reported risk behavioral endpoints.* Rather, focus should be placed on studies that demonstrate efficacy in reducing disease acquisition. The objective must be strategies that can and will be adopted by public health systems, and a level of evidence that demonstrates reductions in disease acquisition. With this in mind, it might be possible to examine the potential of other endpoints, such as HSV-2³¹ or

HPV,^{32,33} that occur with greater prevalence and incidence than chlamydial infection or gonorrhea.

2. *Systems studies are also needed.* While it is important to examine the efficacy of interventions using the highest and most rigorous design standards, it is also important to examine barriers and facilitators to systems' adoption of proven preventive strategies to ensure that efficacious strategies can be put into public health practice.
3. *Maintenance remains a problem and should be addressed specifically.* There is no evidence at present that the impact of any of these interventions lasts beyond 12 months. Examination of maintenance effects is needed along with focus on strategies that can carry changes beyond the end of that time period.
4. *Perhaps we need to change the paradigm.* The individual and small-group interventions follow a kind of brief psychotherapy or "inoculation" model. In this approach, individuals are counseled once and the impact is expected to last indefinitely. Perhaps the model that needs to be evaluated is a systems model in which prevention is incorporated into the fabric of HIV and STI care with multiple interventions employed—assessment, counseling, use of media, STI diagnosis and treatment on a regular basis, and HIV counseling and testing (including assessment of acute infection). Such models might be more comprehensive, and also more effective, in that the system is focused on prevention and individuals returning for follow-up care can be exposed to additional and maintenance doses of prevention.
5. *We should look more seriously at media-based interventions.* Media are important to youth and also represent a primary method by which certain individuals or groups seek out romantic or sexual partners.^{34,35} Further, media strategies might be used beneficially in crowded public health settings where people have to wait for a long time to be seen.³⁶ We recommend that serious attention be paid to exploring more completely the benefits and efficacy of mediated approaches in reducing disease acquisition.
6. *Social and behavioral interventions typically do not address the role of substance use or mental health issues, and these issues may be at the heart of risk-taking and disease acquisition, at least with certain populations.* The role of methamphetamines and other drugs, as well as heavy alcohol use, in risky behavior is well documented.^{37–39} Needed are strategies that can be incorporated into clinical settings that demonstrate efficacy in reducing drug use and the impact of those reductions on HIV or STI disease acquisition or transmission.
7. *Combination prevention strategies should be a priority and should be examined for efficacy.* We have alluded, in this chapter, to the potential of combining social and behavioral interventions with biomedical ones, as in the case of working with couples and using antivirals or antibiotics, or

working with social networks and assessing acute HIV infection, or devising new strategies to reach potentially infected partners. It is time for the field to move beyond single discipline interventions and perhaps use more creative designs (e.g., factorial or other designs) to look at the synergistic effects of combined interventions to determine the ways to enhance the potential of social behavioral and biological interventions. For example, the combination of social/behavioral interventions with anti-retroviral medications (ARVs)²¹ used either to control acute or established infection or used as preexposure⁴⁰ or postexposure prophylaxis^{24,25,23} might be beneficial. The combination of social behavioral interventions with expanded partner therapy is another avenue ripe for investigation.⁴¹ It might also be possible to examine the synergistic effects of social/behavioral interventions with anti-HSV-2 drugs.⁴²

RECOMMENDATIONS FOR PUBLIC HEALTH PRACTICE

1. *Individual, couple, and small-group interventions CAN (but do not necessarily) lead to reductions in acquisition of HIV or STIs.* The studies using biological endpoints are few in number, but the positive findings are heartening. It is important to note, however, that other studies have examined impact on disease acquisition endpoints and have not found such effects. Thus, our conclusion is a bit muted and is qualified to indicate that such interventions CAN but do not necessarily affect disease endpoints. Thus, the evidence seems to indicate that the addition of individual, couple, and small-group interventions to routine STI treatment settings, and other clinical locations where high-risk individuals might present, could be beneficial.
2. *The potential of couples counseling and testing for HIV and STIs should be explored and enhanced.*⁴³ Disclosure of HIV serostatus, and presumably other diseases, remains a problem in HIV and STI prevention.⁴⁴ Strategies for enhancing disclosure might be a useful tool in the HIV/STI prevention armamentarium.

Reinfection with treated STIs or primary infection with viral STIs is common.⁴⁵ Some people presumably reacquire or acquire their STIs from primary partners; thus, innovative strategies for managing such encounters are essential. The literature reports some promising strategies for working with couples,^{11–14} and we are beginning to understand some of the disease cofactors that lead to transmission.^{46,47} Prevention studies in the field are testing the impact of antiretrovirals to prevent transmission of HIV to the uninfected partner, and also the impact of acyclovir to reduce HIV transmission in HSV+/HIV+ and to reduce HIV acquisition in HSV+/HIV– individuals.^{42,48} Other innovative strategies for working with couples involve enhanced partner therapy, whereby the

infected person is given medications for their presumably infected partner(s).⁴¹

Given these developments, it might be useful to continue to examine the impact of couples counseling, with and without combination prevention strategies (such as ARVs and other antivirals or antibacterials) in controlled trials. It might also be useful to examine, in controlled studies, the impact of various strategies for encouraging or increasing disclosure from the diagnosed individual to his or her partner(s). Again, the utility of strategies might be enhanced if such social and behavioral interventions are combined with biological or chemotherapeutic ones.

3. *Some interventions can be effective with minority women.* This can be a heartening finding, given the feminization of the epidemic.⁴⁹ The studies by Shain,¹⁸ Wingood,²⁰ and Baker¹⁹ demonstrated beneficial effects on new STI acquisition among heterosexual women, and these studies worked with substantial numbers of minority women. These results demonstrate the potential of social and behavioral approaches for working with women and suggest that such interventions might be employed routinely for such populations. Interestingly, the interventions in all three studies addressed gender and racial/ethnic/cultural issues, and working with these issues may be vital in securing any intervention effect with these populations. It is also possible that naturally occurring social support systems among women facilitate greater behavioral change and maintenance of those changes to achieve the reductions in disease acquisition noted.

CONCLUSION

The evidence suggests that individual, couples, and small-group social/behavioral interventions can be successful in preventing disease acquisition with some people, and that these interventions are relatively low-cost. We encourage the field to apply now what we know can be effective and, simultaneously move forward to expand the range of strategies at our disposal. In expanding the range of options, the goal should not necessarily be more studies such as reviewed here, but rather expansion to new paradigms and ways of thinking about influencing behavior and disease acquisition or transmission.

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Partner Notification for Sexually Transmitted Infections Including HIV Infection: An Evidence-Based Assessment

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Partner notification, previously referred to as contact tracing, is the process of informing the sex partners or needle-sharing contacts of persons with sexually transmitted infections (STI), including HIV infection, of their potential exposure to an infectious disease and ensuring their evaluation and/or treatment. Partner notification has been a component of public health STI control efforts since at least the eighteenth century, when Danish priests collaborated with local governmental authorities to “notify persons known or suspected of being infected” with syphilis.¹ Similar measures were introduced in Sweden in the nineteenth century and, as in Denmark, linked partner notification to compulsory treatment and free medical care. Public health partner notification programs were incorporated into U.S. and British syphilis control efforts in the 1930s and 1940s and were subsequently expanded in some areas of the United States and Europe to affect persons with gonorrhea, chlamydial infection, and HIV.²⁻⁴

In this chapter, we describe the rationale for partner notification for STI, approaches to STI partner notification in clinical practice, and the evidence supporting the efficacy and effectiveness of these different approaches. Because these approaches vary depending on the resources available and the organization of health service delivery, we discuss partner notification in high-income and low-income nations separately.

RATIONALE FOR PARTNER NOTIFICATION

Partner notification has been justified as a means to reduce ongoing STI transmission, improve the health of individuals, and as a societal obligation to fulfill a duty to warn those potentially exposed to infection. Insofar as partner notification leads to the treatment of infected partners, it has the potential to advance the health of individual patients, and several recent studies of gonorrhea and chlamydial infection have reported reduced rates of index patient reinfection as a consequence of outreach for partner treatment.⁵⁻⁷ The value of partner notification as a means to improve the health of

individual patients is further supported by studies reporting that it is a cost-effective means to avert the complications of chlamydial infection,^{8,9} though some investigators have questioned the parameters used in these cost-effectiveness analyses and their failure to incorporate the dynamic effects of interventions in STI incidence.¹⁰ Moreover, many interventions found to be cost-effective from a societal perspective are too costly for widespread implementation with existing public health resources.

Mathematical models of both gonorrhea and chlamydial infection suggest that increased treatment of sex partners can substantially reduce the prevalence of these infections in the population, particularly when partner notification effectively identifies STI transmitters.¹¹⁻¹⁵ A single dynamic model found that partner notification for chlamydial infection is also cost-effective.¹⁶ However, little empirical data exist to support these findings, and public health partner notification programs have not been shown to affect the prevalence or incidence of STI in the population. Intensified partner notification efforts have occasionally been temporally associated with declines in rates of STI in individual cities or counties that were not observed in areas without intensified partner notification,¹⁷⁻¹⁹ but such studies are essentially anecdotal and the utility of partner notification as a means to prevent STI in the population is uncertain. Some public health authorities have also argued that the insights gained through partner notification programs yield indirect benefits that advance disease control efforts.²⁰

Partner notification programs are primarily justified as a societal good, an effort that diminishes the burden of disease in the population and improves the health of exposed partners. Inherent in this justification is some tension between the welfare of the population and exposed partners and the liberty and right to privacy of persons infected with STIs. The emergence of HIV in the 1980s challenged the traditional view of the balance between these competing concerns. Many patients, HIV political activists, civil libertarians, and some public health authorities concluded that the invasion of privacy and potential to stigmatize persons with HIV

outweighed any potential public health benefits that might be achieved through partner notification.^{21–24} Compared with bacterial STI, identifying the contacts of HIV-infected persons conferred little individual benefit on partners who could not be effectively treated or cured, and the risk of stigmatizing those infected was substantially greater. Increasing social acceptance of homosexuality, data on the acceptability and efficacy of HIV partner notification,²⁵ the introduction of effective treatment for HIV and opportunistic infections, and the advent of effective means to prevent mother to child transmission have all substantially altered the balance of risk and benefits related to partner notification for HIV. However, the fundamental dilemma of balancing the public good and individual rights persists, and public health authorities and clinicians need to remain mindful that partner notification is accomplished in a manner that ensures the voluntary cooperation of infected persons and rigorously safeguards their privacy.

TERMINOLOGY, TYPES OF PARTNER NOTIFICATION

An extensive vocabulary has evolved over the last 60 years to describe different approaches to partner notification and the indices used to measure partner notification program process outcomes. These terms are summarized in [Table 54-1](#).

Three primary approaches to partner notification are now recognized as follows:^{26–29}

- *Patient referral*: Responsibility for partner notification is left to the index patients themselves. This process sometimes involves an interview to elicit the names of contacts. At times, the process may be enhanced through counseling or the provision of referral cards.
- *Provider referral*: A clinician or health department employee interviews an index patient, elicits information about the identity of their sex partners, notifies the identified sex partners, and attempts to ensure their treatment without revealing the identity of the index case.
- *Conditional referral*: Public health staff elicit contact information about index patients' partners but only notify those partners if the index patient does not ensure the partners' treatment within some agreed on time period.

Although these terms provide a basis for describing partner notification, in practice the line between approaches is often blurred, and partner notification activities described with the same term often vary. In particular, patient referral, when implemented within a public health partner notification program, sometimes includes an interview with a health worker to elicit a sexual history and follow-up to ascertain outcomes. When undertaken by individual clinicians, patient referral is more likely to involve only the advice to index cases to inform their sex partners. Recently, some investigators

have divided patient referral into simple patient referral and supported patient referral to differentiate between patient referral in which no assistance is offered (simple patient referral) and patient referral involving contact slips, or some education, interview, enhanced counseling, or follow-up (supported patient referral).⁴

CONTACT PERIODS

Contact periods are the time periods used to define which of an infected person's sex partners are at risk for STI and require evaluation and treatment. These periods are based on what is known about the incubation periods and natural history of each STI, as well as empirical data on case-finding yields observed using different periods. [Table 54-2](#) presents the contact periods recommended by the U.S. Centers for Disease Control and Prevention (CDC) and the British Association for Sexual Health and HIV. Before publication of the UK guidelines, different UK genitourinary medicine (GUM) clinics appeared to employ different contact periods; 3 months was the most commonly used period for gonorrhea and chlamydial infection, and 6 months the most common period for HIV.³⁰ The impact of the UK guidelines on harmonizing contact periods has not yet been assessed.

The adequacy of different contact periods for gonorrhea and chlamydial infection have been evaluated in studies using 120 and 180-day periods for the two infections, respectively.^{31,32} In both studies, public health staff attempted to test all index patients' partners for these periods to define the total population of potentially infected partners. (The study of chlamydial infection attempted to test at least two partners for each index person, using a period longer than 180 days if the patient reported only one partner during the 180-day period.) Among persons with gonorrhea, 30, 60, and 90-day contact periods identified 84%, 96%, and 99% of infected partners, respectively. A 30-day period identified 91% of infected partners of male index cases treated for symptomatic urethral gonorrhea. Among persons with chlamydial infection, 30, 60, and 90-day contact periods identified 79%, 88%, and 92% of infected partners, respectively. These studies suggest that relatively little is accomplished by extending contact periods for these infections beyond 60 days.

PUBLIC HEALTH PARTNER NOTIFICATION PRACTICES IN HIGH-INCOME NATIONS

The role of public health authorities in partner notification varies considerably between countries and among the different STIs. In the United States, health department staff routinely attempt to interview all patients reported with syphilis and typically employ provider referral. In contrast, the approach to other STIs, including HIV, is much more tentative. A survey of partner notification practices in 60 high STI

Table 54-1. Commonly Used Terms in Partner Notification Practice and Research

Term	Alternative Term	Definition
Index patient	Index case, original patient (OP)	The patient who presents for medical care with a newly diagnosed STI
Partner	Contact	Individuals who have been exposed to the index patient through sexual intercourse or needle sharing
Contact period		The time periods used to define which of an infected person's sex partners are at risk for STI and require evaluation and treatment
Contact slip	Referral card	Printed material that clinicians or public health staff give to index patients to give to their sex or needle-sharing partners. Contact slips advise recipients to seek care and are sometimes used to track the number of partners treated.
<i>Partner notification staff</i>		
Disease Intervention Specialists (DIS)	Public health advisors	U.S. health department staff performing PN activities
Health advisers	Contact tracers	UK health professionals performing partner notification, usually in genitourinary medicine clinics
Public health nurses		Dutch health professionals performing partner notification (amongst other duties), based in Municipal Health Services
<i>Types of partner notification</i>		
Patient referral		Index patient is encouraged to notify partners themselves
Provider referral		Health worker notifies partners
Conditional referral		Health worker notifies partners if index case has not done so within an agreed time period
Expedited partner therapy		Goal term of practices that involve treatment of sex partner's without the partner's mandatory prior examination by a clinician
Patient delivered partner therapy (PDPT)		Diagnosed patient is given medication or a prescription for medication to give to their sex partner(s)
<i>Measures of program productivity</i>		
Contact index		Number of contacts for whom information is elicited/number of persons with STI interviewed
Epidemiologic index	Treatment index	Number of contacts treated/number of persons with STI interviewed
Case-finding index	Brought-to-treatment index	Number of infected contacts treated/number of persons with STI interviewed

morbidity U.S. areas found that in 1999, only 17% of persons with gonorrhea and 12% of those with chlamydial infection were interviewed for purposes of partner notification; partner notification services for gonorrhea and chlamydial infection were largely restricted to patients seen in STD clinics, and, when provided, typically involved simply offering to notify patients' partners with no routine follow-up if that

offer was refused.³ In 2001, only 33% of persons reported with newly diagnosed HIV infection in high morbidity parts of the United States were interviewed for purposes of partner notification. As with gonorrhea and chlamydial infection, partner notification services were typically restricted to persons tested in publicly financed HIV testing sites, though some areas routinely attempted to contact all persons with

Table 54-2. CDC and British Association for Sexual Health and HIV Recommended Contact Periods for Pn^{143–146}

Disease	United States	UK
Gonorrhea	Symptomatic—60 d prior to onset of symptoms Asymptomatic—60 d prior to treatment	Symptomatic—2 wks prior to the onset of symptoms Asymptomatic—3 mo prior to treatment ¹²
Chlamydial infection	Symptomatic—60 d prior to onset of symptoms Asymptomatic—60 d prior to treatment	Symptomatic—4 wks prior to the onset of symptoms Asymptomatic—6 mo prior to treatment ¹¹
Primary syphilis	90 d prior to date of onset of primary lesion	90 d prior to the onset of the primary lesion
Secondary syphilis	6.5 mo prior to date of onset of secondary symptoms	Up to 2 yrs prior to treatment in cases of clinical relapse ^a
Early latent syphilis	1 yr prior to start of treatment	2 yrs prior to start of treatment ^a
HIV	1 yr prior to date of positive test (extended interview period may be warranted in some circumstances). 10-y period for current or any previous spouse	No guideline

^a In the UK, early latent syphilis is defined as a new positive serological test for syphilis with no clinical evidence of treponemal infection within 2 years of infection.

Interview periods may be modified if a history of symptoms, a negative test result, or an incidental treatment are documented. Maximum periods are used if symptom history is uncertain. If a patient reports no partners during the interview period, the most recent partner should be notified.

newly reported HIV.³³ A Canadian survey of public health partner notification practices found that most provinces provided partner notification services to the majority of persons with bacterial STI, but that only 33% of health units provided partner notification services to most persons with HIV; provider referral was employed in approximately 50% of instances when partner notification services were provided.³⁴

Partner notification practices in the European Union are highly variable and in many nations somewhat ill-defined.^{4,35} Infected patients and diagnosing clinicians in Sweden and Norway are legally required to notify the sex partners of persons with reportable STIs. Provider referral is used for at least some cases of STI in Scandinavia, the UK, and Ireland. Most other European countries do not have sexual health services that are distinct from their systems of primary medical care and rely on patient referral. Patient referral in some countries involves some sort of interaction with public health authorities, but the nature of that interaction and the proportion of patients that are contacted by public health authorities are not known.

In the UK, a national network of specialist GUM clinics provides free and confidential care for people with STIs. These clinics are thought to treat most diagnosed cases of HIV, syphilis, and gonorrhea, but not chlamydial infection, and most employ specialized staff (health advisors) to undertake

partner notification. Patient referral, including an interview to elicit a sexual history, advice about how to inform partners, and education about reducing the risk of reinfection, is the preferred strategy for syphilis, gonorrhea, chlamydial infection, and HIV infection in over 80% of clinics. Conditional referral is used in almost all other instances,³⁰ and provider referral is very rarely used as an initial approach. Contact slips were formerly used in the UK as a fundamental aid to patient referral and follow-up.²⁷ Sexual contacts could attend any GUM clinic with a contact slip and the slip would be returned to the issuing clinic so that treatment could be recorded in the index patient's notes. Contact slips are not used for HIV partner notification and their use for other infections is diminishing. Clinicians in primary care settings, where increasing numbers of cases of chlamydial infection are being diagnosed, often advise patients to notify their partners but do not necessarily provide risk reduction counseling or follow up the outcomes. A minority of primary care providers send patients with chlamydial infections to GUM clinics^{36,37} and many patients who are referred do not attend.³⁸

In Sweden, the main method for PN is conditional referral. At specialized dermatological and venereological clinics (mainly in the big cities), trained social workers are responsible for partner notification. At primary care clinics, diagnosing clinicians are responsible for partner notification.

Program statistics on PN yields have recently been compiled from published data from the United States between 1995 and 2003 and from both published and unpublished data from the UK from 1995 to 2002 (Table 54-3).^{39,40} The U.S. study compiled data on brought-to-treatment indices, while the UK review evaluated the epidemiologic index (see Table 54-1 for definitions). Assuming that approximately 50% of partners of persons with gonorrhea or chlamydial infection are infected, the results of these reviews are roughly similar, indicating that 3–5 persons with gonorrhea, chlamydial infection, or syphilis need to be interviewed to identify one new infection in a partner, though recent data on syphilis in men who have sex with men (MSM) suggest that current case-finding yields, like those for HIV, are probably lower.⁴¹ The absence of clearly defined partner notification procedures across these studies makes them difficult to interpret or compare, though they provide some basis on which to assess partner notification program success.

Health departments' relatively infrequent application of intensive partner notification efforts for HIV, the most important STI, merits particular discussion. At the outset of the AIDS epidemic, several U.S. states instituted routine PN efforts linked to named-based HIV reporting. Early evaluations of these efforts reported reasonable case-finding yields, with 2–11 index patients interviewed to identify one new case of HIV infection.^{42–48} A small randomized, controlled trial conducted in the early 1990s found that conditional referral was superior to patient referral, when patient referral involved only an interview with public health authorities and no follow-up.⁴⁹ The case finding success of HIV partner notification was subsequently evaluated in a study of 6394 persons receiving public health HIV partner notification services in 23 U.S. cities or states; 13.8 index patients needed

to be interviewed (Number Needed To Interview [NNTI]) to identify one new case of HIV infection. HIV partner notification success was highly variable across different health departments (NNTI ranged among areas from 1 to 196), with fewer new cases identified in areas with higher proportions of AIDS cases occurring in MSM.³³ A multicenter European study reported very similar results, with 28 new cases of HIV infection identified as a result of interviewing 356 index cases (12.7 index cases interviewed to identify one new case of HIV infection).⁵⁰

Despite this evidence, in the United States and UK, relatively little public health effort was devoted to HIV partner notification during the first 2 decades of the AIDS epidemic.^{24,33,51} The failure to more widely employ partner notification likely reflects a combination of concern about the stigma of HIV and potential deleterious effects of partner notification; political considerations, with civil libertarians and community-based organizations (CBOs) purporting to represent MSM frequently opposing the process;^{21–23} the paucity of effective therapies for HIV infection to benefit those with HIV infection identified early in the epidemic; and the culture of HIV-related public health activities, which has often placed a premium on client satisfaction and counseling rather than on more traditional disease control objectives, such as case-finding.^{3,27,52} Recent observational studies have not identified an elevated risk of domestic violence or partnership dissolution associated with HIV partner notification and have found that condom use increases following partner notification.^{53,54} Moreover, persons with HIV, including MSM, typically believe that some form of public health-facilitated partner notification should be routine.^{25,55} Since 2003, CDC has begun to place greater emphasis on HIV partner notification,⁵⁶ and it seems likely that U.S. HIV partner notification programs will expand in the coming years.

HOW CLINICIANS AND PATIENTS APPROACH PARTNER NOTIFICATION

Since public health efforts in most high-income countries affect small numbers of persons and often rely on patient referral, the success of partner notification is often a question of how well diagnosing clinicians and their patients assure partners' evaluation and treatment with little or no assistance. Studies conducted in the United States and Europe have found that clinicians treating patients for STIs typically make very limited efforts to treat partners and seldom know whether their patients' partners are treated. For example, in a U.S. study conducted in King County, Washington, in which clinicians were interviewed about their management of a specific case of *Chlamydia trachomatis* they had reported to the health department, 90% stated that they had told the patient to notify their sex partners but only 17% knew that all of their patient's partners were treated.⁵⁷ Studies surveying

Table 54-3. Partner Notification Indices from Reviews of Recent U.S. and UK Data

	United States ³⁹ Median Brought-to-Treatment Index ^a (range)	UK ⁴⁰ Pooled Epidemiologic Index ^b (range)
Gonorrhea	0.25 (0.09–0.58)	0.58 (0.47–0.71)
Chlamydia	0.22 (0.05–0.53)	0.61 (0.55–0.66)
Syphilis	0.22 (0.05–0.53)	NA
HIV	0.13 (0.03–0.75)	NA

^a Brought to treatment index = Number of infected contacts treated/number of persons with STI interviewed.

^b Epidemiologic index = Number of contacts treated/number of persons with STI interviewed.

providers about their typical practices have found similar results. A study of a national probability sample of 7300 American physicians found that over 80% reported routinely telling patients to notify their sex partners and advise those partners to seek medical care, but fewer than one-third routinely followed up with patients to inquire about partner treatment.⁵⁸ A 1994 survey of British general practitioners found that only 30% referred patients with chlamydial infection to GUM clinics and that only 30% of providers who did not refer to such clinics routinely treated their patients' partners or referred them elsewhere for treatment.³⁶

Although relatively few clinicians seem to actually examine their patients' sex partners, many give their patients medications or prescriptions for medications to give to their sex partners, a practice called patient-delivered partner therapy (PDPT). Approximately half of all U.S. physicians treating persons with gonorrhea or chlamydial infection report at least occasionally using PDPT, though most studies have found that 25% or fewer use it half or more of the time.^{57,59-61} The practice has been less well-studied outside of the United States. A survey of European public health officials reported that PDPT was uncommonly employed.⁴ However, a Danish study of provider practices that included information on how specific patients were managed found that 34% of women and 12% of men treated for *C. trachomatis* were given prescriptions for their current partner.⁶² PDPT also appears to be used relatively commonly in Australia.⁶³ PDPT for gonorrhea and chlamydial infection has been instituted as part of a population-based public health program in a single U.S. city⁶⁴ and is now being promoted in California and in Washington State but is of uncertain legal status in much of the United States⁶⁵ and possibly in Europe. In the UK, PDPT is under investigation and is legal if a health professional (including a pharmacist) has assessed whether such therapy is suitable for a partner, and the doctor prescribing the therapy takes responsibility for the partner. The CDC has issued preliminary advice to state and local health departments suggesting that U.S. health departments should have PDPT available as an option.⁶⁶ Data and controversies related to PDPT have recently been reviewed.⁶⁷ CDC has recently issued guidance related to EPT.⁶⁶

Since health departments frequently do little to promote partner notification, and, in the absence of PDPT, most clinicians do little more than advise patients to notify their sex partners, patients are typically left to assure their partners' treatment with little assistance. Defining the success of patient referral is difficult since ascertaining whether partners have been treated is either dependent on index patient report, which may not be valid, or confirming partners' treatment at a specific clinic, which may fail to ascertain treatment received under an alias or at other venues. In addition, the content of patient referral is variable, reports on patient

referral outcomes have used different contact periods, and health department staff is likely variably successful in defining the number of potentially exposed sex partners used as denominators to calculate the percentage of partners notified or treated. Despite those limitations, numerous studies have attempted to define the success of patient referral, mostly for gonorrhea or chlamydial infection (Table 54-4). Overall, these studies suggest that probably fewer than half of partners of persons with gonorrhea or chlamydial infection are treated. Factors associated with more successful referral of partners include female gender of index patient;⁶⁸⁻⁷⁰ steady, recent and ongoing partnership;^{68,69,71-73} chlamydial infection (vs. gonorrhea);^{68,73} index patients having fewer sex partners;^{57,68,73} nonuse of condoms;^{72,74} index patient self-efficacy⁷⁰; and diagnosis by a private sector clinician as opposed to clinicians in an STD clinic, public health clinic, or an emergency room.⁷³ Index patient age has not been consistently associated with patient referral success.

COMPARATIVE STUDIES OF PARTNER NOTIFICATION

Given the long history of partner notification, there are relatively few studies comparing different approaches to partner notification and very few randomized, controlled trials (Table 54-5). Between 1994 and 2002, three systematic reviews of the partner notification literature were conducted.^{26,28,75} These studies and reviews suggest several conclusions:

- (1) Provider referral or conditional referral conducted by public health professionals among male STD clinic patients with gonorrhea or NGU, and possibly among persons with HIV, increases the proportion of partners who are identified or treated compared to patient referral. Limited existing data do not support the efficacy of partner notification interventions by public health professionals when applied outside of STD clinics. The efficacy of partner notification undertaken by public health professionals is supported by two randomized controlled trials conducted among mostly male STD clinic patients with gonorrhea⁷⁶ and NGU,⁹ as well as by a small randomized trial among persons with HIV.⁴⁹ In addition, a study that compared partner notification outcomes in one U.S. city during two time periods found that brought-to-treatment indices were higher during a period of intensified partner notification involving provider referral than they were during a period of "perfunctory" disease intervention specialist (DIS) partner notification efforts.⁷⁷ In contrast, a randomized trial conducted in the UK among persons with chlamydial infection found that brief partner notification counseling by nurses in primary care clinics or physicians' offices with telephone follow-up was at least as effective as referring patients to receive

Table 54-4. Studies Evaluating Patient Referral Success

Location (y)	Number Index Patients Studied	STI	% Partners Notified or Treated	PN Procedures and Outcome Ascertainment
Colorado Springs (1977) ⁷⁸	93	GC	51	All patients received a routine follow-up call. Partner treatment status based on confirmed treatment in STD clinic
Colorado Springs (1985) ⁷⁷	3368	GC	62	"Perfunctory" PN interviewing performed with no follow-up. Partner treatment status based on confirmed treatment or evaluation
Nova Scotia (1992) ¹⁴⁷	37	CT	68	Partner notification status based on index patient report (treatment outcome not reported)
London (1994) ⁷¹	254	CT	53	Index patients had ocular CT infection. Treatment status based on confirmed treatment
Amsterdam (1997) ⁶⁸	440	GC/CT	40	Patients given referral cards. Partner treatment status based on confirmed in STD clinic or elsewhere
Rotterdam (1998) ⁷²	250	GC/CT	41	Patients routinely counseled by public health nurse and given referral cards. Partner treatment status based on confirmed treatment in STD clinic or elsewhere
Houston (2000) ¹⁴⁸	54	GC/CT	55	Partner treatment status based on index patient report—percentage reflects any partner having been treated
Seattle (1999) ⁵⁷	76	CT	51	Partner treatment status based on index patient report
Seattle (2001) ⁶⁴	698	GC/CT	51	Partner treatment status based on index patient report
Indianapolis (2002) ⁷⁰	241	GC/CT/NGU/TV	65	Partner notification status based on index patient report (treatment outcome not reported)
France (2002) ⁶⁹	145	Any STD	49	Partner notification status based on index patient report (treatment outcome not reported)

GC = gonorrhea, CT = *C. trachomatis*, NGU = nongonococcal urethritis, TV = trichomonas.

partner notification assistance from health advisors in GUM clinics.³⁸ Also, one small, nonrandomized trial did not find that provider referral was superior to patient referral,⁷⁸ and an observational study comparing periods in which DIS services were provided or not provided to

patients with gonorrhea found no difference in the proportion of cases of infection identified through PN.⁷⁹ Possible reasons for disparities across studies include (a) patient referral may be more effective in women, meaning that DIS assistance among women has a smaller effect;⁸⁰

Table 54-5. Experimental and Comparative Studies of Different Approaches to PN

Author (y)	Population	Design	Intervention	Outcome	Comment
Gonorrhea, Chlamydia, and NGU Cleveland (unpublished) ⁷⁶	1898 Dade county STD clinic patients with gonorrhea (94% male, 71% African American)	Randomized controlled trial Test of cure (TOC) performed at 2–5 d Rescreening performed 28 d after treatment (excluded those with positive TOC)	3 arms: (1) Referral cards and instructions to refer partners with no contact elicitation interview (PR) (2) Informational pamphlet, contact elicitation interview, and referral cards (IP) (3) Conditional referral with referral cards (CR)	Epidemiologic Index: PR = 0.37 IP = 0.37 CR = 0.62 Brought-to-treatment index PR = 0.25 IP = 0.24 CR = 0.37 Test of cure (67% tested) PR = 3.5% IP = 2.6% CR = 3.6% Rescreening (54% tested) PR = 6.3% IP = 7.7% CR = 7.2%	Costs per case identified 3.6 × higher in CR than in PR. Statistics to assess significance of PN indices cannot be calculated due to nonindependence of data. No significant difference in TOC or infection at rescreening
Hammer (1972) ⁸⁰	669 STD clinic patients with gonorrhea in Uppsala, Sweden.	Comparison of two time periods	Routine follow-up PN interviews performed during an intervention period. Only an initial interview was performed to elicit partner names during the control period.	Proportion of index cases with at least one infected contact increased from 63% to 74% among men ($p = 0.03$), but decreased from 78% to 68% among women ($p = 0.05$).	The probability of finding the source partners was believed to be higher in men during the intervention period.
Potterat (1977) ⁷⁸	187 El Paso, Colorado male STD clinic patients with gonorrhea	Controlled nonrandomized trial	Conditional referral (CR) vs. patient referral with referral cards (PR) DIS interviewed subjects in PR arm but did not elicit names or contact information	Epidemiologic Index: PR = 1.15 CR = 1.27 Brought-to-treatment index ^a PR = 0.53 CR = 0.53	Excludes partners treated prior to notification ^a
Judson (1978) ⁷⁹	Denver STD clinic patients with gonorrhea	Comparison of two time periods	One period involved DIS interviews with some follow-up provided to 30% of patients. The comparison period involved provision of contact slips to patients by clinicians without any DIS interview	The percentage of all gonorrhea cases diagnosed in the STD clinic as a result of PN did not differ between the DIS and no DIS periods (19.2% vs. 19.4%)	DIS PN procedures ill-defined
Woodhouse (1985) ⁷⁷	Gonorrhea in Colorado Springs, USA	Comparison of two time periods	Study period (1980–82)—intensive PN involving at least some provider referral control period (1977–79)—“perfunctory” patient interviewing	Brought to treatment index increased from 0.17 to 0.28.	Decline in gonorrhea incidence in Colorado Springs was greater than elsewhere in Colorado state (–12.9% vs. –6.6%)

Table 54-5. (Continued)

Author (y)	Population	Design	Intervention	Outcome	Comment
Katz (1988) ⁹	678 Indianapolis male STD clinic patients with nongonococcal urethritis	RCT	3 arms: (1) Patient referral (PR)—nurses caring for subjects advised them to notify partners and gave them referral cards (2) Patient referral with DIS interview (PRD)—DIS elicited contact information but no follow-up done and no referral cards given (3) Provider referral (PrR)—DIS elicited contacts and attempted to contact them	Epidemiologic Index: PR = 0.22 PRD = 0.18 PrR = 0.72	
Solomon (1988) ⁹¹	902 mostly African American (99%) male STD clinic patients	RCT	Intervention: 10 min soap-opera style videotape that emphasized the importance of notifying partners and of returning for test-of-cure followed by DIS interview and receipt of referral cards. No routine DIS follow-up was provided. Control subjects were interviewed by DIS and received referral cards	No difference in PN outcomes as measured by DIS case dispositions or number of partners presenting with referral cards	No numbers presented on PN outcomes. One or more referral cards returned by partners of only 13% of subjects
Montesinos (1990) ⁸⁸	65 university students (74% male) with gonorrhea or nongonococcal urethritis at Southern Illinois University	Two 6 mo periods compared. The first offered counseling only (arm 1) to all subjects, the second randomly assigned subjects to arms 2 and 3	3 arms: (1) Counseling with partner elicitation interview (2) Counseling with partner elicitation interview + referral card + free care for patient and partner (3) Counseling with partner elicitation interview + referral card + follow-up call	More identified partners of persons in arm 3 (90%) sought care than in arm 1 (56%) or arm 2 (62%) ($p < 0.05$)	50 students excluded because they did not have a partner who was also a student at the university. Only 2/19 subjects in arm 3 were called for follow-up. Uncertain if statistical methods accounted for correlated data
Alary (1991) ¹⁴⁹	104 persons with gonorrhea or chlamydial infection (74% female) in Quebec, Canada.	Comparison of number of contacts elicited and number infected contacts	Persons receiving public health PN were interviewed by a PN nurse and managed with conditional referral. Those who refused public	Mean number of contacts elicited was 2.55 in the public health PN group and 1.59 in the physician group ($p = 0.004$). Brought-to-treatment	Acceptance higher among women, though difference in number of contacts identified was higher among those

(Continued)

Table 54-5. (Continued)

Author (y)	Population	Design	Intervention	Outcome	Comment
Gonorrhea, Chlamydia, and NGU	Includes persons diagnosed by general practitioners	identified among persons accepting and refusing public health interviews	health PN had partners elicited by the reporting physician	index higher among persons receiving public health PN (0.66 vs. 0.26)	accepting public health PN after adjustment for gender
Andersen (1998) ¹⁵⁰	96 Danish women with <i>C. trachomatis</i> diagnosed in general practices	RCT	Counseling patient to refer partners vs. providing women with home sampling urine specimen container for male partners	68% of partners in home sampling group and 28% in control group tested ($p < 0.01$)	Completeness of ascertainment of male partner evaluation uncertain
Brewer (2001) ⁸¹	158 MSM (49%), HIV testers, or injection drug users in Seattle, Washington	Comparison of number of partners named before and after use of supplementary techniques. Different supplementary techniques compared in randomized trial	Free recall of sex partners in past year vs. free recall enhanced with supplementary interviewing techniques	Supplementary techniques increased number of sex partners acknowledged by 40% and number of IDU partners acknowledged by 123%	Prompting using alphabetic and locations for meeting partners as cues were most effective
Wright (2002) ⁹⁴	424 heterosexual GUM clinic patients with chlamydial infection in London	Comparison of two 2 month time periods during which different contact slips were used	Contact slip naming chlamydial infection as the index patient's STI diagnosis with attached informational brochure compared to standard contact slip alone	Contacts attending GUM clinics per index patient increased from 0.3 to 0.8 ($p < 0.0005$)	No data provided on number men and women. Significantly, more patients issued slips during time period when experimental slip was used
Brewer (2005) ⁸²	123 persons (43% male) receiving PN services for gonorrhea, chlamydial infection (90%) or syphilis in Colorado Springs, CO.	Comparison of number of sex and needle-sharing partners acknowledged before use of supplementary techniques and after. Different supplementary techniques compared in randomized trial	Location/alphabetic/network/role cues compared to first-name cues and individual characteristic cues (control)	Location/alphabetic/network/role cues resulted in elicitation of 21% more partners and a 0.11 mean increase in partners located	Enhanced elicitation techniques increased number of partners found by 12%

Table 54-5. (Continued)

Author (y)	Population	Design	Intervention	Outcome	Comment
Ostergaard (2003) ⁸³	1826 persons with <i>C. trachomatis</i> randomized prior to enrollment; 562 (74% women) enrolled	Randomized controlled effectiveness trial	Enrolled patients sent home urine specimen collection kits to give to partners; controls received a kit that required them to go to an office for testing	26% of home sampling and 12% office sampling had at least one partner treated ($p < 0.0001$). Among persons enrolled, 67% of home sampling and 34% of office sampling subjects had at least one partner treated	Uncertain how many partners may have been treated outside of study
Schillinger (2003) ⁵	1787 women treated for chlamydial infection in diverse clinical settings in 5 U.S. cities	RCT	Azithromycin PDPT vs. patient-referral	Chlamydia diagnosed in 12% PDPT vs. 15% self-referral at 1 or 4 mo follow-up (OR 0.80, 95% CI 0.62–1.05). NNT to prevent one case of CT = 33	Study did not achieve goal enrollment. Proportions of partners treated not reported
Apoola (2004) ⁸⁹	800 patients with chlamydial infection at Birmingham, U.K. GUM clinic	Comparison of two time periods	2001—patients interviewed by health advisor asked to return to clinic for routine follow-up in 2 wks 2002—patients interviewed by health advisor and 2 wk follow-up telephone call scheduled	Number of contacts treated per case higher in 2002 than 2001 (0.57 vs. 0.45, $p = 0.0006$)	Statistical tests did not account for nonindependence of events
Golden (2005) ⁶	2751 persons (24% men) reported with gonorrhea or chlamydial infection in King Co., WA	RCT	Expedited partner treatment (EPT) vs. standard partner referral. 9% EPT partners treated following direct contact with study staff. Standard partner referral involved patient referral with an offer of assistance notifying sex partners	Infection at 10–18 wk follow-up detected in 9.9% of subjects who received EPT and 13% who received standard partner referral (RR 0.76, 95% CI 0.59–0.98). Partners reported treated 64% EPT vs. 52% standard partner referral	Excluded index patients who reported all partners treated at time of study interview. EPT significantly more effective for gonorrhea (RR 0.32, 95% CI 0.13–0.77) than for chlamydia (RR 0.82, 95% CI 0.62–1.07)
Kissinger (2005) ⁷	977 men treated for urethritis in New Orleans STD clinic; 60% infected with gonorrhea and 20% chlamydial infection	RCT	3 arms: PDPT with azithromycin + ciprofloxacin or cefixime, information booklet (BR), or patient referral (PR) ^a	Infection at follow-up detected in 23% PDPT, 14% BR, and 43% PR ($p < 0.001$). Partners reported treated 56% PDPT, 44% BR, and 34% PR ($p < 0.001$)	Follow-up Interviews performed on 79% of men. STI testing performed on 38% of men interviewed
Low (2005) ³⁸	140 patients with chlamydial infection (44% men) diagnosed	RCT	Patient referral by practice nurse (PN) with telephone follow-up by health adviser vs. referral	Partners reported treated PN 65%, HA 53%, difference 12% (95% CI –2–27%. $p = 0.087$)	31% of patients referred to genitourinary medicine clinic did not attend

(Continued)

Table 54-5. (Continued)

Author (y)	Population	Design	Intervention	Outcome	Comment
	in primary care practices in Bristol and Birmingham, UK		to health adviser at genitourinary medicine clinic (HA)		Persons randomized to HA were interviewed a mean time of 13 d after treatment Cost of two strategies similar
Syphilis					
Peterman (1997) ¹⁵²	1966 patients with syphilis (76% early latent) in Florida or New Jersey	RCT	3 arms: (1) Conditional referral (CPR) (2) Provider referral (PR) (3) Provider referral with bloods drawn from partners in the field (PR+)	Epidemiologic index : CR : 0.67 PR : 0.61 PR+ : 0.62 Cost per partner treated: CR: \$317 PR: \$362 PR+: \$343	Most contacts in CR arm notified by DIS. Cost estimates likely underestimates due to incomplete recording of time spent on activities other than interviews
Trichomonas					
Kissinger (2005) ⁹³	463 New Orleans STD clinic patients with Trichomonas	RCT	3 arms: PDPT with metronidazole, information booklet (BR), or patient referral (PR) ^a	Infection at follow-up detected in 9.4% PDPT, 9.0% BR, and 6.3% PR ($p < 0.001$) Partner treatment reported by 76% PDPT, 58% BR, and 70% PR	81% women tested at follow-up
HIV					
Landis (1992) ⁴⁹	74 persons newly diagnosed with HIV (76% MSM) in publicly funded HIV-testing programs in North Carolina	RCT	Conditional referral (CR) vs. patient referral (PR). DIS attempted to notify partners in patient referral arm after 1 mo	Partners notified and tested 50% in CR arm and 6.5% if PR arm ($p < .001$)	Enrolled subjects constituted 14% of all persons with HIV-positive tests during time period; 46% of those offered participation enrolled

PDPT = Patient delivered partner therapy.

(b) patient referral may be more effective among patients with chlamydial infection than among those with gonorrhea; (c) the quality and intensity of health department-mediated partner notification may have varied substantially between studies; and (d) studies employed different methods to define whether partners

were treated, with recent studies showing no benefit associated with conditional referral relying more on index patient report of partner treatment status, and older studies relying exclusively on confirmed partner treatment, mostly in STD clinics. It should be noted that provider or conditional referral has not been compared

to patient referral in randomized trials involving patients with syphilis, and that the conclusion that conditional referral is superior to patient referral for HIV is based on a single study of only 74 people in the era before highly active antiretroviral medication was available.⁴⁹

- (2) Specific cues can be used to increase the number of partners elicited when interviewing index patients. This finding is supported by two randomized controlled trials.^{81,82} To date, the interviewing techniques studied in these trials have not been widely applied, and the feasibility of widely using these cues and their effectiveness when used outside of a study is unknown.
- (3) Providing women with chlamydial infection with urine self-collection kits to give to their male sex partners increased the number of partners tested and treated in two randomized controlled trials conducted in Denmark.^{63,83} The extent to which self-collection may have increased ascertainment of partner treatment more than total partner treatment in these trials is uncertain.
- (4) PDPT or other means to treat partners without requiring the partners to seek prior medical evaluation increases the proportion of partners treated and decreases STI reinfection rates in persons with gonorrhea or chlamydial infection. This conclusion is based on findings from three randomized controlled trials,⁵⁻⁷ all of which reported increased proportions of partners treated per index patient report and two of which found significantly lower rates of infection at follow-up among persons given PDPT. The third trial found a nonsignificant trend toward lower rates of infection at follow-up among women given PDPT. Findings from two observational studies also support this conclusion.^{84,85} Of note, the benefits of PDPT in women with trichomonas are less clear; a randomized controlled trial of PDPT for trichomonas found no difference in reported partner treatment or infection at follow-up in women randomized to PDPT compared to those who were managed with counseling and patient referral of partners.⁸⁶ In contrast, a randomized controlled trial among women treated for trichomoniasis with tinidazole found that routine treatment of the male partners significantly decreased rates of reinfection in the female index patient compared to no such treatment of male partners, demonstrating that effective partner notification for trichomonas does affect index patient reinfection rates.⁸⁷

Other low-intensity interventions include routine follow-up calls and contact slips for patients to give to their sex partners. A randomized controlled trial conducted among 65 college students in a rural Midwestern town in the United States found that routine follow-up calls could

increase the proportion of partners treated,⁸⁸ a finding that is supported by a UK study in which routine telephone follow-up with index patients with chlamydial infection appeared to result in more partners seeking care, compared to asking index patients to return to the clinic.⁸⁹ Although contact slips are a longstanding component of PN programs, relatively little has been done to evaluate them. Published data on this subject suggest that fewer than 50%, and often less than 20%, of contact slips distributed to index patients are typically returned to STD clinics.^{38,78,90-92} Three recent studies have investigated the utility of contact slips that include some counseling or educational message. In two randomized controlled trials, Kissinger found that using a contact slip that contained a small amount of information about the STI was superior to patient referral alone in men with NGU⁷ but was inferior to patient referral alone in women with trichomoniasis.^{86,93} Wright compared two different contact slips used during different time periods among persons with chlamydial infection in a London GUM clinic; one contained disease specific information and the other did not. She found that more partners attended the clinic when a contact slip with infection specific information was used.⁹⁴

INTERNET-BASED PARTNER NOTIFICATION

Since the mid-1990s, the Internet has emerged as an important avenue through which persons with STI, particularly MSM, meet sex partners.⁹⁵⁻⁹⁷ DIS have successfully used the Internet to trace the sex partners of persons with syphilis,^{98,99} and many patients are interested in using the Internet to notify partners without direct assistance from public health staff.¹⁰⁰ An Internet site, inSpot (<http://www.inspot.org/>), developed by a nonprofit group with funding from the San Francisco Department of Health, has been used to allow persons with STIs to anonymously or confidentially notify their sex partners. During a 3-month period in 2005, 2216 persons sent 3562 notification cards using the Internet site. In 1 month, at least 5 persons seen in the San Francisco STD clinic reported receiving an email notification card.¹⁰¹ It is uncertain whether the Internet site increased the numbers of partners notified or treated.

NETWORK APPROACHES TO PARTNER NOTIFICATION

Over the course of the last 2 decades, partner notification studies have been used to better understand sexual networks, with the implied idea that such an understanding might help direct disease control interventions.¹⁰² To date, new network insights have helped inform modeling efforts but have probably had relatively little practical impact on disease control activities. However, the notion that risk networks might be

exploited for the purpose of STI case-finding has a long history in partner notification programs, many of which have included efforts to test cases' nonsexual contacts (i.e., "suspects") as well as the social and sexual contacts named by uninfected persons initially identified through partner notification activities (i.e., "associates"), a process called cluster tracing or cluster case finding.¹⁰⁵ More recently, increasing research on sexual networks has prompted renewed interest in focusing on social networks as a means to identify persons with undiagnosed syphilis or HIV.¹⁰² Such efforts have met with mixed success. Studies conducted in the 1990s reported interviewing between 9.1 and 500 syphilis cases in order to identify one new case of syphilis among suspects or associates.^{104–108}

Peer referral is a variant on traditional cluster tracing and involves recruiting persons from an at-risk social network to refer other members of the network for HIV or STI testing. To the extent that recruited peers are given an opportunity to become recruiters, it is similar to respondent driven sampling, a procedure sometimes used to sample hard-to-reach populations.¹⁰⁹ Peer recruiters are typically given some incentive for referring others. A small study of HIV-positive patients treated in an inner city Los Angeles HIV clinic suggested that this approach might be effective. In that study, 31 HIV-positive patients referred 79 peers for testing and counseling, of whom 37 (47%) tested HIV positive.^{110,111} More recently, a preliminary evaluation of nine small, CDC-funded peer referral programs conducted by community-based organizations (CBOs) reported that 46 (5.7%) of 814 peers referred by 133 recruiters had previously undiagnosed HIV infection.¹¹² A study of peer referral in Seattle, WA, identified 22 new cases of HIV among 438 peers referred over a 29-month period and reported that peer referral was cost-effective relative to other approaches to HIV case-finding.¹¹³

CONCLUSIONS

The approach to partner notification in high-income nations is now in flux. The emergence of *C. trachomatis* as the most common bacterial STI, the continued HIV epidemic, rising rates of syphilis among MSM, and increased skepticism about the effectiveness and feasibility of applying traditional, labor-intensive approaches to partner notification to all persons with STI have prompted a renewed interest in partner notification research that emphasizes applying variable approaches to larger populations. Although existing data supporting the efficacy of HIV partner notification are limited, they suggest that resource-intensive efforts spearheaded by public health professionals should prioritize persons with HIV. The role of public health professionals in partner notification for other STIs is less certain. Because the number of syphilis cases in most high-income nations remains small, efforts involving intensive investigations by health department staff are feasible. But the efficacy of such efforts among

MSM, now the majority of all early syphilis cases in the United States, is uncertain.⁴¹ Approaches to partner notification that rely on traditional, intensive interviews with public health staff cannot be applied to all persons with gonorrhea or chlamydial infection in most nations. How to best use tools such as PDPT, mailed specimen collection for partners, and less-intensive clinic-based counseling efforts is uncertain, but these tools offer promise as a means to improve partner notification outcomes.

PARTNER NOTIFICATION IN LOW-INCOME NATIONS

Relatively little data are available on current partner notification practices or the efficacy of partner notification in low-income nations. One study, conducted in Chennai, India, found that only 27% of patients diagnosed with STIs in diverse health-care facilities were advised to notify their partners.¹¹⁴ A second study, conducted by the same investigators in Chennai compared how providers and simulated patients reported that a case of STD was managed. Eighty-eight percent of clinicians reported telling patients to notify their partners, but only 33% of patients reported discussing partner notification with their diagnosing clinician; 22% of simulated patients were prescribed medication to give to their partners.¹¹⁵ Studies utilizing simulated STD patients conducted in Peru, Gambia, and Ghana found that pharmacy workers advised fewer than 50% of patients that their partners required treatment or medical evaluation.^{116–118}

Studies evaluating the efficacy of partner notification practices for bacterial STIs or STD syndromes have usually focused on patient referral, typically aided by the use of contact slips, in patients seen in STD clinics or prenatal care clinics. Investigators have generally ascertained outcomes by counting the number of contact slips returned. Summarizing the findings of these studies is complicated by the fact that some investigators have reported epidemiologic indices (for definition, see Table 54-1) as outcomes, while others have reported the total proportion of partners treated. Results from studies evaluating patient referral have been highly variable, with epidemiologic indices varying from 0.13 to 0.7^{119–123} and the proportion of partners treated ranging from 20% to 67%.^{124–131} As in high-income nations, patient referral appears to be most successful among female index cases and in persons in more stable relationships.^{121,127,128,131,132} Studies have also associated greater patient referral success with pregnancy¹²¹ and with genital ulcer disease as opposed to other STD syndromes.¹³⁰ A study conducted in China found that feeling stigmatized by an STI was associated with a reduced willingness to notify spouses.¹³¹

Virtually all studies evaluating partner notification for HIV conducted in low-income nations have involved women seen in antenatal or postpartum care clinics in sub-Saharan Africa. Results have been variable, with 17–86% of

women reporting that their partners were notified. Most studies have reported that index patients inform half or fewer of the partners of their possible exposure to HIV,^{133–137} and that fewer than half of partners believed to have been notified are known to have been tested.^{138,139} Successful HIV partner notification has been associated with greater use of antiretroviral drugs to avoid perinatal HIV transmission, greater adherence with advice to avoid breastfeeding, and higher levels of condom use¹⁴⁰ and could potentially increase a couples' interest in subsequent contraception. Commonly cited barriers to notifying partners include fear of abandonment, rejection, discrimination, violence, or being accused of infidelity.¹³⁶ A review of nine studies assessing the outcomes of HIV partner notification among women in low-income nations found that adverse events occurred in 4–28% of cases, with violence reported by 4–15% of women.

These studies did not report how often these women were victims of domestic violence before disclosing their HIV status to their partners, making the results difficult to interpret.^{136,137} To date, studies of HIV partner notification in women have not included efforts to promote disclosure to partners, and it seems likely that women who notify their partners do so because they feel safer in their relationships than women who do not notify partners. As a result, encouraging more women to disclose their HIV status to partners could result in higher levels of domestic violence. The existing literature on HIV partner notification in low-income nations is notable for the absence of data on how often men notify their partners of their infection, and for the paucity of data from continents other than Africa.

Table 54-6 summarizes studies comparing different approaches to partner notification in developing nations. All but

Table 54-6. Experimental and Comparative Studies of Different Approaches to Partner Notification in Developing Nations

Author (Year)	Population	Design	Intervention	Outcome	Comment
Ogunbanjo (1986) ¹⁵³	64 male STD clinic patients with gonorrhea in Ibadan, Nigeria	RCT	Counseling by health advisor vs. counseling by health advisor plus 5–7 min of additional counseling by a physician	Five partners in counseling group and 10 in experimental counseling group evaluated at clinic	Poor power to detect a difference
Hira (1990) ¹⁵⁴	110 RPR positive women receiving prenatal care in health centers in Lusaka, Zambia	Comparison of birth outcomes in three intervention and three control clinic populations	Health education intervention	Partners treated in 29/74 (39%) intervention clinic women vs. 3/36 (8%) control clinic women	Although populations of clinics were similar overall, partner notification data before the intervention is not presented
Njeru (1995) ¹⁵²	254 Kenyan patients at General medicine or family planning clinic (37% men)	Comparison of PN outcomes in two time periods	5–10 min of individual counseling and collection of names of sex partners. All patients asked to return	33% of partners confirmed as having been treated during intervention period vs. 15% in preintervention period	Data for intervention period limited to 93 (37%) or 254 persons recruited for study, possibly biasing results Index patients reported they notified 58% of partners, and that 40% of partners were treated

(Continued)

Table 54-6. (Continued)

Author (Year)	Population	Design	Intervention	Outcome	Comment
Faxelid (1996) ¹⁵¹	386 Zambian STD clinic patients (76% men) with gonorrhea, chancroid, LGV, syphilis, or trichomonas	RCT	10–20 min of individual counseling, contact slips, and offer of provider referral vs. advice to refer partner for treatment	Per index patient report, more partners were notified (87% vs. 63%) and treated (82% vs. 55%) in the intervention group than in the control group	Index patients not typically given treatment if they did not refer a partner. Impact appeared greater for male index patients
Nuwaha (2000) ¹⁴¹	383 STD clinic patients with STD syndromes in Kampala, Uganda, (52% men). Women with only bacterial vaginosis or candida excluded	RCT	Patient referral with contact slips vs. PDPT	74% of PDPT reported treated vs. 34% of patient referral partners seen in clinic	Primary study outcome ascertained by different mechanisms for two arms of study
Harrison (1999) ¹⁴²	Five pairs of clinics in the Hlabisa health district, South Africa	Clinic-level randomized trial	Clinician training and supervision to improve syndromic management and use of syndrome specific treatment packets that included partner referral cards	Proportion of clinic patients who reported being asymptomatic partners of persons with STD higher in control clinics (8% vs. 5%, RR 0.79, 95% CI 0.68–0.92)	Difference between intervention and control clinics not significant in multivariate analysis. Intervention improved other aspects of STD care
Mathews (2002) ¹⁵⁵	335 STD clinic patients (40% male) with STD syndromes in Kwazuku Natal, South Africa	Comparison of two time periods	Educational video shown in clinic waiting area, nurse educational training, and referral cards compared to referral cards alone	Epidemiologic index in intervention vs. control period were 0.27 vs. 0.20 (95% CI for difference –0.05–0.17)	
Garcia (2003) ¹¹⁶	Seven pairs of districts in Lima, Peru	Community-level randomization of pharmacy workers. Workers in 884 intervention pharmacies participated. Outcomes ascertained using simulated patients	Pharmacy worker training in STD syndromic management	At 3 mo follow-up, 46% of simulated patients in intervention pharmacies and 15% in control pharmacies were advised that partners needed treatment ($p = 0.004$)	Impact on partner treatment in real patients not evaluated

one of these studies was undertaken in sub-Saharan Africa. Five studies evaluated brief counseling or educational interventions, four of which reported significant improvements in the proportion of partners treated or a trend toward such an improvement. A study of PDPT undertaken in Uganda reported higher rates of partner treatment in persons given medication for their partners compared to persons who were simply advised to refer their partners for care but employed different methods to ascertain outcomes in intervention and control groups, possibly biasing the result.¹⁴¹ Two clinic or community-level trials have evaluated partner notification as part of larger, more complex interventions trials. Harrison evaluated an intervention designed to improve clinicians' syndromic management of STI that involved training and the use of syndrome specific treatment packets; slightly lower proportions of clinic patients presented as asymptomatic partners of persons with STI in intervention than in control clinics,¹⁴² suggesting that the intervention did not increase partner notification. Garcia evaluated an intervention designed to improve pharmacy workers' syndromic management of STI in Lima, Peru. She found that trained workers were more likely to advise simulated patients to refer partners than workers randomly assigned to a control training unrelated to STI.¹¹⁶

In summary, due to resource limitations, patient referral is often the only feasible partner notification method in low-income countries. Limited data suggest that the outcomes can be improved through appropriate counseling and the use of contact slips. The information on these slips should be easy to understand and issues of confidentiality should be emphasized, since some persons in low-income countries are illiterate and might seek reading help from relatives and friends. Given the low specificity of vaginal discharge as an STD syndrome, it seems reasonable to prioritize HIV, urethritis, and genital ulcer disease for scarce partner notification resources in countries where microbiologic diagnoses are not available. Particularly as antiretroviral medications become more widely available, improving partner notification for HIV should be a public health and research priority.

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PART 9

Management of STD Syndromes in Women

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Lower Genital Tract Infection Syndromes in Women

King K. Holmes, Walter E. Stamm, and Jack D. Sobel

Differences in male and female anatomy and reproductive physiology account for the greater risk of complications of certain STDs in women and also for the greater difficulty in differential diagnosis of urogenital infections in women. In fact, the difficulty in diagnosing sexually transmitted urogenital infections in women undoubtedly results in delay of proper therapy, which further contributes to the higher risk of complications in women and to the further spread of infection in the community.

In heterosexual men, gonococcal and chlamydial infections appear limited to the anterior urethra in most cases, although the frequency of extension of infection to the posterior urethra and genital adnexae has not been well studied. Symptoms and signs of urethral discharge readily recognizable by both the patient and the clinician have come to represent the most monotonous aspect of venereology; knowledge of variations on this theme is limited.

On the other hand, in women several STD pathogens, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and herpes simplex virus (HSV), have predilection for infection of the urethra, cervix, and rectum simultaneously, producing more variable symptom patterns, each with a wide range of differential diagnostic possibilities. Furthermore, infections at any one site can produce poorly localized symptoms easy to erroneously ascribe to involvement of a contiguous site. For example, infections of the bladder, urethra, or vulva can produce similar symptoms, such as dysuria or dyspareunia. Finally, lack of appreciation of the differing clinical signs of specific genital infections in women can often be attributed to inadequate inspection of the genitalia because of poor clinical skills, paucity of speculums in many developing countries, or simple reluctance to perform the examination (Fig. 55-1). These factors account for the vague terms still used to describe some of the urogenital syndromes in women, such as “nonspecific genital infection” and “lower genital tract infection”—terms that pose a barrier both to understanding these syndromes and to accurate clinical diagnosis and therapy.

The positive predictive values of symptoms or signs for having an STI is a function both of the prior probability of STI in the individual being tested, and of the validity of the symptoms or signs as indicators for such infections. The prior probability of STI in the individual can be measured by risk assessment (see Chapter 48), addressing individual-level risk factors such as history of an STI; history of exposure to an STI; history of individual-level risk behavior(s); age and gender; of partnership-level characteristics such as marital status; and of sexual network and population-level risk, often assessed indirectly through sociodemographic risk markers, such as ethnicity, place of residence, etc. The validity of symptoms and signs as indicators is a function both of (1) the validity of the symptom or sign per se as predictive of one or more specific STIs (e.g., profuse urethral discharge or genital ulceration on physical examination by an STD clinical expert are both highly predictive of certain STI, whereas symptoms of generalized rash, lower abdominal pain, and vaginal bleeding are not) and (2) the validity of ascertainment of the presence of particular symptoms or signs, based on the experience, skill, biases, and efforts of the clinician.¹

Improved detection of gonococcal and chlamydial infections in women by new laboratory tests represents one of the major advances in gynecology and STD during the past 25 years. Beginning in the 1970s, diagnosis of gonorrhea in women by culture became widely available in industrialized countries; and during the past 15 years newer tests for chlamydial and gonococcal infections have also become increasingly available. However, in developing countries there is still almost total reliance on syndromic management and on contact tracing to detect and reduce the “female reservoir” of these infections. Because of the expense and limited availability of facilities for specific detection of *N. gonorrhoeae* or *C. trachomatis* in developing countries, there has been an unwarranted sense of futility about the prospects for diagnosis of lower genital infections in women. Uncertainty about the usual etiologies of inflammatory conditions of the urinary tract, vulva, vagina, and cervix in women, the lack of consistent



FIGURE 55-1. Pelvic examination performed by a clinician not trained in sexually transmitted diseases.

application of available laboratory testing where needed, and the failure to exclude coinfections when analyzing the clinical manifestations of any one particular infection add to the confusion and vagueness concerning classification of urogenital inflammation in women. Clinicians experience further difficulty in differentiating true inflammatory conditions from noninflammatory conditions, including functional, psychosomatic genitourinary complaints.

Although the etiology of certain genitourinary and anorectal inflammatory conditions in women is still not well understood, it is becoming increasingly possible to presumptively identify many common and potentially serious STDs in women on the basis of clinical observations of symptoms and signs, supplemented with selective use of relatively simple screening and confirmatory laboratory tests. More precise diagnosis of urogenital infection in women could make a major contribution to improved control of several important STDs in the community, and should lead to improved management strategies for genital infection in the individual patient. An etiologic classification of urogenital inflammatory and “pseudoinflammatory” syndromes in women is presented in [Table 55-1](#); also, each syndrome is further discussed

Table 55-1. Etiologic Classification of Lower Urogenital Inflammatory or “Pseudoinflammatory” Syndromes in Adult, Premenopausal Women

Syndrome	Usual Microbial Etiology	Other/Idiopathic
Cystitis	Coliform bacteria <i>S. saprophyticus</i>	Interstitial cystitis
Urethritis	<i>N. gonorrhoeae</i> <i>C. trachomatis</i> HSV	
Vulvitis	HSV <i>C. albicans</i>	Vulvar papillomatosis Vulvar vestibulitis Essential vulvodynia Vulvar necrotizing fasciitis
Bartholinitis	<i>N. gonorrhoeae</i> <i>C. trachomatis</i> Facultative or anaerobic bacterial infection	
Vaginitis/Vaginal discharge	<i>T. vaginalis</i> <i>C. albicans</i> <i>G. vaginalis</i> , mycoplasmas, and anaerobic bacteria	Desquamative inflammatory vaginitis Toxic shock syndrome Intravaginal use of detergents, certain microbicides, chemicals, physical agents. Chronic tampon use, other retained foreign bodies Allergic vaginitis
Endocervicitis	<i>C. trachomatis</i> <i>N. gonorrhoeae</i> <i>M. genitalium</i> HSV	
Ectocervicitis	HSV <i>T. vaginalis</i> <i>C. albicans</i>	

in this chapter. Chapter 49 introduces an approach to the anatomy and physical examination of the female genital tract and provides useful background for this chapter. Chapters 42, 43, and 45 discuss the three most common nonviral vaginal infections (bacterial vaginosis [BV], trichomoniasis,

and vulvovaginal candidiasis, respectively), which are therefore not covered in detail here.

CYSTITIS AND URETHRITIS

■ EPIDEMIOLOGY AND ETIOLOGY

In the United States, women with symptoms of lower urinary tract infection (UTI) account for an estimated 7 million office visits to physicians in office practice each year.² In a community-based study in England, symptoms of dysuria and frequent urination occurred in as many as 20% of women per year.³ A prospective study of young women in Seattle initiating contraceptive use demonstrated an incidence of acute cystitis of 0.5–0.7% per year.⁴ Thus, this infection is exceedingly common and its incidence is probably underestimated by surveys dependent on office visits. In addition, recurrent infection is common, occurring in 25% of young women following a first UTI.⁵

Symptoms of dysuria or frequency in women can usually be attributed to acute bacterial cystitis, urethritis, or vulvitis. The incidence of acute bacterial cystitis is highest in women 20–25 years of age, and this condition is a particularly common cause of urinary symptoms among sexually active young women. Recent studies have identified sexual intercourse, spermicide or diaphragm-spermicide use, a history of a prior UTI, and recent antimicrobial exposure as independent risk factors for acute cystitis.^{4,6,7} Almost identical risk factors are seen in young women with pyelonephritis.⁸ Among 263 women presenting to the Seattle STD clinic with urinary symptoms alone, or with both urinary and vaginal symptoms, but without clear signs of vaginal infection, 69 (26%) had “significant” bacteriuria ($\geq 10^5$ organisms/mL of urine).⁹ A separate study of female students at the University of Washington showed that the traditional criterion of $\geq 10^5$ uropathogens per mL of urine is insensitive for diagnosis of acute bacterial cystitis in women who present with dysuria, frequency and pyuria.¹⁰ This criterion was originally established in studies of women with acute pyelonephritis, and in surveys of asymptomatic women who have a low prevalence of bladder infection. However, among female students with symptoms of dysuria, specimens obtained by suprapubic aspiration or urethral catheterization usually confirmed the presence of bladder infection, when voided urines contained lower concentrations of bacteria, ranging from 10^2 to $<10^5$ bacteria per mL.¹⁰ Subsequent studies have confirmed these observations and it is now accepted that among women with dysuria and frequency, from one-third to one-half of those with acute bacterial cystitis have “low-count” bacteriuria, with cultures yielding uropathogenic bacteria in concentrations between 10^2 and $<10^5$ organisms per mL of urine. Almost all episodes of bacterial cystitis, irrespective of the urinary colony count, are accompanied by pyuria, and about

20% of patients have gross hematuria. The etiologic agents in women with acute uncomplicated cystitis are highly predictable, with *E. coli* causing 80% of cases. *S. saprophyticus* is the second most common pathogen, causing 5–15% of cases.¹¹ This organism has a seasonal variation in incidence (summer fall) and preferentially infects adolescents. Infections due to *E. coli* and *S. saprophyticus* cannot be distinguished clinically. *Proteus mirabilis*, *K. pneumoniae*, *Enterobacter* and enterococci collectively cause about 10% of cystitis cases.

The syndrome of dysuria and frequency in women whose urine does not contain $\leq 10^2$ of the preceding uropathogens has been called the “urethral syndrome” or, in the presence of pyuria, the “dysuria-sterile pyuria syndrome.”^{12–14} In a 1980 study of female university students with the urethral syndrome who had sterile bladder urines, the etiology was found to be related to the presence or absence of pyuria. Infection with *C. trachomatis* was demonstrated in 10 of 16 women with pyuria but in only 1 of 16 women without pyuria ($p = 0.002$).¹² Pyuria was defined as more than eight leukocytes per mL of uncentrifuged midstream urine, approximately equivalent to 10 leukocytes per $400\times$ microscopic field when 10 mL of urine have been centrifuged and the sediment resuspended in 1 mL of urine for microscopic examination under a coverslip. *N. gonorrhoeae* was not associated with the urethral syndrome in this population of university students.

However, in a 1970s study of indigent women attending a hospital emergency room, gonococcal infection was significantly correlated with dysuria, accounting for 8 (61%) of 13 cases whose urine samples contained $<10^5$ uropathogens per mL.¹⁵ Cultures for *C. trachomatis* were not obtained in that study. The role of *Mycoplasma genitalium* in women with dysuria and pyuria remains undefined, though one recent Swedish study of STD clinic patients and their sex partners¹⁶ found a significant association of *M. genitalium* with urethritis (mostly nonsymptomatic pyuria), as well as with cervicitis in women. In another study,¹⁷ a nonsignificant trend toward an association with increased numbers of polymorphonuclear (PMN) leukocytes in urethral smears was found. Thus, among young women with the urethral syndrome, and without bladder infection by uropathogens, the relative importance of gonococcal and chlamydial infection probably depends on the relative background incidence of these two infections in young women. HSV infections (especially primary infection), although not commonly found among women with the urethral syndrome, clearly can produce urethritis, dysuria, and pyuria in young sexually active women, and can be mistaken for bacterial cystitis if vulvar lesions are not prominent or carefully sought. Dysuria in women who do not have bacteriuria or urethral infection with STD pathogens is often attributable to vulvar inflammation caused by genital herpes or candida vulvovaginitis.^{18–20} For example, Komaroff et al. reported that in

young women, dysuria was attributable to vaginitis more often than to UTI because vaginitis was so much more common than UTI.^{20,21}

■ DIAGNOSIS AND THERAPY

The characteristic features that help to differentiate the three major conditions that can result in dysuria in women are summarized in Table 55-2. The medical history, physical examination, and simple laboratory tests are all helpful in the differential diagnosis of dysuria. The optimal diagnostic approach to dysuria and/or frequency varies, depending on the clinical setting and the likelihood of STD. Thus, in STD clinics, family planning clinics, teen clinics, or other settings where the prevalence of STDs is high, speculum exam is warranted to rule out STDs. In clinical settings or individual patients where the likelihood of an STD is low, the pelvic exam can be omitted. Urinalysis should be performed in all women with dysuria or frequency to detect pyuria. Microscopic examination of unspun urine by using a hemocytometer or calibrated chamber is the most sensitive and specific test for the presence or absence of pyuria.²² Alternatively, leukocytes can be counted after centrifugation of the urine followed by resuspension of the sediment in

1 mL of urine and enumeration of white cells in one to two drops of urine placed on a microscope slide under a coverslip. This method is slightly less accurate than the first method. Another simple test for pyuria involves the use of a “dipstick” to detect leukocyte esterase in urine. Although the sensitivity of the leukocyte esterase test appears lower than that of the chamber microscopy method for detection of pyuria, the simplicity and low cost of the test make it useful for screening women with dysuria in the clinic.^{22,23} Among women with dysuria, pyuria usually is indicative of acute bacterial cystitis in women at low risk for STDs and may indicate either cystitis or urethritis in women at high risk for STDs. If pyuria is found microscopically or by leukocyte esterase test, the urine can also be examined microscopically for bacteriuria, either by (1) preparation of a Gram’s stain of a fresh, midstream, clean-catch, uncentrifuged urine specimen and examination with an oil immersion lens (the presence of one bacterial organism per field is correlated with quantitative isolation of $\geq 10^5$ bacteria per mL of urine); or (2) by examination of unstained, centrifuged urinary sediment of fresh urine under high dry objective (detection of 100 organisms per field also correlates well with isolation of $\geq 10^5$ bacteria per mL of urine). These simple procedures should be readily available in any clinic. However, bacteria present in concentrations of

Table 55-2. Characteristic Features That Differentiate the Three Major Causes of Dysuria in Women

	Acute Bacterial Cystitis	Urethritis	Vulvitis
Predisposing factors	Previous cystitis Spermicide onset of symptoms within 24h after intercourse	New sex partner	History of genital herpes Partner with genital herpes Antibiotic use History of recurrent vulvovaginal candidiasis
Symptoms	Internal dysuria Duration of symptoms ≤ 4 days Frequency and urgency Gross hematuria	Internal dysuria Duration of symptoms often ≥ 7 days with chlamydial urethritis	External dysuria Vaginal discharge Vulvar irritation, burning, pruritis, or lesions
Signs	Suprapubic tenderness	Endocervical mucopus Vulvar lesions (with herpes)	Vulvar lesions Vulvitis Curdlike vaginal exudate
Laboratory	Pyuria Microscopic hematuria Rapid nitrite test Urine Gram stain Urine culture	Pyuria Urethral discharge or Bartholinitis Endocervical exudate Cervical and urethral tests for <i>C. trachomatis</i> and <i>N. gonorrhoeae</i> Test lesion for HSV	No pyuria Test lesion for HSV Test vaginal discharge for <i>C. albicans</i>

$<10^5$ per mL of urine are not likely to be seen on Gram's stain; hence this is not a sensitive test for bacteriuria. The use of urine cultures to confirm the diagnosis of acute cystitis, once universally recommended for all suspected cases, is now considered unnecessary for most women. In women with typical symptoms and signs of acute cystitis and a low risk of STDs, the uropathogens that would be identified by culture and their antimicrobial susceptibility profiles are highly predictable, obviating the need for culture (see Table 55-2). Cultures are most useful to confirm the diagnosis in cases of persistent or recurrent symptoms of UTI, when there are signs of pyelonephritis or other complications, or when there is a history of recent use of antimicrobials. If the patient has pyuria without bacteriuria and is considered to be at risk for STD, or has signs of mucopurulent endocervicitis, specimens from the endocervix and urethra should be tested for *N. gonorrhoeae* and *C. trachomatis*.

The diagnosis of urethritis owing to *C. trachomatis*, *N. gonorrhoeae*, or HSV rather than the diagnosis of bacterial cystitis is favored by a recent history of acquiring a new sex partner. Genital herpes is suggested by history of genital herpes, exposure to a partner with genital herpes, or the presence of genital lesions (which can also result in external dysuria). Symptoms or signs of abnormally yellow vaginal discharge, or pelvic pain or tenderness, or other signs of pelvic inflammatory diseases (PIDs) in the woman with internal dysuria suggest gonorrhea or chlamydial infection. Infection with *N. gonorrhoeae* or *C. trachomatis* is suggested by the presence of expressible urethral discharge (Fig. 55-2), inflammation of Skene's glands (Fig. 55-3), Bartholin's glands (Fig. 55-4), mucopurulent cervicitis (MPC) (Figs. 55-5 and 55-6), or proctitis. Findings that favor cystitis rather than urethritis include a history of previous cystitis, history of onset of symptoms within 24 hours after sexual intercourse, prominent frequency

or urgency as well as dysuria, and history of gross hematuria.^{7,12} Cystitis is also suggested by a history of current spermicide or diaphragm use, which appear to increase the risk of cystitis in young women by altering the vaginal bacterial



FIGURE 55-3. Purulent discharge from Skene's gland. This can be caused by *N. gonorrhoeae* or *C. trachomatis*.



FIGURE 55-2. Urethritis in a female caused by *N. gonorrhoeae*. Pus can be expressed from the urethral orifice by compressing the urethra against the pubic symphysis.



FIGURE 55-4. Acute Bartholin's glanditis caused by *N. gonorrhoeae*. Pus is expressed from the orifice of Bartholin's duct, which opens in the posterior portion of the labia minora and runs posteriorly toward the rectum.

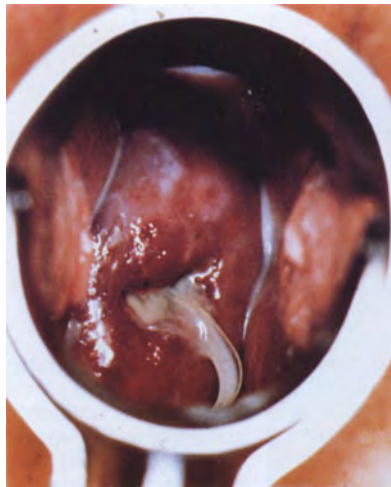


FIGURE 55-5. Mucopurulent cervicitis caused by *C. trachomatis*. Note pus mixed with mucus (indicating source from the endocervix); also note ectopy, edema, and bleeding.

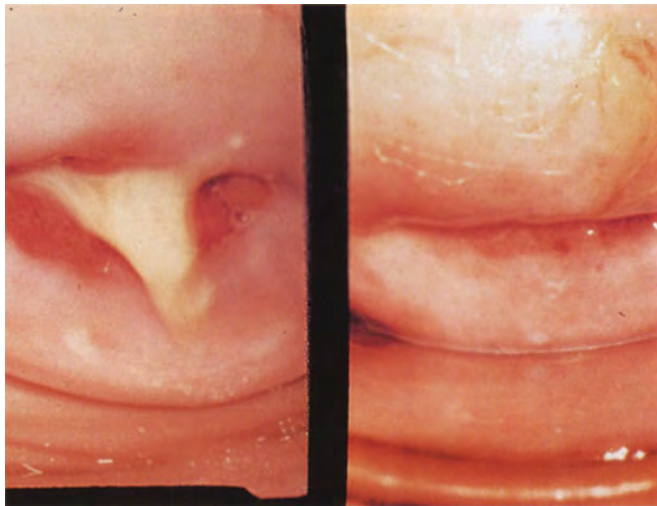


FIGURE 55-6. Mucopurulent cervicitis caused by *C. trachomatis*, before and after treatment with doxycycline.

flora,^{4,6} but which may be associated with decreased risk of cervical infection. Acute onset of severe dysuria leading to consultation within 4 days after onset favors a diagnosis of bacterial cystitis (or perhaps gonococcal urethritis), whereas a history of gradual onset of milder symptoms and long duration of symptoms before seeking therapy (≥ 7 days) suggests chlamydial urethritis.¹² Suprapubic tenderness and microscopic hematuria are also highly suggestive of cystitis in the acutely dysuric patient.¹²

External dysuria (vulvar burning during urination) owing to vulvitis is produced most commonly by genital herpes or by vulvovaginal candidiasis.^{19,20} Perhaps the less common conditions discussed in Chapters 62 and 64 can also produce this symptom. With trichomoniasis, no significant correlation was found with dysuria or frequency, after adjustment for coinfections.²⁴ The patient with external dysuria should be questioned about history of genital herpes or exposure to

herpes, or about risk factors for vulvovaginal candidiasis, such as recent antibiotic use, or history of VVC.

Women with clinical findings suggestive of uncomplicated bacterial cystitis (or with microscopic evidence of pyuria and bacteriuria as well) should generally be treated with a 3-day course of antimicrobial therapy.^{25,26} If the temperature exceeds 38.3°C (101°F), symptoms have been present for longer than 1 week, or there is costovertebral angle pain or tenderness, the presence of pyelonephritis should be considered, and longer treatment is needed.²⁶ Over 25% of coliform isolates from women with acute cystitis are currently resistant to sulfonamides, ampicillin, tetracyclines, and first-generation cephalosporins. These organisms, as well as *S. saprophyticus* generally remain susceptible to sulfamethoxazole-trimethoprim, trimethoprim alone, nitrofurantoin, the fluoroquinolones, or amoxicillin-clavulanic acid.²⁷ However, an increasing proportion (now up to 15–20% in the United States and even higher in southern Europe, Asia, and Israel) are now resistant to TMP/SMX, which limits the effectiveness of this agent in those areas where resistance is frequent.²⁸ Resistance to fluoroquinolones among *E. coli* strains causing acute cystitis remains infrequent in the United States but has increased to 5% or more in the same areas in which TMP resistance has increased.^{29,30} Thus, the clinician needs to know the epidemiology of resistance among *E. coli* strains causing cystitis in order to select empiric therapy.³¹ Three days of treatment with TMP, TMP/SMX, or a fluoroquinolone provides excellent results when treating acute cystitis caused by uropathogens sensitive to those drugs.²⁵ TMP or TMP/SMX should be used as the preferred empiric regimen in areas in which the prevalence of resistance does not exceed 20%.³¹ Specific regimens include trimethoprim (100 mg PO q12h); TMP/SMX (160 plus 800 mg q12h); ciprofloxacin (250 mg q12h); or levofloxacin 250 mg daily.²⁶ These 3-day regimens are more effective than single-dose therapy and are as effective as 7 days of therapy. Further, both cost and rates of side effects are lower than those seen with 7 days of therapy. However, β -lactams and nitrofurantoin generally provide better cure rates with 7 days of therapy than with 3 days. Despite appropriate antibiotic therapy, recurrent infections occur in 25–35% treated women, most commonly among women given amoxicillin or amoxicillin-clavulanic acid.^{5,27}

Recurrent infections should likewise be treated with a 3-day regimen of TMP/SMX or a fluoroquinolone such as ciprofloxacin or levofloxacin. There is no benefit in investigating most such women urologically or with imaging procedures as almost all are normal. If recurrences continue to occur, low dose antimicrobial prophylaxis is effective.³²

Women suspected of having urethritis owing to chlamydia (because of pyuria without microscopic evidence of bacteriuria, together with other compatible clinical or epidemiological findings) should be treated with azithromycin (1.0 gm) or with

a tetracycline regimen such as 100 mg doxycycline twice daily for 1 week while urine cultures are pending. The latter regimen was significantly more effective than placebo in curing symptoms of the urethral syndrome in women with pyuria and would also be adequate in many bladder infections caused by common uropathogens.¹² Male sex partners of women with suspected or confirmed gonococcal or chlamydial urethritis should be examined and tested to exclude urethral infection, or should be treated for exposure to these agents.

VULVOVAGINITIS AND VAGINAL DISCHARGE SYNDROMES

■ AGE-DEPENDENT DIFFERENCES IN VAGINAL ANATOMY, PHYSIOLOGY, AND FLORA

The normal anatomy, physiology, and microbial ecology of the vagina are age-dependent, and there are also obvious age-dependent differences in the source and microbial etiology of vaginal infections (see Chapters 8 and 42).³³ These factors account for very different etiologies of vaginitis in neonates, infants and toddlers, prepubertal girls, and pre- and postmenopausal adults.

During the first month of life, the neonatal vagina, still under the influence of maternal estrogen, is lined by stratified squamous epithelium. From about 1 month of age until puberty, the vagina is lined by cuboidal cells, and the pH of vaginal fluid is normally about 7. After puberty, under the influence of estrogen, the vagina becomes lined by stratified squamous epithelium containing glycogen (Fig. 55-7). With growth of facultative H₂O₂-producing species of lactobacillus, such as *L. crispatus* to concentrations of approximately 10⁹/mL of vaginal fluid, lactic acid is produced from

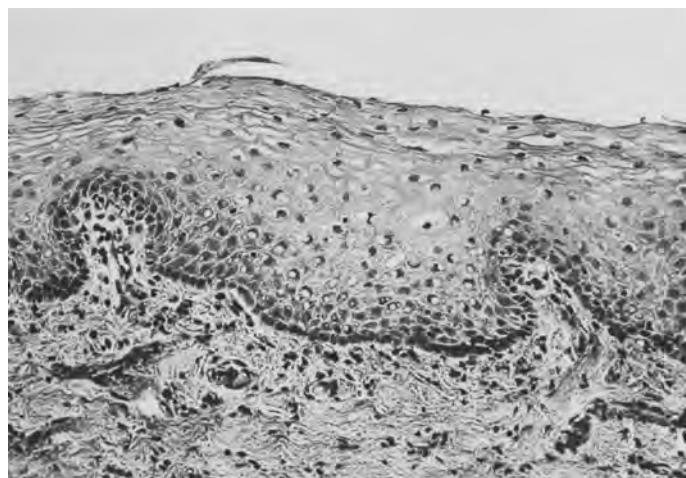


FIGURE 55-7. Normal adult vaginal epithelium, showing the basal cell layer with overlying stratum spinosum. Note the absence of an overlying stratum corneum. The transit time for cells moving from the basal layer to the superficial surface of the vaginal epithelium has been estimated to be about 4 days, perhaps one-third that of normal epidermis.

glycogen, and the pH falls to between 4.0 and 4.5 in normal adult women. The fall in pH, as well as the H₂O₂ production, are considered important in regulating the vaginal flora (see Chapter 18).^{34,35} The oxidation–reduction potential (Eh) at the surface of the vaginal epithelium is approximately 0 ± 50 mV in the absence of BV, but is much lower in BV.³⁶

The relative concentration of vaginal microbes has not been extensively characterized in neonates, infants, or prepubertal girls, but the facultative flora most often includes diphtheroids, *S. epidermidis*, γ-hemolytic streptococci, lactobacilli, and coliforms.^{37,38} Coliforms are more common in the vagina before puberty (especially among toddlers still in diapers) than after puberty, whereas the reverse is true for lactobacilli, which dominate the vaginal flora of normal postpubertal women.

■ VAGINITIS IN PREMENARCHAL GIRLS

The neonatal vaginal squamous epithelium resists perinatally transmitted *N. gonorrhoeae* and *C. trachomatis* but is susceptible to perinatally transmitted vaginal candidiasis. Among older infants, the cuboidal vaginal epithelium is susceptible to *N. gonorrhoeae* and *C. trachomatis* but is resistant to candidiasis. Vaginal shedding of *C. trachomatis* does indeed sometimes appear after about 1 month of age in infants who were exposed perinatally but is not generally associated with overt signs of vaginitis in young infants. Vaginal infection by *N. gonorrhoeae* is rare among infants, and with few exceptions it is thought to represent postnatal acquisition.³⁹

Among older premenarchal girls, the etiology of vaginal symptoms is correlated with puberty status and with the presence or absence of objective signs of abnormal vaginal discharge. For example, in a study of 54 premenarchal patients with suspected vaginitis and 52 age-matched controls, a microbial pathogen was isolated from the vagina from 14 of 26 with abnormal vaginal discharge, none of 26 with suspected vaginitis who had no vaginal discharge, and none of 52 control subjects (Table 55-3).⁴⁰ *N. gonorrhoeae* accounted for one-third of cases of abnormal discharges in prepubertal girls, whereas *C. albicans* or “yeast” was isolated only from those premenarchal girls who were considered to be pubertal (Tanner stages II, III, or IV) on the basis of breast growth.

Streptococcus pyogenes (group A β-hemolytic streptococci) and *Shigella* sp. are also recognized as causes of purulent or bloody vaginal discharge in prepubertal girls.^{41–44} Any species of *Shigella* may cause vaginitis in children, but *Shigella flexneri* has been most often implicated and represented a significantly higher proportion of isolates from the vagina than from all other sites in one retrospective study.⁴³ *Shigella* vaginitis is often chronic, causes a bloody vaginal discharge in about 50% of recognized cases, and is associated with

Table 55-3. Pathogens Isolated from Vaginal Cultures from 52 Premenarcheal Girls with Suspected Vaginitis and 52 Age-Matched Controls

Pathogens Isolated	Prepubertal		Pubertal		Control Subjects (n = 52)
	Discharge Present (n = 12)	Discharge Absent (n = 24)	Discharge Present (n = 14)	Discharge Absent (n = 2)	
<i>Strep. pyogenes</i>	0	0	1	0	0
<i>N. gonorrhoeae</i>	4	0	0	0	0
<i>Shigella sonnei</i>	1	0	0	0	0
<i>C. albicans</i> or "yeast"	0	0	8	0	0
<i>C. trachomatis</i> ^a	0	0	0	0	0

^aSpecimens from 27 of 36 prepubertal girls with suspected vaginitis were cultured for *C. trachomatis*.

From Paradise et al. Vulvovaginitis in premenarcheal girls: Clinical features and diagnostic evaluation. *Pediatrics* 1982; 10: 193.

diarrhea in only about one-quarter of cases. The predilection of shigella for prepubertal rather than adult vaginitis may be partly attributable to poor survival of this organism below a pH of 5.5.

The etiologic roles of group B *Haemophilus influenzae* and coagulase-positive staphylococci in prepubertal vaginitis are controversial. Group B streptococcal vulvovaginitis has been described in a case series of 13 adolescents and young adults.⁴⁵ As indicated in Table 55-3, no specific bacterial pathogen is found in a large proportion of prepubertal girls with abnormal vaginal discharge. However, intravaginal foreign body and poor perineal hygiene are among the leading predisposing factors in young girls, among whom *Enterobius vermicularis* (pinworm) is an acknowledged cause of vulvovaginitis. Although *C. trachomatis* has not been implicated as a common cause of prepubertal vaginitis, this agent was isolated from the vagina from about one-quarter of girls with gonococcal vaginitis and appeared responsible for post-gonococcal vaginitis following penicillin treatment in such cases.⁴⁶ The occurrence of *C. trachomatis* infection in prepubertal sexually abused girls has been documented in several studies (see Chapter 105).

VULVOVAGINAL SYNDROMES IN ADULT WOMEN

Vaginal infections in adult women ranked among the 25 most common reasons for consulting physicians in private office practice in the United States in a 1979 report from the U.S. CDC. The three most common types of vaginal infections

in adult women are BV, vulvovaginal candidiasis, and trichomoniasis (see Chapters 42, 43, and 45).⁴⁷

In the United States, the number of initial visits to private physicians' offices for trichomonal vaginitis declined slowly from an estimated 579,000 in 1966 to 190,000 in 1988, remaining fairly stable since then, with 165,000 visits in 2005.⁴⁸ However, the estimated number of new cases of trichomoniasis in the United States, is much higher—7.4 million cases in 2000.⁴⁹ Initial visits for other conditions classified as "vaginitis" (presumably including BV, not generally regarded as true vaginitis, vulvovaginal candidiasis, and undiagnosed cases of trichomoniasis) increased from an estimated 1,155,000 in 1966 to nearly 4.5 million per year during 1989, then declined to 3.1 million in 1997 followed by a steady increase to 4.1 million in 2005.⁵⁰ (Genital herpes is discussed in Chapter 24 and vulvovaginal papillomavirus infections in Chapter 28.)

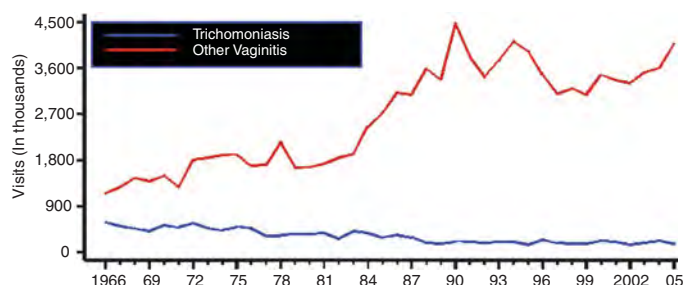


FIGURE 55-8. Trichomoniasis and other vaginal infections in women – Initial visits to physicians' offices: United States, 1966–2005. (Source: Adapted from CDC and IMS Health)

Other types of relatively well-characterized vaginitis syndromes in adults are attributable to microbial or chemical toxins or those associated with physical agents. The most serious and important to rule out is a destructive type of ulcerative vaginitis associated with vaginal infection by toxic shock syndrome (TSS)-associated *Staphylococcus aureus*^{51,52} and currently attributed at least in part to the action of the TSS toxin 1 on vaginal epithelial cells, upregulating several chemokine and cytokine genes, with influx of lymphocytes into vaginal tissue.⁵³ Vaginal ulceration and mixed infections have also been associated with the use of vaginal tampons or other retained foreign bodies.^{54,55} Cervical caps, detergent spermicides, such as nonoxynol-9, or a vaginal antiseptic preparation actually still sold commercially to consumers in some countries containing policresulín (a condensation product of metacresol sulfonic acid and formaldehyde) can cause vaginitis and vaginal ulceration,⁵⁶ as can various chemicals used in douching.^{57–59} Vaginal inflammation also has been associated with the use of various traditional vaginal preparations in some developing countries.^{60–62}

In postmenopausal women, vaginal symptoms are very prevalent, and the usual forms of vaginal infection need to be considered and differentiated from symptoms attributable to vaginal atrophy.^{63,64} Postmenopausal women have a relative depletion of vaginal lactobacilli, which in turn is associated with a higher frequency of vaginal colonization by *E. coli*.⁶⁵ The vaginal epithelium becomes thin with estrogen withdrawal, with decreased glycogen and increased pH. Lubrication occurs less often with sexual arousal, the introitus narrows, and the depth of the vagina decreases. These atrophic changes have been negatively correlated with frequency of intercourse and with circulating concentrations of gonadotrophins and androgens in postmenopausal women.⁶⁶ Treatment with intravaginal or systemic estrogen is effective. A possibly related syndrome, puerperal vaginal atrophy with dyspareunia, occurs postpartum in relation to the duration of breast-feeding and is sometimes treated with topical estrogen.

A number of other perplexing, chronic vulvovaginal syndromes tend to involve women older than those most often affected by STD.^{50,67} These include desquamative inflammatory vaginitis, a syndrome associated with purulent vaginal discharge, massive vaginal cell exfoliation with increased numbers of parabasal cells on vaginal smear, elevated vaginal pH, and gram-positive cocci on Gram's stain of vaginal fluid; this syndrome often responds to intravaginal 2% clindamycin cream.⁶⁸ Some experts view this syndrome as the most severe manifestation of what may represent a continuum of vaginitis caused by facultative or aerobic microbial pathogens. Various other forms of irritant or allergic vulvovaginitis have also been described, including those caused by various intravaginal medications, spermicidal products, personal hygiene products, local anesthetics, components of lubricants, latex condoms, and occasional instances in which vulvovaginitis seems to

follow intercourse with a particular sex partner.⁶⁹ There is some published evidence from small case series for localized vaginal hypersensitivity to human seminal plasma;^{70–74} and even for penicillin-induced anaphylactic reactions attributed to sexual exposure to partners who are taking penicillin.⁷⁵ Vulvar vestibulitis and essential vulvodysnia are other poorly understood vulvovaginal syndromes. Since the etiology of these syndromes remains unknown, treatment is empiric and should be as conservative as possible. Vaginal aphthae, like oral and esophageal aphthae, have been described among women with HIV infection. Among women who present vulvovaginal symptoms with or without dyspareunia, but without objective physical evidence of vulvitis or vaginitis, psychological factors may sometimes be involved.⁷⁶ In a recent analysis of a prospective clinical data base of women with chronic vaginitis, the most common diagnoses were contact dermatitis (21%), recurrent vulvovaginal candidiasis (20.5%), atrophic vaginitis (14.5%), and vulvar vestibulitis syndrome (12.5%).⁷⁷ Women with desquamative inflammatory vaginitis were older; those with vulvar vestibulitis more often complained of dyspareunia. Psychiatric disorders (44%) and atopy (43%) were common.

■ DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF VAGINAL DISCHARGE

Symptoms or signs of abnormal vaginal discharge are usually attributable to vaginal infection. As shown in [Table 55-4](#), in analyses adjusted for detection of cervical or vaginal infections, signs of increased profuse vaginal discharge among STD clinic patients were associated only with isolation of *T. vaginalis*; foul or fishy odor volatilized after adding 10% KOH to vaginal fluid was associated strongly with BV and also with *T. vaginalis*; and yellow color of vaginal discharge was significantly and independently associated with detection of HSV, *T. vaginalis*, *N. gonorrhoeae*, and *C. trachomatis*.¹⁸ The relationship of symptoms or signs of abnormal vaginal discharge to cervical infection has undergone reevaluation in recent years. Few recent studies have found statistically significant associations between symptoms of vaginal discharge and cervical infection; and where found, such associations could represent coincidental sexual acquisition of cervical infection together with trichomoniasis or BV. Several studies have demonstrated no association of cervical gonococcal or chlamydial infection with symptoms or signs of abnormally increased amount or abnormal odor of vaginal discharge.^{18,78,79}

In contrast, and not surprisingly, symptoms and signs of abnormal vaginal discharge have been predictive of vaginal infections. For example, in a large 1998–1999 survey of healthy women in rural Peru, over half of the women with symptoms of malodorous vaginal discharge, or signs of abnormal discharge, or both had BV or trichomoniasis⁸⁰ and thus could benefit from metronidazole therapy.

Table 55-4. Infections Associated with Signs of Vaginitis and Cervicitis on Physical Examination Among 779 STD Clinic Patients

	Unadjusted OR (95%CI) ^a	<i>p</i> -Value	Adjusted OR (95%CI) ^{a, b}	<i>p</i> -Value
Speculum examination—yellow vaginal discharge ^c (<i>n</i> = 69)				
GC	2.71 (1.73,4.24)	<0.01	1.76 (1.06,2.92)	0.03
CT	2.79 (1.81,4.3)	<0.01	3.06 (1.88,4.99)	<0.01
GC or CT	2.85 (1.97,4.12)	<0.01	2.79 (1.88,4.14)	<0.01
TV	4.34 (2.8,6.72)	<0.01	4.71 (2.84,7.79)	<0.01
BV	1.76 (1.25,2.46)	<0.01	1.30 (0.86,1.95)	0.21
TV or BV	1.94 (1.39,2.72)	<0.01	1.84 (1.27,2.69)	<0.01
CA	0.64 (0.42,0.96)	0.03	0.83 (0.65,1.06)	0.14
HSV	6.91 (3.1,15.4)	<0.01	11.52 (5,26.56)	<0.01
Speculum examination—profuse vaginal discharge (<i>n</i> = 56)				
GC	1.44 (0.7,2.96)	0.32	1.23 (0.57,2.67)	0.60
CT	1.11 (0.53,2.34)	0.78	1.33 (0.61,2.91)	0.47
GC or CT	1.05 (0.56,1.96)	0.89	1.14 (0.59,2.21)	0.70
TV	2.85 (1.54,5.25)	<0.01	2.64 (1.31,5.32)	0.01
BV	1.72 (1,2.96)	0.05	1.49 (0.79,2.81)	0.22
TV or BV	1.94 (1.12,3.36)	0.02	2.18 (1.19,4.02)	0.01
CA	1.22 (0.67,2.24)	0.51	1.20 (0.85,1.69)	0.29
HSV	1.92 (0.64,5.72)	0.24	2.34 (0.76,7.17)	0.14
Speculum examination—foul/fishy odor (<i>n</i> = 149)				
GC	1.58 (0.97,2.58)	0.07	0.79 (0.43,1.45)	0.45
CT	0.80 (0.47,1.37)	0.42	0.78 (0.4,1.52)	0.46
GC or CT	1.24 (0.82,1.87)	0.30	0.82 (0.5,1.34)	0.43
TV	5.63 (3.6,8.81)	<0.01	3.35 (1.91,5.88)	<0.01
BV	20.88 (12.31,35.44)	<0.01	18.97 (10.61,33.93)	<0.01
TV or BV	29.11 (15.41,55.01)	<0.01	33.95 (16.76,68.77)	<0.01
CA	0.57 (0.36,0.91)	0.02	1.02 (0.74,1.4)	0.90
HSV	0.91 (0.37,2.27)	0.84	1.47 (0.47,4.56)	0.51
Speculum examination—cervical mucopus (<i>n</i> = 182)				
GC	3.72 (2.37,5.83)	<0.01	2.81 (1.69,4.66)	<0.01
CT	5.64 (3.63,8.76)	<0.01	5.14 (3.2,8.24)	<0.01
GC or CT	4.94 (3.4,7.2)	<0.01	5.10 (3.43,7.59)	<0.01
TV	1.91 (1.23,2.97)	<0.01	1.86 (1.1,3.15)	0.02
BV	1.05 (0.74,1.49)	0.77	0.83 (0.55,1.25)	0.37
TV or BV	1.18 (0.84,1.66)	0.34	0.94 (0.64,1.39)	0.76
CA	0.68 (0.45,1.03)	0.07	0.90 (0.71,1.14)	0.39
HSV	2.83 (1.37,5.86)	0.01	4.20 (1.95,9.04)	<0.01
Speculum examination—cervical ectopy (<i>n</i> = 379)				
GC	1.33 (0.88,2)	0.18	1.33 (0.82,2.14)	0.24
CT	2.99 (1.95,4.58)	<0.01	3.48 (2.16,5.59)	<0.01
GC or CT	1.92 (1.37,2.68)	<0.01	2.23 (1.57,3.17)	<0.01
TV	0.68 (0.45,1.01)	0.06	0.67 (0.42,1.06)	0.09
BV	0.76 (0.56,1.02)	0.07	0.76 (0.54,1.06)	0.10
TV or BV	0.74 (0.55,0.98)	0.04	0.64 (0.47,0.88)	0.01
CA	1.01 (0.72,1.4)	0.97	1.02 (0.85,1.23)	0.83

Table 55-4. (Continued)

	Unadjusted OR (95%CI) ^a	p-Value	Adjusted OR (95%CI) ^{a,b}	p-Value
HSV	1.22 (0.54,2.75)	0.64	1.51 (0.63,3.65)	0.36
Speculum examination—cervical bleeding on touch (n = 286)				
GC	1.41 (0.91,2.18)	0.13	1.02 (0.63,1.65)	0.94
CT	2.62 (1.7,4.04)	<0.01	2.81 (1.77,4.45)	<0.01
GC or CT	1.78 (1.25,2.53)	<0.01	1.76 (1.22,2.54)	<0.01
TV	1.32 (0.87,2.02)	0.19	1.53 (0.95,2.46)	0.08
BV	1.34 (0.98,1.82)	0.07	1.30 (0.91,1.84)	0.15
TV or BV	1.31 (0.96,1.77)	0.09	1.30 (0.93,1.81)	0.12
CA	0.81 (0.57,1.16)	0.26	0.91 (0.75,1.11)	0.37
HSV	3.07 (1.43,6.61)	<0.01	3.66 (1.67,8.01)	<0.01

^aThe odds ratios (OR) are in relation to those without stated sign.

^bThe adjusted confidence intervals are based on a logistic model that includes GC (*N. gonorrhoeae*), CT (*C. trachomatis*), TV (*T. vaginalis*), BV (bacterial vaginosis), CA (*Candida albicans*), and HSV. The adjusted confidence intervals for GC or CT and TV or BV are based on a logistic model that includes these each as single variables as well as CA and HSV.

^cColor detected on white dacron swab.

Modified with permission from Ryan CA, Courtois BN, Hawes SE, Stevens CE, Eschenbach DA, Holmes KK. Risk assessment, symptoms and signs as predictors of vulvovaginal and cervical infections in urban U.S. STD clinic: implications for use of STD algorithms. *Sex Transm Infect* 1998; 74(Suppl 1): S59–S76.

The initial assessment of the patient for vulvovaginal infection ideally should begin with an open-ended question about the reason for the clinic visit (i.e., the chief complaint), since a chief complaint of vaginal discharge is most predictive of vaginal infection. An alternative or intermediate step is a semistructured but nonleading question (e.g., “Do you have any abnormal genital symptoms?” or “Do you have any new symptoms that make you think you might have a vaginal infection or an STD?”). A leading question, such as “Do you have a vaginal discharge?” generates very nonspecific responses of low predictive value for vaginal infection. More specific questions concerning abnormal vaginal discharge, as a follow-up to an initial open-ended question should probe the following three main types of abnormality and focus on recent changes in symptoms to further increase specificity of positive responses, such as “Have you recently developed (1) an abnormal increase in the amount of vaginal discharge? (2) an abnormal and unpleasant odor of vaginal discharge? (3) an unusually yellow color of vaginal discharge?” Unfortunately, the terminology commonly used in clinical practice (i.e., “leukorrhea,” “physiologic leukorrhea,” or the equivalents in other languages) may have little utility.

Specific questions directed toward vulvar disease also should focus on the main types of vulvar abnormality and on recent changes in symptoms, such as (1) “Have you recently developed abnormal itching or burning pain at the opening of the vagina (the vulva)? (2) any open sores or painful lesions at the opening

of the vagina? (3) any lumps or swellings at the opening of the vagina?” Positive responses should lead to probing about past history of such symptoms, because of the recurrent nature of genital herpes or vulvovaginal candidiasis, and the chronicity of other conditions described above.

Vulvar and perineal inspection and speculum examination are indicated to detect signs of vulvovaginitis, and also to identify other types of ectocervicitis (e.g., herpetic ulcerations, and “strawberry cervix” with trichomoniasis), and to identify manifestations of cervico-vaginal HPV infection, epithelial dysplasia, and cancer; to detect vulvovaginal ulcers, and less common types of severe vulvovaginal pathology (see the following); to establish the presence or absence of MPC; and to obtain specimens to test for specific microbial pathogens.

The amount, consistency, and location of the discharge within the vagina should be noted. A sample of discharge should then be removed with a swab from the vaginal wall, avoiding contamination with cervical mucus. The color of vaginal discharge should be noted in comparison with the white color of the swab. The pH should be determined directly by rolling the swab containing the specimen onto appropriate pH indicator paper, which should show color variation with pH above and below 4.5. An additional specimen should be removed with a swab and mixed first with a drop of saline, then with a drop of 10% KOH, on a microscope slide. Any abnormal fishy (amine) odor released after mixing the specimen with KOH is noted, and separate coverslips are placed on both the saline and KOH wet

mounts for microscopic examination to detect the presence and quantity of normal epithelial cells, clue cells, PMN leukocytes, motile trichomonads, or fungal forms, especially fungal hyphae. The presence of any three of the four criteria described by Amsel et al. (homogeneous adherent white discharge, pH >4.5, clue cells and amine odor after mixing the discharge with 10% KOH) provides the usual basis for a clinical diagnosis of BV.⁸¹ Where microscopic examination of vaginal fluid is not possible, various rapid point-of-care tests can be used by the clinician to screen for BV.^{82,83} For example, the QuickVue Advance® test for pH \geq 4.7 and amines;⁸⁴ the QuickVue Advance® test for proline aminopeptidase; and the OSOM BV Blue test for sialidase have correlated fairly well in a few studies with results of the Amsel criteria and with Gram stain criteria for diagnosis of BV. Gram stain criteria or oligonucleotide probe testing are used on an increasing but still very limited basis for laboratory diagnosis of vaginal conditions (see Chapter 42).

Although the sensitivity and specificity of individual symptoms and signs as outlined above and in Table 55-5 are not high, in many patients, symptoms and signs combined with risk assessment and with pH and amine tests and microscopic wet mount findings correspond to a consistent pattern, and further diagnostic tests are unnecessary. However, when symptoms or signs suggest a vaginal infection that cannot be confirmed by microscopic wet mount examination, further microbiological studies are indicated. Depending on the clinical findings, these further studies may include culture for *C. albicans*, culture for *T. vaginalis*, or Gram's stain of vaginal fluid to differentiate between normal flora and the flora characteristic of BV or other forms of vaginitis.^{18,19} In women with prominent vaginal symptoms but no abnormal findings, all three of these additional microbiological tests may be indicated to differentiate vaginal infection from other causes of vaginal symptoms, including psychosexual factors.⁷⁶ Although evaluation and treatment of sex partners is not currently recommended for partners of women with BV or vulvovaginal candidiasis, male partners of women with vaginal trichomoniasis should be treated with metronidazole 2 gm single oral dose (probably this should also be offered to any female partners); and recent progress in diagnosis of trichomoniasis in men⁸⁵ has improved the likelihood of detecting trichomoniasis in the male partner.

A proposed pH based algorithm for diagnosing vaginal infections

Because of the lack of specificity of clinical symptoms and signs in allowing practitioner-based diagnosis, or self-diagnosis, a pH based algorithm has been suggested⁸⁶ as a practical guide for practitioners in facilitating diagnosis and therapy of vaginitis which is no longer based on empiricism (Fig. 55-10). This transition from symptom- or sign-based (syndromic) clinical assessment to an objective data-driven process represents a further step towards specific diagnosis. The pH based system rests on the premise that during acute vulvovaginal candidiasis

whether uncomplicated or complicated, the vaginal pH remains unchanged and within the normal range of 4–4.5. It further utilizes the remarkable stability of the vaginal pH at 4–4.5 found in healthy women throughout most of the menstrual cycle, although an elevation does occur during menses. While it is recognized that a variety of physiologic and nonphysiologic short- and long-term causes of altered pH can occur in the absence of infection, the measurement of the vaginal pH represents a useful, simple signpost directing clinical decision making.

Vaginal pH is best measured by avoiding cervical mucous as well as not using the vaginal secretions that normally accumulate in the lower blade of a speculum. The most reliable method requires using a conventional swab to rub the middle third of the vaginal walls until the cotton swab becomes moist. The pH should be immediately determined using conventional techniques with pH paper. Several commercial interests are attempting to expedite measurement of pH by the practitioner as well as by patient self-interpretation of a self-obtained specimen. Physiologic causes for an elevated pH in excess of 4.5 include menses, bleeding from any source, the presence of semen for up to approximately 8–12 hours, recent and particularly prolonged use of systemic and local antibiotics, which may deplete the physiologic vaginal flora, as well as pH elevation in the absence of estrogen. Thus, an elevated pH in a postmenopausal woman is an early indicator of local vaginal estrogen deficiency. The normal vaginal pH reflects the production of vaginal organic acids, which include lactic acid. The local production of organic acids by indigenous vaginal flora is predominantly attributable to lactobacilli but also, potentially, partially attributable to other bacterial species. The substrate for the lactic acid production is predominantly glycogen. Another frequent cause of elevated vaginal pH includes recent and perhaps chronically repeated vaginal douching.

Accordingly in a symptomatic patient, the finding of a normal pH usually indicates the absence of BV, trichomoniasis, or atrophic vaginitis (Fig. 55-9). This also serves to exclude a number of rare causes of inflammatory vaginitis of noninfectious etiology e.g., desquamative inflammatory vaginitis

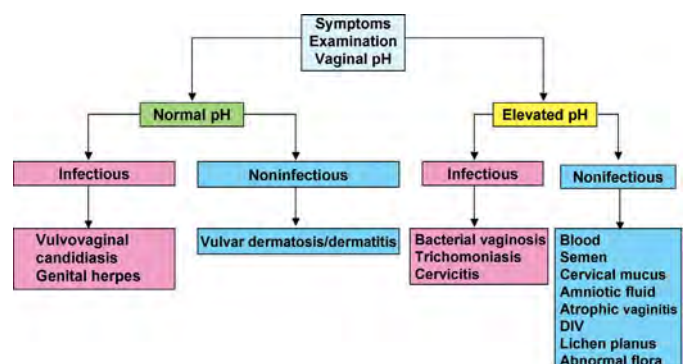


FIGURE 55-9. pH-based algorithm for diagnosing vaginal infection. (Modified from Nyirjesy P, Sobel JD. Advances in diagnosing vaginitis: development of a new algorithm. *Curr Infect Dis Rep* 2005; 7: 458–462.)

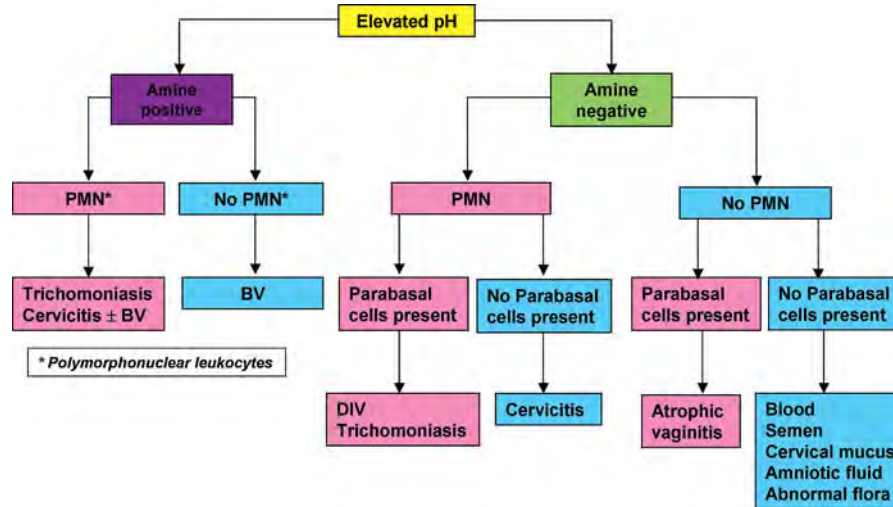


FIGURE 55-10. Use of vaginal pH and amine test, and of screening for polymorphonuclear leukocytes (PMNs) and para basal cells, in diagnosis of vaginal infections. (From Nyirjesy P, Sobel JD. Advances in diagnosing vaginitis: development of a new algorithm. *Curr Infect Dis Rep* 2005; 7: 458–462.)

(DIV). In contrast, an elevated pH while not excluding *Candida*, increases the likelihood of BV or trichomoniasis. Little additional information is gleaned from quantitation of the pH once it is elevated above 4.5. (i.e., a pH of 6 appears to be of no greater diagnostic specificity than a pH of 5.)

With vaginal pH >4.5, a positive amine or “whiff” test further increases the likelihood of abnormal bacterial flora as found in BV and trichomoniasis. A positive amine test does not reliably differentiate BV and trichomoniasis, which frequently coexist. In this diagnostic algorithm, with an elevated pH and positive amine test, the finding of increased PMN leukocytes by microscopic examination of vaginal fluid mixed with saline, strongly suggests trichomoniasis rather than BV. Saline microscopy is also useful in identifying motile trichomonads.

Lactobacillus depletion may follow many types of systemic or local antibiotic therapy—especially after topical intravaginal clindamycin therapy—and a conventional course of therapy with clindamycin may result in an elevated pH for several weeks. The accompanying algorithms have not been validated in prospective studies for diagnosing the cause of vulvovaginal symptoms but reflect the clinical experience of one of the authors (JS) of this chapter.

Treatments recommended in the CDC 2006 STD Treatment Guidelines⁸⁷ (see Appendix B and Chapters 42, 43, and 45) for vaginal infections including newer approaches to managing; and chronic or recurrent vaginal infections are briefly summarized in Table 55-5. It is still a common practice to prescribe metronidazole for BV only for those who have complaints related to this condition, despite the associations of BV with PID, preterm delivery, and increased risk of HIV acquisition (see Chapter 42).

Vulvar symptoms

Symptoms of vulvar pruritis or burning, of painful vulvar lesions, and of external dysuria, are most often associated with

isolation of HSV or *C. albicans*. Primary genital herpes with cervicitis may also produce symptoms of increased or yellow vaginal discharge, whereas such symptoms do not typically seem to occur with vulvovaginal candidiasis (see Table 55-4).¹⁸

■ BARTHOLINITIS

Bartholin’s gland infection can involve the main duct (which opens near the junction of the anterior two-thirds and posterior one-third of the labia majorum) as well as the minor ducts and glandular acini. Ductal inflammation and obstruction can lead to Bartholin’s abscess or cysts, which can reach 1–8 cm in diameter. The etiology of Bartholinitis commonly involves *N. gonorrhoeae*, or *C. trachomatis*; abscesses often contain enteric and vaginal gram-negative rods and anaerobes.^{88–91} The role of *M. genitalium* has not yet been assessed. The potential role of BV as a risk factor for Bartholinitis (analogous to the role of BV or PID) remains undefined. Unusual etiologies include the respiratory pathogens *Streptococcus pneumoniae* and *Haemophilus* species.^{92–94} Ductal exudate or aspirates from abscesses or cysts provide material for microbiologic diagnoses. The differential diagnosis of cysts includes benign tumors such as adenomas and hamartomas as well as carcinoma, especially in postmenopausal women. Treatment of Bartholinitis and Bartholin’s abscess probably should cover gonococcal and chlamydial infection, as well as anaerobic bacteria—analogous to treatment of PID. Drainage of abscesses, and excision or marsupialization of cysts are commonly employed.

■ CERVICITIS

Two types of cervicitis can be distinguished—*endocervicitis* (also known as *mucopurulent cervicitis* [MPC]) and *ectocervicitis*. Causes of endocervicitis include *C. trachomatis*, *N. gonorrhoeae*, and herpes simplex virus. Several recent

Table 55-5. Diagnostic Features and Usual Management of Vaginal Infection in Premenopausal Adults

	Normal Vaginal Examination	Yeast Vaginitis	Trichomonal Vaginitis	Bacterial Vaginosis
Etiology	Uninfected; <i>Lactobacillus</i> predominant	<i>Candida albicans</i> and other yeasts	<i>Trichomonas vaginalis</i>	Associated with <i>G vaginalis</i> , various other cultivable and non cultivable anaerobic bacteria, and mycoplasma
Typical symptoms	None	Vulvar itching or irritation	Profuse purulent discharge	Malodorous, slightly increased discharge
Discharge: Amount	Variable; usually scant	Scant to moderate	Profuse	Moderate
Color ^a	Clear or white	White	Yellow	Usually white or gray
Consistency	Nonhomogeneous, floccular	Clumped; adherent plaques	Homogeneous	Homogeneous, low viscosity; uniformly coating vaginal walls
Inflammation of vulvar or vaginal epithelium	None	Erythema of vaginal epithelium, introitus; vulvar dermatitis common	Erythema of vaginal and vulvar epithelium; colpitis macularis	None
pH of vaginal fluid ^b	Usually ≤ 4.5	Usually ≤ 4.5	Often ≥ 5.0	Usually ≤ 4.7
Amine ("fishy") odor with 10% KOH	None	None	May be present	Present
Microscopy ^c	Normal epithelial cells; lactobacilli predominate	Leukocytes, epithelial cells; yeast, mycelia, or pseudomycelia in up to 80%	Leukocytes; motile trichomonads seen in 80–90% of symptomatic patients, less often in the absence of symptoms	Clue cells; few leukocytes; lactobacilli outnumbered by profuse mixed flora, nearly always including <i>G vaginalis</i> plus anaerobic species, on Gram stain
Usual treatment	None	Miconazole, clotrimazole, or other imidazoles (See Chapter 45)	Metronidazole or tinidazole 2.0 g orally (single dose) Metronidazole 500 mg orally twice daily for 7 days	Metronidazole 500 mg orally twice daily for 7 days Intravaginal metronidazole gel or clindamycin cream
Usual management of sex partners	None	None; topical treatment if candidal dermatitis of penis is present	Examine for STD; treat with metronidazole, 2 g po	Examine for STD; no treatment if normal

^aColor of discharge is determined by examining vaginal discharge against the white background of a swab.

^bpH determination is not useful if blood is present.

^cTo detect fungal elements, vaginal fluid is digested with 10% KOH prior to microscopic examination; to examine for other features, fluid is mixed (1:1) with physiologic saline. Gram's stain also is excellent for detecting yeasts and pseudomycelia and for distinguishing normal flora from the mixed flora seen in bacterial vaginosis, but is less sensitive than the saline preparation for detection of *T. vaginalis*.

studies have also implicated *Mycoplasma genitalium*.^{16,95–97} HSV infection can also be associated with ectocervicitis, and will be discussed separately in the following. The presence of cervical infection is not synonymous with the term “cervicitis,” since not all infections are associated with demonstrable inflammation, and vice versa. For example, a positive test for *C. trachomatis* in an endocervical specimen leads to a diagnosis of chlamydial infection of the cervix, not of necessarily to a diagnosis of chlamydial “cervicitis.”

MPC caused by *C. trachomatis* or *N. gonorrhoeae* must be differentiated from endo- and ecto-cervicitis caused by HSV, from ectocervicitis caused by *T. vaginalis*, from vaginitis, and from simple cervical ectopy without inflammation, a common condition (Fig. 55-11). Columnar epithelium lies in an exposed position on the ectocervix in the majority of adolescent girls at the onset of menarche. The prevalence of ectopy gradually declines through young adulthood.⁹⁸ The term ectropion has also been used to describe the patulous parous cervix, which opens as the blades of a vaginal speculum are spread, to expose the endocervix. Ectopy or ectropion, when not associated with visible or microscopic evidence of mucopurulent exudate, or with colposcopic epithelial abnormalities, is a normal finding and requires no therapy. Recurrent genital herpes involving the cervix alone produces lesions of the endocervical columnar epithelium and the ectocervical squamous epithelium. Ectocervicitis caused by trichomoniasis and vulvovaginal candidiasis are generally associated with vaginitis, as discussed below.

■ ENDOCERVICITIS

Urethritis in men represents the tip of the iceberg of infections caused by *C. trachomatis*, *N. gonorrhoeae*, and probably

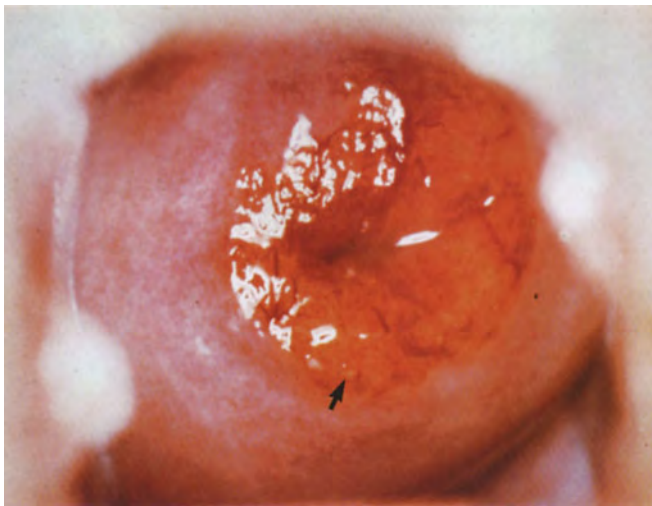


FIGURE 55-11. Cervical ectopy. Endocervical columnar epithelium is present in an ectopic position on the exocervix, giving a bright-red circumferential appearance. Note that the cervical mucus is clear, not purulent. However, also note the small vesicle (arrow) indicative of a very early primary HSV lesion, within the zone of ectopy.

by *M. genitalium*. Endocervical infection, together with sub-clinical urethral infections in both sexes, represents the portion of the iceberg that often goes unrecognized. The fact that urethritis in the male can result in detection and treatment of cervical infection led to the old adage in venereology: “The man who develops a discharge after sex with a woman could become that woman’s best friend.” At present, in most of the world, control of these infections unfortunately is based largely on the clinical diagnosis of urethritis in the male and on treatment of the female sex partners of men with urethritis. This is particularly so in the poorest developing countries, where specific laboratory tests for *N. gonorrhoeae* and *C. trachomatis* are rarely available. Because endocervicitis produces symptoms less often than male urethritis, and symptoms of endocervicitis that may occur (e.g., yellow vaginal discharge) are less distinctive than symptoms of urethritis, the careful assessment of clinical signs of MPC, and the appropriate use of laboratory tests for confirming the microbial etiology of MPC, as well as for screening for sub-clinical infection of the female, are of paramount importance in the control of gonococcal and chlamydial infections.

Infection of the cervix represents a reservoir for sexual or perinatal transmission of pathogenic microorganisms, and also might lead to at least two possible types of complications in the female: (1) ascending intraluminal spread of pathogenic organisms from the cervix, producing endometritis and salpingitis; (2) ascending infection during pregnancy, resulting in chorioamnionitis, premature rupture of membranes, premature delivery, amniotic fluid infection, and puerperal infection.

The lack of widely recognized objective signs of cervical inflammation is illustrated by the confusing nomenclature for endocervicitis. Terms such as acute and chronic cervicitis, cervical erosion, cervical discontinuity, MPC, papillary cervicitis, follicular cervicitis, and hypertrophic cervicitis have all been used. This confusion results in part from the changes that occur in the cervix over the reproductive period and in part from difficulty in differentiating normal ectopic columnar epithelium from endocervicitis.^{98–101} The latter differentiation is complicated by the fact that cervical ectopy (Fig. 55-11) has been correlated with the detection of cervical infection by *C. trachomatis* in most studies.^{98,102–104} Ectopy is present in the majority of younger teenage girls, and decreases steadily in prevalence with increasing age. Further, ectopy is significantly positively correlated with oral contraceptive use, and inversely correlated with smoking, independent of age.⁹⁸

In this chapter, the term *mucopurulent endocervical discharge* (or *endocervical mucopus*) refers to yellow endocervical exudate or increased numbers of neutrophils in endocervical mucus as demonstrated by Gram’s stain (see the following). The yellow color is thought to be caused by the presence of the “green enzyme” myeloperoxidase contained within PMN neutrophils.

Mucopurulent endocervicitis refers to the appearance of the inflamed endocervix on physical examination—optimally by colposcopy—with manifestations such as yellow endocervical discharge, edema and erythema of the zone of ectopy, and easily induced endocervical bleeding. *Endocervicitis* refers to histopathologic features of endocervical inflammation.

Definition and etiology of mucopurulent cervicitis

Rees et al.¹⁰⁵ and then Brunham et al.¹⁰⁶ initially established the relationship of *C. trachomatis* to MPC.¹⁰⁵ Brunham studied randomly selected women attending an STD clinic in Seattle for the correlation of selected cervical abnormalities with isolation of *C. trachomatis*, *N. gonorrhoeae*, and HSV.¹⁰⁶ *C. trachomatis* was isolated from 22%, and *N. gonorrhoeae* from 16%. The presence of yellow endocervical exudate, confirmed by the simple identification of yellow exudate on a white cotton-tipped swab specimen of endocervical secretions, correlated only with isolation of *C. trachomatis*. Mucopurulent secretions were present in 62% of women with cervical chlamydial infection and 12% of women with no cervical pathogen. Bleeding produced by collection of culture specimens from the endocervix, erythema (owing to increased vascularity), and edema of the zone of ectopy were also more common among women with *C. trachomatis* infection (Fig. 55-12). Examples of some of these findings are also shown in Figs. 55-5 and 55-6. Microscopic detection of increased numbers of neutrophils demonstrated by Gram's stain within the faintly pink strands of endocervical mucus, collected after first removing ectocervical vaginal cells with a large swab, and examined as described in the following, was also correlated with isolation of *C. trachomatis* (Figs. 55-13 and 55-14).

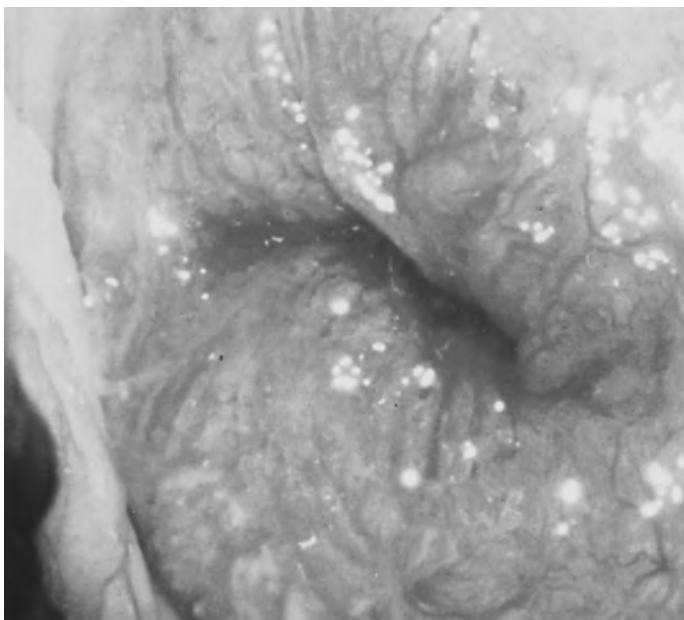


FIGURE 55-12. Colpophotograph of the cervix infected with *C. trachomatis*, showing proliferation and dilation of subepithelial capillaries in the zone of ectopy.

In a 1984–1986 study of a larger series of 779 consecutive women attending the Seattle STD clinic, when the prevalence of endocervical chlamydial and gonococcal infection by culture were 15% and 14%, respectively, we found that the presence of yellow mucopus collected from the endocervix and visualized on a white swab was independently correlated not only with isolation from the cervix of *C. trachomatis*, but also with isolation of *N. gonorrhoeae* and of HSV from the endocervix, and with isolation of *T. vaginalis* from the vagina.¹⁸ A subsequent retrospective analysis of endocervical specimens from 719 of these 779 patients studied during 1982–1984 also found that *M. genitalium* was associated with MPC. We identified *M. genitalium* by PCR in 24 (11.2%) of 215 patients with MPC (defined either as visible mucopus or ≥ 30 PMNs) versus 26 (5.2%) of 504 patients without MPC.⁹⁵ (Fig. 55-15) displays the proportion of women with endocervical mucopus in that study found to have *N. gonorrhoeae*, *C. trachomatis*, HSV, *T. vaginalis*, or *M. genitalium* alone or in mixed infections; 36% of those with MPC had none of these pathogens. In populations with lower prevalence of these pathogens (including the same

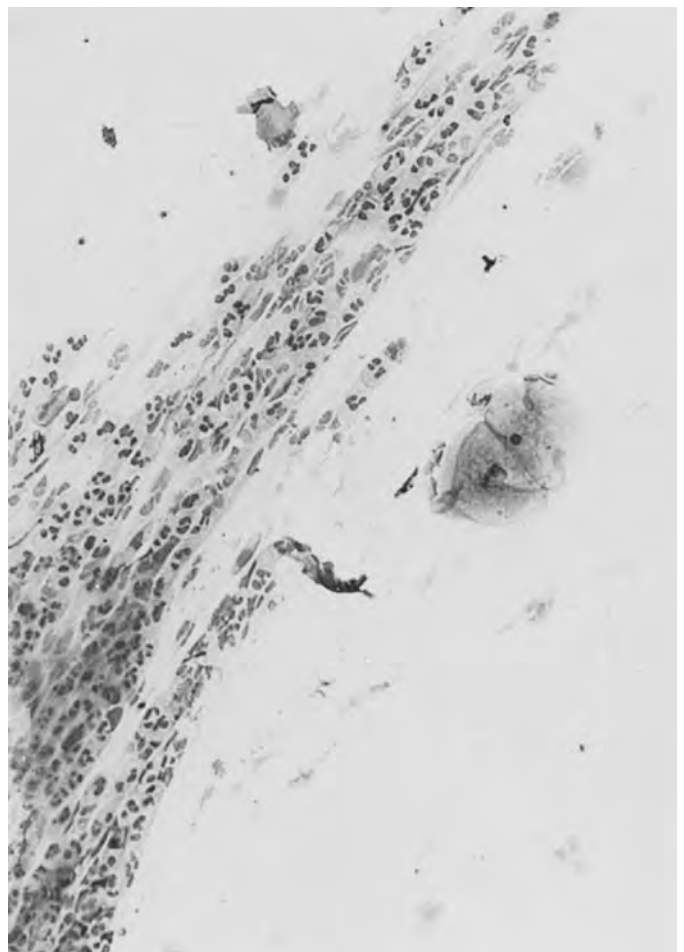


FIGURE 55-13. Satisfactory smear of endocervical mucus from chlamydial mucopurulent cervicitis, showing many neutrophils in strands of mucus, with few contaminating vaginal squamous cells or bacteria.

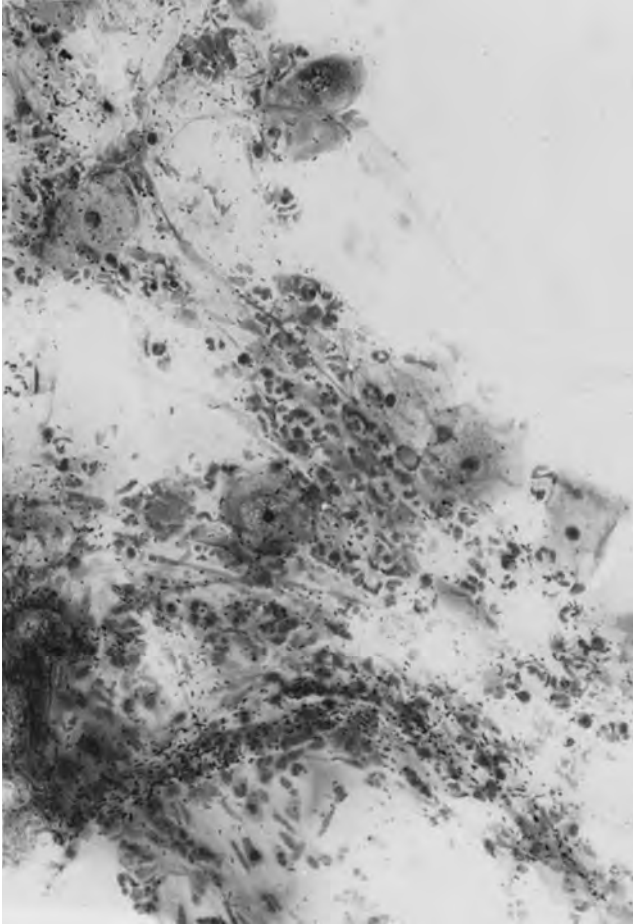


FIGURE 55-14. Unsatisfactory smear of cervical mucus. Although moderate numbers of neutrophils are seen, the presence of many vaginal squamous cells and bacteria makes it difficult to tell whether the neutrophils originate in the cervix or the vagina.

Seattle STD Clinic today¹⁰⁷), smaller proportions of those with mucopus would have these infections. *N. gonorrhoeae* or *C. trachomatis* were isolated from 45% of those with endocervical mucopus and 14% of those without endocervical mucopus in this 1982–1984 study. By multivariate analysis adjusting for other infections, chlamydial infection was also significantly associated with cervical ectopy and with cervical bleeding that was easily induced with a dacron swab (commonly misnamed cervical “friability,” see Table 55-4.) Gonococcal and chlamydial infection, cervical HSV infection, and trichomoniasis all were also associated with signs of yellow vaginal discharge on speculum examination, but neither gonococcal nor chlamydial infection was associated with objective signs of profuse vaginal discharge.

Initial efforts to develop clinical algorithms for syndromic management of STDs were based on the premise that symptoms of vaginal discharge could identify women with increased risk of gonococcal and chlamydial infection, and that this could be the basis for improved control of these infections in the population. When this approach failed to identify women with increased prevalence of cervical infection,

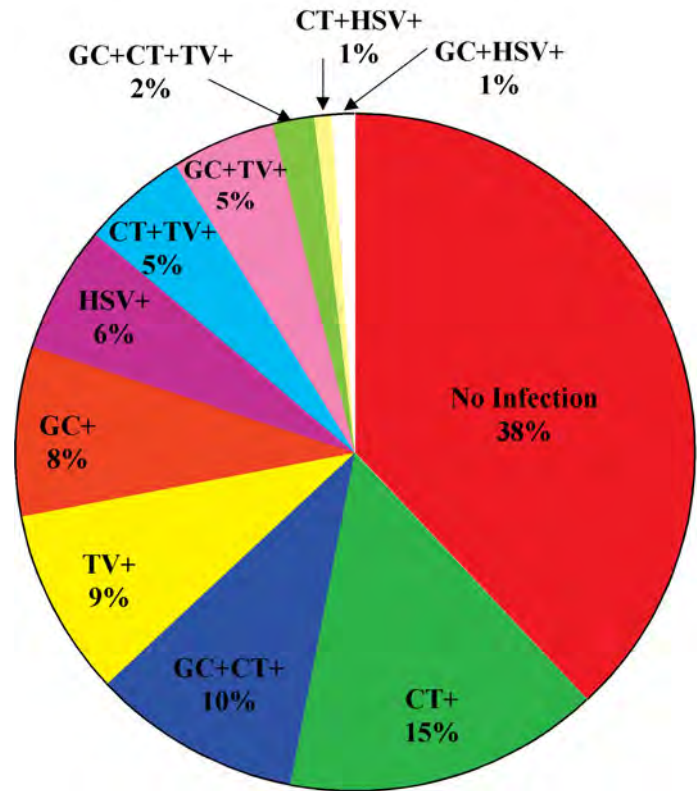


FIGURE 55-15. Among 779 consecutive female STD clinic patients, 182 (23.4%) had signs of endocervical mucopus. This pie chart shows the percentage of those with endocervical mucopus no cervical infection, or cervical infection by *C. trachomatis* (CT), *N. gonorrhoeae* (GC), herpes simplex virus (HSV), or *T. vaginalis* (TV).

especially after adjusting for the presence or absence of BV or trichomoniasis, which tend to be associated with gonococcal or chlamydial infection, a modified approach was proposed by the World Health Organization, in which risk assessment was added to try to identify a subset of women with vaginal discharge who might have a higher prevalence of cervical infection, sufficient to warrant presumptive treatment for cervical infection. In general, although various locally derived strategies for risk assessment did help to identify those with increased prevalence, the positive predictive values for cervical infection were still too low to warrant routine treatment in most settings; the basic flaw was the lack of correlation of symptoms of an increased amount of vaginal discharge with cervical infection in most studies.¹⁰⁸ The question then arises: If endocervical mucopus or easily induced cervical bleeding are the true clinical manifestations of cervical infection, would addition of risk assessment *after detection of mucopus*, help to further discriminate those with from those without cervical infection; and prove more useful for syndromic management algorithms in which speculum examination was performed? Applying this more logical approach to the above data set for 779 Seattle women who had an overall prevalence of cervical gonococcal or chlamydial infection of 24%, the prevalence of

Table 55-6. Performance of Risk Assessment (RA) in Identifying Gonococcal and Chlamydial Infection Among Women With and Without Signs of Endocervical Mucopus

	Endocervical Mucopus Present		Endocervical Mucopus Absent	
	RA Positive (N = 119) ^a	RA Negative (N = 63)	RA Positive (N = 314)	RA Negative (N = 283)
% GC+	35%	10%	14%	5%
% CT+	37%	27%	12%	7%
% GC or CT+	57%	21%	23%	11%
Sensitivity ^b	78%		70%	
Specificity ^b	45%		51%	
Positive P.V. ^b	57%		23%	
Negative P.V. ^b	69%		89%	

^aRisk assessment positive = partner with gonorrhea or chlamydia or 2 or more of the following: age <21, no use of barrier contraception, new partner in past 30 days, multiple partners in past 30 days.

^bSensitivity, specificity, and positive and negative predictive values for detection of GC and/or CT are presented separately for those with, and those without endocervical mucopus.

cervical gonococcal or chlamydial infection was 57% among those with mucopus and positive risk assessment versus only 11% among those with no mucopus and negative risk assessment (Table 55-6). Such an approach might prove useful in various settings for deciding who to treat empirically and when to initiate presumptive partner treatment as well, who to test while deferring treatment, and who to offer neither treatment nor testing nor partner treatment.

In various published studies, the recommended cutoff value indicative of MPC for the number of PMN leukocytes per 1000× microscopic field in endocervical mucus on Gram's stain for diagnoses of endocervical mucopus has been ≥10, ≥20, or ≥30. As shown in Table 55-7, in our study of 779 women, cutoff values of ≥10 neutrophils and ≥30 neutrophils per 1000× field in endocervical mucus both were significantly and independently associated with isolation of *N. gonorrhoeae*, *C. trachomatis*, and HSV, but only the lower value (≥10) was also associated with isolation of *T. vaginalis*.¹³ With respect to detection of *N. gonorrhoeae* or *C. trachomatis*, the finding of ≥10 PMN(1000× field in cervical mucus had a sensitivity of 80.4%, a specificity of 48.3%, and a positive predictive value of 33% in this population, with its 24% prevalence of either infection. The finding of ≥30 PMN had a lower sensitivity of 46.6%, a higher specificity of 80.2%, and higher positive predictive value of 43%. Neither finding was as accurate as detection of yellow endocervical mucopus, which had a sensitivity of 52%, specificity of 82%, and positive predictive value of 48%.¹⁸

Changing prevalence and etiology of mucopurulent endocervical discharge

In recent years, at the Public Health Seattle-King County STD Clinic at Harborview Medical Center the proportion of new problem male visits associated with a diagnosis of urethritis has fallen, as has the proportion of men with urethritis who have associated with gonococcal or chlamydial infection. Similarly, among 6230 women visiting Seattle STD clinics from 1995–1999¹⁰⁷ (i.e., 12–15 years after the 1982–1984 study of MPC, when the prevalence of gonorrhea or chlamydial infection or both was 24%) the prevalence of either or both of these infections had fallen to 10%. Endocervical gonococcal or chlamydial infection were independently associated with age less than 25 years, endocervical mucopus or induced bleeding, or >30 PMNs on endocervical Gram stain, but the positive predictive value of any of those signs of endocervicitis was considered high enough to warrant presumptive treatment only in those younger than 25 years of age—with results of specific laboratory tests now recommended to guide treatment for women 25 years of age or older.¹⁰⁷

Several published studies on the prevalence of endocervical gonococcal and chlamydial infections, and on the prevalence of endocervical mucopus on speculum examination, are summarized in Table 55-8, in relation to the year and type of population studied.^{18,106,109–125} Some but not all of these studies enrolled only women with symptoms,

Table 55-7. Percentage of Infection Among 779 Randomly Selected Female STD Clinic Patients With and Without Increased Concentrations of Polymorphonuclear (PMN) Leukocytes in Cervical Mucus or Vaginal Fluid^a

	% Infected with Finding	% Uninfected without Finding	Unadjusted OR (95%CI) ^b	Adjusted OR (95%CI) ^{b, c}
Cervical PMNs ≥ 10 ($n = 457$)				
GC	83.0	54.8	4.03 (2.38,6.81)	3.20 (1.82,5.63)
CT	79.5	55.0	3.17 (1.98,5.09)	2.82 (1.71,4.66)
GC or CT	80.4	51.7	3.84 (2.59,5.69)	3.73 (2.49,5.57)
TV	72.6	56.2	2.07 (1.34,3.2)	1.75 (1.07,2.86)
BV	61.3	55.6	1.27 (0.94,1.71)	1.04 (0.74,1.46)
TV or BV	63.5	55.1	1.42 (1.06,1.9)	1.24 (0.9,1.7)
CA	55.1	60.2	0.81 (0.58,1.13)	0.99 (0.83,1.2)
HSV	82.4	57.2	3.49 (1.44,8.5)	4.13 (1.67,10.23)
Cervical PMNSs ≥ 30 ($n = 205$)				
GC	44.3	23.5	2.60 (1.7,3.96)	2.23 (1.38,3.62)
CT	50.4	22.1	3.60 (2.4,5.4)	3.69 (2.37,5.74)
GC or CT	46.6	19.8	3.52 (2.48,5)	3.59 (2.48,5.18)
TV	33.3	25.1	1.49 (0.98,2.28)	1.17 (0.71,1.94)
BV	27.5	24.8	1.15 (0.83,1.61)	1.07 (0.73,1.58)
TV or BV	28.0	25.1	1.16 (0.84,1.6)	0.97 (0.68,1.39)
CA	18.7	28.9	0.57 (0.38,0.85)	0.82 (0.66,1.04)
HSV	47.1	24.9	2.68 (1.34,5.37)	3.67 (1.75,7.74)
Vaginal PMNs ≥ 10 ($n = 491$)				
GC	77.4	61.2	2.16 (1.34,3.5)	1.99 (1.17,3.39)
CT	79.5	60.6	2.52 (1.57,4.05)	2.41 (1.46,3.99)
GC or CT	76.2	59.3	2.19 (1.51,3.18)	2.45 (1.66,3.61)
TV	70.1	62.2	1.42 (0.93,2.17)	1.44 (0.88,2.34)
BV	63.8	63.8	1.00 (0.74,1.36)	1.03 (0.73,1.45)
TV or BV	63.2	63.6	0.99 (0.73,1.32)	1.03 (0.75,1.42)
CA	71.1	61.1	1.57 (1.1,2.25)	1.34 (1.1,1.63)
HSV	94.1	61.2	10.1 (2.47,41.7)	10.43 (2.51,43.39)
Vaginal PMNs ≥ 30 ($n = 277$)				
GC	50.0	33.3	2.00 (1.33,3.03)	2.13 (1.33,3.42)
CT	55.6	32.0	2.65 (1.78,3.96)	2.93 (1.89,4.53)
GC or CT	50.8	30.7	2.33 (1.67,3.26)	2.67 (1.87,3.81)
TV	39.3	34.9	1.21 (0.81,1.81)	1.11 (0.7,1.78)
BV	36.6	36.2	1.02 (0.75,1.38)	1.06 (0.75,1.51)
TV or BV	35.9	35.3	1.02 (0.76,1.38)	1.02 (0.73,1.41)
CA	41.2	33.8	1.37 (0.98,1.92)	1.29 (1.07,1.56)
HSV	70.6	33.6	4.75 (2.23,10.09)	5.66 (2.54,12.62)

^aNumber of PMN leukocytes per 1000 x microscopic field.

^bThe odds ratios (OR) are in relation to the those without stated sign.

^cThe adjusted confidence intervals are based on a logistic model that includes GC,CT, TV, BV, CA, and HSV. The adjusted confidence intervals for GC or CT and TV or BV are based on a logistic model that includes these each as single variables as well as CA and HSV. Models will exclude BV, TV or TV/BV if finding is used as criteria for diagnosis.

Modified with permission from: Ryan CA, Courtois BN, Hawes SE, Stevens CE, Eschenbach DA, Holmes KK. Risk assessment, symptoms and signs as predictors of vulvovaginal and cervical infections in urban U.S. STD clinic: implications for use of STD algorithms. *Sex Transm Infect* 1998; 74(Suppl 1): S59-S76.

Table 55-8. Prevalence of Endocervical Gonococcal and Chlamydial Infection (GC and CT) and of Mucopurulent Endocervical Discharge in Published Studies, and the Relationship of GC and/or CT to Various Manifestations of Cervicitis

Author, Year	Clinical Setting	% With Mucopus	% With GC ± CT	Findings Associated With GC ± CT	Odds Ratio ^a
Brunham '82 ¹⁰⁶	Seattle STD clinic	24%	28.0%	Mucopus ≥10 PMN/1000 x field	4.8 8.0
Ryan '84-'86 ¹⁸	Seattle STD clinic	23.4%	24.0%	Yellow vaginal discharge Induced bleeding Mucopus Ectopy ≥30 PMN/1000 x field	2.8 5.1 5.5 2.2 3.6
Handsfield '84 ¹¹¹	Seattle Family planning	14.2%	9.7%	Mucopus Induced bleeding	3.0 2.3
Thomas '94 ¹¹²	Nairobi antenatal	7.3%	10.8%	Mucopus Induced bleeding	2.6 2.1
Mayaud '92-93 ¹¹³	Tanzania antenatal	4.5%	8.4%	Cervical discharge ≥10 PMN/HPF	2.7 2.0
Behets ¹¹⁴	Jamaica STD clinic	NA	34.0%	Mucopus Induced bleeding	2.1 1.5
Mosure '95-'96 ¹¹⁰	US family planning Region IX	10.5% ^b	3.7% ^b	Mucopus Induced bleeding	2.3 2.1
	Region X	8.2% ^b	2.7% ^b	Mucopus Induced bleeding	2.8 2.5
Sellors '89-'92 ¹¹⁵	Canada family planning, student and abortion Clinics	—	6.3%	Yellow mucopus Opaque cervical discharge Induced bleeding	2.8 2.9 2.3
Alary '93-'94 ¹¹⁶	Benin STD, antenatal	14.3%	7.8%	Mucopus Pos. swab test	2.8 3.3
Daly '94 ¹¹⁷	Malawi hospital outpatient clinic	19.5%	19.5%	Abnormal color of vaginal discharge Cervical motion tenderness Mucopus ≥10 WBCs/HPF on vaginal wet mount	2.4 8.7 2.7 2.3
Sanchez '96 ¹¹⁸	Peru gynecology and family planning clinic	27.7%	12.2%	Profuse yellow vaginal discharge Induced bleeding ≥10 PMN/HPF	4.1 2.8 2.3
Ryan '95-'96 ⁷⁸	Morocco primary care, family planning	35.9% 50.7%	10.1% 5.4%	Yellow vaginal discharge Mucopus	2.0 2.1

Table 55-8. (Continued)

Author, Year	Clinical Setting	% With Mucopus	% With GC ± CT	Findings Associated With GC ± CT	Odds Ratio ^a
Diallo '92-'93 ¹¹⁹	Côte d' Ivoire sex workers	20.2%	35.0%	Mucopus Induced bleeding Cx motion tenderness WBC ≥ 10/HPF	4.8 2.2 1.6 3.8
N'doye '90 ¹²⁰	Senegal sex workers	11.8%	24.9%	Mucopus WBC ≥ 10/HPF in cervical fluid WBC ≥ 10/HPF in vaginal fluid	2.6 3.5 6.6
Wi '94 ¹²¹	Manila, Philippines sex workers	20.7%	23.3%	Mucopus	3.0
	Cebu City	2.8%	37.0%	≥ 20PMN/1000 x field ≥ 20PMN/1000 x field	2.5 2.4
Behets '95 ¹²⁵	Jamaica family planning	4.3%	14.1%	None	–
Kapiga '95 ¹²²	Tanzania family planning	7.7%	8.2%	Induced bleeding Cx motion tenderness	2.5 2.4
Mayaud '94 ¹²³	Tanzania antenatal	Not assessed	7.4%	Yellow vaginal discharge ≥ 20PMN/HPF ≥ 5PMN/HPF	2.0 6.3 4.0
Schneider '94 ¹²⁴	South Africa family planning	22%	14%	Mucopus and/or induced bleeding	2.4
Marrazzo 2002 ¹⁰⁷	Seattle, WA, USA STD clinic			Mucopus induced bleeding >30 PMN/1000x field	
Pepin 2005 ⁹⁷	Ghana, Benin sex workers			Mucopus induced bleeding "Inflammatory cervix"	

^aLimited to statistically significantly elevated odds ratios.

^bData for ages 20–24 only.

^cMucopus defined as yellow or "brown" cervical mucus in this study.

such as abnormal vaginal discharge or lower abdominal pain; many did not test for HSV or *T. vaginalis* infection. The prevalence of gonococcal or chlamydial endocervical infection ranged from as low as 2.7% in the U.S. Region X family planning clinics in 1995–1996 to as high as 37% in female sex workers (FSWs) in Cebu City, the Philippines.¹²¹

The reported prevalence of endocervical mucopus observed by speculum ranged from 2.8% in Cebu FSWs (perhaps representing insensitive screening for mucopus) to 50.7% (probably representing nonspecific detection of mucopus) in Moroccan family planning clinics enrolling women with symptoms of vaginal discharge or lower

abdominal pain.^{78,121} This wide range reflects the importance (and difficulty) of training health-care providers to accurately screen for this finding. It is also not surprising that surveys of healthy women in the general population (as opposed to studies of women seeking care for genital symptoms or exposure to an STI) have shown only weak correlations of symptoms and signs of cervical inflammation with detection of *C. trachomatis* or *N. gonorrhoeae*.⁸⁰ Nonetheless, of the 19 studies cited, 16 found significant associations of endocervical mucopus (usually defined as a positive “swab test,” meaning yellow color of endocervical discharge visualized on a white swab) with endocervical gonococcal or chlamydial infection (with odds ratios [OR] ranging from 2.1 to 5.5); and the remaining three (all done in family planning or antenatal clinics) did find associations with increased numbers of PMN leukocytes in cervical mucus, or with induced endocervical bleeding. Some studies also assessed and found associations of endocervical gonococcal or chlamydial infections with yellow vaginal discharge, or with increased numbers of leukocytes in vaginal smears.^{18,115,118,126} This finding may be easier for clinicians to demonstrate in some settings than the demonstration of endocervical mucopus, but can reflect vaginal trichomoniasis as well. Many of these studies found no relationship of symptoms of vaginal discharge to presence or absence of endocervical gonococcal or chlamydial infection, as discussed earlier.

Although MPC has been significantly correlated with endocervical infection in most of these studies, the sensitivity, specificity, and predictive value have varied in different settings.^{18,106,111–125,127–129} It is difficult to assess to what extent the variability is attributable to differences in patients, to differences in assessing MPC, or to differences in detection of infection. Our experience suggests that the correlation of detection of *C. trachomatis* or *N. gonorrhoeae* in the cervix with detection of mucopurulent (yellow) endocervical discharge by an inexperienced clinician is initially low (in which case identification of increased numbers of neutrophils in cervical mucus by an experienced laboratory technician is more reliable); but with training and experience, the correlation improves.

In the absence of proven gonococcal, chlamydial, *M. genitalium* or HSV infection or trichomoniasis, the causes of MPC remain uncertain. Various other genital pathogens have been implicated in single studies, and it is likely that false negative tests for *C. trachomatis*, *N. gonorrhoeae*, or HSV account for some cases. Just as new microbial etiologies of urethritis and cervicitis (such as *M. genitalium*) have been discovered, it seems likely that further causes will be identified in the future. Hence, the positive predictive values of clinical manifestations of MPC for the detection of *N. gonorrhoeae* and *C. trachomatis* may greatly underestimate the predictive value for infection per se, and may even underestimate the proportion that would respond to syndromic treatment with currently recommended antimicrobial therapies. Similarly,

the specificity of signs of cervical inflammation, in terms of cervical infection, are likely to be understated when gonococcal and chlamydial infections are the only infections considered. In addition, it remains possible that oral contraceptive use and cervical ectopy per se, and perhaps some vaginal infections,¹³⁰ may be associated with endocervical inflammation.

■ ECTOCERVICITIS

Routine colposcopic examination of female STD clinic patients has shown that cervical HSV infection is highly correlated with cervical ulcers or necrotic lesions (Fig. 55-16), whereas trichomoniasis is correlated with colpitis macularis (“strawberry cervix”), and both *C. trachomatis* and cytomegalovirus infection of the cervix are correlated with colposcopic features of immature metaplasia.¹³¹ Immature metaplasia has been defined as faint acetowhite epithelium (white after application of acetic acid) with diffuse distal borders, occurring as finger-like projections within the transformation zone, at the central margin of a squamocolumnar junction advancing centrally into the zone of ectopy. In a further analysis, colpitis macularis (Fig. 55-17) was identified without magnification in only 2 (2%) of 108 women with trichomoniasis; but by colposcopy was identified in 49 (45%) of the 108 with trichomoniasis versus only 6 (1%) of 509 without trichomoniasis.²⁴ In the 1984-Seattle study of 779 women mentioned above, cervical ulcerations or necrotic lesions were detected by colposcopy in 22 (65%) of 34 women with positive cervical cultures for HSV, and 11 (1.5%) of 745 with negative cultures for HSV.¹³² *C. albicans*, like *T. vaginalis*, also can produce ectocervicitis, but both are associated with other manifestations of inflammation of the contiguous stratified squamous vaginal epithelium (Figs. 55-18 and 55-19).

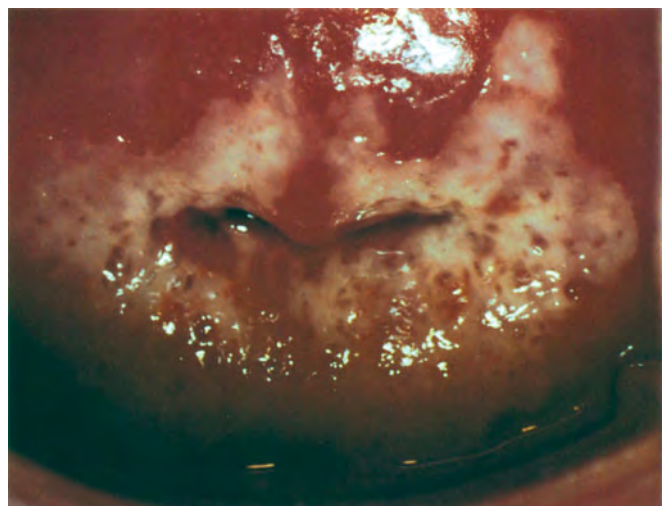


FIGURE 55-16. Severe primary HSV-2 cervicitis. HSV-2 produces both endocervicitis and ectocervicitis.

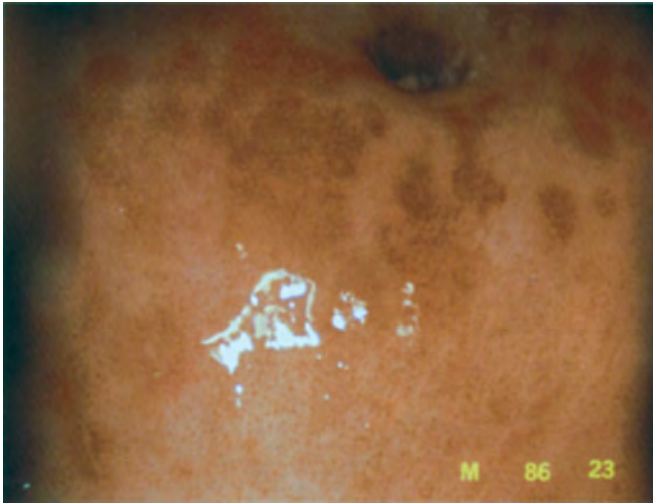


FIGURE 55-17. Colpophotograph of “strawberry cervix” showing petechiae on the ectocervix in a patient with trichomonal vaginitis and ectocervicitis.

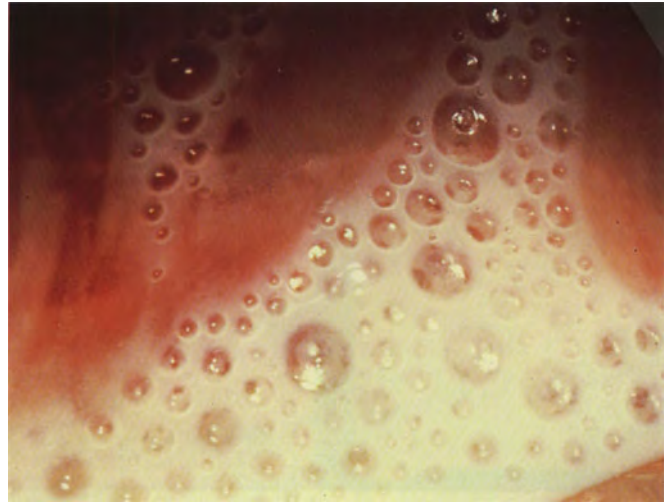


FIGURE 55-19. Profuse purulent vaginal discharge due to trichomoniasis. Color is yellow when viewed on a white swab. Appearance is occasionally frothy, as seen here.

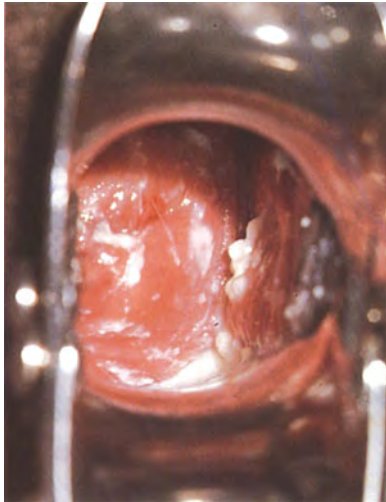


FIGURE 55-18. Cervical-vaginal candidiasis. Note the white nonhomogeneous curd-like, clumped exudates characteristic of candida infection.

Special diagnostic procedures for cervicitis

The presence of endocervicitis can be confirmed by a variety of supplementary diagnostic procedures, most of which should be available to clinicians specializing in treatment of genital infections of women. These include Gram’s stain of endocervical mucus, cervical cytology, colposcopy, and cervical biopsy. The gonococcal etiology of endocervicitis can be presumptively established when Gram’s stain of endocervical mucus shows gram-negative diplococci; the microbial etiology of cervicitis can be further substantiated by isolation of *C. trachomatis*, *N. gonorrhoeae*, or HSV, by detection of specific microbial antigens, or by detection of specific nucleic acid sequences from these pathogens or from *M. genitalium*.

Endocervical Gram stain

Just as sputum is difficult to evaluate microscopically when contaminated by oropharyngeal cells and flora, the endocervical mucus is difficult to evaluate microscopically when contaminated by vaginal cells and flora. The ectocervix is therefore generally wiped clean with a large swab before endocervical mucus is obtained for microscopy. (NOTE: this is recommended to facilitate microscopic examination of endocervical secretions, not necessarily to improve sampling for other specific diagnostic tests such as culture or nucleic acid amplification tests.) Mucus is then obtained from the endocervical canal, rolled in a thin film over a slide, heat-fixed, and stained by Gram’s stain. The slide is screened at low magnification ($\times 100$) to identify strands of cervical mucus containing PMN, as well as to evaluate the extent of contamination by vaginal squamous cells, and to select representative areas of cervical mucus for closer examination with the oil immersion lens. The number of PMN neutrophils per $\times 1000$ field (oil immersion magnification) within strands of cervical mucus should then be counted in several representative fields. The presence of increased concentrations of PMN in mucus strands supports the diagnosis of cervicitis, unless heavy contamination by vaginal squamous cells (e.g., > 100 squamous cells per slide) and by vaginal flora (e.g., > 100 bacteria per $1000\times$ field overlying cervical mucus) suggest that the neutrophils may have originated in the vagina rather than in the endocervix. Common mistakes are to search areas of the smear other than cervical mucus strands to enumerate PMNs, or to enumerate mononuclear leukocytes rather than PMN. Contamination of the specimen with vaginal flora can also obfuscate the detection of gonococci in endocervical mucus by Gram’s stain. As discussed elsewhere, detection of gram-negative diplococci within neutrophils in properly

collected endocervical mucus is highly specific, but gonococci can be identified by Gram's stain in only about 50–60% of women with cervical gonococcal infection.

■ CYTOPATHOLOGY

An estimated 50 million cervical Pap smears are performed by physicians in private office practices in the United States each year for detection of cervical neoplasia. Cervical cytological screening also can help identify women with cervicitis who require further microbiological studies.

The correlation of cervical intraepithelial neoplasia with human papilloma virus infection is described in Chapter 57. Cytological studies in STD clinic patients and in pregnant women have shown that *C. trachomatis* infection is significantly correlated with certain other epithelial cell changes and inflammatory cell patterns.¹³³ The epithelial cell changes include so-called reactive changes of metaplastic cells and endocervical cells. Inflammatory changes, which are significantly correlated with *C. trachomatis* infection include the presence of transformed lymphocytes and of increased numbers of histiocytes and plasma cells, as well as increased numbers of neutrophils. Large, inclusion-containing vacuoles in endocervical and metaplastic cells also are correlated with *C. trachomatis* infection, but they are relatively nonspecific and are not present in the majority of women with chlamydial infection. Use of cytopathology to identify cervical inflammation in addition to cervical neoplasia, represents a potential but little used approach to control of cervical infections. This can now be facilitated by nucleic acid amplification testing of liquid Pap smear media.^{134,135} “Reflex testing” by nucleic acid amplification for cervical pathogens of specimens yielding inflammatory cervical Pap smears should be viewed as analogous to reflex testing for HPV of liquid Pap smear medium specimens when Pap smears show atypical squamous cell changes of uncertain significance (ASCUS).

■ COLPOSCOPY

Colposcopy has been increasingly used to evaluate women who have cervical cytological smears consistent with cervical intraepithelial neoplasia, and to obtain directed biopsies of colposcopically visible lesions. Colposcopy has potential utility for use in high-risk patients (e.g., in STD clinics) for screening examinations for cervical dysplasia, and for cervical infection.¹³¹ Colposcopic features of papillomavirus infection and of dysplasia, and the use of simple techniques for visual screening for cervical dysplasia and cancer in developing country settings, where cytology and colposcopy may not be available, are described in Chapter 57. Colposcopic features of MPC are described in the preceding and are illustrated in Figs. 55-16, 55-5, 55-6, 55-18, 55-17, and 55-13.

■ HISTOPATHOLOGY

In patients with endocervicitis due to *C. trachomatis*, cervical biopsy may show intraepithelial inclusions, which are located in columnar or metaplastic cells. Such inclusions are best demonstrated by immunofluorescence or immunoperoxidase staining (Fig. 55-20). By electron microscopy with special stains, these can be shown to contain typical elementary and reticulate bodies of *C. trachomatis* (Figs. 55-21 and 55-22). Inflammation surrounds endocervical glands in a patchy distribution, and lymphoid follicles, containing germinal center cells (transformed lymphocytes) can be identified in about two-thirds of patients (Fig. 55-23). The majority of cervical biopsy specimens from patients with chlamydia-positive endocervicitis show superficial focal endocervical micro-ulcerations, reactive endocervical cellular changes, stromal and epithelial cellular

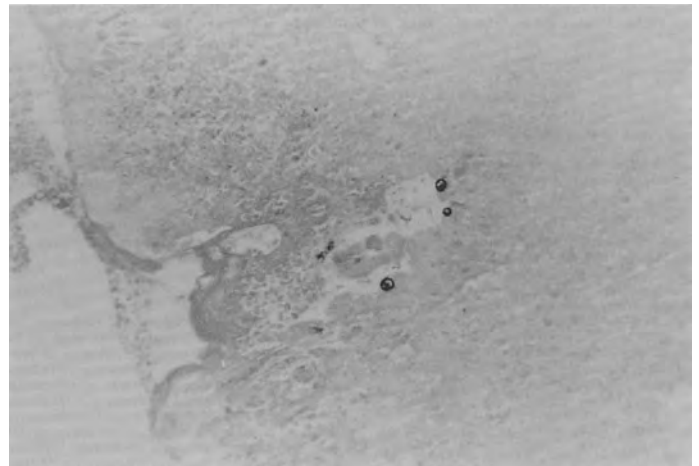


FIGURE 55-20. Immunoperoxidase stain of a cervical biopsy specimen using monoclonal antibodies to *C. trachomatis* showing cervical intraepithelial chlamydial inclusions. (Courtesy of N. Kiviat.)

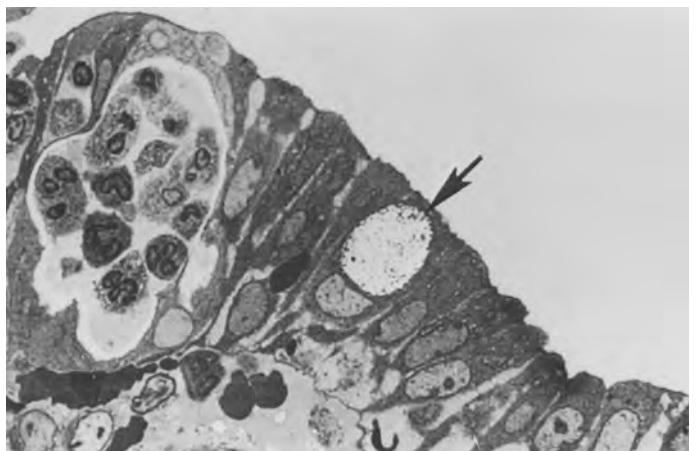


FIGURE 55-21. Thin section of cervical biopsy showing a chlamydial inclusion in a columnar epithelial cell, compressing the nucleus to the base of the cell. Toluidine blue O stain, phase contrast, $\times 1000$ magnification. (Courtesy of J Swanson.)

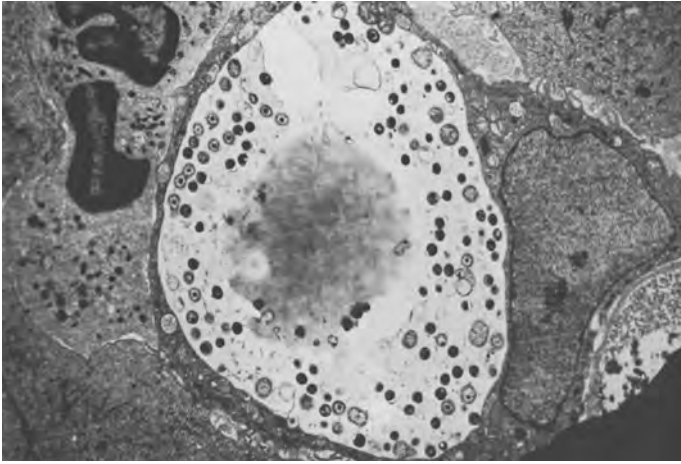


FIGURE 55-22. Electron micrograph of a chlamydial inclusion in cervical biopsy tissue, showing compact elementary bodies, larger reticulate bodies, and intermediate forms that resemble bull's eyes. Uranyl acetate, lead citrate, 12,000 \times magnification. (Courtesy of J. Swanson.)

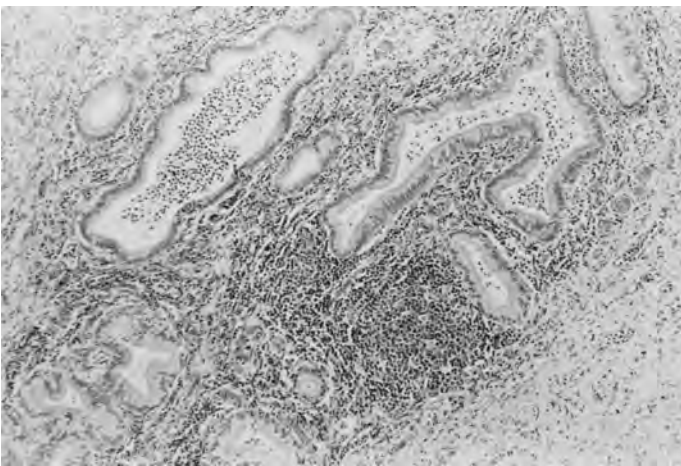


FIGURE 55-23. Endocervical biopsy showing patchy periglandular inflammation associated with chlamydial infection. Several gland lumina are filled with neutrophils, with intraepithelial infiltration by neutrophils, and are surrounded by mononuclear cells, predominantly plasma cells. A rounded germinal center containing transformed lymphocytes is present.

edema, dilatation and proliferation of subepithelial capillaries, and stromal inflammatory infiltration, predominantly by plasma cells.¹³⁶ These changes resemble those described in ocular trachoma.

There is surprisingly little recent information on the histopathology of cervical infection with *N. gonorrhoeae* or of initial and recurrent episodes of HSV cervicitis, or on the histopathology of cervical *M. genitalium* infection. We have observed that HSV infections differ from chlamydial and gonococcal infections in showing deep, necrotic ulceration with stromal infiltration predominantly by lymphocytes; whereas chlamydial cervicitis differs from gonococcal or HSV cervicitis in showing germinal centers and stromal infiltration predominantly by plasma cells.¹³⁶

CONFIRMATORY MICROBIOLOGICAL STUDIES

To provide the best guide to therapy, patient counseling, and management of sex partners, a specific microbiological diagnosis is desirable in patients with cervicitis. This can be accomplished by isolation of *N. gonorrhoeae*, *C. trachomatis*, HSV, or *T. vaginalis*; by immunologic detection of microbial antigens; or increasingly by use of nucleic acid probes or DNA amplification/detection methods. A Gram stain of endocervical mucus is useful in patients with suspected endocervicitis, for detection of gram-negative diplococci associated with neutrophils, as well as for quantitation of neutrophils. However, even if gonococci are identified by Gram's stain, confirmatory testing for *N. gonorrhoeae* is desirable, and culture testing has the advantage of allowing tests for beta-lactamase production, and antimicrobial sensitivity. The presence of cervical lesions suggestive of HSV infection warrants confirmatory testing for HSV (see Chapter 21). Viral isolation and nucleic acid amplification tests can permit differentiation of HSV-1 from HSV-2, which has prognostic importance, since HSV-1 is less likely than HSV-2 to cause recurrent genital herpes. If colpitis macularis is seen, wet mount examination for motile trichomonads is usually positive.

■ TREATMENT FOR MUCOPURULENT CERVICITIS

The 2006 Centers for Disease Control Guidelines for Treatment of STD⁸⁷ (see Appendix B) recommend "the results of sensitive tests for *C. trachomatis* and *N. gonorrhoeae* (e.g., nucleic acid amplification tests) should determine the need for treatment subsequent to the initial evaluation." A negative endocervical Gram stain for *N. gonorrhoeae* does not exclude gonorrhea. The guidelines also recommend that management of sex partners of women with MPC should be "appropriate for the identified or suspected STD," and should include examination and treatment for that STD; and further note that management of persistent MPC is unclear, since infection is not often found, and the need for or benefit of further treatment is unproven.

However, among women with coexistent gonococcal and chlamydial infection of the cervix, persistence of *C. trachomatis* has been more common after single-dose ampicillin therapy than after therapy with trimethoprim-sulfamethoxazole; and persistence or development of cervicitis after therapy was correlated with persistence of *C. trachomatis*.¹³⁷ Treatment of women with gonococcal infection with 4.8 million units of procaine penicillin G plus probenecid was associated with a significantly higher rate of post-treatment cervicitis and PID than was treatment with drugs effective against *C. trachomatis* (tetracycline or trimethoprim-sulfamethoxazole).¹³⁸ Treatment of cervical *C. trachomatis* infection with effective therapy for this pathogen (e.g., 500 mg of tetracycline hydrochloride four times daily for 7 days) has eliminated

mucopurulent endocervical discharge in nearly all women within 3 weeks after completion of therapy.¹³⁹ In another small study, women with mucopurulent cervical discharge who also had BV, were all treated with doxycycline plus ofloxacin, and were additionally randomized to also receive treatment either with metronidazole gel for 5 days or with placebo gel. The MPC resolved in 24 (89%) of 27 given the metronidazole gel, versus 15 (62.5%) of 24 given placebo ($p = 0.03$). This small study raises the question as to whether MPC was related as cause or effect to BV, or whether metronidazole might have activity against other organisms involved in causing MPC.¹³⁰ The emerging data in treatment of *M. genitalium*-associated cervicitis is reviewed in Chapter 40.

PREVENTION OF LOWER GENITAL TRACT INFECTION IN WOMEN

When used correctly, consistent and correct condom use can be regarded as highly effective in preventing sexual transmission of pathogens that infect the columnar epithelium of the urethra and endocervix (e.g., *N. gonorrhoeae*, *C. trachomatis*);¹⁴⁰ and recent prospective studies also indicate effectiveness in reducing sexual acquisition of pathogens that can infect the squamous epithelium of the vulva and penis (e.g., HPV and HSV^{141,142}); although undoubtedly ineffective in reducing sexual transmission of ectoparasites pathogens that infect the cornified skin or the cutaneous appendages (i.e., *Sarcoptes scabiei*, *Phthirus pubis*) (see Chapter 47). The efficacy of other intravaginal barrier contraceptives, such as the diaphragm, in reducing transmission of *N. gonorrhoeae* and *C. trachomatis* is being evaluated.

OBSTETRIC, GYNECOLOGIC, AND SYSTEMIC COMPLICATIONS OF LOWER GENITAL TRACT INFECTIONS IN WOMEN

A high index of suspicion for local complications or systemic disease is essential in evaluating women with symptoms or signs of lower genital tract infection.

The differential diagnosis of vulvovaginitis, or Bartholinitis includes potentially catastrophic diseases, including toxic shock syndrome (TSS) and necrotizing fasciitis of the vulva.^{143–153} TSS associated with tampon use and menses is associated with temperature $>38.9^{\circ}\text{C}$; systolic blood pressure <90 mm Hg; rash with subsequent desquamation—especially on palms and soles; involvement of ≥ 3 of the following organ systems: GI, muscular, mucous membranes (vagina, conjunctiva, pharynx), renal, liver, blood (thrombocytopenia), or central nervous system; and negative tests for causes of similar illnesses (e.g., measles, leptospirosis, Rocky Mountain spotted fever).

Necrotizing fasciitis of the vulva arises from obstetrical or other trauma or episiotomy, vulvar abscess, or Bartholin's abscess, with predisposition for diabetic, alcoholic, or otherwise immunocompromised patients.^{143–153} The process involves the superficial fascia and subcutaneous tissue (as opposed to necrotizing cellulitis, which occurs beneath deep fascia and involves muscle). Symptoms and signs often begin with severe tenderness, swelling, and erythema, progressing to an ecchymotic appearance with bullae and skin breakdown, eventually leading to anesthesia and loss of pain following destruction of superficial innervation. The etiology generally is either group A *Streptococcus pyogenes* or anaerobic plus/minus facultative anaerobic species that can produce gas in the tissue with foul odor. The histopathology includes PMN infiltration, with necrosis of fat and superficial fascia, microabscesses and thrombi, and the presence of causative organisms visualized with special stains. Superantigens produced by β -hemolytic streptococci may contribute to local and systemic manifestations. Diagnosis is prompted by a high index of suspicion, and best confirmed by surgical exploration. Management is guided by the phrase, “Be bloody, bold, and resolute” with surgical debridement; together with prompt antimicrobial therapy that covers streptococci and staphylococci, gram-negative pathogens, and anaerobes. In particular, clindamycin is commonly used, and some clinicians use hyperbaric oxygen or immunoglobulin therapy, although the benefits of these adjunctive approaches warrant further study.

Perhaps the most important aspect of the differential diagnosis of MPC is careful evaluation for complicating endometritis or salpingitis. As discussed in the following and in Chapter 49, endometritis, manifested by midline abdominal tenderness or menorrhagia, often with elevation of the erythrocyte sedimentation rate, C-reactive protein, or peripheral white count, and with characteristic histopathological evidence of endometritis, is often present among women with MPC. Among STD clinic patients with MPC studied at the University of Washington, at least 40% had histopathological evidence of plasma cell endometritis.¹⁵⁴ The classic study of Jacobsen and Westrom required the presence of purulent discharge in the vagina (leukocytes must outnumber other cell types) for the diagnosis of salpingitis.^{155,156} It seems likely that such discharge is probably attributable to MPC in most if not all cases. Jacobsen and Westrom once stated they had never seen salpingitis laparoscopically in a patient who did not have a purulent vaginal discharge.¹⁵⁷ In contrast, U.S. gynecologists have not required the presence of MPC as a criterion for salpingitis, and in fact guidelines developed for diagnosis of salpingitis by a group of U.S. gynecologists and approved by the Obstetrics and Gynecology Infectious Disease Society did not include this criterion.¹⁵⁸ Nonetheless, detection of MPC is useful in increasing the odds that symptoms of lower abdominal or pelvic pain are attributable to PID (see Chapter 56), or that upper abdominal pleuritic pain is attributable to perihepatitis.

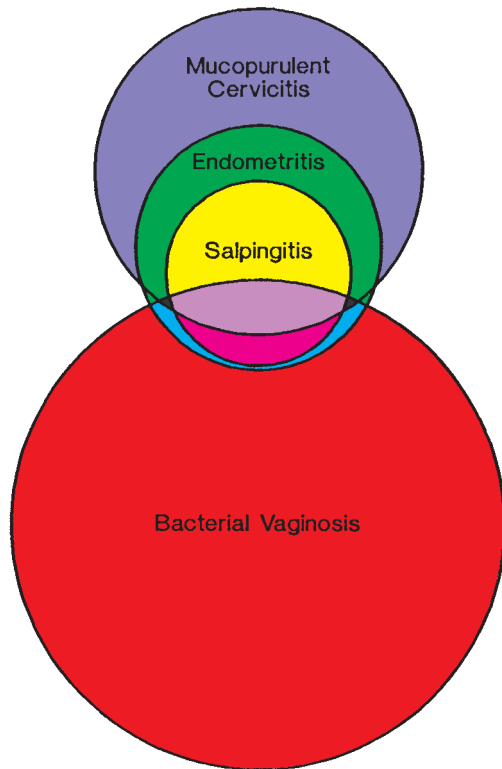


FIGURE 55-24. Hypothetical relationship of upper genital tract infections to lower genital tract infection. In this model, among women with mucopurulent cervicitis, upper tract infections are attributable to *C. trachomatis* and *N. gonorrhoeae*, while among women with bacterial vaginosis, upper tract infections are attributable to bacterial vaginosis-associated vaginal organisms. Upper tract infections in women with both bacterial vaginosis and mucopurulent cervicitis may be owing to either or both sets of organisms. A second hypothesis advanced here is that salpingitis complicating mucopurulent cervicitis or bacterial vaginosis is associated with endometritis.

BV may also predispose to endometritis and salpingitis caused by those pathogens characteristically found in the vagina in BV.¹⁵⁹ Among the set of randomly selected 1984–1986 Seattle STD clinic patients described in the preceding, BV was significantly associated with a clinical diagnosis of PID; and even after adjusting for coinfections and other potential confounders, BV was significantly associated with moderate to severe adnexal tenderness.¹⁶⁰ The role of MPC and the potential role of BV in predisposing to endometritis and salpingitis are illustrated in Fig. 55-24. Simultaneous MPC and BV may be responsible for mixed tubal infections caused by the cervical pathogens (*N. gonorrhoeae*, *C. trachomatis*), together with the BV-associated organisms. HIV infection with immunosuppression may increase the risk of PID, given cervical chlamydial or gonococcal infection or BV; and may increase the risk of tuboovarian abscess among women who develop PID. Evaluation of these and other possible models for the interrelationship between upper and lower genital tract infection could lead to clearer understanding of the pathogenesis of salpingitis. As discussed in Chapter 81, there is also a great deal of evidence for the importance of cervical

and vaginal infection in causing complications of pregnancy, including chorioamnionitis and premature delivery; and evidence for a beneficial impact of detecting and treating such infections early in pregnancy. Increasing emphasis on proper management of these lower genital tract infections in pregnant women can be anticipated. Finally, there is ample evidence that mucopurulent endocervicitis, and endocervical gonococcal and chlamydial infections, are associated with increased risk of acquiring HIV infection, and with increased cervical shedding of HIV; and considerable evidence for an association of BV, trichomoniasis, and vulvovaginal candidiasis with acquisition of HIV. Cervicitis has also been associated with increased probability of shedding of human T-lymphotrophic virus type 1 (HTLV-1)¹⁶¹ among HTLV-1 seropositive sex workers. It is likely that the quantitative shedding of endocervical pathogens per se is also greatest among women with cervicitis, and that quantitative shedding of *T. vaginalis* is greatest among women with vaginal inflammation. Therefore, as with men, early detection and treatment of women with lower genital inflammatory syndromes associated with their LGTI would likely have a greater, impact per case detected—both in terms of the women’s individual benefit and the population benefit—than would screening and treatment for subclinical, nonsymptomatic LGTI in women.

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DEFINITION

Pelvic inflammatory disease (PID) comprises a spectrum of upper genital tract inflammatory disorders among women, which includes any combination of endometritis, salpingitis, tuboovarian abscess, and pelvic peritonitis.¹ Use of the term *pelvic inflammatory disease* is restricted to infections of the upper genital tract caused by microorganisms that ascend from the cervix or vagina; the term excludes blood-borne infections such as tuberculosis. Infections following delivery or induced abortion are also categorized separately as puerperal or postabortion infection.

Salpingitis, or infection of the fallopian tubes, is the most important feature of PID, and the terms *PID* and *salpingitis* are often used synonymously. In this chapter, the term *salpingitis* is reserved for women with visual confirmation of fallopian-tube infection. About two-thirds of women with a clinical diagnosis of PID in fact have salpingitis, while the remaining one-third have either other conditions or normal pelvic organs when laparoscopy is used to confirm a clinical diagnosis of PID.² A small proportion of women with clinical PID have infection and inflammation of the endometrium and/or blood vessels and lymphatics adjacent to the uterus, but without visually recognized salpingitis.³

Women with salpingitis/PID present with a vast array of clinical manifestations that range from virtually none to severe. No symptom, clinical sign, or laboratory result or combination thereof is pathognomonic for PID. In most women with mild or uncharacteristic manifestations, the diagnosis of salpingitis is just not made. In fact, about two-thirds of cases of PID are probably unrecognized.⁴ Attempts were made to sharpen the diagnostic criteria for PID and to grade the severity of clinical manifestations,^{5,6} but there are no accepted criteria or classification in the clinical diagnosis of salpingitis/PID. Chronic PID is an even more poorly defined entity that is often used for patients with chronic pain or infertility, caused by pelvic adhesions and other abnormalities from a prior episode of PID. Thus, the term *PID* has different meanings in various settings.

HISTORICAL REVIEW

In ancient Greece, Aetius described surgical drainage of pus through the vagina, indicating that early physicians not only diagnosed pelvic abscesses but also provided surgical treatment.⁷ In the seventeenth and eighteenth centuries, when direct observations and dissection of human cadavers became acceptable, Mauriceau described inflammatory tumors of the uterine adnexa in puerperal infections in 1683.⁸ In the 1700s, “adnexitis” was described in autopsy reports.

Noeggerath was the first physician to link sexual transmission with infertility in 1876,⁹ 3 years before Neisser identified the gonococcus. In the late nineteenth century, advances in bacteriology, pharmacology, anesthesiology, asepsis, and surgery opened the era of modern medicine. By the turn of the century, a number of important observations were made with respect to PID; some immediately increased our understanding, but others were not fully understood until half a century later. Von Bumm established the sequence of cervical gonorrhoea progression to endometritis, salpingitis, and pelvic peritonitis in 1887.¹⁰ Between 1892 and 1914, Wertheim, Schauta, Kelly, Martin, Schottmüller, and Barfuth isolated a variety of aerobic and anaerobic bacteria from the fallopian tubes and pelvic cavities of women with PID.¹¹

Nocard and Roux in 1898 identified the causative organism of pleuropneumonia in cattle, later to be named *mycoplasmas*.¹² Kelling described the fundamentals of laparoscopy in 1902, and Jacobaeus reported laparoscopy in humans by 1910–1912.¹³ In 1907, Halberstaedter and von Prowazek described inclusion conjunctivitis in experimental primate infections,¹⁴ and in 1910 Fritsch et al.¹⁵ linked inclusion conjunctivitis with genital infection, later recognized as chlamydia. Successful attempts at conservative treatment of PID began in the 1920s¹⁶ and were generally accepted by the 1930s. Sulfonamides were first used to treat PID in the 1930s.

In 1937, mycoplasmas were first isolated from the human genital tract.¹⁷ By 1946, Falk clearly demonstrated the ascending route of spread in PID,¹⁸ and Ruddock in the United States and Palmaer in Paris pioneered modern laparoscopy.¹³

Chlamydia trachomatis was identified by T'ang and coworkers in 1957,¹⁹ and by 1959 the organism was isolated from the human genital tract.²⁰

During the 1960s, laparoscopy was systematically used to provide an accurate diagnosis of salpingitis, and the vast array of clinical presentations became apparent.² Laparoscopy made possible accurate studies of the microbial etiology of salpingitis, and laparoscopy became the gold standard for diagnosis and research in PID. Mycoplasmas in 1970²¹ and chlamydia in 1977^{22,23} were isolated from the fallopian tubes of women with PID, and in 1975 the polymicrobial etiology of PID was described.²⁴ Echoing Noeggerath's theories, Weström in 1975²⁵ quantitated the incidence of infertility and ectopic pregnancy (EP) following salpingitis. During the 1980s and first half of the 1990s, our understanding of PID further increased due to progress in microbiology, immunology, epidemiology, experimental animal models, and social and behavioral sciences.

In recent years, many societies and organizations have published practice guidelines to diagnose and treat PID. Since PID is the only preventable cause of infertility and adverse pregnancy outcome, increased efforts are now focused on PID prevention.

MICROBIAL ETIOLOGY

PID is caused when microbes ascend from the vagina/cervix into the endometrium, fallopian tubes, and contiguous structures. Since a large number of species colonize the vagina and cervix, the microbial etiology of PID is best established by direct culture of upper genital tract tissue. Specimens potentially contaminated by vaginal/cervical flora include endometrium obtained by transcervical biopsy,^{26,27} peritoneal fluid obtained by cul-de-sac puncture,²⁸ or material from transvaginal abscess drainage.²⁶ Direct uncontaminated specimens can be obtained from the pelvic cavity at laparoscopy or laparotomy.^{21,26,29,30} Specimens from the cul-de-sac or peritoneal cavity may also contain microorganisms not necessarily present in infected tubes.^{30,31} Further, comparisons among studies is difficult because of marked differences in the sample method (tissue biopsy, scraping, swabbing, and aspiration), specimen transport (media, time, and temperature), laboratory culture techniques, and spectrum of microorganisms sought.² Finally, modern DNA technology is only now being used for PID.³²

Isolates from the upper genital tract and abdominal cavity in PID are usually classified into sexually transmitted organisms (those never normally isolated from the genital tracts) and endogenous organisms (those often present in the lower genital tract), some of which may also be sexually transmitted.³¹

SEXUALLY TRANSMITTED ORGANISMS

C. trachomatis and *Neisseria gonorrhoeae* both cause PID, while the role of genital mycoplasmas remains unclear.

Herpes simplex virus (HSV),^{21,33} cytomegalovirus, and *Trichomonas vaginalis*^{29,34} occasionally are isolated from the pelvis, but systematic studies provide no convincing evidence that viral pathogens or protozoa cause PID, although HSV may rarely cause peritonitis.

Isolation of more than one sexually transmitted pathogen from the lower genital tract is common in acute PID. From one-fourth to three-fourths of young women with acute PID have *N. gonorrhoeae* and/or *C. trachomatis* isolated from the lower genital tract, although these bacteria are isolated less frequently from the upper genital tract of women with PID.^{21,24,29,30,35,36} *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *T. vaginalis* are also commonly present in the lower genital tract in PID.

■ *N. GONORRHOEAE*

N. gonorrhoeae is the "classic" bacterial cause of PID. *N. gonorrhoeae* has been recovered from the cervix, endometrium,^{31,37} fallopian tubes,^{29,33,35,37} peritoneal fluid,^{10,11,24,37} and serosal surface of the liver^{38–40} in women with PID. The organism is not isolated from normal fallopian tubes. Koch's postulates to establish an organism as the causative agent of disease are not fulfilled because of difficulty to infect animals with *N. gonorrhoeae*.⁴¹ *N. gonorrhoeae* causes a cytotoxic effect^{42,43}; gonococcal endotoxin causes tubal cilia damage in human organ culture experiments.⁴⁴

Ten percent to 19% of women with *N. gonorrhoeae* in the cervix have clinical signs of acute PID.^{45–47} Certain characteristics of *N. gonorrhoeae* appear to predispose to tubal infection, including specific auxotypes and penicillin resistance,^{48,49} the formation of transparent colonies on agar,^{50,51} and certain serovars.^{51,52} Women with *N. gonorrhoeae* and PID tend to have the onset of pain in the first part of the menstrual cycle, suggesting rapid ascent of *N. gonorrhoeae* into the upper genital tract after cervical mucus is lost with menses.⁵³ In women with cervical *N. gonorrhoeae* and PID, the rate of recovery of gonococci from the upper genital tract is inversely related to the duration of symptoms.^{29,54,55}

The endometrium serves as a transition zone between uncomplicated cervical infection and salpingitis. Cervical infection is frequently asymptomatic, and symptomatic gonorrhea may occur only when the organism reaches the upper genital tract. Ultrastructural studies of the pathogenesis of gonococcal endometrial infection indicate that gonococci utilize multiple mechanisms to associate with endometrial epithelial ciliated and secretory cells.⁵⁶ Thus, gonococcal endometritis is a well-characterized clinical syndrome. CDC guidelines include endometritis as well as salpingitis, tuboovarian abscess, and pelvic peritonitis—as manifestations of PID.¹

In (Table 56-1), 42% of 185 women with cervical *N. gonorrhoeae* and PID had *N. gonorrhoeae* isolated from

Table 56-1. Rates of Isolation of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* from the Cervix, and *N. gonorrhoeae* from Fallopian Tubes Among Women with Acute Pelvic Inflammatory Disease

Study	Number of Patients	Cervical Infection		Tubal/Abdominal Infection	
		<i>C. trachomatis</i>	<i>N. gonorrhoeae</i>	<i>C. trachomatis</i>	<i>N. gonorrhoeae</i>
Henry-Suchet et al., France, 1980	17	6/16 (38%)	0/4	4 (24%) ^a 4/6 ^b	1/4 (24%) ^a 0/4 ^b
Møller et al., Denmark, 1981	166	37 (22%)	9 (5%)		
Mårdh et al., Sweden, 1981	60	23 (38%)	4 (7%)		
Gjonnaess et al., Norway, 1982	65	26/56 (46%)	5 (8%)	5/31 (16%) 4/5	0/65 0/5
Bevan et al., England, 1995	104	37 (36%)	14 (13%)	13 (13%) 13/37	3 (3%) 3/14
Mardh et al., Sweden, 1977	53	19 (36%)	11 (17%)	6/20 (30%) 6/7	1/14 (7%) 1/2
Adler et al., England, 1982	78	4 (5%)	14 (18%)		
Ripa et al., Sweden, 1980	206	52/156 (33%)	39 (19%)		
Osser and Persson, Sweden, 1982	209	52/111 (47%)	41 (20%)		
Paavonen, Finland, 1979	106	27 (25%)	27 (25%)		
Paavonen, et al., Finland, 1981	101	32 (32%)	25 (25%)		
Paavonen, et al., Finland, 1980	228	69 (30%)	60 (26%)		
Eilard et al., Sweden 1976	22	6 (27%)	7 (32%)	2 (9%) 1/6	1/22 (5%) 1/7
Bowie and Jones, Canada, 1981	43	22 (51%)	15 (35%)		
Livengood et al., United States, 1992	23	6 (26%)	9 (39%)	1 (4%) 1/6	6 (26%) 6/9
Eschenbach et al., United States, 1975	204	20/100 (20%)	90 (44%)	1/54 (2%)	7/54 (13%) 7/21
Sweet et al., United States, 1981	39	2 (5%)	18 (46%)	0/35 0/2	8/35 (23%) 8/18
Cunningham et al., United States, 1978	104	N.D.	56 (54%)		30/104 (29%) 30/56
Soper et al., United States, 1992	36	6 (17%)	25 (69%)	0 0/6	12 (37%) 12/25
Thompson et al., United States, 1980	30	3 (10%)	24 (80%)	3/30 (10%)	10/30 (33%) 10/24
Totals	1,904	449/1,528 (29%)	493/1,891 (26%)	35/372 (9%) ^a 29/75 (39%) ^b	79/491 (16%) ^a 78/185 (42%) ^b

^aIsolation (%) of *C. trachomatis* and *N. gonorrhoeae* from the peritoneum of the total number of women studied.

^bIsolation of *C. trachomatis* from the abdomen of those with *C. trachomatis* cultured from the cervix and isolation of *N. gonorrhoeae* from the abdomen of those with *N. gonorrhoeae* cultured from the cervix.

N.D. = Not Done

fallopian-tube or cul-de-sac specimens.^{22–24,53,57–71} Many women with PID and *N. gonorrhoeae* also have *C. trachomatis* in the cervix or other bacteria isolated from the fallopian tubes or peritoneum.²⁴ Thus, mixed infections are common.

In populations with high endemic rates of gonorrhea, a high proportion of PID is associated with gonorrhea.

N. gonorrhoeae can be isolated from the lower genital tract in up to 70–80% of women in such populations with acute PID (see Table 56-1).^{70,71} In regions with reliable statistics, the proportion of PID associated with gonorrhea increased in the 1960s, leveled, and then decreased in the 1980s, paralleling changes in the incidence of gonorrhea (Fig. 56-1).^{46,47,72} In

many U.S. populations, gonorrhea was found in 40–50% or more of patients with PID (Table 56-1). However, in current populations in the United States and elsewhere without endemic gonorrhea, less than 5% of young women with PID have gonorrhea (Fig. 56-1).^{47,72} For example, gonorrhea is now uncommon in most European countries. In addition, the rapid decrease of endemic gonorrhea paralleled reduced hospitalization rates for patients with PID. One explanation is that gonococcal PID tends to clinically manifest as peritonitis and be severe enough to require hospitalization.

■ C. TRACHOMATIS

C. trachomatis is now an established important etiological agent in PID. *C. trachomatis* has been isolated from the cervix, endometrium,^{27,72–75} fallopian tubes,^{22,23,62,75,76} and the liver capsule of women with PID.⁷⁷ Specific serum IgM and IgG antibody and titers increase significantly with primary PID associated with chlamydia.²⁴ In experimental infection of human fallopian-tube organ culture, *C. trachomatis* can be recovered for 5–7 days, and inclusions contain all forms of chlamydia in ciliated and nonciliated tubal cells for 72 hours

after inoculation.^{78,79} Disruption of cell junctions and rupture of the cell occur with the release of elementary bodies.⁷⁹ Experimental chlamydial infection in primates produces salpingitis.^{80,81} A single inoculation of *C. trachomatis* directly into the oviducts produces acute infection for several days, after which the organism is no longer recovered and inflammation subsides. The cellular response is complex, and severe inflammation can result, particularly with repetitive *C. trachomatis* infection.⁸¹ Repeat infection contributes to development of a delayed hypersensitivity response, resulting in severe tubal epithelial inflammation and damage with frequent sequelae.⁸²

In contrast to gonorrhea, which tends to produce severe symptoms with mild tubal disease, chlamydial salpingitis tends to produce only mild clinical manifestations with severe tubal disease. The age distribution of women with chlamydia-associated PID parallels that of uncomplicated cervical chlamydia in the same population, with a peak incidence in sexually active teenagers. An estimated 10% of *C. trachomatis* cervical infections ascend to cause PID, although this proportion is less well established than with *N. gonorrhoeae*. In a population-based study, the mean annual incidence of infection per 1000 sexually active teenagers was 97 for genital chlamydial infection and 14 for symptomatic chlamydial PID; among women aged 25–29 years, the annual incidence was 46 for genital chlamydial infection and 3 for chlamydial PID.⁸³

Incidence rates of PID following cervical chlamydial infection may also have decreased in recent years, because of improvement in clinical diagnosis and treatment, including use of sensitive nucleic acid amplification test (NAAT)-based diagnosis and a single-dose azithromycin-containing regimen to treat *C. trachomatis*. Prior diagnostic studies used cervical culture, which required a relatively high bacterial load for detection of *C. trachomatis*. NAAT detects chlamydia at a low bacterial load that may not be associated with ascending infections at as such a high rate. Further, opportunistic screening programs detect more asymptomatic uncomplicated chlamydial infection, which may help explain why the rate of PID associated with chlamydial cervical infection has decreased.

Among women with PID in (Table 56-1), *C. trachomatis* was isolated from the cervix of 29% of 1528 (range 5–51%); by comparison, *N. gonorrhoeae* was isolated from the cervix of 26% of the 1891 women (range 5–80%). Patients in studies with high rates of cervical *C. trachomatis* tended to have low rates of cervical *N. gonorrhoeae* and vice versa. However, 20–30% of patients with *C. trachomatis* also have *N. gonorrhoeae*, and a similar percent with *N. gonorrhoeae* have *C. trachomatis*.^{60,63–66,84} The combined results of most studies from Europe during the 1970s and 1980s indicated that *C. trachomatis* was isolated from 25–50% of women with PID, while *N. gonorrhoeae* was found only in 5–25%. American studies at the time showed higher rates of gonorrhea and lower rates of chlamydial infection than the European studies. A fourfold or greater

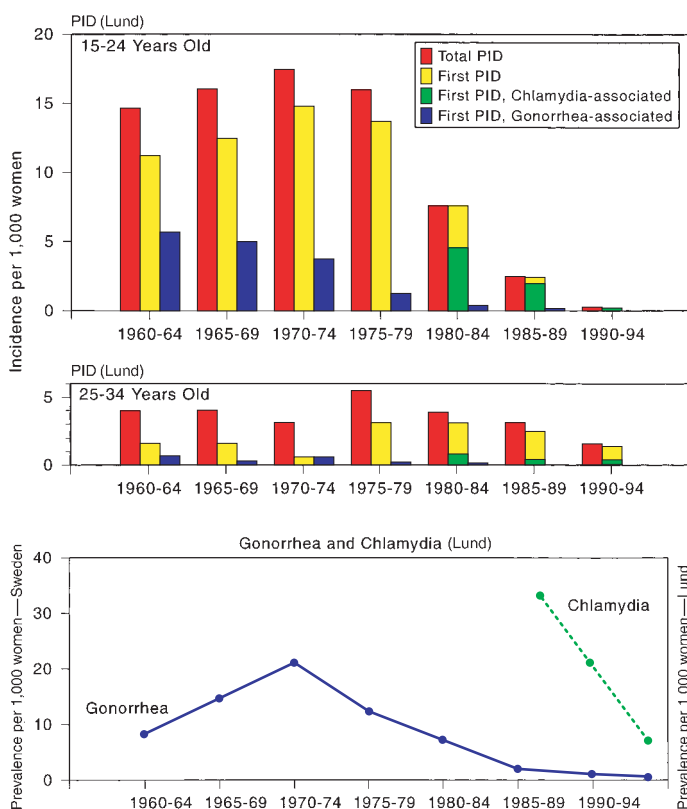


FIGURE 56-1. Mean annual incidences of PID in women 15–24 and 25–34 years of age during 5-year periods 1960–1964 through 1990–1994 in the city of Lund, Sweden, as well as the prevalences of gonorrhea in Swedish women less than 25 years of age from 1960 to 1994 and of genital chlamydial infection in women in Lund from 1987 to 1994.

change in IgG antibody titer to *C. trachomatis* was present in 25% of women with laparoscopically verified PID.^{24,84}

In acute salpingitis, *C. trachomatis* was isolated from the tubes/abdomen in 39% of those with cervical *C. trachomatis* infection, a percentage similar to that for recovery of *N. gonorrhoeae* from tubes of PID patients with gonorrhea (see Table 56-1). *C. trachomatis* was isolated from the fallopian tubes of women with “chronic PID”^{31,85–87} and occasionally from normal-appearing fallopian tubes.^{87–89} *C. trachomatis* is uncommonly recovered from the cul-de-sac.⁹⁰

■ MYCOPLASMAS AND UREAPLASMAS

M. hominis has been isolated from the cervix, the endometrium,⁹¹ and the fallopian tubes of women with laparoscopically verified salpingitis (Table 56-2).^{21,24,59,71,90} The microbe has not been isolated from normal fallopian tubes.^{21,91} Direct inoculation of *M. hominis* into the oviducts of grivet monkeys provoked oviductal infection,^{92,93} and a cytopathogenic effect was demonstrated after inoculation of human fallopian-tube organ culture with *M. hominis*.⁹⁴

M. hominis is recovered frequently from the cervix^{21,91,95,96} but infrequently (0–17%) from the upper genital tract of women with PID (see Table 56-2). Twenty percent to 40% of women with acute PID had significant change of antibody to *M. hominis* demonstrated by enzyme immunoassay (see Table 56-2).^{96–98} In contrast to PID associated with *N. gonorrhoeae* and *C. trachomatis*, PID associated with *M. hominis* was evenly distributed in all age groups.⁹⁵

On the other hand, *M. hominis* is frequently isolated from the lower genital tract of sexually active women^{21,99} and is associated with bacterial vaginosis (BV) (see Chapter 42). BV has been implicated as a risk factor for PID. Thus, *M. hominis* may be either a risk marker or an independent risk factor for PID.

Mycoplasma genitalium is associated with nongonococcal urethritis.¹⁰⁰ *M. genitalium* produces oviductal infections in marmosets, grivet monkeys, and baboons.^{101,102} *M. genitalium* adheres to human fallopian-tube epithelial cells in organ cultures.¹⁰³ Using a polymerase chain reaction (PCR) assay, *M. genitalium* can be detected in vaginal, cervical, and endometrial specimens.^{104,105} *M. genitalium* has been associated with cervicitis¹⁰⁶ and with clinically diagnosed PID¹⁰⁷ and was more common in women with (16%) than without (2%) symptomatic histologic endometritis.¹⁰⁸ Among women with laparoscopically confirmed acute salpingitis, *M. genitalium* was identified by PCR in the cervix or endometrium of 7% and in the fallopian tubes of one.¹⁰⁹

U. urealyticum has been isolated from the fallopian tubes from 2% to 20% of women with PID (see Table 56-2), and a significant increase of serum metabolism-inhibiting antibody to *U. urealyticum* was documented in 20% of women with acute PID.²⁴ However, attempts failed to produce tubal infection in monkeys with *U. urealyticum* failed.⁹³ *U. urealyticum*

Table 56-2. Evidence of Genital Mycoplasma Infection Among Women with Acute Salpingitis

Study	Cervical Isolation (%)	Tubal Isolation (%)	Antibody Titer Change (%)
<i>M. hominis</i>			
Sweet et al., United States, 1979	73	4	
Eschenbach et al., United States, 1975	72	4	20
Mårdh and Weström, Sweden, 1970	62	8	
Thompson et al., United States, 1980	60	17	
Møller et al., Denmark, 1981	55		30
Mårdh et al., Sweden, 1981			40
Bevan et al., UK, 1995	38	0	
<i>U. urealyticum</i>			
Eschenbach et al., United States, 1975	81	2	18
Mårdh and Weström, Sweden, 1970	56	4	
Sweet et al., United States, 1979	54	15	
Thompson et al., United States, 1980	33	20	
Henry-Schet et al., France, 1980	24	17	
Sweet et al., United States, 1981		9	

is commonly found in the lower genital tract of sexually active women, and isolation rates are similar in healthy women and women with PID.^{21,91,99,110} The role, if any, of *U. urealyticum* in PID appears minimal.

■ HUMAN IMMUNODEFICIENCY VIRUS

There is no evidence that human immunodeficiency virus (HIV) infection per se causes PID. Infection with HIV does influence the clinical manifestations of PID, as discussed below in the section “Epidemiology and Risk Factors.”

ENDOGENOUS AND OTHER ORGANISMS

Facultative and anaerobic bacteria are commonly isolated alone or together with *N. gonorrhoeae* or *C. trachomatis* from the endometrium, fallopian tubes, cul-de-sac, and/or abscesses of women with acute PID.^{21,24,30,53,111–113} *Bacteroides* spp. (*disiens*, *fragilis*, and *melaninogenicus*), *Prevotella bivia*, *Escherichia coli*,

Gardnerella vaginalis, *Peptostreptococcus* spp. (*asaccharolyticus*, *anaerobius*, and *magnus*), staphylococci, group B–D streptococci, *Actinomyces israeli*, *Campylobacter fetus*, clostridia, and others have all been isolated from the upper genital tract of women with acute PID. Most of these bacteria are also found in normal vaginal flora, and several occur more often and in increased concentrations among women with BV. Even respiratory pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and group A streptococci occasionally cause salpingitis.^{24,30,31} Often more than one species from the vaginal flora are isolated from the patient, leading to the concept of “polymicrobial” PID.²⁴

Microbial species associated with BV are frequently recovered from upper genital tract or cul-de-sac specimens of women with acute PID and deserve special mention.¹¹⁴ BV has been associated with a clinical diagnosis of PID¹¹⁵ and with histologic endometritis.¹¹⁶ For example, the presence of cervicitis among women with BV was associated with the absence of H₂O₂-producing *Lactobacillus*. The presence of BV flora may increase the susceptibility of both the cervix and the upper genital tract to bacterial invasion by the local production of enzymes, such as sialidase and cytokines that enhance both the invasion and the susceptibility of cells to the effect of bacteria.¹¹⁷ Among patients with a clinical diagnosis of PID, “BV-associated” bacteria were associated with histologic endometritis even when controlling for gonorrhea or chlamydia.¹¹⁸ “BV-associated” bacteria were also isolated from the upper genital tract of women with gonorrhea and PID in a polymicrobial infection.^{24,111} More efficacious screening and treatment of BV may reduce PID rates.¹¹⁹ BV is almost three times more prevalent among black women than among white women.¹²⁰ However, more research is needed on adverse sequelae of BV. Isolation of “endogenous” bacteria from the upper genital tract appears more common in older women²⁹ and may be associated with severe suppurative disease,²⁴ intrauterine device (IUD) use,¹²¹ recurrent PID,⁵³ and tuboovarian abscess.^{24,111} Tuboovarian abscesses virtually always contain a mixture of facultative and anaerobic bacterial species.¹²² In contrast, women with early mild salpingitis at laparoscopy generally have no anaerobic bacteria recovered from the upper genital tract.³¹

These observations could indicate a dynamic infectious process that evolves over time, where a large proportion of cases of PID initially are ascending gonococcal or chlamydial infections. If not treated, such infections might be followed days or weeks later by a “polymicrobial” stage and eventually by abscess formation. Alternatively, endogenous bacteria may ascend into the upper genital tract without a preexisting cervical infection. At present, it is not fully known how or under what circumstances endogenous, predominantly vaginal, bacteria cause infection in an otherwise healthy fallopian tube, or if the tube needs to be “primed or compromised” by an earlier pathological process to enhance tissue invasion.

PID OF UNKNOWN ETIOLOGY

Although many different microbial species can be recovered from the upper genital tract in acute PID, no microorganisms are recovered from 20–30% of patients in recent studies. In one study, 30 (20%) of 151 women with laparoscopically verified acute salpingitis had no evidence of microbial infection. In comparison to patients with PID of proven etiology, those with unknown etiology were older, had a longer average duration of pelvic pain, and relatively mild inflammation at laparoscopy.¹²³ Study of the microbiology of PID also is hampered by what appears to be a large number of unculturable species in the genital tract, which are only identifiable by DNA techniques. The microbial picture in the fallopian tube may well mirror that of the vagina; species identified in the vagina of women with BV in the highest quantity in recent research were unculturable bacteria identified only by PCR.¹²⁴ Newer diagnostic techniques, such as PCR and antigen detection assays, may help refine the etiology of PID.

PATHOGENESIS

By definition, PID associated with sexually transmitted infections (STIs) is caused by spread of microbes from the lower to the upper female genital tract.¹ The spread is canalicular, along mucosal surfaces from the vagina/cervix through the cervix to the endometrial cavity, the fallopian tubes, and into the abdominal cavity. The initial infection involves the mucosa and not the muscularis.⁸⁰ *N. gonorrhoeae* and *C. trachomatis* are demonstrated by culture or antigen detection in epithelia of the cervix, endometrium, and fallopian tube in women with salpingitis.^{75,125} Interruption of the fallopian tubes by cornual resection prevents salpingitis.¹⁸

Some observations indicate that intermittent ascent of microbes into the endometrial cavity and even fallopian tubes might be a physiological phenomenon.^{2,126} Spermatozoa, dyes, and particulate matter are rapidly transported from the vagina/cervix into the pelvic cavity.^{127–129} With menses, the cervical mucus plug is lost, potentially allowing bacteria access to the endometrium. Endometrial blood is commonly present in the abdomen at menses.¹³⁰ Observations in animal experiments also suggest that microbes may be transported through the genital tract without causing infection.¹³¹ The fate of such microbial ascent would depend on their virulence and load, as well as on local defense mechanisms.

The immunopathogenesis of *C. trachomatis* infection is an important focus of recent research. As an intracellular pathogen, *C. trachomatis* induces an antigen-specific cell-mediated immune response. Some individuals are more susceptible to *C. trachomatis* infection and associated sequelae than others, suggesting involvement of genetic factors. Specifically, chlamydial heat shock proteins (CHSP60) are major targets of both humoral and cell-mediated immune

mechanisms. The outcome of *C. trachomatis* infection may depend not only on its virulence but also on the host response. CHSP60-specific cell-mediated immune response is associated with specific HLA types and IL-10 polymorphism, which may reduce the Th1 response needed to eradicate *C. trachomatis*.^{132–134}

Comparisons of immune markers in individuals with non-complicated and complicated chlamydial infection are needed to further understand risk factors or including immunologic factors, associated with the development of long-term sequelae of *C. trachomatis* infection.

FACTORS INFLUENCING ASCENDING CANALICULAR SPREAD

■ COITUS-RELATED FACTORS

PID is rare in virgins,¹³⁵ and the frequency of sexual intercourse appears related to PID among monogamous women.¹³⁶ The role of spermatozoa in the active transport of microbes in PID is unknown. However, “bacteriospermia” occurs, and spermatozoa with adherent microbes migrate through cervical secretions.^{137,138} Spermatozoa with attached *C. trachomatis* were identified in cul-de-sac fluid of women with salpingitis.¹³⁹ Experimental *C. trachomatis* infection in the cervix of pig-tailed macaques produced plasma-cell infiltrates in the tubes of mated but not of unmated animals, suggesting that coitus helped introduce chlamydia to the tubes.¹⁴⁰ On the other hand, symptoms of PID may begin weeks following sexual intercourse, and the use of condoms in women already infected with *N. gonorrhoeae* or *C. trachomatis* does not protect against PID.¹³⁶

■ IATROGENIC PROCEDURES

Diagnostic and therapeutic procedures that disrupt the protective cervical barrier—such as dilatation and curettage, induced abortion, IUD insertion, and hysterosalpingography—introduce bacteria into the endometrial cavity. These procedures preceded the onset of acute PID in up to 12% of women with PID.²

The association of BV with iatrogenic PID or with upper tract infections after hysterectomy or induced abortion has led to a common strategy to treat such patients with prophylactic antibiotics, including use of metronidazole to cover BV-associated organisms.¹¹⁸

■ SEXUAL STEROID HORMONES

Sexual steroid hormones might influence the pathogenesis of PID. Cervical mucus provides a barrier against ascent of microbes into the endometrial cavity; mucous production and characteristics are highly influenced by such hormones.

During the estrogen phase of the menstrual cycle, cervical mucus is watery, with glycoprotein molecules arranged in parallel rows, allowing penetration by spermatozoa.¹⁴¹ In contrast, during the progesterone-dominated luteal phase, the water content of the secretion is low and glycoprotein molecules are arranged in an interlacing network that inhibits spermatozoa penetration.¹⁴¹ Thus, the likelihood of microbes spreading from the cervix to the endometrium might be higher in follicular- than in luteal-phase mucus. In ovulating women, gonorrhea has been diagnosed more often in the follicular than in the luteal phase of the menstrual cycle,¹⁴² and symptoms of STI-associated salpingitis more often start at menses or shortly thereafter than in the luteal phase; this suggests that retrograde menstruation may play a role to transport bacteria into the fallopian tubes.^{130,143,144}

In women not using oral contraceptives, subendometrial myometrial contractions increase in frequency and amplitude at midcycle ovulation, and most contractions move toward the fundus. This pattern is essentially reversed in the luteal phase.¹⁴⁵ These observations underline the pivotal role of ascending infection in the pathogenesis of PID.

Combination oral contraceptive pill (OCP) use is associated with protection against acute salpingitis.¹⁴⁶ The 36-month PID-related discontinuation rate was lower in women using levonorgestrel-medicated IUDs than among women using copper IUDs.¹⁴⁷ In vitro, progesterone suppresses the growth of *N. gonorrhoeae*,¹⁴⁸ while 17- β -estradiol enhances the adherence and growth of *C. trachomatis* in a dose-dependent manner in human endometrial cells.¹⁴⁹ However, the addition of contraceptive progestins (and ethinyl estradiol) to cell cultures had no effect on the replication of *C. trachomatis*.¹⁵⁰

In animal experiments, it has been found that administration of estradiol to ovariectomized guinea pigs prolonged genital infection with the guinea pig inclusions conjunctivitis agent and thus promoted upper genital tract infection.¹⁵¹ Mestranol/norethynodrel enhanced the course of the infection and produced ascending infection not seen in untreated animals.¹⁵² Progesterone alone given to the animals prevented acute endometritis.¹⁵³ By contrast, the duration of experimental *C. trachomatis* infections in monkeys was not influenced by combined OCPs.¹⁵⁴

The apparent protective effect of progestins against ascending infection may be explained by the production of luteal-type cervical mucus, which inhibits bacterial penetration, and by the production of an inactive endometrium, which may inhibit bacterial attachment. OCPs appear to protect against PID in women infected with *C. trachomatis* but not in those with gonorrhea.¹⁴⁶ Thus, the mechanism of protection by sex steroid hormones remains unclear, but protection against overt *C. trachomatis* salpingitis raises the possibility that sex steroids may also downregulate the immune response to *C. trachomatis*.

■ OTHER FACTORS

The ecological disturbance in the vaginal flora of women with BV includes a significant increase in the concentration of potentially pathogenic species (see Chapter 42), which may predispose to upper genital infection if the cervical barrier is breached. An increased risk of PID was documented among women who douche.^{155,156} Induced abortion also predisposes to PID,¹⁵⁷ presumably by the introduction of pathogenic cervical or vaginal bacteria into the upper genital tract.

The role of the IUD in the ascending spread of infection in the female genital tract remains controversial. A majority of epidemiological studies report higher incidences of PID in IUD-using women than in nonusers. With IUD insertion, bacteria from the vagina/cervix are introduced into the endometrium along with the IUD.¹⁵⁸ The risk for PID appears mainly increased during the first 3 months after IUD insertion.¹⁵⁹ However, bacteria are also found to colonize both the string and the main body of the IUD months to years after insertion.¹⁶⁰ IUDs also enhance cervical colonization by bacteria such as actinomyces,¹⁶¹ predispose to BV,¹⁶² and cause impressions in the endometrium,¹⁶³ all of which should increase the risk for PID.

TUBAL INFLAMMATION

The presence of *N. gonorrhoeae* and *C. trachomatis* on genital mucosal surfaces starts a cascade of events involving humoral and cellular defense mechanisms. These mechanisms either can clear the infection and/or provoke tissue damage. This damage can have important reproductive consequences by interfering with fallopian-tube function. In a human fallopian-tube culture model, *N. gonorrhoeae* selectively adheres to and enters nonciliated cells, leaving ciliated cells uninfected. However, the ciliated cells soon undergo ciliostasis and sloughing.^{42,43,164} Ciliary activity of tubes is significantly reduced within 24 hours of initiation of gonococcal infection, as well as after exposure to gonococcal supernatant,⁴⁴ suggesting that the reduction of ciliary activity is mediated by a toxic cell-free product. Reduced tubal ciliary activity also occurs from purified *N. gonorrhoeae* lipopolysaccharide¹⁶⁵ and from monomeric peptidoglycan fragments of *N. gonorrhoeae*.¹⁶⁶ Once inside nonciliated cells, gonococci are protected from immune-defense factors, traverse the cells, and eventually are released from the basal surfaces of the cells by exocytosis.^{42,43}

In the natural disease, antibody binding to gonococcal lipooligosaccharide molecules and peptidoglycan in the fallopian tubes activates complement and initiates the prostaglandin cascade,¹⁴⁴ resulting in an intense acute inflammatory reaction that includes purulent secretion, edema, vasodilatation, and tissue destruction. Gonococcal infection may produce more severe inflammation and symptoms that lead women to seek health care quickly, while other

pathogens may produce more indolent symptoms that result in delayed seeking of health care.^{123,167}

Immunological defense mechanisms induced by a gonococcal infection appear to offer some defense against recurrent gonococcal salpingitis. Antibody against the principal outer-membrane protein of *N. gonorrhoeae* was associated with reduced risk of PID among women with recurrent gonococcal infection in a small 1970s study,⁵² and antibodies to gonococcal opacity proteins reduced gonococcal salpingitis among prostitutes.¹⁶⁸

C. trachomatis attaches to tubal epithelium and is engulfed by endocytosis in a membrane-lined vacuole.⁷⁸ *C. trachomatis* replicates within the cell, protecting it from immune recognition. Infectious *C. trachomatis* elementary bodies are eventually released from the cytoplasmic inclusions into the fallopian-tube lumen.⁷⁸ In human fallopian-tube organ culture, elementary bodies replicate with inclusion formation in both ciliated and nonciliated cells, during a 5–7-day maintenance period of the cultures.⁷⁹ Similar findings occurred in the oviducts of mice infected with murine-*C. trachomatis*.¹⁶⁹ Both cilia and ciliated cells are lost in chlamydial salpingitis of the pig-tailed macaques.⁸⁰

Chlamydial infections induce cytokines, including tumor necrosis factor (TNF), interferon (IFN), and interleukins (IL).^{170–172} In PID, monocytes produce increased levels of IL-1 and IL-6, which in turn can induce scarring and tissue damage.¹⁷³ IFN- γ is present in cervical secretions of women with chlamydial cervicitis¹⁷⁴ and in the sera of women with acute PID.¹⁷⁵ IFN- γ may elicit a further increase in monokine production, and it may induce expression of major histocompatibility complex (MHC) class II molecules on epithelial and endothelial cells and on macrophages. Expression of MHC II-bound exogenous antigens on epithelial cells activates an immune response that in salpingitis could result in tubal cell destruction, analogous to that demonstrated in ocular trachoma.¹⁷⁶

Genital chlamydial infection also elicits a humoral immune response of local and serum antibodies. Serum IgG antibody to *C. trachomatis* is detected up to 6 years after chlamydia-associated PID.¹⁷⁷ Partial protection against reinfection with *C. trachomatis* is present in animal experiments,^{178–180} but this protection appeared both short lived and serotype specific.¹⁸¹ On the other hand, studies on mice^{182,183} indicate that cell-mediated immune mechanisms rather than antibody play a dominant role in the resolution of chlamydial infection.

In experimental studies of primates and mice, repeated *C. trachomatis* inoculations produced progressive tubal scarring.^{81,184} A single direct tubal *C. trachomatis* inoculation in previously uninfected pig-tailed macaques produces a self-limited infection with edema that leaves no tubal scarring.⁸¹ By contrast, tubal inoculation after either repeated cervical or tubal inoculations causes tubal occlusion and peritubal

adhesions.⁸⁰ These findings are analogous to clinical and experimental findings after repeated infection in ocular trachoma,^{185,186} suggesting damage from an immunologic response to chlamydial antigens.⁸² A cytokine response involving INF- γ and IL-2, IL-6, and IL-10 occurs with experimental fallopian-tube infection.¹⁸⁷ While INF- γ helps eradicate *C. trachomatis*, it also stimulates macrophages to intensify the inflammatory response. With acute infection, about 60% of the lymphocytes were CD8 cytotoxic lymphocytes.¹⁸⁷ Repetitive inoculation of *C. trachomatis* appears to result in severe permanent tissue damage from immunopathogenic T-cell responses.

Since CD4 T-cell loss induced by HIV infection increases the risk of *C. trachomatis* salpingitis, it may be that CD8 T cells are relatively more important in immunopathology than are CD4 T cells. This is supported by the observation that chlamydial salpingitis in humans is associated with an increased number of individuals with HLA-A31.¹⁸⁸ HLA-A31 is an HLA class I molecule that presents cytoplasmically processed peptide antigen to CD8 cells.

CD4 T cells may also play a role in immunopathology by T-cell delayed-type hypersensitivity (DTH). In experimental ocular trachoma, DTH was reproduced by placing a 60-kilodalton (kD) chlamydial heat shock protein (CHSP-60) on the conjunctiva of previously infected animals.¹⁸⁹ A human 60-kD heat shock protein (HHSP-60) is present in humans, and both heat shock proteins share extensive amino-acid sequence homology.¹⁹⁰ A proliferative response by lymphocytes to conserved epitopes CHSP-60 and HHSP-60 was demonstrated in five of 10 women with two or more episodes of PID, one of nine with a single episode of PID, and one of 32 control women.¹⁹⁰ Preexisting antibody to CHSP-60 was associated with a fivefold increased risk of developing chlamydial PID.¹⁸⁸ Antibody to CHSP-60 is also associated with severe tubal disease at acute infection¹⁹¹ and perihepatitis,¹⁹² infertility,¹⁹³ and tubal pregnancy.¹⁹⁴ These findings support the likelihood that *C. trachomatis* PID is, in part, an immune-mediated disease, where particularly severe inflammation results from an immune response to CHSP-60.^{82,195}

Antibody response to CHSP-60 appears to be genetically determined.¹⁹⁶ Several mechanisms could explain the role of CHSP-60 in the immunopathogenesis of chlamydial PID. First, antibody to CHSP-60 could reflect a shift in the immune response to a Th-2-dominant response away from a protective cellular immune response. Second, immune complexes involving CHSP-60 antibody could stimulate excessive tissue inflammation. Third, because of the homology between CHSP-60 and human HHSP-60, antibody to CHSP-60 could initiate an autoimmune response to self-HHSP-60, precipitating further tissue injury.

In summary, clinical and experimental studies suggests a profound difference in host-parasite interactions of tubal

infections caused by *N. gonorrhoeae* compared to *C. trachomatis*. *N. gonorrhoeae* appears to induce an acute neutrophilic inflammatory response, while *C. trachomatis* often results in a more indolent, cell-mediated lymphocytic response, possibly a DTH response. In naturally occurring chlamydial salpingitis, however, neither a DTH nor a human heat shock protein expression on tubal cells has been confirmed.

TUBOOVARIAN ABSCESS

Abscess formation is a late manifestation of PID. Neither *N. gonorrhoeae* nor *C. trachomatis* alone produces abscesses in animals or humans.¹⁹⁷ Instead, tuboovarian abscess typically results from a mixture of facultative and anaerobic bacteria, where facultative bacteria dominate the early phase of infection and bacterial metabolic products produce an environment of low oxygen tension that favors the growth of anaerobic bacteria.^{122,197} Anaerobic bacteria dominate the infection in tuboovarian and pelvic abscesses.^{24,34,122}

TISSUE REPAIR

In the repair process, the replacement of dead tubal epithelial cells by ingrowing fibroblasts causes tubal scarring and eventual tubal function impairment. Tubal deciliation,⁸⁰ intraluminal adhesions,¹⁹⁸ tubal occlusion, and peritubal adhesions occur after both natural infection in women¹⁹⁹ and experimental infections in animals.^{197,200–202} These sequelae appear irreversible and can lead to infertility or tubal pregnancy (see below).

Tubal infection and scarring can be rapid; tubal infection and inflammation are initiated within hours for gonorrhea and within days for chlamydia, and tubal scarring begins within days of infection. In follow-up studies of women with STI-associated salpingitis, a delay in seeking care for more than 2 days after the onset of pain was associated with a threefold increase in infertility or EP.¹⁶⁷ Infertility after chlamydial salpingitis in mice was inversely proportional to the time between inoculation and the start of tetracycline treatment.²⁰¹

EPIDEMIOLOGY AND RISK FACTORS

We do not usually accurately know the incidence and prevalence of acute PID in a population, and considerable variation between populations occurs. Patient surveys, outpatient visits, hospital discharge rates, retrospective self-reporting, and extrapolations from incidence figures of gonorrhea and chlamydia were used to study the epidemiology of PID. PID is not a notifiable disease, and different methods have been used to obtain information, including the use of ICD codes, reporting agencies, and self-reporting. Further, accurate

clinical criteria do not exist for the diagnosis, and the diagnostic accuracy of a clinical diagnosis (as assessed by laparoscopy) is only about 65%.² In addition, about two-thirds of women with PID have so few or such mild symptoms that the diagnosis is not even made. These latter cases are only identified if and when the late complications of tubal infection become evident. Thus, published figures on the epidemiology of PID are difficult to compare. A number of factors influenced trends in the incidence of PID over time, most importantly the prevalences of STIs in the population. Other influential factors include demography (parous and/or married women have a lower incidence of PID than nulliparous, single, divorced, or widowed women²⁹), economics, health-care characteristics of the population, sexual risk-taking behavior, douching, smoking and drug habits, and contraceptive use.

REPORTED INCIDENCES AND TRENDS

In the United States, widely divergent figures on the estimated incidence of PID illustrate the difficulties with such estimates. In the 1980s, the annual estimated number of cases of PID varied from 857,000 cases²⁰³ to 1,477,000 cases (based on average numbers of hospitalized cases in 1987–1988 and outpatient cases in 1985–1989)²⁰⁴ to 2,000,000 cases (a 1984 community survey).²⁰⁵ Hospitalization occurred in 30% of cases of PID in the 1980s, falling to 9% by 2001.^{206,207} Of U.S. women 15–44 years, 14.2% in 1982 and 10.8% in 1988 reported that they had received treatment for PID.²⁰⁸

American data indicate a particularly high incidence of PID among young, nonwhite, single, or divorced urban women.^{203–206,208} Between 1972 and 1981, hospitalized cases of PID per 100,000 women per year had decreased among African American teenagers from 1000 to 750 and had increased among white teenagers from 250 to 300 cases.²⁰⁹ Since 1980, the number of hospitalizations of women for acute PID peaked in 1992 at nearly 200,000; the number has fallen fairly steadily since then, to less than 90,000 in 1993 and 70,000 in 2001 (Fig. 56-2).^{207,210} The number of initial visits to physicians' offices for PID peaked in the mid-1980s at over 450,000 visits; the number has fallen sharply since 1993 (Fig. 56-3).²¹⁰ From 1993 to 2001, annually, an estimated 769,858 women 15–44 years of age were diagnosed with PID.^{207,211}

In England and Wales, hospital admissions for PID in women 15–44 years of age increased from 11,300 to 16,000 between 1975 and 1985. The incidence per 1000 women increased from 1.3 to 1.8 in the 20–24-year age group and from 1.1 to 1.2 in the 25–29-year age group but was virtually constant among teenagers and older women.²¹²

In Sweden, hospital discharge rates for PID peaked in 1977 and have significantly decreased since.⁷² The incidence of PID

was followed from 1960 in one region in Sweden, where one gynecological department cared for the female population, and about 90% of all cases were verified by laparoscopy. The total incidence of PID per 1000 women 15–24 years of age increased to a peak of 17.5 in the mid-1970s and subsequently decreased to less than one in 1990–1994 (Fig. 56-1).²¹³ Only minor changes in the incidence of PID occurred in the 30–34-year age group over this time. The incidence of gonorrhea-associated PID per 1000 women 15–24 years of age decreased from six in 1960–1964 to none in 1990–1994, paralleling a significant nationwide drop in gonorrhea rates after 1975. The incidence of chlamydia-associated PID per 1000 women 15–24 years of age decreased from 6.3 in 1977 to less than one in 1994, in parallel with a local chlamydial-control program that markedly reduced chlamydial infection in women. Additionally, recurrent episodes of PID decreased from 21% of the total in 1960–1964 to 4% in 1990–1994, possibly from a lower risk of gonorrhea and chlamydia.²¹³ Thus, trends in STIs significantly influence the epidemiology of PID.

In developing countries, hospital admissions for PID provide a crude marker of PID as a public-health problem. PID

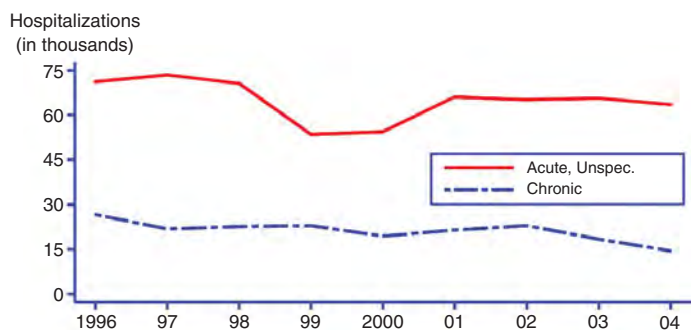


FIGURE 56-2. Pelvic inflammatory disease. Initial visits to physicians' offices by women 15 to 44 years of age: United States, 1996–2005. *Note:* The relative standard error for these estimates range from 19% to 30%.

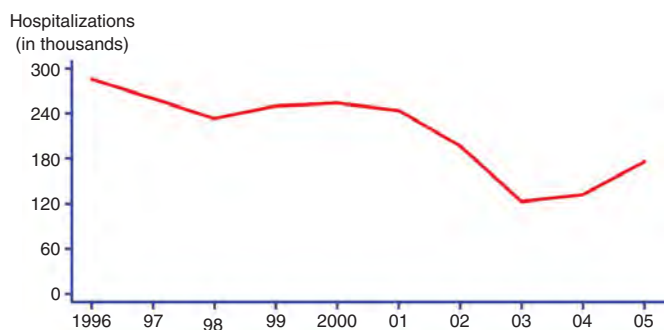


FIGURE 56-3. Pelvic inflammatory disease. Hospitalizations of women 15 to 44 years of age: United States, 1996–2004. *Note:* The relative standard error for these estimates of the total number of acute unspecified PID cases ranges from 8% to 11%. The relative standard error for these estimates of the total number of chronic PID cases ranges from 11% to 18%. Data only available through 2004. (Source: National Hospital Discharge Survey. National Center for Health Statistics, CDC).

has accounted for 17–40% of all gynecological admissions in the sub-Saharan region of Africa, for 15–37% in Southeast Asia, and for 3–10% in India.²¹⁴ However, the exact proportion of PID associated with STIs is not known, because postpartum and postabortal infections are also common.

As expected, tubal infertility is common in developing countries. Some sub-Saharan communities reported that up to 80% of infertility was associated with previous PID and that 30–50% of reproductive-age women are infertile.²¹⁵ EP was the most common surgical emergency in one center in Nairobi.²¹⁶ The ratio of ectopic to intrauterine pregnancy prior to 1980 was 1:88 in Benin and 1:91 in Kampala,²¹⁷ compared with 1:133 in Finland.²¹⁸ In summary, limited data indicate that PID and its consequences are common in most developing nations. Poverty, urbanization, lack of education, prostitution, and the low status of women constitute formidable challenges to control STIs and PID.

RISK MARKERS AND RISK FACTORS

Risk factors for PID that are possibly in the causal pathway after acquiring an STI include age, contraceptive use, coital frequency, douching, invasive diagnostic procedures, health-care behavior, and HIV infection. Knowledge of how risk factors cause PID could allow reduction of PID through education, counseling, or treatment.¹³⁶ By contrast, risk markers are variables associated with PID, which in themselves do not cause the acquisition of microbes that cause PID, nor do they cause the ascent of microbes into the upper genital tract. Risk markers for PID include age, socioeconomic status, smoking, and drug and alcohol abuse. Risk markers and risk factors are interrelated to form a complex network.

SEXUALLY TRANSMITTED DISEASES

Risk factors for the acquisition of STIs are discussed in Chapter 4. As discussed above, gonorrhea, chlamydial infection, and probably BV represent the most important risk factors for PID, based on epidemiologic and etiologic studies.^{47,136} A genital infection was diagnosed in about 50–65% of sexual partners of young women with PID, irrespective of the etiology of PID.^{69,219} Declining rates of PID parallel control of gonorrhea and chlamydial infection in Sweden (see Fig. 56-1) and the United States. In Wisconsin, the institution of a chlamydial treatment program was followed by a drop in the rate of PID.²²⁰ In Seattle, a randomized trial of screening high-risk women for chlamydial infection coupled with chlamydia treatment demonstrated a 60% reduction in the rate of PID, compared to a control group of high-risk women assigned to receive usual care without chlamydia screening.²²¹

AGE

Age is associated with PID, probably as a risk marker rather than a causal risk factor.^{49,210} The risk to acquire acute salpingitis is 1:8 for sexually active 15-year-olds, 1:16 for 16-year-olds, and 1:80 for women 24-year old.²²² The high number of sexual partners in younger women is associated with more frequent acquisition of STIs in this group. Women 20–24 years of age have the highest incidence of both STIs and PID, closely followed by teenagers.²²² After adjusting for sexual activity, however, sexually active teenage females have higher incidences of both gonorrhea and chlamydial infection than any other age group. The incidences of both STIs and PID decrease significantly with increasing age beyond the age of 24 years. Additionally, age is no longer associated with PID after adjusting for gonorrhea and chlamydial infection, which further suggests that young age is related to PID through increased rates of these two STIs.²²³ The impact of history of these STIs on risk of PID should be viewed as a risk factor independent of the physiologic attributes of age per se.

CONTRACEPTIVE USE

The magnitude of the effect of contraception on PID is difficult to ascertain. Experimental studies of the influence of contraceptives on the pathogenesis of PID have been cited above. The use of different methods of contraception influences the risk of acquiring STIs, as well as the risk of progressing to PID. Some contraceptives, such as barrier methods, reduce the acquisition of STIs, while oral contraceptives may enhance the acquisition of chlamydial infection yet reduce the development of PID among those who have acquired chlamydial infection.¹⁴⁶ Use of IUDs has no known influence on STI acquisition, but it enhances the movement of bacteria from the cervix to the uterus/tubes. Behaviors that influence both contraceptive choice and PID potentially confound studies of the association of contraceptives with PID. Women using no contraception may tend to take sexual risks and pregnancy risks and have poor health-care utilization, which in concert can increase the rates of STIs, PID, and pregnancy. Contraceptives have not been randomly assigned to women to examine the influence of contraception per se on PID, so the influence of contraception on PID is generally assessed from case-control studies.

Barrier methods, such as condoms and probably diaphragms, decrease the acquisition of STIs by women. Spermicidal agents offer a partial protection against cervical pathogens by a direct inhibitory effect on bacteria. Thus, barrier and spermicidal use has been associated with modest reduction in PID.^{136,224}

Overall, OCP use has generally been associated with a reduction of 40–60% in the rate of PID.¹³⁶ Among women with chlamydial infection, OCP use was associated with a 70% reduction in risk of PID,¹⁴⁶ but OCPs do not appear to protect women with gonorrhea from PID.¹⁴⁶ The protective

effect of OCPs on chlamydial PID, but not other forms of PID, raises the possibility that OCPs might influence the immune response to chlamydial infection and thereby reduce fallopian-tube inflammation. This hypothesis is consistent with the finding that OCP users have had less severe damage of the fallopian tubes when PID is visualized laparoscopically, compared to IUD users or women who use no birth control.²²⁵ Women in these studies used first- and second-generation combination OCPs with higher doses than most OCPs used today, however, and there is a complex interaction of OCP use with age, ectopy, and cervical infection, and perhaps with health-seeking behavior and health-care access as well.²²⁶

At least 20 controlled studies from the 1960s through the 1980s reported a two- to fourfold increased risk of PID or consequences of PID among users of IUDs, compared to women using other or no contraceptives.^{227,228} Women who use IUDs clearly have an increased risk of PID in the first 1–3 months following insertion of the device, probably related to the introduction of bacteria into the uterus during insertion.¹⁵⁹ After this immediate postinsertion period, the rate of PID decreases but remains above that of non-IUD users, based on data from case-control studies of PID,²²⁹ tubal infertility,^{230,231} and EP.²³² Later infections are probably related to the long-term colonization of the IUD and string surface demonstrated by bacteriologic and scanning electron microscope studies.^{160,233} Uncontrolled prospective cohort studies of IUD users report low rates of PID, but since they lack non-IUD-using controls, they fail to examine the sensitivity to detect PID.²²⁸ Thus, prospective cohort data are not consistent with case-control study data. Women who use IUDs appear to have more non-STI-associated PID than do non-IUD users.^{234,235} The rate of PID among IUD users can be reduced by screening for gonorrhea and chlamydia before insertion and by recognizing early signs of infection such as abnormal vaginal discharge, vaginal bleeding, and mild abdominal pain. Progesterone-releasing IUDs may reduce the rate of PID compared to copper or nonmedicated IUDs.¹⁴⁷

Studies of the association of prior IUD usage with tubal infertility and EP are not subject to the bias of underdiagnosis or misdiagnosis of PID. Women using only copper IUDs have a threefold increased rate of tubal infertility, after adjustment for variables associated with infertility.²³⁶ Copper IUD users also had a threefold increased rate of EP following IUD removal and after adjustment for variables associated with EP.²³² The data on tubal infertility and EP following IUD use are consistent with the increased rates of salpingitis noted in case-control studies of IUD users.

■ DOUCHING AND BV

In the United States, douching is practiced more commonly among African Americans and is associated with low socioeconomic status. Women with PID report frequent douching

more commonly than controls, even after adjustment for gonorrhea and chlamydial infection.¹⁵⁵ A recent confirmation of the link between douching and PID and a link between douching and EP²³⁷ raises the possibility that douching upsets the vaginal ecology or in some way enhances bacterial invasion of the uterus.

Among women undergoing induced abortion, those with BV have a threefold increased rate of postabortion PID compared to those without BV. The increased rate of PID was reduced to baseline in a randomized treatment trial of BV.¹⁵⁷ Frequent intercourse has been implicated as a risk factor for PID.¹³⁶ BV, with its 1000-fold increased concentration of a variety of bacteria in the lower genital tract, might interact with the frequency of intercourse to cause ascending infection.

■ SURGICAL PROCEDURES

Surgical procedures such as dilatation and curettage, hysterosalpingography, and IUD insertion spread microbes to the upper genital tract, by breaching the protective cervical barrier. Such procedures preceded the onset of PID in about 12% of cases.²

■ SMOKING, ALCOHOL, AND ILLICIT DRUG ABUSE

Cigarette smoking was related to a twofold relative risk of PID.^{136,238} However, a dose-response relationship was not observed,²³⁸ and the relationship between smoking and PID is not consistent. The association between alcohol and illicit drug use, particularly cocaine and the risk of PID, may occur because of high STI rates in this population.¹³⁶

■ HIV INFECTION

Patients with HIV infection may have increased risk of PID, although several potential biases could distort the recognition and incidence.²³⁹ The seroprevalences of HIV were 15–17% among patients with PID compared to 2–3% among control women in two U.S. studies,^{240,241} and they were elevated in patients in Nairobi with PID.²⁴² HIV infection may also influence the course and clinical manifestations of PID, particularly among patients with markedly suppressed immunity. Patients with PID who were also HIV positive tended to have more abscesses^{243,244} and more frequent surgical intervention,^{244,245} compared to HIV-seronegative women with PID. The Centers for Disease Control and Prevention (CDC) recommends early hospitalization and intravenous antibiotics for HIV-infected women with PID.²⁴⁶

CLINICAL MANIFESTATIONS

In response to the spread of microbes from the lower to the upper genital tract and, in some instances, the abdominal cavity, inflammatory mediators cause endometritis, salpingitis, peritonitis, or perihepatitis. Different etiologic agents

(*N. gonorrhoeae*, *C. trachomatis*, etc.) tend to cause different clinical presentations, ranging from mild to severe (Fig. 56-4). Mild symptoms may not prompt patients to seek care and may allow physicians to miss the diagnosis. About two-thirds (range 30–75%) of infertile women with postinfection tubal obstruction report no history of prior PID,^{4,247–250} indicating that subclinical infection accounts for the majority of PID and tubal infertility following PID. On the other hand, many patients with suspected PID have other conditions. When a clinical diagnosis of PID is made, the specificity of any one clinical and laboratory diagnostic procedure is low; in general, the clinical diagnosis of PID is incorrect about one-third of the time. Up to one-third of women with pain and other clinical findings suggestive of PID, in fact, have other diseases or no disease.^{251–257}

■ SUBCLINICAL DISEASE (ATYPICAL PID, “SILENT” PID)

Historically, low abdominal or pelvic pain was regarded as the symptom sine qua non to suspect acute PID.² However, as noted above, individuals with apparent subclinical infection identified in studies of postinfection sequelae of salpingitis, such as tubal occlusion, hydrosalpinx, infertility, and EP, often give no past history of treatment for PID. On the other hand, in detailed focused interviews of infertile women with “no history of PID,” medical visits for abdominal pain were reported by 60% of those with tubal occlusion, compared to only 19% of those without tubal disease.²⁵⁸ Thus, many who recall no treatment for PID, nevertheless, may have experienced symptomatic PID and even have sought medical care.

Inflammation or microbes in the endometrium and fallopian tubes, and abnormal tubal ciliary function, can be found in women with no or few symptoms of PID. Histopathologic evidence of endometritis (≥ 10 plasma cells in any of six tissue sections) was found in 45% of women with mucopurulent cervicitis (MPC), including 65% of those with chlamydia-associated MPC.²⁷ Some of these patients had abnormal uterine bleeding or mild uterine tenderness, but no overt signs of salpingitis. Other studies demonstrated *C. trachomatis* in the endometrium in 26% of asymptomatic infertile women with serum antibody to chlamydia,²⁵⁹ and in the fallopian tubes

of 15% of infertile women without clinical or laparoscopic evidence of acute salpingitis.²⁶⁰ Among asymptomatic women undergoing laparoscopic sterilization, plasma cells were present in the tubal mucosa of 47% of IUD users and 1% of those who have never used IUDs.²⁵⁰

Some evidence suggests that *C. trachomatis* infection can persist without symptoms in fallopian tubes after treatment. In one study, *C. trachomatis* DNA and/or antigen was detected in fallopian-tube biopsy specimens of 19 of 24 women undergoing surgery for postinfection tubal factor infertility (TFI).⁸⁵ Eight women had been treated for PID and six for chlamydial cervicitis. However, these data have not been confirmed.

Another study suggests that tubal pathology from prior PID appears unrelated to presence or absence of history of previous clinical symptoms. Among 59 women with TFI, abnormal ciliary-beat frequency in fallopian-tube specimens and structure measured by scanning and transmission electron microscopy were identical in women with and without a history of overt PID.²⁶¹

Thus, ascending infection can cause endometrial and tubal inflammation, resulting in tubal scarring, impaired tubal function, tubal occlusion, and infertility, even among those who report no prior treatment for PID. *C. trachomatis* is particularly implicated in subclinical PID, on the basis of (1) lack of prior history of PID among chlamydia-seropositive women with tubal damage,^{4,247} (2) detection of chlamydial DNA or antigen among asymptomatic women with tubal infertility,⁸⁵ and (3) mild clinical manifestation when acute PID infection occurs in symptomatic PID, as discussed below. These data further imply that the best method to prevent PID and its sequelae is the surveillance and control of lower genital tract infection, particularly chlamydia and gonorrhea. Promotion of early symptom recognition and health-care seeking may also reduce the sequelae of PID.

Endometritis is generally thought to represent an intermediate phase of PID. However, endometritis has also been described as a distinct pathologic syndrome. Among women with suspected PID, the histopathologic manifestations of endometritis are associated with clinical manifestations of infection and specific risk factors that were intermediate in frequency between women with salpingitis and women with neither endometritis nor salpingitis.²⁶² The potential for the progression to salpingitis would seem to warrant antimicrobial therapy, although the natural history of endometritis with or without treatment remains unclear. In particular, the frequency with which endometritis clears with menstruation, persists without spreading to the fallopian tubes, or progresses to salpingitis needs further study.

The PEACH study was a multicenter randomized clinical trial designed to compare the effectiveness of inpatient and outpatient treatment for mild-to-moderate PID. PEACH investigators also studied the association between endometritis and reproductive morbidity. Surprisingly, endometritis was

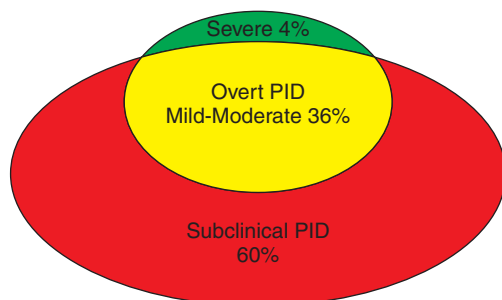


FIGURE 56-4. Illustration of the probable proportions of clinical manifestations of PID.

not associated with reduced pregnancy rates, recurrent PID, or chronic pelvic pain.^{263,264} The conclusion from the PEACH study was that, among women with clinically suspected mild-to-moderate PID treated with standard antibiotics, endometritis was not associated with reproductive morbidity. These findings suggest that, although endometritis can accompany salpingitis, endometrial inflammation alone does not predict future morbidity among women with acute PID. Alternatively, endometritis and PID may be separate clinical entities and not necessarily different aspects of the same disease condition. Another PEACH report addressed clinical predictors of endometritis in women with symptoms and signs of PID. The finding most highly associated with endometritis was a positive test result for *C. trachomatis* or *N. gonorrhoeae*. It is clear that not just one or a few clinical criteria are enough to accurately diagnose upper genital tract infection. Combinations of clinical criteria can increase predictive values for PID. Sensitivity is increased by using the presence of adnexal tenderness as a minimal criterion to diagnose PID. Criteria that support the probability of endometritis include abnormal cervical or vaginal discharge, elevated temperature, elevated leukocyte count, and positive test results for *N. gonorrhoeae* or *C. trachomatis*.²⁶⁵

■ MILD AND MODERATELY SEVERE PID

Most laparoscopically verified cases of overt PID have mild-to-moderate symptoms and physical signs (see Fig. 56-4).²⁹ Up to 75% of women with mild or moderate PID are sexually active, are less than 25 years of age, and have gonococcal or chlamydial infection.^{47,222}

In (Table 56-3), consecutive women routinely laparoscoped because of assumed PID all had low abdominal or pelvic pain

for less than 3 weeks, cervical motion tenderness, and an increase of inflammatory cells in the cervical/vaginal secretion on microscopic wet mount.^{2,29} Salpingitis was identified at laparoscopy in 65% of those with a clinical diagnosis of PID, but some of the remaining women without salpingitis had lower genital tract infection.² The prevalence of selected symptoms in (Table 56-3) was similar among women found to have salpingitis and those with no salpingitis; no symptom helped to distinguish the group with salpingitis.

Various combinations of symptoms and signs are also given in (Table 56-4), for the proportions of 2220 women in the Swedish study with and without salpingitis. A minimum of clinical and laboratory abnormalities (lower abdominal pain plus signs of a lower genital tract infection and cervical motion tenderness) was present in 16% of women with salpingitis. Sixty-one percent of women with salpingitis and 39% without salpingitis had these minimum abnormalities. The addition of an elevated ESR or temperature or an adnexal mass (especially two to three of these abnormalities) increased the possibility of salpingitis. In fact, 84% of the women with salpingitis had the minimum criteria and at least one of the three additional abnormalities; however, so did 36% of those with no salpingitis.

The general condition of the patient with mild or moderately severe PID is good. Pain associated with PID is usually subacute and slow in onset, bilateral, and dull in character and present in the lower abdomen or pelvis. Of women with PID who experienced pain within 7 days of the first menstrual day, 81% had gonococcal or chlamydial infection compared to 66% of those with premenstrual onset of pain.¹⁴³ A short period of pelvic pain (<3 days) at time of presentation to the clinic was significantly correlated with gonorrhea-associated PID and with age >30 years.²⁹ Women with chlamydia-associated

Table 56-3. Percent Prevalence of Symptoms, Signs, and Laboratory Abnormalities Among 807 Women Subjected to Laparoscopy Because of Clinically Suspected Salpingitis

Symptoms	Laparoscopic Diagnosis		Signs and Laboratory Abnormalities	Laparoscopic Diagnosis	
	Salpingitis, % (n = 623)	No Salpingitis ^a , % (n = 184)		Salpingitis, % (n = 623)	No Salpingitis ^a , % (n = 184)
Abnormal discharge	55	56	Temperature > 38.°C	41	20
Irregular bleeding	36	43	Palpable mass	49	25
Dysuria	19	20	ESR ≥ 15mm/h	76	53
Vomiting	10	9	WBC > 10,000/mL blood ^b	59	33
Anorectal symptoms	7	3	Acute phase reactants ^c	79	24
			Decreased isoamylases ^d	90	20

^aNormal intraperitoneal findings; assumed to have lower genital tract infection or endometritis.

^bWBC was determined in 186 cases of salpingitis and 54 controls with no salpingitis.

^cAntichymotrypsin, orosomuroid, or acute-phase reactants including CRP, determined in 40 cases of salpingitis and 15 controls with no salpingitis.

^dDetermined in peritoneal fluid in 57 cases of salpingitis and 20 controls without salpingitis.

Table 56-4. Correlation of Clinical and Laboratory Abnormalities with Laparoscopic Findings in 2220 Cases, Given a Clinical Diagnosis of Acute Salpingitis

Clinical and Laboratory Abnormalities	Laparoscopic Salpingitis, %	Diagnostic Normal or Other, %	Percentage of Women with Salpingitis Presenting the Symptoms or Signs
Low abdominal pain plus signs of an LGTI ^a plus cervical motion tenderness	61	39	16
As above plus one or more of the following: ESR \geq 15 mm/h; temperature > 38.0°C; palpable adnexal mass:			
+ one of the above abnormalities	78	22	28
+ two of the above abnormalities	90	10	39
+ all three abnormalities	96	<u>4</u>	<u>17</u>
		75	100

^aLGTI = lower genital tract infection, as defined by the presence of inflammatory cells outnumbering other cellular elements on wet-mount examination of vaginal fluid.

Table 56-5. Prevalence of clinical and Laboratory Abnormalities in Women with Laparoscopically Verified Acute Salpingitis Associated with Cervical Infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or Neither Organism

Clinical and Laboratory Abnormality	Gonorrhea, % (n = 19)	Prevalence of Clinical and Laboratory Abnormalities	
		Chlamydia, % (n = 68)	Neither, % (n = 64)
Duration of pelvic pain:			
≤ 3 days	32	15	38
> 10 days	21	41	27
Temperature > 38.0°C	52	22	30
Palpable adnexal mass	52	25	20
ESR \geq 30 mm/h	32	65	19
Irregular bleeding	25	40	30

PID more often reported a period of pain exceeding 1 week in duration (Table 56-5).¹²³ Deep dyspareunia is frequent in women with PID.²⁹

A fever was reported by about one-half of women with gonorrhea-associated PID, but only by 22% of those with chlamydial PID (Table 56-5). A palpable mass occurred slightly more often in women with gonorrhea than the other groups, and ESR >30 mm/h was associated with *C. trachomatis*. Irregular vaginal bleeding was also common and significantly associated with chlamydia-associated PID (Table 56-5).¹²³ Abnormal bleeding appears to be a manifestation of endometritis. Bleeding is often the only symptom (other than

pelvic pain) of chlamydial PID.²⁵⁸ One-fifth of women with PID reported dysuria,^{2,29} reflecting the urethritis caused by gonorrhea and chlamydial infection. Nausea and vomiting are infrequent in mild-to-moderate PID and, if present, should raise suspicion of an appendicitis or a ruptured EP.

Despite increased inflammatory cells in the cervical/vaginal discharge of all cases in the Swedish series, only slightly more than one-half of the patients with PID reported symptoms of increased or changed vaginal secretion (see Table 56-3).²⁹ Thus, symptoms of lower genital tract infection preceding PID go unnoticed or are not present.

Clinical symptoms and signs do not accurately predict the extent of tubal disease observed at laparoscopy.²⁶⁶ Patients with tubal occlusion or moderate-to-severe tubal adhesions are fairly equally distributed among patients with mild-to-moderate and severe clinical symptoms and signs.^{25,249,267}

■ SEVERE PID

Clinical manifestations of severe PID correspond to classic textbook descriptions of PID, but severe manifestations occur in only 5–10% of those with overt PID, at least in industrialized settings. Severe PID has two general etiologic categories: (1) young patients with florid peritonitis, usually from gonorrhea, and (2) older patients with an abscess and no STI-associated disease.^{2,29,222,267} In fact, severe PID was diagnosed in only about 3–4% of all patients with PID in Swedish and American studies.^{29,222,267} This group represents only the tip of the iceberg of PID cases (see Fig. 56-4).

Patients with peritonitis appear very ill, usually with a short duration of symptoms (e.g., <3 days), fever, chills, purulent vaginal discharge, nausea, vomiting, abdominal guarding, and other signs of diffuse peritonitis. The white blood count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are usually elevated. Patients with an abscess have a more varied duration and severity of pain, but they are usually febrile with clinical or ultrasonographic evidence of an abscess.

■ CLINICAL MANIFESTATIONS OF EXTRAGENITAL INTRA-ABDOMINAL SPREAD OF *N. GONORRHOEA*E AND *C. TRACHOMATIS*: PERIAPPENDICITIS AND PERIHEPATITIS

Both *N. gonorrhoeae* and *C. trachomatis* may enter the abdominal cavity and cause inflammation of serosal surfaces.^{268,269} Spread of gonococci from gonococcal salpingitis, causing periappendicitis, was described by Moritz in 1912,²⁷⁰ and gonococcal perihepatitis was described in 1930 by Curtis²⁷¹ and in 1934 by Fitz-Hugh.³⁸

Periappendicitis is serositis not involving the intestinal mucosa. Periappendicitis alone is found in 1–15% of appendices removed because of a preoperative diagnosis of acute appendicitis.²⁷² The majority (32/41) of patients with periappendicitis in one study were young women, and eight of the 32 had “tubal abnormalities.”²⁷³ Periappendicitis must always be kept in mind; when an appendix is removed from a young woman, the appendix should be opened and the mucosal surface inspected. A normal-looking mucosal surface strongly suggests periappendicitis secondary to salpingitis. All seven appendices removed from 112 women with bilateral salpingitis had histologically confirmed periappendicitis, and all had chlamydial salpingitis. The appendix was adherent to the right fallopian tube in six women, indicating a direct spread

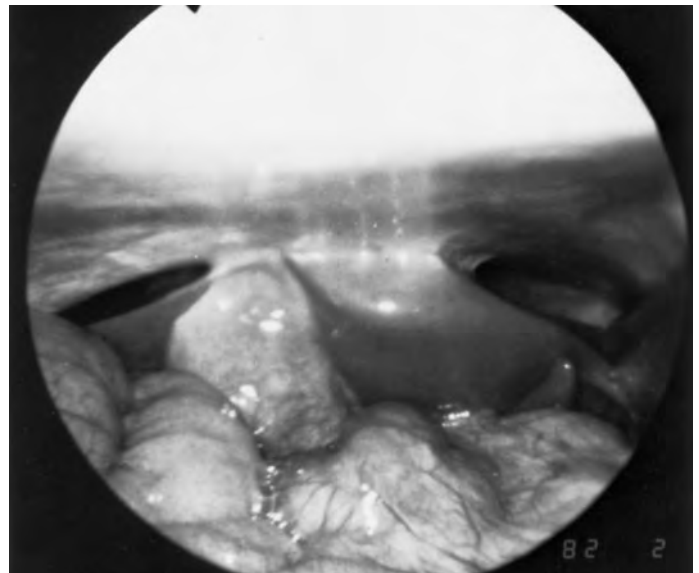


FIGURE 56-5. Laparoscopic view of an early-stage Fitz-Hugh–Curtis syndrome with the liver surface closely adherent to the anterior abdominal wall.

of organisms from the infected tube to the appendiceal serosa, but *C. trachomatis* was not detected in the removed appendices.²⁷⁴ By contrast, an inflammatory mass of both the appendix and the right tube with a normal left tube indicates primary appendicitis.²⁹

Perihepatitis involves inflammation of the liver capsule and the adjacent peritoneum associated with PID. The liver parenchyma is normal.^{38,269} In acute perihepatitis, filmy fibrinous deposits develop on the reddened liver capsule (“pepper-and-salt appearance”), and avascular, initially soft, adhesions form between the liver capsule and the adjacent parietal peritoneum under the ribs (Fig. 56-5).^{275,276} The adhesions eventually form dense “violin-string” adhesions between the liver capsule and the abdominal wall (Fig. 56-6); dense adhesions indicate prior perihepatitis.²⁷⁶

Although some women with laparoscopic perihepatitis report no local symptoms,²⁷⁶ acute severe pleuritic right-upper-quadrant abdominal pain is a cardinal clinical sign of perihepatitis.^{269,276} Its sudden dramatic onset mimics pleuritis or cholecystitis. Right-upper-abdominal tenderness, guarding, and slight liver enlargement on palpation are present. A friction rub is occasionally auscultated over the liver.³⁸

The results of conventional laboratory tests (ESR, WBC, and CRP) with perihepatitis usually are within the ranges seen in other cases of acute salpingitis.^{192,276} Liver enzymes are usually normal.^{192,275–277} A small amount of basal pleural fluid may be found on X-ray.²⁷⁸ Ultrasonic examination of the gall bladder is normal in perihepatitis but should be performed to differentiate perihepatitis from gall-bladder disease.

Perihepatitis has been observed by laparoscopy in 5–15% of patients with acute salpingitis,^{279,280} although a smaller proportion have clinical signs of perihepatitis.^{275–280} Twenty-four of

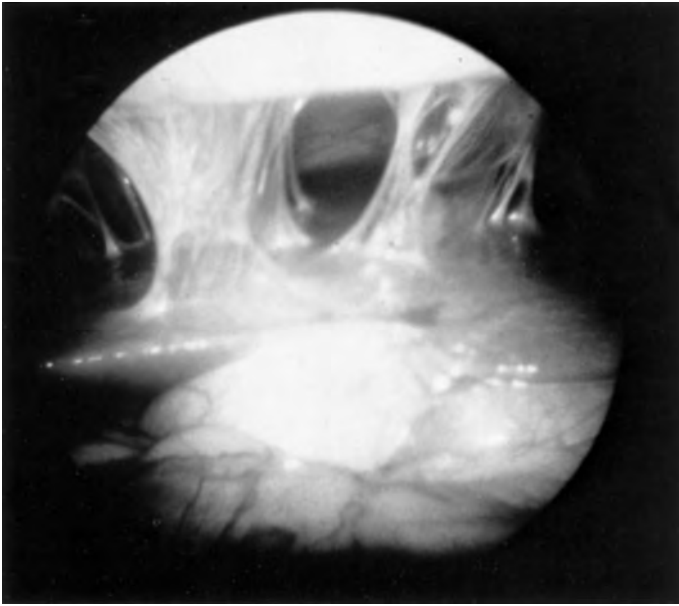


FIGURE 56-6. Laparoscopic view of a later-stage Fitz-Hugh–Curtis syndrome demonstrating fibrous adhesions, including “violin-string adhesions,” between the liver surface and the anterior abdominal wall.

38 women with laparoscopic signs of perihepatitis and salpingitis had right-upper-quadrant abdominal pain.²⁷⁹ Other conditions can cause upper-quadrant pain, and laparoscopy can establish a definite diagnosis of acute perihepatitis.

Perihepatitis was initially associated with gonococcal PID,^{38,211} but in most recent reports it was associated with *C. trachomatis*.^{269,277,280–282} *C. trachomatis* was isolated from the liver capsule in women with perihepatitis.^{276,282} An elevated serum antibody to *C. trachomatis* of $\geq 1:32$ occurs in 70–75% of women with perihepatitis^{269,277,280}; the geometrical mean titer of *C. trachomatis* antibody is higher among women with perihepatitis than among those with salpingitis alone.²⁷⁷

The pathogenesis of perihepatitis remains unclear. Fluid and particulate matter in the cul-de-sac rapidly move to the subdiaphragmatic spaces.²⁸³ As suggested by the recovery of *N. gonorrhoeae* and *C. trachomatis* from the liver capsule in perihepatitis, microbes may move with this fluid film. An additional factor might involve a delayed hypersensitivity reaction to CHSP-60 or other chlamydial antigens, analogous to the proposed role of DTH in chlamydial salpingitis. Antibody to CHSP-60 was associated with laparoscopically verified perihepatitis.¹⁹² In addition to the particularly high levels of antichlamydial serum antibody, noted above, women with perihepatitis are more likely to have serologic evidence of a prior infection with a heterologous chlamydial immunotype,²⁷⁷ and less frequent use of OCPs,^{256,276,278} which may reduce the cellular immune response.²⁸⁴

The clinical importance of perihepatitis lies in the differential diagnosis. Many women with perihepatitis lack or do not

report symptoms from concomitant genital infection. Perihepatitis should always be considered in a young woman presenting with right-upper-quadrant abdominal pain or right-sided pleuritic pain. Chest X-ray, ultrasonographic examination of the gall bladder, and gynecological examination, including tests for *N. gonorrhoeae* and *C. trachomatis*, can exclude other disease and reveal salpingitis and predisposing cervical infection.

DIAGNOSIS

As mentioned, no symptom or sign is pathognomonic of PID, and, in fact, all symptoms have a low positive and negative predictive value for the diagnosis of PID.^{2,29,252–256}

CLINICAL SIGNS

An increase in the inflammatory cells in the vagina is common in PID. However, this criterion is imprecise, lacks an accepted definition, and can reflect either cervical or vaginal inflammation. MPC is correlated with cervical infection^{285,286} and, therefore, is a more logical sign for the presence of upper genital tract infection in women with pelvic pain. However, MPC is common in populations at high risk of gonorrhea and chlamydia, where it has a low positive predictive value for diagnosis of PID. By contrast, in a primary-care setting, where cervical infection is less common, the clinical diagnosis of cervicitis among 95 women presenting with pelvic pain was 75% sensitive and 95% specific to diagnose PID.²⁵⁴ Since PID usually arises from lower genital tract infection, the absence of MPC or inflammatory cells is a valuable negative predictor to exclude PID. In fact, none of the Swedish patients with laparoscopically documented PID had both an entirely normal vaginal wet mount and a clear cervical secretion.^{2,29} Similarly, in women with histologic endometritis but without symptoms of PID, finding vaginal neutrophils was 91% sensitive, although only 26% specific.²⁸⁷

A vaginal wet mount with three or more WBC per high-powered field was more sensitive (87%) but less specific (38%) than the ESR, CRP, or peripheral WBC, among patients with signs of overt PID documented by endometrial biopsy or laparoscopy.²⁶⁶ Vaginal wet mount and endocervical Gram stain for white blood cells are most useful for the presumptive diagnosis of chlamydial or gonococcal infection, only in settings with a relatively high prevalence of infection or when taken together with other predictors that can increase the likelihood of infection.²⁸⁸

In a meta-analysis of data from 14 studies on the diagnosis of PID, adnexal tenderness had a sensitivity of 95% but a low specificity of 74%; a palpable adnexal mass had a sensitivity of 48% and a specificity of 75% in predicting PID.²⁵⁷ Other physical findings were even less predictive.

Simple pragmatic clinical algorithm may be useful in practice to lower the risk of under- or overtreating PID (Fig. 56-7). If pelvic examination findings suggest PID in a patient with a negative pregnancy test, the presence of MPC or an increased number of WBCs on a wet mount of vaginal fluid (e.g., number of WBCs exceeds number of epithelial cells) suggests PID, and treatment should be initiated. However, PID is unlikely if the patient is not sexually active or if the wet mount shows normal lactobacilli and no WBCs.

LABORATORY TESTS

Most laboratory tests used to diagnose PID are nonspecific. Further, the sensitivity and specificity of laboratory tests have not been compared with the laparoscopic diagnosis in large series. No laboratory test is either highly sensitive or specific for PID. However, a pregnancy test is required in all cases of suspected PID to exclude possible EP, which represents a life-threatening complication.

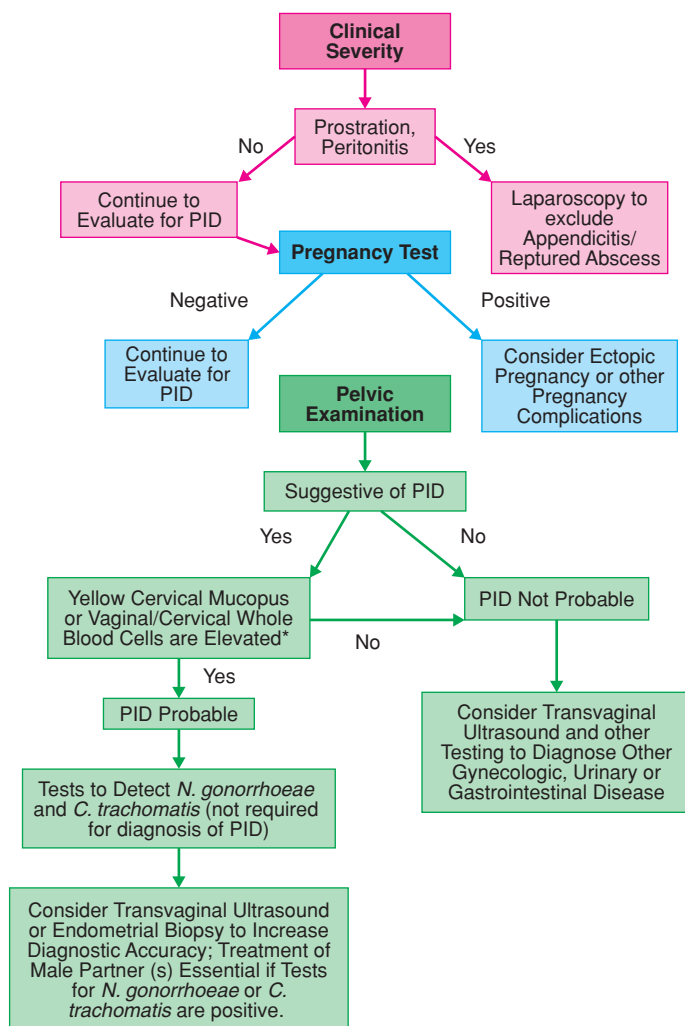


FIGURE 56-7. A stepwise algorithm in the differential diagnosis of acute PID.

Laboratory findings from Jacobson and Weström's study of Swedish women with PID are presented in (Table 56-3).^{2,29} An ESR >15 mm/h was present in 76% of patients with, but also in 53% of patients without, laparoscopically verified PID. An elevated ESR was significantly associated with laparoscopic staging of the inflammatory reactions (mild 60%, moderate 84%, and severe 89%)²⁹ and, in another data set, with chlamydia-associated PID.¹²³

Elevated levels of CRP had a sensitivity ranging from 70% to 93% and a specificity ranging from 67% to 90% for PID.^{251,289-291} The level of CRP also appears to reflect the severity of laparoscopically proven PID. The mean CRP was 47 mg/L (range 32–63) for mild tubal abnormalities and 83 mg/L (range 65–103) for severe tubal disease.²⁹⁰ An elevated CRP is a more sensitive and specific predictor of PID than an elevated ESR.²⁹⁰ Further, changes in CRP more accurately reflect the course of the infection and the effect of treatment than changes in ESR.

In the Jacobson–Weström study, the peripheral WBC exceeded 10,000 mm³ in 59% of patients with laparoscopically verified PID and in 33% of patients with no PID.^{2,29} The WBC was normal in 63% of patients with laparoscopically mild disease and in 20% of those with severe disease.²⁹ An elevated WBC was particularly associated with gonococcal PID in a Seattle study.²⁶⁷

Other serum markers examined in patients with PID remain investigational. Antichymotrypsin levels were increased (>140% of a reference pool) in 23 of 40 patients with PID and in none of 15 control women.^{29,291} Ovarian cancer-associated tumor markers, both CA125 and tumor-associated trypsin inhibitor have been elevated in one-fourth to one-third of patients with proven PID.^{245,292,293} Specific genital isoamylases (SGI) are produced in fallopian-tube epithelium and are present in peritoneal fluid.²⁹⁴ The SGI level is high in peritoneal fluid of healthy women but is diminished or absent in tubal infections and pregnancy.²⁹⁵ Ratios of the level of nonpancreatic isoamylases in peritoneal fluid and serum (P/S quotient) <1.5 were found in 45 of 56 of patients with PID, in none of 22 women with lower genital tract infection, and in one of 18 control women.²⁹⁵ This commercially available test is easy to perform, but it demands a cul-de-sac puncture. Larger studies are needed to confirm these results.

Since the diagnosis of PID is extremely difficult, a search for accurate diagnostic tests continues. One recent small study found enhanced erythrocyte aggregation in PID.²⁹⁶ Erythrocyte aggregation testing is simple, rapid, and of low cost, but it should be further evaluated. Another recent study found an association between elevated neutrophil defensin levels and endometritis.²⁹⁷ High levels of neutrophil defensins in the vagina were associated with endometritis. Neutrophil defensins process antimicrobial properties and are elevated in body fluids from patients with severe infections such as meningitis, sepsis, or intrauterine infection in pregnancy.

INVASIVE DIAGNOSTIC TECHNIQUES

■ CULDOCENTESIS

Peritoneal fluid can be obtained by culdocentesis, which is easy to perform, especially with vaginal ultrasonography to guide the needle.²⁹⁸ An increased WBC level in peritoneal fluid indicates intra-abdominal inflammation. Combining two studies,^{29,298} 21 out of 24 patients with proven PID and none of 36 control women had WBC counts >3100/mm in cul-de-sac fluid. Pure nonclotting blood in the aspirate indicates intra-abdominal bleeding and usually is an indication for laparoscopy or laparotomy to exclude EP or ruptured ovarian cyst.

Microbiological results on peritoneal fluid obtained by culdocentesis must be interpreted with caution, because of potential contamination from vaginal organisms or unrecognized bowel puncture. Additionally, species recovered by culdocentesis in PID have often been different from those recovered from tubal specimens obtained simultaneously by laparoscopy.^{30,31} *C. trachomatis* is rarely isolated from peritoneal fluid even in chlamydial salpingitis,³¹ although detection of *C. trachomatis* antigen or DNA in peritoneal fluid has not been evaluated.

In recent years, culdocentesis became less common to diagnose PID.

■ ENDOMETRIAL BIOPSY

Endometrial biopsy is a simple outpatient procedure.²⁹⁸ Histologic evidence of endometritis includes polymorphonuclear leukocytes (PMNs) migrating through the endometrial epithelium and present within lumina of endometrial “glands,” dense infiltration of the subepithelial stroma by plasma cells and lymphocytes, and germinal centers within the stroma.³⁷ Demonstration of histologic endometritis, based on detection both of plasma cells and of intraepithelial PMNs, had a sensitivity of 92% and a specificity of 87% with respect to detection of salpingitis by laparoscopy.²⁹⁸ However, the distribution of endometrial inflammation may be patchy, and results are not immediately available. Still, endometrial biopsy has been increasingly used for the outpatient diagnosis of PID.^{299–301}

It should be emphasized that plasma cells are also found in small numbers in the endometrium of healthy women, suggesting that plasma cells alone may not signify upper genital tract infection.³⁰² One central question in management of endometritis is whether endometritis and PID are different aspects of the same disease or separate clinical entities. The answer is not straightforward, and whether endometritis alone requires treatment³⁰³ has been thoroughly assessed in the PEACH study.³⁰¹ Clearly, endometritis can be a distinct clinical syndrome requiring treatment in symptomatic women,³⁰⁰ but evidence is not available for or against screening and treatment of endometritis in asymptomatic women.³⁰³

■ LAPAROSCOPY

Laparoscopy was introduced to study PID in the 1950s. After a series of publications during the 1960s through the 1980s,^{2,23,252,253} laparoscopy became the gold standard to diagnose PID and obtain specimens directly from the fallopian tubes.¹¹³ Criteria used to define salpingitis observed through the laparoscope include tubal erythema, swelling, and exudate.² Laparoscopy is a valuable research tool to study the accuracy of the clinical diagnosis of PID, to correlate symptoms and signs with laparoscopy findings, and to study the microbiology, pathology, and prognosis. However, laparoscopy is not practical for the majority of women with PID. Interpretation of laparoscopic findings is subjective and in need of interobserver and intraobserver reproducibility; the procedure has slight risks, and it is costly. Still, laparoscopy is valuable in selected circumstances; about 5% of women with clinically suspected PID have serious surgical conditions such as EP, appendicitis, or a ruptured abscess.^{2,29,30} Laparoscopy has been used to guide the percutaneous placement of catheters to drain abscesses or to directly puncture a tuboovarian abscess.³⁰⁴ Laparoscopy also benefits patients unresponsive to antibiotics, where the only objective finding is pelvic tenderness; such patients usually have no active infection, and laparoscopy identifies other conditions such as endometriosis.

The true accuracy of laparoscopy in the diagnosis of PID has never been formally validated. Although generally considered as the gold standard, observer agreement may be poor. In one study, where histopathologic diagnosis based on endometrial biopsy and fimbrial mini biopsy were used as the gold standard, laparoscopy had a sensitivity of 50%.²⁵⁴ This study was performed among primary-care physicians referring patients with suspected PID to gynecologists for laparoscopy and suggested that the clinical diagnosis of PID was no more accurate than chance. In addition, specificity of 80% suggested only a modest agreement between clinical, visual, and histopathologic assessments.

A recent observer-agreement study also showed low accuracy of the laparoscopic diagnosis of PID, when histopathologically proven PID was used as the gold standard. The overall accuracy of the laparoscopic diagnosis of PID was 78%, the sensitivity was 27%, and the specificity was 92%.³⁰⁵ The intraobserver reproducibility of the diagnosis of PID was only modest, and the interobserver reproducibility was only fair. When specific diagnostic features such as tubal erythema, edema, adhesion, or cul-de-sac fluid were separately analyzed, the results were not different, suggesting only poor-to-fair reproducibility. However, in this study, experienced gynecologists performed better than residents in training. These studies suggest that while the clinical diagnosis of PID is extremely difficult, laparoscopy seems to only partially solve the diagnostic problem.

■ ULTRASONOGRAPHY

Ultrasound provides a noninvasive test to diagnose and follow the course of severe PID. Findings in cases of severe PID include tuboovarian abscess, dilated fallopian tubes suggestive of pyosalpinx, excess fluid in the cul-de-sac, and enlarged polycystic ovaries.^{306,307} These ultrasound findings were consistent with PID in 94% of patients with proven severe PID, in 80% of patients with moderate PID, but in only 64% of patients with mild PID.³⁰⁷ Transvaginal ultrasound, which found dilated tubes, thickening of the wall of the tube, or fluid within the tube, was 85% sensitive and 100% specific, compared to plasma-cell endometritis among outpatients with pelvic pain.³⁰⁸

Transvaginal power Doppler sonography (TVS) is increasingly used among women admitted for suspected PID. Specific TVS findings, including wall thickness above 5 mm, cog-wheel sign, incomplete septa, and cul-de-sac fluid, best discriminate women with acute PID from women with hydrosalpinx formation.³⁰⁹ Power Doppler TVS also reveals hyperemia in women with acute PID, which is not usually present in women without acute inflammation. Power Doppler TVS is hampered by motion artifacts and the need for a high level of expertise. Ultrasonography may also be used to guide needles for the drainage of tuboovarian abscess in selected cases.^{310,311}

■ MAGNETIC RESONANCE IMAGING

Magnetic resonance imaging (MRI) has been extensively used in the characterization of adnexal masses, but only a few studies have used MRI to diagnose gynecologic infection. Recent development of fast MRI technology shortens the imaging time. In one study, MRI turned out to be more accurate than transvaginal ultrasound to diagnose PID among patients who underwent laparoscopy. Thus, MRI is useful not only to establish the diagnosis of PID but also to detect other processes such as tubal torsion or severe endometriosis. Although transvaginal ultrasound is far more cost effective than MRI, MRI may still be cost effective if proper therapy can be provided early and laparoscopy is avoided.³¹²

COMBINATIONS OF SYMPTOMS AND SIGNS IN THE DIAGNOSIS OF PID

Individual symptoms and signs of PID have a low diagnostic accuracy. Two comprehensive surveys on the diagnosis of PID^{255,257} used a syndromic approach to evaluate the diagnosis of PID. As expected, increasing the number of positive indicators of PID increased the specificity but decreased the sensitivity, and a high sensitivity and good specificity were achieved only by integrating laparoscopy into the logistic models.²⁵⁷ Still, in clinical practice, even in developed countries, a syndromic approach supplemented by simple laboratory tests for

WBC and CRP and for pregnancy, together with vaginal wet mount examination and cervical tests for gonorrhea and chlamydial infection, remains the usual practice.

In conclusion, the diagnosis of PID remains difficult. In the absence of laparoscopy, the most obvious challenge is to discriminate whether or not a genital infection has extended to the fallopian tubes. In the future, TVS ultrasound and analyses of vaginal, cervical, and endometrial specimens seem to offer the best combination to diagnose PID without the use of laparoscopy.

High diagnostic accuracy is essential for effective patient management. Unfortunately, there is insufficient evidence from clinical research to support the existing commonly used diagnostic criteria for PID. Thus, a new evidence base is urgently needed; this will require either new studies of the association between clinical presentation and PID based on gold standard diagnoses or the development of new innovative diagnostic tests. However, a new major study of the clinical presentation of proven PID would be costly and time consuming.³¹³

DIFFERENTIAL DIAGNOSIS

PID is one of many diagnoses that must be considered in women with abdominal or pelvic pain. In the largest series of 814 consecutive women laparoscoped because of a clinical diagnosis of salpingitis, 12% had intra-abdominal disorders other than PID.² The differential diagnosis of PID includes other gynecological conditions and disorders of the gastrointestinal and urinary tract. EP and acute appendicitis are the most serious intra-abdominal conditions to exclude. Despite the limitations of a direct microscopy of vaginal secretion, a completely normal wet mount argues strongly against PID.²⁹

GYNECOLOGICAL CONDITIONS OTHER THAN PID

EP is the most common and important differential diagnosis in PID.^{314,315} It is difficult to differentiate between an unruptured EP and mild-to-moderate PID on clinical criteria alone. Thus, a pregnancy test should be done in all potentially fertile women with acute abdominal/pelvic pain, and it also should be performed irrespective of contraception use.

Other common gynecological diagnoses to consider include rupture, bleeding, or torsion of an ovarian cyst. In such instances, the pelvic pain is usually acute in onset, unilateral, and severe. Laboratory tests are generally normal, and ultrasound most often reveals a pelvic mass or fluid in the cul-de-sac. Pelvic endometriosis may mimic PID, but the history of pelvic pain is often of longer duration than in PID. The microbiologic tests will be normal, but CRP may be elevated, and only laparoscopy will establish the diagnosis.

GASTROINTESTINAL DISEASES

Acute appendicitis is the most important differential diagnosis to exclude in this group. The clinical signs and laboratory test results overlap between appendicitis and PID, and up to 3% of women treated for PID have appendicitis.² A brief period of abdominal pain, pain originating in the central abdomen and moving to the right lower quadrant, nausea and vomiting, favoring a supine position, pallor, and abdominal guarding suggest appendicitis. If appendicitis cannot be excluded, laparoscopy should be performed and expectant management should not be considered.

Mesenteric lymphadenitis, regional ileitis, enteritis, and other manifestations of *inflammatory bowel disease* are other considerations in the differential diagnosis of PID.

URINARY TRACT DISORDERS

Urinary tract infection and colic from renal or ureteral stones are unusual differential diagnostic problems in PID. Microscopy and culture of urine usually will reveal the diagnosis. About 20% of women with STI-associated PID have urinary symptoms.²

A STEPWISE ALGORITHM

A simple stepwise algorithm for the differential diagnosis of PID includes the following: (1) A patient with prostration and signs of peritonitis needs hospitalization and an explorative laparoscopy to exclude appendicitis or a ruptured abscess. (2) A positive pregnancy test in patients with pelvic tenderness points to EP or other pregnancy complications. (3) If a pelvic examination suggests PID in a patient with a negative pregnancy test, but the patient is sexually inactive or the wet mount or Gram stain of cervical/vaginal secretions is normal (i.e., shows no increase in PMNs or evidence of BV [see Chapter 42]), consider ultrasonography to diagnose other gynecological conditions, or a gastrointestinal/urinary disorder. (4) If the patient is sexually active and there is yellow cervical mucopus or the wet mount reveals WBCs outnumbering the number of epithelial cells, PID is probable, but other intrapelvic conditions are not completely excluded; consider TVS and endometrial biopsy to increase the accuracy of diagnosis. Testing for *N. gonorrhoeae* or *C. trachomatis* in the cervix or urine by nuclear amplification testing is indicated, and a positive test for either strongly increases the probability of PID.

TREATMENT

Antimicrobial therapy is required to treat infection present in PID. As previously noted, early antibiotic treatment in the first 3 days after the onset of symptoms reduced tubal

infertility.¹⁶⁷ The choice of antimicrobial is empiric. The ideal to provide antimicrobial therapy, based on the isolation, identification, and antimicrobial susceptibility of the offending pathogen, is rarely achieved, because collection and microbial testing of fallopian-tube specimens are not practical in the majority of cases and test procedures are still too slow to guide initial therapy. Thus, the antimicrobial regimen must cover at least the most frequently expected microbes, including *N. gonorrhoeae*, *C. trachomatis*, and common aerobic and anaerobic isolates. At least two drugs are recommended by the CDC for syndromic treatment of PID (Table 56-6).

Guidelines for the hospitalization of patients are available.¹ A randomized trial has compared clinical and long-term outcomes with inpatient versus outpatient PID therapy. Among 831 women with clinical signs and symptoms of mild-to-moderate PID, there was no difference in reproductive outcomes of women randomized to inpatient treatment with intravenous cefoxitin and doxycycline versus outpatient treatment of a single intramuscular injection of cefoxitin and oral doxycycline.³⁰¹ Short-term clinical and microbiologic improvements were similar for inpatient versus outpatient treatment. After a mean 35 months of follow-up, pregnancy rates were nearly equal between groups. No statistically significant differences occurred between groups in the time to become pregnant or the proportion of women with recurrent PID, chronic pelvic pain, or EP.³⁰¹

Large numbers of women are hospitalized for PID each year, but, without an apparent difference in effectiveness, the large cost savings gained by treating women with PID outside hospital certainly favors outpatient management of those with symptoms of mild-to-moderate PID.

Comprehensive assessment of the efficacy of antimicrobial treatment of acute PID must include (1) evaluation of the clinical response to acute infection, (2) elimination of at least *N. gonorrhoeae* and *C. trachomatis*, (3) evaluation for subsequent relapse and/or recurrence, and (4) incidence of late sequelae, including infertility, EP, and pelvic pain. The vast majority of studies have evaluated only the initial clinical response to infection. Factors that influence efficacy, besides the interval between symptoms and treatment, include the presence of *N. gonorrhoeae* (which is associated with better clinical outcome), abscesses, and prior PID (associated with worse clinical outcome).

A report summarizing the rates of clinical cure for inpatient and outpatient regimens found that clinical cure rates ranged from 60% to 100%.³¹⁶ Only five inpatient studies reported clinical cure rates less than 84%. Of these, one used metronidazole and penicillin, two used metronidazole and doxycycline, one used cefoxitin-doxycycline, and the other used sulbactam-ampicillin-doxycycline. In a meta-analysis of 21 studies that met inclusion criteria, pooled cure rates were similar for the multiple-drug inpatient regimens, which consisted of clindamycin-aminoglycosides (92%), cefoxitin-doxycycline

Table 56-6. Inpatient and Outpatient PID Treatment Regimen**Inpatient***Regimen A*

Cefotetan 2 g i.v. every 12 h or cefoxitin 2 g i.v. every 6 h
 plus
 Doxycycline 100 mg orally or i.v. every 12 h

Regimen B

Clindamycin 900 mg i.v. every 8 h
 plus

Gentamicin loading dose i.v. or i.m. (2 mg/kg of body weight) followed by maintenance dose (1.5 mg/kg) every 8 h. Single dosing may be substituted. Because of pain with infusion, doxycycline should be administered orally, when possible.

The intravenous regimen should be continued for at least 24 h after substantial clinical improvement, then followed by doxycycline 100 mg orally twice daily or clindamycin 450 mg orally four times daily for a total of 14 d of therapy.

Alternative parenteral regimens include ofloxacin or levofloxacin (with or without metronidazole) or ampicillin/sulbactam plus doxycycline.

Outpatient*Regimen A*

Ceftriaxone 250 mg i.m. in a single dose or Cefixitin 2 g i.m. plus probenecid 1 g orally administered concurrently as a single dose or other parenteral third-generation cephalosporins (e.g., ceftizoxime or cefotaxime)
 plus

Doxycycline 100 mg orally twice daily for 14 d with or without metronidazole 500 mg orally twice daily for 14 d

Regimen B

Ofloxacin 400 mg orally twice daily for 14 d or levofloxacin 500 mg orally once daily for 14 d
 with or without

Metronidazole 500 mg orally twice daily for 14 d

From Centers for Disease Control and Prevention. Sexually transmitted disease guidelines 2002. *MMWR* 2002;51(RR6):1–80.

(93%), cefotetan-doxycycline (94%) and ciprofloxacin (94%).³¹⁶ Thus, the CDC-recommended regimens A and B (Table 56-6) have provided virtually identical clinical cure rates. Metronidazole-doxycycline had a pooled cure rate of only 75%. Single reports of multiple-drug inpatient regimens combining other cephalosporins (ceftizoxime and cefotaxime) or sulbactam ampicillin with doxycycline and ofloxacin alone also provided clinical cure rates of 88–100%.³¹⁶ Quinolones could also be combined with doxycycline and metronidazole for coverage. However, note that all of these studies were carried out before the widespread and continuing emergence of gonococcal resistance to fluoroquinolones.

In a review of trials between 1980 and 1990, the overall clinical cure rate was 90.4%. Six antibiotic regimens (clindamycin-aztreonam, cefoxitin-doxycycline, ticarcillin-clavulanic acid, moxalactam alone, clindamycin-aminoglycoside, and cefoxitin alone) provided clinical cure rates of 91–98%.³¹⁷ All the regimens achieved over a 90% clinical response rate, as reported in

three or more papers, and all had significantly greater clinical response rates than penicillin combined with tetracycline, aminoglycosides, or metronidazole. Superior regimens, judged on the highest clinical response rates, lowest toxicity, and adequate coverage of *C. trachomatis*, included clindamycin-aztreonam and cefoxitin-doxycycline, where the clinical response rates were 98% and 95%, respectively.³¹⁷

One recent trial compared azithromycin 500 mg IV daily for 1–2 days with or without metronidazole to combinations of doxycycline, cefoxitin, and metronidazole, and doxycycline and amoxicillin/clavulanic acid in 309 hospitalized patients in whom laparoscopy confirmed the diagnosis in 75%. Cure rates ranged from 95% to 98%, and *N. gonorrhoeae* and *C. trachomatis* eradication did not differ between groups.³¹⁸

Currently, no single intravenous drug provides satisfactory coverage of both *N. gonorrhoeae* and *C. trachomatis*; two drugs must be used to cover these two bacteria. As shown in (Table 56-6), most facultative and anaerobic bacteria found in

PID are effectively treated by the cephalosporins in regimen A, and by gentamicin and clindamycin in regimen B. Intravenous clindamycin provides adequate but not optimal coverage of *C. trachomatis*.^{319,320} Microbiologic cure rates were over 85%, with the exception of two studies: one of metronidazole-doxycycline-gentamicin (71% microbiologic cure) and one of cefoxitin-doxycycline (85% microbiologic cure).³¹⁶

Outpatient regimens recommended by the CDC for the treatment of PID are also listed in (Table 56-6). As with the intravenous regimens, they are designed to provide excellent *N. gonorrhoeae* and *C. trachomatis* inhibition and some aerobic and anaerobic coverage. Metronidazole could be added to improve coverage of anaerobic bacteria. Physicians must ensure that those treated as outpatients comply with treatment. In the UK, a significant improvement in the clinical cure rate of outpatient management of PID was observed following a change in therapy that added ceftriaxone. (In the UK, many genitourinary medicine clinics had used oral doxycycline and metronidazole to treat PID.) Ceftriaxone 250 mg intramuscularly was added to cover quinolone-resistant gonorrhea. Women receiving ceftriaxone, doxycycline, and metronidazole had a clinical cure rate of 72%, compared with 55% among women who received only doxycycline and metronidazole. This UK study, reported in 2005, suggests that doxycycline and metronidazole alone are not a suitable regimen to treat PID.³²¹

Little data exist on the effectiveness of azithromycin for PID treatment in the outpatient setting. Nonetheless, azithromycin might be more effective than doxycycline for eradicating persistent *in vivo* infection³²² and appeared to reduce upper genital tract inflammation in experimental primate infection.³²³

As expected, microbiologic cure rates of *N. gonorrhoeae* and *C. trachomatis* in the cervix are high with all regimens.³¹⁶ Virtually no valid data on microbiologic cure rates at the fallopian-tube site exist following therapy.

Also, few studies have followed patients for more than a few weeks to provide reliable data on relapse and recurrence of infection after therapy. Further, few studies assessed infertility, EP, and chronic pain after therapy.^{199,263,301,324,325} Weström found that the subsequent infertility rate was 11–13% among patients treated with regimens such as penicillin-streptomycin, penicillin-chloramphenicol, ampicillin, and doxycycline.³²⁶ The data suggested that most of the permanent damage occurred before antibiotic therapy was given, reinforcing the finding that the most important predictor of subsequent infertility is the degree of tubal damage when the infection was first observed and treatment was initiated.^{25,326} However, more data are needed on tubal patency following therapy. In one small study reported in 1985, patients given doxycycline-metronidazole had a higher post-treatment rate of tubal patency based on hysterosalpingogram than those given penicillin-ampicillin-metronidazole.³²⁷

Women with an IUD should have it removed, usually after some interval of antibiotic therapy. All recent male sexual

contacts of women with acute STI-associated salpingitis, including those who are asymptomatic, should be empirically treated for both gonococcal and chlamydial infection.

Radical surgery during the acute phase of PID has decreased significantly. Immediate surgical exploration is necessary to prevent septic shock in patients with a ruptured pelvic abscess. Early operative transvaginal drainage is the preferred method of treating a fluctuant pelvic abscess that becomes attached to the vagina in the midline of the cul-de-sac. More difficulty arises when an abscess that is not attached to the vagina requires transperitoneal drainage. Because even large masses do not always represent abscess formation, our current recommendation is to start antibiotic therapy that includes effective coverage of anaerobes and continue antibiotics if the mass size declines. Surgical exploration can then be delayed unless a definite abscess is identified by the clinical course, when the patient fails to improve clinically or the mass remains unchanged in size. If an abscess is of substantial size (greater than 6 cm in diameter), as demonstrated by TVS, transabdominal drainage may provide a shorter hospitalization and reduce recurrences.

If surgical drainage is required, laparoscopy is used to guide percutaneous placement of catheters into the large abscess. A catheter is used to drain pus and gently irrigate the abscess cavity. The catheter may be left to drain for 24–48 hours or until drainage decreases and the patient's condition improves. Care must be taken to avoid bowel injury and to identify multiloculated abscesses. About 90% of large abscesses can be cured with drainage^{328,329} plus appropriate antibiotics with the advantage of obviating extensive surgery. For more complex clinical courses, simple drainage or even removal of a unilateral abscess at laparotomy without removal of the opposite tube and ovary and the uterus is usually successful when a patient receives an adequate antibiotic regimen that includes antibiotics to inhibit anaerobes. This conservative approach is particularly mandatory for young women with a first episode of acute PID who may desire children in the future. A limited number of patients with salpingitis suffer persistent abdominal pain without evidence of an abscess or adnexal pathology, except for mild tenderness. If pain continues, diagnostic laparoscopy should be performed.

PROGNOSIS AND SEQUELAE

■ PROGNOSIS

The vast majority of women have a complete clinical recovery, regardless of treatment.³²⁶ The clinical course of acute PID is protracted in only a few women. In the industrialized countries, mortality from PID is unusual. In the United States, the mortality rate for PID was 0.29 per 100,000 female population 15–44 years of age in 1979.³³⁰ The most common cause of

death is rupture of an abscess with generalized peritonitis, a condition still capable of causing death.^{331,332}

■ SEQUELAE

Despite prompt diagnosis and treatment, sequelae are common. The most-feared complication of PID for women is tubal infertility (Fig. 56-8).^{25,213,332–335} Tubal and peritubal damage after PID can result not only in infertility but also in EP, chronic pain, and other gynecological morbidity. Appropriate, timely antibiotic treatment helps to reduce these complications. The mean pregnancy rates in women attempting pregnancy after conservatively treated PID were 28% in 1026 patients before antibiotics and 73% in 954 patients after antibiotic therapy.¹⁹⁹

In the United States and Europe, an estimated 15% of married and cohabiting couples fail to conceive after 1 year of unprotected sexual intercourse.³³⁶ Among infertile couples, a global study reported a wide range in prevalence of postinfection tubal occlusion from a low number to over 50% of women, with wide geographical variations.^{335–338} In studies from industrialized countries, 10–15% of women in infertile couples have tubal abnormalities and/or pelvic adhesions.³³⁹ The corresponding figure in African women has been up to 64%.³³⁷

As mentioned, many tubal infections severe enough to cause tubal infertility have no or mild symptoms. In 23 sero-epidemiologic studies of IgG antibody to *C. trachomatis* among infertile women, a serum antibody titer of $\geq 1:8$ was present in 68% of 1466 women with, and 27% of 1544 women without, TFI.²⁴⁹ IgG antibody was found in about 33% of 1130 fertile controls. A titer of $\geq 1:32$ was present in 75% of those with tubal infertility and 21% of those with other reasons for infertility.²⁴⁹ In these studies, 30–60% of the infertile women reported no history of PID.

The most extensive prospective follow-up study on reproductive events after overt PID was conducted at the University of Lund in Sweden, over the 25 years from 1960 through 1984.^{25,29,213,249,326,333,340} In a brief review of these studies, 1730 women underwent routine diagnostic laparoscopy because of clinical suspicion of acute salpingitis. PID was diagnosed in 1282 and entirely normal conditions in 448 women. The latter group served as controls. Women exposed to pregnancy during the follow-up, and who either conceived or consulted because of infertility were compared to controls. Details of the methods are given in Ref. 199 and the results are provided in (Table 56-7).

Fertility

In this series, 96% of the controls and 78% of the patients with salpingitis developed an intrauterine pregnancy following the index laparoscopy. Among those with intrauterine pregnancies, no difference was observed between patients and controls

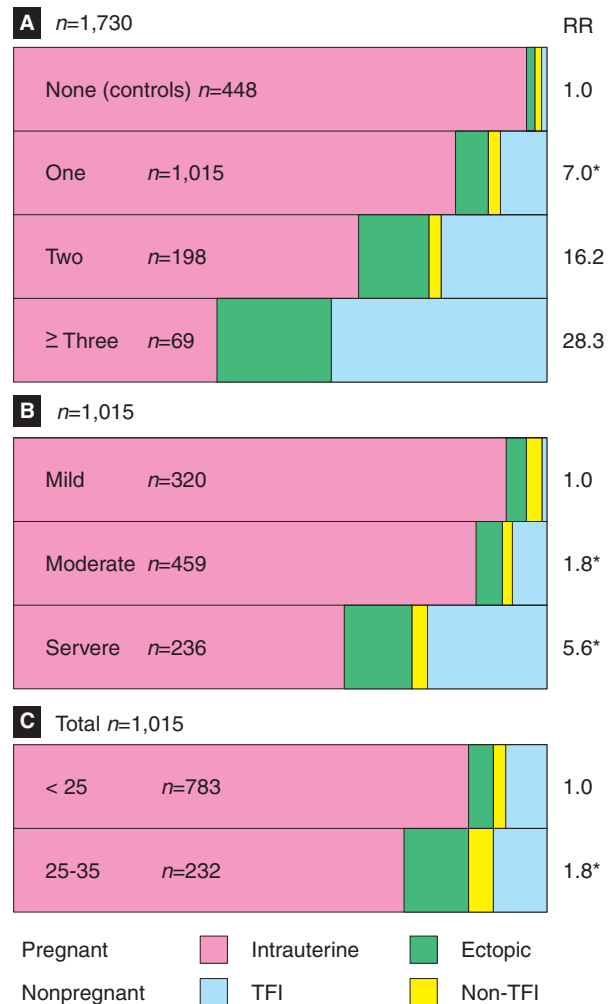


FIGURE 56-8. Fertility and infertility after PIDs: **A.** related to the number of PID episodes in one and the same woman; **B.** related to laparoscopic severity of the inflammatory reactions in women with only one episode of PID; and **C.** related to the age of the patient at the time of her only episode of PID.

in the proportion resulting in normal-term delivery, preterm delivery, stillbirth, and induced or spontaneous abortions.²⁵

Infertility

Among patients with salpingitis at laparoscopy, 12.1% had postinfection TFI and 2.1% were infertile for other reasons (Table 56-7). The corresponding figures in controls were 0.9% and 1.1%. An independent and significant risk factor for post-PID TFI was both the number of PID episodes (Fig. 56-8A)^{25,326} and, among women with only one PID episode, the severity of the infection determined at laparoscopy (Fig. 56-8B).^{25,326} Mild tubal disease was observed significantly more often at laparoscopy among women who used OCPs than among women who did not use contraception or used other methods.³⁴¹ With noncontraceptors as a reference group, tubal infertility after salpingitis was reduced by one-third ($p < 0.01$) in women who used combined OCPs at the time of the index laparoscopy, one-half in IUD users ($p < 0.05$), and not at all in users of barriers or other

Table 56-7. First Pregnancies (Uterine and Ectopic) and Infertility (Tubal and Nontubal Factor Infertility) in 1282 Patients and 448 Control Women Followed After Index Laparoscopy Related to Number of PID Episodes, Severity of Infection, and Age at Infection

PID	N	Pregant		Infertile		RR ^c
		Uterine ^a	Ectopic ^a	TFI ^b	Other	
None	448	433	6	4	5	1.0
One (Total)	1015	852	61	79	23	6.3
Mid	320	300	9	4	7	(1.0)
Moderate	459	404	19	26	10	(2.4)
Severe	236	148	33	49	6	(8.5)
Age < 25	783	676	34	60	13	(1.0)
Age 25–235	232	176	27	19	10	(1.8)
Two	198	124	24	46	4	16.2
≥Three	69	24	15	30	0	29.6
All PID	1282	1000	100	155	27	9.1

^aFirst pregnancy after PID.

^bTFI = tubal factor infertility.

^cRR = Relative risk of postinfection tubal dysfunction (TFI/ectopic pregnancy).

methods.³²⁶ These results should be interpreted with caution, because there was no information on the contraceptive method used after the PID episode. In an analysis of 443 women with STI-associated PID in this series, women who consulted after ≥ 3 days of abdominal pain had a 2.8-fold (95% confidence interval 1.3–6.1) increased risk of impaired fertility (tubal infertility or EP), compared with those who consulted within 3 days.¹⁶⁷

Among women with only one episode of PID, post-PID TFI did not correlate with the antibiotic treatment administered.³²⁶ A more favorable prognosis may have occurred after gonorrhea-associated PID than after nongonococcal PID,²⁵ but no such difference was observed in other reports.^{249,333,342,343} *C. trachomatis*-associated PID has produced high rates of infertility in other studies,^{193,334} and recent reanalysis of the series from Lund also indicated increased infertility after chlamydia-associated PID than after PID without genital chlamydial infection.³⁴³ However, no difference was observed between women with chlamydia- and gonorrhea-associated PID in a prior report from that same group.³⁴²

Women less than 25 years of age have an overall better fertility prognosis after PID than older women (Fig. 56-8C). There was no difference between the age groups in tubal infertility after PID; however, the difference was accounted for by a higher proportion of fertility from other causes and from EP in older women, factors only partly related to PID (Fig. 56-8C).

Among women with one episode of PID with severely damaged tubes, fertility nonetheless remained in 62.7% (Table 56-7). Similarly, fertility was preserved in 63% in a series of women treated by colpotomy for pelvic abscess.³⁴⁴ Thus, even in women with severely diseased tubes, fertility is preserved in over one-half.

Seroepidemiological studies of infertile and fertile women suggest significant causal roles for *N. gonorrhoeae*,^{345–347} *C. trachomatis*,^{247,342,345–348} and possible roles for *M. hominis*^{348,349} and *M. genitalium*) in TFI.^{348,350,351}

Since *C. trachomatis* is the leading cause of permanent tubal damage world wide, chlamydia antibody testing (CAT) is increasingly used in the evaluation of infertility.^{352–354} Detection of past chlamydial infection using serology is non-invasive, simple, and quick. Also, chlamydial antibodies persist for years as serologic evidence of past infection. Further, a linear trend exists between serum CAT results and the likelihood of tubal damage.³⁵⁴ However, the choice of cut-off level used for CAT screening depends on the prevalence of chlamydial infection in the population and the antibody test used. By using CAT more extensively, it may be possible to reduce the use of laparoscopy to diagnose TFI. In many infertility clinics, CAT is already an integral part of the infertility work-up. Medical history alone or transvaginal ultrasound appearance are insensitive to detect TFI in infertile women.³⁵⁵ Cost-effectiveness studies suggest that the diagnostic work-up to detect tubal pathology should start with CAT.³⁵⁶ One study from a university-based tertiary care infertility clinic reported that CAT was more accurate than hysterosalpingography in predicting TFI.³⁵⁷

Ectopic pregnancy

The ratio of EP to intrauterine pregnancy is related to the prevalence of fertile women exposed to pregnancy and the presence of risk factors for EP. Risk factors for EP besides salpingitis include older age, past and current use of an IUD, postoperative tubal damage, and other tubal pathology.^{218,358} Since 1970, significant increases occurred in EP in industrialized countries.^{359–362} A 64% increase in annual hospital admissions for EP was observed in one study between 1970–1974 and 1980–1984.³⁶¹ In the United States, hospital admissions for EP continued to increase until 1989 and then began to fall (Fig. 56-9). The decline may reflect a growing trend toward outpatient management of EP rather than a true decline in incidence; nearly half of all women with EPs in the United States are treated as outpatients.³⁶² Thus, the estimated number of EPs in the United States in 1992 was 108,800 (19.7 cases per 1000 pregnancies), the highest level in more than two decades.³⁶²

The epidemic increase in EPs until the early 1990s was explained by better diagnostic methods, increased use of IUDs, postponing the first pregnancy to an older age, and the epidemic of STIs. The impact of any individual factor is difficult

to evaluate, but, in one report, the increase in EP paralleled an increase in STIs in the 1980s, and the risk increased with the number of episodes of salpingitis.³⁶³

In the series from Lund, the first pregnancy after documented salpingitis was ectopic in 7.8% of patients compared to 1.3% of the control women. The ratio of EP to intrauterine pregnancy in all first pregnancies was 1:73 among control women, and 1:15, 1:6, and 1:2.6 after one, two, and three episodes of salpingitis, respectively (Table 56-7; Fig. 56-8A). In women with only one episode of salpingitis, the corresponding figures were 1:36, 1:25, and 1:5.4 after mild, moderately severe, and severe PID, respectively (Table 56-7; Fig. 56-8B).

Age is consistently related to EP.^{358,360} Women who used an IUD in the past have an increased rate of EP.²³² In seven sero-epidemiological case-control analyses, the mean prevalence of chlamydial serum antibody was 60% (range 32–71) in patients with EP and 24% (range 4–39) in control women.²⁴⁹ PID has a “carryover” effect for increased risk of EP, even if the first pregnancy was intrauterine, such that an increased percentage of EP was parallel to the severity of tubal damage (observed by laparoscopy) and the number of episodes of prior salpingitis.³⁶³ If the first pregnancy was ectopic, the risk for an EP in the following pregnancies was about 20%.³⁶³

Chronic pain

Abdominal or pelvic pain lasting longer than 6 months occurred in 17–18% of patients after one or more episodes of PID, compared to only 2–5% in control women.^{29,199,253,364} Chronic pain is related to the number of PID episodes, occurring in 12% with one episode, 30% with two episodes, and 67% after three or more episodes of PID.³⁶⁴ In patients with chronic pain after PID, peritubal and periovarian adhesions at a second-look laparoscopy revealed that pain occurred in 9% with no visible adhesions and 91% in those with extensive adhesions.³⁶⁴ Chronic pelvic pain correlated better with the extent of pelvic adhesions than to the number of PID episodes.³⁶⁴

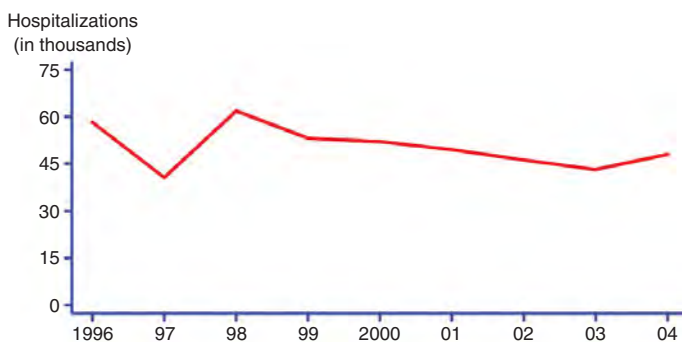


FIGURE 56-9. Ectopic pregnancy. Hospitalizations of women 15 to 44 years of age: United States, 1996–2004. *Note:* The relative standard error for these estimates ranges from 10% to 14%. Data only available through 2004. (Source: National Hospital Discharge Survey. National Center for Health Statistics, CDC).

General gynecologic morbidity

In a study of 1200 women hospitalized for PID and followed for 6.5–8.5 years, compared to 10,507 control women, there was a 4.5–9.8-fold increased risk of hospitalization for abdominal pain, “gynecologic” pain, endometriosis, hysterectomy, and EP.³⁶⁵ The rate of total gynecological operations (excluding laparoscopy for repeat PID) was 0.8 procedures per woman in 415 patients after PID, compared to 0.1 per woman in 100 controls followed for 6–14 years.^{25,366}

It is evident that many long-term sequelae can result from PID. It was estimated that one in four women with acute PID will suffer from one or more of the following: tubal infertility, EP, chronic pelvic pain, or PID-related gynecological surgery. Apart from the economic and public-health consequences of PID and its sequelae,²¹¹ the human suffering is enormous in terms of a lowered quality of life and childlessness.

PREVENTION

Because treatment of PID has so far had only a limited impact upon sequelae of PID, prevention of PID is a high priority. Prevention of PID would not only reduce the morbidity and costs from acute infection, but it would also potentially offer large lower cost savings of treating sequelae. Widespread clinic-based screening for chlamydial infection reduces the prevalence of chlamydial infection at the population level, and public-health efforts to control gonorrhea and chlamydia reduce the rate of PID. In fact, recent data indicate that control programs for chlamydia have a major impact on reducing PID rates.^{220,221,367}

One report demonstrated that women randomized to chlamydia screening subsequently experienced only half the rate of PID in half compared to an unscreened control group.²²¹ Another randomized trial from Denmark screened 5500 female high-school students for *C. trachomatis* by home sampling, with an overall uptake of 42%. The relative risk reduction for PID also was 50%.³⁶⁷

It is apparent that screening and treatment of asymptomatic women for *C. trachomatis* reduce the prevalence of chlamydial infection in the population and lower the risk of acute PID for the individual. As a result, the CDC, the U.S. Preventive Services Task Force, and several international agencies recommend chlamydia screening of sexually active women less than 26 years of age.³⁶⁸ Despite these recommendations, U.S. women aged 16–26 years had only a 26% screening rate in commercial health plans and a 38% screening rate in Medicaid plans in 2001.³⁶⁸ While about one-half of women with acute PID have *C. trachomatis* identified by culture, NAATs increase the detection of chlamydia by about 30%.³⁶⁹ Thus, chlamydia-associated PID probably causes greater morbidity than currently estimated, because, until recently, the proportion of all cases of PID associated with

C. trachomatis had been determined only by culture. Because *C. trachomatis* is also particularly likely to produce mild symptoms¹¹⁵ and may cause a disproportionate amount of unrecognized PID,²⁵⁶ tubal infertility,³⁴² and EP^{194,249} a more widespread adherence to recommended screening is called for.

Unfortunately, *C. trachomatis* infection is still not controlled in most populations. Efforts to control chlamydia in the United States and elsewhere are increasing very slowly. Some barriers to *C. trachomatis* control relate to indecisiveness about who to screen. While *C. trachomatis* causes specific clinical manifestations in women such as cervicitis²⁸⁵ and the urethral syndrome,³⁷⁰ most *C. trachomatis* infections in women are asymptomatic or produce only nonspecific or mild symptoms,³⁷¹ resulting in a large reservoir of asymptomatic *C. trachomatis* infection. Effective control programs require screening of both men and women, rather than reliance only on the identification and treatment of syndromes related to chlamydial infection.

■ CONTROL STRATEGIES

Disease prevention can be primary, secondary, or tertiary. Clinicians and other health-care providers have an important role in the primary prevention of STI. Primary prevention occurs through lifestyle counseling and health education, asking questions about risk-taking sexual behaviors, encouraging screening tests for those at risk, ensuring the proper management of sex partners, and counseling about safe sex practices. Partner notification and expedited treatment of sex partners are important but often ignored steps to prevent further sexual transmission of infections. Many sex partners of individuals with gonorrhea or chlamydial infections go untreated, leading to reinfections and further transmission. Strategies for expedited partner treatment, for example, by giving patients undergoing treatment for gonorrhea or chlamydial infection, have been found in a randomized trial to decrease rates of such infections in the index patient at follow-up—presumably by preventing reinfection from an untreated partner.³⁷²

Screening for *C. trachomatis* infection represents secondary prevention at the population level, leading to early treatment and reduced further transmission, and also represents secondary prevention of complications and sequelae at the individual level. Because *C. trachomatis* is a major cause of upper genital tract infection and tubal damage, it is logical to focus a major prevention effort on chlamydia. Chlamydial infection fills all prerequisites for disease prevention by screening, because chlamydial infections are prevalent, associated with significant morbidity, readily diagnosed, and effectively treated. Current screening programs are important steps to limit complications of chlamydial infection. Major long-term reductions in the prevalence of chlamydial infections in the population seem unlikely unless men also

are targeted, clinic-based screening is maximized, and innovative strategies are developed to encourage young people to be screened.³⁷³ Prevention of PID is also clearly a testing issue. To date, screening rates are surprisingly low among sexually active young people, which can be explained by specific system, provider, and patient factors.^{366,374} System factors include lack of availability of urine-based screening tests, which eliminate the need for gynecologic examination, insufficient reminder systems about screening, and inadequate organizational commitment to increase the availability of this preventive service. Provider factors include lack of awareness of high chlamydia prevalence in adolescents, misperceptions that adolescent patients are not sexually active, discomfort with discussing or lack of time to assess sexual activity, and lack of knowledge of the availability of urine-based chlamydia screening tests. Patient factors include the stigma associated with STIs, lack of awareness of the high prevalence of asymptomatic chlamydial infection, and fears about breaches of confidentiality regarding sexual health services or diagnoses in medical records.³⁶⁸ One intervention that increased screening from 5% to 65% involved informing providers about high chlamydia prevalence and providing urine tests and monthly provider feedback on screening rates.³⁷⁴ Another intervention, which included routine placement of chlamydia specimen collection materials next to Pap test collection kits, increased screening from 61% to 83%.³⁶⁸

■ COST EFFECTIVENESS OF PID PREVENTION

Cost-effectiveness analyses strongly support *C. trachomatis* screening to prevent PID.³⁷⁵ By screening men and women between age 15 and 24 years, the prevalence of asymptomatic infections in women can be reduced from 4.2% to 1.4% over 10 years.³⁷⁶ In particular, school-based screening programs are likely to be cost effective.³⁷⁷ The average per person lifetime cost of PID ranges between \$1060 and \$3180. This suggests that successful PID prevention efforts may save substantial costs. These redefined estimates of the average lifetime cost of PID may improve future cost-effectiveness analysis.³⁷⁸

In many countries, reported rates to chlamydial infection have increased several fold since the early 1990s. An increasing incidence of genital *C. trachomatis* infection might be expected to lead to a rise in the incidence of PID. However, on a population level, trends in the incidence of PID generally do not parallel those of reported chlamydia rates. Such ecological disassociation may be surprising and should be interpreted with caution. For example, in Australia, chlamydia rates increased fourfold at a time when admission rates for PID significantly decreased.³⁷⁹ This obvious discrepancy can be explained in many ways; one explanation is that the proportion of women with PID admitted to the hospital has decreased over the same time.³⁸⁰ Further, early detection and treatment may prevent PID. Increased use of azithromycin

may improve compliance and prevent more complications. Population-level ecological data cannot show that chlamydia screening is directly responsible for a declining PID rate. In Sweden and many other European countries, despite continued screening, chlamydia rates have actually increased since early 1990s. In British Columbia, Canada, it has been argued that a resurgence in reported chlamydial incidence and rise in rates of *C. trachomatis* reinfections might reflect waning population-level immunity to *C. trachomatis* attributable to early detection of infection and attenuation of the average duration of infection to a period too short to generate protective immunity.³⁸¹ Nonetheless, increasing screening appears to be at least temporally associated with decreasing rates of PID in recent years and continued scale-up of screening seems warranted, while simultaneously pursuing other approaches to alter sexual networks. Ecological, time series analyses should be interpreted with caution.³⁸²

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Cervical Neoplasia and Other STD-Related Genital Tract Neoplasias

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PAST SUCCESSES AND CURRENT CHALLENGES FOR PREVENTION AND TREATMENT OF GENITAL TRACT NEOPLASIA

It is now well established that specific types of sexually transmitted human papillomaviruses (HPV) play a central role in the pathogenesis of most squamous cell cancers and adenocarcinomas of the male and female genital tract. This makes HPV an STD with potentially life-threatening consequences. Fifty years ago, cervical cancer was considerably more common in the United States and other developed countries than it is today. This success is primarily due to the establishment of early detection through cytology-based screening programs. Such programs are only rarely available in much of the developing world, where cervical cancer continues to be the most common cause of cancer-related mortality among women. Worldwide, it is second only to breast cancer.¹

In the last decade, our rapidly expanding knowledge of HPV carcinogenesis (reviewed in Chapter 27) and epidemiology (reviewed in Chapter 28) has allowed us to make great strides in our approach to control cervical cancer. As discussed in Chapter 58, HPV DNA testing is now recommended for use in cervical cancer screening programs in both developed and developing countries. At present, however, neither HPV DNA testing nor cytological screening have been recommended for early detection of other HPV-related genital cancers, in part because such cancers are less common than cervical cancer. More recently, a prophylactic recombinant HPV vaccine aimed at preventing cervical cancer as well as other HPV-related cancers and genital warts was approved in many countries for use in young women (reviewed in Chapter 28). The challenge of the next decade will be to implement and sustain HPV immunization programs that optimize public health benefits in both developed and developing countries.

This chapter summarizes recent trends in the incidence of invasive cervical and other anogenital tract cancers (vagina, vulva, penis, and anus), and discusses evidence that links genital and anal cancers with HPV and with other factors including behavioral and biological characteristics of the

host. Practical guidelines for diagnosis and early treatment of genital and anal precancers and cancers are also provided.

DEFINITIONS AND CLASSIFICATION OF LESIONS

■ INVASIVE SQUAMOUS CELL CANCER

A variety of different types of malignancies occur at all genital and anal sites, but the majority of tumors are of the squamous cell type (Table 57-1). As discussed below, all have been associated with HPV infection. Squamous cell lesions of the anal and genital tract that are felt to be neoplastic in nature are generally divided into (1) invasive cancer and (2) noninvasive or preinvasive lesions. The term *invasive* refers to tumors in which the malignant cells have penetrated the underlying basement membrane and have infiltrated into the stroma. Invasive squamous cancers are graded as well, moderately, or poorly differentiated. Grade 1, or well-differentiated carcinoma, most resembles normal squamous epithelium, with many keratinizing cells and keratin pearls present. Grade 2, or moderately differentiated cancer, shows less keratin formation, with greater nuclear polymorphism and more mitoses present. Grade 3, or poorly differentiated squamous cell cancer, is composed of cells with a high nuclear/cytoplasmic ratio and many mitotic figures, but no keratin formation.² Invasive cervical cancers are further classified as being either frankly invasive or microinvasive. The Society of Gynecologic Oncologists (SGO) guideline defines microinvasive cervical lesions as those in which the malignant cells have not penetrated more than 2 mm below the basement membrane and in which lymphatic or vascular invasion is absent. More recently, it has been proposed that lesions in which the malignant cells have penetrated to a depth of 5 mm without vascular and/or lymphatic invasion, or lesions in which malignant cells penetrate to a depth of 3 mm but where vascular and/or lymphatic invasion is present, should be classified separately as *occult carcinoma*.³ The term *microinvasive vulvar cancer* has also been introduced.

Table 57-1. Distribution (Percent) of Genital and Anal Cancers by Histologic Type Surveillance, Epidemiology, and End Results (SEER) Program, United States, 1993–2002

Total N	Cervix 35876	Vagina 2663	Vulva 7634	Female Anus 4130	Male Anus 2706	Penis 2418
Histologic types:*						
Carcinoma, NOS	7.0	5.4	3.6	1.5	1.8	2.3
Papillary carcinoma, NOS	0.4	1.8	2.3	1.0	1.5	7.4
Squamous cell carcinoma, NOS	72.3	65.4	69.0	54.2	52.8	79.2
Transitional cell carcinoma, NOS	<0.1	0.2	0.3	24.5	14.9	0.4
Adenocarcinoma, NOS	10.3	7.0	1.0	9.4	15.6	0.2
Melanomas	<0.1	4.5	3.9	1.6	1.0	1.0
Other tumors	10.0	15.6	20.0	7.8	12.3	9.4

*NOS = not otherwise specified

Data from SEER (the Surveillance Epidemiology and End Results Program of the National Cancer Institute).

■ NONINVASIVE SQUAMOUS CELL EPITHELIAL LESIONS

Histologic classification and natural history of noninvasive squamous cell epithelial lesions of the cervix

The concept of precancerous lesions was first developed around the beginning of the 1900s, when it was noted that the normal cervical epithelium cells adjacent to invasive squamous carcinomas were often replaced by a full-thickness layer of cells morphologically identical to invasive tumor cells.^{4,5} Such areas were termed *carcinoma in situ* (CIS). On the basis of retrospective studies of women with invasive squamous cell carcinoma in whom prior biopsies showed CIS,⁶ as well as on the basis of prospective studies,⁷ it became widely accepted that such lesions represented incipient cancers. In fact, the exact proportion of cases that would progress from CIS to invasive cervical carcinoma (ICC) if left untreated is still unknown, because virtually all women with CIS are treated. Estimates of progression (based on eight studies) range from 0% to 71%, with a median of 34%.⁷ However, median follow-up for these prospective studies has been less than 5 years, which is not sufficient time to accurately estimate rates of progression to invasion, persistence, or clearance. As discussed below, it is quite likely that most CIS lesions would persist or progress if left untreated, and there-

fore, cervical cancer control today is based on detection and subsequent treatment of women harboring such lesions.

Other types of cervical lesions composed of less worrisome cells were subsequently described. The significance of these lesions was even less clear, but because the cells in these lesions shared some morphologic features of cells seen in CIS, it was proposed that these lesions (initially called *dysplasias*, and later termed *cervical intraepithelial neoplasia* or *squamous intraepithelial lesions*) represented the earliest morphologic changes associated with cervical cancer. Despite the fact that little was known about the natural history of such lesions, several hierarchical systems for their classification were developed, which supposedly reflected their potential biological behavior. In the most popular of these classification schemes, noninvasive cervical epithelial lesions were classified as mild, moderate, or severe dysplasia or CIS. Subsequently, natural history studies in which women with varying degrees of dysplasia were followed by cytology alone (as it was felt that biopsies might alter the natural history) were undertaken to clarify the nature of these lesions and to provide a basis for clinical management of women harboring such lesions. As summarized in [Table 57-2](#), with the exception of the Richart and Barron study, most investigators reported extremely low rates of progression of mild dysplasia to CIS. Nevertheless, on the basis of results from this natural history study, the investigators concluded and popularized the idea that “dysplasia is simply an early cervical

Table 57-2. Development of Carcinoma In Situ Among Women with Cytologic Evidence of Dysplasia: Summary of Four Studies

Principal Author, Year	Cytologic System ^a	Cytologic Entry Criterion	Cohort Definition	Number in Cohort	Months of Follow-Up	% Progressing to \geq Carcin In Situ
Richart, 1969 ^b	O ^c	3 dysplastic smears	Mild dysplasia	NS ^d	Projected progression at 60 mo (life table analysis)	50
			Mod. dysplasia	NS		70
			Severe dysplasia	NS		95
			Any dysplasia			48
Patten, 1978 ^e	P ^e	1 dysplastic smear	Mild dysplasia	3299	60 mo	0.5
			Mod. dysplasia	661		2.4
			Severe dysplasia	125		10.4
Jordan, 1981 ^f	WP ^g	2 negative smears	Mild dysplasia	708	60 mo	1.1
			Mod. dysplasia	164		1.8
			Severe dysplasia	52		7.7
		3 dysplastic smears	Any dysplasia	65		19.0
Nasiell, 1983 ^h , 1986 ^{i,j}	W ^g	1 dysplastic smear	Mild dysplasia	555	Projected progression at 60 mo (life table analysis)	15.0
			Mod. dysplasia (no.biopsy)	410		26.0
			Severe dysplasia (biopsy)	484		21.0

^aOrganization of cytologic classification scheme used to classify cytologic findings: O = Okagaki, P = Patten, W = World Health Organization.

^bRichart RM, Barron BA. A follow-up study of patients with cervical dysplasia. *Am J Obstet Gynecol* 1969; 105(3): 386–393.

^cOkagaki T, et al: Diagnosis of anaplasia and carcinoma in situ by differential cell counts. *Acta Cytol* 1962; 6: 343.

^dNumbers of subjects followed not specified.

^ePatten SF: *Monographs in Clinical Cytology: Diagnostic Cytopathology of the Uterine Cervix*. New York: Karger, 1978, p. 141–145.

^fJordan SW, Smith NL, Dike LS. The significance of cervical cytologic dysplasia. *Acta Cytol* 1981; 25(3): 237–244.

^gCharles Eh, Savage EW: Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstet Gynecol Surv* 1980; 35: 539–548.

^hNasiell K, Nasiell M, Vaclavinkova V. Behavior of moderate cervical dysplasia during long-term follow-up. *Obstet Gynecol* 1983; 61(5): 609–614.

ⁱNasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasia during long-term follow-up. *Obstet Gynecol* 1986; 67(5): 665–669.

^jNo difference in biopsied vs. nonbiopsied group for the mild dysplasia group.

Data from SEER (the Surveillance Epidemiology and End Results Program of the National Cancer Institute).

neoplasm and ... although some spontaneous regressions do occur in the mild lesions, the vast majority of dysplasias ultimately evolve to carcinoma in situ and invasive carcinoma.”⁸ This view of dysplasia is inherent in the *cervical intraepithelial neoplasia* (CIN) classification scheme for cervical lesions, and the concept that mild, moderate, and severe dysplasia and CIS represent a morphologic and biologic continuum of progressive, consecutive stages in the development of invasive cancer. Lesions are classified as cervical intraepithelial grade lesion 1 (CIN1), cervical intraepithelial grade lesion 2 (CIN2), cervical intraepithelial grade lesion 3 (CIN3), or carcinoma *in situ* (CIS), according to the proportion of epithelium occupied by basaloid, undifferentiated cells (cells resembling the basal cell

layer of the epithelium). CIN 1 lesions are conceptualized as having neoplastic, basaloid cells occupying the lower third of the epithelium, while in CIN 2 lesions, basaloid cells occupy the lower third to two-thirds of the epithelium, and in CIN 3, the full thickness of the epithelium is occupied by undifferentiated basal-type cells. The belief inherent in this system is that these are successive stages in development of invasive cancer and that most CIN 1, if left untreated, will progress to CIS. This view of the natural history of CIN 1 is dramatically different from that suggested by most natural history studies (see [Table 57-2](#)), which provide support for the view that mild dysplasia is generally a benign self-limited lesion with little malignant potential. The high rate of progression of CIN 1 detected in the

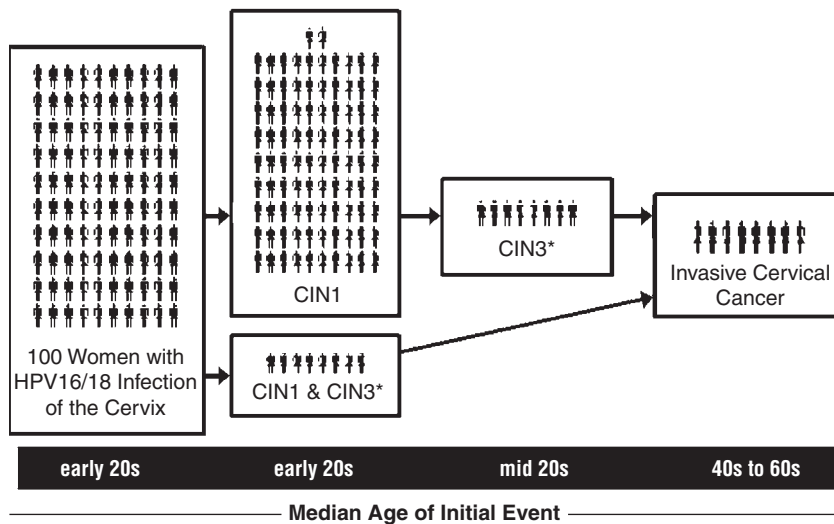


FIGURE 57-1. Natural history of HPV16/18-related cervical cancer in the absence of screening.

Richart and Barron study most likely resulted from the specific study entry criteria and the unique cytologic classification scheme employed. The fact that only women who had had three consecutive Pap smears showing mild dysplasia during the previous 12 months were eligible for enrollment in Richart and Barron's study that biased the study population toward women with mild dysplasias that were unlikely to regress. Furthermore, the Okagaki cytologic classification used in Richart and Barron's study differed markedly from that used today or from that used in the other studies shown in Table 57-2. Nevertheless, over the last 30 years, the CIN classification system has been widely used for histologic classification of cervical pathology, and has served as the basis for clinical management of women with cervical epithelial abnormalities. The view of carcinogenesis inherent in the CIN classification system has led to aggressive treatment of all lesions classified as CIN. Such an approach is increasingly being questioned in the light of what we have learned about the role of HPV as a common, self-limited, sexually-transmitted viral infection as well as the etiologic agent of most genital tract neoplasia.

All genital HPV types appear to be capable of causing CIN1, which is now widely accepted as the transient manifestation of a productive cervical HPV infection. Even without treatment, most CIN1 clears within less than 12 months.^{9,10} CIN3, which is caused by oncogenic HPV types, is the precancerous cervical lesion that, if left untreated, is more likely to persist or progress to invasion than to spontaneously clear.^{11,12} CIN2 is a histologically ambiguous presentation of CIN1 or CIN3. Current evidence indicates that regardless of the patient's age at detection, CIN3 requires treatment because spontaneous clearance is unlikely, and long-term persistence with the potential for invasion is likely. CIN2 is also treated because current technologies do not distinguish between lesions that will spontaneously clear and those that will persist and progress.

Recent knowledge of the role of oncogenic HPV in the pathogenesis of cervical cancer has led to the consideration of a new natural history paradigm (Fig. 57-1). This figure depicts the course of infection for 100 young women with HPV-16 or HPV-18 infection of the cervix. As in the analysis of Goldie and colleagues,¹³ the estimated lifetime risk of cervical cancer in the underlying population of infected and uninfected women is estimated to be ~3.6%. Another feature of this paradigm is that all women with a cervical HPV-16 or HPV-18 infection are shown to develop CIN1. Although others¹⁴ suggest that only about 20% of cervical HPV infections result in CIN1, it is probably closer to 100% because CIN1 is the lesion that produces infectious virions. A CIN1 lesion may never be detected because it is small and located outside of the transformation zone or in a glandular crypt, and because it is transient and often resolves before it is identified on a Pap test (median duration of CIN1/LSIL is 6 months or less^{10,15}). Also, some HPV DNA that is detected in a cervical swab sample is from a vaginal, not a cervical infection and, thus, would not be expected to cause CIN.¹⁶ While natural immune surveillance usually clears infectious virus, which leads to resolution of the associated CIN1 lesion and regeneration of uninfected (virally quiescent?) epithelium, immunity appears to be relatively ineffective at clearing the proliferating immature cells of CIN3.

Although the natural history of HPV at genital sites other than the cervix is less well understood, both productive and precancerous HPV-related lesions of the vagina, vulva, anus, and penis have been described.

Histologic Classification and Natural History of Noninvasive Squamous Cell Epithelial Lesions of the Vagina, Vulva, Anus, and Penis

The nomenclature for the precancerous states of vaginal, vulvar, anal, and penile squamous epithelium is similar to that of the cervix,¹⁷ being termed as vaginal intraepithelial neoplasia

(VaIN 1, 2, 3), vulvar intraepithelial neoplasia (VIN 1, 2, 3), anal intraepithelial neoplasia (AIN 1, 2, 3), and penile intraepithelial neoplasia (PIN 1, 2, 3). It is preferable to avoid using terms such as “Bowen’s disease” or “Bowenoid papulosis.” Although there appears to be a remarkable morphologic similarity between CIN3 and VIN3, the risk for progression of VIN3 to invasive carcinoma is thought to be much lower than for CIN3, with less than 10% progression among young women with normal immune systems.^{18–20} Given this apparent low risk of progression, the management of patients with VIN should be as conservative as possible. Similarly, management of VaIN and PIN is conservative. Invasive vaginal carcinoma is rare, and less is known about the relationship between intraepithelial and invasive disease. VaIN is most often found in the upper third of the vagina, and the lesions are usually multifocal. In one study, approximately one-half of the lesions were associated with concomitant cervical or vulvar intraepithelial neoplasia. Progression to invasive vaginal carcinoma occurred in two cases (9%), persistence of VaIN occurred in three (13%), and regression of VaIN occurred in 18 (78%).²¹ Perianal high-grade AIN has a well-defined rate of progression to invasive anal cancer.²² Intra-anal high-grade AIN has also been demonstrated to have precancerous potential but the progression rate is not well defined.²³

INCIDENCE AND PREVALENCE

■ INVASIVE CERVICAL CANCER

International Trends

Carcinoma of the uterine cervix is the second most common cancer in the world among women, and the most common

cancer among women in many developing countries of Africa, South and Central America, Asia, and the Pacific, with crude incidence rates ranging from 4 cases per 100,000 in western Asia to 35 per 100,000 in the Caribbean.²⁴ In 2002, it was estimated that there were 493,000 new cases and 274,000 deaths from cervical cancer detected worldwide. It was the seventh most common cancer among both sexes, preceded by cancers of the lung, breast, colon/rectum, stomach, prostate, and liver.¹ Figure 57-2 shows the incidence of cervical and penile cancer estimated from the data collected from tumor registries that were maintained in several countries in the years 1968–1972 and 1993–1997 (figure taken from Partridge and Koutsky [2005]²⁵). The incidence of cervical cancer declined in all of the areas shown except Israel and Zaragoza, Spain, whereas the incidence of penile cancer increased in many areas between the two periods studied. Although the overall incidence of cervical cancer has been declining in countries with organized screening programs, rates of cervical adenocarcinomas have been on the rise.^{26–28} This could be due to the fact that cervical cytology testing has a relatively low sensitivity for adenocarcinoma compared to squamous cell carcinoma.²⁴

US Trends

Data on the incidence, mortality, and survival rates of invasive cancer in the United States come from the Surveillance, Epidemiology, and End Results (SEER) Program, the part of the Surveillance Program at the National Cancer Institute (NCI) that routinely collects cancer data from nine population-based cancer registries located throughout the United States. The National Center for Health Statistics (NCHS) provides cancer mortality data for the entire United States. The

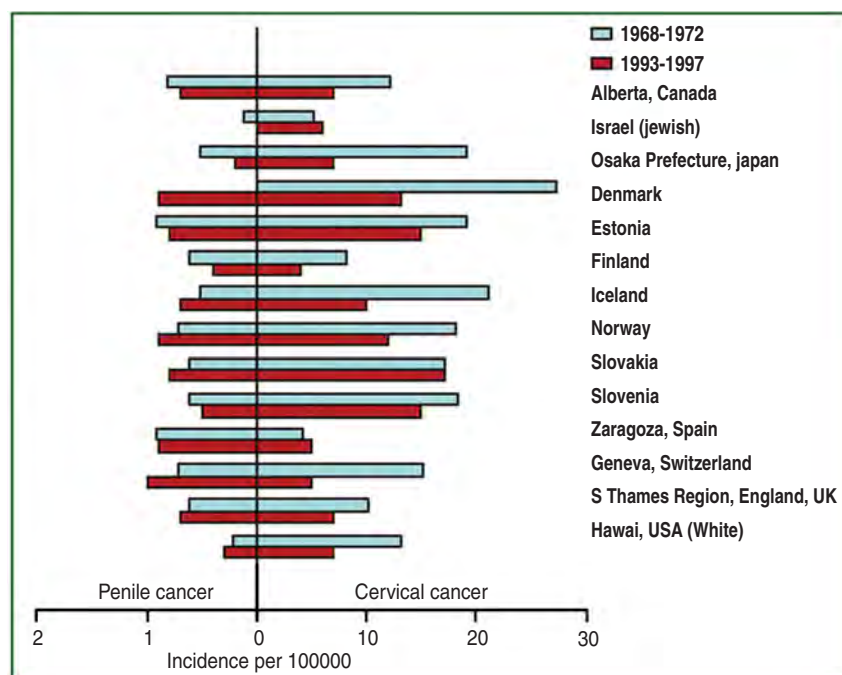


FIGURE 57-2. Age-adjusted incidence of cervical and penile cancers in countries with tumour registries during the years 1968–972 and 1993–1997. (Reprinted from Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. *Lancet Infect Dis* Jan 2006; 6(1): 21–31.)

SEER data presented below are calculated only for women and are age-adjusted to the 2000 U.S. standard population.

From 1950 to 1991, the incidence of cervical cancer in the United States declined by 76.6% among white women, with an estimated annual percentage change of about 3.3.²⁹ The incidence has continued to decline, with an estimated annual percentage change of 4.5 for all women of all ages between 1997 and 2003. From 1975 to 2003, mortality from cervical cancer declined by 53.2% among whites and 64.7% among blacks. The 5-year relative survival among white women has increased from 58% (1960–1963) to 74.6% (1996–2002); among black women it has increased from 47% (1960–1963) to 66.3% (1996–2002).³⁰ The development and implementation of Pap smear screening for early detection of precancerous cervical lesions in the 1950s has generally been credited with a major portion of the dramatic decline in incidence and mortality.

The changes in incidence of cancers of the cervix, vagina, vulva, penis, and anus since 1973 are shown in [Table 57-3](#). While rates of cervical cancer have generally declined, the incidence of carcinomas at each of the other genital sites has remained relatively low and steady over the past two decades, at least five times lower than the rates of cervical cancer, despite the fact that there is no routine screening for such lesions. Thus, the combined incidence of cancers of the vagina, vulva, and penis equaled 29.5% of the incidence of cervical cancer in 1973–1982, increasing to 44.1% in 1993–2002. On the other hand, the incidence of anal cancer has risen substantially in both men and women.

In 2002, there were an estimated 12,085 new cases and 3952 deaths from invasive cervical cancer in the United States.³¹ The U.S. age-adjusted mortality rate (2000–2002) for cervical cancer was 2.6 per 100,000 women per year (standardized to

the 2000 population), and for women diagnosed between 1996 and 2002, the 5-year relative survival rate for 17 SEER geographical regions was 71.6%. With an incidence of 8.8 cases per 100,000 during 2000–2003, cancer of the cervix uteri was the third most common female genital tract malignancy, following cancers of the corpus uteri (23.3 per 100,000) and ovary (13.7 per 100,000). In comparison, the incidence of breast cancer among women was considerably higher (129.1 per 100,000). The incidence of cervical cancer declined during the 1975–2003 period by 52.0%, cancer of the corpus uteri declined by 32.7%, and cancer of the ovary declined by 19.0%, but the incidence of breast cancer rose by 18.3%.³⁰

Although carcinomas of the cervix, penis, vagina, vulva, and anus are morphologically similar and share a common sexually transmitted etiology, the incidence of cervical cancer is 5 to 50 times higher than other genital tract cancers ([Table 57-3](#)). The exception is anal cancer among homosexual men. While anal cancer was rare among the general population even prior to the advent of HIV, the incidence of anal cancer among homosexual men at that time approached that of cervical cancer prior to Pap screening (i.e., 36/100,000).³² Why cervical cancer and anal cancer in homosexual men are so much more common than the other HPV-related genital tract cancers is unclear. Interestingly, however, both of these cancers arise in areas where HPV commonly infects metaplastic epithelium. Metaplasia is the process by which much of the mucus-secreting columnar epithelium in a particular anatomic location is replaced by stratified squamous epithelium. As shown in [Fig. 57-3](#), the surface epithelium of the endocervix and ectocervix undergoes dramatic changes (squamous metaplasia) throughout a woman's lifetime, presumably as a

Table 57-3. Age Adjusted Genital and Anal Cancer Incidence for 1973–1982, 1983–1992, and 1993–2002, All Races; Surveillance, Epidemiology, and End Results (SEER) Program, United States

	1973–1982 Incidence Per 100,000		1983–1992 Incidence Per 100,000		1993–2002 Incidence Per 100,000	
	Females	Males	Females	Males	Females	Males
Cervix	13.2		10.4		8.6	
Vagina	0.8		0.8		0.7	
Vulva	2.0		2.2		2.3	
Penis		1.1		0.9		0.8
Anus	1.0	0.7	1.2	0.9	1.4	1.2

Source: http://seer.cancer.gov/csr/1975_2003

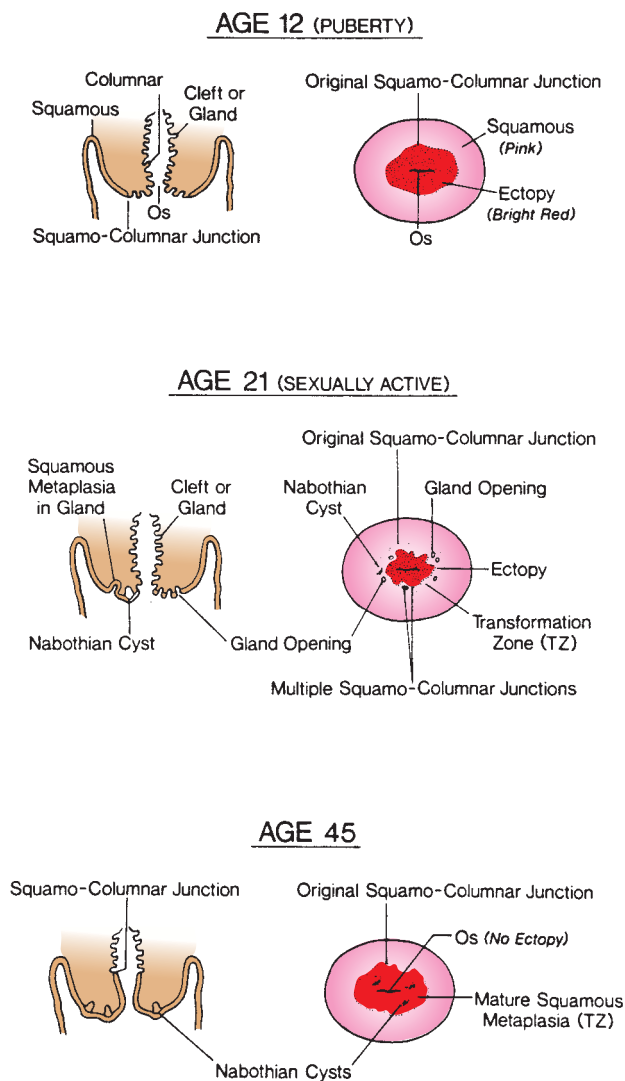


FIGURE 57-3. These diagrams show the change in location of the squamo-columnar junction on the uterine cervix from menarche (12 years) through initiation of sexual activity (21 years) and menopause (45 years).

result of hormonal and physical influences as well as infection with various agents, including HPV. As this change occurs, the point at which the squamous epithelium abuts columnar epithelium (termed the squamocolumnar junction) progressively recedes up into the endocervical canal. The area of the cervix where the native mucus-secreting columnar epithelium has been replaced by squamous epithelium is termed the transformation zone, and it is within this area of metaplastic epithelium that most cervical pathology, including early cancer, occurs. A similar zone of active epithelial metaplasia has been observed in the anal canal.

Age-specific rates in the US

Between the years 2000–2003, the median age of diagnosis for carcinoma of the cervix was 48 years, about 20 years younger than the median age of diagnosis of carcinoma of

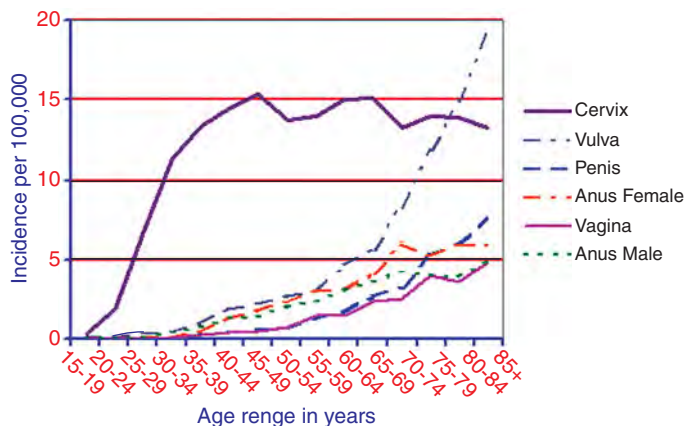


FIGURE 57-4. Age- and sex-specific incidence of invasive cancers of the cervix, vulva, penis, anus, and vagina in the United States. (Data from the Surveillance, Epidemiology, and End Results (SEER) Program, United States, 1993–2002.)

the vagina (68 years), vulva (69 years), anus (females, 63 years; males, 58 years), and penis (68 years).³⁰ As shown in Fig. 57-4, the incidence of all genital tract and anal cancers increases with age. The incidence of invasive cervical cancer increases with age, rising sharply to 11 per 100,000 between the ages of 30 and 34 years (premenopausal years), then fluctuating around 13–15 cases per 100,000 through the ninth decade of life. The age-specific incidence for other HPV-associated genital tract and anal cancers increases much more slowly and remains relatively low throughout life, except that of vulvar cancer, which increases sharply among women 60 years of age or older, up to about 20 cases per 100,000 for those in their 80s.

Ethnic Comparisons in the US

For all genital tract cancers except cancer of the vulva, the incidence is higher and the 5-year survival rate lower among African Americans than among whites. Overall in 2003, the incidence of carcinoma of the cervix was 10.5 as compared to 6.6 per 100,000 for black and white women, respectively. The disparity in cervical cancer incidence between white and black women is greatest among those over 50 years of age.

Mortality rates for HPV-related genital tract cancers have also remained considerably higher among African Americans of all ages since the early 1970s. This may be related to the fact that compared to cervical tumors diagnosed in black women, tumors diagnosed in white women are more likely to be localized at the time of diagnosis.³⁰ These racial differences in age and stage of cancer diagnosis may be related to varying access to and utilization of screening and treatment. However, the fact that survival is better for white women than for black women for each diagnostic stage of cancer³⁰ suggests other factors are also important. Regardless of race, women among lower

socioeconomic groups (lower income and education level), who until recently have had less access to Pap screening and gynecological services, have a higher risk of cervical cancer.^{33,34}

■ CERVICAL CARCINOMA *IN SITU*

In countries with early detection programs, the incidence of cervical carcinoma in situ (CIS) is much higher than the incidence of invasive cervical cancer through the fourth decade of life. The estimated age-specific incidence rates of CIN 3/CIS and invasive cervical cancer (CC) are shown for three European cancer registries (Fig. 57-5). As seen in the figure, CIN 3/CIS has a younger age distribution than CC, with incidence rates peaking in the 25–30 years age group in all three countries. The incidence of CIN 3/CIS peaked at about 400 per 100,000 women in the UK and Iceland, thus being at least 400-fold greater than the incidence of CC. In Finland, which has a long-standing, centralized cervical screening program, the incidence of CIN 3/CIS is an order of magnitude lower, peaking between 25 and 30 per 100,000 women at the highest. Similarly, the population-based ratio of CIN 3/CIS to invasive cancer calculated over all ages is lowest in Finland. In all three countries, a second mode of CIN 3/CIS and CC cases is seen in the 50–65 years age group. The reason for this second mode is uncertain. It is possible that screening coverage may be poorer or cytology screening may have decreased sensitivity at older age groups. Alternatively, immunosuppression in older women may induce activation of latent HPV infections. Finally, the possibility of newly acquired HPV infections during middle age cannot be ruled out.²⁴

It is likely that CIN3/CIS is often established at an age earlier than is depicted in Fig. 57-5. CIN3/CIS is asymptomatic and, therefore, will only be detected with screening followed by histological diagnosis. Delays in detection occur for the following reasons (1) in the United States women are screened only once every two years on average;³⁵ (2) Pap testing is only about 60% sensitive;³⁶ (3) cells from CIN3 lesions are difficult to identify on Pap tests when there is coexisting CIN1/LSIL, which is a common occurrence in young women;^{37,38} (4) diagnostic biopsies often are not scheduled until after two or more abnormal Pap tests;³⁹ and (5) the lesion is initially misdiagnosed as normal, atypia, CIN1, or CIN2.⁴⁰ Moreover, in European countries, routine screening may not begin until the age of 25 or 30, and recommended screening intervals tend to be longer than in the United States.^{41–43}

There is little information on the incidence of intraepithelial neoplasia of the vagina, vulva, anus, or penis in the general population, but it is likely that these lesions are less common than cervical neoplasia. VaIN 2–3 in the upper vagina usually represents a distal extension of CIN.^{44,45} A recent report indicates that the incidence of vulvar in situ

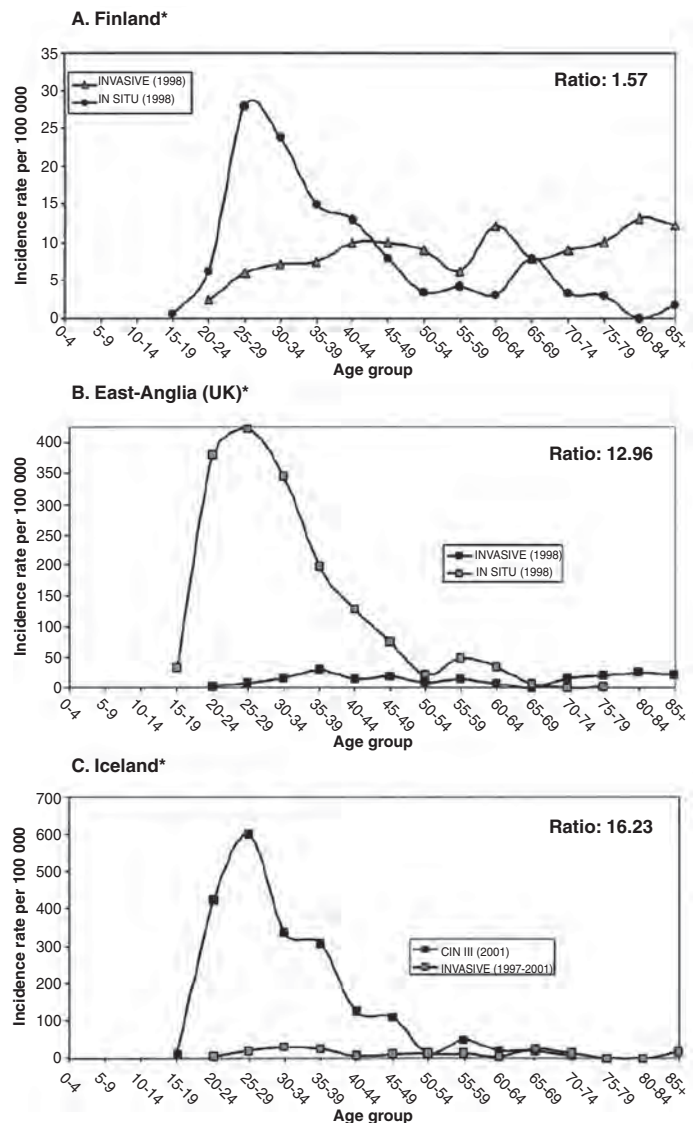


FIGURE 57-5. Age-specific incidence rate of CIN 3/carcinoma in situ and of invasive cervical cancer in selected populations. Ratio: Number of cases of CIN 3/in situ carcinoma of the cervix over the number of cases of invasive cancer diagnosed in the same population over the same time period across all age groups. (From Bosch FX, de Sanjose S. Human papillomavirus and cervical cancer—burden and assessment of causality. *J. Natl Cancer Inst Monogr* 2003; 31: 3–13.)

carcinoma increased more than 400% in the United States between 1973 and 2000.⁴⁶ The rate also appears to be increasing worldwide.⁴⁷

HISTORICAL OVERVIEW of ETIOLOGY: EPIDEMIOLOGICAL DATA SUGGESTING THAT CERVICAL CANCER IS AN STD

The association between cervical cancer and sexual activity was noted as early as 1842, when Rigoni–Stern reported that cancer of the uterus (site unspecified) occurred less frequently among cloistered nuns than among married women.⁴⁸ Since this initial report, other studies have con-

firmed the association between various measures of sexual exposure and development of squamous cell neoplasms of the cervix,⁴⁹ anus,³² and vulva.⁵⁰ Since 1950, at least three studies have documented a low incidence of mortality from cervical cancer among nuns.^{51–53} In contrast, subsequent wives of husbands whose previous wife had cervical cancer are at an increased risk.⁵⁴ In most studies, total number of sex partners is strongly associated with the risk of cervical neoplasia.^{55,56} In 1981, Buckley et al. reported that among women reporting only one lifetime sex partner, those whose husbands reported six or more sex partners appeared to have approximately a fourfold higher risk of cervical neoplasia than women whose husbands reported having had fewer than six partners.⁵⁷ Zunzunegui showed that among South American women residing in California, the occurrence of invasive cervical cancer was highly associated with the total number of sex partners of the husband but not with the woman's sex partner history.⁵⁸ Studies have reported an increased occurrence of cervical cancer in partners of men with penile carcinoma.^{59–61} Increased numbers of sex partners has also been associated with carcinoma of the anus³² and penis.⁶²

The epidemiologic evidence correlating sexual behavior with CIN and ICC, as well as with cancers of the penis and anus^{32,56,63,64} led to an extensive search for specific STD agents acting as carcinogens in genital and anal cancers. Until the 1980s attention had shifted from one organism to another about every ten years, from syphilis in the 1940s^{65,66} to gonorrhea^{67–70} and trichomoniasis.^{71–75} Other pathogens implicated in one or more studies include mycoplasmas, *Gardnerella vaginalis*, cytomegalovirus,^{76–81} and Epstein–Barr virus.^{82–85} The relationship of other sexually transmitted bacterial, chlamydial,^{79,86–89} protozoan, and fungal infections to genital tract neoplasia has also been evaluated, and although it is now clear that they are not independent causes of genital and anal cancers, their capacity to induce chronic inflammation or to produce mutagenic metabolites⁹⁰ may increase the risk of genital and/or anal carcinogenesis.

During the 1970s and early 1980s, there was considerable interest in HSV 2 and cervical cancer.^{56,91,92} The major problem in most seroepidemiologic studies linking cervical cancer to various STDs, including HSV, has been the lack of careful matching of cases and controls for potential confounding factors, most importantly sexual behavior. With HSV 2 there was the additional difficulty in initial seroepidemiologic studies of discriminating between serum antibody responses to HSV 1 and HSV 2.^{93–96} Epidemiologic and laboratory-based studies suggest that once HPV is taken into account, there is little evidence of an important role for HSV in the pathogenesis of cervical cancer,^{97,98} but that it may act as a cofactor by enhancing host susceptibility to HPV-induced neoplastic changes.^{99,100}

HPV TYPE AND GENITAL TRACT CANCERS

Within the taxonomic family of papillomaviruses, there are many species of HPVs, and within each species, the numerous HPVs are classified into types, subtypes, or variants based on DNA homology.¹⁰¹ Clinical epidemiologic studies undertaken during the last two decades have strongly supported the central role for specific types of HPV in the pathogenesis of squamous cell cancers of the genital tract. In addition, as discussed in Chapter 27, the molecular and biochemical evidence supporting a link between specific types of HPV and cancers of the genital tract and anus is quite strong.

Bosch et al. examined over 1000 cases of invasive cervical cancers from 22 countries from around the world for HPV DNA by PCR, using the L1 consensus primer and 26 type-specific probes. Over 93% of cancers in this series were positive for HPV DNA¹⁰² (Fig. 57–6)¹⁰³. It was hypothesized that the failure to detect HPV DNA in 7% of the samples may have been an indication of false-negative PCR results rather than the absence of HPV. Integration of HPV DNA into the host genome can disrupt the L1 open reading frame or the PCR primer sequences, leading to negative PCR results. Amplification of the E6 or E7 region of HPV DNA avoids this problem. With this in mind, the HPV DNA-negative samples were retested by type-specific E7 PCR targeting 14 HPV types. Combining the data from the two studies, HPV DNA was found to be present in 99.7% of cervical carcinomas.¹⁰⁴

A number of case-control studies examining the association between specific HPV types and invasive cervical cancer have been performed, with most studies reporting relative risks for the association of HPV DNA and invasive cervical cancer ranging from about 10 to over 40 for PCR-based studies.^{105,106} Recently, a pooled analysis was conducted that included 1918 squamous cell cervical cancer cases and 1928 controls taken from 11 case-control studies from around the world. All the studies included had used PCR-based methods to detect HPV DNA. Detection of HPV of any type was associated with a 158-fold increased risk for cervical cancer. Thirteen HPV types were classified as “high-risk” types because the odds ratios for cervical cancer associated with these types exceeded 45. These types were HPV-16, -18, -31, -33, -35, -45, -51, -52, -56, -58, -59, -68, and -73. In addition, types 39 and 82 were also classified as “high-risk” because they were detected in some cases but no controls. HPV types 26, 53, and 66 were classified as “probable high-risk” because they were detected in only a few cases and in no controls. HPV-16 was associated with the highest risk for squamous cell carcinoma (OR = 435, 95% confidence interval 278–679). In general, HPV types that are phylogenetically related to HPV-16 and HPV-18 conferred the highest risk.^{101,107} Prospective studies of HPV infection and risk of CIN2 or worse show similar findings.^{10,108–117}

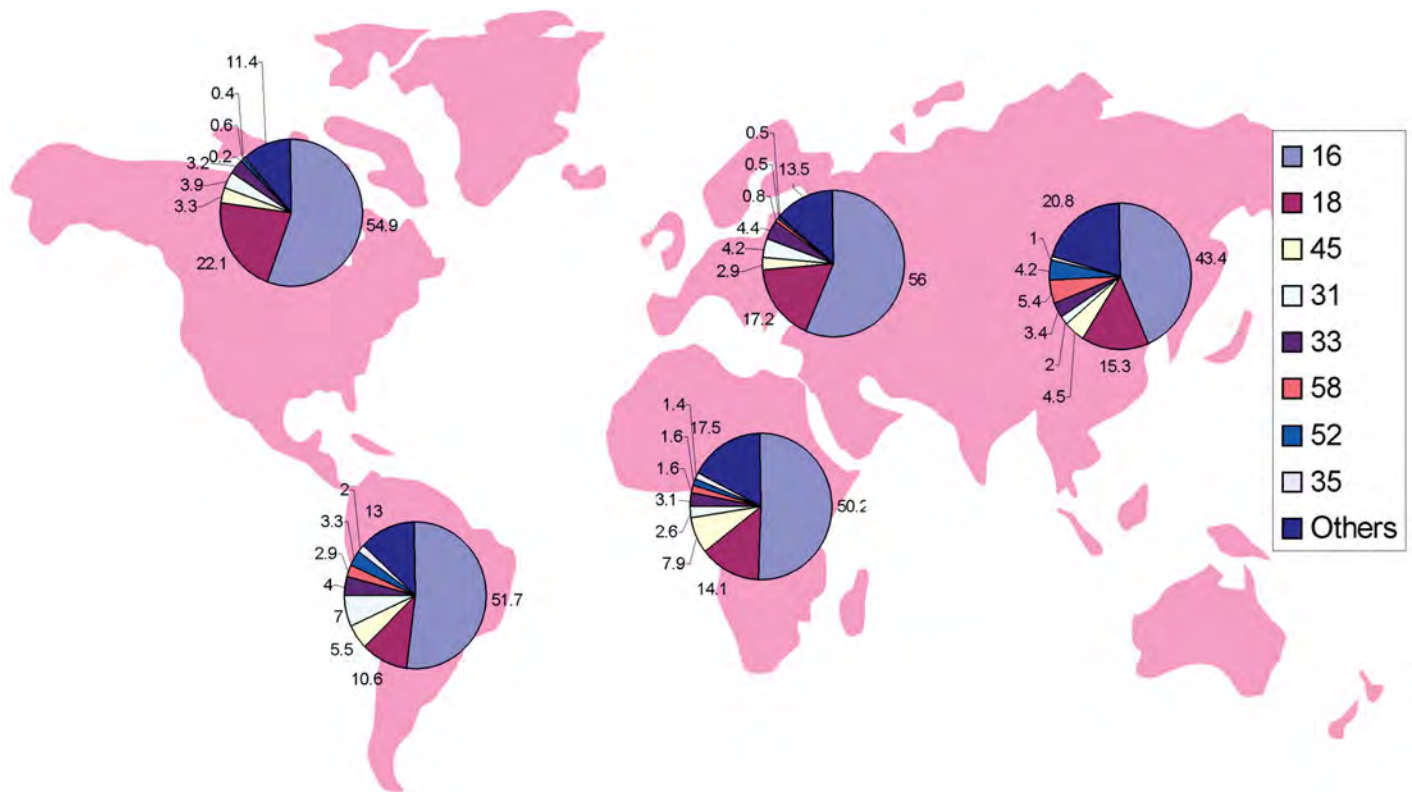


FIGURE 57-6. Detection of HPV types in cervix cancers from different regions of the world. (Data from Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: A meta-analysis. *Br J Cancer* 2003; 88(1): 63–73.)

The overall distribution of HPV types in cervical cancer is similar across the world (Fig. 57-6). In a meta-analysis, Clifford et al. found that HPV DNA is significantly more likely to be detected in squamous cell carcinomas (SCC) than in adenocarcinomas, but HPV-16 is the predominant type in both types of cancers. Throughout the world, HPV-16 and HPV-18 were the first and second most common types present in SCC, accounting for about two-thirds of the cases worldwide. In North and South America, Europe, and Australia, HPV-45 and HPV-33 were the next most prevalent types in SCC. In Africa, HPV-45 was more than twice as prevalent as HPV-31 or HPV-33, while in Asia HPV types 58 and 52 were found more commonly than HPVs-45, -31, and -33.¹⁰³

The role of HPV in anal carcinoma has been extensively studied and is now well established.¹¹⁸ There is no clear distinction between HPV-positive and HPV-negative tumors. Basaloid anal cancers are similar to squamous cell anal cancers with respect to prevalence of HPV DNA, and are more likely to be a histologic variant rather than a separate entity. HPV has also been shown to substantially increase the risk of other anogenital cancers. In a case-control study, Carter et al. investigated the effect of HPV seropositivity on the risk of cervical, vulvar, vaginal, penile, and anal invasive and in situ cancers among men and women in western Washington state. HPV-16 seropositivity was associated with

an increased risk of all the anogenital cancers, with risk estimates ranging from 1.8 for cervical adenocarcinoma to 5.9 for vaginal cancer. HPV-18 seropositivity was associated with an increased risk of cervical, vulvar, vaginal, and anal but not penile cancer. HPV DNA was detected in >80% of all anogenital cancers tested.¹¹⁹ Bjorge and colleagues performed a nested case-control study, using data from a cohort of individuals in Norway and Finland who developed noncervical anogenital cancers.¹²⁰ HPV-16 seropositivity was associated with a significantly increased risk of vulvar and vaginal cancers. HPV-18 seropositivity was associated with a significantly increased risk of preinvasive lesions at these sites. Nonsignificant but elevated risk for penile cancer was associated with seropositivity for HPV-16 and HPV-33. The fact that this study is based on prospectively collected data adds further credence to the role of HPV in these anogenital cancers. In contrast to cervical and anal cancer, however, HPV DNA is not as frequently detected in all other genital cancers. In penile tumors, HPV DNA positivity varies from 42% to 80%.^{62,121–123} Similar findings have been made for vulvar tumors.²⁵ The relationship between HPV and penile cancer resembles vulvar cancer more than cervical cancer. Warty and basaloid cancers of the penis have a higher prevalence of HPV infection than verrucous and keratinizing cancers of the penis. Verrucous carcinomas are associated with low-risk HPV types.

COFACTORS FOR HPV CARCINOGENESIS

Because only a minority of women infected with oncogenic types of genital HPV go on to develop cervical neoplasia, investigators have studied other factors that may work in conjunction with HPV to contribute toward an increased risk of neoplastic behavior. These factors can be broadly classified as (1) viral cofactors; (2) host cofactors; and (3) environmental cofactors.

■ VIRAL COFACTORS: VIRAL PERSISTENCE, VARIANT, VIRAL LOAD AND INTEGRATION

Persistent detection of infection

The majority of genital HPV infections appear to be transient,^{124–128} with most new infections being detectable for less than 2 years.^{124,125,128,129}

While it has been generally accepted that persistent HPV infection is crucial for development of neoplasia, uncertainties and controversies remain. Long-term persistence (that is, repeated detection of the same HPV type on two visits at least 5 years apart) is about the same for high-risk and low-risk HPV types, with the possible exception of HPV-16.¹⁰⁸ Furthermore, in a longitudinal study with active biannual follow-up,¹¹¹ risk of a precancerous cervical lesion was greatest within 6 months of the first positive HPV test, not after 12 or more months of persistent HPV infection. Results from another natural history study¹⁰ and from 3.5 years follow-up post-dose 3 of the placebo arm of the monovalent HPV-16 vaccine trial¹³⁰ are similar. Thus, as Woodman and Collins¹³¹ have discussed, persistence per se does not appear to predict progression. Rather, it is likely that a persistent high-risk HPV infection is more of a “risk marker” for underlying CIN3 than a “risk factor” for future development of CIN3.

HPV variants

HPV viruses are classified into separate “types” if they differ by more than 10% in the nucleotide sequences of specified regions of the genome.^{101,132,133} Viruses that differ by 2–10% in these regions are considered “subtypes” while those that differ by less than 2% in these regions are considered to be “variants.”^{101,132,133} Because only a minority of women infected with oncogenic HPV types go on to develop cervical cancer, there is now considerable interest in the idea that different HPV variants might have differing biological behaviors. Although most of the research in this area has tended to focus on HPV-16, investigators have begun expanding their studies to include other oncogenic HPV variants as well.

The first HPV-16 to be cloned was from a cervical cancer removed from a German patient. This HPV is considered the

HPV-16 prototype variant, and is the variant commonly used in molecular studies of HPV. Nucleotide sequencing of E6, L1, L2, and the long control region (LCR) of viruses in different parts of the world revealed the existence of multiple HPV variants, which segregate geographically, suggesting that the virus coevolved with its human host.^{132–140} Based on their suspected origin, HPV-16 variants have been classified into five phylogenetic lineages: European (E), Asian (As), Asian American (AA), African-1 (Af1), and African-2 (Af2). Yamada et al. examined invasive cervical cancers from 22 countries and found that 92% belonged to previously reported HPV-16 lineages, with 7.8% of cancers harboring HPV-16 variants with novel hybridization and/or nucleotide changes. Most variants from European and North American samples were phylogenetically classified as European prototype (E), while samples from Africa were primarily classified as African.¹³⁷ Stewart et al. examined 135 invasive cervical cancers from the same 22 countries, in addition to 11 cancers from New Mexico, for variations in the genomic sequences of HPV types -18, -33, -35, -39, -45, -51, -52, -58, -59, -68, -73, and -82. They found that within a given HPV type, nucleotide sequence varied from 0.2% to 2.9% and amino acid diversity was between 0% and 5.1%.¹³⁹

It is possible that differences in certain amino acid sequences might have functional importance for biologic properties related to the development of malignancy. As discussed in Chapter 27, E6 and E7 genes of HPV are vital to oncogenic transformation. Their gene products interact with various cellular proteins involved in cell-cycle regulation, most notably p53 and Rb, respectively. Transcription of E6 and E7 genes is controlled by promoter and enhancer elements in the long control region and by the E2 protein of HPV. Thus, nucleotide sequence variation in E6, E7, E2, and LCR genes may have functional significance that impacts the malignant potential of the different variants. Evidence of this has begun to emerge from *in vitro* studies. HPV-16 E6 variants have been observed to have varying abilities to generate differentiation-resistant human foreskin keratinocyte (HFK) colonies and to target the degradation of p53.^{133,141} Nucleotide alterations in the non-coding region of HPV-16 have been shown to enhance promoter and transcriptional activity^{142–145} or alter oncogenic potential in the presence of *ras* oncogene and hormone.¹⁴⁶ The influence of variant differences on promoter activity of E6/E7 has also been observed *in vitro* for HPV-18.¹⁴⁷

Early epidemiologic studies of the association between HPV variants and risk of neoplasia (reviewed in Ref. 132) yielded conflicting findings. It is now accepted that the early data were rather homogeneous, being predominated by European variants.¹³² Thus, significant differences in the risk of neoplasia were not always observed in the variants included in these projects. Later studies, conducted largely in North and South America, demonstrated that the non-European lineages of HPV-16 confer higher risk of cervical neoplasia.^{144,148–152} In a

cohort study in Seattle, we found that compared to women infected with prototypelike (PL) variants of HPV-16, women infected with non-prototypelike (NPL) variants are at increased risk of developing CIN2-3.^{144,151} This finding was also seen in a cohort study performed in Brazil.¹⁵⁰

A few studies^{150,153,154} have provided evidence that as with HPV-16, NPL variants of HPV-18 confer increased risk of developing high grade cervical neoplasia. The limited epidemiologic data on variants of other oncogenic HPV types have so far indicated that certain polymorphisms of HPV-33¹⁵⁵ and HPV-58¹⁵⁶ may be associated with CIN3 and invasive squamous cell carcinoma.

It is possible that the oncogenic potential of HPV variants may vary in different populations if certain amino acid changes present in certain variants, in association with specific host HLA haplotypes, influence the host immune response to different HPV types or variants.^{149,157-162} It has also been suggested that specific HPV variants might work in concert with certain p53 polymorphisms to increase a woman's risk for cervical cancer¹⁶³ or risk of transitioning from CIN3 to invasive cancer.¹⁶⁴ Such data are currently sparse and suffer from low sample sizes, but suggest that the oncogenic potential of HPV could be determined by the particular combination of molecular factors present in the cellular milieu.

Viral load

Several studies have shown that HPV-16 viral loads are higher among women with cervical neoplasia than among those without,¹⁶⁵⁻¹⁶⁹ but a similar trend has not been reported for other oncogenic HPV types.¹⁷⁰ In a nested case-control study conducted in Sweden, viral load measured using quantitative PCR was able to predict CIS even in samples collected 13 years before diagnosis.¹⁷¹ Repeated detection of high viral load was associated with risk of incident CIS, but the magnitude of this risk decreased with increasing length of time between HPV testing and diagnosis of CIS.¹⁶⁶ In another study using quantitative PCR, women with high viral loads had increased likelihood of developing CIN 2-3 and decreased risk of viral clearance. Furthermore, among women with Pap abnormalities, a consistently high viral load was predictive of progression to a higher grade lesion.¹⁶⁵ Although the relationship between high HPV-16 viral load and cervical neoplasia is consistent, the association is not strong enough to propose the use of HPV-16 viral load as a screening test for cervical cancer.

Viral integration

In vitro studies with HPV-16 have shown that cell populations in which the virus is integrated into the host genome possesses a growth advantage compared to cells in which the virus is retained in its episomal form.¹⁷² During integration, the E1 and/or E2 genes of HPV are often disrupted, while the

E6 and E7 oncogenes are retained. The disruption of the open reading frame of E2 is thought to augment the levels of mRNAs encoding E6 and E7. The proteins expressed by the latter two genes are critical in HPV carcinogenesis through their interactions with p53 and Rb proteins in the host, respectively. Thus, disruption of E2 during the viral integration process may be an irreversible step that leads to a chain of events resulting in genomic instability and cell immortalization.¹⁷² HPV-16 integration has been reported to occur to different degrees in variously graded cervical lesions, from low-grade lesions to invasive cancer.¹⁷²⁻¹⁸² Some studies show that the frequency of integration increases with increasing disease severity,¹⁷⁶⁻¹⁷⁹ and integration has also been linked with poorer prognosis of cervical cancer.^{183,184} These findings have not been confirmed in other investigations, and the importance of integration in development of neoplasia is still being debated.^{172,180-182} As was the case with the early studies of the role of HPV DNA in cervical neoplasia, much of the reason for this uncertainty may lie in the limitations of laboratory assays to measure integration. Methodologic challenges include the fact that HPV often coexists in integrated and episomal form, and that the sites of integration are highly variable. Also, assays that measure levels or relative levels of E2 and E6 or E7 DNA without taking into account the inherent variability of the nucleotides for different variants of a given HPV type are likely to provide inaccurate results.

■ HOST FACTORS: ASSOCIATIONS BETWEEN HLA HAPLOTYPE AND RISK OF HPV-RELATED CANCER

Since human leukocyte antigen (HLA) molecules are responsible for presenting foreign antigens to the immune system, there was a strong a-priori hypothesis that HLA molecules may influence the risk of developing neoplasia mediated by clearance of HPV infection. Most research on the association of HLA molecules with cervical neoplasia has focused on HLA Class II molecules, which present antigenic peptides to CD4⁺ T-helper cells to initiate cell-mediated immunity.¹³² The most consistent findings to date point toward a decreased risk of CIN3/CIS and SCC associated with HLA Class II DRB1*13 (DRB1*1301-5) and DQB1*0603 alleles (these two alleles are in linkage disequilibrium and, therefore, often occur on the same haplotype).¹⁸⁵⁻²⁰² In a recent study, Sastre-Garau et al. observed that after controlling other factors including HPV-16/-18 infection, the DRB1*13 allele is associated with increased probability of regression of CIN 1 lesions.²⁰³

■ ENVIRONMENTAL FACTORS: MEASURES OF SEXUAL BEHAVIOR, HORMONE AND CONTRACEPTIVE USE, SMOKING AND DIET

After taking into account HPV, the previously reported associations of cervical cancer with many risk factors, such as

number of sex partners, early age of first intercourse, parity, or other infectious agents, disappear or are greatly reduced. Likewise, while several case control studies during the 1980s linked current cigarette smoking with cancers of the cervix,^{55,204} vulva,⁵⁰ anus,³² and penis,²⁰⁵ these studies did not adequately take into account confounding sexual exposures not measured by the number of sex partners, or (most importantly) laboratory evidence of HPV infection. Recent studies have evaluated the independent effect of smoking on neoplasia by restricting analyses to include only women who are HPV-infected. These studies have indicated that smoking imparts a 1.5-fold to 5-fold increased risk for high grade cervical neoplasia and invasive cancer, and that there is a trend of increasing risk associated with increasing amounts of exposure to tobacco smoke, as measured by the duration or intensity of smoking.^{206–214} Interestingly, investigators are beginning to find that this elevated risk for squamous cell cervical cancer is not seen for cervical adenocarcinoma.^{210,215,216} There is evidence that cervical mucus from cigarette smokers is more likely than mucus from nonsmokers to contain carcinogens.^{217–219} Various mechanisms have been proposed for the pathway through which tobacco smoke might induce neoplastic changes. Exposure to tobacco may suppress one's immune response to HPV infection, allowing the virus to persist for a longer period of time, as cigarette smokers have a reduced Langerhans cell population in the cervix.^{220,221} A prospective study has provided evidence that compared to nonsmokers, smokers take longer to clear oncogenic HPV infections.²²² Cigarette smoke has also been shown to directly induce malignant transformation in HPV-infected cells.^{223–225} Finally, it has been proposed that smoking alters normal epithelial cell proliferation by increasing cell division and inducing metaplasia.²⁰⁷

As regards hormonal contraceptives (HC), a recent meta-analysis of HC use and cervical cancer among women with HPV infection showed a 2.5-fold increased risk of cervical cancer for long-term users.²²⁶ While this finding supports a causal association, the hormonal contraceptives that were available to many of these women during their reproductive years, which mostly coincided with years in the 1960s and 1970s, contained levels of hormones that were much higher than those of present-day hormonal contraceptives. Other studies among HPV-infected women have shown either no significantly elevated risk or significant associations limited to particular histologic types or only in subgroups of the study participants.^{208,211,212,214,227,228} (For a detailed discussion on the possible reasons for these conflicting findings, refer to the cited studies or to a review by Castellsague and Munoz.²²⁹)

There also appears to be an increased risk for high grade cervical neoplasia and cervical cancer among women with high parity compared to those with low parity or nulliparous women, even after restricting the analyses to HPV-infected

women.^{211,214,228} In studies in North America and Denmark, significant associations were not seen with parity,^{208,212,228} but this may be because most participants in these studies had low parity. High parity may increase a woman's risk for cervical neoplastic changes by maintaining the transformation zone exposed on the exocervix for a longer duration of time, thus increasing the likelihood of exposure to HPV. Hormonal changes during pregnancy could also play a role, particularly given the observed association with hormonal contraceptive use. Increased levels of estrogen and progesterone during pregnancy could reduce the immune response to HPV. Further, estrogen could promote HPV-related malignant transformation in cervical cells by facilitating viral integration into the host genome and stimulating transcription of E6 and E7 oncogenes of HPV.²²⁹ Such hormone-induced mechanisms would explain the associations with high parity and hormonal contraceptive use.

As mentioned earlier in this chapter, other sexually transmitted infections could enhance host susceptibility to HPV-induced changes by causing chronic inflammation, which can result in the production of reactive oxygen species that can cause DNA damage. Recent epidemiologic evidence points to HSV-2 and Chlamydia trachomatis as cofactors.^{99,230} Lastly, after HPV infection is taken into account, it does not appear that specific nutritional factors or combinations of factors affect cervical cancer risk; however, such studies have only been conducted in populations with adequate nutrition.²³¹

IMMUNOSUPPRESSION, INCLUDING HIV-INFECTION-RELATED IMMUNOSUPPRESSION

The importance of immune surveillance for prevention of HPV-associated neoplasia of both the skin and genital tract has been well documented.^{232–234} For example, patients with a rare genetic defect of cell-mediated immunity, epidermodysplasia verruciformis, are particularly prone to developing multiple common skin warts, with up to one-third of these individuals going on to develop skin cancers at the site of such lesions.²³⁵ Renal transplant patients also have increased risk for various manifestations of HPV infection, including genital warts and cervical neoplasia.^{233,234,236,237}

The prevalence of HPV is high among women with HIV infection.^{238–245} Some studies indicate that HPV infection is more likely to occur at higher viral loads²⁴⁶ and with multiple types of HPV²⁴⁶ in HIV-positive as compared to HIV-negative women. Follow-up studies have also shown that HPV infection is more likely to be persistently detected in HIV-positive women.^{247–251} Infection with HIV has also been associated with a higher prevalence of cytologic abnormalities and histologically confirmed CIN.^{239,240,242–245,249,250,252–257} In longitudinal studies, HIV infection has been associated with a greater incidence and persistence of CIN.^{247,258,259} There have been few studies on the natural history of CIN in HIV-infected women, but it appears that lesions are more

likely to progress and less likely to regress in the presence of HIV.^{259,260} Detection of HPV, as well as the frequency of detecting CIN, increases with worsening immunosuppression as measured by CD4 cell counts.^{240–242,247,251,253,256,258,259} Other mechanisms such as HIV-targeting of specific genes and direct viral–viral interactions may also play a role in HPV-related neoplasia.^{261,262}

The association with HIV infection has also been demonstrated for other HPV-related genital neoplasias including anal^{263–268} and vulvovaginal intraepithelial neoplasia.^{269,270} While the effect of HIV has been clearly demonstrated for precancerous HPV-related lesions, its relationship with HPV-related genital cancers is not as firmly established despite the addition of invasive cervical cancer to the list of AIDS-defining illnesses. The association between prevalence of HIV and invasive cervical cancer varies from country to country, being influenced by a number of factors including access to cervical screening and follow-up care and life expectancy following HIV infection. In North America, Europe, and Australia, no significant change was seen in the incidence of cervical cancer between 1992 and 1999.²⁷¹ Similarly, no increase in cervical cancer was seen among HIV-positive women in Kenya.²⁷² On the other hand, an increase in cervical cancer incidence was observed in South Africa.²⁷³ Some studies in the United States and Southern Europe have also shown an increased risk of cervical cancer among HIV-positive women.^{274–276}

It is not yet clear whether using highly active antiretroviral therapy (HAART) to control HIV replication alters the course of HPV-related lesions. A number of studies have explored this issue, with mixed findings.^{277–282} Although current findings are based on studies with relatively short-term follow up, any effect of HAART on reducing the risk of HPV and/or CIN appears to be modest.²⁸³

THE ROLE OF COLPOSCOPY IN CERVICAL CANCER CONTROL

During the last 50 years, colposcopy has been used to evaluate women with atypical cervical cytology or with vaginal and vulvar intraepithelial neoplasia, to determine where to carry out biopsy and to follow the evolution of lesions over time.²⁸⁴ Colposcopic identification of epithelial pathology is possible because as cancers or intraepithelial lesions develop, the normal epithelium is replaced by a proliferating and crowded epithelium that is characterized by an altered optical density and an abnormal vasculature. With the cervix, the colposcopist first determines whether the colposcopic examination is adequate (i.e., whether the squamocolumnar junction and the whole lesion are visible). If the entire squamocolumnar junction cannot be seen (because a portion or the entire junction lies within the endocervical canal), the colposcopic examination is termed inadequate or unsatisfactory. This situation occurs in approximately 15–20% of women, especially older women, and

requires endocervical curettage for diagnosis of any pathology present. Next, severity of the lesions is estimated and biopsies obtained from what appear to be the most serious lesions. Colposcopic criteria for diagnosis of different pathologic diagnoses have been established, and the reader is referred to the American Society for Colposcopy and Cervical Pathology website (<http://www.asccp.org/>) for resources that provide visual presentations and detailed discussions of this issue. Generally, the size of the lesion, its appearance with and without the application of acetic acid, and its vascular pattern (best assessed with the use of a green filter) are used to classify changes. If a two-stage or greater discrepancy exists between colposcopically directed biopsies and cervical cytology, in which the severity of the cytology is greater than that of the biopsy, it is important to consider diagnostic or therapeutic conization by performing large-loop excision of the T zone (LLETZ). Colposcopy has also been used to aid in evaluation of cervicitis and other cervical vaginal infections. A major problem with colposcopy is poor accuracy and reliability even among experienced colposcopists.^{285,286} However, even with these shortcomings, colposcopic examinations are needed to guide practitioners to areas of abnormality that require biopsy and histopathological diagnosis.

COLPOSCOPIC EXAMINATION OF THE PENIS AND ANUS

Colposcopic examination of the penis and anus has been used for evaluation of intraepithelial neoplasia at these locations.^{266,287–289} Colposcopic examination of the penis is usually performed after application of 5% acetic acid to the penis, whereas 3% acetic acid is used in the anal canal. There have been reports that application of 5% acetic acid and colposcopy augment the detection and diagnosis of subclinical HPV infections and PIN. Common manifestations of subclinical HPV infection of the penis, including PIN, include sharply demarcated, slightly raised macules, and papules with fine punctation. Detection of acetowhite epithelium, although useful for clinical examination, is not sufficiently specific and should not be used as a screening tool for penile lesions or as a sole criterion for the diagnosis of HPV infection.²⁹⁰

When used to assess anal disease, the technique, known as high resolution anoscopy (HRA) has been recommended by some experts to visualize anal intraepithelial neoplasia (AIN). Similar to assessment of CIN, HRA is used to direct biopsies to establish the histologic grade of the lesion to guide treatment.²⁹¹

TREATMENT OF GENITAL SQUAMOUS CELL NEOPLASIA

■ CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

Once invasion has been ruled out by histologic examination of tissue and the extent of a lesion has been accurately established

by colposcopy, the lesion can be destroyed by a variety of methods, including excision or ablation. Although treatment of CIN by various methods may be followed by recurrence of CIN, subsequent development of invasive cancer is quite rare.

Local biopsy excision

Local biopsy excision is appropriate for excision of a small, single focus of CIN 1 completely visualized by colposcopic examination, but it is not appropriate for multifocal disease or for lesions which extend into the endocervical canal.

Hysterectomy

Hysterectomy is an alternative treatment for CIS, if fertility is not important and when concomitant gynecologic indications for hysterectomy are present.

Cold-knife or CO₂ Laser Conization

Cold-knife conization has been widely employed as a definitive therapy for CIN in the past, but it has recently been replaced by simple outpatient procedures such as CO₂ laser conization, and most recently by loop electrosurgical excision procedure (LEEP). The recurrence rates after cold-knife or CO₂ laser conization are generally low if margins are negative; however, there is a relatively high complication rate, including postoperative hemorrhage, cervical stenosis and scarring, increased risk for subsequent preterm deliveries, and infertility. Both procedures offer the opportunity of histopathologic evaluation for degree of pathology and margins.

Electrocautery

Although electrocautery was popular in the past, this approach is no longer recommended because of frequent complications and failure to eradicate lesions with deep crypt involvement.

Cryocautery

Introduced by Townsend and Ostergard²⁹² 25 years ago, cryocautery involves liquid nitrogen freezing of lesions. Treatment usually involves one or two 2–3 minute applications of a cold probe, which causes necrosis of the targeted area. Cryocautery is virtually painless and bloodless, and total reepithelialization is complete in 7–10 weeks. The value of cytology and colposcopy after treatment may be reduced as a result of scarring and of the fact that the squamocolumnar junction often recedes high up into the endocervical canal after squamous metaplasia during reepithelialization. Published failure rates (i.e., persistence of disease) after initial cryotherapy for CIN range from 4% to 24%.²⁹³ Failure is especially common among women with a positive endocervical curettage specimen (ECC), inadequate colposcopic examination, extensive lesions, or glandular involvement. Given the high rate of treatment failures, cryotherapy is no longer considered the treatment of choice for CIN lesions and is

contraindicated in patients with CIN who have inadequate colposcopy, positive ECC, or extensive lesions.

CO₂ laser

Laser vaporization treatment of CIN can be performed as an outpatient procedure, and allows for precise tissue destruction under colposcopic guidance, minimal damage to surrounding tissue, low risk for postoperative hemorrhage, rapid healing with practically no scarring, and decreased risk for postoperative infections. A new squamocolumnar junction is formed at the external os and usually remains visible colposcopically, facilitating posttreatment cytologic and colposcopic evaluation. Concomitant multifocal intraepithelial lesions in the vagina or vulva can easily be treated simultaneously. However, relative to cryotherapy, CO₂ laser vaporization is costly and requires more training and skills. Failure rates have ranged from 4% to 30%,²⁹³ with the best designed studies showing a failure rate of 17%.²⁹³

Large-loop excision of the T zone (LLETZ)

Large-loop excision of the T zone (LLETZ) is also called LEEP.^{294–298,295} This Procedure uses a fine wire loop diathermy for biopsy or excision of the whole T zone. This is a safe, effective, inexpensive, easily mastered outpatient procedure,^{299–302} which provides excellent quality tissue for histologic evaluation.²⁹⁷ Reported recurrence rates have ranged from 5%, when lesions involved only one quadrant, to 26% when the lesions involved all four quadrants.²⁹⁷ Morbidity of this procedure, as with laser or cold-knife cone biopsies, is related to the volume and depth of endocervical tissue excised. Potential problems include intra- and postoperative bleeding in 4–7% of women treated,^{299–303} a figure well below the average complication rates reported with cold-knife conization or CO₂ laser conization,³⁰⁴ and removal of excessive amounts of tissue, which can result in an increased risk of preterm delivery and low birth weight.^{305–308} Although there was initially a great deal of enthusiasm for a “see and treat” approach using the LLETZ, this approach has led to the overtreatment of minor cytological abnormalities, with recent reports showing that 5–41% of “see and treat” LLETZ specimens are free of disease.^{296,299,301,309}

Topical chemotherapy

Topical chemotherapy (bleomycin, 5-fluorouracil, beta-all-trans-retinoic acid, or interferons) has been used in the treatment of CIN with relatively poor success rates, due to its inability to eradicate CIN involving glandular crypts.

■ VAGINAL AND VULVAR INTRAEPITHELIAL NEOPLASIA

Although during the 1960s, vulvectomy, and more recently skinning vulvectomy, were the standard treatments for vulvar

carcinoma in situ (VIS), the high rate of spontaneous regression of VIN has prompted less aggressive treatment modalities. Excisional biopsy and CO₂ laser treatment have now largely replaced skinning vulvectomy in the treatment of VIN, including VIS. The CO₂ laser is useful because it is an efficient treatment of multifocal disease to a depth that allows for rapid healing with minimal scarring.³¹⁰

■ PENILE AND ANAL INTRAEPITHELIAL NEOPLASIA

The spontaneous regression rate of PIN and specifically Bowenoid papulosis (PIN 3) is not known; however, these lesions appear to have a low risk of progression. Lesions suggestive of PIN should be biopsied, and preferably treated with local ablation using CO₂ laser surgery or cryotherapy under colposcopic guidance.

Treatment of anal lesions depends on the location and extent of the lesions.²⁹¹ Although it has not yet been confirmed, it is presumed that treatment of high-grade AIN will reduce the risk of progression to invasive anal cancer, analogous to the reduction in cervical cancer due to treatment of high-grade CIN. Small internal lesions may be treated with 85% trichloroacetic acid (TCA) and small external lesions may be treated with cryotherapy or 85% TCA. Perianal condyloma may also be treated by patients themselves with imiquimod or podophyllotoxin. Larger lesions inside the anal canal may be treated in the office with infrared coagulation (IRC).³¹¹ Lesions too large for IRC may be treated in an outpatient surgical setting with electrocautery, laser or cold scalpel excision.³¹²

Lesions that are too diffuse may be difficult or impossible to remove without causing excessive morbidity, and some experts recommend that patients with high-grade AIN be monitored on a regular basis for development of invasive anal cancer.

■ CERVICAL CARCINOMA

Treatment for early microinvasive carcinoma ranges from cervical conization to radical hysterectomy with pelvic node dissection and radiotherapy or chemotherapy. The overall recurrence rate is approximately 1%, regardless of the criteria used for case definition or the method of treatment. Hysterectomy with excision of the vaginal cuff is the current treatment of choice in cases with less than 3 mm invasion depth, without evidence of stromal or vascular involvement, and in which there is no confluence of tongues of invasive cells. Treatment of other forms of invasive cervical carcinoma (ICC) is based on the stage of disease defined by the International Federation of Gynaecology and Obstetrics (FIGO) classification.

■ VAGINAL AND VULVAR CARCINOMA

Treatment of vaginal cancer is more difficult because of anatomic considerations. The selection of treatment is based on the stage of the disease, the tumor volume, and location

within the vagina. Most superficial lesions can be treated with vaginectomy. However, in general, surgical treatment can rarely be conservative because of the close proximity of the rectum and the bladder. Hence, ultraradical surgery with pelvic exenteration is often necessary. Cure rates are generally poor except in stage I disease. During the 1960s, VaIN was treated by partial or total vaginectomy with or without radiation. Currently, less traumatic treatment modalities are used, including colposcopically directed excisional biopsies, cryotherapy, laser therapy, and topical 5-fluorouracil (5-FU). Laser therapy has reported cure rates of 85–90%, whereas 5-FU has a high recurrence rate and can result in local toxicity, with frequent development of genital ulcerations.

■ ANAL AND PENILE CARCINOMA

In the past, anal cancer was usually treated by excision of the rectum and anus and formation of a permanent colostomy. More recently, first-line therapy is a combination of chemotherapy and radiation therapy, with abdomino-perineal resection usually reserved for recurrent anal cancer. As with cervical cancer, the success rate of therapy varies inversely with the stage at which the cancer is diagnosed. Although often successful, this regimen is frequently complicated by radiation proctitis, with anal pain and bleeding that may last for years. Treatment of HIV-positive men and women may be particularly challenging due to inability to tolerate a full course of therapy. Recent data suggest, however, that patients successfully treated with antiretroviral therapy are often able to tolerate a complete course of therapy. Cancers at the earliest stage of invasion may potentially be treated with wide local excision, but the outcome of this approach has not yet been determined.

Treatment of localized, stage I penile cancer has a high cure rate. If the cancer is on the glans, its treatment may involve fluorouracil cream and microsurgery (removal of the cancer). If the tumor begins in the glans and involves other tissues, its treatment may involve partial penectomy and lymph node removal, external radiation therapy, and microsurgery. If the cancer is limited to the foreskin, its treatment is likely to be wide local excision and circumcision. Stage II cancers are often treated with partial, total, or radical penectomy, or radiation therapy followed by penectomy. Stage III involves cancer that has spread beyond the penis, and in addition to penectomy, lymph node removal on both sides of the groin, radiation therapy, and chemotherapy may be required. Treatment of Stage IV cancer may involve chemotherapy and radiation therapy for palliation.

PREVENTION OF HPV-RELATED CANCERS

Primary prevention of cervical and other HPV-related genital cancers relies on preventing HPV acquisition. Secondary prevention, which requires screening and treatment for

precancerous lesions or early cancers, is discussed in Chapter 58. Certain behavioral interventions including life-long mutual monogamy and use of male condoms with sex partners can be undertaken to reduce one's risk of acquiring or transmitting HPV (see Chapter 28). Condoms have also been shown to reduce the risk of high-grade cervical neoplasia and cervical cancer, as well as to increase the regression rate of cervical and penile lesions.^{313–316}

A prophylactic vaccine designed to prevent infection by four HPV types (HPV-6, HPV-11, HPV-16, and HPV-18), was recently approved in many countries for immunizing young women aged 9–26 years of age (discussed in Chapter 28). Briefly, among an HPV-16 and HPV-18 susceptible population, this vaccine was highly effective (>90%) in preventing infection with these four HPV types, as well as in HPV-16/-18-related precancerous lesions of the cervix, vagina, and vulva. Similarly, high efficacy was observed for prevention of HPV-6/-11-related genital warts.³¹⁷ Clinical trials of a bivalent HPV-16/-18 prophylactic vaccine³¹⁸ with encouraging early results are ongoing and licensure is expected in 2007. Both vaccines have the potential to reduce the global incidence of cervical and anal cancers by about 70%, the incidence of vaginal, vulvar, and penile cancers by about 30%, and the incidence of oral and oral-pharyngeal cancers by about 15%. Due to the long latency period between infection and cancer, it will take decades of high vaccine coverage among preadolescents to achieve such reductions. Whether high levels of vaccine coverage will be achieved in the future depends on information developed over the next decade concerning societal acceptability, long-term durability and safety profiles, and pricing schemes that allow for cost-effective vaccination strategies in all countries, particularly in developing countries where the need is the greatest.

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Stephen E. Hawes and Nancy B. Kiviat

INTRODUCTION

Over the last 30 years we have gained important insights into the pathogenesis of cervical cancer.¹ It is now well established that specific types of sexually transmitted human papillomaviruses (HPV) play a central role in the pathogenesis of the essentially all squamous cell cancers of the cervix, most of those of the vagina and vulva, as well as many of the adenocarcinomas of the endocervix.² In the United States and other industrialized countries, the incidence and mortality of the most important HPV-related cancer, invasive cervical cancer (ICC), have dramatically decreased, presumably as a result of cytologic detection and eradication of preinvasive cervical lesions, termed *intraepithelial lesions* or *cervical dysplasia*. However, worldwide cervical cancer remains the second most common malignancy in women, with 83% of cases occurring in the developing world, where Pap screening is only rarely available.¹ Further, while the incidence of ICC has markedly decreased in the United States, the cost of cervical cancer control has dramatically increased over the last decade due to the practice of referring up women with atypical squamous cells of undetermined significance (ASCUS) and cervical intraepithelial neoplasia grade 1 (CIN-1) findings for additional follow-up, colposcopy, biopsy, and often treatment. As a result, it was recently estimated that the yearly cost of cervical cancer prevention and treatment of HPV-associated disease in the United States exceeds \$4 billion.³

In the past decade, HPV testing has become available and gained widespread acceptance as an adjunct to cytology in developed nations,⁴ while other low-technology approaches, such as visually aided inspection, have been proposed for use in less developed areas.⁵ While these approaches may improve and extend cervical cancer control efforts, the recently developed HPV vaccines are likely in the long term to be central to cervical cancer control. However, for the reasons explained below, some form of continued screening and treatment of cervical cancer precursor lesions will be required for at least the next 50 years. Importantly, as an increased proportion of the population becomes immunized for those types of HPV most

commonly associated with cervical cancer, we will need to identify new approaches to cervical cancer screening.⁶ The challenge of the next decade will be to develop new cost-effective approaches for screening in the developed world and to bring inexpensive screening and vaccination programs to areas without current screening programs.

This chapter reviews the successes and failures of the current approaches to cervical cancer control and of our current histologic and cytologic classification systems. We also present an overview of emerging technologies that have recently been proposed for the identification, diagnosis, and management of these lesions in the future. Lastly, we examine the changing epidemiology of cervical cancer screening in the setting of the new HPV vaccines.

BURDEN OF DISEASE

■ CURRENT INCIDENCE AND MORTALITY OF ICC GLOBALLY

Cervical cancer remains the second most common cancer in women, being exceeded only by breast cancer, and represents the third most common cause (after breast and lung cancer) of cancer-related mortality. Worldwide, nearly 500,000 new cases of cervical cancer arise each year, and approximately 275,000 deaths from cervical cancer occurred in 2002.^{1,7} The incidence of ICC varies dramatically across populations, in large part, as discussed below, depending on the availability of screening and treatment of cervical cancer precursor lesions. Since genital HPV, the acknowledged cause of cervical cancer,^{2,8-11} is a very common sexually transmitted disease, factors such as sexual behavior and reproductive history are also of importance,¹²⁻¹⁴ Over 80% of cases of ICC now arise in the developing world, where cervical cancer remains the leading cause of cancer-related death in women¹⁵ and accounts for 15% of female cancers, with an estimated cumulative risk of 1.5% before age 64 years. The highest rates occur in sub-Saharan Africa, Melanesia, Latin America, and South Central Asia (Fig. 58-1), which suffer incidence rates of

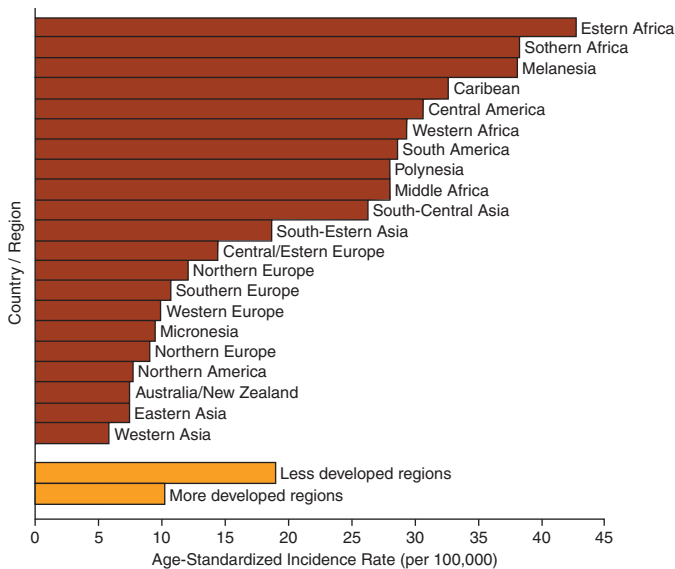


FIGURE 58-1. Age-standardized incidence for cervical cancer, per 100,000 women. GLOBOCAN 2002, International Agency for Research (IARC).¹⁷

greater than 25 cases per 100,000 women and lifetime risks of cervical cancer as high as 6–7%.¹⁶ In contrast, in developed countries where cytology-based screening is widely available, cervical cancer accounts for only 3.6% of new cancer cases, with a cumulative lifetime risk of 0.8%. Country-specific factors associated with high rates of cervical cancer include lacking adequate public health infrastructure, having a low number of doctors per capita, high rates of fertility, sexual activity, early age of birth of first child, and high rates of HIV infections.¹⁷

Survival from cervical cancer is strongly associated with stage at diagnosis and varies substantially by region: 21% in sub-Saharan Africa, 42% in India, 51% in Eastern Europe, 55% in South America, 65% in Japan, 66% in Western Europe, and 70% in the United States.¹ Women with localized cancer experience over 90% 5-year survival, as compared to less than 15% survival with distant disease.¹⁸ In sub-Saharan Africa, patients typically seek care only when their cancer is advanced, resulting in poor prognosis.^{19,20} Dramatic improvements in cervical cancer survival rates can result from improvements in health service infrastructure and accessibility, as has been observed in Singapore, where 5-year age-standardized survival increased from 45% to 65% in a recent 20-year time period.²¹

■ INCIDENCE AND MORTALITY IN THE UNITED STATES

In the United States, as Pap smear screening has increased over the past few decades, the incidence and mortality of ICC has steadily declined. In 2005, 9710 new cases of ICC occurred, with 3700 deaths.²² The probability of developing cervical cancer during a woman's lifetime is approximately 1 in 135 (0.74%).²³ Five-year survival rates in women

diagnosed with ICC in the United States rose slightly from 69% in 1974–1976 to 73% by 2001, with 92.4% and 54.7% 5-year survival of women with local and regional disease, respectively. Survival is considerably lower among women with distant disease (16.5%).¹⁸ In the United States, incidence is higher in African Americans and Hispanics compared to Asian, whites, and native Americans. Likewise, survival rates tend to be higher for white (75%), compared to African American (66%) women.

CLASSIFICATION OF DISEASE

■ HISTOLOGIC CLASSIFICATION OF CERVICAL NEOPLASIA

Cervical neoplasia is classified as either *invasive* or *intraepithelial*. A lesion is classified as ICC if the neoplastic (i.e., cancer) cells have extended through the basement membrane into the underlying tissue. In contrast, in CIN, the neoplastic cells remain limited to areas normally populated by epithelial cells and are not found below the basement membrane. Our current approach to cervical cancer control is based on the concept that ICC arises from intraepithelial precursor lesions termed *cervical intraepithelial lesions grade 3* (CIN-3) and/or *carcinoma in situ* (CIS) and that treatment of these precursor lesions prevents progression to invasive cancer.

■ CLASSIFICATION OF ICC PRECURSOR LESIONS

ICC precursor lesions include CIN grades 1, 2, and 3, and CIS. This classification system was developed over 45 years ago, prior to any understanding of the importance of HPV infection in the pathogenesis of ICC.²⁴ At that time, it was believed that CIN grades 1, 2, and 3 represented a morphologic and biologic continuum of progressive, consecutive stages in the development of invasive cancer. It was thought that the majority of women with CIN-1 would progress to CIN-3 and, if untreated, to ICC.²⁵ As we have gained insights into the molecular pathogenesis of ICC and the central role of infection with “oncogenic” or “high-risk” (HR) types of HPV in this process, the relationship of CIN-1, CIN-2, CIN-3, CIS, and ICC has been reassessed. It has become apparent that most CIN-1 lesions simply represent morphologic manifestation of infection with HPV and that the overwhelming majority of such lesions regress within 1–2 years.^{26–28} Further, previous studies as well as data from the recent large multicenter ASCUS/low-grade squamous intraepithelial lesions (LSILs) triage study (ALTS) suggests that, in many cases, morphologic changes that are classified as CIN-2 and CIN-3 are found early after infection with “oncogenic” types of HPV.^{9,29} CIN-3 and CIS are considered to be the immediate precursors of ICC. This idea is supported

by the fact that these lesions are often present adjacent to invasive cancers and, in the few prospective studies that were undertaken prior to our understanding of the malignant potential of these lesions, untreated CIN-3/CIS were the lesions that appeared to be most likely to progress to ICC.³⁰ Available data concerning the risk of development of invasive cancer associated with untreated CIS come primarily from a small series of women with CIS who inadvertently were not treated, and several series undertaken before ablative treatment became the accepted standard of care, from women repeatedly undergoing biopsies rather than definitive treatment.^{30,31} These data suggest that, if left untreated, 12–40% would develop invasive disease within the span of a normal lifetime.^{28,32,33} Pathologists do not routinely attempt to differentiate between CIN-3 and CIS, as such morphologic differentiation is known to be difficult and nonreproducible.³⁴ and the clinical management of these lesions is similar. Unfortunately, using morphology (microscopy), we are unable to differentiate those cases of CIN-3/CIS, which, if untreated, would progress from those that carry little or no risk of progression, and therefore all such lesions are treated. It is likely in the future that ICC precursor lesions will be defined by the presence of specific cancer-associated molecular changes. Interestingly, studies have demonstrated that the molecular profiles (expression and methylation profiles) of ICC resemble those of a subset of approximately 30% of CIN-3 and CIS lesions, with such changes being only rarely present in CIN-1 lesions.^{35,36}

The classification of CIN lesions as grade 1, 2, and 3 or CIS described in 1968²⁴ was originally based on the proportion of the epithelium that was replaced by abnormal, less differentiated cells. While many CIN-3/CIS lesions do appear to be comprising a full-thickness layer of poorly differentiated cells under the microscope, molecular studies demonstrate that CIN-1 lesions also are composed of a full-thickness layer of abnormal cells. Other criteria for classification of these lesions include the presence of dividing cells (i.e., mitotic figures) at different levels of the epithelium. Normally, mitotic figures are limited to the basal epithelial cells; however, they are present throughout the full thickness of CIN-3/CIS lesions but are less frequent and only present at lower levels in lesions classified as CIN-1 or CIN-2.³²

■ ADENOCARCINOMA

Historically, cervical adenocarcinoma has been relatively uncommon,³⁷ constituting approximately 5% of all ICCs.³⁸ However, over the last 25 years, there has been both an increase in the proportion of cancer cases attributable to adenocarcinoma and an increase in the overall rate of adenocarcinoma.^{38–46} In the United States (Fig. 58-2), the age-adjusted rate of adenocarcinoma increased 29.1% between 1973–1977 (1.34 per 100,000 women) and 1993–1996

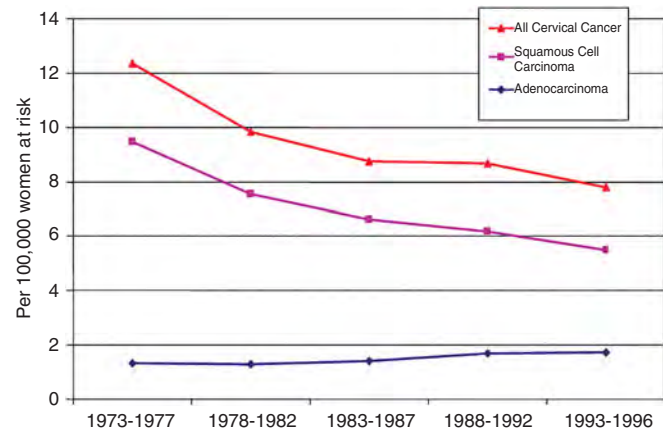


FIGURE 58-2. SEER age-adjusted incidence rates of invasive cervical cancer, by histologic type, in the United States 1973–1996.³⁸

(1.73 per 100,000 women), while the proportion of incident ICCs, which were adenocarcinomas, nearly doubled from 12.4% to 24.0%.³⁸ Similar patterns of increasing adenocarcinoma with decreasing squamous cell carcinoma rates have been observed in Canada⁴² and Europe.^{39,47} Presently, adenocarcinoma accounts for approximately 20% of all ICCs.^{38,48,49} Such changes may be related to the fact that although current screening practices target squamous cell cancer precursor lesions, they are much less sensitive for detection of adenocarcinoma precursor lesions.^{42,43,50,51} As in squamous cell cervical carcinoma, HPV is central to the pathogenesis of cervical adenocarcinoma, with HPV 16 and 18 accounting for the majority of adenocarcinoma cases.^{52–54}

CYTOLOGY-BASED CERVICAL CANCER CONTROL

■ HISTORY

The Pap smear was first described in 1928,⁵⁵ and, while it is generally agreed that cytology-based screening for, and treatment of, CIN is highly effective for prevention of ICC,⁵⁶ cytology-based cervical cancer control requires the establishment and maintenance of an extensive clinical and laboratory infrastructure, and thus extensive screening has largely been limited to industrialized countries. European countries generally implemented organized screening programs in the early 1960s, while in the United States, opportunistic screening has been in effect since the 1950s, with most of the population being screened by the 1970s.⁵⁷ A recent national population-based survey found that 93% of American women have had at least one Pap smear in their lifetime,⁵⁸ although this varies somewhat by geographic region.⁵⁹ In contrast, less than 5% of women in developing countries have been screened for cervical dysplasia in the past 5 years.²²

IDENTIFICATION AND TREATMENT OF LESIONS TO PREVENT PROGRESSION TO ICC

It is also well established that a single Pap test is insensitive for CIN 2–3/CIS, detecting from 30–87% of underlying CIN-3 lesions.^{60,61} Effective identification of the great majority of women harboring lesions at HR for progression has traditionally been achieved by repeated (annual) Pap testing over long periods of time. This approach is possible because progression from CIN-3/CIS to ICC is extremely slow, with transit times from CIN 2–3/CIS occurring over an average of 10 or more years.⁶² Furthermore, these lesions increase in size (and presumably increase shedding of abnormal cells) over time. Importantly, CIN-3/CIS lesions are easily removed without significant morbidity, with such treatment being highly effective in preventing progression to invasive cancer.

CLASSIFICATION OF ABNORMAL CELLS: BETHESDA SYSTEM OF CLASSIFICATION

The morphologic changes Papanicolaou originally used decades ago on vaginal aspirates to make a cytologic diagnosis of invasive squamous cancer are the same used today and include the presence of cells with characteristic nuclear and cytoplasmic changes in a background containing necrotic debris, old blood, and inflammation. Over time, to support clinical management of women with Pap smear abnormalities, a number of different schemes have been developed to attempt to classify the other abnormal, but not malignant, cells identified. In 1988, the Bethesda system was introduced to attempt to standardize nomenclature and improve inter- and intrapathologist reproducibility.⁶³ Using this system, which was updated in 2001,⁶⁴ abnormal squamous cells are classified as suggestive of the presence of invasive squamous cell cancer; high-grade squamous intraepithelial lesion (HSIL), which now encompasses moderate and severe dysplasia, i.e. CIN 2–3/CIS (a comment is added, if necessary, to alert the clinician to the possibility of invasion); or LSIL, which encompasses changes associated with HPV and mild dysplasia/CIN-1. Abnormal cells that are not definitively dysplastic are termed *atypical squamous cells of uncertain significance*, and if such equivocal atypical cells are thought to possibly arise from a CIN 2–3/CIS, they can be classified as *atypical squamous cells, cannot exclude HSIL (ASC-H)* (Table 58-1). Although the traditional cytologic diagnoses of moderate and severe dysplasia are now regrouped with CIS into HSILs, a corresponding revision of the histologic classification system has not formally occurred, although some pathologists have adapted such an approach.

EFFECTIVENESS OF CYTOLOGY-BASED CERVICAL CANCER CONTROL

Although it is widely accepted that the implementation of cervical cancer control based on cytologic identification of,

and treatment for, women with CIN 2–3/CIS has been responsible for the decrease in the incidence of cervical cancer in the developed world over the last 50 years, there have never been clinical trials verifying the effectiveness of this approach.⁶⁶ The fact that the incidence of cervical cancer strongly reflects the availability of routine screening strongly supports the contention that identification and treatment of precursor lesions are central to the observed decline in cervical cancer incidence. Age-standardized incidence rates of ICC declined by 27–77% in 11 of 17 populations after the introduction of screening,⁶⁷ and cervical cancer incidence rates are now below eight cases per 100,000 in Western Asia, China, Australia/New Zealand, North America, and Japan, where most women regularly undergo Pap screening. In the United States, the age-adjusted incidence of cervical cancer decreased from 17.2 to 7.2 cases per 100,000 between 1973 and 2002 (Fig. 58-3), and cervical cancer mortality has fallen from 7.7 (1969) to 2.5 deaths per 100,000 in 2002. Cervical cancer is currently only the 14th most common type of cancer in U.S. women.⁶⁸ It is estimated that 93% of American women aged 18 years and older have had at least one Pap smear in their lifetime, with over 80% of women in the United States having had a Pap test in the last 3 years, and over half participating in annual Pap testing.^{58,59,69,70} The lack of Pap smear screening is now the most important risk factor for development of ICC in the United States, with most cases of ICC developing in women who did not undergo regular screening^{71–73} or who did not receive appropriate follow-up.^{74,75}

Factors associated with lack of screening include low family income, low educational attainment, and a lack of a usual source of health care or insurance.^{69,76,77} In an attempt to increase screening, since 1990, cervical (and breast) cancer screening and diagnostic services have been provided in the United States to low-income women without health coverage, through The National Breast and Cervical Cancer Early Detection Program (NBCCEDP). Nearly 2 million Pap tests have been performed as part of the program; however, this

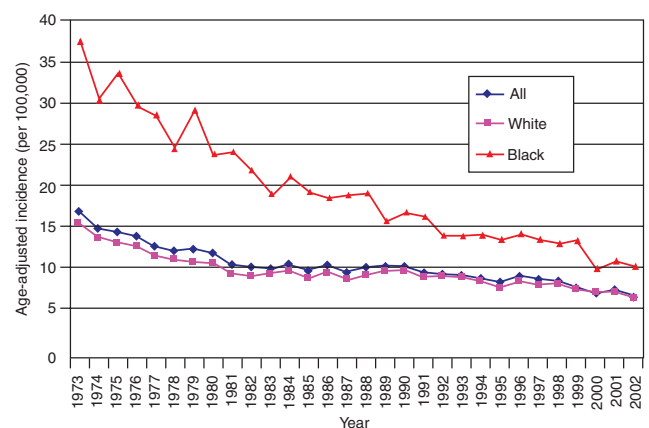


FIGURE 58-3. SEER age-adjusted incidence rates of cervix uteri cancer, by race, in the United States 1973–2002.¹⁸

Table 58-1. The 2001 Bethesda System (Abridged)

Specimen Type: *Indicate conventional smear (Pap smear) vs. liquid based vs. other*

Specimen Adequacy

- Satisfactory for evaluation (*describe presence or absence of endocervical/transformation zone component and any other quality indicators, e.g., partially obscuring blood, inflammation, etc.*)
- Unsatisfactory for evaluation (*specify reason*)
 - Specimen rejected/not processed (*specify reason*)
 - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (*specify reason*)

General Categorization (*optional*)

- Negative for intraepithelial lesion or malignancy
- Epithelial cell abnormality: see interpretation/result (*specify 'squamous' or 'glandular' as appropriate*)
- Other: see interpretation/result (*e.g., endometrial cells in a woman ≥ 40 years of age*)

Interpretation/Result

Negative for Intraepithelial Lesion or Malignancy (*when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report, whether or not there are organisms or other non-neoplastic findings*)

Organisms:

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida* spp
- Shift in flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces* spp.
- Cellular changes consistent with Herpes simplex virus

Other Non-Neoplastic Findings (*Optional to report; list not inclusive*):

- Reactive cellular changes associated with
 - inflammation (includes typical repair)
 - radiation
 - intrauterine contraceptive device (IUD)
- Glandular cells status post hysterectomy
- Atrophy

Other

- Endometrial cells (*in a woman ≥ 40 years of age*) (*Specify if 'negative for squamous intraepithelial lesion'*)

(Continued)

Table 58-1. (Continued)**Epithelial Cell Abnormalities**

Squamous Cell

- Atypical squamous cells
 - of undetermined significance (ASCUS)
 - cannot exclude HSIL (ASC-H)
- Low-grade squamous intraepithelial lesion (65) encompassing: HPV/mild dysplasia/CIN 1
- High-grade squamous intraepithelial lesion (HSIL) encompassing: moderate and severe dysplasia, CIS/CIN 2 and CIN 3
 - with features suspicious for invasion (*if invasion is suspected*)
- Squamous cell carcinoma

Glandular Cell

- Atypical
 - endocervical cells (NOS *or specify in comments*)
 - endometrial cells (NOS *or specify in comments*)
 - glandular cells (NOS *or specify in comments*)
- Atypical
 - endocervical cells, favor neoplastic
 - glandular cells, favor neoplastic
- Endocervical adenocarcinoma in situ
- Adenocarcinoma
 - endocervical
 - endometrial
 - extrauterine
 - not otherwise specified (NOS)

Other Malignant Neoplasms: (*specify*)**Educational Notes and Suggestions** (*optional*)

Suggestions should be concise and consistent with clinical follow-up guidelines published by professional organizations (references to relevant publications may be included).

Source: National Cancer Institute Bethesda Workshop, 2001

represents fewer than 15% of women eligible to participate in the program.⁷⁸ Further, in 2000, the Breast and Cervical Cancer Prevention and Treatment Act (BCCPTA) offered states Medicaid coverage for treatment services for women screened under the NBCCEDP.⁷⁹

Similar to decreases described in the United States, decreases in the age-adjusted incidence rates of invasive squamous cervical cancer as a result of screening have been noted in Canada,⁴² Australia,⁸⁰ and Europe (including Scandinavia).^{40,41,67,81} Screening intervals and the age of onset of screening vary

across programs; however, screening every 3 years of women aged 20–60 years is the most common approach used.⁸² Estimated coverage varies from 30–40% in Hungary and Luxemburg to 93% in Finland, with most countries falling in the 70–85% range.^{82–84} Few Asian countries have established routine screening programs, although in Singapore, high-level opportunistic screening has taken place since 1987, resulting in increased survival in cervical cancer patients, presumably due to increased awareness and utilization of prevention measures resulting in early detection.²¹ More recently in Vietnam, a grassroots effort has attempted to establish a nationwide Pap smear cervical cancer prevention program in 10 districts in south and central Vietnam.⁸⁵

■ COST EFFECTIVENESS OF CERVICAL CANCER SCREENING PROGRAMS

Cytology-based cervical prevention and treatment programs are extremely expensive. In the United States alone, over 55 million Pap smears are performed each year,^{86,87} and while actual costs incurred remain unknown, total direct costs for the prevention of HPV-relative disease were estimated to be U.S. \$3–4 billion in 2000.^{3,88} In 1998, a large U.S. health plan estimated annual cervical cancer prevention and treatment costs to be \$26 per female enrollee, with 63% of the costs being attributed to screening, 17% attributed to management of CIN, 10% attributed to treatment of cervical cancer, and 9% attributed to costs associated with false-positive results.⁸⁹ Costs associated with the now widespread use of HPV testing and thin-layer cytology were not included.

Various mathematical models have been developed to assess the cost effectiveness of different cervical cancer-screening strategies,^{87,90–103} including a number evaluating the cost effectiveness of HPV DNA testing for triage of equivocal cytologic abnormalities, primary HPV testing in countries with existing screening programs, and the introduction of various screening strategies in nations without current screening programs.¹⁰⁴ Most studies suggest that screening intervals of 3–5 years are the most cost effective.⁹⁶ Increased screening frequency generally leads to detection and treatment of greater numbers of low-grade lesions, which generally regress without intervention.¹⁰⁴ It is thought that the cost efficiency of existing screening programs can be increased by increasing the age of onset of screening and/or by lengthening the screening interval.⁹⁶ The benefit of screening appears to decline rapidly in women over 65¹⁰⁴; however, determining the upper-age limit for discontinuing cervical cancer screening is controversial. Modeling studies suggest that cessation of screening of women over age 50 years with a recent history of negative smears might provide an approximate 25% cost savings; however, this approach is also

predicted to increase in cancer incidence by 16–21%.¹⁰⁵ If withdrawals began later, at age 60 years, screening costs were reduced about 4.0%, with a less than 2% increase in cancer rates, suggesting that terminating screening after age 60 years would not lead to a substantial saving in resources,¹⁰⁶ and therefore there is no reason to impose an upper-age limit for cervical cancer screening.¹⁰⁷

■ CYTOLOGY-BASED CERVICAL CANCER CONTROL IN THE DEVELOPING WORLD

Cytology-based screening programs are rare outside the industrialized world. Further, while a few developing countries in Central and South America established screening programs during the 1970s, these programs have had limited success.¹⁰⁸ For example, a cervical cancer screening program established in the early 1970s screened over 80% of married women in Chile at least once, while a 5-year program initiated in Columbia in 1990 trained nurses, gynecologists, and pathologists to provide cytology screening, follow-up, and treatment to over 60% of women aged 25–69 years. Nevertheless, cervical cancer mortality data suggest that cancer rates remained unchanged. In Cuba, over 80% of women aged 20–60 years have been screened at least once, without a reduction of cervical cancer.¹⁰⁸ In Mexico, a national annual cervical screening program has been in place since 1974, but the lack of sufficient infrastructure led to screening of less than 30% of women in rural areas.¹⁰⁹ Further, an evaluation of cervical cytology testing showed that >50% of the smears were of insufficient quality.¹¹⁰ Perhaps not surprisingly, there has not been a decline in mortality from cervical cancer in Mexico.¹¹¹ A key barrier to establishing effective screening programs appears to be difficult in establishing and maintaining high-quality Pap screening. In part, this is due to a shortage of well trained cytology technicians and cytopathologists.¹¹² Encouragingly, however, in Costa Rica nationwide cytology services have been available since the 1970s, with 85% of eligible women receiving screening. While cervical cancer rates remained unchanged from 1983 to 1991, a more recent decline has been observed.

Currently, there are no organized or opportunistic screening programs for cervical cancer prevention in sub-Saharan Africa. A recent situational analysis of cervical cancer services in five African nations (Kenya, Lesotho, Uganda, Tanzania, and Zimbabwe) reported a serious lack of both supplies and qualified staff (gynecologists, pathologists, and cytotechnicians) necessary for carrying out screening, biopsy, and treatment.¹¹³ Our experience in West Africa over the last 20 years is similar: There is a severe lack of qualified cytology screeners, pathologists, and colposcopists, as well as a lack of necessary materials. In South Africa, an attempt in the late 1980s to organize the infrastructure for mass screening of women in Soweto resulted in poor participation. The South African government has adopted a policy of three lifetime smears,

at ages 30, 40, and 50 years, and it has been suggested that, while the necessary infrastructure is in place, the necessary funds are not, as the government perceives other health problems, such as malnutrition, diarrheal diseases, tuberculosis, and HIV/AIDS as more urgent.²⁰ While screening services are widely available, a recent survey found that 80% of women had never been screened.¹¹⁴ In India, which accounts for one-fifth of the world burden of cervical cancer, there are no organized or opportunistic screening programs for cervical cancer, although as discussed below, visual inspection-based approaches to cervical cancer screening have been extensively investigated.¹¹⁵

The introduction of annual screening in developing countries could reduce cancer incidence by up to 93% (Table 58-2) but would require performing 45 tests per women to identify 33 cases of cancer for every 100,000 tests.¹¹⁶ Every 3-year screening would result in significantly fewer tests (approximately 15 tests per woman) to identify 96 cases for every 100,000 Pap smears performed¹¹⁶ and could reduce the cumulative incidence of ICC by at least 75%.^{116,117} Thus, as compared to annual screening, every 3-year screening would significantly reduce the cervical cancer burden in a more

economic fashion.¹¹⁶ The effectiveness of a 3-year interval is supported by a study of 25,000 Dutch women, in which incidence of squamous cervical cancer declined from 0.38 per 1000 to zero within 12 years.¹¹⁸ Mathematical models suggest that once per lifetime cytology or HPV testing in women 30–59 years old would lead to a 23–30% reduction in annual incidence of ICC, given 80% coverage.⁹¹ In a modeling study in Hong Kong, compared with no screening, opportunistic screening using cytology was predicted to reduce lifetime risk of cervical cancer by 40% but would be less effective than cytology at 3-, 4-, or even 5-year intervals, which was associated with 90%, 87%, and 83% reductions, respectively.¹¹⁹ For all cytology-based screening strategies, organized screening programs were less costly and more effective than opportunistic screening. In simulations utilizing data from Thailand, well-organized screening programs reduced cervical cancer mortality at low costs.⁹⁴ However, as discussed below, given the recent development of highly efficacious vaccines for prevention of infection with those HPV types most frequently associated with development of cervical cancer, it is unclear whether such an approach would be cost effective.

Table 58-2. Reduction in Cervical Cancer Incidence with Effective Screening

Screening Frequency	Potential Reduction, ^a IARC, 1986	Potential Reduction, ^b Goldie, 2001	Potential Reduction, ^c Mandelblatt, 2002
Every year	93.5%	90–93%	NA
Every 2 yr	92.5%	86–91%	NA
Every 3 yr	90.8%	75–88%	NA
Every 5 yr	83.6%	NA	8–52%
Five times lifetime	NA	61–74%	NA
Every 10 yr	65.1%	NA	5–32%
Three times lifetime	NA	35–55%	NA
Two times lifetime	NA	29–42%	2–11%
One time per life	NA	17–32%	1–6%

^aScreening and potential reduction in cumulative cervical cancer rates. (Adapted from IARC Working Group on Evaluation of Cervical Cancer Screening Programmes. Screening for squamous cervical cancer: Duration of low risk after negative results of cervical cytology and its implication for screening policies. *Br Med J (Clin Res Ed)* 1986; 293: 659–664.)

^bScreening and potential reduction in cumulative cervical cancer rates (Alliance for Cervical Cancer Prevention). (Adapted from Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings: Clinical benefits and cost-effectiveness. *JAMA* 2001; 285: 3107–3115.)

^cPotential reduction in cervical cancer incidence in a well-organized screening program (with Pap, HPV, and/or visual inspection) in the developing world. (Adapted from Mandelblatt JS, Lawrence WF, Gaffikin L, et al. Costs and benefits of different strategies to screen for cervical cancer in less-developed countries. *J Natl Cancer Inst* 2002; 94: 1469–1483.)

■ LIMITATIONS OF CYTOLOGY-BASED CERVICAL CANCER CONTROL

Despite the past proven successes, primary screening based on cytology has serious shortcomings. Most importantly, cytology has low *test sensitivity* (i.e., the sensitivity of a single test) for CIN 2–3, with a single Pap smear detecting as few as 47–62% of these lesions.^{60,120–123} Traditionally, to increase the overall *program sensitivity*, women undergo repeated Pap testing. Further, any women having abnormal cells detected on their smear, regardless of whether such changes were only weakly associated with an increased risk of cancer, were referred for additional testing. Thus, all women with cytologic diagnosis of CIN were referred for colposcopy and biopsy, while those with atypia (ASCUS) returned for repeat Pap testing and, if the abnormality did not resolve, for colposcopy and biopsy. Since ASCUS is diagnosed in 5–15% (over 3 million) of the over 5.5 million U.S. women undergoing Pap screening each year,⁸⁶ considerable numbers of women were required to undergo additional testing. Further, Pap smear-based identification and classification of cervical abnormalities is characterized by poor inter- and intraobserver reproducibility.^{34,86,124} This is especially true for a cytologic diagnosis of ASCUS. This approach, although successful in terms of decreasing the incidence of cervical cancer, was becoming increasingly costly and burdensome.

Over the last 20 years, a number of changes have been made to attempt to increase the sensitivity of Pap-based screening. Liquid-based cytology (LBC) for screening for cervical cancer was developed in the 1960s and approved by the Food and Drug Administration (FDA) in 1995, for use in the United States as an alternative to conventional cytology. There are currently two commercially available liquid-based preparation technologies: ThinPrep (Cytyc Corp., Boxborough, MA) and SurePath (TriPath Imaging Inc., Burlington, NC). Unlike conventional cervical smears, LBC cell samples are rinsed into a vial of liquid to produce a suspension of cells to produce a thin monolayer on slides, thus reducing the clustering of cells, which may obscure abnormalities. This technique is designed to reduce the number of inadequate smears and increase the sensitivity for the detection of SIL.^{125–127} Additionally, the method provides for enough cells for the detection of infectious agents, including HPV as well as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and herpes simplex virus, through molecular biology techniques.¹²⁸ Presently, approximately 80% of the estimated 55 million Pap smears performed annually in the United States currently utilize LBC¹²⁹ and the UK has also incorporated LBC into screening programs.¹³⁰ However, Canada, New Zealand, and Australia have been reluctant to adopt LBC without more conclusive clinical evidence as to its accuracy and cost effectiveness. Numerous studies have compared the adequacy, accuracy, and/or cost effectiveness of LBC to that

of conventional cytology.^{60,130–135} Cells on thin-layer preparations appear to be more easily viewed, making smear less frequently inconclusive,¹³¹ and a study from the UK National Institute for Clinical Excellence reported that the percentages of unsatisfactory slides decreased from 9.1% to an average of 1.6% with the introduction of LBC,¹³⁶ although whether there is an overall improvement in adequacy remains unclear.^{130,132,133}

Another far-reaching change has been the introduction of testing for HR types of HPV. With the understanding of the central role of HPV in the pathogenesis of cervical cancer, assays for detection of HR types of HPV have become available and, as discussed below, are now widely used as an adjunct to cytologic screening. Lastly, another shortcoming of our current morphology-based approach (i.e., cytology and histology) to identification of women at risk of cancer is the fact that, although all HSIL are treated, it is expected that a minority of women with CIS would eventually have progressed to invasive cancer if untreated. Cytology- and histology-based cervical cancer control is unable to identify those women who are truly at risk of progression to invasive disease. However, as discussed below, this is also an important limitation of HPV DNA testing.

ALTERNATIVE APPROACHES TO IDENTIFICATION OF WOMEN AT RISK OF ICC

■ HPV TESTING IN CERVICAL CANCER SCREENING

HPV as an adjunct to cytology

As noted above, a major shortcoming of cytology-based identification of women with CIN 2–3/CIS is the low sensitivity of a single smear and the need to refer the large number of women receiving an ASCUS diagnosis for additional testing. The ASCUS/LSIL triage study, or ALTS, recently examined the potential of HPV testing to aid in the clinical management of women with an ASCUS or an LSIL diagnosis by identifying those who truly at HR of CIN 2–3. Women in this study either were randomized to repeated cytology with referral to colposcopy on the basis of a cytologic HSIL diagnosis, immediate colposcopy, and biopsy or were triaged to colposcopy and biopsy on the basis of HPV testing (i.e., referred to colposcopy if they tested positive for HR types of HPV DNA). HPV testing was noted to be of little benefit among women with LSIL, as 83% of women with LSIL were positive for HPV DNA, and thus women receiving an LSIL diagnosis are directly referred to colposcopy without HPV testing.¹³⁷ Referral of women solely on the basis of a positive HPV DNA test allowed identification of approximately 90% of CIN 2–3/CIS lesions.¹³⁸ This trial demonstrated that triage of women with ASCUS to colposcopy on the basis of testing

for HR types of HPV testing was not only highly sensitive for identification of women with CIN 2–3/CIS, but importantly, using this strategy, approximately 50% of women with ASCUS (i.e., those who test negative for HR HPVs) were returned to normal screening without undergoing unnecessary colposcopy or additional Pap smear testing.¹³⁹ Testing for HR types of HPV is currently being used in many settings as an adjunct to cytology-based screening to support the clinical management of women with ASCUS. In 2000, the U.S. FDA approved HPV DNA testing with the Digene Hybrid Capture 2 (HC2) test for triage of all women with equivocal Pap smears,^{66,140–142} and in 2003, HPV testing was approved as an adjunct to Pap screening in women aged 30 years and above.

The cost effectiveness of the three management strategies examined in ALTS were recently analyzed.⁸⁷ Management costs per ASCUS case for HPV testing (\$183) fell between those associated with conservative management strategies with one or two follow-up cytology visits (\$100 and \$179, respectively) and immediate colposcopy (\$196) or conservative management with three visits (\$252). HPV testing had the highest sensitivity (66%) for CIN-3, compared to 51% or less for the other strategies; conservative management with a single cytology was the least sensitive (37%) strategy. HPV DNA testing appeared to be the most cost-effective strategy for management of ASCUS. However, while this approach may be among the most sensitive and cost-effective approaches currently available, its lack of specificity is problematic. While millions of U.S. women with HPV-positive ASCUS can undergo colposcopy and biopsy each year, relatively few (7–20% in the ALTS multicenter trial¹³⁷) have significant underlying disease.^{62,143} While women with ASCUS cytology who were HPV 16 DNA positive at baseline had 2-year cumulative absolute risk for CIN-3 or worse of 32.5%, women with ASCUS who were positive by HC2 for the other oncogenic HPV types combined had an 8.4% risk for CIN-3 or worse, which was similar to the risk posed by having ASCUS (8.8%) without knowledge of the oncogenic HPV DNA status.¹⁴⁴ Further, HPV testing is likely to be of little benefit among young sexually active women initiating sexual behavior, many of whom experience sequential self-limited infections with different HPV types. Use of this approach in such a population could result in overtreatment of HPV-positive women, who most likely have self-limiting, transient infections, which would clear with no clinical effects within months.^{145–148} Further, while using HPV testing as an adjunct to cytology-based screening is of interest for the developed world, as discussed above, this approach is not currently practical in resource-poor settings. Cervical cancer control strategies, which involved referral of women with cytologic abnormalities, would be particularly ineffectual in areas with endemic HIV infection, given that the rate of CIN-1 and ASCUS is much higher among women with, as compared to those without, HIV infection.^{149–151} Thus, while, in the setting of a

cytologic diagnosis of ASCUS, detection of HPV 16 appears to be useful, this may not be the case for detection other HPV types.

HPV testing for primary screening

Given the central importance of HPV in the development of cervical cancer, primary screening on the basis of HPV detection is theoretically of considerable interest. In the last 15 years, several large cross-sectional studies have evaluated HPV DNA detection of HR HPV types as a primary screening method and have compared HPV testing to cytology been completed (Table 58-3).^{169–171} In these studies, HR HPV viral DNA has been detected either by PCR-based research assays using consensus primers MY09/MY11 or GP5+/6+ or by the commercially available and now FDA-approved HC2 test (Digene Corp, Gaithersburg, MD), which uses RNA-based probes and detects 13 types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). Both assays are widely accepted to be reliable for detecting HPV in clinical samples.^{172,173}

HPV DNA testing has extremely high sensitivity for detecting CIN-2 lesions or worse, with a mean sensitivity in the 19 studies of 89%, a median sensitivity of 91%, and an interquartile range (IQR, defined as the 25th to 75th percentiles) of 84–97%. In comparison, conventional Pap smear cytology testing had a mean sensitivity of 62%, a median of 63%, and an IQR of 46–78%, varying greatly by study population. In no study was the sensitivity of HPV testing less than that of the Pap smear. Further, the median increase in test sensitivity of HPV testing in paired comparisons to conventional cytology in the 19 studies was 23%, with an IQR of 16–34%. In contrast, the specificity of the Pap smear was consistently high and usually greater than that of HPV testing. In these studies, the mean specificity of conventional cytology was 93%, with a median of 96% and an IQR of 94–98%. In comparison, the mean specificity of HPV testing was 85%, with a median of 88% and an IQR of 82–98%, varying somewhat across populations and by HPV detection method. Only in one study in Finland¹⁶⁷ was the specificity of HPV testing greater than that of cytology, and in that study, the specificity values were somewhat low and not substantially different from each other (78% compared to 77%, respectively). Overall, the median increase in specificity of cytology compared to HPV testing across the 19 studies was 6%, with an IQR of 3–13%.

The relative performance of primary HPV testing in screening for cervical cancer precursors tends to vary by age. In a combined summary of eight European and North American studies assessing cytology and HPV testing, Cuzick et al.¹⁷⁴ demonstrated a similar sensitivity for CIN-2 or greater (96%) for HPV testing across all age groups (<35, 35–49, and 50+ years), whereas the specificity of HPV testing with respect to CIN increased with increasing age (87%, 93%, and 95%, respectively). In contrast to what was seen in HPV testing, the

Table 58-3. Primary Screening Based on Detection of High-Risk Types of HPV Compared to Pap Smear

Study	Site	Sample Size	HPV Sensitivity	Pap Sensitivity	HPV Specificity	Pap Specificity
Cuzick et al. (1995) ¹⁵²	UK	2009	75	46	96	96
Clavel et al. (1999) ¹⁵³	France	1518	100	79	86	96
Cuzick et al. (1999) ⁹²	UK	2981	95 (HC2) 76 (PCR)	79	94 (HC2) 95 (PCR)	99
Kuhn et al. (2000) ¹⁵⁴⁹	South Africa	2944	88	78	82	97
Ratnam et al. (2000) ¹⁵⁵	Canada	2098	68	27	91	96
Schiffman et al. (2000) ¹⁵⁶	Costa Rica	8554	88	78	89	97
Wright et al. (2000) ¹⁵⁷	South Africa	1365	84	61	83	96
Schneider et al. (2000) ¹⁵⁸	Germany	4761	89	20	94	99
Belinson et al. (2001) ¹⁵⁹	China	1997	95	87	85	94
Blumenthal et al. ^{64,160}	Zimbabwe	2073	80	44	61	91
Clavel et al. (2001) ¹⁶¹	France	7932	100	68	87	95
Kulasingam et al. (2002) ¹⁵⁸	United States	4075	91 (HC2) 88 (PCR)	57	73 (HC2) 79 (PCR)	90
Petry et al. (2003) ¹⁶²	Germany	8468	98	44	96	98
Cuzick et al. (2003) ¹⁶³	UK	10358	97	77	93	96
Ferreccio et al. (2003) ¹⁶⁴	Costa Rica	8551	85	63	88	94
Salmeron et al. (2003) ¹⁶⁵	Mexico	7868	93	59	92	98
Lee et al. (2004) ¹⁶⁶	Korea	593	92	76	52	66
Nieminen et al. (2004) ¹⁶⁷	Finland	2032	98	93	78	77
Agorastos et al. (2005) ¹⁶⁸	Greece	1296	81	50	98	99
			Mean = 89 Median = 91	Mean = 62 Median = 63	Mean = 85 Median = 88	Mean = 93 Median = 96
All Studies	<i>N</i> = 19	81473	IQR = 84–97	IQR = 46–78	IQR = 82–98	IQR = 94–98

sensitivity of cytology testing increased with increasing age group (49%, 55%, and 79%, respectively). Similar to HPV testing, the specificity of cytology increased with increasing age (95%, 97%, and 98%, respectively).

Given that infection with HR types of HPV is exceedingly common, with a 2-year cumulative HPV prevalence of up to 80%,¹⁷⁵ it is not surprising that a single HPV screening is sensitive but not specific with respect to presence of CIN, especially among young sexually active women. Many studies suggest that women with persistent infections with HR HPV

are at greatest risk of developing cervical precursor lesions and carcinoma.^{176–180} Two HPV tests, for example, at a 6-month interval, might be an effective way to differentiate transient HPV infections from those that will persist and develop into relevant precursor lesions. However, such a strategy is associated with other problems (such as the need for additional follow-up). Given the inability of a single HPV assay to distinguish transient infection from infection associated with neoplasia, there has been a reluctance to have HPV testing replace cytology as a method for primary screening.¹⁴⁵ HPV

testing may have a role in primary screening, if it can reliably distinguish between women who would benefit from more intensive Pap testing (more frequent, different technologies, or extended over longer periods) and women for whom screening can be less intensive or even discontinued.

It is important to keep in mind that in these cross-sectional studies, the sensitivity of the screening tests may be overestimated and the specificity underestimated due to verification bias, since in most study designs, only women with a positive test result by one of the tests were referred for colposcopy and biopsy, preventing an unbiased estimate.¹⁶⁹ However, in some of these studies, verification bias was averted by use of the gold standard (colpo/biopsy) on all study subjects^{166,181} or by extrapolation of results from a subset of negative testers undergoing colpo/biopsy^{138,155,158} to the entire study population. A further limitation of these studies is that, thus far, none have reported on long-term follow-up for incident high-grade lesions, and none were randomized controlled trials.

Other randomized controlled trials of HPV testing alone (by PCR or HC2) or with cytology compared to cytology alone (conventional or liquid based), with long-term follow-up, are currently being conducted in Europe and North America.^{174,182} The largest of these, the Finnish Randomised Public Health Trial, will ultimately randomize 200,000 women aged 25–65 years to HPV or Pap smear screening and was initiated in 2003.¹⁸³ In Canada, the Canadian Cervical Cancer Screening Trial (CCCaST)¹⁸⁴ enrolled 9667 women between 2002 and 2004, randomizing the order of Pap and HPV testing within study subjects. Another randomized study comparing HPV to cytology is being conducted in Mexico.¹⁶⁵ The remaining trials study HPV as an adjunct to cytology in comparison to cytology alone. One such population-based study, POBASCAM (Population Based Screening Study Amsterdam), is taking place in the Netherlands and has enrolled 44,102 women.¹⁸⁵ Additional trials are taking place in Sweden (Swedescreen),¹⁸⁶ the UK (ARTISTIC—a Randomised Trial in Screening to Improve Cytology,¹⁸⁷ and HART (HPV in Addition to Routine Testing¹⁶³)), as well as Italy (NTCC—New Technologies for Cervical Cancer screening¹⁸⁸), and all will be completed by 2010.

Cost effectiveness of HPV-based screening

Most cost-effectiveness studies suggest that the HPV testing costs per quality-adjusted life-year are less than for repeat cytology^{95,98,189,190} and that the costs associated with screening strategies combining HPV testing and cytology (either for primary screening or triage of ASCUS) are within the range of acceptability, as compared to screening for other cancers.^{191,192} However, small changes in specificity can greatly influence the outcome of cost-effectiveness modeling, and, as described above, since HPV DNA testing is 25–30% more sensitive but 5–10% less specific than cytology for high-grade lesions, the true cost effectiveness of such approaches

remains unknown. Mathematical models indicate that adoption of recent guidelines to include HPV testing with cytology as a screening option for women aged 30 years and over is likely to be cost effective¹⁹² but only with an increase of the routine screening interval.^{96,104}

As discussed below, immunization against infection with HR types of HPV will become increasingly available. However, some form of screening will likely need to be carried out for the next several decades. The decreasing prevalence of CIN 2–3/CIS in the population may make cytology- as well as HPV-based screening for identification of women at risk of cervical cancer even less efficient. Development of novel, molecular-based biomarkers for identifying women at true risk of cervical cancer will be necessary. As described below, a number of new approaches have recently been developed to try to overcome the problems associated with cytology-based screening.

DETECTION OF HPV IN SELF-COLLECTED VAGINAL SPECIMENS OR URINE

Detection of HPV DNA by testing of self-collected vaginal samples has been proposed as an alternative to testing of clinician-collected cervical samples.^{193–196} Two published studies have compared HPV DNA testing of self-collected samples with clinician-collected samples for conventional Pap test screening and HPV testing and with biopsy findings. Among 1415 previously unscreened black South African women,¹⁵⁷ the sensitivity of an HPV test of the self-collected vaginal swab sample for detecting CIN 2–3 (66.1%) was similar to that of the conventional Pap test (67.9%), but both had lower sensitivity than the clinician-collected HPV sample (83.9%). However, comparison of these test indices may be misleading because of verification bias, since women who had negative HPV test results were not followed up for colposcopic assessment with the same intensity as those who had positive HPV test results. In another study of 200 Canadian women,¹⁹⁶ the sensitivity of the self-collected vaginal sample for detecting CIN 2–3 was 86.2%, compared to 77.6% for the Pap test and 98.3% for the clinician-collected HPV sample.

Developing urine-based cervical cancer control is of interest, as it offers the possibility of freeing screening from the need of a clinic visit and pelvic examination. Most studies, thus far, have focused on detection of HPV DNA in urine as a biomarker for cervical neoplasia or cervical HPV infection. HPV DNA is detected less frequently in urine than at the cervix.^{196–201} For example, Brinkman¹⁹⁷ detected any HPV DNA in 58% of cervical and 48% of urine specimens. However, concordance of any, HR, or low-risk type of HPV in urine and the cervix was high (70%, 71%, and 78% women, respectively, for the distributions of any, low-risk, and HR HPV in the cervix and the urine, respectively), and detection of HPV DNA in urine was associated with an

abnormal Papanicolaou smear to the same extent that detection of HPV DNA in a cervical swab specimen was. HPV DNA was detected in 89% of nine cervical cancer cases, 45% of 29 HSIL cases, and 13% of 39 LSIL cases identified in Greece,²⁰² with the relative sensitivity of urine compared to cervical HPV detection being 89% in cancers, 77% in HSIL cases, and 46% in LSIL cases. HPV types were 100% concordant in cases where both cervical swab and urine samples were HPV DNA positive. However, in a study of 80 sexually active adolescents,¹⁹⁹ detection of HPV was significantly higher in the cervix (90.0%) than in urine (75.0%), and HR HPVs were 50% more common in the cervix than in urine. With recent techniques, urine HPV DNA detection is 100% specific for cervical HPV DNA, and there are no positive urine samples when the cervical sample was negative,^{202,203} although, historically, this is not universal.¹⁹⁸ In summary, detection of HPV DNA in urine samples is generally lower than in cervical samples, but it is generally considered more acceptable than self-collected vaginal sampling.¹⁹⁶ The main advantage is that urine sampling allows for self-collection of the specimen, which may be valuable in resource-limited settings.²⁰²

While detection of HPV DNA by itself in urine appears to have limited sensitivity and specificity for CIN 2–3, the sensitivity and specificity of urine-based approaches to cervical cancer control might be increased by combining detection of HPV DNA in urine with other biomarkers for cervical cancer. For example, in a recent study Feng²⁰⁴ examined the potential utility of detection of hypermethylated genes in combination with the detection of HR types of HPV for cervical cancer screening in urine. Urine samples from Senegalese women with, and without, same-day biopsy-proven cervical neoplasia were examined for the presence of HR HPV and hypermethylation of four genes that we have previously shown to be associated with cervical neoplasia.³⁵ Hypermethylation of at least one of the four genes identified 62% of ICC and 28% of CIN 2–3/CIS and was present in only 4% of CIN-1 or normal urines. HR HPV DNA was detected in urine in 70% of those with biopsy-proven ICC, 59% of those with CIN 2–3/CIS on biopsy, 44% of those with CIN-1 on biopsy, and only 11% of women negative for cervical neoplasia on biopsy. Urine-based detection of either HR HPV and/or hypermethylation of any of the four genes (DAPK1, RARB, TWIST1, and CDH13) identified 84% of ICC, 64% of CIN 2–3/CIS, 44% of CIN-1, but only 19% of women negative for cervical neoplasia. The sensitivity for detection of CIN 2–3/CIS/ICC by HR HPV DNA and/or aberrant DNA methylation of four genes appears to be comparable to that of an exfoliated cervical cytology.

■ SCREENING BASED ON VISUALIZATION OF THE CERVIX

Since it is not currently feasible to set up and maintain the extensive laboratory and clinical infrastructure necessary

for cytology-based cervical cancer screening in many resource poor settings, there have been numerous attempts to identify “low-technology” approaches to cervical cancer screening and prevention. One approach that has received a great deal of attention is visual inspection, with or without low-level magnification. Detection of cervical abnormalities by visual examination with magnification has been practiced for over 75 years, with the use of a colposcope.²⁰⁵ In the early 1930s, Schiller added the use of a topical iodine solution to dissolve mucus and promote vasoconstriction to facilitate identification of cervical abnormalities.²⁰⁶ Several other “low-technology” methods of visual inspection have been described (recently summarized by Wright²⁰⁷), including direct visual inspection (DVI), (also called direct visual inspection with acetic acid (VIA), aided visual inspection (AVI), the vinegar or acetic acid test, or cervicoscopy), visual inspection with acetic acid involving a low-level magnification device (VIAM), and visual inspection with Lugal’s iodine (VILI). The International Academy of Cytology task force recommends the term DVI to be used to refer to inspection of the cervix with the naked eye after application of acetic acid.¹⁰⁴ DVI involves examination of the cervix after application of a 3–5% solution of acetic acid. Several countries have begun prevention programs that include immediate treatment of women with positive examination by DVI or VIAM. Ablative treatment of CIN-3 or CIS lesions with cryotherapy is simple and may prevent subsequent development of cervical cancer in many cases. However, since cryotherapy results in wide areas of cervical ulceration, which is known to increase risk of HIV transmission,^{208,209} such an approach to treatment would be appropriate only if the primary screening approach was highly specific for identification of women with CIN-3/CIS.

A number of large clinical trials have been conducted to evaluate DVI alone or compared with the performance of cytology and/or HPV testing (Table 58-4). Definitions of a positive DVI test have varied across studies, as have the thresholds for cervical disease (LSIL or HSIL). Training techniques have varied as well. Most studies have used a cross-sectional design and have been limited by verification bias, in that the gold standard (usually colposcopy or biopsy) has only been applied to those with positive tests.²¹⁰ This bias results in an overestimate of the specificity of DVI, since test-negative subjects are assumed not to have disease. In addition, this bias also results in an overestimation of the sensitivity, since test-negative cases with disease are not identified.

DVI is generally associated with a high rate of test positivity, similar to HPV testing. In the 26 studies summarized above, the median percentage of subjects testing positive by AVI was 21%, with the middle 50% of the studies (IQR) reporting positivity rates between 13% and 30%. Results of

Table 58-4. Primary Screening Based on Direct Visual Inspection of the Cervix

Author	Country	% AVI Positive	Sensitivity for HSIL or Worse	Specificity	PPV	Referral to Gold Standard
Ottaviano and La Torre (1982) ²¹¹	Italy	312/2384=13%	62/62=100%	2072/2322=89%	62/312=20%	Colposcopy on all
Slawson et al. (1992) ²¹²	United States	113/2753=4%	9/31=29%	2583/2659=97%	9/85=11%	Colpo/biopsy only VIA/cytology +
Cecchini et al. (1993) ²¹³	Italy	535/2105=25%	7/8=88%	1528/2097=75%	7/535=1%	Colpo/biopsy on DVI or cytology or cervicography + only
Frisch et al. (1994) ²¹⁴	United States	71/95=75%	4/4=100%	24/91=26%	4/71=6%	51/95=55% of subjects
Megevand et al. (1996) ²¹⁵	South Africa	76/2426=3%	20/31=65%	2339/2395=98%	20/76=26%	Colpo/biopsy only DVI or cytology +
Sankaranarayanan et al. (1998) ²¹⁶	India	298/3000=10%	46/51=90%	2697/2949=91%	46/298=18%	Colpo/biopsy of DVI or cytology + plus 8% of test -
Sankaranarayanan et al. (1999) ²¹⁷	India	452/1268=55%	68/71=96%	813/1197=68%	68/452=15%	Colpo/biopsy on DVI or cytology + plus 14% of test -
Chirenge (1999) ²¹⁸	Zimbabwe	849/2130=40%	158/206=77%	1233/1924=64%	158/849=19%	Colpo/biopsy on all
Denny et al. (2000) ²¹⁹	South Africa	534/2944=18%	58/86=67%	2382/2858=83%	58/534=11%	Colpo/biopsy only on VIA/HPV/ cytology +
Cronje et al. (2001) ²²⁰	South Africa	1095/6147=18%	169/342=49% (65)	4879/5805=84%	169/1095=15%	Biopsy on VIA + and 20% of VIA -
Singh et al. (2001) ²²¹	India	167/402=42%	118/135=87%	218/267=82%	49/167=29%	Colpo/biopsy on all
Belinson et al. (2001) ¹⁶⁴	China	552/1997=28%	61/86=71%	1420/1911=74%	61/552=11%	Colpo/biopsy on all
Denny et al. (2002) ²²²	South Africa	683/2754=25%	85/117=73%	2009/2581=78%	85/657=13%	Colpo/biopsy only on test +
Rodriguez-Reyes et al. (2002) ²²³	Mexico	176/371=47%	47/51=92%	191/320=60%	47/176=27%	Colpo/biopsy on all
Cronje et al. (2003) ²²⁴	South Africa	577/1093=53%	71/90=79%	490/1003=49%	71/577=12%	Biopsy on all
Basu et al. (2003) ²²⁵	India	1092/5843=19%	68/122=56%	4697/5727=82%	68/1092=6%	Colpo/biopsy on all
Ngelangel et al. (2003) ²²⁶	Philippines	331/3316=10%	30/82=37%	2933/3234=91%	30/331=9%	Colposcopy/biopsy on all
Claeys et al. (2003) ²²⁷	Nicaragua	322/1076=30%	45/51=88%	748/969=77%	45/266=17%	Colpo/biopsy only VIA/cytology +
Sankaranarayanan et al. (2003) ²²⁸	India	1075/4444=24%	132/149=81%	3352/4295=78%	132/1075=12%	Colpo/biopsy on all

Table 58-4. (Continued)

Author	Country	% AVI Positive	Sensitivity for HSIL or Worse	Specificity	PPV	Referral to Gold Standard
Ghaemmaghami et al. (2004) ²²⁹	Iran	191/1190=16%	71/87=82%	983/1103=89%	71/191=37%	Colpo/biopsy test + and 25% test -
Sankaranarayanan et al. (2004) ¹¹⁵	Multiple countries	8848/54,981=16%	817/1063=77%	45887/53924=85%	817/8848=9%	Colpo/biopsy on all
Shastri et al. (2005) ²³⁰	India	508/4009=13%	54/85=64%	3470/3924=88%	54/508=11%	Colposcopy on all/ biopsy on colpo +
Doh et al. (2005) ²³¹	Cameroon	1044/4813=22%	245/348=70% (65)	3666/4465=82%	245/1044=23%	Colpo/biopsy test + and 10% test -
Goel et al. (2005) ²³²	India	50/500=10%	12/13=92%	449/487=92%	12/50=24%	Colpo/biopsy only VIA/cytology test +
Sarian et al. (2005) ²³³	Brazil	1377/11,834=12%	80/162=49%	10,375/11,672=89%	80/1377=6%	Colpo/biopsy all at 1 clinic and 1/3 at other 3 clinics
De Vuyst et al. (2005) ²³⁴	Kenya	177/653=27%	44/60=73%	460/593=78%	44/177=25%	Colpo/biopsy on all
All Studies	<i>N</i> = 26	Mean = 25% Median = 21% IQR = 13–30%	Mean = 74% Median = 77% IQR = 65–88%	Mean = 79% Median = 82% IQR = 75–89%	Mean = 16% Median = 14% IQR = 11–23%	
Studies with colpo/ biopsy of all subjects	<i>N</i> = 10	Mean = 31% Median = 28% IQR = 19–42%	Mean = 73% Median = 77% IQR = 71–81%	Mean = 74% Median = 78% IQR = 64–82%	Mean = 16% Median = 12% IQR = 9–25%	

previous studies in resource-poor settings have shown a wide range of sensitivity and specificity for visual inspection methods. Median sensitivity across the published studies was 77%, with an IQR of 65–88%, while the median specificity was 82%, with an IQR of 75–89%. These wide ranges may reflect the relative subjectivity of DVI and differences in the training and experience of observers.²⁰⁷ The median positive predictive value (PPV) of studies evaluating DVI was 14%, with half of the studies observing values between 11% and 23%. In the 10 studies that have eliminated ascertainment bias by conducting colpo/biopsy on all study subjects, the median percentage of test positives was 28%, and studies had a median sensitivity of 77%, a specificity of 78%, and a PPV of 12%.

Similar to other screening methods, test performance varies with the age of women screened. In the IARC study, specificity of DVI for HSIL generally increased with increased age,¹¹⁵ from specificity for HSIL being 83% in women 25–29 years old and 87% in women 50–59 years old. However, increased specificity was associated with a loss of test sensitivity, with the sensitivity of DVI for HSIL being

89% in young women as compared to only 72% of in older women. VIA may be less effective in older women, reflecting the tendency for the transformation zone and associated lesions to recede into the endocervical canal, making inspection difficult.²³⁵ Although the specificity of VIA was significantly lower in HIV-positive women,²²² the test performance of DVI does not appear to vary with the presence of most other sexually transmitted infections. Magnification does not appear to substantially improve the accuracy of VIA but may reduce specificity.^{222,236}

DVI has been reported to have a higher sensitivity but lower specificity for high-grade cervical lesions. For example, in a study in Zimbabwe, the sensitivity of VIA (77%) was considerably greater than that of cytology (44%), although the specificity of VIA was lower than that of cytology (67% vs. 91%).²¹⁸ Similarly, in a South Africa-based study,²²⁴ the sensitivity of VIA was greater than that of cytology (79% vs. 53%), while specificity was much lower (49% vs. 95%). A Nicaraguan study found that while VIA detected twice as many HSIL lesions and cancers than did

cytology, for every additional true-positive case identified, there were eight false-positive cases, all of which had to be referred for additional examination.²²⁷ In contrast, a study of over 4000 women in India found that the sensitivities of VIA, cytology, and HPV testing were similar (near 60% for all methods), while the specificity of cytology (99%) was greater than that of HPV testing (93%) or VIA (88%).²³⁰ Finally, in a multicenter study in Latin America, VIA had a sensitivity (50–53%) similar to that of cytology but had a lower specificity (99% vs. 90%). In that study, HPV detection by hybrid capture had a considerably higher sensitivity (83%) with a lower specificity (86%).²³³ The PPV of cytology was considerably higher (73%) than the PPV of HPV testing (9%) or VIA (7%). HPV DNA testing tends to have higher sensitivity and similar (low) specificity as compared to DVI.^{207,237}

Visual screening strategies, combined with immediate ablative treatment of visually identified lesions, without confirmation of the presence of disease, have been widely advocated for use in resource-poor settings,^{150,238} as these eliminate the need for cytology and histology. However, given the low specificity of visual screening approach, on average, for every woman with HSIL or worse treated who is correctly identified by visual screening, seven women *without* disease would receive treatment. This approach may have some merit in areas where HIV infection is rare. However, ablative therapy creates large areas of cervical/endocervical ulceration, which may, in populations with a high HIV prevalence rate, result in increased rates of HIV acquisition or transmission to offspring or sexual partners.^{208,209}

In summary, compared to conventional cytology, visual inspection methods generally have similar sensitivity but lower specificity. Because of the low specificity and PPVs, concerns exist regarding diagnostic workups and/or unnecessary treatment of the large numbers of women with false-positive tests, and it remains to be seen if test specificity can be improved by improved reporting or training, without undue loss in sensitivity.¹¹⁵ As a number of these studies have involved highly trained staff with quality control procedures in place, it seems unlikely that even the level of performance observed in these studies would be obtained in a routine service setting in the developing world.²⁰⁷ Nonetheless, despite these limitations, mathematical modeling studies have suggested that visual inspection is likely to be more cost effective than cytology or HPV testing for cervical cancer screening in the developing world.^{94,102,117} In a recent cost-effectiveness study in five developing countries, once per lifetime screening with a one- or two-visit strategy involving VIA reduced lifetime risk of cancer by 25–31%, similar to that of HPV DNA testing, and was somewhat better than two- and three-visit cytology.¹⁰⁰ However, real-life evidence regarding the long-term programmatic performance and

effectiveness of VIA-based programs does not currently exist,²³⁹ and the results of ongoing prospective trials and actual programs will help determine the potential utility of this screening method for more widespread use worldwide.

■ NON-HPV RELATED MOLECULAR MARKERS

As discussed above, once it became apparent that HPV infection played a central importance in the pathogenesis of cervical cancer, a number of proposals for incorporating HPV into cervical cancer control were put forth and tested. Testing for HR types of HPV is now widely used as an adjunct to cytology, whereby women with ASCUS are either triaged to colposcopy and biopsy or returned to routine screening on the basis of detection of HR types of HPV. This approach has the limitations discussed earlier, especially in young women. Similarly, primary screening based on detection of HR types of HPV may be sensitive, but not adequately specific for detection of CIN 2–3. Given the limitations of HPV-based testing, it is of great importance to develop other sensitive and specific markers for detection of women at risk of development of ICC. Further, for reasons discussed below, development of such markers will become increasingly important in the era of HPV vaccines. A number of different molecular markers have been proposed for cervical cancer control screening, including antigens involved in cell proliferation, tumor suppression, DNA repair, apoptosis, and other aspects of the cell cycle (PCNA, Ki-67, cdc6/mcm5, telomerase, cyclin E, and P16), and markers related to control of gene expression, which are also briefly reviewed below.

PCNA

Many of the proposed biomarkers for HPV-associated cervical neoplasia, including proliferating cell nuclear antigen (PCNA), are molecules involved in cell cycle control and thus cellular proliferation. PCNA is an S-phase-associated nuclear protein, which is a cofactor of DNA polymerase.²⁴⁰ Monoclonal antibodies to PCNA have been used in a variety of assays, including flow cytometry and on paraffin-embedded tissue.^{241,242} On immunohistochemical staining, normal cervical epithelium shows only rare intranuclear staining of basal epithelial cells. A number of tissue-based studies report that the level of PCNA-positive nuclei staining correlates with the increasing severity of dysplasia.^{43,243–245} However, HPV infections induce cell proliferation so that this marker is generally positive in the setting of HPV infection, and PCNA can be used as a surrogate of HPV gene expression.²⁴⁶ Thus, in relation to HPV testing, PCNA does not provide any significant gain in specificity for CIN-3.²⁴⁷ The utility of this marker is also limited by the fact that the number of basal cells staining is markedly increased in the presence of inflammation (without neoplasia), and in normal squamous metaplastic epithelium, but not atrophic epithelium.²⁴⁸

Ki-67 (MIB-1)

Detection of intranuclear Ki-67 (MIB-1) antigen, a nonhistone protein expressed in all active parts of the cell cycle, but not in G₀,²⁴⁹ has gained popularity for identification of proliferating cells. As with PCNA, in normal mature squamous epithelium, Ki-67 staining occurs only in rare basal cells (second and third cell layers). Hence, Ki-67 has been proposed as a biomarker for identification of cervical neoplasia. Since HPV infection activates host cell cycle progression, Ki-67 staining is increased in the presence of HPV infection. Although all HPV-related neoplasia stains positive, some studies suggest that the pattern of Ki-67 staining differs with increasing grade of neoplasia,^{250–252} and increased Ki-67 may have prognostic value for progression.²⁵³ In LSILs, some studies report that staining is located in the areas of cytopathic effect (i.e., in upper epithelial layers), while staining is more diffuse with a higher index of cell nuclei in HSIL. However, the index of Ki-67-positive cells changes throughout the menstrual cycle (i.e., is hormone dependent), increasing in the luteal, as compared to the follicular phase, and increasing during pregnancy.²⁵⁴ Atrophic epithelium stains at a lesser level, so it has been speculated that Ki-67 may be useful in cases of ASCUS in postmenopausal women.²⁵⁵ However, although there appears to be no significant difference in Ki-67 expression with and without inflammation, recent studies suggest other serious limitations of this marker, including the fact that criteria for a positive result are subjective (defined as staining in the upper two-thirds of the epithelium) and false positives are common in tangentially sectioned tissues.²⁵⁶ These problems make this marker of limited use for cervical cancer screening or classification.

cdc6 and mcm5

Since *cdc6* and minichromosome maintenance 5 (*mcm5*) have been used as markers of active DNA replication, they might be of interest for cervical neoplasia.^{185,257,258} These are both proteins involved in regulating DNA replication and have been shown to mark dysplastic cells. However, similar to Ki-67, these markers cannot precisely distinguish dysplastic cells from normal proliferating cells.²⁵⁹

Telomerase

Telomeres are repetitive DNA sequences at the ends of eukaryotic chromosomes, which are shortened with each cell division. Decreased length of telomeres is associated with instability and cell death. Telomerase is a ribonucleoprotein enzyme that plays an important role in maintaining telomere length during normal cell proliferation.²⁶⁰ Since telomerase has been noted to be upregulated in most cancers, detection of this enzyme has been proposed as a potential cancer biomarker. The clinical utility of this marker has been somewhat limited by its low level of expression, making it difficult to

detect with conventional immunohistochemical methods. More importantly, with regard to identification of women with CIN-3, HPV 16 E6 oncoprotein expression has been shown to induce telomerase activity by a p53-independent mechanism,²⁶¹ so that HPV cervical infections and HPV-related neoplasia resulting from HR types of HPV are all positive for telomerase. Thus, while greater than 90% of HSILs are positive for telomerase, approximately 50% of LSILs, 56% of reactive atypias, and 18% of normal cervical mucosa samples are also positive,²⁶² making this marker of limited interest for cervical cancer screening by itself. Recently, telomerase activity has been suggested as a possible adjunct to cytology or HR HPV,^{263,264} although the utility of this approach has not been extensively studied.

Cyclin E

Cyclin E is a regulatory protein that complexes with the cyclin-dependent kinase (CDK) *cdk2* to control the G₁–S-phase transition in the cell cycle. The intervention of the cyclin E–*cdk2* complex during S phase is required for progression through the cell cycle. The oncogenic E7 gene of HPV 16 has been shown to upregulate cyclin E activity. Cyclin E also interacts with the E1 gene of HPV 16, which is involved in viral replication. Thus, in the presence of oncogenic HPV types such as HPV 16, overexpression of cyclin E not only deregulates the cell cycle but also facilitates viral replication.^{265,266} In tissue-based studies, cyclin E staining is associated with preinvasive and invasive cervical neoplasia, with some studies reporting increasing levels of immunohistochemical staining for cyclin E, with increasing severity of diagnoses. However, other studies report that 95% of LSILs also show nuclear staining.²⁶⁷ This, along with difficulty in interpretation as a result of high background staining of inflammatory cells and cervical stromal cells, makes this marker of limited interest.²⁵⁶

p16^{INK4a}

p16^{INK4a} is the gene product of cyclin-dependent kinase inhibitor type 2A (CDKN2A), which inhibits *cdk4/6* interaction with cyclin D1 to prevent progression through the cell cycle G₁–S transition checkpoint. In normal cells, accumulation of E2F-1 induces transcription of *p16^{INK4a}*, thus limiting G₁ kinase activity by feedback inhibition. It is well established that the *p16* CDKN2A gene is frequently altered (decreased) in many cancers. In contrast, in HPV-related cervical cancers and precursor lesions, nuclear and cytoplasmic *p16^{INK4a}* protein immunoreactivity is normally present and increased. Although it is not known why *p16^{INK4a}* overexpression occurs in HPV-associated lesions, it is thought that a positive feedback linked to increase in E2F transcription factor is a likely cause.²⁶⁸ A number of studies have used histologic or cytologic immunostaining methods to evaluate the

presence of p16 in normal and dysplastic cervical biopsy or cytology samples.^{269–280} In general, the proportion of p16-positive cases has been closely associated with severity of diagnosis, with 0–18% of normal, compared to 81–100% of high-grade and nearly 100% of squamous cancer cases.²⁸¹ Staining is highly correlated with the infection with HR types of HPV, and, not surprisingly, the majority of both CIN-1 and CIN 2–3 lesions associated with such HPV infections stain positively. In a study of 400 subjects comparing identification of cervical neoplasia by HC2 HPV testing and p16^{INK4a} staining, HC2 had somewhat greater sensitivity, while p16^{INK4a} had greater specificity for HSIL/CIN 2–3.²⁷⁹ p16^{INK4a} was positive in 78% of HSIL specimens, 42% of LSIL specimens, and 36% of ASCUS specimens, whereas HC2 was positive in 92% of HSIL specimens, 81% of LSIL specimens, and 45% of ASCUS specimens.²⁷⁹ However, high levels of p16^{INK4a} expression have also been noted in endocervical and metaplastic cells,²⁷² and a number of studies have reported a lack of positive staining from a subpopulation of CIN 2–3 and ICC cases. Labeling of normal cells and bacteria may preclude the use of p16^{INK4a} in automated screening or nonmorphologic assays.²⁷⁹

While it is generally now agreed that p16^{INK4a} staining is not likely able to distinguish CIN-1 from CIN 2–3, several recent studies have attempted to correlate p16^{INK4a} expression with risk of disease progression.^{184,280} A retrospective analysis of p16^{INK4a} expression on cervical biopsy samples from women with LSIL reported that those with diffuse p16^{INK4a} staining on biopsy had a significantly higher tendency to progress to a high-grade lesion than p16^{INK4a}-negative cases. Importantly, the presence of HR types of HPV in the LSIL was not considered. Wang et al. also explored the potential of p16^{INK4a} as a marker of risk of progression and assessed its relationship to the presence of HR HPV infection. p16^{INK4a} was highly associated with oncogenic HPV infection. Risk of progression of LSIL was associated with p16^{INK4a} staining, when the presence of HPV was not taken into account.⁴³ In a larger study,²⁷⁷ p16^{INK4a} was associated with detection of HR HPV, and there was a significant linear relationship between the lesion grade and intensity of p16^{INK4a} staining, but p16^{INK4a} staining did not predict clearance or persistence of HR HPV after treatment of CIN. Similarly, despite a slightly more favorable survival in women with strong/intense p16^{INK4a} staining in univariate analysis, p16^{INK4a} expression was not an independent prognostic predictor in multivariate survival analysis. In summary, p16^{INK4a} has emerged as a promising complementary marker in the detection of CIN^{282,283} and may improve the diagnostic accuracy of HPV and cytology screening²⁸⁴ but, like most other markers, appears to have limited usefulness in cervical cancer screening on its own.

Epigenetic changes

As discussed above, assays based on detection of antigens involved in cell cycle are generally positive in the setting of oncogenic HPV infection and thus do not provide any clear

advantage over HPV testing, which is sensitive but not specific for CIN 2–3/ICC. An alternative strategy is development of biomarkers based on changes that are highly associated with oncogenesis, rather than with cell proliferation or HPV infection. Such changes include various genetic mutations, and/or *epigenetic* changes (heritable changes in gene expression without alterations of the primary nucleotide sequence), associated with loss and/or gain of function of genes regulating tumor suppression, DNA repair, apoptosis, or facilitating development of malignancy. Epigenetic changes, especially DNA promoter hypermethylation,^{285,286} have been of particular interest, as such changes are believed to be an early event in carcinogenesis and are often present in the precursor lesions of a variety of cancers, including cervical cancer.^{27,35,287–292} Further, while mutations found in cancers from different individuals occur at many different locations in a specific gene, DNA hypermethylation of genes always occurs in the same region (the promoter region). This makes development of a clinical assay, based on detection of DNA promoter hypermethylation, considerably easier than development of an assay based on mutations. A variety of different genes have been found to have aberrant DNA hypermethylation in ICC, including genes related to cell cycle, tissue differentiation regulation (*CDKN2A*, *p16*, *p14ARF*, *CDKN2B*, *CCND2*, *TP73*, *RBI*, *RASSF1*, *RARB*, *TWIST1*, *PRDM2*, *SFN*, *HIC1*, *APC*, *BRCA1*, and *MYOD1*), genes related to cell growth regulation (*SOCS1*, *SOCS2*, *CALCA*, *VDR*, *RNR1*, *HSD17B4*, *PGR*, *TYMS*, *TGFBR2*, and *ESR1*), genes related to DNA repair, detoxification, and chromosomal stability (*MGMT*, *MLH*, *BRCA1*, *GSTP1*, *FHIT*, *TERT*, *FANCF*, and *PTGS2*), and genes related to metastasis and invasion (*CDH1*, *TIMP3*, *TIMP2*, *APC*, and *CDH13*).^{204,293–307} In the largest study thus far, Feng et al. reported that a panel of three genes (*DAPK1*, *RARB*, and *TWIST1*) detected 73.9% of 92 cases of ICC and 56.5% of 23 CIN-3/CIS cases, while 95.0% of 181 with CIN-1 or less were negative for all three genes.³⁵ These gene methylation markers may have great potential as surrogates of clinical disease or as indicators of risk during follow-up.³⁰⁸

HPV VACCINES

■ VACCINE DEVELOPMENT

It is now clear that the development of ICC requires infection with HR types of HPV^{2,54}; therefore, vaccines preventing HPV infection have the potential to dramatically reduce the incidence of cervical cancer and its precursor lesions.³⁰⁹ In June 2006, a Merck (Whitehouse Stations, NJ, USA) vaccine (Gardasil®) for prevention of infection with HPV types 16 and 18, which together account for approximately 70% of all cervical cancer, was approved by the U.S. FDA for use in girls and women aged 9–26 years and has been approved by the European Medicines Agency (EMA). Gardasil® also protects

against infection with HPV 6 and 11 types, which are associated with 90% of genital warts but not with cervical cancer. Another vaccine (Cervarix™), manufactured by Glaxo-SmithKline (Philadelphia, PA, USA) for prevention of HPV 16 and 18, is also now under review in Europe, and the company hopes to apply for U.S. FDA approval by the end of 2007.³¹⁰ Three proof-of-principle randomized controlled trials have assessed the efficacy of these vaccines to prevent HPV infection and cervical abnormalities to date^{311–313} and demonstrated high levels of efficacy (at least 89%) for prevention of incident/transient, persistent HPV infections as well as for prevention of type 16 or 18 high-grade disease.^{178,314,315} In the Merck-sponsored monovalent type 16 HPV vaccine study,³¹¹ 1533 U.S. women aged 16–23 years and without a history of cervical abnormalities were enrolled and followed for up to 48 months after receiving an HPV 16 virus-like particle capsid vaccine (or placebo). No serious side effects were observed, and antibody titers were 60 times greater in those vaccinated compared to titers that occur in natural genital HPV infection. Similarly, in the GSK-sponsored study,³¹² 1113 women aged 15–25 years in the United States, Canada, and Brazil were vaccinated with a bivalent (HPV 16 and 18) VLP capsid vaccine (or placebo). Again, serious side effects were not noted, and antibody titers were 50–80 times greater in vaccines compared to individuals with naturally acquired HPV 16 or 18 infection. Most recently, the approved Merck quadrivalent vaccine, Gardasil®, containing L1 protein antigens from HPV types 6, 11, 16, and 18, showed 90% efficacy against persistent infection or disease. Ongoing clinical studies are expected to provide further evidence of efficacy in preventing high-grade CIN. It is important to note that these vaccines did not prevent development of HPV 16 or 18 related CIN 2–3 in women who were infected or who had baseline evidence of serum antibodies to HPV 16 or 18.

While these vaccines will clearly lower the incidence of cervical cancer and will be of tremendous importance for cervical cancer control, many questions must be addressed, including what additional HR HPV types should be included in future vaccines, whether development of vaccines containing many HPV types is achievable, and whether there is any cross protection between different related HPV types. More than 40 HPV types infect the genital tract and at least 15 of these are significantly associated with progression to ICC.^{316,317} A recent meta-analysis of HPV types in over 10,000 cases of squamous cervical cancer worldwide⁵³ showed that 69% of cases were associated with HPV 16 (51%) or 18 (16%), making inclusion of these types logical for first-generation vaccines. HPV types 45, 31, 33, 58, and 52 each accounted for less than 10% of all invasive cancers and collectively accounted for 18% of cases. While a majority of ICC was associated with HPV 16 or 18 in all regions, the distribution of other types in ICC varied by region. A vaccine that contained the seven most common HPV types could potentially prevent

approximately 87% of cervical cancers worldwide, with little geographic variation. Gains in type coverage rapidly diminish beyond inclusion of four HPV types and potentially cause increased manufacturing challenges.³¹⁸ Similar findings have been observed in adenocarcinoma, where HPV 16 (52%) and HPV 18 (39%) were detected in a vast majority of cases across eight studies.⁵² Which HPV types in addition to 16 and 18 will be added to future vaccines is unclear, as early studies show some evidence of cross protection among certain HPV types.³¹⁹ However, the extent of such cross protection will be defined by larger ongoing studies.

Other issues that will need to be addressed are the duration of protection and the cost effectiveness of various vaccination strategies. At present, for example, it is not clear whether young adolescent females or both young females and males should be vaccinated. Natural history studies have reported that HPV infection occurs shortly after the onset of sexual activity,³²⁰ necessitating early vaccination of individuals before they become sexually active. Sexually active males and females both become infected with HPV^{321,322} and transmit HPV between each other, so it has been suggested that vaccination should be considered for both genders. Males have been included in clinical trials only recently, to determine whether vaccination protects them from penile and anal infections and potentially from cancers, caused by HPV 16 and 18; this would then be expected to also protect their female partners from cervical cancer. Vaccinating males could thus help reduce HPV infection transmission through herd immunity, especially since vaccine coverage of women is likely to be less than 100%.³²³ However, recommendations for male vaccination will require data from research studies of prevention currently underway.³²⁴ Unfortunately, the duration of vaccine efficacy is unknown and remains a key issue that will have a major impact on the timing of vaccination regimens and affordability.³²⁵ Presently, both vaccines have shown proven immunization for up to 5 years, and there is strong evidence that the protective effect of the vaccines will be long lasting, but it is still unknown whether both vaccinees will require booster shots.

The impact of these vaccines will obviously be highly significant. In the developed world, where full implementation of cervical cancer screening has shifted the burden of HPV infection from cervical cancer mortality to management of precancerous lesions, HPV vaccination might decrease the costs associated with management of abnormalities detected by Pap testing and CIN.³¹³ Inclusion of HPV 6 and 11, which are not causally associated with ICC, in a vaccine could diminish the incidence of genital warts and low-grade CIN, which are benign but costly to treat.

Theoretical models suggest that an HPV vaccine will have the greatest effect where screening programs are not in effect.³²⁶ In the developing world, the logistics of delivering a new vaccine will be formidable, particularly since the present vaccines require multiple injected doses and are likely to

target adolescents, a group that is not currently reached by any global health-care program.³²⁷ Public health-care systems are generally understaffed and underfunded, and the health-care community faces numerous challenges in organizing implementation of HPV vaccine programs of the future.³²⁴ The WHO, the Bill and Melinda Gates Foundation, IARC, and PATH (a Seattle-based NGO) are all involved in facilitating implementation of vaccination programs in the developing world and are hopeful that the introduction of HPV vaccination will bring about greatly needed reductions in cervical cancer incidence.

■ SCREENING IN THE AGE OF HPV VACCINES

Vaccine implementation will have important implications for cervical cancer screening protocols in countries with established screening programs. The currently available vaccines will protect uninfected women from infection with HR types HPV 16 and 18 and from development of HPV 16- and 18-related HSIL and (presumably) cancer. However, HPV 16 and 18 only account for approximately 70% of all cervical cancers, and the current vaccines probably will not provide protection from infection and development of pathology related to the many other oncogenic HPV types. If many HPV 16- and 18-associated lesions and cancer will be avoided, it is possible that lesions caused by other HR types not included in a vaccine might increase in frequency.³²³ Further, the current vaccines are not therapeutic and hence will not protect women already infected with HPV 16 or 18, from subsequent development of related HSIL and cancer.³²⁸ Thus, many sexually active women will not derive any benefit from these vaccines. In light of these problems, some sort of cervical cancer screening will be needed for the foreseeable future.

Mathematical modeling of the impact of an HPV vaccine on screening for cervical cancer suggests that the interval for Pap smear screening in vaccinated women could be lengthened as a result.^{99,309,329} HPV vaccination might decrease the costs associated with management of abnormalities detected by Pap testing and CIN.³¹³ Inclusion of HPV 6 and 11, which are not causally associated with ICC, in a vaccine could diminish the incidence of genital warts and low-grade CIN, which are benign but costly to treat. Vaccination will likely affect HPV DNA testing and screening practices and result in changes to screening time intervals and clinical management algorithms.³³⁰ The current approach of frequent screening using cytology may prove too expensive and inefficient for many countries as they implement HPV vaccination, particularly for those that publicly fund most of their health care; countries that introduce HPV vaccination may eventually switch to HPV DNA testing as the primary screening test, and HPV genotyping will allow for monitoring long-term vaccine protection.³²⁸ The impact of vaccination on these issues will

need to be evaluated prospectively and will depend on the timing of regional vaccine implementation, the extent of coverage, whether other HR HPV types are added to future vaccines, and the duration of vaccine protection. A significant reduction of cervical cancer rates as a result of vaccination in young girls will not be observed for years to come, and it is clear that countries will need substantial resources to support both vaccination and screening programs at the same time for years to come.³³¹

CURRENT SCREENING RECOMMENDATIONS

Cervical cancer screening recommendations have been issued by a variety of organizations, including the American Cancer Society⁶⁶ and the American College of Obstetrics and Gynecology (ACOG).³³² These guidelines are summarized below, but the reader is referred to these original publications for the evidence-based rationale and a broader discussion of these recommendations.

■ ONSET OF SCREENING

It is recommended that cervical cancer screening start 3 years after first vaginal intercourse or no later than 21 years of age. However, cervical cancer screening should not be the only basis for the onset of gynecologic care, with all adolescents being given information on preventive health care, counseling regarding health risks, contraception, along with screening and treatment of sexually transmitted diseases.

■ DISCONTINUATION OF SCREENING

Women 70 years of age or older who have had three or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening. Women with a history of cervical cancer, DES exposure before birth, HIV infection, or a weakened immune system should continue to have screening as long as they are in good health.

■ SCREENING AFTER HYSTERECTOMY

Women who have had a total hysterectomy (removal of the uterus and cervix) may choose to stop having cervical cancer screening, unless the hysterectomy was performed for treatment of cervical cancer or precancer. Women who have undergone hysterectomy for treatment of CIN2/3 should continue screening until they receive three consecutive, satisfactory normal/negative cervical cytology tests and no abnormal/positive cytology tests within a 10-year period. Those with a history of treatment of cancer and/or a history of in utero diethylstilbesterol (DES) exposure should continue

screening after hysterectomy for as long as they are healthy. Women who have had a hysterectomy without removal of the cervix should continue to follow the guidelines below.

■ SCREENING INTERVAL

Cervical screening should occur annually if conventional cervical cytology smears are used or every 2 years with LBC. For women 30 years or older, those with three prior consecutive, satisfactory normal/negative cytologies may be screened every 2–3 years (unless they have a history of in utero DES exposure, are HIV+, or are immunocompromised by organ transplantation, chemotherapy, or chronic corticosteroid treatment).

■ HPV DNA TESTING WITH CYTOLOGY FOR SCREENING

Some have advocated HPV DNA testing with cytology for primary cervical cancer screening for women over 30 years. This is an option for women over 30 years, since Digene-based detection of HPV DNA has been approved for primary screening with cytology for women aged 30 years. As an alternative to cervical cytology testing alone, cervical screening may be performed every 3 years (but not more frequently), using conventional or LBC combined with a test for DNA from HR HPV types.

MANAGEMENT OF ABNORMAL CYTOLOGY RESULTS

As discussed above, approximately 3.5 million women are diagnosed with cervical cytologic abnormalities each year. To encourage standardized clinical care, the American Society for Colposcopy and Cervical Pathology (ASCCP) hosted a consensus conference in 2001³³³ to develop evidence-based guidelines for clinical management of the women with abnormal cytologic findings (<http://www.asccp.org>). These recommendations are summarized below.

■ MANAGEMENT OF WOMEN WITH ASCUS

Repeat cervical cytological testing, immediate colposcopy, HPV DNA testing for HR types, or combined repeat cervical cytological testing with another adjunctive method are all acceptable methods for managing women with ASCUS (Fig. 58-4). Reflex HPV DNA testing (automatic testing of the original specimen if cytology shows ASCUS) is of interest, as it eliminates the need for an additional clinical examination for specimen collection and reduces by 40–60% the number of women with ASCUS who are referred for colposcopic examination. Further, a negative test essentially

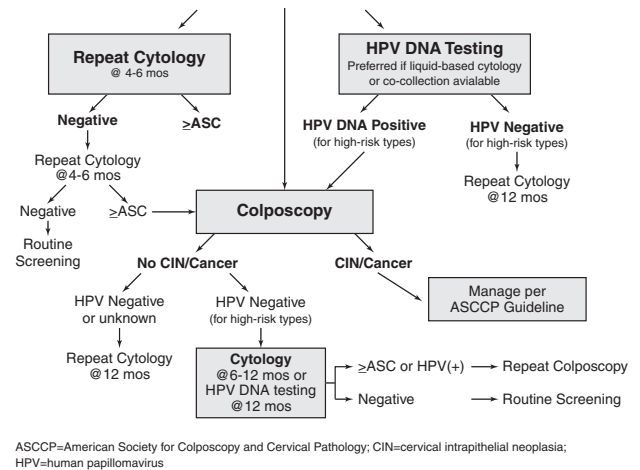


FIGURE 58-4. Management of women with atypical squamous cells of undetermined significance (ASCUS).³³⁸

eliminates the presence of a significant cervical neoplastic lesion and allows the women to return to normal screening. All women who test positive for HPV DNA should be referred for colposcopy and biopsy. The use of excisional loop electrosurgical excision procedure (LEEP) as a means of diagnosis is not recommended in women with ASCUS on cytology, as this is likely to result in overtreatment of large numbers of women. Women positive for HR types of HPV, but without CIN on colposcopy and biopsy, should have either repeat HPV DNA testing at 12 months or cytological testing at 6 and 12 months. Those with a cytologic diagnosis of ASCUS or greater, or a positive HPV test should be referred back to colposcopy. If women with ASCUS are followed by cytology, repeat cytological testing should be performed at 4–6-month intervals until they receive two consecutive “negative” results, at which time women can be returned to routine screening. Those with ASCUS or greater on the repeat tests should be referred for colposcopy. If immediate colposcopy is used to manage women with ASCUS, those who are not found to have CIN should have repeat cytology at 12 months. Women with CIN on biopsy should be managed according the 2001 Consensus Guidelines for the Management of Women with Cervical Histological Abnormalities.³³⁴ Postmenopausal women with ASCUS may be managed by a course of intravaginal estrogen followed by a repeat cervical cytology with subsequent management, based on these results. All immunosuppressed women with ASCUS should be referred for colposcopy.

■ MANAGEMENT OF WOMEN WITH ASC-H

Women with ASC-H should be directly referred for colposcopic evaluation. If no lesion is found on colposcopy, cytology, colposcopy, and histology, results should be reviewed, and if ASC-H is confirmed, HPV DNA testing at 12 months or repeat cytology at 6 and 12 months should be performed.

■ MANAGEMENT OF WOMEN WITH LSIL

Women with LSIL on cytology should be referred for colposcopic evaluation. HPV DNA testing and LEEP are not considered useful for the initial management of women with LSIL, as most women with LSIL are HPV positive and LEEP is frequently normal.

■ MANAGEMENT OF WOMEN WITH LSIL BUT NO CERVICAL LESIONS

Few data are available regarding management of women with LSIL on cytology in whom CIN is not identified after satisfactory colposcopic examination. While some such women do have underlying CIN, the risk of missing a significant lesion in this situation is relatively low.³³⁵ Endocervical sampling lowers the risk of missed endocervical lesions in women with LSIL, with or without satisfactory colposcopic examinations. Endocervical sampling is acceptable for nonpregnant women with satisfactory colposcopic findings and a lesion identified in the transformation zone but is preferred for those without identifiable lesions. Women in whom CIN is not identified can be managed by either repeat cytology at 6 and 12 months with referral to colposcopy if ASCUS or greater is diagnosed or HPV DNA testing at 12 months with referral for colposcopy if testing is positive for an HR HPV.

■ MANAGEMENT OF POSTMENOPAUSAL WOMEN WITH LSIL

Postmenopausal women with LSIL can be managed as above, or alternatively with either repeat cytology at 6 and 12 months with referral for colposcopy for ASCUS or greater, or with HPV DNA testing at 12 months with referral for colposcopy if positive for HR types of HPV. Women with LSIL, who have clinical or cytological evidence of atrophy, and who are without contraindications to use of intravaginal estrogen, can be managed by a short course of intravaginal estrogen treatment with repeat cytology approximately a week after completion of estrogen therapy. Those with ASCUS or greater should be referred to colposcopy, while those with a cytologic diagnosis of “negative for intraepithelial lesion or malignancy” should have repeat cytology in 4–6 months. Patient can return to routine cytological screening, if both repeat cytology test results are “negative for intraepithelial lesion or malignancy.” Women should be referred for colposcopy if either repeat result is ASCUS or greater.

■ MANAGEMENT OF ADOLESCENTS WITH LSIL

Adolescents with LSIL can be managed without initial colposcopy with either repeat cytology at 6 and 12 months or of HPV DNA testing at 12 months. Those with ASCUS or

ASC-H on repeat cytology, or who are positive for HR HPV DNA should be for referral for colposcopy.

■ MANAGEMENT OF PREGNANT WOMEN WITH LSIL

For the recommended management of pregnant women with a diagnosis of LSIL, see the “HSIL in Special Circumstances” section.

■ MANAGEMENT OF WOMEN WITH HSIL

Women with HSIL on cytology should be referred for colposcopy with endocervical assessment. Repeat cytological testing or triage by HPV DNA testing is unacceptable. Omission of endocervical sampling is acceptable when a diagnostic excisional procedure is planned. The approach of managing nonpregnant women with HSIL by immediate LEEP of the transformation zone (i.e., “see and treat”) has been shown to be safe; however, studies of women undergoing immediate LEEP for cytological abnormalities show that histologically confirmed CIN will frequently not be present (reviewed by Wright),³³³ so this approach should be reserved for populations with an HR of being lost to follow-up and for older patients where effects of LEEP on fertility does not have to be considered.

Women with a cytologic HSIL, which cannot be identified on colposcopy and biopsy, need additional consideration, as up to 35% of such women have been found to have high-grade lesions after additional workup.^{336,337} Therefore, in situations where a woman has an HSIL cytology without a high-grade lesion on biopsy, a careful re-review of the colposcopic, biopsy, and cervical cytology results should be undertaken to confirm the initial HSIL diagnosis. Nonpregnant patients in whom the cytological diagnosis of HSIL is upheld after review can be managed by a diagnostic excisional procedure. Ablation is unacceptable in this situation.

HSIL in pregnant women also requires special attention. Lesions suspicious for high-grade disease or cancer should be biopsied, while biopsy of other lesions is acceptable. Colposcopic evaluation and detection of HSIL are sometimes more difficult in the setting of pregnancy, and endocervical sampling is proscribed. Pregnant women with unsatisfactory colposcopic findings should have a repeat colposcopic examination 6–12 weeks after an unsatisfactory colposcopy, as colposcopy may become satisfactory as the pregnancy progresses. If invasive disease is not present, the patient should have additional colposcopic and cytological examinations, with biopsy only of lesions whose appearance has worsened or when cytology suggests invasive cancer. A diagnostic excisional procedure is recommended only if invasion is suspected. Reevaluation with cytology and colposcopy should take place no sooner than 6 weeks postpartum.

Young women of reproductive age with HSIL on cytology but in whom biopsy-confirmed CIN 2–3 is not identified on (satisfactory) colposcopy and biopsy (including negative endocervical sampling) can be managed by observation with colposcopy and cytology at 4–6-month intervals for 1 year, and the patient accepts the risk of occult disease. Cytologic persistence of HSIL or colposcopic progression to high grade should be handled by a diagnostic excisional procedure.

■ MANAGEMENT OF WOMEN WITH AGC AND AIS

Glandular cell abnormalities less severe than invasive adenocarcinoma include (1) atypical glandular cells endocervical, endometrial, or “glandular cells” not otherwise specified (AGC NOS), (2) atypical glandular cells, either endocervical or “glandular cells” that favor neoplasia (AGC “favor neoplasia”), and (3) endocervical adenocarcinoma in situ (AIS).

Women with all subcategories of AGC, with the exception of women with atypical endometrial cells, should initially be evaluated by colposcopy with endocervical sampling. Those with atypical endometrial cells should initially be evaluated with endometrial sampling. In younger women with AGC with unexplained vaginal bleeding and in women older than 35 years with AGC, endometrial sampling should be performed in combination with colposcopy. Women with AIS on cytology should undergo endocervical sampling. Repeat cytologic testing is not an acceptable management strategy for women with AGC or AIS. Further, it is not known whether HPV DNA testing has a role in the management of women with AGC or AIS.

■ WORKUP OF WOMEN WITH AGC OR AIS IN WHOM LESIONS ARE NOT IDENTIFIED

If initial colposcopic examination and endocervical sampling do not identify invasive disease, women with AGC “favor neoplasia” or endocervical AIS should undergo a diagnostic excisional procedure, preferably cold-knife conization for women with AGC or AIS. Biopsy-confirmed CIN (of any grade) identified during the initial workup for AGC NOS should be managed as are other CINs. Women with AGC NOS without neoplasia on initial workup should be followed by repeat cervical cytological testing at 4–6-month intervals until four consecutive “negative for intraepithelial lesion or malignancy” results are obtained, at which point the woman may return to routine screening. If ASC or LSIL is diagnosed on any of the repeat cytology, repeat colposcopic examination or referral to a clinician experienced in the management of complex cytological situations is appropriate.

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PART 10

Management of STD Syndromes in Men

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David H. Martin

DEFINITIONS

Urethritis, manifested by urethral discharge, dysuria, or itching at the end of the urethra, is the response of the urethra to inflammation of any etiology. The characteristic physical finding is urethral discharge, and the pathognomonic confirmatory laboratory finding is an increased number of polymorphonuclear leukocytes (PMNL) on Gram stain of a urethral smear or in the sediment of the first-voided urine. Urethritis is called gonococcal, or gonorrhea, when *Neisseria gonorrhoeae* is detected, and nongonococcal if *N. gonorrhoeae* cannot be detected. The term *nongonococcal urethritis* (NGU) is preferable to the term *nonspecific urethritis*, because NGU has specific causes and many of these have been elucidated. Of those that are clearly established as causes of NGU, *Chlamydia trachomatis* and *Mycoplasma genitalium* are the most frequent. NGU occurring soon after curative therapy for urethral gonorrhea is called *postgonococcal urethritis* (PGU).

HISTORY

In the 1800s, even prior to the discovery of *N. gonorrhoeae*, the existence of several types of urethritis was already suspected. By the 1880s, after the isolation of *N. gonorrhoeae* and the introduction of the Gram stain, differentiation of gonococcal from NGU became possible. In the early part of the twentieth century, intracytoplasmic inclusions, which today are considered characteristic of chlamydiae, were seen in urethral smears of some men with urethritis. The development that had the greatest impact on clinical differentiation of GU and NGU, however, was the introduction of the sulfonamides and penicillins for treatment of urethritis. With penicillin in particular, GU was curable, but NGU usually was not. Progress in therapy of NGU came with the introduction of tetracyclines and macrolides. Further insight into the etiology of NGU came with the discovery of *Ureaplasma urealyticum* in 1954,¹ the development of cell culture isolation techniques for *C. trachomatis* in 1965,² and the development

of nucleic acid amplification tests (NAATs) for sexually transmitted diseases (STDs) in the 1990s.

ETIOLOGY

Organisms that are proved or are possible causes of sexually transmitted urethritis are listed in [Table 59-1](#).

■ NEISSERIA GONORRHOEAE

The causal role of *N. gonorrhoeae* in male urethritis is well established. Several aspects that are important for management of GU deserve reemphasis here. These include the frequency of asymptomatic infection, the increasing resistance of isolates of *N. gonorrhoeae* to traditional treatments, and the high frequency of concurrent *C. trachomatis* infection. Although most new cases of GU are symptomatic, a number of studies have shown that GU can be asymptomatic or minimally symptomatic.³ As many as two-thirds or more of men in the community who are found to have urethral gonorrhea by routine screening or by contact-tracing have no symptoms at all, or they have such mild symptoms that they ignore them. These men are likely to remain sexually active and to spread the infection. For example, a population-based study of 5867 men in rural Tanzania found that 27% had a positive urine leukocyte esterase dipstick test, and 2.5% reported a complaint of urethral discharge. Of those with a positive dipstick test or with symptoms, 158 had urethral gonorrhea (by Gram stain) or chlamydial infection (by antigen-detection immunoassay). Only 24 (15%) of those with either infection complained of symptoms or signs, and an additional 30 (19%) had a discharge on examination, leaving 66% with neither symptoms nor signs.⁴ Asymptomatic men in a U.S. study appeared especially likely to have the arginine-, hypoxanthine-, and uracil-requiring auxotrophs of *N. gonorrhoeae* that have often been associated with disseminated gonococcal infection.⁵

N. gonorrhoeae is a textbook example of how overuse of antibiotics induces resistance that eventually spreads around the

Table 59-1. Etiology of Sexually Transmitted Urethritis in Males

Gonococcal:

N. gonorrhoeae^a

Nongonococcal:

C. trachomatis, 15–40%*M. genitalium*, 15–25%

Neither, 20–50%

T. vaginalis, 5–15%?*U. urealyticum*, <15%?

HSV, 2–3% (in the absence of skin lesions)

Adenovirus, 2–4% (seasonal, associated with receptive oral sex)

Haemophilus sp., rare

Unknown

^aRare cases of *N. meningitidis* urethritis presenting like GU have been reported (see text). Question marks reflect uncertainty concerning the percent of cases attributable to the organism.

world resulting in increased morbidity due to treatment failures. Gradually increasing resistance of *N. gonorrhoeae* to penicillins in the 1960s resulted in the need for progressively higher doses of penicillin in conjunction with probenecid to obtain a cure. Penicillinase-producing *N. gonorrhoeae* strains appeared in 1976; they were initially most prevalent in Southeast Asia and Africa, but then spread worldwide. More recently, quinolone resistance also first appeared in Asia and from there has spread to become an increasing problem in the West including the United States. Treatment guidelines have changed significantly as a consequence (see Chapter 35 for details).^{6,7}

■ CHLAMYDIA TRACHOMATIS

Since 1972, many studies have shown that *C. trachomatis* could be isolated from the urethras of 25–60% (usually 30–40%) of men who have NGU, 4–35% (usually 15–25%) of men with urethral gonorrhea, and 0–7% of men without obvious urethritis (see Table 59-2). *C. trachomatis* has been less frequently isolated from men who have sex with men (MSM) with NGU in most studies.^{8,9} However, a more recent report based on an NAAT for diagnosis suggests that at least in some areas the organism is equally common among MSM with NGU as in heterosexual men.¹⁰

Most patients with NGU seen in STD clinics have existing antibody to *C. trachomatis* demonstrable in acute-phase sera by microimmunofluorescence (micro-IF). It is unusual to

document seroconversion or a fourfold increase in micro-IF antibody in such patients.¹¹ However, in a selected group of men who had relatively few sex partners and no previous history of urethritis, and who have had symptoms of NGU for less than 10 days, 9 of 10 who were culture-positive for *C. trachomatis* seroconverted.¹² IgM micro-IF antibody, a transiently detectable antibody that allows diagnosis of recent infection despite preexisting antibody, was detected in specimens from 16 of 20 men whose cultures were *C. trachomatis*-positive, compared with 3 of 39 with NGU whose cultures were negative ($p > 0.0001$).¹² These results suggested that recent acquisition of chlamydia, rather than reactivation of latent infection, was associated with urethritis in these men.

PGU provides an opportunity for prospective assessment of the ability of *C. trachomatis* to produce urethritis. Gonorrhea has a shorter incubation period than chlamydial urethritis, so men with both infections can present with gonorrhea while the chlamydial infection is still incubating. When gonorrhea is treated with antimicrobials that do not eradicate *C. trachomatis*, such as single-dose penicillin, ampicillin, ceftriaxone, fluoroquinolones, or spectinomycin, PGU develops in most men who have concurrent *C. trachomatis* infections (see Table 59-2).

Selective eradication of *C. trachomatis* results in alleviation of urethritis in men infected with the organism.^{12–14} Use of sulfonamides or rifampin that are active against *C. trachomatis* but which overall have a poor record in the treatment of NGU, resulted in clinical responses in most men infected with *C. trachomatis*, but in a significantly smaller proportion of men without *C. trachomatis*.^{12–14} However, a better response in *C. trachomatis*-positive NGU patients than in chlamydia-negative NGU is also observed with a broader-spectrum antimicrobial, tetracycline.¹⁵ Persistence or recurrence of NGU within 6 weeks of initiation of a 7-day course of tetracycline, 2 g per day, was seen in 17% of men whose cultures were *C. trachomatis*-positive, compared with 47% of those whose cultures were *C. trachomatis*-negative ($p = 0.01$). In a subsequent study with minocycline, persistent or recurrent NGU developed within 6 weeks of initiation of therapy in 17% of 78 *C. trachomatis*-positive men, compared with 35% of 133 men without *C. trachomatis* infection ($p > 0.005$).⁸ In summary, the accumulated data unequivocally have established *C. trachomatis* as a cause of NGU.

Etiology of *Chlamydia trachomatis*-negative NGU

Chlamydia culture is difficult to perform optimally and it has always been thought that the sensitivity of culture is less than optimal. Because of this fact, it has been suspected that a certain proportion of *C. trachomatis*-negative NGU cases may have been false-negative cases of chlamydial urethritis. However, several different lines of evidence have suggested that this is not the case or at least is uncommonly so. It has

Table 59-2. Recovery of *C. trachomatis* from Males with NGU, GU, PGU, and Asymptomatic Controls

Country	Investigator	Year	NGU ^a	GU ^a	PGU ^a	Controls ^a	Refs.
UK	Dunlop et al.	1972	44/99 (44)				123
UK	Oriel et al.	1972	49/135 (36)			0/31 (0)	16
UK	Richmond et al.	1972	40/103 (30)	32/99 (32)	17/21 (81)	5/92 (5)	124
UK	Oriel et al.	1975		15/44 (34)	11/23 (48)		125
UK	Oriel et al.	1975	33/133 (25)				126
USA	Schachter et al.	1975	27/76 (36)	2/18 (11)		0/57 (0)	127
USA	Smith et al.	1975	34/131 (26)				128
USA	Holmes et al.	1975	48/113 (42)	13/69 (19)	12/20 (60)	4/58 (7)	11
UK	Oriel et al.	1976	125/262 (48)	35/141 (25)		3/74 (4)	129
UK	Prentice et al.	1976	43/136 (32)				130
USA	Bowie et al.	1976	36/91 (40)				13
Sweden	Johannisson et al.	1977	44/103 (43)		11/15 (73)		131
UK	Alani et al.	1977	116/385 (30)	13/118 (11)	9/59 (15)		17
UK	Vaughan-Jackson et al.	1977		30/95 (32)	26/49 (53)		25
USA	Bowie et al.	1977	23/69 (33)			1/39 (3)	12
USA	Segura et al.	1977	71/180 (39)				132
USA	Wong et al.	1977	21/67 (31)	4/99 (4)		3/85 (4)	42
Finland	Paavonen et al.	1978	39/75 (52)				18
Finland	Terho	1978	93/159 (58)			0/64 (0)	116
Norway	Csango	1978	36/81 (44)				133
Sweden	Ripa et al.	1978	74/284 (26)	15/88 (17)			134
Switzerland	Perroud et al.	1978	124/238 (52)	32/139 (23)	15/19 (79)	1/40 (3)	135
USA	Bowie et al.	1978		23/121 (18)	10/26 (38)		24
USA	Smith et al.	1978		31/143 (22)			136
USA	Swartz et al.	1978	35/107 (33)	12/61 (20)		6/112 (5)	53
Finland	Lassus et al.	1979	75/181 (45)				19
UK	Coufalik et al.	1979	93/217 (43)				14
UK	Taylor-Robinson et al.	1979	263/726 (36)				137
Canada	Bowie et al.	1980	80/200 (40)				20
USA	Root et al.	1980	19/96 (20)				23
USA	Bowie et al.	1981	78/211 (37)				8
Denmark	Ibsen et al.	1988	82/188 (44)				114
France	Lefevre et al.	1990	52/202 (26)	5/23 (22)			138
USA	Hooton et al.	1990	60/152 (39)				112
USA	Stamm et al.	1995	69/452 (15)				108

^aNumber culture or NAAT-positive/number examined (percent culture or NAAT-positive).

been shown that when initial urethral specimens are negative for *C. trachomatis* they usually remain negative when untreated patients are cultured repeatedly on follow-up.¹⁵ It has also been shown that cervical cultures from female sex partners of men with *C. trachomatis*-negative NGU are likely to be *C. trachomatis*-negative.^{11,16–19} Another study has shown that in most cases of *C. trachomatis* culture-negative NGU, there is no serologic evidence of recent *C. trachomatis* infection.¹² Finally, *C. trachomatis*-negative NGU cases have been demonstrated to respond poorly to certain antimicrobials that are active against *C. trachomatis* such as the sulfonamides, rifampin, and the tetracyclines.^{8,12,13,15,20} Though NAATs have proven that *C. trachomatis* culture sensitivity is relatively poor (see Chapter 32), the data indicate that though a small proportion of *C. trachomatis* culture-negative NGU cases are actually caused by this organism, other organisms, some of which remain unknown, are more important.

■ MYCOPLASMAS

Of the 13 mycoplasma species known to infect or colonize humans, four are found in the genital tract. These are *Mycoplasma hominis*, *M. genitalium*, *Ureaplasma parvum*, and *U. urealyticum*. The latter two were included previously in the single species *U. urealyticum*. Recent genetic studies have shown that the genus actually comprises of the two species, a finding that eventually may help clarify the confusion surrounding the role of these organisms in NGU.²¹ In reading the older literature, it is important to remember that whenever *U. urealyticum* is referred to, the authors are really talking about a mixture of the two. *Ureaplasma sp. M. hominis* does not appear to have a role in NGU having been found in numerous studies to be equally present in men with disease and in normal men.

The best evidence for a pathogenic role for *Ureaplasma sp.* in NGU, came from studies of men who were relatively inexperienced sexually and were having their first episodes of urethritis. In such men, the rate of isolation and the concentration of *Ureaplasma sp.* in first-voided urine were significantly greater in those with *C. trachomatis*-negative NGU than in those with *C. trachomatis*-positive NGU or in a comparison group without urethritis.¹² In that study, the comparison group without urethritis had actually had more sex partners than the other groups.¹² Data compiled from three Seattle studies^{8,12,13} showed that *Ureaplasma sp.* were isolated significantly more often from men with a first episode of urethritis than from those who had a history of previous episodes or from men without urethritis.

The results of studies of selective eradication of *Ureaplasma sp.* also support a pathogenic role in NGU. Sulfonamides and rifampin are active against *C. trachomatis*, whereas spectinomycin and streptomycin are active

against *Ureaplasma sp.*, but not against *C. trachomatis*. In men whose cultures were *C. trachomatis*-negative but *Ureaplasma sp.*-positive, urethritis responded poorly to sulfonamides and rifampin.^{12–14} Furthermore, urethritis responded well to streptomycin or spectinomycin when *Ureaplasma sp.* were eradicated, but not when they persisted.¹³ In another study, NGU persisted 6–12 days after onset of minocycline therapy significantly more often in men infected with tetracycline-resistant *Ureaplasma sp.* than in those infected with tetracycline-sensitive strains, and persistent NGU correlated with persistence of the tetracycline-resistant strains.²² Root et al. also demonstrated that there was a strong correlation between tetracycline resistance of *Ureaplasma sp.* and the persistence of the organism after tetracycline treatment.²³ In contrast to these results, the evidence for the involvement of *Ureaplasma sp.* in PGU is very weak.^{11,24,25}

Intraurethral inoculation of *Ureaplasma sp.* has been performed in two men and several nonhuman primates. The first man developed dysuria and frequency of urination, associated with pyuria and positive cultures for *Ureaplasma sp.*²⁶ Symptoms and signs disappeared with eradication of the *Ureaplasma sp.* by minocycline. The second man developed PMNL-containing mucus threads in his urine, which persisted after minocycline treatment despite the eradication of *Ureaplasma sp.*²⁶ Intraurethral inoculation of *Ureaplasma sp.* into nonhuman primates has resulted in colonization of the urethra for various periods of time, and it has been associated with increased numbers of PMNL in the endourethral smear in some animals.^{27,28}

Despite the evidence cited earlier, confusion has persisted concerning the role of *Ureaplasma sp.* in NGU. This has resulted largely from the relatively uniform finding in NGU survey studies among men at high risk for STDs that *Ureaplasma sp.* are found as often among controls as in cases. Case-control studies of the association of *Ureaplasma sp.* with NGU must account for the fact that urethral colonization is common in men without urethritis, and is strongly correlated with the total number of female sex partners.²⁹ In general, *Ureaplasma sp.* are isolated more often from patients with NGU than from control groups when the control group is less sexually active than the NGU group, but not when the sexual activity of the two groups is comparable (reviewed by McCormack et al.³⁰).

As noted earlier and discussed in greater detail in Chapter 41, the genus *Ureaplasma* is now known to contain two species, *U. urealyticum* and *U. parvum*. The latter is named “parvum” as its genome size is significantly smaller than that of *U. urealyticum*. Limited studies have suggested that *U. urealyticum* but not *U. parvum* is associated with NGU. Deguchi et al. found *U. urealyticum* in 18% of men with chlamydia-negative NGU compared to 7.3% of controls while *U. parvum* prevalence was 9.9% and 13.2%, respectively.³¹

Povlsen used a different polymerase chain reaction (PCR) assay and found that *U. urealyticum* was associated with NGU, but after multiple regression analysis, the *p* value was only 0.15.³² Another study utilizing molecular genotyping has suggested that only a subpopulation of *U. urealyticum* is actually associated with NGU.³³ These data combined with those from the earlier studies cited before support a role for *U. urealyticum* as a cause of NGU and suggest that *U. parvum* is a colonizer. However, it appears that the organism causes only a small proportion of chlamydia-negative NGU cases. Clearly, there is a need for further research to better understand the role of *Ureaplasma* sp. in urethritis and hopefully this will be forthcoming over the next few years.

In contrast to the strong association between PGU and *C. trachomatis*, the association between PGU and *Ureaplasma* sp. is weak. Among *C. trachomatis*-negative men with gonorrhea who received treatment with penicillins, which are not active against mycoplasmas, PGU developed in 11 (61%) of 18 who had *Ureaplasma* sp., compared with 5 (28%) of 18 without *Ureaplasma* sp. infection (*p* = 0.09).²⁴ In two other studies involving cultures for *C. trachomatis* and *Ureaplasma* sp., *Ureaplasma* sp. were not shown to be associated with PGU.^{11,25}

The greatest advance in our understanding of the etiology of urethritis over the last 15 years has been the unequivocal establishment of the important role of *M. genitalium* in NGU. *M. genitalium* was first implicated as a cause of NGU in 1981.³⁴ Further understanding of the role of this organism had to await the advent of modern DNA amplification technology as this organism is very difficult to grow in vitro. Early studies using the PCR assay showed that *M. genitalium* is present in as many as 25% of men with NGU,^{35,36} but it is present in only 6% of normal men.³⁷ These data have withstood the test of time and a number of studies supporting these early observations have been reported since publication of the last edition of this book as reviewed by Jensen (see Fig. 41-1 in Chapter 41).³⁸ Combining the data from 19 studies, the percentage of patients with NGU harboring *M. genitalium* is 21.1% as compared to 6.7% in controls without NGU. The pooled odds ratio for this difference is 3.8 (95% confidence interval 3.0–4.9) For combined chlamydia-negative NGU cases, the *M. genitalium* prevalence is 21.7% compared to 6.0% for a pooled odds ratio of 5.15 (95% confidence interval 3.6–7.4). Clearly, *M. genitalium* is a cause of a significant number of the NGU cases that were referred to as “etiology unknown” in the last edition of this chapter. At least, in part, *M. genitalium* may explain why nonchlamydial NGU cases appear to respond less well to treatment than cases caused by *C. trachomatis* (see the section on therapy for more details). Finally, based on genotyping analyses of concurrently infected couples, there is now strong evidence that *M. genitalium* is sexually transmitted.³⁹

■ TRICHOMONAS VAGINALIS

As reviewed by Krieger, numerous studies largely from Europe have suggested that *T. vaginalis* is a significant pathogen in men causing a variety of genitourinary syndromes including urethritis.⁴⁰ In many cases, these studies were not controlled or poorly controlled and results varied widely (see Chapter 43). In North American studies from the 1970s, the proportion of cases of NGU in which *T. vaginalis* was detected was small.^{11,41–43} For these studies, the diagnosis was entirely dependent on observing the organism by direct microscopy which is relatively insensitive or culture using a variety of media for which quality control was poor. However, in a cross-sectional study involving 447 men including 147 contacts to women with trichomoniasis and 300 randomly selected STD clinic clients, Krieger and colleagues convincingly demonstrated that the organism was associated with NGU. Among men with NGU in this study, 18% were infected with *T. vaginalis* compared to 8% of men without urethritis. Detection of *T. vaginalis* was optimized in this study by culturing both urethral secretions and urine in well-standardized Diamond’s medium.^{44,45} Though data accumulated over last decade largely based on PCR assays have supported these findings, the magnitude of the contribution of *T. vaginalis* is, if anything, even less clear. In another culture-based study, evidence was presented that the older the NGU patient, the more likely it was that *T. vaginalis* may have been the cause of the problem.⁴⁶ However, in a population-based study in Africa, Watson-Jones et al. showed that asymptomatic male carriage rates of *T. vaginalis* also increased significantly with age.⁴⁷

The advent of PCR assays for the diagnosis of *T. vaginalis* infection has shown that the organism is found frequently in the urethra of both symptomatic and asymptomatic men. Schwebke and Hook found *T. vaginalis* in 17% and 13% of men with urethral symptoms and urethral inflammation, respectively, but also found it in 14% of asymptomatic men and 11% of men without Gram stain evidence of inflammation.⁴⁸ Wendel et al. found *T. vaginalis* in 17% of urethritis cases and 12% of those without evidence of disease.⁴⁹ The differences between cases and controls were not significant in both studies.

The prevalence rate of *T. vaginalis* among African women is high suggesting that *T. vaginalis* might play an even greater role in African men with NGU. *T. vaginalis* PCR assays have been used to address this question in several recent studies. Rates in NGU or nonchlamydial NGU varied from 15% to 23% while rates in controls varied from 6% to 11% and these differences were highly significant. Unfortunately these studies utilized controls from settings very different than those where cases were enrolled and it is possible that STD risk factors differed significantly between cases and controls. Therefore, the true relative risk of *T. vaginalis* infection in symptomatic versus asymptomatic men in these studies cannot be estimated.^{50–52}

In summary, while it seems clear the *T. vaginalis* is a cause of urethritis in men, the relative contribution of the organism to urethritis-associated morbidity is difficult to estimate especially now that recent studies have found high carriage rates in men without urethritis drawn from the same populations as the cases. Additionally, these studies have shown high coinfection rates between *T. vaginalis* and the other known urethral pathogens further complicating the task of estimating the contribution of *T. vaginalis* to incident urethritis case rates.

As can be seen in Table 59-3, in a series of recent studies the median percent of NGU cases that are *C. trachomatis*-positive is 30% compared to 19% for *M. genitalium*. Though the data as yet are incomplete and are subject to the limitations discussed in the paragraph above, 10–20% of NGU cases are at least associated with *T. vaginalis*. Based on two studies that met criteria for inclusion in Table 59-3 and which included *U. urealyticum* as diagnosed by a new, specific PCR assay, this

organism may account for about the same number of NGU cases as does *T. vaginalis*. New studies of urethritis utilizing well-standardized NAATs for all four of these pathogens are needed to understand clearly the relative contribution of each to the NGU syndrome. Moreover, such studies should define more precisely the proportion of cases for which the causative agent or agents remain to be discovered.

■ OTHER CAUSES OF NGU

As noted earlier, despite recent advances in our understanding of the etiology of NGU, there remains a significant proportion of urethritis cases in heterosexual males for which the etiology is unknown. Moreover, in the majority of NGU cases in MSM, the etiology is unknown.⁸

Most studies of the aerobic and anaerobic urethral flora excluding the mycoplasmas have not yet revealed significant differences between *C. trachomatis*-positive and

Table 59-3. Etiology of NGU in Studies Published Since 1992

Country	Year	# NGU cases	<i>C. trachomatis</i>	<i>M. genitalium</i>	<i>T. vaginalis</i>	<i>U. urealyticum</i>	None	GC Rate ^c	Ref.
UK	1993	96	40% ^b	23%	nd	nd	44%	nd	37
Denmark	1993	48	29%	27%	nd	nd	46%	8%	35
Japan	1998	74	55%	13%	nd	nd	31%	51%	139
Malawi	1999	61	0%	nd	23%	nd	77%	66%	50
Italy	2000	178	39%	30%	nd	nd	47%	nd	140
Sweden	2000	115	36%	15%	nd	nd	50%	nd	141
Denmark	2000	50	28%	26%	nd	nd	46%	7%	142
USA	2001	121	30%	22%	2%	nd	48%	nd	68
W. Africa ^a	2001	251	21%	19%	18%	nd	42%	62%	52
S. Africa	2002	96	16%	17%	nd	nd	67%	47%	143
USA	2002	52	38%	31%	nd	nd	44%	46%	83
Japan	2003	317	49%	13%	nd	16%	34%	45%	31
USA	2003	151	25%	nd	20%	nd	60%	nd	48
Sweden	2004	271	22%	12%	nd	nd	63%	1%	144
S. Africa	2004	45	64%	18%	11%	nd	16%	79%	145
Australia	2006	329	20%	9%	<1%	13%	58%	nd	69

Papers were chosen for inclusion in the table based on the following criteria: (1) Study published in the last 15 years. (2) GU clearly differentiated from NGU and at least one other putative NGU pathogen other than *C. trachomatis* was studied. (3) The data were presented in such a way that organism prevalence in NGU cases could be calculated. Urethritis was defined differently in several of the studies. Organisms were identified using NAATs in most of these studies.

^aSeven West African countries were involved in this study.

^bPercents exceed 100% as multiply infected cases are included two or three times.

^cFor studies in which the data were provided, this figure represents the proportion of urethritis cases attributable to *N. gonorrhoeae* seen in the facilities where each study was conducted (nd: data not available).

C. trachomatis-negative patients with NGU.^{41,53} Early studies suggested a possible role for *Bacteroides ureolyticus*,^{54,55} but more recent work has not demonstrated this organism more frequently among men with NGU than among normal men.⁵⁶ *Haemophilus influenzae* and *Haemophilus parainfluenzae* appear to cause urethritis infrequently.^{57,58} Similarly, coliforms may cause a few cases of urethritis in MSM.⁵⁹ *Neisseria meningitidis* has been reported as a cause of urethritis relatively more often in areas such as Western Europe where the incidence of gonorrhea has dropped to very low levels. Today, men with urethral smears positive for Gram-negative diplococci in these countries may be relatively likely to have an infection caused by this organism in view of the rarity of *N. gonorrhoeae*.^{60,61} Oral-genital sex is the presumed mode of transmission. This hypothesis has been strengthened recently by the isolation of an *N. meningitidis* strain from the pharynx of a woman which matched the strain isolated from her symptomatic male partner as determined by pulsed field gel electrophoresis.⁶²

Recently, molecular approaches to the study of vaginal flora have revealed a number of previously unknown organisms such as *Atopobium vaginae* that are important members of the genital tract bacterial ecosystem.^{63,64} Many of these organisms are most closely related to strict anaerobes and some have never been cultivated. Keane et al. showed an association between NGU in males and bacterial vaginosis in their partners suggesting the possibility that one or a combination of the organisms associated with this syndrome could infect their male partners resulting in urethritis.⁶⁵ Molecular methods have been applied to a few patients with NGU and controls and, indeed, there is at least one unknown organism that is present in symptomatic men and not in controls.⁶⁶ More extensive investigations focusing specifically on the organisms now known to be associated with bacterial vaginosis is likely to advance our understanding of nonchlamydial NGU.

Only two viruses have been implicated as a cause of male urethritis. Urethritis occurs in approximately 30% of men with primary genital herpes simplex virus (HSV) infection and in a much lower percentage of men with recurrent genital HSV infection.⁶⁷ Most, but not all, such patients have penile lesions. HSV was not isolated at higher frequency from the urethra of men with NGU than from controls in two older studies.^{11,42} Two recent studies using PCR assays were similar in that HSV was detected in 2–3% of cases.^{68,69} However, only the Bradshaw et al. study had sufficient numbers of patients enrolled to demonstrate a significant difference between cases and controls. In this study, HSV-1 was more common than HSV-2 and unprotected oral sex was a major risk factor.⁶⁹

Adenoviruses were first reported in men with urethritis in Perth, Australia.⁷⁰ Swenson et al. reported isolating adenovirus from 0.3% of 7000 patients attending the Seattle STD clinic and other health department clinics. Of 20 infected

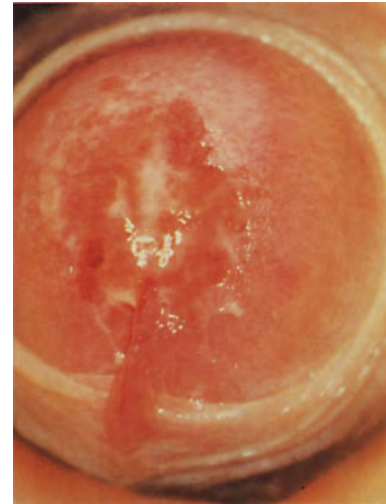


FIGURE 59-1. NGU and meatitis associated with Stevens–Johnson syndrome due to *Mycoplasma pneumoniae* pneumonitis. NGU also occurs as a manifestation of other systemic diseases, such as Reiter’s syndrome.

men, 75% had urethritis.⁷¹ Six additional cases were reported more recently from New Zealand.⁷² Bradshaw et al. studied 329 NGU cases and compared them to 307 controls in the Melbourne, Australia, Sexual Health Center. Adenovirus was identified in 4% of cases and only 0.3% of controls thus providing strong support for the addition of this virus to the list of urethral pathogens in men.⁶⁹ In summary, both HSV, especially type 1, and adenovirus appear to be causes of NGU though the proportion of cases is small.

■ NONSEXUALLY TRANSMITTED CAUSES OF NGU

The proportion of cases of NGU that are not sexually transmitted has not been defined since *C. trachomatis* was recognized as a cause of NGU. Bacterial urethritis may occur in association with urinary tract infection, bacterial prostatitis, urethral stricture, phimosis, and secondary to catheterization or other instrumentation of the urethra. In fact, a recent study from England suggested that as many as 6% of clinical NGU cases actually have a urinary tract infection.⁷³ Urethritis is also described with congenital abnormalities, chemical irritation, and tumors. Allergic etiologies have been postulated, but the supporting evidence is very meager. Similarly, there is no proof as yet that repeated stripping of the penis, masturbation, use of caffeine and alcohol, too little or too much sexual activity, or eating of certain foods will result in urethritis. Stevens–Johnson syndrome may produce urethritis (see Fig. 59-1).

EPIDEMIOLOGY

Details for the epidemiology of the various organisms causing male urethritis may be found in the chapters devoted to each. Surveillance of urethritis as a syndrome generally is not done.

France is an exception. There, a network of primary care providers reports urethritis cases to a national database. Nationwide, the annual incidence of urethritis dropped from 630 cases per 100,000 males older than 14 years to 180 cases between 1989 and 1995 and then rose to 270 cases per year between 1996 and 1998. Thereafter, the incidence rate has remained relatively stable.⁷⁴ GU is not differentiated from NGU in this surveillance system. Data from individual studies show that the relative proportion of GU cases versus NGU cases is strikingly different in different parts of the world. As can be seen in [Table 59-3](#), which is based on recent studies of urethritis, GU is now uncommon in the Scandinavian countries while it predominates as a cause of urethritis in Africa. There have been no recent studies from the United States comparing GU rates to NGU rates, but generally areas with high STD rates tend to see relatively more GU cases than those such as the Northwest where gonorrhea is less common. In individual STD clinics during the 1970s, the relative proportion of cases of urethritis that were nongonococcal varied from 19% to 78%,⁷⁵ and, on college campuses, more than 85% of urethritis was nongonococcal.⁷⁶

For both gonorrhea and NGU, the peak age group affected is 20–24 years, followed by 15–19 years, and then 25–29 years. Some behavioral and demographic characteristics of men with gonorrhea and NGU differ, but not to the extent that the differences are diagnostic in individual cases. In a comparison between 113 men with NGU and 69 men with urethral gonorrhea, those with NGU were more often white, better educated, more likely to be students and less likely to be unemployed, members of a higher socioeconomic stratum, older at the age of first intercourse, and involved with fewer total sex partners.¹¹ A history of previous gonorrhea was more frequent among men who had gonorrhea, while a history of NGU was more frequent among men with NGU.^{11,77} Men with two or more previous episodes of NGU have a lower isolation rate of *C. trachomatis* than those with one or no previous episode.¹⁷ Unfortunately, data comparing the epidemiology of gonorrhea in men and NGU more recent than the 1970s are not available.

CLINICAL MANIFESTATIONS

■ EXAMINATION OF THE MAN WITH URETHRITIS

A thorough examination is helpful in guiding appropriate therapy for all patients with STDs including urethritis. Details of the male examination are provided in a separate chapter (see Chapter 50). The quantity of discharge may be categorized as profuse (spontaneously flowing from the urethra), scant (apparent only after stripping the urethra), and intermediate (between profuse and scant). Unless an attempt has been made to “strip” or “milk” the urethra, it cannot be said that there is no discharge. The color or character of the

discharge should be noted. A yellowish color (most common) or greenish color (seen only occasionally) can be described as “purulent.” A grey or white discharge often mixed with clear fluid should be labeled “mucoid” or “mixed.” The third category is “clear.” The presence or absence of meatal inflammation (meatitis) should be noted. Finally, the presence or absence of penile edema and enlarged inguinal lymph node should be determined.

Although it is usually not done in practice, when patients give a history of dysuria and/or urethral discharge but a discharge is not detected, the patient should be examined the next morning, after not voiding overnight, to enhance the likelihood of reaching a firm diagnosis.⁷⁸ In a study by Simmons in an STD clinic, 200 men with genitourinary symptoms in whom no firm diagnosis was made on the first visit were asked to return for reexamination in the morning prior to voiding. Among these men, 108 infections were confirmed; 5 had gonorrhea and 103 had NGU.⁷⁸ Another study of symptomatic men with few or no PMNL on urethral smear also showed the value of repeat examination after a longer interval without voiding.⁷⁹ Furthermore, in that study, using pyuria as the criterion for urethritis, almost 80% of men with *C. trachomatis* had urethritis, whereas only one-third of symptomatic men without *C. trachomatis* had pyuria at the initial or on repeat visits. This approach is probably most useful in ruling out urethral inflammation as a cause of symptoms in a patient with chronic or multiply recurring urethritis or with minimal complaints. In practice, most clinicians treat patients complaining of dysuria and/or discharge as if they have urethritis regardless of the physical findings because of the difficulty of getting the typical STD client back for another examination and the increased probability of infection despite lack of objective evidences of urethritis.⁷⁸ The downside of this approach is overtreatment with antibiotics and potential problems with partner treatment.

■ COMPARISON OF THE CLINICAL PRESENTATION OF GU AND NGU

The symptoms and signs of GU and NGU are similar, but differ significantly in severity though there is a great deal of overlap. Both may cause urethral discharge, dysuria, or urethral itching. Discharges are more profuse and usually purulent in men with gonorrhea, but are generally scant and mucoid in men with NGU (see [Figs. 59-2](#) and [59-3](#)). Especially with NGU, discharge may be detected only in the morning or noted as crusting at the meatus or as staining on underwear. Frequency, hematuria, and urgency are infrequent with either infection. The usual incubation period is also shorter with gonorrhea. Gonorrhea usually develops 2–6 days after exposure, whereas NGU generally develops between 1 and 5 weeks after the likely time of acquisition of infection, with a peak at around 2–3 weeks. Longer incubation periods for both



FIGURE 59-2. GU. Note profuse purulent urethral discharge and meatal erythema.

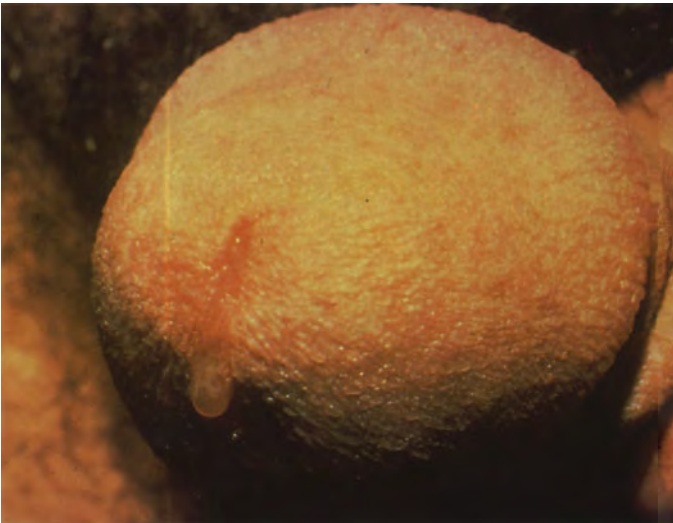


FIGURE 59-3. Chlamydial urethritis. Note the scant minimally purulent urethral discharge.

infections are seen, however, and a significant proportion of both groups of men remain asymptomatic.

In one study, 71% of 185 men with gonorrhea, but only 38% of 214 men with NGU, complained of both discharge and dysuria.⁷⁷ All but one man with urethral gonorrhea had urethral discharge, but 19% of men with NGU did not. Men with gonorrhea had a more abrupt onset and sought medical care sooner. More than three-fourths of the men who had gonorrhea, but less than one-half of those who had NGU, sought treatment within 4 days of onset of symptoms.⁷⁷

■ CLINICAL MANIFESTATIONS OF NGU CAUSED BY ORGANISMS OTHER THAN *CHLAMYDIA TRACHOMATIS*

In urethritis caused by HSV and adenovirus, dysuria is usually severe, significantly more so than that reported on average by

men with bacterial NGU.^{69,80–82} Despite the severity of dysuria, discharge is scant and mucoid or clear rather than purulent. Most men with viral urethritis also present with meatitis, which is seen in a minority of cases caused by bacteria. O'Mahony has published an excellent color photograph of adenovirus-associated meatitis.⁸¹ Adenovirus cases tend to occur in the fall and winter and are often associated with conjunctivitis.^{69,72,80–82} Regional lymphadenopathy and constitutional symptoms may be seen with primary HSV urethritis.⁸²

Kreiger presented detailed comparisons of the clinical manifestations of gonococcal, chlamydial, and trichomonal urethritis.⁴⁵ Only 55% of men with trichomoniasis had a discharge on examination compared to 82% of men with chlamydial infection and 93% of those with gonorrhea. The discharge caused by *N. gonorrhoeae* was almost always moderate to large in amount and was purulent in nearly 80% of cases. In contrast, the discharges associated with chlamydial and trichomonal infections were virtually indistinguishable with almost all patients having small or moderate amounts that were either clear or mucoid in character.

Relatively few studies have provided detailed clinical descriptions of *M genitalium*-associated urethritis. Based on the available data, however, it appears that this organism causes relatively mild disease and is indistinguishable from chlamydial urethritis.^{51,68,83}

■ ASYMPTOMATIC URETHRAL INFECTION

It is important to recognize that asymptomatic urethral, gonococcal, and chlamydial infections in males are relatively common, especially the latter. These asymptomatic cases constitute a large reservoir of undetected infection in the general population. As shown in Table 59-2, the rate of isolation of *C. trachomatis* is lower in asymptomatic controls, but still substantial should they be representative of the male population as a whole. However, population rather than clinic-based studies are necessary to estimate the true burden of asymptomatic infections. In three studies, *C. trachomatis* was isolated from 11% of asymptomatic soldiers, 11% of asymptomatic men attending an urban emergency department, and 7% of asymptomatic college students.^{84–86} More recent studies have used NAATs for chlamydial diagnosis rather than culture. Cecil et al. studied urine specimens in 2245 United States Army recruits and found that 4.6% had asymptomatic *C. trachomatis* infection and 0.2% had asymptomatic gonococcal infection. In a clinic-based study of MSM in San Francisco, it was found that 2.7% of nearly 5000 men had asymptomatic urethral *C. trachomatis* infections. Forty-two percent of all chlamydial urethral infections detected in this population were asymptomatic.⁸⁷ Among male contacts of infected women, Thelin et al. detected *N. gonorrhoeae* in 78% of male contacts of women with gonorrhea, and they detected *C. trachomatis* in 53% of male contacts

of women with *C. trachomatis*.⁸⁸ Only 50% of the male partners infected with either organism were symptomatic.⁸⁸

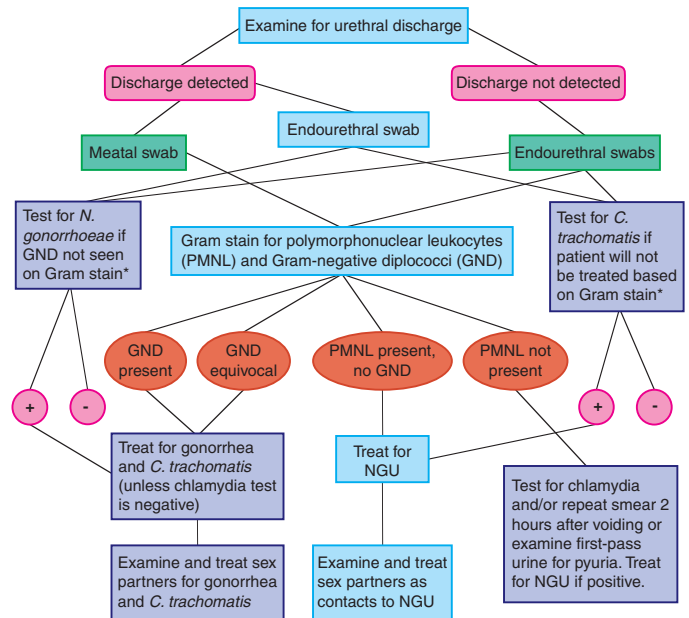
Clearly, a large reservoir of asymptomatic male urethral infection exists in the general population. The possibility of asymptomatic infection in the male partner should always be discussed with women who are being treated for proven or suspected chlamydial and gonococcal infections. Otherwise, male partners who believe they cannot have an STD unless they have symptoms are not likely to seek therapy.

OTHER MANIFESTATIONS OF URETHRITIS

Other manifestations of urethritis are unusual. A small proportion of patients with gonococcal or chlamydial urethritis will have conjunctivitis caused by *N. gonorrhoeae* or *C. trachomatis*, especially the latter, probably as a result of autoinoculation. Epididymitis develops infrequently today. Some patients with NGU present with the reactive arthritis syndrome (formerly known as Reiter's syndrome), or they develop it soon after their initial presentation. Inguinal lymphadenopathy is unusual, though it is occasionally seen in men with gonorrhea and a severely inflamed urethra. Severe gonorrhea may also produce edema of the foreskin and/or edema of the penile shaft. Rarely, a periurethral abscess involving the penile shaft may develop.⁸⁹ In the pre-antibiotic era, it was said that prostatitis was a frequent complication of gonorrhea, but this is not the case today. In a study by Holmes et al.,¹¹ prostatic enlargement or tenderness was not significantly more common among patients with NGU (13%) than among those with gonorrhea or with no urethritis (4%). If present, it was always of minimal severity. Symptoms of hematuria, chills, fever, frequency, hesitancy, nocturia, urgency, perineal pain, scrotal masses, postvoid dribbling, or genital pain other than dysuria or urethral pain are not typical of urethritis; these suggest the presence of other genitourinary abnormalities such as classic urinary tract infection, acute prostatitis, a flare-up of chronic prostatitis, or acute epididymitis or orchitis.

DIAGNOSIS

In men with symptoms of urethritis, the diagnosis of gonorrhea requires demonstration of *N. gonorrhoeae* by Gram stain, culture, or a reliable nonculture technique. The diagnosis of NGU requires exclusion of urethral infection with *N. gonorrhoeae* by microscopic examination of stained urethral secretions and objective demonstration of urethritis based on the presence of an abnormal discharge on examination and/or demonstration of PMNL in the urethral smear (Fig. 59-4, Table 59-4). Though there are now many reliable nonculture tests available for the diagnosis of *C. trachomatis*, unfortunately, there are no sufficiently sensitive point-of-care tests such as the Gram stain available for this organism (see Chapters 32 and 52).



*In many public health clinics, testing is performed on all or most patients for surveillance purposes.

FIGURE 59-4. Initial diagnosis and management in men with suspected urethritis.

CRITERIA FOR THE DIAGNOSIS OF URETHRITIS

For research purposes, the criteria used for diagnosis of urethritis in some of the first studies included presence of urethral discharge and of 20 or more PMNL in two or more of five random $\times 400$ microscopic fields of the sediment of the first 10–15 mL of urine collected when the patient has not voided for 4 hours or longer.¹² In a study of men with minimal or no discharge, there was a bimodal distribution of the numbers of PMNL in Gram-stained urethral specimens and in the first-voided urine; the presence of 15 or more PMNL in any of five random $\times 400$ microscopic fields of the sediment of the first-voided urine correlated with a mean of more than four PMNL per field in five $\times 1000$ oil-immersion fields in Gram-stained specimens of urethral exudate.⁹⁰ Swartz et al. independently concluded that a mean of more than four PMNL per oil-immersion field on urethral smear correlated with urethritis.⁵³ In that study, there was more of a continuum from normal to abnormal. Thus, the criterion of ≥ 5 PMNL in at least five oil immersion microscopic fields became the more commonly used laboratory component of the definition of urethritis in the male.

Subsequent studies among symptomatic men with minimal or no urethral discharge showed similarly strong correlations between the Gram stain and the first-voided urine sediment.⁷⁹ However, *C. trachomatis* was isolated from some men when neither the urethral Gram stain nor the first-voided urine sediment contained PMNL. In many

Table 59-4. Management of Urethritis

<ol style="list-style-type: none"> 1. Establish presence of urethritis <ol style="list-style-type: none"> a. Examine for urethral discharge b. Gram-stain urethral secretions for PMNL c. Reexamine if necessary in a.m. prior to voiding 2. Establish presence or absence of <i>N. gonorrhoeae</i> <ol style="list-style-type: none"> a. Gram stain b. Culture or nonculture test for <i>N. gonorrhoeae</i> if Gram stain is negative 3. Diagnostic test for <i>C. trachomatis</i> (optional) 4. If gonorrhea, treat with ceftriaxone 125 mg im or a single, oral dose of cefixime 400 mg, ciprofloxacin 500 mg, ofloxacin 400 mg, 	<p>or levofloxacin 250 mg plus a single 1 gram dose of azithromycin or 7 days of doxycycline 100 mg p.o. twice daily. (see text for special considerations concerning quinolone resistance)</p> <ol style="list-style-type: none"> 5. If NGU, treat with a single 1 gram dose of azithromycin or 7 days of doxycycline 100 mg p.o. twice daily. 6. Evaluate and treat partner(s) appropriately—generally with same regimen used to treat the patient with urethritis, or guided by results of additional diagnostic tests. 7. Follow-up examinations (optional—usually not done) <ol style="list-style-type: none"> a. 3–5 days after completing therapy with gonorrhea b. 2–4 weeks after completing therapy for NGU
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other *C. trachomatis*-positive men, only the urine or the smear, but not both, showed increased PMNL. In another study, Root et al. noted that 7 of 18 *C. trachomatis*-positive men had five or fewer PMNL in “several representative fields” on urethral Gram stain.²³ More recent studies using NAATs for diagnosis demonstrated even greater proportions of infected men among those not meeting laboratory criteria for urethritis.^{36,69,91}

Semiquantization of PMNL in urine or in stained smears is very much dependent on the skills and/or diligence of the microscopist. This fact no doubt explains much of the performance variation of the PMNL criterion for the diagnosis of urethritis reported in the literature.⁹² Thus, the use of smears or urines to provide objective evidence of urethritis is only a rough guide to the presence of urethral pathogens. Therefore, for both *N. gonorrhoeae* and *C. trachomatis* in men with minimal or no evidence of urethritis, a sensitive diagnostic test is necessary to rule out infection. This is reflected in the urethritis diagnostic algorithm presented in Fig. 59-4.

In men who are symptomatic without objective evidence of urethritis (i.e., either discharge on examination or the presence of PMNL in the stained urethral smear), nonsexually transmitted causes of urethritis-like symptoms such as urinary tract infection should be considered. However, before initiating a more extensive evaluation for such problems, further evaluation for urethritis should be done. The patient should be reexamined in the morning without having voided overnight. The urethra should be stripped from the base to the meatus three or four times to detect urethral discharge. For Gram stain, any expressible urethral exudate can be obtained with a swab from the urethral meatus. When discharge is minimal or absent after an attempt to express discharge, a

thin urethral swab should be inserted 3–4 cm into the urethra. The patient should be warned that the procedure is moderately painful and that the next urination will also be painful. The swab is then rolled gently back and forth over a glass slide to cover an area of approximately 1 cm². The slide is Gram-stained and scanned at a magnification of $\times 100$. Areas that have the largest numbers of PMNL are examined under oil ($\times 1000$), and the number of PMNL in each of five such fields is recorded. While the PMNL are being enumerated, the slide should also be examined for gram-negative diplococci. For research purposes or for patients in whom the establishment of objective evidence of inflammatory urethritis is especially important (i.e., the male with recurrent urethritis), examination of a first-voided urine specimen is worthwhile. To detect PMNL in urine, the first 10–15 mL of urine voided should be collected and centrifuged at $400 \times g$ for 10 minutes. All but 0.5 mL of the supernatant is decanted, and the sediment is resuspended in the residual urine. Sufficient sediment is placed on a slide to cover an area of approximately 1 cm², and a coverslip is placed on the slide. The area under the coverslip is examined at a magnification of $\times 400$, and the number of PMNL in each of five randomly selected fields is enumerated. Based on two studies about half of the men having such follow-up evaluations, either GU or NGU will be confirmed.^{78,79} Those without clear evidence of urethritis can then be referred for further evaluation.

■ LABORATORY DIFFERENTIATION BETWEEN GONORRHEA AND NGU

Although clinical suspicion that a patient with urethritis has either gonorrhea or NGU may be strong, the final distinction

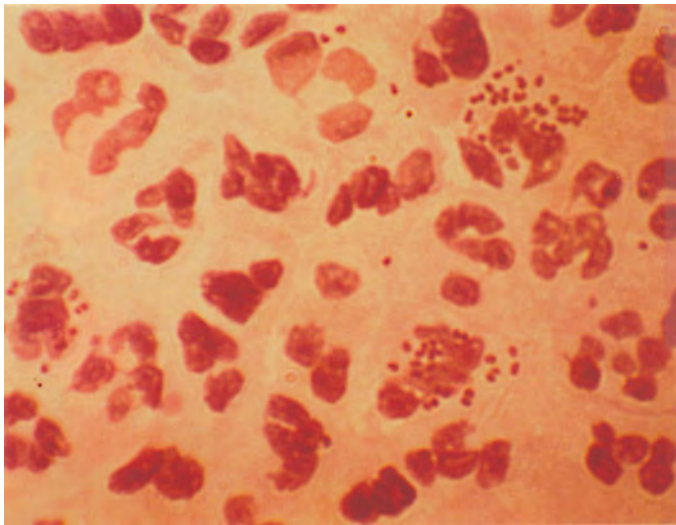


FIGURE 59-5. Gram stain of GU, showing number of gram-negative intracellular diplococci.

requires laboratory examination to determine if *N. gonorrhoeae* is present. The most rapid and least expensive procedure is microscopic examination of stained urethral exudate or material obtained with an endourethral swab. For experienced microscopists, the sensitivity, specificity, and positive predictive value of the finding of typical gram-negative diplococci inside the PMNL for the diagnosis of gonorrhea are close to 100% in men with urethritis (see Fig. 59-5). A simple, one-step procedure using a stain such as methylene blue probably works equally well, though careful comparative studies have not been done. This procedure relies solely on morphologic characteristics, since color differences are not obtained with the single staining reagent. It should be noted that in most clinical settings there is insufficient time to enumerate PMNL carefully in the urethral smear. Therefore, most clinicians accept the presence of any PMNL in smears from symptomatic men as adequate support for the diagnosis of NGU (see Fig. 59-6). Thus, in a symptomatic case where the urethral smear contains increased numbers of PMNL, gonorrhea can be differentiated from NGU at the initial visit, and specific therapy can be given. Since the Gram stain misses up to 5% of gonococcal infections in men with urethritis under usual clinical circumstances, patients clinically diagnosed as having NGU on the basis of Gram stain should undergo further testing for *N. gonorrhoeae*. Specific tests for the agents known to cause NGU will not influence therapeutic decisions at this point. When Gram-stained specimens are interpreted as being equivocal, with only extracellular typical or intracellular atypical gram-negative diplococci being detected, cultures for *N. gonorrhoeae* have been positive in 25%.⁷⁷ Such patients should be treated for gonorrhea (see Fig. 59-1), but cultures or DNA-based tests will establish the diagnosis definitively. Cultures are

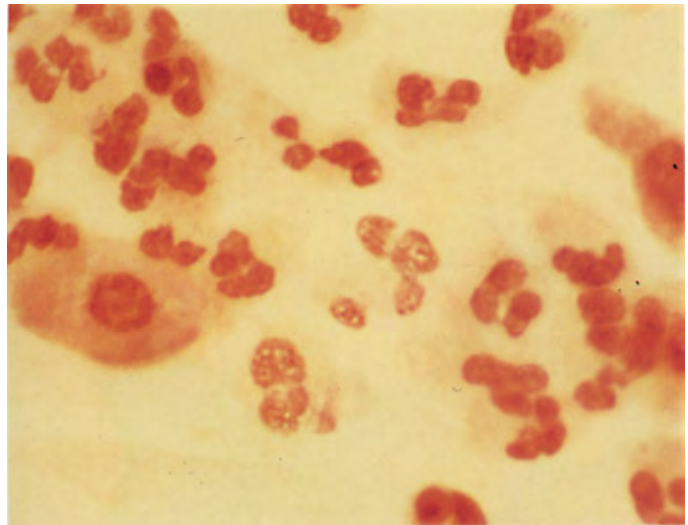


FIGURE 59-6. Smear from NGU. Note the presence of both PMNL and occasional mononuclear leukocytes in the absence of gram-negative diplococci.

necessary in cases that are positive by Gram stain when prior treatment has failed. The laboratory should be alerted that antibiotic resistance may be a problem, so that the organism can be referred to a laboratory that is able to perform susceptibility testing.

■ DETECTION OF SPECIFIC AGENTS ASSOCIATED WITH NGU

Specific diagnosis of *C. trachomatis* urethritis requires culture or detection by a nonculture technique (see Chapters 23 and 52). While the diagnosis may be confirmed in some cases serologically, this approach is not practical.¹² Because *C. trachomatis* is an intracellular parasite of columnar epithelial cells, the preferable specimen is endourethral material rather than urethral exudate. NAATs have been studied extensively for the diagnosis of *C. trachomatis* infections over the last decade and there are several of these that were cleared by the FDA for clinical use (see Chapters 32 and 52 for details). However, in most clinical circumstances, identification of *C. trachomatis* as the cause of NGU is not necessary, as recommended antibiotic therapy currently is the same for both chlamydia-positive and chlamydia-negative disease (see Fig. 59-4). Furthermore, it is recommended that the partners of men with NGU be treated regardless of the etiology. As with the gonococcus, a specific diagnosis of *C. trachomatis* may be useful for the purposes of surveillance, partner notification, and may be desired by some patients who wish to know the specific etiology of their disease. The issue of who is paying for the test is often the deciding factor here. Diagnostic tests for *U. ureaplasma*, *M. genitalium*, and *T. vaginalis* either lack sensitivity or specificity or are for research use only at this point.

THERAPY

■ DUAL THERAPY FOR URETHRITIS: SYNDROMIC MANAGEMENT AND GONORRHEA

In many parts of the world, and in many smaller public health and primary care clinics, specific diagnostic tests for urethral pathogens are not available. Unfortunately, as noted previously, the clinical presentation is not adequately specific to differentiate between the causative organisms. In these circumstances, treatment should be based on the pathogens most likely to result in long-term sequelae, namely, *N. gonorrhoeae* and *C. trachomatis*. While this approach seems intuitively correct, clinicians in the past frequently attempted to provide specific therapy based on their clinical impressions. In many cases, this resulted in inadequate treatment and continued chronic infection with one pathogen or the other. Recently, increased emphasis has been placed on “syndromic management” of STDs as an alternative to specific disease treatment, particularly in resource-poor settings (see Chapters 48 and 102). In a study of syndromic management of all STD syndromes, this approach decreased rates of HIV transmission.⁹³

Since the late 1980s, STD treatment guidelines from the Centers for Disease Control and Prevention (CDC) have recommended dual-antibiotic therapy of men with GU for the syndromic management of urethritis.⁶ The primary rationale for this approach is that *C. trachomatis* is found in 15–40% of women with endocervical gonorrhea and 15–25% of men with GU. Providing effective therapy for *C. trachomatis* in these patients eliminates the major cause of PGU and also reduces the number of potential male carriers of *C. trachomatis* who would otherwise disseminate the organism to future sex partners. The hypothesis that this approach benefits society as a whole by decreasing the population prevalence of *C. trachomatis* is very reasonable, but it has never been tested. Nonetheless, decreases in the prevalence of *C. trachomatis* in the United States since this policy was put in place suggest that this policy may have had the desired effect, though a variety of public health measures designed to control chlamydial infections were also instituted during this time. Another theoretical benefit of antibiotic therapy with two drugs active against *N. gonorrhoeae* is that it could slow the development of antibiotic resistance though this approach did not prevent the emergence of quinolone resistance in the United States.

Arguments against dual therapy include increased cost and higher adverse event rates. Since the added cost of doxycycline is small and experience does not suggest substantial increases in toxicity rates, on balance, the arguments favor dual-antibiotic therapy for GU in males. In areas such as Western Europe, where the incidence of both gonorrhea and chlamydial infections have decreased dramatically in the

past decade, the argument for dual therapy becomes less compelling.

Therapy for *N. gonorrhoeae* is described in detail in a separate chapter (see Chapter 35). The most convenient treatment is oral therapy with cephalosporins or quinolones. However, rising resistance rates to the latter worldwide including the United States is increasingly limiting the use of these drugs. Four hundred milligrams of cefixime orally as a single dose is an excellent choice but there are few companies that manufacture the drug resulting in unavailability in some regions of the world including the United States. Ceftriaxone given as a single 125 mg intramuscular dose is also highly effective for GU, but intramuscular administration is inconvenient and relatively expensive, since additional supplies and personnel time are required. There are two oral cephalosporins which studies have shown to be effective for treated GU, but the number of patients studied thus far has been relatively small. These are cefpodoxime proxetil and cefuroxime axetil.

Tetracycline, doxycycline, and azithromycin have been used most commonly as the antichlamydial component of dual-drug combinations for the syndromic management of male urethritis (see Chapter 32 for details). Doxycycline is easier to comply with than tetracycline as it is administered as two daily 100 mg doses with food, if desired, in contrast to tetracycline, which must be taken as 500 mg four times daily on an empty stomach. Alternatives to doxycycline or tetracycline that could be included as part of dual-treatment regimens are erythromycin, four times daily for a week, but the single 1 g oral dose of azithromycin is a much better alternative. There are few studies of dual-antibiotic therapy of urethritis, probably because there is little reason to doubt the efficacy of drugs already proven to be useful for treating *N. gonorrhoeae* and *C. trachomatis* infections individually. More data on tolerance would be helpful, though experience suggests that significant increases in adverse events have not been a problem. The combination of cefixime, 400 mg orally, and azithromycin, 1 g orally, given together for the treatment of GU has been evaluated in only one small pilot study; a relatively high rate of gastrointestinal toxicity was noted (HH Handsfield, personal communication).

Two drugs currently are approved in the United States for the treatment of both *N. gonorrhoeae* and *C. trachomatis*. Ofloxacin, 400 mg followed by 300 mg b.i.d. to complete a 7-day course, is effective for both organisms, as is azithromycin, 2 g as a single dose. However, cost and emerging antibiotic resistance have limited the use of the former while the single 2 g dose of azithromycin frequently causes gastrointestinal side effects.⁹⁴

It should be remembered that empiric dual-antibiotic therapy of urethritis in males requires that sex partners also be treated empirically for both organisms.

■ TREATMENT OF NGU

Results of treatment for NGU are not as good as for gonorrhea, even though almost every antimicrobial in clinical usage has been tried. In the 1950s, tetracyclines, erythromycin, and a combination of sulfonamides and aminocyclitols were recognized as being the most effective therapy for NGU. The basis for these observations was elucidated by subsequent research that showed that all three regimens were capable of eradicating *C. trachomatis*^{12,13,15,95} and had significant activity against the mycoplasmas. In compliant patients who were not reexposed to new or untreated partners, all but 5% of men showed definite and often total improvement by the end of treatment. However, in one study, among men who initially responded and were followed for 4–6 weeks posttreatment, 30–35% had a recurrence or incomplete resolution of pyuria.⁸ About one-half of these men had symptoms of urethritis. In this study, the critical determinant of response was the etiology of the NGU rather than the amount of drug given or the duration of therapy. Response to treatment was best in men infected with *C. trachomatis*, significantly worse in men infected with *U. urealyticum* alone, and significantly worse still in men from whom neither organism was initially isolated from urethral specimens.

In compliant patients, the high rates of recurrent urethritis or persistence following treatment for NGU are not due to failure to eradicate *C. trachomatis*. Tetracycline-resistant isolates of *C. trachomatis* have not been described. *Ureaplasma* sp. tetracycline resistance has been shown to be associated with treatment failure in one study done before it was known that the genus has two species rather than just one.²² Preliminary data suggest that *M. genitalium* is relatively resistant to the tetracycline class of antibiotics^{96,97} and that some strains may be resistant to the erythromycin class.⁹⁸ In an as yet unpublished randomized treatment study, we found that a 7-day course of doxycycline failed to eradicate *M. genitalium* in 20/31 (64%) of men with NGU who were examined at least once following treatment compared to a failure rate of 4/25 (16%) among men treated with a single dose of azithromycin (L. Mena, personal communication). These data clearly indicate a need for the development of better therapeutic approaches to NGU.

STD treatment guidelines from the CDC and the World Health Organization currently recommend doxycycline 100 mg twice daily for 7 days.^{6,7} A few investigators have concluded that longer courses of antimicrobial therapy are more effective than shorter courses.^{99–101} Holmes et al. showed that a 7-day course of tetracycline was more effective than a 4-day course,⁹⁹ and, in a nonblinded study, John showed that 21 days were better than 10 days, which, in turn, were better than 5 days.¹⁰⁰ Thambar et al. concluded that 3 weeks of triple tetracycline was better than 1 week of therapy, but patients on the longer regimen had a much shorter follow-up after

cessation of therapy—a critical problem, as discussed later.¹⁰¹ In contrast to these studies, others have not found a significant difference with longer courses of therapy.^{8,102,103} Grimble and Amarasuriya did not show any marked differences between results with 4- to 10-day regimens of several different tetracyclines.¹⁰² Helmy and Fowler had essentially identical results in a double-blind comparison between tetracycline, 500 mg four times daily for 7 days, and 250 mg four times daily for 14 days, and the results were also similar between 4- and 21-day regimens.¹⁰³ A double-blind comparison of two doses and two durations of minocycline has been performed in a study that included cultures for *C. trachomatis* and *Ureaplasma* sp.⁸ Overall, persistent or recurrent NGU within 6 weeks of initiation of therapy was seen in 32% of men. Prolonging therapy from 7 to 21 days delayed, but did not diminish, the rate of recurrence, and the use of 100 mg daily gave results that were as good as those obtained with twice-daily treatment. More recently, it has been shown that minocycline, 100 mg nightly for 7 days, was equal to doxycycline, 100 mg twice daily for 7 days, for the treatment of NGU.¹⁰⁴ Whether regimens employing a tetracycline class drug for less than 7 days would be effective for eradicating *C. trachomatis* and *U. urealyticum*, and for producing similar clinical responses in NGU, requires further study, but the weight of evidence argues strongly against treating for more than 7 days.

A single 1 g dose of azithromycin is the other most frequently recommended therapy for NGU and has the advantage of directly observed treatment thus eliminating compliance as an issue though studies have not shown benefit in terms of bacterial eradication as compared to multidose doxycycline. Martin et al. clearly demonstrated the efficacy of azithromycin, 1 g orally as a single dose, for uncomplicated chlamydial infections in women and men, including those with NGU.¹⁰⁵ Two small nonblinded studies suggested that single-dose azithromycin would be effective also for chlamydia-negative NGU.^{106,107} In a large randomized double-blind study of men with NGU regardless of etiology, Stamm et al. showed that the 1 g dose of azithromycin was equivalent to doxycycline, 100 mg twice daily for 7 days.¹⁰⁸ In this study, both chlamydia-positive and -negative cases did equally well with azithromycin. Azithromycin is now a generic drug and, therefore, cost is no longer a major impediment to its use.

Alternative choices are 7 days of erythromycin base or stearate, 500 mg orally four times daily, or erythromycin ethylsuccinate, 800 mg orally four times daily, which are very cheap but the gastrointestinal tolerance of these regimens is poor.

Trimethoprim-sulfamethoxazole is active against *C. trachomatis*,¹⁰⁹ but has poor activity against the mycoplasmas. Among the marketed quinolones in the United States, ofloxacin and its congener levofloxacin have the best in vitro activity against *C. trachomatis*. Quinolones, in general, have variable activity against genital mycoplasmas.¹¹⁰ Clinically,

ciprofloxacin has been associated with frequent treatment failures in men with chlamydia-positive NGU,^{111,112} while ofloxacin, 200–300 mg twice daily for 7 days, has proven to be effective.^{113,114} The latter dose is recommended as an alternative therapy for NGU in the United States as is levofloxacin 500 mg once daily for 7 days.⁶

■ TREATMENT OF SEX PARTNERS

As part of the management of urethritis, every attempt should be made to evaluate and treat the patient's sex partner(s) as soon as possible. This approach is widely accepted for partners of men with either gonorrhea or chlamydial infection, and it is equally appropriate for partners of men with NGU. Waiting for the results of laboratory tests before treating the partners increases the time interval between patient and partner treatment and runs the risk of sexual reexposure to a potentially infected partner. This approach also decreases the probability that the partner will be treated at all. Though it has not been clearly demonstrated that treatment of the partner diminishes the rate of recurrence of NGU in men, female partners need treatment for their own benefit. *C. trachomatis* is isolated from 30 to 60% of the female partners of men with GU or NGU and has important sequelae in women.^{11,15,16,19,115,116} Furthermore, infected women (and men) constitute a major undiagnosed and untreated reservoir of *C. trachomatis* infection; ultimate control of *C. trachomatis* infection is unlikely to be achieved without reduction of this reservoir of infection. In general, the same regimens used to treat males with urethritis should be used to treat their female partners, though the tetracycline class of antibiotics should be avoided in pregnant women.

■ MANAGEMENT OF RECURRENT URETHRITIS

As discussed earlier, recurrent NGU is a relatively common problem. If current dual therapy guidelines have not been followed for treating GU, PGU can be expected in 10–20% of cases. *C. trachomatis* is the most common cause of this problem as 10–20% of men with gonorrhea have *C. trachomatis* coinfection. It seems likely that *M. genitalium* would also contribute to this problem given that it too is found in men with gonorrhea, but how frequently this occurs is not yet known. Given the evidence discussed earlier that suggest that this *M. genitalium* may be relatively resistant to doxycycline, PGU following a doxycycline-containing treatment regimen might be particularly likely to be caused by this organism.

The median time for recurrence following treatment for NGU is about 2 weeks after completing therapy.⁸ Most men with recurrences of NGU are culture-negative for *C. trachomatis* unless the interval following treatment is several weeks or more and they have had intercourse with an

untreated partner. The initial step in management requires that the presence of urethritis again be documented by examining urethral secretions for the presence of PMNL to exclude patients with functional complaints or other disorders. The patient should be questioned about compliance and unprotected sexual intercourse. In persistent (as opposed to recurrent) NGU, the possibility of HSV urethritis should be considered. Primary HSV urethritis typically lasts about 2 weeks. Urethral foreign bodies, periurethral fistula, and abscess should be excluded by palpation. Cultures or nonculture tests for *N. gonorrhoeae* and *C. trachomatis* should be repeated. Since tetracycline-resistant mycoplasmas may be the cause of recurrent or persistent infection, treatment with azithromycin should be given if doxycycline or another tetracycline class drug had been used for initial therapy. Moreover, azithromycin would be expected to eradicate *C. trachomatis* should the patient have been reinfected with this organism. As the initial NGU treatment recommendations do not include metronidazole, men with recurrent or persistent NGU are more likely to have *T. vaginalis* than at the time of the initial presentation. When an exudate is present, *T. vaginalis* can be sought by mixing a drop of exudate with saline solution and looking for motile organisms, but this is not standard laboratory procedure and most healthcare providers are not proficient in performing this test. If possible, culture for *T. vaginalis* should be performed. Kreiger et al. recently pointed out that culture sensitivity is significantly enhanced by culturing both urethral secretions obtained by a swab and the sediment of a first-voided urine specimen.⁴⁴ Regardless of what studies are performed, it is recommended that men with their first episode of recurrent NGU be treated empirically with 2 g of metronidazole as a single dose. Tinidazole is a suitable substitute though more expensive.⁶ If the female partner has been appropriately treated as a contact to NGU and intercourse has not occurred until both partners completed treatment, the partner does not require retreatment unless the man is proven to have a chlamydial, gonococcal, or trichomonal infection as the cause of his recurrence.

■ MANAGEMENT OF THE MALE WITH PERSISTENT URETHRITIS OR WITH MULTIPLE RECURRENCES

Most men will be cured after a second course of treatment, but some will have further recurrences or persistence of symptoms. Management of these men with NGU represents one of the most difficult problems in venereology. It is important to document that the cause of the symptoms is an inflammatory process. If, indeed, this is the case, there are several considerations. If the second round of chlamydial and gonococcal cultures were negative but *T. vaginalis* studies were not done, special effort should be made to do these tests. If the patient received metronidazole empirically for treatment of the first recurrence and persistent *T. vaginalis*

infection can be documented, the problem could be due to a metronidazole-resistant organism. The timing of the patient's treatment relative to that of the partner and to sexual reexposure should be reviewed carefully to eliminate any possibility of reinfection. The female partner should be evaluated carefully for all sexually transmitted infections (STIs) if this has not been done. Urinary tract infection and recurrent herpes should be ruled out with cultures' and/or NAATs. If there is no evidence of a known infectious agent, is there any value of further treatment with drugs normally effective for NGU? Hooton et al. suggested that a 3-week course of erythromycin, 500 mg four times daily, may be of benefit.¹¹⁷ They found evidence of prostatic inflammation in many men with persistent urethritis, and it was this group that benefited most from treatment. Nonetheless, relapse rates were high. These observations may be explained, at least, in part, by the fact that *M. genitalium* is now known to be a common cause of NGU and that some strains of this organism may be relatively resistant to antibiotics. There is some experience suggesting that a 5-day course of azithromycin or a 10-day course of moxifloxacin may be successful in these cases.^{97,98,118} Men with inflammatory urethritis that persists after the above treatment approaches have been tried should be evaluated by an urologist who is experienced in dealing with such patients. The urologist should be made aware of the details of the patient's workup and treatment history in order to avoid unnecessarily repeating expensive tests and, more important, to avoid further empiric antibiotic trials. After urologic evaluation has ruled out anatomic problems (as it usually does¹¹⁹), whether or not chronic suppressive antibiotic therapy is justified is unknown. The best advice is not to treat further, but to reassure the patient, using the counseling points listed below. Many cases will resolve spontaneously over time. In the future, it will be possible to use PCR techniques to evaluate these patients for antibiotic-resistant mycoplasmas and/or currently unknown urethral pathogens.

The following issues should be discussed with the patient:

1. The likelihood of long-term sequelae such as infertility or cancer appears to be exceedingly low even in men who continue to have recurrent urethritis after two or three treatment attempts have failed.
2. The risk of transmission of disease to partners is exceedingly low because these men do not have ongoing *C. trachomatis* infection, and other pathogens are usually not identified or are not important causes of sequelae in women. For example, as yet it is not known if *M. genitalium* causes significant morbidity in women.
3. Even if no further treatment is given, symptoms likely will disappear over time.
4. If the man has an ongoing monogamous sexual relationship (and this is true of the partner as well), there is no need for further treatment of the partner if both received an initial course of therapy active against the known STIs and refrained from intercourse until both completed treatment.
5. Most recurrences will arise independent of resumption of sexual activity, and these episodes do not mean that the partner has been "unfaithful."
6. Persistent or recurrent urethritis is not a presentation of AIDS.

It is important to be aware of the fact that many patients complaining of persistent or recurrent symptoms of urethritis after treatment for a documented episode do not have any evidence of an inflammatory process, even after a careful search. In the authors' experience, these are often well-educated men who are very health conscious, sometimes to the point of being obsessive. Not infrequently this problem develops in a monogamous man who originally acquired a documented episode of urethritis following an illicit sexual encounter, suggesting that unresolved guilt feelings are a contributing factor. Typically, these patients self-refer to multiple "experts" either concurrently or sequentially. Since most of these simply prescribe antibiotics without attempting to document the presence or absence of an inflammatory process, the specialist often sees such patients after they have received many courses of a variety of antibiotics. Such inappropriate treatment reinforces the notion in the patient's mind that he has an "incurable" infection. These patients may benefit from an urological examination as much for reassurance as for anything else, though an urethral stricture occasionally may be discovered. However, the most important point to be made here is that, rather than launching into a prolonged series of evaluations and empiric therapies as recommended earlier for the patient with documented inflammatory disease, counseling should be initiated early in the course for the patient with symptoms but without objective evidence of urethritis.

PROGNOSIS

Although frequent in the preantimicrobial era, local complications of urethral gonorrhea are now unusual in developed countries. Epididymitis occurs in 1–2%, seminal vesiculitis is rare, and prostatitis and prostatic abscess are almost never seen. Other unusual complications include abscess of Tyson's glands, penile edema secondary to dorsal lymphangitis or thrombophlebitis, inflammation of the urethral wall including periurethral abscesses and fistula, and regional lymphadenitis. Urethral strictures secondary to urethritis rarely occur now in the developed countries, but remain significant problems in certain areas of the world. Other complications include inflammation of other concurrently infected sites such as proctitis or systemic spread as is seen with the disseminated gonococcal infection syndrome. NGU is generally a self-limited disease, and, even without therapy, the physical consequences to the individual are slight. One percent to two percent of

both *C. trachomatis*-positive and *C. trachomatis*-negative men with NGU develop epididymitis, and another 1–2% develop conjunctivitis.¹¹⁶ Urethritis is a manifestation of the reactive arthritis syndrome (formerly known as Reiter's syndrome), but it is unclear how frequently this problem develops as a consequence of NGU. Two studies indicate that the rate of development of reactive arthritis is not high in HLA-B27-positive men after initiation of therapy with a tetracycline for *C. trachomatis*-positive or *C. trachomatis*-negative NGU.^{120,121} In one of the studies, however, men who were positive for *C. trachomatis* had more reactive arthritis than men who were chlamydia-negative.¹²⁰ Although approximately 20% of men with NGU have an increased number of PMNL in expressed prostatic secretions,¹¹ development of overt prostatitis is rare. In contrast to the infrequent physical consequences, the psychological impact of persistent urethritis or frequent recurrences of urethritis may be great. A thorough discussion with the patient of the issues reviewed earlier will usually greatly alleviate this distress.

PREVENTION

Preventive measures offered by healthcare providers and health departments should include (1) diagnosis and treatment of patients with STDs, (2) treatment of gonorrhea with regimens that will eradicate *C. trachomatis*, (3) improved contact-tracing to detect and treat partners exposed to either *N. gonorrhoeae* or *C. trachomatis* infection, and (4) increased availability of adequate diagnostic tests, especially for asymptomatic *C. trachomatis* infection. Urine-based diagnostic tests are now available. These tests are useful for screening hard-to-reach asymptomatic populations such as adolescents who are unlikely to attend a clinic for screening by one of the conventional tests. Hopefully, the resources can be found to support the widespread application of this approach. Although much progress has been made in understanding the immunobiology of these infections, effective vaccines are not presently available.

A sexually active male can take several preventive measures. He can choose his sexual partners carefully, avoid multiple partners, and use condoms. There is no way that one can determine by intuition that a prospective new partner is free of genital pathogens. Proper use of a condom diminishes acquisition and transmission of many STDs. Prophylactic antimicrobials are partially efficacious for prevention of urethritis (for example, 200 mg of minocycline or doxycycline soon after intercourse),¹²² but this approach cannot be justified from a public health point of view.

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DEFINITION, HISTORY, AND OVERVIEW

Epididymitis is defined as an inflammatory process involving the epididymis. Many cases are related to genitourinary tract infections, especially sexually transmitted infections and bacterial urinary tract infections. The process causes scrotal pain and swelling that is characteristically unilateral and relatively acute in onset.

Embryologically, the epididymis and vas deferens arise from the Wolffian system and mesonephric duct. The epididymis is a sausage-shaped structure positioned on the posterior aspect of the testicle. It consists of a single, delicate convoluted tubule 12–15 feet long. The epithelium of the epididymis possesses stereocilia that have no directional movement. Because of its embryological origin and associated anatomic structures, it is easy to understand why congenital genitourinary tract abnormalities are associated with an increased susceptibility to epididymitis in children and adolescents. Anatomists divide the epididymis into six sections based on histological characteristics, which likely correspond to different functional capacities. Fluid and particulate matter are both secreted and absorbed by the epididymis. During passage through the epididymis, sperm achieve motility and the potential to fertilize an ovum.

In 1804, Monteggia was probably the first to describe the gross pathology of epididymitis and to differentiate epididymitis from orchitis. In 1879, Despres suggested that epididymitis was due to retention of semen related to the pain of urethritis. Subsequently, specific infectious forms, such as tuberculosis and gonococcal epididymitis, have been well recognized. With the advent of specific diagnostic criteria and effective antimicrobial therapy for gonorrhea and tuberculosis in the 1940s and 1950s, an increasing proportion of cases were regarded as “idiopathic,” often attributed to “straining” or reflux of sterile urine into the epididymis. More recent studies established the infectious etiology of most cases of epididymitis and the importance of sexually transmitted urethritis and bacteriuria as precursors of epididymitis.

With improved understanding of the etiology, the diagnosis and management of epididymitis is becoming more rational, leading to decreased morbidity and, possibly, to prevention of recurrences. Epididymitis usually occurs as a complication of urethral infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*, or a complication of genitourinary infection with coliforms or *Pseudomonas aeruginosa* (Table 60-1). In rare cases, epididymitis may occur as a complication of systemic infection with various bacterial, fungal, viral, or parasitic pathogens or may be due to noninfectious causes. In children, epididymitis may be related to concomitant presence of genitourinary tract anomalies.

Effective management of epididymitis depends on accurate etiologic diagnosis. The responsible infectious causes must be identified, and attention must be directed toward correction of contributing anatomical, physiological, and behavioral factors. For example, for patients with sexually transmitted epididymitis caused by *N. gonorrhoeae* or *C. trachomatis*, this would most certainly include examination and treatment of the patient’s sexual partners. Patients with epididymitis secondary to coliform urinary tract infection may benefit from correction of primary genitourinary disorders.

We prefer to avoid the term “nonspecific epididymitis.” In the past this terminology was used to describe patients with epididymitis associated with “nonspecific” urethritis or without obvious infection. Only those unusual cases for which no etiologic agent can be determined after thorough investigation should be referred to as “idiopathic” or “nonspecific.”

EPIDEMIOLOGY AND ETIOLOGY

Epididymitis is common, and it carries much morbidity in terms of suffering and loss of time from work. Because of epididymitis, an estimated 634,000 patients sought treatment by American physicians in 1977.¹ In 1981, the National Institutes of Health estimated 500,000 cases of acute epididymitis occurred annually.² Researchers have reported that the incidence of epididymitis may range from one to four per 1000 men per year.^{3,4} In Great Britain, from 1963 to 1964,

Table 60-1. Classification of Acute Epididymitis

- I. Epididymitis due to infectious agents
 - A. Associated with urethritis
 - B. Associated with bacteriuria
 - C. Associated with systemic bacterial, fungal, viral, or parasitic infections
- II. Epididymitis due to noninfectious causes
 - A. Associated with trauma
 - B. Associated with drugs (amiodarone)
 - C. Associated with a postinfectious etiology
 - D. Associated with a systemic vasculitis

From Berger RE. Acute epididymitis. *Sexually Transmitted Diseases*, 3rd edn. US: McGraw-Hill, 1999, pp. 847–858.

13,600 claims were made for workman's compensation for epididymoorchitis.⁵ In 1984, Baumgarten reported that 82% of men with work-related epididymitis returned to work after an average of 6 days.⁶ However, 18% had prolonged symptoms or required surgical therapy. Epididymitis was reported to account for more days lost from military service than any other disease, with over 20% of urologic admissions being caused by epididymoorchitis.^{7–9}

■ EPIDIDYMITIS ASSOCIATED WITH BACTERIURIA

In prepubertal males, epididymitis is frequently associated with coliform or *Pseudomonas* infection of the genitourinary tract (Table 60-2).^{10,11} These children frequently have predisposing structural, functional, or neurologic abnormalities, often congenital. Gierup et al. found that 10 (45%) of 22 children with epididymitis confirmed by surgical exploration had significant bacteriuria (e.g., $>10^5$ *E. coli*/mL of urine).¹⁰ Prepubertal children had bacteriuria more often than postpubertal children, while pyuria with negative urine cultures occurred more often in older children. Cultures for *C. trachomatis* or *N. gonorrhoeae* were not performed, but these agents are important among sexually active adolescents. In a retrospective study, Gislason et al. found that approximately two-thirds of boys with epididymitis were postpubertal. Although 29% had pyuria, only 12.5% had positive urine cultures for conventional pathogens.¹² In adolescents with epididymitis, a detailed sexual history should be elicited, along with appropriate evaluation for sexually transmitted pathogens.

In postpubertal males younger than 35 years of age, epididymitis is usually not attributable to coliforms, and the

Table 60-2. Microbial Etiology and Predisposing Factors in Acute Epididymitis

Prepubertal children
Usual etiology: Coliforms, <i>P. aeruginosa</i>
Unusual etiology: Hematogenous spread from primary infected site
Predisposing factors: Underlying genitourinary pathology
Men younger than 35
Usual etiology: <i>C. trachomatis</i> , <i>N. gonorrhoeae</i>
Unusual etiology: Coliform or <i>P. aeruginosa</i> , <i>Mycobacterium tuberculosis</i>
Predisposing factors: Sexually transmitted urethritis
Men older than 35
Usual etiology: Coliforms or <i>P. aeruginosa</i>
Unusual etiology: <i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , <i>M. tuberculosis</i>
Predisposing factors: Underlying structural pathology or chronic bacterial prostatitis

From Berger RE. Acute epididymitis. *Sexually Transmitted Diseases*, 3rd edn. US: McGraw-Hill, 1999, pp. 847–858.

presence of *P. aeruginosa* is unusual, unless the patient has a documented history of anatomic urinary tract abnormalities (i.e., neurogenic bladder or previous urinary tract surgery). In various series, from 0% to 35% of sexually mature young men with epididymitis had infection with coliform bacteria or *P. aeruginosa*.^{1,9,13,14} This low prevalence may reflect the low frequency of structural disorders predisposing to urinary tract infections in this population. Most males with significant congenital urinary tract anomalies have been diagnosed and treated at an earlier age. In contrast, most acquired structural or functional disorders of the male urinary tract, such as benign prostatic hypertrophy, develop later in life.¹ Berger et al. reported that 6 (12%) of 51 men younger than 35 years had coliform infections and one (2%) had infection with *Haemophilus influenzae* (Table 60-3).^{1,15} All seven of these patients were men who have sex with men (MSM) infected with Gram-negative rods, who regularly practiced anal-insertive intercourse.¹⁵ No pathogen was identified in the two additional MSM in this series, but all nine MSM had many neutrophils per 400× microscopic field on Gram stain of midstream urine. Drach had previously noted that a history of anal intercourse was associated with chronic bacterial prostatitis.¹⁶ Barnes et al. found that bacteriuria was more common among MSM than among heterosexual men in a venereal

Table 60-3. Etiology of Acute Epididymitis in 68 Consecutive Men

Etiology	Heterosexual Men >35 Years Old (n = 17)	Heterosexual Men <35 Years Old (n = 42)	MSM ^a <35 Years Old (n = 9)
Coliforms, <i>Pseudomonas</i>	12	0	6
<i>N. gonorrhoeae</i>	0	9	0
<i>C. trachomatis</i>	1	18	0
<i>N. gonorrhoeae</i> plus <i>C. trachomatis</i>	0	1	0
<i>H. influenzae</i>	0	0	1
Trauma	0	2	0
Tuberculosis	1	0	0
Idiopathic	3	12	2

^aMSM, men who have sex with men.

From Berger RE, Alexander ER, Harnisch JP, et al.: Etiology, manifestations and therapy of acute epididymitis: prospective study of 50 cases. *J Urol* 1979; 121: 750–754; Berger RE, Kessler D, Holmes KK, et al. Etiology and manifestations of epididymitis in young men: correlations with sexual orientation. *J Infect Dis* 1987; 155: 1341–1343; Berger RE, Alexander ER, Monda GD, et al. *Chlamydia trachomatis* as a cause of acute “idiopathic” epididymitis. *N Engl J Med* 1978; 298: 301–304.

disease clinic population.¹⁷ Of those with bacteriuria, 61% had urethral discharge, presumably owing to *E. coli* urethritis. Thus, the occurrence of *E. coli* epididymitis in MSM is most likely attributable to the more frequent exposure of the urethra to pathogenic enteric bacteria during anal intercourse. Although Stamey et al. showed in 1971 that enteric pathogens isolated from the urine of women with urinary tract infections could be isolated from the urethra of their male sexual partners, coliform epididymitis appears to be uncommon in young heterosexual men.¹⁸

In contrast, among men older than 35 years with epididymitis, up to 80% have coliform or *P. aeruginosa* urinary tract infection.¹⁹ This high proportion of epididymitis caused by coliform infections in older men may reflect the decreasing prevalence of sexually transmitted disease and an increased prevalence of acquired genitourinary abnormalities. These patients may have a history of prostatic calculi, recent genitourinary or prostate instrumentation, neurogenic bladder, benign prostatic hypertrophy, or chronic bacterial prostatitis. Berger et al. identified only one sexually transmitted infection among 17 patients (6%) older than 35 years with epididymitis. In contrast, 12 of the 17 (71%) patients had coliform or *Pseudomonas* infections (Table 60-3).^{1,15,19} Almost one-half of the patients older than 35 years had pre-existing genitourinary pathology.

In military populations, epididymitis secondary to coliform bladder infections is unusual.^{9,13,14,20,21} This may reflect the predominantly young age and low rate of underlying structural urinary abnormalities in the military populations. Mittemeyer found underlying urinary abnormalities in only 3.4% of 610 patients with epididymitis.¹⁴ In this series, 70.1% were between the ages of 20 and 39; and in Shapiro's study, 75% of military patients were between the ages 18 and 32.^{13,14}

It has been postulated that straining may cause reflux of sterile urine down the vas deferens leading to epididymitis. The popularity of this theory may partly reflect the previous inability to identify pathogens in many patients. However, Shapiro noted only 2 (4%) of 52 patients had a history of straining prior to the onset of epididymitis.¹³ Similarly, Mittemeyer noted a history of straining in only 6.6% of his population.¹⁴ Berger et al. studied two patients who had a history of strenuous lifting just before the onset of epididymitis. *C. trachomatis* was isolated from both patients.¹⁹ Cathcart reported that 12 (86%) of 14 epididymitis cases had a history of “strain”, but these patients also had urethral discharge.²² Taken together, these observations suggest that reflux of infected urine into the vas deferens may be important in the pathophysiology of epididymitis. In contrast, reflux of sterile urine has not been shown to play an important role in causing epididymitis.

■ EPIDIDYMITIS ASSOCIATED WITH URETHRITIS

Epididymitis caused by *N. gonorrhoeae* or *C. trachomatis* is rare in prepubertal children and suggests the possibility of sexual abuse. In contrast, sexually transmitted infections represent important considerations in sexually active adolescents presenting with epididymitis. To date, no study of postpubertal children with epididymitis has assessed the sexual history, or has utilized appropriate diagnostic testing for sexually transmitted organisms as well as for conventional uropathogens.

Sexually transmitted organisms represent the most common cause of epididymitis in heterosexual men younger than 35 years old (Table 60-4).^{1,15,16} In the preantibiotic era, Pelouze reported that epididymitis complicated 10–30% of gonococcal urethritis cases.²³ More recently, Watson found that 16% of patients with epididymitis in a young military population had gonorrhea, although only 50% of those with gonorrhea had urethral discharge.²⁴

In a series of studies, Berger et al. reported that 28 (67%) of 42 men younger than 35 years had acute epididymitis secondary to *N. gonorrhoeae* or *C. trachomatis*.^{1,15,19} *N. gonorrhoeae* alone was isolated from the urethra from nine, *C. trachomatis* infection alone was found in 18, and both agents were recovered from one patient (Table 60-3). *C. trachomatis* was isolated as the sole pathogen from the epididymis in 5 of 6 men with *C. trachomatis* infection who underwent epididymal aspiration.

Characteristically, patients with *N. gonorrhoeae* or *C. trachomatis* epididymitis are young and sexually active; they may have multiple sexual partners. Symptoms or signs of urethritis may not be present. Nonetheless, patients who deny symptoms of urethritis may have expressible urethral discharge. Gram-stained smear of an endourethral swab specimen may reveal ≥ 5 polymorphonuclear leukocytes per 1000 \times field, or a urinalysis may reveal pyuria. Thus, either

Table 60-4. Etiology of Acute Epididymitis

Study	Total Number of Men	Age < 35; No./Total (%)			Age > 35; No./Total (%)		
		GC	Ct	<i>E. coli</i>	GC	Ct	<i>E. coli</i>
Berger et al. (1978)	23		11/13 (85)			8/10 (80)	
Scheibel et al. (1983)	52	1/31 (3)	13/31 (42)			6/13 (46)	
Kristensen et al. (1984)	16	4/16 (25)	14/16 (88)				
Hawkins et al. (1986)	40		13/27 (48)		2/13 (15)	3/13 (23)	
Hawkins et al. (1986)	40	2/27 (7)	13/27 (48)	0/27	3/13 (23)	2/13 (15)	3/13 (23)
Berger et al. (1987)	51	9/51 (28)	19/51 (37)	6/51 (12) ^a			
Grant et al. (1987)	54	2/42 (5)	29/40 (73)	3/42 (7)		3/12 (25)	8/12 (67)
Melekos et al. (1987)	31		10/17 (59)	4/17 (24)		3/14 (21)	7/14 (50)
Mulcahy et al. (1987)	40	4/40 (10)	13/40 (33)	0			6/11 (55)
De Jong et al. (1988)	25	1/13 (8)	11/13 (85)	1/13 (8)		1/12 (8)	10/12 (83)
Kojima et al. (1988)	45	3/30 (10)	21/30 (70)			10/15 (67)	
Pearson et al. (1988)	27	1/27 (4)	7/29 (24)	0			
Doble (1989)	24 ^b	1/24 (4)	10/24 (42)				
Hoosen et al. (1993) ^c	144	76/134 (57)	46/134 (34)	4/134 (3)	1/10 (10)	2/10 (20)	3/10 (30)

^aSix of nine MSM had coliform infection; one other had infection with *Haemophilus influenzae*. None of 42 heterosexual men had coliform infections.

^bAll younger than 45 years

^cCut-off between younger and older men was age 40 years.

GC, gonorrhea; ct, *Chlamydia trachomatis* infection.

or both of these evaluations are indicated routinely. Because underlying urinary tract abnormalities are seldom found in this population, routine structural urological evaluation is not indicated.

Berger et al. found that 13 (68%) of 19 men with *C. trachomatis* epididymitis were referred from sexually transmitted disease clinics.^{1,15,19} This could represent a biased population that might overestimate the proportion of cases actually associated with *C. trachomatis*. However, other studies confirmed their findings.^{25,26} Among men with acute epididymitis, *C. trachomatis* infection was found by Melekos and Asbach in 9 (53%) of 17 men younger than 40 years; by Colleen and Mårdh in 14 (33%) of 42 men younger than 35 years; and by Mulcahy et al. in 65% of men younger than 35 years.^{25–27} Hawkins et al. and Lee et al. found that men presenting with epididymitis often had nongonococcal urethritis (NGU), even in the absence of positive tests for *Chlamydia trachomatis*.^{28,29} These cases could be attributed to urethritis caused by less common pathogens. Eley et al. were unable to increase *C. trachomatis* detection in acute epididymitis by employing polymerase chain reaction-based (PCR) testing.³⁰ Future use of nucleic acid amplification testing for *C. trachomatis*, *N. gonorrhoeae*, and other urethral pathogens may facilitate more accurate determination of the role of these organisms in epididymitis.

■ MISCELLANEOUS CAUSES OF EPIDIDYMITIS

While most cases of epididymitis are due to bacterial pathogens associated with sexually transmitted urethritis or bacteriuria, less common causes include localized or systemic infectious and noninfectious disorders.

Bacterial infections

Epididymitis is well documented as a complication of hematogenous dissemination of a number of bacterial infections.

Mycobacteria. Epididymitis may occur in systemic tuberculosis. In Mittermeyer's military series, 0.8% of patients had epididymitis due to tuberculosis.¹⁴ Ross found the age of patients with tuberculosis epididymitis to be between 20 and 40 years.³¹ Tuberculosis epididymitis commonly presents with bilateral involvement. In contrast, epididymitis caused by coliforms, *N. gonorrhoeae*, or *C. trachomatis* is nearly always unilateral. Because tuberculosis epididymitis results from disseminated infection, patients may present with clinical disease involving other organs, including the kidneys,^{32,33} adrenal glands,^{34,35} lymphatics (retroperitoneal, abdominal, or mediastinal),^{36,37} and other male accessory glands.³² Halker reported that 75% of patients with renal tuberculosis had an episode of epididymitis.³² Medlar reported that no case of tuberculosis epididymitis occurred without renal, prostate, or

seminal vesicle involvement.³³ Tuberculosis epididymitis may also occur after intravesical Bacillus Calmette-Guerin (BCG) instillation for treatment of carcinoma of the bladder.^{38–41}

Several clinical clues suggest the possibility of tuberculosis epididymitis. The two classic physical findings associated with tuberculosis epididymitis are “sterile pyuria” and “beading of the vas.” While the presence of sterile pyuria should suggest the possibility of genitourinary tuberculosis, this finding may be confused with other causes of sterile pyuria, such as nonspecific urethritis or urinary stone disease (which may present with referred scrotal pain).⁴² “Beading of the vas” is the physical finding of a “string of beads” on palpation of the vas deferens that occurs with tuberculosis. Another, less specific, finding that we have noted with genitourinary tuberculosis is prostatic calculi that may be detected on digital rectal examination. According to urologists who practiced before effective antimicrobial therapy, this was noted in a reasonable proportion of cases. (Victor Marshall personal communication to JNK, 1977.)

Several mycobacterial species other than *M. tuberculosis* have been associated with epididymitis, including *M. chelonae*, *M. avium-intracellulare*, *M. kansasii*, *M. xenopei*, and *M. bovis*.^{43–46} Leprosy, especially erythema nodosum leprosum, may present clinically as a multisystem disorder that includes epididymitis.^{47,48}

Other Bacteria. Numerous other bacteria have been reported as infrequent causes of epididymitis, probably due to hematogenous dissemination. These organisms include *Streptococcus pneumoniae* and *equisimilis*, *Brucella* spp., *N. meningitidis*, *Treponema pallidum*, *Nocardia* spp., and *Tropheryma whippelii*.^{49–59} *H. influenzae* type B has been isolated from the epididymis of children with acute epididymitis as well as in an MSM with epididymitis.^{15,60,61} Salmonella epididymitis has also been reported in children with enteric salmonella infection.⁶² Epididymitis attributed to *Plesiomonas shigelloides* and to *Listeria monocytogenes* has been reported in immunosuppressed individuals.^{63,64}

Fungal infections

Epididymitis may occur as a manifestation of disseminated fungal infections, such as histoplasmosis, coccidioidomycosis, blastomycosis, and cryptococcosis.^{65,66} Candidal epididymitis (both *C. albicans* and non-*albicans* spp.) has also been reported.^{67–70}

Viral infections

Epididymo-orchitis is the most common complication of mumps in postpubertal men,⁷¹ and is commonly unilateral.^{71–73} Cytomegalovirus epididymitis has been reported in a patient with AIDS.⁷⁴

Parasitic infections

Trichomonas vaginalis is an etiologic agent of NGU and, in case reports, has been reported to cause epididymitis.^{75,76} Other parasitic etiologies for epididymitis, including schistosomiasis, sparganosis, and Bancroftian filariasis are typically endemic in regions outside the United States. Patients may present with eosinophilic urethritis or cystitis, and may have a more subacute or chronic clinical course.^{77–79} Diagnosis of parasitic epididymitis is often made upon pathologic evaluation of surgical specimens.

■ POSTINFECTIOUS EPIDIDYMITIS

Studies of epididymitis in pediatric and adolescent patients suggest that a postinfectious etiology may account for some cases. Somekh et al. prospectively studied epididymitis in 44 patients 2–14 years old.⁸⁰ They found significantly higher serologic titers to *Mycoplasma pneumoniae*, enteroviruses, and adenoviruses compared with controls.⁸⁰ Epididymoorchitis has been reported as a complication of *Streptococcus pyogenes* pharyngitis.⁸¹

■ VASCULITIS

Systemic vasculitis represents an infrequent cause of epididymitis. Epididymitis has been reported in Behcet's disease, Henoch-Schönlein purpura (HSP), and polyarteritis nodosa.^{82–90} Epididymitis, sometimes recurrent, has been reported in 5–12% of patients with Behcet's disease.^{84–87} In a large study of 780 male patients with Behcet's disease by Cho et al., 36 patients with epididymitis were significantly more likely to have genital ulcers, cutaneous involvement, arthritis, central nervous system involvement, and a positive pathergy test.⁸⁴ These findings suggest a tendency toward more severe Behcet's disease manifestations in patients who have epididymitis.⁸⁴ HSP may present with bleeding into the epididymis with associated inflammation and pain.^{88,90} The scrotal pain and swelling in HSP-associated epididymitis may be severe, mimicking testicular torsion; clinical features and color and power Doppler ultrasonography can be useful in excluding torsion and preventing unnecessary surgery.⁸⁸ Our clinical experience also includes a few patients with epididymitis associated with Wegener's granulomatosis.

■ DRUG-ASSOCIATED EPIDIDYMITIS

A new cause of epididymitis was reported by Gasparich, Krieger, and colleagues, who reported a syndrome of epididymitis in 6 (11%) of 56 men taking the antiarrhythmic drug amiodarone.³ Epididymal biopsy showed lymphocytic infiltration and fibrosis. Amiodarone levels in the epididymis were found to be 400 times higher than therapeutic blood levels in one patient. Reduction of the amiodarone dosage resulted in resolution of epididymitis. Subsequent reports

have confirmed amiodarone as an etiology for epididymitis.^{91,92} In amiodarone-associated epididymitis, pyuria and urethritis are absent. This sterile epididymitis is usually bilateral; however, it may be unilateral.³

PATHOGENESIS OF EPIDIDYMAL INFECTION

The route of spread of infection to the epididymis has been a subject of considerable debate. Much of the controversy arose with the original concept that “idiopathic” epididymitis was caused by “sterile” inflammation from urine refluxing down the vas deferens while straining with a full bladder. This theory had implications both for workman's compensation from results of injuries sustained while working, and for the military, where prevention of epididymitis and loss of time from service was of great importance. Currently, most cases of epididymitis are thought to be infectious in origin. Therefore, the route of spread to the epididymis may be of more than academic interest, since the spread of naturally occurring infection from the urethra, bladder, or prostate does not carry the same legal implications as reflux of sterile urine caused by strenuous work.

The second historical area of controversy concerns the recommendation for routine “prophylactic” vasectomy to prevent epididymitis following prostatectomy. Experimentally, infective epididymitis has been produced by inoculation and intraluminal spread.⁹³ On numerous occasions, it has been demonstrated that bladder urine can reflux first into the ejaculatory ducts, then into the vas deferens in patients undergoing prostatectomy or in those with serious urinary pathology. Thind et al. documented high voiding pressures and sphincter dysinergia in many patients with acute epididymitis.^{94,95} In contrast, Kohler was unable to produce reflux of radiographic contrast into the vas in patients recovering from acute epididymitis.⁹⁶ Herwig was also unable to demonstrate urinary reflux into the vas in patients with sterile urine.⁹⁷ Pelouze pointed out that because the ejaculatory ducts lack circular muscles, retrograde peristalsis of urine down the vas would require the seminal vesicle to first fill with urine and then contract forcing urine down into the epididymis.²³ Inflammation of the seminal vesicle during acute epididymitis has been demonstrated by ultrasound.⁹⁸ Since the seminal vesicle is subject to the same intraabdominal pressures as the bladder, perhaps straining could force infected seminal vesicle contents down the vas and into the epididymis. Reflux of urine would not be necessary to explain the sudden onset of epididymitis with straining in these patients. Kendall documented positive vas cultures in only 15% of men with prostatic obstruction and positive urine cultures without a catheter, compared to 36% of infected patients who had a urethral catheter.⁹⁹ Orandi evaluated patients undergoing prostatectomy: 32 (48%) of 67 patients with positive urine cultures also had positive vas cultures.¹⁰⁰ In contrast, none of the

74 patients with negative urine cultures had a positive vas culture. Reeves ligated only one vas deferens in 505 pre-prostatectomy cases and found a higher rate of epididymitis on the nonligated side.¹⁰¹ Perhaps a catheter or similar irritation from infection of the verumontanum may allow reflux of infected urine from the bladder down the vas deferens or lead to seminal vesiculitis with infection subsequently spreading to the epididymis. Taken together, these findings suggest that retrograde ascent of infected urine may cause postoperative epididymitis following urological procedures but that epididymitis is an unlikely complication of urological procedures in patients with sterile urine.

Other theories have been proposed to explain the pathogenesis of epididymitis. Wesson suggested that bacteria could reach the epididymis via lymphatics adjacent to the vas, and he noted frequent swelling of the spermatic cord in patients with epididymitis.¹⁰² Since the epididymis drains to hypogastric and iliac nodes while the prostate and seminal vesicles drain to the same area, spread by the way of lymphatic drainage was postulated. Lack of testicular involvement in some cases was attributed to the different lymphatic drainage of the two organs. Rolnick suggested that bacteria could advance along the sheath of the vas, since this sheath is a continuation of the sheath of the prostate and seminal vesicles.¹⁰³ Thus, infection from the prostate or seminal vesicles could travel along the sheath of the vas to the tail of the epididymis. Some infections, such as tuberculous, pneumococcal, fungal, and other infections, might well spread to the epididymis by a hematogenous route. However, this route is probably unusual for coliform or sexually transmitted organisms because the infecting organism can usually be identified in the urethra or bladder.

CLINICAL MANIFESTATIONS

Characteristically, patients with epididymitis complain of testicular or scrotal pain and may also complain of inguinal pain.¹⁹ In severe cases, acute swelling of the spermatic cord may result in flank pain from obstruction of the ureter as it crosses over the spermatic cord.²³ Of 92 men in the military service with epididymitis, one-third had a sudden onset, and two-thirds a gradual onset.²¹ A history of lifting or straining on onset of pain is probably not significant in determining the etiology of the epididymitis or in its differentiation from other intrascrotal conditions.

In coliform epididymitis, a history of bacteriuria or symptoms suggestive of urinary tract infection may or may not be present.^{21,104} Frequency, urgency, or dysuria may be present. There may be a history of symptoms suggestive of urinary tract obstruction (e.g., hesitancy or slow urinary stream), indicating conditions predisposing to urinary tract infection (e.g., stricture and benign prostatic hypertrophy). Men with epididymitis secondary to sexually transmitted pathogens

often have a history of urethral discharge or dysuria, and they usually have a history of recent sexual exposure. Berger et al. found that only 1 (10%) of 10 patients with coliform infections versus 6 (43%) of 14 patients with *C. trachomatis* infections had dysuria.¹ Patients with tuberculosis epididymitis often have a prior history of pulmonary tuberculosis or a history of exposure to tuberculosis.

On examination, the scrotum on the involved side may be red and edematous. The testicle tends to lie in the normal position in the scrotum. The tail of the epididymis, which connects with the vas deferens near the lower pole of the testes, is swollen first. Later, swelling spreads to the head of the epididymis, near the upper pole of the testes. The groove between the epididymis and the testicle should be examined, as this will help to show whether the maximum swelling is in the testicle or the epididymis. The spermatic cord may be swollen and tender (termed, “funiculitis”). The degree of scrotal erythema and epididymal edema may be less in patients with chlamydial epididymitis compared with those with epididymitis of other etiologies.¹⁰⁵ However, massive erythema and edema may also occur with untreated *C. trachomatis* epididymitis. If the patient has not voided recently, a urethral discharge may be apparent. However, it is important to recognize that asymptomatic urethral infection without discharge may occur. Watson found that 50% of gonococcal epididymitis cases did not have urethral discharge.²⁴ If no spontaneous discharge is noted, the urethra should be stripped and examined again. Digital rectal examination may reveal abnormalities suggesting bacterial prostatitis in some cases.^{13,20}

PATHOLOGY OF ACUTE EPIDIDYMITIS

The pathology usually begins in the tail of the epididymis, then spreads to the rest of the epididymis. Subsequent spread to the testicle may result in a diffuse pathologic process, properly termed “epididymoorchitis.”

Pelouze noted in 98% of epididymitis cases that the clinical course suggested the epididymis was inflamed before the vas.²³ Initially, the epididymal ducts become distended with polymorphonuclear and mononuclear leukocytes that may actively phagocytize sperm.¹⁰⁶ The epithelium of the epididymis may be destroyed, and small abscesses form in the connective tissue, which is intensely hyperemic. In the stroma, lymphocytes may outnumber the polymorphonuclear leukocytes. Microabscesses may be present after 48 hours.¹⁰⁶ Later the columnar epithelium of the epididymis may become squamoid in appearance and plasma cells more frequent.

Cronquist reported seven cases of epididymitis in which sperm penetrated the epithelium and basement lamina of the epididymis with a marked inflammatory reaction.¹⁰⁷ In a biopsy study, Wolin noted that 13 (54%) of 24 patients had epididymal tubular destruction with microabscesses and a predominance of polymorphonuclear leukocytes.⁹ However,

in the remaining 11 cases, there was predominantly lymphocytic infiltration with no tubular involvement. Perivascular mononuclear cell infiltration was prominent in some of these cases. Kiviat et al. also noted a mononuclear cell infiltrate in the epididymis of men with chlamydial infection proven by fluorescent monoclonal antibody staining.¹⁰⁸

Often, the epididymal interstitium is infiltrated by neutrophils, small lymphocytes, plasma cells, and transformed lymphocytes. Neutrophils are often seen in the epididymal tubules and migrating through the epithelium.¹⁰⁸ Wolin and Nilsson et al. described testicular inflammation,^{9,109} the latter reporting that Sertoli's cells were vacuolated with cloudy cytoplasm. Furthermore, the organism responsible for epididymitis was isolated from the testicle in four patients. After 2–7 months, repeat biopsies showed decreased inflammation with an increased proportion of lymphocytes, macrophages, and plasma cells. After 2–3 years, there was atrophy that was proportional to the degree of initial inflammation. There have been rare reports of xanthogranulomatous epididymitis, in which chronic bacterial infection of the epididymis leads to destructive granulomatous inflammation accompanied by a cellular infiltrate of lipid-laden macrophages.^{110–112}

In summary, available data suggest that most cases begin in the tail of the epididymis, with an acute intraluminal exudate, tubular epithelial damage, and subjacent microabscesses formation. However, some cases show predominantly mononuclear and perivascular infiltration. Subsequently, testicular involvement occurs that may lead to testicular atrophy. Unfortunately, these pathological studies did not employ comprehensive microbiological studies of etiology.

EXPERIMENTAL PATHOLOGY

Møller and coworkers developed a primate model of *C. trachomatis* epididymitis.⁹³ Injection of *C. trachomatis* into the vas deferens of grivet monkeys produced marked infiltration with a polymorphonuclear leukocytes and lymphocytes through all layers of the spermatic cord, and in the epididymis. The ducts were filled with polymorphonuclear leukocyte exudate. Although *C. trachomatis* was isolated from the vas deferens, it was not isolated from the epididymis. Berger et al. used *Macaca nemestrina* as a primate model.¹¹³ After inoculating *C. trachomatis* through the vas deferens, they observed mononuclear perivascular inflammation in the area of the epididymis.¹¹³

Other models for acute and chronic epididymitis have been developed in mice and rats.^{114–116} Lucchetta et al. developed a model for epididymitis caused by *E. coli* in the rat, and Hackett et al. developed a similar model in the rabbit.^{117,118} Both models demonstrated a marked decrease in spermatogenesis following epididymitis. In a rat model, See et al. found that the concentration of the antibiotic amdinocillin was actually increased in the infected testicle compared to the

noninfected side.¹¹⁹ Likewise, in a rat model, Tartaglione et al. found increased antibiotic concentrations on the infected side for sulfamethoxazole, tobramycin, doxycycline, and ampicillin.¹²⁰ Trimethoprim had similar levels in the infected and noninfected sides, and doxycycline had the best tissue penetration of any antibiotic evaluated. Vieler et al. compared the efficacy of different antibiotic regimens in rats with experimental *E. coli* epididymitis.¹²¹ Ofloxacin was the most effective at decreasing the number of organisms and histologic changes; doxycycline was more effective than cefotaxime. Nielsen found that antibiotic therapy had no effect once abscess formation occurred.¹²² Finally, in a study of *E. coli* epididymitis in rats, Ludwig et al. reported that sparflaxacin therapy eradicated the organisms and reduced the degree of epididymal damage compared with untreated controls.¹²³ However, the initial inflammatory reaction persisted as a nonbacterial process, possibly compromising fertility. These experimental observations suggest that acute epididymitis may resemble acute pyelonephritis, with persistent immunological processes causing ongoing tissue damage despite elimination of the infecting bacteria.

ETIOLOGIC DIAGNOSIS

Gram stain of a urethral swab specimen will often indicate the presence of urethritis and establish with a high degree of certainty whether its etiology is gonococcal or nongonococcal. Berger et al. demonstrated that the presence or absence of intracellular Gram-negative diplococci on Gram stain or urethral smear correlated with culture results for *N. gonorrhoeae*.¹ Two-thirds of the cases of epididymitis not caused by Gram-negative rods or *N. gonorrhoeae* in men younger than 35 years of age were secondary to *C. trachomatis*.¹ Urethral specimens should be tested for *N. gonorrhoeae* and *C. trachomatis* in all cases. While culture has been the traditional diagnostic test for chlamydia and gonorrhea, tests of first-voided urine for *N. gonorrhoeae* and *C. trachomatis* using highly sensitive and specific nucleic acid amplification techniques may prove just as or even more useful, though more experience with these tests is needed in men with epididymitis.

First-voided and midstream urine specimens should next be examined for bacteria and white cells. Comparison of the urinary sediments in the first-voided and midstream urine may reveal whether pyuria is coming from the urethra or the bladder. Gram stain of uncentrifuged midstream urine can be used to presumptively establish the diagnosis of bacteriuria in cases of coliform or *Pseudomonas* infections. Presence of greater than one Gram-negative rod per oil immersion field on Gram stain of unspun midstream urine correlates with the presence of greater than 10⁵ coliform or *Pseudomonas* spp. per milliliter. Quantitative midstream urine culture should be obtained in all cases of acute epididymitis when bacteriuria is suspected because culture also provides antimicrobial susceptibility data.

In certain difficult cases, diagnosis may be facilitated by epididymal aspiration cultures.¹²⁴ Such cultures may be useful in patients with (1) indwelling urethral catheters, (2) failure to respond to initial antimicrobial therapy, (3) epididymitis found on surgical exploration for torsion of the testicle, and (4) recurrent epididymitis in which the etiologic agent is uncertain. If the patient had received prior antimicrobial therapy and the urine is sterile, the responsible pathogen may still be culturable from aspirate samples. Nucleic acid amplification tests for gonorrhea and chlamydia using epididymal aspirates may also be useful though little clinical experience has been reported. Patients with indwelling urethral catheters often have multiple organisms in the urine, and therapy may be best selected on the basis of the organism(s) found on epididymal aspiration.

DIFFERENTIAL DIAGNOSIS OF ACUTE EPIDIDYMITIS

An algorithm for the initial diagnostic evaluation of the patient with the acute scrotum syndrome is presented in Fig. 60-1.¹²⁵

■ TORSION OF THE TESTIS

Acute epididymitis must be differentiated from torsion of the testicle. In infants and prepubertal children, torsion of the testicle is much more common than acute epididymitis. In these populations, any acute scrotal swelling must be presumed to be torsion of the testicle unless proven otherwise. Quinto found that only 12 (8%) of 158 pediatric patients with scrotal swelling had epididymitis.¹²⁶ Children with epididymitis often have pyuria. In contrast, children with torsion generally do not have pyuria.

Torsion of the testis requires urgent surgical exploration to perform detorsion and orchidopexy to preserve testicular viability. Cases of suspected epididymitis in adolescents or young adults should be confirmed by Doppler or radionuclide scanning, since the incidence of torsion is also higher than the incidence of epididymitis for most populations in this age group. In consecutive cases of acute testicular swelling, Devillar noted that 11 (85%) of 13 patients younger than 20 years old, had torsion of the testicle.¹²⁷ In contrast, among patients 20–30 years old only 10% had torsion of the testicle. Of 29 patients with acute epididymitis, only eight (28%) were younger than 20 years old. Barker also found that epididymitis was much more likely in patients older than 18 years old than in patients younger than 18 years old presumably because of increasing sexual activity and the decreasing incidence of torsion with age.¹²⁸ As the age at first intercourse has decreased, the incidence of epididymitis has increased in patients younger than 18 years old.

A history of previous scrotal pain is more common in torsion of the testicle than in epididymitis, presumably reflecting

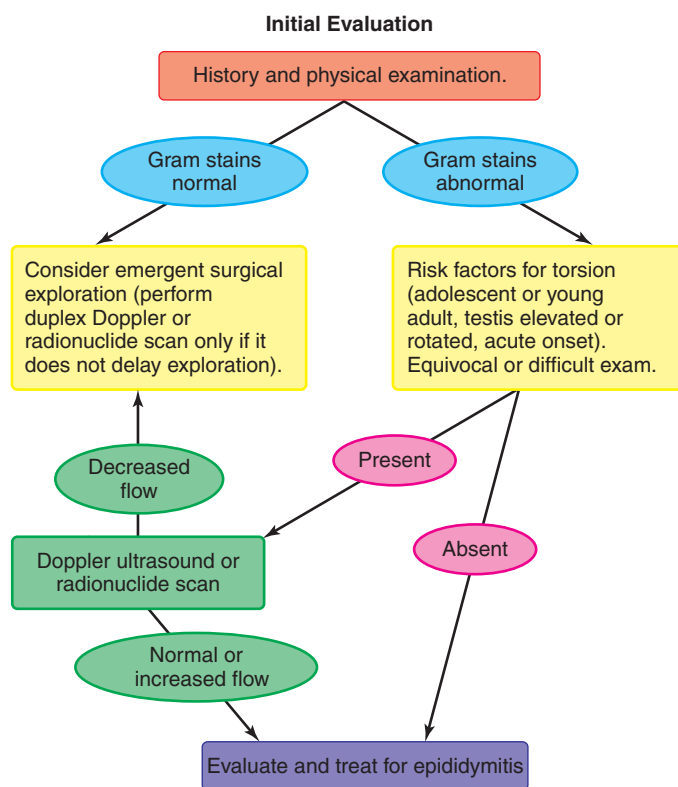


FIGURE 60-1. Algorithm for initial evaluation of the acute scrotum syndrome.

previous intermittent torsion. History of trauma to the testicle or of extreme exertion at the onset of pain may occur with either epididymitis or torsion. Unless performed early in the course of the acute scrotum syndrome, physical examination may be very similar in torsion and epididymitis. Devillar noticed swelling of the testes in 28% of patients with epididymitis and in 77% of cases of torsion.¹²⁷ Swelling of the epididymis alone occurred in 59% of cases of epididymitis and in 15% of torsion cases. In torsion, examination of the opposite testicle may reveal that the epididymis is anterior. This diagnostic clue indicates that the congenital abnormality that allows torsion of the testicle may also be present on the opposite side. Also in torsion, the testicle is often high in the scrotum, whereas in epididymitis this is unusual. In epididymitis, the spermatic cord in the inguinal canal may be quite tender, whereas in torsion tenderness is generally limited to the scrotal contents.

Examination of the urine and urethral smear may prove helpful in differentiating epididymitis from torsion. Barker and Raper noted that 31 (97%) of 32 patients with epididymitis had bacteriuria or leukocytes in their urine, compared to none of 38 patients with torsion.¹²⁸ In Doolittle's series, 8 (73%) of 11 patients with epididymitis had pyuria, compared to none of 19 with torsion.¹²⁹ Ideally, evaluation should include examination of the first-voided urine, which may demonstrate a higher concentration of leukocytes than the midstream urine in patients with urethritis. In Madsen's series, 49 (98%) of 50 patients with acute epididymitis had expressed prostatic secretions with increased leukocyte

counts.¹³⁰ Although Madsen did not examine urethral smears routinely, finding clear evidence of urethritis on smear would limit the need for prostate examination in most cases. Some authors consider a rigorous prostate exam to be contraindicated in patients with epididymitis because of the risk of exacerbating symptoms or because of a possible risk of causing bacteremia in men with coliform or *P. aeruginosa* infection. Neither Madsen nor Berger¹ reported such exacerbations. However, Berger avoided prostatic massage in older patients with suspected coliform or *P. aeruginosa* infection.¹

Recent studies suggest that inflammatory markers may help distinguish epididymitis from noninflammatory conditions, such as torsion and tumor. Rivers et al. found that serum interleukin-6 (IL-6) was significantly elevated in epididymitis compared with testicular torsion, and had a positive predictive value of 79% in diagnosing epididymitis versus a negative predictive value of 100% for torsion.¹³¹ Doehn et al. reported that 50 (96%) of 52 patients with epididymitis had at least a fourfold elevation in serum C-reactive protein, compared to none of the 17 patients with tumor and only 1 (9%) of 11 with torsion.¹³² Thus, an elevated C-reactive protein had a sensitivity of 96%, specificity of 94%, negative predictive value of 94%, and positive predictive value of 94%.¹³² Matalliotakis et al. found that in 82 infertile men, levels of soluble IL-6 receptor in the seminal plasma were significantly higher in cases of accessory genital gland infection than in other groups.¹³³ While these laboratory measures of inflammation may help support the diagnosis of epididymitis, diagnosis of epididymitis is primarily based on the clinical history and examination.

Doppler ultrasound has proven very useful in differentiating the diagnosis of torsion from epididymitis.¹³⁴ This examination may demonstrate increased blood flow to the acutely inflamed epididymis and decreased blood flow to a testicle that has undergone torsion, cutting off its blood supply. The opposite testicle is used as a control. Care must be exercised in interpreting Doppler ultrasound examinations, as hyperemia surrounding a necrotic testicle may produce a false positive signal for epididymitis. Compression of the spermatic cord at the external ring may cause the Doppler pulse to disappear if blood flow is coming from the testicle, but not if it is coming from scrotal vessels. Similarly, a hydrocele surrounding an inflamed epididymis may produce a falsely decreased signal. Ultrasound may also prove useful in evaluating complications of epididymitis, such as testicular abscess, testicular infarction, or pyocele of the scrotum.¹³⁵

Color-coded duplex and power Doppler ultrasonography have also proven valuable in differentiating epididymitis and torsion, and currently, these are the imaging methods of choice in many institutions. Color and power Doppler ultrasound use visual coding of flow velocities in blood vessels superimposed on the gray scale ultrasonography. Increases or decreases in blood flow can be determined.^{136,137} Wilbert et al.

found that color-coded Doppler ultrasonography had a sensitivity of 82% and a specificity of 100% for torsion.¹³⁸ For epididymitis, the sensitivity was 70% and specificity was 88%. False negative scans in torsion generally resulted from intermittent or partial torsion with some residual blood flow in the testicle and epididymis. Magnetic resonance imaging has also been found to be accurate in the differential diagnosis of epididymitis and torsion in a small series.¹³⁹

The use of radionuclide testicular scanning is also based on a finding of increased blood flow in epididymitis (Fig. 60-2). In Holder's series, all 22 patients with acute epididymitis had increased blood flow and were correctly diagnosed.¹⁴⁰ In a retrospective study of 4 patients with torsion, 13 patients with inflammatory testicular diseases, and 3 healthy persons, Wu et al. found all were correctly diagnosed by radionuclide imaging (based on the final surgical and pathologic diagnosis) and this imaging was more accurate than ultrasonography.¹⁴¹ Abu-Sleiman et al. found that a correct diagnosis could be made in 86% of cases.¹⁴² False positives were noted in hydroceles and false negatives in late torsions and patients with retracted scroti.^{143,144} Testicular tumor may also produce increased flow on testicular scan, resembling epididymitis.¹⁴⁵

In summary, multiple imaging modalities are available to assist in distinguishing torsion from epididymitis. In all cases, unless the examiner and imaging can unequivocally rule out torsion of the testicle, scrotal exploration should be undertaken. Some experts believe surgical exploration without

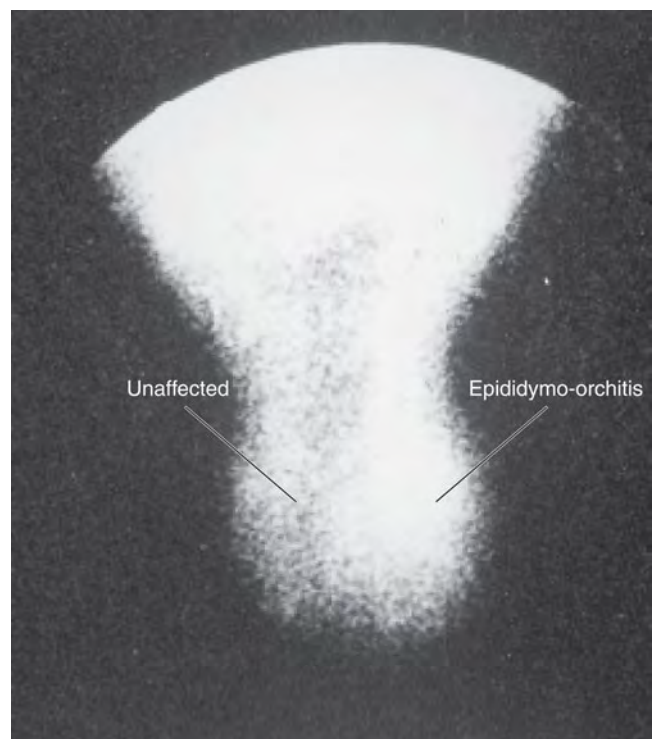


FIGURE 60-2. Technetium radionuclide scan of a patient with typical acute unilateral epididymo-orchitis, showing increased uptake of Tc⁹⁹ on the affected side, with normal uptake on the unaffected side.

prior imaging is appropriate for presumed torsion, given that after 4 hours of torsion, there is a significant risk of irreversible testicular infarction. A “wait and see” attitude is never justified.

■ TESTICULAR TUMOR

Testicular tumor is another important consideration in the differential diagnosis of epididymitis (Fig. 60-3). The peak incidence for epididymitis and testicular tumors occur in similar age groups. The presentation of a painless or persistent testicular mass suggests the possibility of testicular tumor. However, approximately one-quarter of patients with testicular tumors present with testicular or scrotal pain. Therefore, the presence of testicular or scrotal pain does not rule out a tumor, especially since hemorrhage or rapid tumor growth may, on occasion, cause such pain. In the early stages of epididymitis, swelling is limited to the epididymis, and differentiation from testicular tumor usually is not difficult. However, as epididymitis progresses and the testicle becomes more involved, the limits of inflammation are not easily defined. Further, a testicular tumor may invade the epididymis and thus, on physical exam, mimic exactly the findings of acute epididymitis. Reactive hydrocele formation may further limit the usefulness of physical examination. In testicular tumors, the urine and urethral smear should show no evidence of inflammation. Failure of improvement in the size of swelling or pain in any young man being treated for epididymitis should lead to the suspicion that an incorrect diagnosis has been made. Imaging, and possibly scrotal exploration through an inguinal incision, should be considered to rule out carcinoma of the testicle. Transscrotal open or needle biopsy should never be performed when carcinoma of the testicle is suspected for fear of spreading the tumor to the

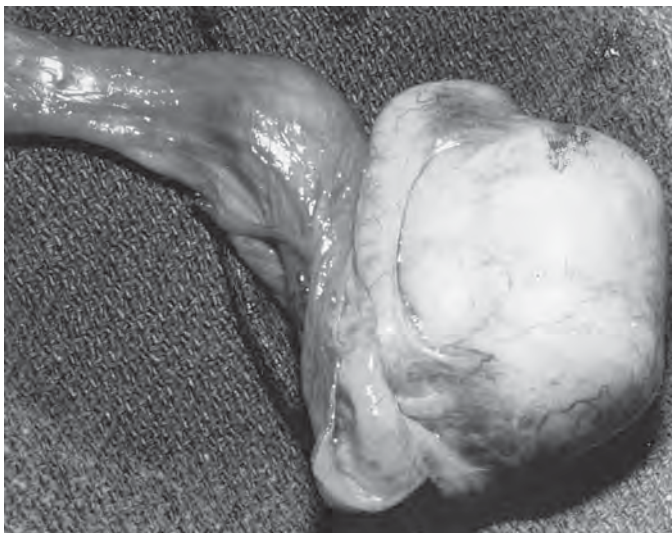


FIGURE 60-3. Testicular seminoma that was misdiagnosed as epididymitis by three urologists. The cancer is sausage-shaped and the epididymis is elevated.

inguinal lymph system; the usual lymphatic drainage of the testis is to the nodes at the level of the renal hilum, and not to the inguinal nodes.

■ MISCELLANEOUS

Other common intrascrotal conditions that may present difficulties in diagnosis are presented in Table 60-5. Spermatocele and hydrocele are easily differentiated by transillumination or by ultrasound. The scrotal varicosities of a varicocele disappear on assuming the supine position. A hernia protruding into the scrotum may sometimes present difficulties in diagnosis. However, this may be reducible as the patient lies down. Hernias are not transilluminable, and bowel sounds may occasionally be heard in the hernia contents.

TREATMENT

■ ANTIMICROBIAL THERAPY

Because most cases of acute epididymitis are caused by infections, antimicrobials are the cornerstone of therapy. Nilsson provided evidence that antibiotic treatment is superior to placebo in patients with and without coliform epididymitis.¹⁴⁶ Appropriate empiric antimicrobial therapy can be chosen based on whether initial Gram stain evaluation of an endourethral specimen and first-voided and midstream urine specimens suggest urethritis or bacteriuria as the inciting event, as outlined in Fig. 60-4.

In patients with bacteriuria, broad-spectrum antimicrobial therapy appropriate for a tissue-invasive urinary tract infection should be initiated promptly. For ambulatory therapy in those with mild or moderate epididymitis, either oral ofloxacin 400 mg twice daily or levofloxacin 500 mg once daily for a 10-day treatment course is appropriate;¹⁴⁷ if *P. aeruginosa* is a concern, then levofloxacin would be more appropriate. Because ciprofloxacin is less effective against *C. trachomatis* than ofloxacin or levofloxacin, it is not recommended. Traditionally, trimethoprim-sulfamethoxazole was recommended as an empiric option for treating uncomplicated epididymitis attributed to coliform infection. However, with increasing resistance of *E. coli* and other coliforms to trimethoprim-sulfamethoxazole, trimethoprim-sulfamethoxazole is no longer an ideal empiric antimicrobial option.

For febrile individuals or those with more severe or complicated epididymitis, intravenous broad-spectrum therapy directed against coliforms and *P. aeruginosa*, including the addition of an aminoglycoside, should be considered. Therapy can be modified based on susceptibility testing results for organisms cultured from the urine. In patients with indwelling urethral catheters who may have multiple organisms isolated from the urine and in patients who have

Table 60-5. Common Differential Diagnosis of Acute Epididymitis in Adult Men

	Usual Age	Pain	Onset	Past History of Pain	Spermatic Cord Tenderness	Scrotal Tenderness	Transill Umination	Decrease in Swelling on Lying Down	Fever	Location of Swelling	Urethritis, Pyuria, Bacteriuria	Activity on Testicular Scan	Blood Flow on Doppler Ultrasonic
Epididymitis	Any	Mild–severe	Gradual to sudden	Infrequent	Frequent	Severe	No	No	Frequent	Posterior to testes	Yes	≠	≠
Torsion of testes	<30	Severe	Sudden	Frequent	Infrequent	Severe	No	No	Infrequent	Testes ^a	No	∅	∅
Testes tumor	18–32	None–mild	Gradual	Infrequent	No	None–mild	No	No	No	Testes	No	≠ or ∅	Normal
Hydrocele	Any	None–mild	Gradual	Infrequent	No	None	Yes	No	No	Entire hemiscrotum	No	∅	Normal or ↓
Spermatocele	Any	None–mild	Gradual	Infrequent	No	None	Yes	No	No	Above testes ^b	No	∅	Normal or ↓
Varicocele	Any	None–mild	Gradual	Infrequent	No	None	No	Yes ^c	No	“Bag of worms”	No	Normal or ≠	Normal ^d
Hernia	Any	None–moderate	Gradual	Frequent	Frequent	None–mild	No	Yes ^e	No	Above testes	No	Normal	Normal

^aIn torsion of testicle, epididymis of normal testicle may be anterior.

^bSpermatocele may feel like “third testicle.”

^cVaricocele should disappear on lying down.

^dMay get increased venous flow.

^eHernia may be reducible on lying down.

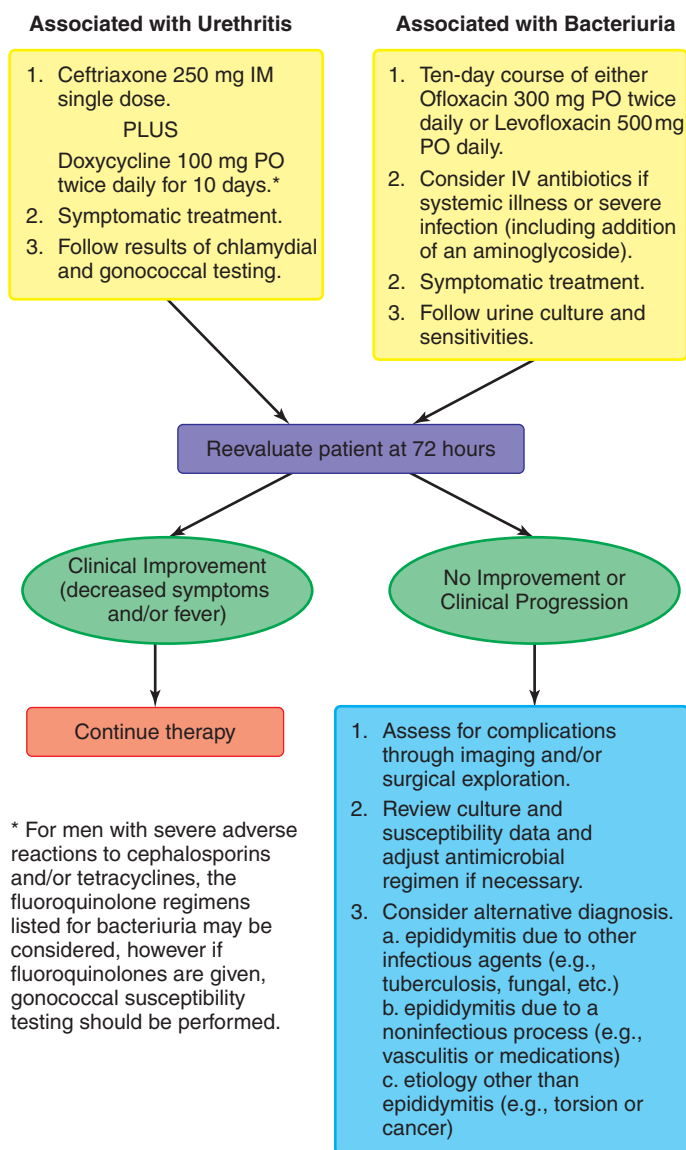


FIGURE 60-4. Algorithm for management of epididymitis.

been started on antibiotics who may have sterile urine, the use of epididymal aspiration cultures may identify the causal pathogen and also provide needed antimicrobial sensitivity information.¹²⁴ Antibiotic treatment may need to be prolonged in more complicated cases.

In patients with epididymitis associated with urethritis or a suspected sexually transmitted pathogen, antimicrobial therapy directed against *N. gonorrhoeae* and *C. trachomatis* should be initiated promptly. Treatment for both organisms is necessary because chlamydiae can be isolated from the urethra from approximately 20% of patients with gonorrhea, and theoretically could cause epididymitis even when *N. gonorrhoeae* is isolated. A treatment regimen active against beta-lactamase positive strains of *N. gonorrhoeae* (e.g., ceftriaxone 250 mg intramuscularly), followed by 10 days of oral doxycycline 100 mg twice daily to adequately cover chlamydial infection is recommended.¹⁴⁷ Due to an increase in fluoroquinolone

resistance among *N. gonorrhoeae* strains, fluoroquinolones are no longer recommended as first-line therapy for epididymitis associated with urothrits (<http://www.cdc.gov/std/treatment/2006/updated-regimens.htm>). If fluoroquinolones are used in this setting, than susceptibility testing should be performed consultation with a specialist may be considered.

■ NONANTIMICROBIAL MEDICAL THERAPY

Symptomatic treatment of the patient with epididymitis is always indicated. Scrotal elevation provides for maximum lymphatic and venous drainage. The patient should be placed at bed rest with the scrotum elevated on a towel between his legs. The use of constricting scrotal supports while the patient is supine often only holds the scrotal contents between the patient's legs in a dependent position. If the patient is standing, gravity limits proper drainage of the tissues and may increase swelling. The patient should remain at bed rest until the scrotal contents are no longer tender. If the pain returns after ambulation, the patient should return to bed rest and scrotal elevation. Analgesics should be given as necessary for pain.

Several other nonantimicrobial treatments have also been proposed for epididymitis. Smith found that patients with epididymitis had dramatic relief of pain after one or two injections of the spermatic cord with procaine hydrochloride.¹⁴⁸ He noted that the pain relief was both immediate and lasting well beyond the period of local relief.¹⁴⁸ Kamat et al. reported on outcomes of medical therapy in three groups of patients: one group received antibiotics only; the second was treated with antibiotics plus oxyphenbutazone; and the third was treated with antibiotics plus infiltration of the spermatic cord with xylocaine hydrochloride.¹⁴⁹ The patients treated with antibiotics plus oxyphenbutazone or antibiotics plus spermatic cord infiltration recovered more quickly than patients on antibiotics alone.¹⁴⁹ His study was not blinded, however, and he did not report bacteriologic results. McClellan reported that the addition of paraenzyme or varidase also decreased the amount of swelling and percentage with residual chronic epididymitis.¹⁵⁰ Lapidus found that 35 (74%) of 47 patients with acute epididymitis were relieved by oxyphenbutazone alone.¹⁵¹ He described decreased pain in these patients but no decrease in the amount of erythema or swelling. In a multicenter, placebo-controlled study, Moore et al. found that prednisone had no value as an adjuvant to antibiotic therapy in the treatment of epididymitis.¹⁵² Thus, some clinicians believe that anesthetic infiltration of the spermatic cord and the use of oxyphenbutazone in addition to antibiotics and oral analgesics may increase the comfort of a patient. However, it is not clear whether these other forms of treatment provide better symptomatic relief than the use of analgesics with antibiotics. The effect of such adjuvant therapy on the long-term sequelae of epididymitis remains uncertain.

■ SURGERY

Drainage of testicular abscesses or orchiectomy is seldom necessary in patients who receive early appropriate antimicrobial therapy with bed rest and scrotal elevation. Vordermark et al. found that in patients who do not respond to antibiotics within 4 hours, epididymectomy hastened convalescence.^{153–155} However, this has not been subjected to a controlled study, and many patients with epididymitis will require up to 48–72 hours to show improvement, but then do well. Epididymectomy might be indicated in an older group of patients after unsuccessful conservative treatment. Prophylactic vasectomy of the contralateral testicle has also been advocated during such procedures.¹⁵⁶ Surgical therapy (generally orchiectomy) may be necessary for complications of severe epididymo-orchitis, such as testicular infarction, abscess formation, or development of a pyocele of the scrotum (i.e., an infected hydrocele).

■ FOLLOW-UP

Patients should be reevaluated at 72 hours following initiation of antimicrobial therapy (Fig. 60-4). Failure to clinically improve within 72 hours of the initiation of medical treatment requires reevaluation of the initial diagnosis and the current therapy. Swelling and tenderness that persists following completion of antimicrobial therapy needs to be evaluated more comprehensively through other means, including imaging or surgical exploration. The differential diagnosis includes testicular tumor, abscess or infarction, or a different infectious etiology (e.g., tuberculosis or fungal epididymitis).

■ ADDITIONAL ASPECTS OF MANAGEMENT

In patients in whom the etiologic agent is a sexually transmitted pathogen, treatment of epididymitis is not complete without evaluation and treatment of the sexual partner(s). This limits the risk of reinfection of the patient and prevents disease in the partner. In a study by Berger et al., two (25%) of eight female partners of men with epididymitis had chlamydial infections.¹ Robinson et al. found that 14 (88%) of 16 female consorts of chlamydia-infected men had chlamydial cervicitis.¹⁵⁷

Whether to evaluate possible anatomical or functional urological disorders depends on the clinical presentation. Svend-Hansen found abnormal excretory urograms in only 6 (14%) of 43 in patients younger than 50 years old of age; all six with abnormal findings had symptoms suggesting urologic disease.¹⁵⁸ He concluded that patients younger than 50 years old with epididymitis did not require radiographic evaluation. Berger et al. found that no patient younger than 35 years old had concurrent genitourinary pathology, whereas 7 (58%) of 12 patients older than 35 years old with coliform infections had underlying urological pathology.¹ Kaver et al. also identified urological abnormalities only in patients older than 50 years old.¹⁵⁹ All abnormalities were secondary to lower urinary

tract outflow obstruction. Certainly, the presence of urethritis caused by *N. gonorrhoeae* or *C. trachomatis* does not suggest that the patient has an underlying anatomic problem. In contrast, a coliform urinary infection in a male always requires investigation. Patients with epididymitis caused by coliform or *P. aeruginosa* infection should also be considered, after completion of antimicrobial therapy, for further evaluation for bacterial prostatitis (see Chapter 61), as this may be a predisposing factor to recurrent epididymitis.

Recurrence of acute epididymitis may occur and usually reflects a lack of adequate treatment, failure to identify factors predisposing to recurrence (e.g., untreated sexual partners, persisting genitourinary abnormality, etc.), or inadequate suppression of a source of chronic infection. Evaluation of these patients should address these factors.

COMPLICATIONS OF ACUTE EPIDIDYMITIS

■ SURGICAL COMPLICATIONS

Since the availability of effective antibiotics, the incidence of surgical complications from epididymitis has decreased. From 1951 to 1955, Gartman infrequently used antibiotics and had a 30% incidence of surgical complications.²⁰ From 1955 to 1959, he used antibiotics much more frequently, and had an 8% incidence of surgical complications. He noted an overall 10% complication rate in patients with “idiopathic epididymitis”; and a 16% rate when a definite pathogen was found in the urine or urethra.

The most serious local complications of epididymitis are abscess formation and infarction of the testicle (Fig. 60-5).



FIGURE 60-5. Infarcted testis with infected epididymis in a man with *Escherichia coli* epididymitis.

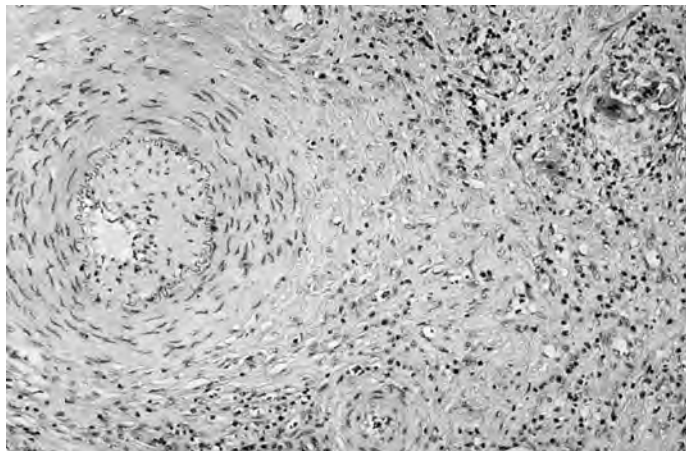


FIGURE 60-6. Thrombosed artery in spermatic cord of a man with *Escherichia coli* epididymitis.

Both complications are suggested by failure of the patient to improve clinically with appropriate bed rest and antibiotic therapy. Testicular infarction probably results from thrombosis of the spermatic vessels secondary to severe inflammation (Fig. 60-6).^{19,160,161} Gangrene of the testicle may take place while the epididymis remains viable (Fig. 60-5). Costas suggested that the swollen spermatic cord may become compressed at the external ring and lead to vascular compromise of the testicle.¹⁶² In Gartman's series, 3 (1%) of 310 cases resulted in gangrene of the testicle.²⁰ Abscess may be suggested by a "cold" area in the middle of a "hot" region on a radionuclide scan. See et al. found that serial gray scale ultrasonography revealing progressive inhomogeneity was highly correlated with the development of abscess and the need for orchiectomy.¹³⁵ In Mittermeyer's series, 19 (3%) of 610 patients developed abscesses that required surgical drainage.¹⁴ Treatment requires surgical drainage and, often, orchiectomy. In Gartman's series, 22 (7%) of 310 patients developed hydroceles; however, only 11 of these failed to resolve after treatment of epididymitis and required surgical repair.²⁰

■ INFERTILITY

Another complication of acute epididymitis, although poorly documented, is decreased fertility. Patients with bilateral epididymitis and bilateral occlusion of the vas deferens or epididymis have virtually no potential for fertility. In some parts of sub-Saharan Africa where urethritis often goes untreated, epididymitis is a leading cause of male infertility.¹⁶³ Campbell noted that 40% of patients with bilateral epididymitis secondary to gonorrhea were sterile.¹⁶⁴ Pelouze reported involuntary infertility among 11% of men with only a history of gonococcal urethritis, 23% of men with history of unilateral epididymitis, and 42% of men with history of bilateral epididymitis (Fig. 60-7).²³ Gartman reported that among 18 azoospermic men with normal testes biopsies and patent vasa deferentia, only four (22%) had histories of bilateral



FIGURE 60-7. Bilateral epididymitis in a young man with *C. trachomatis* infection.

epididymitis, but all were found to have fine scars that transected the epididymal tubules.²⁰ Gerris et al. found elevated antichlamydia antibody titers in *tunica vaginalis* fluid from men with oligoasthenospermia, suggesting previous undetected chlamydial infection.¹⁶⁵ These data suggest that patients may have a subclinical form of epididymitis that may lead to asymptomatic scarring and decreased fertility. This intriguing observation may be analogous to the observation that in many infertile women who have bilateral tubal obstruction (many of whom have serological evidence of past *C. trachomatis* infection), only about half have a past history of salpingitis (see Chapter 56).

Since sperm transit through the epididymis is necessary for development of normal sperm function, it is possible that acute inflammation and damage to the epididymis could ultimately lead to decreased fertility even in the absence of occlusion of the epididymal tubules. Epididymal obstruction reverses spontaneously in some patients. Pelouze reported one patient who had a return of sperm and fertility after 5 years of apparent epididymal occlusion following gonococcal epididymitis.²³

Inflammation with acute epididymitis is not limited to the epididymis but also involves the testicle. On testes biopsy during acute epididymitis, Wolin found that 20 (71%) of 28 patients had decreased spermatogenesis, and 9 (32%) of 28 had testicular inflammation.⁹ Nilsson et al. did aspiration biopsies on testicles in patients with acute epididymitis, and found that 16 (73%) of 22 had inflammatory cells.¹⁰⁹ Follow-up biopsy of these testicles after 2–3 years showed that 5 (56%) of 9 had reduced or absent spermatogenesis. Bietz found nonspecific toxic changes in the opposite testis 150–280 days following the onset of epididymitis.¹⁶⁶ Osegebe found thickened basement membranes, decreased spermatogenesis, and fibrosis in the contralateral testicles of men with clinical unilateral epididymitis.¹⁶⁷ Both Tozzo and Berger et al. found low sperm counts in a high proportion of patients with acute epididymitis.^{1,168} Ludwig followed

46 patients with unilateral epididymitis from 8 days to 1 year.¹⁶⁹ Initially, two-thirds had oligoasthenospermia. However, only 20% had long-term decreases in semen analysis parameters, and only one had persisting sperm agglutinins after 1 year.

Decreased fertility has been demonstrated in other unilateral testicular conditions, such as cryptorchidism and torsion.^{170, 171} Whether unilateral testicular involvement in acute epididymitis can decrease fertility has not been definitively evaluated. However, several observations support this possibility. Bandhauer found that 9 (19%) of 48 men with acute unilateral epididymitis developed sperm agglutinins.¹⁷² Ingerslev et al. found that following epididymitis, 27% of men developed serum antisperm agglutinating antibodies.¹⁷³ Heidenreich et al. and Ingerslev et al. both found that antibodies often appeared in the early period after acute epididymitis.^{173, 174} Later, the titers usually decreased to insignificant levels. Greskovich et al. found experimentally that early antibiotic therapy suppressed the antibody response, perhaps through a direct immunosuppressive effect, or through decreased antigenic load of killed sperm secondary to eradication of infection.¹⁷⁵ Other studies found that men without a history of clinical epididymitis but with anti-*C. trachomatis* antibodies had a significantly greater chance (50%) of having antisperm antibodies than men without anti-*C. trachomatis* antibodies (16%).¹⁷⁶

In summary, bilateral epididymitis may lead to bilateral epididymal occlusion, azoospermia, and infertility. Whether unilateral epididymitis, subclinical epididymitis, or epididymitis without occlusion, can result in infertility remains unproven.

■ CHRONIC EPIDIDYMITIS

Chronic epididymitis is a poorly defined clinical syndrome. Patients labeled as having chronic epididymitis account for a significant number of outpatient urology visits. Until recently, there was no clear definition of this syndrome or its clinical course. In 1966, Mittemeyer et al. reviewed 610 cases of epididymitis requiring hospitalization and reported that 15% of patients were diagnosed with chronic or recurrent epididymitis after the initial episode.¹⁴

A study by Nickel et al. in 2002 began to address many of the unknown or unclear aspects of chronic epididymitis, starting with the clinical definition.¹⁷⁷ Based on the available literature, chronic epididymitis was defined as: symptoms of discomfort and/or pain at least 3 months in duration in the scrotum, testicle, or epididymis localized to one or both epididymides on clinical examination.¹⁷⁷ Nickel et al. then performed a comprehensive clinical survey of 50 men meeting this definition and compared the findings to a control group. From their survey, a chronic epididymitis classification system (inflammatory, obstructive, and epididymalgia) and a

symptom assessment index (based on pain and quality of life) were developed, that may provide the basis for further epidemiological and clinical studies.¹⁷⁷

It remains unclear whether chronic epididymitis is related to persistence of bacteria or bacterial antigens in the epididymis or whether this syndrome reflects an ongoing immunological reaction (as occurs with chronic interstitial nephritis following some renal infections), scarring, neurological injury, or other factors. Chronic epididymitis is generally considered idiopathic and traditionally felt to be unresponsive to antimicrobial therapy, which in some instances has led to epididymectomy^{178–180} and other procedures^{181–184} for pain relief. Strebel et al. (Strebel RT, Luginbuehl T, Leippold T, Hauri D. Chronic Epididymitis – Management among Urologists in Switzerland, Abstract 118, American Urological Association Annual Meeting, San Antonio, May 2005) conducted a survey study of all urologists in Switzerland. The Swiss urologists see a median of five patients per month (range 1–30) with chronic epididymitis, with each patient having a mean of 2.5 visits. The treatments most often prescribed for chronic epididymitis were nonsteroidal anti-inflammatory agents and antibiotics. Of urologists surveyed, most considered surgery as the second line therapy, especially epididymectomy, “semicastration,” microscopic spermatic cord dissection and denervation. The estimated failure rates were 48% for medical treatment and 18% for epididymectomy.

Our clinical experience includes numerous patients who have failed such procedures. Thus, our current approach to chronic epididymitis is to evaluate possible contributing anatomical and infectious causes. We then evaluate the response to anti-inflammatory therapy, spermatic cord blocks using local anesthetics and/or steroids, and other measures. To our knowledge, there is little evidence-based data suggesting that a substantial proportion of patients benefits from more invasive therapies.

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Prostatitis Syndromes: Causes, Differential Diagnosis, and Clinical Management

John N. Krieger

OVERVIEW

Although prostatitis and prostate disease have been well known since antiquity, these syndromes continue to present major diagnostic and therapeutic challenges. Prostatitis is the diagnosis given to a large group of adult men who present with a variety of complaints referable to the lower urogenital tract and perineum.^{1,2} By one estimate, 50% of men experience symptoms of prostatitis at some time in their lives.¹ Data from the National Health Center for Health Statistics indicate that there were 76 office visits per 1000 men per year for genitourinary tract problems, with prostatitis accounting for approximately 25% of these visits.^{3,4}

Many men remain symptomatic for prolonged periods. Patients frequently relate the onset of their condition to sexual activity, commonly to an episode of acute urethritis.⁵ Antimicrobial treatment often results in transient relief of symptoms. Based on these observations, standard practice is to prescribe multiple courses of antibacterial therapy in the frequently vain hope that patients will experience lasting relief.^{1,6,7} For example, in one report of 75 men with chronic prostatitis the average patient had received 10 weeks of unsuccessful antimicrobial treatment during the 3 months before evaluation.⁸ Many other treatments are commonly prescribed for empirical therapy, with unproven success.

Clinical characterization of patients with prostatitis syndromes has not been carefully correlated with the pathologic classification of prostatitis.^{1,7} Pathologic studies have not included sufficient clinical or microbiologic data. On the other hand, clinical studies rarely have found pathologic specimens to be helpful, probably reflecting the focal nature of the inflammatory response in patients with prostatitis.^{9–11}

From a clinical standpoint, it is critical to distinguish men with lower urinary tract complaints associated with bacteriuria from the larger number of patients without bacteriuria.⁷ Careful lower urinary tract localization studies classify most patients in four diagnostic groups: acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), and asymptomatic inflammatory

prostatitis.^{12–14} Considerable progress has been made in understanding the pathophysiology and developing rational approaches for treatment of patients with acute and chronic bacterial prostatitis. Unfortunately, few reliable data are available on the etiology of either CP/CPPS or asymptomatic inflammatory prostatitis. Thus, current therapy is unsatisfactory for most patients with prostatitis syndromes. Occasionally, men develop granulomatous prostatitis, a characteristic histological reaction of the prostate to a variety of insults. Treatment of granulomatous prostatitis depends on accurate etiologic diagnosis.

HISTORY

Prostate disease, stones, obstruction, and infection were well known in antiquity. The Ebers Papyrus refers to prostatitis, urethritis, urinary retention, incontinence, and cystitis.¹⁵ Bladder stones, often a consequence of prostatic or urethral obstruction, were found in Egyptian mummies. The ancient Egyptians used reeds, copper and silver tubes, and rolled palm leaves to treat urinary retention. This may have been due to stones or prostatic obstruction, or probably both. Practitioners who used these instruments most became known as lithologists, the first specialists in medicine.

The Hindu Vedas contain procedures to relieve obstruction caused by prostatic disease and bladder stones, which may be 4000–5000 years old. The Vedas also describe cannulas of wood and metal. Uroscopy, or examination of the urine, was a highly developed art before the time of Hippocrates (460–377 BC), who paid much attention to this examination. Herophilus of Chalcedonia, a well-known lithotomist, is credited with what is probably the earliest gross description of the prostate in his anatomic texts. Rufus of Ephesus described the “parastatus glandulus,” meaning “standing before,” a likely origin of the term prostate. Aristotle used the term “varicose parastatae,” for what may well have been seminal vesicles.

At the beginning of the Christian era, Celsus (25 BC to 50 AD) described catheterization and urethrotomy. This procedure

would have been needed for treatment of obstruction related to prostate and urethral infection and inflammation. “Circumstances sometimes render it necessary to draw off the urine by an operation; as in retention, or when the urethra has become collapsed from old age, or when a calculus or grumous blood has produced internal obstruction; even a moderate degree of inflammation often prevents natural micturition. Now this operation is necessary not only in males, but sometimes in females, also. Hence, copper catheters are made for this purpose. The practitioner should keep by him three for men, and two for females...They ought to be somewhat curved.”

By 1500, cystostomy, generally perineal, was in widespread use for removal of stones. On occasion, this approach would also treat prostatic obstruction, because it was necessary to remove portions of the prostate to obtain access to the stone (Fig. 61-1).¹⁵ The first prostatic surgery was probably unintentional and through a perineal incision. In summary, prostatitis and urethritis were well recognized in antiquity and represented reasons for the development of medicine, surgery, and numerous specialties, especially infectious diseases, genitourinary medicine, dermatology, and urology.

HOST DEFENSES

Prostatitis syndromes occur despite the wide variety of defenses of the male lower urogenital tract. These defenses include nonspecific mechanisms, such as mechanical factors and antimicrobial secretions, and the humoral and cellular limbs of the immune system.

■ NONSPECIFIC DEFENSES

Most infections of the urogenital ducts and accessory sex organs are caused by organisms that ascend through the urethra.¹ Thus, mechanical factors including urethral length, micturition, and ejaculation should provide some protection against infection, although the relative importance of such defenses is unclear. The oblique courses taken by some prostatic ducts and by the ejaculatory ducts have also been proposed as mechanical defense mechanisms.

Prostatic secretions contain several substances with activity against a wide spectrum of microorganisms.^{1,16} A zinc-containing polypeptide, known as the prostatic antibacterial factor, is the most important antimicrobial substance secreted by the prostate. The prostate has higher concentrations of zinc than any other organ, and prostatic secretions of normal men contain high zinc levels.^{17–21} The bactericidal activity of prostatic secretions against a wide range of Gram-negative and Gram-positive organisms is a direct function of zinc concentration. Zinc also inhibits other genital pathogens, including herpes viruses,^{22,23} *Candida albicans*,^{24,25} *Trichomonas vaginalis*,^{6,26,27} and *Chlamydia trachomatis*.²⁸ Men with well-documented chronic bacterial prostatitis have



FIGURE 61-1. The arrogant Frenchman about to undergo lithotomy. Lithotomy position prior to surgery for removing a stone due to obstructing prostate adenoma. (From Tolet F. *Trait de la Lithotomie*, 4th edn. Paris, 1689; after Herman JR. *Urology: A View Through the Retrospectroscope*. Hagerstown, MD: Harper & Rowe, 1973, p. 27.) Lithotomy was developed for removal of bladder stones, usually resulting from prostatic and/or urethral obstruction due to previous infection and inflammation.

significantly lower levels of zinc in their prostatic fluid than controls,^{18,19} but their serum zinc levels are within normal limits.¹⁹ It is unclear whether reduced concentrations of zinc in the prostatic secretions of men with bacterial prostatitis precede development of prostatic infection or reflect secretory dysfunction resulting from such infections.²⁰ Oral zinc supplements did not increase the concentration of zinc in prostatic secretions of men with bacterial prostatitis.¹⁹

The prostate gland secretes a number of other substances with antibacterial activity. Spermine and spermidine, which are responsible for the characteristic seminal aroma, have been studied in most detail.^{21,29} These compounds possess activity primarily against Gram-positive bacteria and appear

to be of secondary significance in protecting the male lower genitourinary tract against infection.^{21,30}

■ HUMORAL IMMUNITY

Many investigators studied the serologic responses of men with bacterial prostatitis. Sera obtained from men with acute bacterial prostatitis contain specific agglutinating antibodies against the infecting bacterial strains.^{31–33} Titers remain elevated during persistent bacterial infection of the prostate, and changes in antibody titers reflect the response to antimicrobial therapy in some patients.^{31,32} Controls had low titers of antibodies against Gram-negative organisms of their own fecal flora, and similar low titers are present in men whose urethras are colonized by *Escherichia coli*. Serologic studies of men with bacterial prostatitis have two significant technical limitations. First, most studies employed an assay that does not distinguish specific immunoglobulin classes. Second, some patients with well-documented bacterial prostatitis have low titers of agglutinating antibodies.^{1,31}

Local immunoglobulin production by the prostate appears to be an important defense of the lower urogenital tract against infection. Prostatic secretions from men with bacterial prostatitis contain high concentrations of immunoglobulin.^{34–36} Several studies demonstrated antigen-specific antibody coating of bacteria isolated from patients with prostatitis.^{37,38} An indirect solid-phase radioimmunoassay was used to measure the local immunologic response in a limited number of patients with well-documented bacterial prostatitis.^{39–42} The antigen-specific antibody response in prostatic secretions (predominantly secretory immunoglobulin A [IgA]) was significantly greater than the serologic response.^{39,41,42} The antigen-specific IgA response in prostatic secretions persisted longer than either the prostatic IgG antigen-specific antibody or the serum antigen-specific responses.⁴⁰ Patients with nonbacterial prostatitis had a modest nonspecific increase in local class-specific immunoglobulins, whereas normal control men, with no history of urologic disease, had even lower levels of local prostatic antibodies.^{42,43}

Men with prior episodes of *E. coli* bacteriuria, but with no bacteriologic evidence of prostatitis, had similar increases in antigen-specific antibody levels in their prostatic secretions.^{42,43} These data suggest that bacteriuria in men may be associated with subclinical colonization of the prostate.^{42–44} Comparable increases in local immunoglobulins were not detected in men with *Staphylococcus epidermidis* apparently localized to their prostates.⁴² This finding suggests that Gram-positive cocci that occasionally appear to colonize the prostate (according to culture results) are predominantly urethral contaminants.

The data on immunological function in prostatitis patients with no history of bacteriuria are limited. One study compared monthly seminal fluid specimens from 35 prostatitis

patients to 96 specimens from normal controls.⁴⁵ These investigators found that levels of interleukin-6 and IgA correlated with patients' clinical symptoms, consistent with an inflammatory process. Other investigators⁴⁶ found no significant difference in immune responses to the expressed prostatic secretions (EPSs) of 44 prostatitis patients without histories of bacteriuria and 25 control men.

■ CELLULAR IMMUNITY

Leukocytes

Presence of leukocytes characterizes many conditions of the male lower urinary tract, including cystitis, urethritis, and some prostatitis syndromes. Variations in prostatic leukocyte populations occur among men with prostatitis. Patients with acute disease have a predominance of mononuclear cells, while patients with chronic disease have few cells of the monocyte-macrophage series.⁴⁷ One longitudinal study of prostatic secretions from 106 patients with prostatitis found that inflammation resolved in most patients with acute bacterial prostatitis and was episodic in patients with chronic bacterial or abacterial prostatitis.⁴⁸ The observation of phagocytosis of abnormal sperm by leukocytes in infertile men with pyospermia suggests that leukocytes may have a functional role in inflammatory conditions of the male lower urogenital tract.^{49,50} However, the clinical importance of lower urinary tract leukocytes in patients with prostatitis is currently the subject of intense controversy, as outlined below in the laboratory evaluation section.

Cytokines

Abnormal cytokine levels in EPS and/or seminal fluid occur in patients with chronic prostatitis.^{51–57} EPS leukocyte count, the usual marker of inflammation measured by the traditional, qualitative method of counting leukocytes/high-powered microscopic field,⁵⁸ does not correlate with the predominant symptoms of prostatitis.⁵¹ In contrast, quantitative assays suggest that prostatitis patients may have an imbalance toward increased proinflammatory and decreased anti-inflammatory cytokines that might correlate with pelvic pain symptoms.⁵¹ In some men, this imbalance may result from polymorphisms at the cytokine loci.^{51,54} Other data suggest that an autoimmune process might be involved, and experimental evidence indicates that this can be under hormonal influence, such as defects in the androgen receptor.^{51,59–61}

PATHOLOGY

The pathologist's view of prostatitis differs markedly from the clinical picture of "prostatitis," as seen by most clinicians.⁶² In the pathology literature, diagnosis and characterization of "prostatitis" is based entirely on the evaluation and

characterization of inflammatory infiltrates in prostate tissue. In clinical practice, such tissue is usually removed for diagnosis and treatment of prostate diseases, such as benign prostate hypertrophy (BPH) and cancer, or in the differential diagnosis of these conditions. Systematic evaluation of tissue removed for treatment of prostate cancer or BPH demonstrates presence of inflammatory infiltrates in almost every case, an observation that has led many investigators to hypothesize that prostatic inflammation, whether symptomatic or asymptomatic, may be important in the etiology and pathogenesis of cancers and BPH.⁶³⁻⁶⁹

Pathologically, prostatitis is usually a focal process, with areas of acute or chronic inflammatory cells in close apposition to areas with normal architecture (Fig. 61-2). Histological findings compatible with prostatitis occur commonly in adult males. In an autopsy series, McNeal⁹ found evidence of prostatitis in 40 of 91 adult prostates. Two cases involved the central zone only, 24 cases involved the peripheral zone only, and 14 cases involved both zones. These data suggest that prostatitis usually arises as a focal inflammation in the peripheral zone that spills over into the periurethral zone in severe cases. Kohnen and Drach found some inflammation in 98% of 162 surgically resected hyperplastic prostates.⁷⁰ Both histological and bacteriologic evidences of prostatitis may occur without endoscopic signs of inflammation.¹⁰ Blacklock suggests that these findings may be explained by differences in the drainage patterns of prostatic ducts.¹⁰ The peripheral prostatic ducts tend to drain at right angles to the ejaculatory ducts and, therefore, are vulnerable to infection by organisms ascending through the urethra. In contrast, ducts draining the central zone tend to parallel the ejaculatory ducts and are more resistant to infection by organisms in the urethra.

Clinical characteristics of men with prostatitis syndromes have not been carefully correlated with pathologic criteria.^{1,7} Pathologic studies rarely included sufficient clinical or microbiological data.^{9,70} Conversely, clinical studies seldom found pathologic specimens helpful, reflecting the focal nature of inflammation in patients with prostatitis.^{9,11} In one study, 60 men with “chronic abacterial prostatitis” had transrectal prostatic ultrasound with transperineal biopsy of abnormal areas. Histological examination revealed chronic inflammation, predominantly of low grade, in 53 (88%) of 60 patients.⁷¹ No uropathogens were cultured. The same investigators found intraprostatic antibody deposition in men with chronic abacterial prostatitis but not in controls, suggesting an earlier active role of an infectious agent. Although the authors describe sonographic findings characteristic of “prostatitis,”⁷² extensive clinical experience indicates that such grey-scale ultrasound findings lack specificity.⁷³⁻⁷⁵ Other critical problems with these data include patient selection and limited attempts to correlate objective inflammation in EPSs with inflammation in prostatic parenchyma or with microbiological finding.

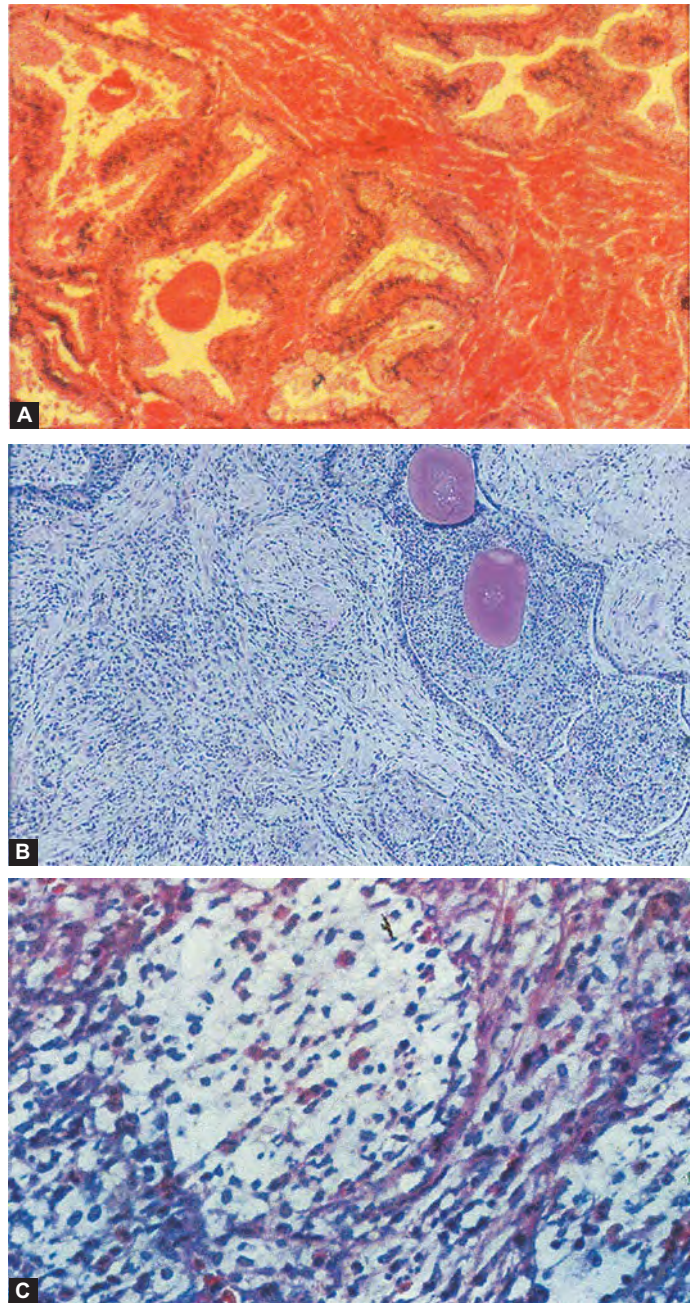


FIGURE 61-2. **A.** Benign prostatic adenoma (BPA) tissue removed during transurethral resection of the prostate for obstructive urinary symptoms. Note the glandular tissue with surrounding stroma (H and E stain). **B.** Chronic prostatitis. Note the intense active inflammatory infiltrate. This patient underwent prostatectomy following multiple episodes of acute urinary retention with bacterial urinary tract infection (H & E stain). **C.** Prostate biopsy showing granulomatous prostatitis. The patient had a prostate nodule suspicious for carcinoma. The biopsy revealed nonspecific granulomatous inflammation (H & E stain). (Data from Krieger JN, Nakagawa M and Nyberg LM. Epidemiology and pathogenesis of prostatitis. In: *6th International Consultation on Prostate Diseases*. Paris, France: International Consultation on Urological Diseases, 2005.)

A major difference between the clinician's view of “prostatitis” and the pathologist's diagnosis occurs in symptomatic patients with no history of bacteriuria. In one study of prostate histopathology in 368 needle biopsies from 97 patients, prostatic inflammation was detected in only 33% of patients.⁶² In the

minority of patients with inflammation, 88% had only mild (less than 10 leukocytes per 1 mm field) and only 12% of the patients with inflammation had moderate (between 10 and 200) or severe (more than 200) infiltrate. Overall, only 5% of 97 patients had moderate or severe inflammation.

EPIDEMIOLOGY

We reviewed the epidemiology of prostatitis using evidence-based recommendations to identify 3848 references, including 65 that merited detailed review.⁷⁶

■ INCIDENCE AND PREVALENCE OF PROSTATITIS SYMPTOMS

The nine studies included in our final analyses possessed at least four of the following five criteria⁷⁷: (1) population based, excluding studies of referral patients from tertiary care institutions, (2) a clear and standardized case definition, (3) a standard survey strategy, (4) large enough population to provide reasonable statistical power, and (5) use of a recognized and validated survey instrument. Currently, the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI, [Table 61-1](#)), described below, represents the most desirable survey instrument.⁷⁸ To facilitate evaluation of varied populations, the NIH-CPSI has been translated and validated for use in English,⁷⁸ Spanish,⁷⁹ Japanese,⁸⁰ Chinese,⁸¹ Malay,⁸¹ and German.⁸² A recent population-based study documented low agreement between physician-diagnosed prostatitis and the NIH-CPSI, suggesting that the index, by itself, may have limited ability to document the presence or absence of prostatitis.⁸³ Thus, use of the NIH-CPSI was considered desirable but was not required for inclusion. Of the nine studies that met the inclusion criteria, five were from North America,^{84–88} three were from Asia,^{81,89,90} and one was from Europe⁹¹ ([Table 61-2](#)).

The prevalence of prostatitis-like symptoms could be compared in six studies that surveyed varied ambulatory populations.^{81,84,86,88–90} Of 9260 total men included in these studies, 636 participants met criteria for symptoms of prostatitis, representing an overall rate of 6.9%. In these studies, the prevalence of prostatitis symptoms ranged from 2.2%⁸⁸ to 9.7%,⁸⁶ with a median rate of 6.9%.

Three other studies met the inclusion criteria but were not directly comparable, because the studies employed different denominators or different outcome measures.^{85,87,91} Collins and coworkers studied 58,955 outpatient physician visits by men >18 years old in the U.S. National Ambulatory Medical Care Survey database.⁸⁵ Randomly selected physicians completed visit forms documenting the reasons for patient visits and diagnoses. Of 58,955 visits, 5% included genitourinary symptoms. These data suggest that prostatitis was a diagnosis in 2,000,000 physician visits annually, including 700,000 visits by men 18–50 years old and 900,000 visits by men >50 years

old. Of visits for prostatitis, 46% were to urologists and 47% were to primary-care physicians. Prostatitis was diagnosed in 8% of all visits to urologists and 1% of all primary-care visits. The odds of a prostatitis diagnosis were 13-fold greater for visits to urologists than for visits to primary-care physicians. Patients with prostatitis received antimicrobial therapy 45% of the time, compared to 27% of the time for patients without genitourinary symptoms.

Subsequently, this group evaluated the prevalence and correlates of prostatitis symptoms among U.S. health professionals without prostate cancer.⁸⁷ Of the 31,681 men, 16% reported a history of prostatitis. Men reporting a history of benign prostatic hyperplasia had a 7.7-fold greater odds of a history of prostatitis. Participants with severe lower urinary tract symptoms had 2.8-fold greater odds of a history of prostatitis, while men with moderate lower urinary tract symptoms had a 1.8-fold greater odds of prostatitis. Other factors associated with a history of prostatitis were a history of sexually transmitted disease (OR 1.8), stress at home (OR 1.5), and stress at work (OR 1.2). The 2163 men with prostatitis alone were younger and had less severe urinary symptoms than the 4575 men with BPH alone.

Mehik and associates determined the prevalence of prostatitis symptoms among 2500 randomly selected men living in the two most northerly provinces of Finland (Oulu and Lapland).⁹¹ Surveys were completed by 1832 men 20–59 years old. The overall lifetime prevalence of prostatitis was 14.2%. The risk for prostatitis increased with age: Compared to 20–39-year-old men, the risk of prostatitis was 1.7 times greater for 40–49-year-old men and 3.1 times greater for 50–59-year-old men. The incidence of prostatitis was 37.8/10,000 person years. Among the 261 men who had symptoms of prostatitis, 27% suffered at least once a year, including 16% who suffered from persistent symptoms. These authors noted a seasonal variation, with 63% of participants with prostatitis experiencing their worst symptoms during the winter months. Divorced and single men had a lower risk of prostatitis than married men.

■ NATURAL HISTORY OF PROSTATITIS SYMPTOMS

We identified only two studies that considered the natural history of prostatitis symptoms and that met the criteria for inclusion in this systemic review.^{92,93} Both studies evaluated North American patients after clinical treatment for symptoms of prostatitis.

Nickel and associates conducted a 1-year follow-up study of 40 prostatitis patients and 119 age-matched controls from Eastern Canada.⁹² Fifteen men (38%) with prostatitis in the initial survey did not report similar symptoms 1 year later, while 25 men (63%) experienced persistent symptoms. Four men (3%) in the control group reported prostatitis-like symptoms in the follow-up survey. Thus, about one-third of men with prostatitis-like symptoms in this general population had

Table 61-1. National Institutes of Health Chronic Prostatitis Symptom Index^{a,b}

- | | |
|--|---|
| <p>1. In the last week have you experienced pain or discomfort in the (Yes/No):</p> <ul style="list-style-type: none"> • Area between rectum and testicles (perineum) • Testicles • Tip of penis (not related to urination) • Below your waist, in your pubic or bladder area <p>2. In the last week have you experienced (Yes/No):</p> <ul style="list-style-type: none"> • Pain or burning during urination • Pain or discomfort during or after sexual climax (ejaculation) <p>3. How often have you had pain or discomfort in any of these areas over the last week? (0–5 scale)</p> <ul style="list-style-type: none"> • Never • Rarely • Often • Usually • Always <p>4. Which number describes your AVERAGE pain or discomfort on the days that you had it, over the last week? (0–10 scale)</p> <ul style="list-style-type: none"> • 0 (no pain) • 10 (pain as bad as you can imagine) <p>5. How often have you had a sensation of not emptying your bladder completely after you finished urinating, over the last week? (0–5 scale)</p> <ul style="list-style-type: none"> • Not at all • Less than 1 time in 5 • About half the time • More than half the time • Almost always | <p>6. How often have you had to urinate again less than two hours after you finished urinating, over the last week? (0–5 scale)</p> <ul style="list-style-type: none"> • Not at all • Less than 1 time in 5 • About half the time • More than half the time • Almost always <p>7. How much have your symptoms kept you from doing the kinds of things you would usually do, over the last week? (0–3 scale)</p> <ul style="list-style-type: none"> • None • Only a little bit • Some • A lot <p>8. How much did you think about your symptoms, over the last week? (0–3 scale)</p> <ul style="list-style-type: none"> • None • Only a little bit • Some • A lot <p>9. If you were to spend the rest of your life with your symptoms just the way they have been during the last week, how would you feel about that? (0–6 scale)</p> <ul style="list-style-type: none"> • Delighted • Pleased • Mostly satisfied • Mixed (about equally satisfied and dissatisfied) • Unhappy • Terrible |
|--|---|

^aOf the nine items in the index, four concern pain or discomfort (items 1–4), three concern urinary symptoms (items 5 and 6), two concern the impact of symptoms (items 7 and 8), and one concerns quality of life (item 9). The index can be scored as a total score (maximum score of 43). Scores can also be obtained in each of three domains: pain domain (items 1–4, maximum score of 21), urinary symptoms domain (items 5 and 6, maximum score of 10), and the quality of life domain (items 7–9, maximum score of 12). (From Litwin MS, McNaughton-Collins M, Fowler FJ, Jr., et al. The National Institutes of Health Chronic Prostatitis Symptom Index: Development and validation of a new outcome measure. *Chronic Prostatitis Collaborative Research Network. J Urol* 1999;162:369–375.)

^bExclusion criteria for CP/CPSP include duration less than 3 months, presence of lower genitourinary tract cancer (e.g., transitional cell carcinoma, carcinoma in situ, and prostate cancer), active urinary stone disease, active genitourinary tract infection (e.g., bacteriuria genitourinary tuberculosis), gastrointestinal disorders (e.g., inflammatory bowel disease and perirectal disease, such as fissure or fistula), radiation cystitis, chemical cystitis (i.e., postchemotherapy), active urethritis, acute epididymitis, acute orchitis, functionally significant urethral stricture, or neurological disease affecting the bladder.¹²

resolution after 1 year (usually those with a shorter duration and less severe symptoms). The severity of symptoms of men with persistent prostatitis symptoms remained relatively unchanged over the year.

Turner and associates studied 286 men with physician-diagnosed prostatitis in a large health-maintenance organization.⁹³ Interviews were conducted at baseline, 3-, 6-, and 12-month follow-up. On average, symptoms improved substantially from months 1 to 3, modestly from months 3 to 6,

then remained unchanged. Men whose initial visit was for a first lifetime episode had better outcomes compared to men with a recurrent episode. Participants with more severe symptoms were more likely to report symptoms 1 year later. The authors concluded that men who make physician visits for new prostatitis episodes usually improve during the next 6 months. However, chronic or recurrent symptoms are common. Patients with previous episodes and more severe symptoms are at higher risk of chronic pelvic pain.

■ PROSTATITIS AS A RISK FACTOR FOR BPH AND PROSTATE CANCER

Limited epidemiological data suggest that a history of prostatitis may be associated with an increased risk of BPH and/or prostate cancer. In the health professionals' follow-up study outlined above, men reporting a history of BPH had 7.7-fold greater odds of a history of prostatitis.⁸⁷ This observation appears consistent with current concepts about symptomatic BPH. The natural history of BPH includes two phases: a pathologic phase and a clinical phase.⁹⁴ The pathologic phase may be subdivided further into two stages: a microscopic stage, developed by nearly all men if they live long enough, and a macroscopic stage, associated with enlargement. Because only half of men with microscopic prostatic hypertrophy develop macroscopic enlargement, it is likely that additional factors are necessary for progression. The second, or clinical BPH phase, involves progression of pathologic hypertrophy to clinical BPH, in which the patient develops symptoms. Of men with macroscopic prostatic hypertrophy, half progress to clinical disease. Although macroscopic enlargement of the prostate is necessary for development of clinical BPH, such enlargement is

not sufficient by itself for progression. Prostatitis has been suggested as one possible factor leading to progression of pathological BPH to clinical BPH.⁹⁴ Clearly, further studies are needed to validate this theoretical connection between prostatitis and BPH.

Other epidemiologic data also suggest the possibility that prostatitis may be associated with an increased risk of prostate cancer.^{95–97} Dennis and associates completed a meta-analysis evaluating available studies.⁹⁵ In this study, men with a history of prostatitis had an increased risk of prostate cancer (OR = 1.6), particularly with population-based case-control studies (OR = 1.8). This study also found an increased relative risk of prostate cancer among men with a history of syphilis and a history of gonorrhea (conditions that are also associated with prostatitis).

A recent report investigated the potential association between prostatitis and prostate cancer by reviewing the medical records of 409 residents of Olmsted County, Minnesota, with histologically proven prostate cancer and 803 matched controls.⁹⁸ The risk for prostate cancer was increased in men with history of any type of prostatitis (OR = 1.7; 95% CI = 1.1–2.6) or acute prostatitis (OR = 2.5; 95% CI = 1.3–4.7). The mean time from most recent episode

Table 61-2. Epidemiological Studies of Prostatitis in Adult Men

Authors Year, Country Reference	Population	Number, Age Range (Y)	Prevalence of Prostatitis-Like Symptoms
Roberts et al. (1998) ⁸⁴	Minnesota, USA	2115 men, 40–79	9%
Collins (1998) ⁸⁵	National Ambulatory Medical Care Survey, USA	58,955 visits, >18	5% Overall Urology: 8% Primary care: 1%
Mehik et al. (2000) ⁹¹	Oulu and Lapland Provinces, Finland	1832 men, 20–9	Lifetime prevalence (incidence) 14.2%
Nickel et al. (2001) ⁸⁶	Patients of family practitioners Lennox and Addington counties, Canada	868 men, 20–74	9.7%
Tan et al. (2002) ⁸⁹	Cross-sectional study, Singapore	1087 men, 21–70	2.7%
Kunishima et al. (2002) ⁹⁰	Random sample, Hokkaido, Japan	502 men, 20–79	5%
Cheah et al. (2003) ⁸¹	Random sample, Penang, Malaysia	3147 men, 20–50	8.7%
Collins et al. (2002) ⁸⁷	Health care professionals without prostate cancer, USA	31681 men	Self-reported history: 16%
Roberts et al. (2002) ⁸⁸	Random community-dwelling men, Minnesota, USA	1541 men, 40–79	16% GU pain 2.2% Prostatitis

Data from Krieger JN, Nakagawa M, Nyberg LM. Epidemiology and pathogenesis of prostatitis. In: *6th International Consultation on Prostate Diseases*, Paris, France: International Consultation on Urological Diseases, 2005.

of acute prostatitis to diagnosis of prostate cancer was 12.2 years. Chronic bacterial prostatitis was weakly associated with prostate cancer (OR = 1.6; 95% CI = 0.8–3.1), while CPPS was not.

Although these associations suggest that prostatitis may represent one mechanism through which BPH and prostate cancer develop, causality is unclear. This is because recall bias and detection bias cannot be ruled out.⁹⁶ Self-reporting and review of medical records are the most common methods used to assess past exposures. However, studies have shown that such information may not be consistent. This problem appears to be especially common with prior genitourinary diseases that have less explicit diagnostic criteria, such as BPH and prostatitis.⁹⁹ These observations suggest that prostatitis may increase the risk of both BPH and prostate cancer but that additional studies are necessary to verify that there is indeed a biological relationship between these conditions.

These observations are controversial. For example, a recent study of the epidemiology of prostate cancer used random digit dialing to select a group of aged-matched controls aged 40–64 years without prostate cancer.¹⁰⁰ The “control group” was then divided into those who reported a diagnosis of prostatitis (cases) and those who denied ever having had prostatitis (controls). Of the 645 control men with no history of prostate cancer, 58 (9.0%) reported a prostatitis diagnosis. The prostatitis cases more frequently reported urinary ($P \leq 0.05$) or urethral infections ($P \leq 0.01$) before diagnosis. Men with prostate cancer reported a diagnosis of prostatitis more often than the noncancer controls (13.6% vs. 9.0%), but after controlling for the number of prostate-specific antigen tests this difference disappeared. Clearly, further studies are needed to determine whether prostatitis (symptomatic or asymptomatic) is indeed a risk factor for either BPH or prostate cancer.

LABORATORY ASSESSMENT

■ MICROBIOLOGY

Uropathogenic bacteria

The critical clinical issue is to distinguish patients with lower urinary tract complaints associated with bacteriuria, i.e., patients who may have bacterial prostatitis, from the larger number of patients without bacteriuria.^{1,20} Careful studies have shown that <10% of men, given the clinical diagnosis of “prostatitis,” have bacterial prostatitis.⁸ Further classification of patients with prostatitis is based on careful bacteriologic assessment of the lower urinary tract, preferably using the technique of Meares and Stamey.^{101,102} This method is based on cultures of sequential specimens that are obtained during micturition (Table 61-3).

Attention to several technical points is necessary to assure useful and reliable information.^{1,2,7,102} Precise bacteriologic

Table 61-3. Procedure for Localization of Infection in the Male Lower Urinary Tract by Use of Segmented Urine Cultures

Specimen	Abbreviation	Description
Voided bladder 1	VB ₁	Initial 5–10 mL of urinary stream
Voided bladder 2	VB ₂	Midstream specimen
Expressed prostatic secretions	EPS	Secretions expressed from prostate by digital massage after midstream specimen
Voided bladder 3	VB ₃	First 5–10 mL of urinary stream immediately after prostate massage

Terminology is from Drach GW, Meares EM, Jr., Fair WR, Stamey TA. Classification of benign disease associated with prostatic pain: Prostatitis or prostatodynia? *J Urol* 1978;120:266.

methods and rapid transport to the laboratory are critical. The midstream urine should be sterile during the localization procedure. The prepuce of uncircumcised men should be retracted, the glans cleansed, and the soap removed because small amounts of detergent may falsely reduce bacterial counts. It is important to collect the initial few drops of the first-void urine (VB₁) specimen, since the bacterial concentrations may be significantly reduced a few milliliters later. Finally, it may be necessary to repeat the localization procedure for men with inconclusive findings.

Unequivocal diagnosis of bacterial prostatitis requires that the colony count in the postmassage (VB₃) specimen exceed the count in the first-void (VB₁) specimen by at least 10-fold.^{1,7,12,101,102} However, many men with chronic bacterial prostatitis harbor only small numbers of bacteria in their prostates. Direct culture of the prostatic secretions is useful in this situation.^{1,101,105} Often the colony counts in the EPS specimens are 1 or 2 logs higher than comparable counts in the VB₃ specimen. This difference reflects dilution of the small volume of prostatic secretions by urine in the VB₃ sample. A prominent characteristic of bacterial prostatitis is that the organism present in VB₃ or in EPS in significantly greater numbers than in the VB₁ may be isolated on multiple occasions and is identical to the uropathogen-causing episodes of bacteriuria.^{101,103}

Under certain circumstances, lower urinary tract localization studies may be misleading.³ False impressions concerning excessive concentrations of leukocytes in the EPS occur in urethral disorders, such as urethritis, strictures, condylomata, or diverticula; or in men with noninfectious conditions of the prostate, such as uninfected prostatic calculi; or after

ejaculation.¹⁰⁴ Isolated analysis or culture of the ejaculate without concomitant study of urethral and bladder specimens may be more misleading than isolated examination of prostatic secretions.³ Semen contains fluids from several accessory glands besides the prostatic fluid. Further, cytological examination of semen is complicated by the difficulty of distinguishing immature sperm from leukocytes.^{1,3}

Organisms not cultivated on routine urine cultures

Many other infectious agents, including sexually transmitted infections, have been implicated in prostatitis. These data are considered in the section below considering the etiology of CP/CPPS. Thus, it appears critical to consider an individual patient's risk factors and whether he has evidence of urethritis with appropriate diagnostic testing.

■ LEUKOCYTE EVALUATION

Microscopic evaluation of the EPS has traditionally been recommended to identify inflammation.^{1,2,20} Presence of leukocytes and "oval fat bodies" (large lipid-laden macrophages) is characteristic of the prostatic inflammatory response. Various criteria have been used by researchers to define an abnormal number of leukocytes.^{1,105,106} Most investigators agree that >20 leukocytes per high-power microscopic field (hpf) represent significant inflammation. Many reports use a criterion of ≥ 10 leukocytes/hpf.^{2,20,105,107} There appears to be little value in counting the numbers of leukocytes in the EPS of men with objective evidence of urethral inflammation, especially among men at risk of sexually transmitted diseases.⁷ Thus, we examine a urethral smear for inflammation, before proceeding with a lower urinary tract localization study.^{8,58,102,108} Further, it is clear that the traditional method of counting leukocytes/hpf in an EPS wet mount is inaccurate compared to determining leukocyte concentrations in a counting chamber.¹⁰⁶ Recent studies comparing EPS wet mount to counting chamber concentrations have shown that the wet mount is especially inaccurate for distinguishing inflammation for patients with ≤ 20 EPS leukocytes/hpf.^{58,108}

■ CONTROVERSIES

Gram-positive bacteria in prostatitis

Long-standing controversies surround the role of Gram-positive bacteria in prostatitis, whether (and how) to evaluate lower urogenital tract inflammation. Isolation of Gram-positive organisms, such as staphylococci and diphtheroids, that appear to "localize" to the prostate is a major source of confusion to clinicians and in the literature.^{1,20,109,110} In most cases, such patients have neither a history nor a bacteriologic documentation of bladder infection with these organisms.^{1,20,02} Technical problems, e.g., failure to collect the initial portion of the VB₁,

or having some of the detergent used to cleanse the glans fall into the collection bottle for the VB₁, account for part of the problem.¹ Further, the VB₁ is the control for the VB₃. The EPS is useful in borderline cases only. Relying on the EPS may introduce some artifacts, since prostatic fluid may acquire organisms during transit through the urethra, especially if the EPS drops "hang" at the fossa navicularis.

Some authorities maintain that Gram positives are pathogens responsible for patients' symptoms when these bacteria increase by at least 10-fold (e.g., "localize") in quantitative cultures of "prostate-specific" specimens (EPS or VB₃).^{111,112} Antimicrobial therapy is recommended to resolve "chronic bacterial prostatitis" and to ameliorate patients' symptoms. Others maintain that Gram positives rarely cause bacteriuria and that Gram-positive localizations usually represent non-pathogens that do not cause patients' symptoms.¹ To help resolve this issue, one recent study determined the rate of Gram-positive localizations in 470 chronic prostatitis patients and whether repetitive cultures demonstrated consistent localization of Gram-positive bacteria.¹¹³ Tenfold increases in the concentrations of Gram-positive bacteria were noted when postprostate massage (VB₃) or EPS cultures were compared with first-void urine (VB₁) cultures from 29 patients (6%). This was similar to the 7% rate of Gram-negative chronic bacterial prostatitis. Of the 29 patients with Gram-positive localizations, 27 (94%) did not have consistent localization of Gram-positive species. These findings suggest that Gram-positive bacterial localization results were seldom reproducible in untreated patients. Gram-positive localizations may represent nonpathogens, transient bacterial colonization of the lower urinary tract, or intermittent shedding of prostatic pathogens. These limitations of traditional cultures highlight the need for better diagnostic approaches and improved recommendations for antimicrobial therapy.¹¹³

■ LEUKOCYTE EVALUATION

It is appealing to think that patients with objective evidence of inflammation differ from patients without inflammation. Traditionally, emphasis was limited to evaluation of the EPS.^{1-3,16,40,102,105,114} The traditional classification of prostatitis classified patients with no history of bacteriuria and leukocytes in their EPS as having "nonbacterial prostatitis" to distinguish them from those with no evidence of inflammation in their EPS, termed "prostatodynia." However, despite more than 20 years of effort, no clinical difference either in etiology or in response to therapy was demonstrated between these two populations.

This lack of progress provided a major impetus, supporting reevaluation of the traditional classification scheme leading to development of the NIH consensus classification, emphasized in this chapter.^{12,13,115} One critical aspect of these new prostatitis initiatives was expansion of the definition of

Table 61-4. NIH Consensus Classification of Prostatitis Syndromes¹²⁻¹⁴

Prostatitis Category	Systemic Illness ^a	Bacteriuria ^b	Inflammation ^c	Abnormal Prostate Examination ^d
I. Acute bacterial	+	+	+	+
II. Chronic bacterial	+/-	+	+	-
III. Chronic prostatitis/ chronic pelvic pain syndrome				
a. Inflammatory subtype ^e	-	-	+	-
b. Non-inflammatory subtype ^f	-	-	-	-
IV. Asymptomatic inflammatory	-	-	+	+/-

^aSystemic findings frequently include fever and rigors and may include signs of bacteremia.

^bBacteriuria documented with the same organism that can be shown to localize to a prostatic focus of infection when the midstream urine culture is negative.

^cElevated concentrations of leukocytes in the expressed prostatic secretions, semen, postprostate massage urine, prostate tissue or semen.

^dAbnormal prostate examination findings include exquisite tenderness and swelling that may be associated with signs of lower urinary tract obstruction. In asymptomatic patients, a prostate nodule may prompt biopsy.

^eFormerly termed nonbacterial prostatitis (when limited to examination of the prostatic secretions).

^fFormerly termed prostatodynia (when limited to examination of the prostatic secretions).

urogenital tract inflammation to include patients with increased concentrations of leukocytes in their EPS, post-prostate massage urine (VB₃), or semen in a new “inflammatory” subtype (Table 61-4). Studies using a counting chamber and special stains to determine leukocyte concentrations in 100 chronic prostatitis patients found poor correlation between inflammation in the EPS and inflammation in the seminal fluid.¹¹⁶ Another study of 235 subjects with symptoms of chronic prostatitis found that, compared with an examination of a urethral swab specimen, examination of either first-void urine or midstream urine had low sensitivity for detecting urethral inflammation. Thus, our preference is to examine both the EPS and the VB₃ proved best for detecting prostatic fluid inflammation. Combining the urethral smear with lower urinary tract localization (“four-glass test”) represents an optimal approach for detecting urethral and prostatic inflammation.^{58,108}

The critical question is to determine whether there is any clinical difference in the inflammatory response between prostatitis patients with inflammation and those with no evidence of inflammation. For example, the NIH Chronic Prostatitis Cohort Study evaluated 488 men.¹¹⁵ Although 50% of participants had urethral leukocytes, they were not evaluated for recognized urethral pathogens. The prevalence of inflammatory chronic prostatitis ranged from 90% to 54%, depending on the composite set of cut-points. In a subsequent study, these investigators compared leukocyte counts and bacterial localization rates for 463 men enrolled

in the NIH chronic prostatitis Cohort Study and 121 age-matched men without urinary symptoms.¹¹⁷ Men with Chronic Prostatitis had statistically higher leukocyte counts in all segmented urine samples and EPS, but not in semen compared to asymptomatic control men. However, the control population also had a high prevalence of leukocytes. These investigators questioned the clinical usefulness of the standard four-glass test as a diagnostic tool. Thus, the optimal diagnostic approach to patients with chronic prostatitis is an area of intense debate.

CLASSIFICATION OF PROSTATITIS SYNDROMES

Until the last decade, the characteristic symptoms of prostatitis were poorly defined.^{118,119} This situation changed dramatically following general acceptance of the concept that most cases of prostatitis are diagnosed clinically, based on patients’ symptoms rather than physical findings or laboratory tests.

The preferred classification of prostatitis syndromes was developed by an NIH-sponsored conference that includes four categories: acute bacterial prostatitis, chronic bacterial prostatitis, chronic prostatitis/chronic pelvic pain syndrome CP/CPPS and asymptomatic inflammatory prostatitis (Table 61-4).¹² In addition, some patients develop granulomatous prostatitis, a category that is not considered specifically in the consensus classification.

■ ACUTE BACTERIAL PROSTATITIS (CATEGORY I)

Acute bacterial prostatitis is an acute, symptomatic bacterial infection of the prostate associated with bacteriuria and often with systemic signs and symptoms. Patients have evidence of an inflammatory response in their prostatic secretions and semen and often have an abnormal prostate on digital rectal examination.

■ CHRONIC BACTERIAL PROSTATITIS (CATEGORY II)

Chronic bacterial prostatitis is a persistent bacterial infection of the prostate gland that results in recurrent episodes of bacteriuria. During acute exacerbations, patients may have systemic symptoms, but this is uncommon. Inflammation characteristically occurs in the prostatic secretions. Patients seldom have an abnormal prostate on examination.

■ CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME (CP/CPPS) (CATEGORY III)

Patients with CP/CPPS account for the largest population of patients presenting with prostatitis symptoms. Characteristic complaints include a variety of perineal and pelvic symptoms, voiding, and sexual dysfunction. These men have no history of bacteriuria and lack objective evidence of bacterial infection of their prostatic secretions on careful localization studies. On examination, their prostate glands are usually normal.

Currently, two subtypes of CP/CPPS are distinguished. There is an inflammatory subtype (category III a), characterized by objective evidence of inflammation in the prostatic secretions, postprostate massage urine, or semen. Patients with no evidence of inflammation in any of these specimens/samples are classified as having noninflammatory CP/CPPS (category III b).

■ ASYMPTOMATIC INFLAMMATORY PROSTATITIS (CATEGORY IV)

The consensus classification includes a category for patients who have histological evidence of prostatic inflammation. These patients often do not have symptoms associated with other prostatitis syndromes. Asymptomatic prostatic inflammation is usually diagnosed for patients with elevated prostate-specific antigen levels who undergo prostate biopsy to rule out prostate cancer, examination of prostate tissue removed for treatment of bladder outlet obstruction, or patients undergoing evaluation for infertility.

■ GRANULOMATOUS PROSTATITIS

Although not formally noted in the NIH consensus classification, granulomatous prostatitis represents a distinct and important prostatitis syndrome. Granulomatous prostatitis represents the characteristic histological reaction of the prostate to a

variety of insults. Some patients have symptoms, while others present with a nodular prostate or with bladder outlet obstruction. Accurate diagnosis is important because any cases are related to infections requiring specific antimicrobial therapy.

CLINICAL MANIFESTATIONS, TREATMENT, AND COMPLICATIONS

The sections below consider diagnosis, clinical management, and potential complications of the major prostatitis syndromes.

■ CATEGORY I. ACUTE BACTERIAL PROSTATITIS

Acute bacterial prostatitis is characterized by the abrupt onset of symptoms and dramatic findings on physical examination. Laboratory findings include bacteria in the midstream urine, EPS, and post-massage urine passed after prostatic massage. Most patients respond readily to appropriate treatment, and the disease is self-limited in most cases. Rarely, patients develop complications, such as urinary retention, chronic bacterial prostatitis, prostatic abscess, or granulomatous prostatitis.

Clinical presentation

Acute bacterial prostatitis is seldom a subtle or difficult diagnosis.^{1,20,103} Characteristic symptoms are those associated with lower urinary tract infection, such as increased urinary frequency, urgency, and dysuria. Patients may also complain of bladder outflow obstruction due to acute edema of the prostate. Signs of systemic toxicity are common and may include fever, malaise, and myalgias. Physical examination may show a high temperature and lower abdominal or suprapubic discomfort due to bladder infection or urinary retention. The rectal examination is frequently impressive, with an exquisitely tender, tense, “hot” prostate on palpation. Urinalysis is abnormal with pyuria, and cultures will be positive for Gram-negative aerobic rods or *Streptococcus faecalis*. Systemic leukocytosis is common, with increased numbers of segmented cells. Bacteremia may be present spontaneously or may result from vigorous rectal examinations.

Treatment

Antimicrobial therapy usually results in dramatic improvement of signs and symptoms of acute bacterial prostatitis. Many drugs that do not penetrate into the prostate under normal conditions have proven effective for treating acute bacterial prostatitis.^{1,20} Thus, drugs appropriate for treatment of bacteremia caused by Enterobacteriaceae, pseudomonads, or enterococci should be started after specimens have been obtained for urine and blood cultures. For men who require hospitalization, conventional therapy is the combination of an aminoglycoside plus a beta-lactam drug.^{3,7} However, the fluoroquinolones or third-generation cephalosporins represent attractive alternatives for monotherapy.^{120,121} For men with

less severe infections, the conventional choice is the combination of trimethoprim and sulfamethoxazole.^{1,20} However, the fluoroquinolones have proven useful as oral therapy for patients with acute bacterial prostatitis who do not require hospitalization, with most data being available for ciprofloxacin and levofloxacin.^{112,122–126}

Patients with acute urinary retention require bladder drainage. In this situation, placement of a suprapubic cystostomy tube, either using a percutaneous trocar apparatus or by open surgery, is preferred. An indwelling transurethral catheter would pass through and obstruct drainage of the acutely infected prostate, increasing the risk for bacteremia and prostatic abscess.^{1,7} However, there has never been a direct comparison between suprapubic and transurethral catheterization in this situation. Some authorities suggest that a transurethral catheter may work well in the absence of persistent fever or signs, suggesting a possible prostatic abscess.¹²⁷ General measures, including hydration, analgesics, and bed rest, are also indicated.^{1,7,20,103}

Complications

A few patients with acute bacterial prostatitis experience complications.^{1,6,121} Chronic bacterial prostatitis occasionally follows an episode of acute bacterial prostatitis. Men with chronic bacterial prostatitis often remain asymptomatic between acute episodes of bacteriuria.

Prostatic abscess is a rare complication among patients who receive appropriate antimicrobial therapy for acute bacterial prostatitis.^{6,7,121,128,129} In one series of 28 patients referred for persistent fever following treatment for acute bacterial prostatitis, transrectal ultrasonography detected only two prostatic abscesses (7%).¹³⁰ The classical presentation of prostatic abscess is a fluctuant area in the prostate that is felt during rectal examination.^{128,131,132} However, many patients present with more subtle findings. Transrectal ultrasound and computerized tomography are especially valuable for diagnosis of prostatic abscess in men with such subtle findings.^{133–136} Treatment includes drainage of the abscess, using a perineal, percutaneous, or transurethral approach, besides appropriate antimicrobial therapy.^{135,136} In most situations, the transurethral approach is optimal.

Granulomatous prostatitis may occur during resolution of an episode of acute bacterial prostatitis.^{1,137} Usually, the patient is asymptomatic but has a hard area on rectal examination that arouses the suspicion of carcinoma. Areas of prostatic infarction may also complicate acute bacterial prostatitis. Such areas usually present as firm portions of the prostate, and their chief importance lies in the differential diagnosis of carcinoma.

■ CATEGORY II. CHRONIC BACTERIAL PROSTATITIS

Although chronic bacterial prostatitis is uncommon, it is critical to distinguish these patients. Chronic bacterial

prostatitis is an important cause of bacterial persistence in the male lower urinary tract.^{1,20,103} Patients characteristically experience recurrent episodes of bacteriuria caused by the same bacterial species.^{1,102} It has been stated that the most common cause of relapsing urinary tract infections in adult men is the persistence of small numbers of bacteria in the prostate.¹ Patients are often asymptomatic between episodes of bladder bacteriuria. The prostate gland is usually normal on either rectal or endoscopic evaluation. Thus, careful lower urinary tract localization studies are critical for diagnosis of chronic bacterial prostatitis.¹⁰¹ Diagnosis based solely on symptoms, numbers of leukocytes in EPS or semen, or prostate biopsy is inadequate. Appropriate antimicrobial therapy results in cure or amelioration of symptoms for the great majority of patients.

Clinical presentation

Men with chronic bacterial prostatitis occasionally present with signs of a systemic illness. Small numbers of bacteria in the prostate do not cause systemic illness. However, with acute exacerbations, bladder bacteriuria and secondary sepsis may result from the prostatic focus of infection. This is especially true among older men, who may have the combination of prostatic obstruction and infection.

Traditional thinking is that Gram-negative rods, Enterobacteriaceae, and pseudomonads are, by far, the most important pathogens in chronic bacterial prostatitis.^{1,20,102,103} Gram-positive cocci, such as *S. faecalis* or *Staphylococcus saprophyticus*, may be the etiologic organisms in a few cases.^{20,138} Reports implicating many other organisms in the etiology of chronic bacterial prostatitis are difficult to evaluate because of methodological problems with case definitions, lack of documentation of bacteriuria caused by the alleged pathogen, or lack of an immunological response by the prostate.^{3,7,46,139}

This traditional view of the critical organisms has been challenged. First, electron microscopic studies suggest that some Gram-positive bacteria may be identified in intraprostatic biofilms in a few patients with antibiotic-refractory prostatitis.^{140–143} Second, some investigators consider Gram-positive bacteria to be pathogens meriting antimicrobial therapy, if these organisms are shown to localize to the prostate on segmented cultures, despite absence of bacteriuria.^{111,112} Third, Gram positives represented the preponderance of bacterial species treated in studies, leading to FDA approval of trovafloxacin, gatifloxacin, and levofloxacin for treatment of chronic bacterial prostatitis.¹¹²

Chronic bacterial prostatitis is associated with secretory dysfunction of the prostate gland.²⁰ Alterations include increased pH of prostatic secretions, changes in the ratio of LDH isozymes, and secretion of immunoglobulins. Other changes include decreased specific gravity of prostatic secretions, prostatic antibacterial factor, cation concentrations

(zinc, magnesium, and calcium), citric acid, spermine, cholesterol, acid phosphatase, and lysozyme. These findings suggest that bacterial prostatitis is associated with a generalized secretory dysfunction of the prostate gland.

Men with chronic bacterial prostatitis characteristically have episodes of symptomatic bladder bacteriuria caused by the same organism; these episodes are separated by asymptomatic intervals of varying length.^{1,20} Lower tract localization studies during episodes of bladder bacteriuria are worthless^{1,101}; patients must be evaluated when their midstream urine is sterile. Occasionally, it may be necessary to eradicate organisms present in the bladder urine and urethra with drugs, such as penicillin G or nitrofurantoin, to obtain diagnostic localization studies.¹

Medical therapy

Medical management is effective in curing or suppressing bacterial prostatitis.^{1,3,121} Effective antimicrobial therapy for localized bacterial infections depends on achieving sufficient levels of an appropriate drug at the infected site. Unfortunately, many drugs penetrate prostatic parenchyma poorly^{114,144} and may even be less useful if the prostate gland contains bacteria within infected biofilms.¹⁴¹ Other antimicrobials, such as erythromycin, which achieve good tissue levels, have an inappropriate spectrum for the pathogens in prostatitis.²

Trimethoprim–sulfamethoxazole is the traditional “gold standard” for treating chronic bacterial prostatitis.^{3,121} Trimethoprim has two useful characteristics: It achieves adequate levels in prostatic parenchyma and is effective against the common bacterial pathogens. Available studies usually employed the combination of trimethoprim and sulfamethoxazole for men with well-documented chronic bacterial prostatitis. Long-term therapy with trimethoprim (80 mg) plus sulfamethoxazole (400 mg) taken orally twice daily for 4–16 weeks was superior to shorter treatment courses.^{145,146} Follow-up studies showed that such long courses result in symptomatic and bacteriologic cure in approximately one-third of patients, symptomatic improvement during therapy in approximately one-third of patients (who relapse after stopping treatment), and no improvement in the remaining patients.^{20,145–148} Single-agent treatment using trimethoprim alone has been studied less well. In theory, trimethoprim alone should produce comparable results to combination therapy, since sulfamethoxazole diffuses poorly into the prostatic parenchyma.^{2,77}

During the last decade, considerable success has been reported using several newer fluoroquinolones to treat chronic bacterial prostatitis. In contrast to the beta-lactams, concentrations of many fluoroquinolones are high in prostatic fluid, in prostatic tissue, and in seminal fluid, compared to blood plasma levels.^{124,125,149–152} Good results have been reported for men with chronic bacterial prostatitis, including some patients who failed therapy with trimethoprim–sulfamethoxazole.^{124,125,149–151} Promising results have been described with a number of agents,

including norfloxacin, ciprofloxacin, ofloxacin, enoxacin, temafloxacin, gatifloxacin, trovafloxacin, and levofloxacin.^{123–126,150,151,153,154} Available studies are difficult to compare because investigators used varying diagnostic criteria, there was a considerable range in duration of treatment and of follow-up, and few studies compared effective agents. Because relapse rate is the critical issue for evaluating treatment of prostatitis, patients cannot be considered cured without long-term follow-up. On balance, the newer quinolone agents appear to provide the best results.^{155,156} The largest clinical and clinical trials experience is with ciprofloxacin,¹⁵⁷ for which excellent, long-term data are available,¹²² and with levofloxacin,^{155,156} which has recently been approved by the FDA for this indication (Table 61-5).

Many other orally administered antimicrobials have been used to treat patients with chronic bacterial prostatitis. Most reports are hampered by imprecise case definitions, lack of sufficient microbiologic documentation or follow-up, or an abundance of patients “infected” with organisms generally considered urethral contaminants. Although it is difficult to draw definitive conclusions, the indanyl ester of carbenicillin,^{158,159} doxycycline,¹⁶⁰ rosamicin,¹⁶¹ erythromycin plus urinary alkalization with bicarbonate,^{162,163} or drug combinations employing rifampicin plus trimethoprim¹⁶⁴ might prove useful for selected patients. Some investigators report success using aminoglycosides, administered parenterally¹ or by local injection into the prostate^{165,166} for men with prostatitis who failed oral therapy.

Bacteria isolated from men with chronic bacterial prostatitis are generally antimicrobial-sensitive strains, even after multiple symptomatic episodes and prolonged courses of therapy.^{1,7,20} However, these bacteria tend to have multiple virulence factors characteristic of invasive uropathogens.^{167–171} Although bacterial resistance is seldom a major problem in chronic bacterial prostatitis, an infected prostate may become the focus of a persistent infection with recurrent bouts of bacteriuria and a risk for blood stream infection. Although often identified in the prostates of asymptomatic men,^{75,172} some studies suggest that calculi occur more often among men with chronic bacterial prostatitis. Infection of prostatic stones may serve as a persistent focus for bacteria that is difficult to eradicate with antimicrobial agents.^{3,173–177} Other reasons offered for the difficulty in curing chronic bacterial prostatitis include difficulties in achieving high levels of drug in areas of infection within the prostate, changes in the pH of the prostatic fluid associated with infection that influence the diffusion of drugs into the prostate,^{178–180} and presence of biofilms^{140,141} that protect bacteria from antimicrobial agents.

Men with chronic bacterial prostatitis who are not cured by antimicrobial therapy may be rendered asymptomatic by long-term suppressive treatment, using low-dosage antimicrobial agents.^{1,20} Since most patients are asymptomatic between episodes of bacteriuria, the goal of suppressive therapy is to

Table 61-5. Prostatitis Treatment Strategies^a

Category	First-Line	Second-Line	Other	Evidence
I. Acute bacterial prostatitis	Antimicrobial Fluoroquinolone	Antimicrobial Trimethoprim- sulfamethoxazole	Bladder drainage Supportive	Case series, multiple
II. Chronic bacterial prostatitis	Antimicrobial Fluoroquinolone	Antimicrobial Trimethoprim- sulfamethoxazole	Antimicrobial Suppression Various drugs	Case series, multiple
III. Chronic prostatitis/ chronic pelvic pain syndrome	Antimicrobial Fluoroquinolone— newly diagnosed	Alpha-blocker	Various	Case-series-variable results Expert opinion
IV. Asymptomatic inflammatory prostatitis	No therapy	Antimicrobial	Anti-inflammatory	Debate among Experts
Granulomatous	Antimicrobial Depending on etiologic agent	None-if asymptomatic with nonspecific findings		Case reports, small series

^aPlease refer to appropriate sections of the text for discussion of the diagnosis and treatment strategy for each category.

prevent symptomatic episodes, despite persistence of bacteria in the prostate. Very low doses of agents are remarkably effective in preventing episodes of symptomatic bladder bacteriuria among men with chronic bacterial prostatitis. Available drugs include penicillin G, tetracyclines, nitrofurantoin, naladixic acid, cephalexin, or trimethoprim–sulfamethoxazole.

The data above form the basis of a rational approach to antimicrobial therapy for men with chronic bacterial prostatitis (Table 61-5). It is important to document a prostatic source of organisms causing bacteriuria by careful lower urinary tract cultures. If cultures indicate chronic bacterial prostatitis, then a prolonged course of therapy should be employed in an effort to cure the infection, using an appropriate drug that achieves good levels in the prostate. During and after such therapy, lower urinary tract studies should be repeated to evaluate the therapeutic response. A second course of treatment using a different drug or a drug with a different mechanism of action may be indicated for men with a persistent focus of prostatic infection. Men who are not cured may be treated with long-term, low-dose, suppressive medication, to prevent colonization of the bladder and urethra with organisms from the prostate.

Surgical therapy

Surgery has a limited role in the treatment of patients with chronic bacterial prostatitis. Although complete surgical removal of the prostate by radical prostatectomy or cystoprostatectomy will cure bacterial prostatitis,¹ such surgery is

a major undertaking that is associated with a significant incidence of complications. Thus, radical surgery is best reserved for patients with localized prostate cancer. For the rare men who have both carcinoma of the prostate and chronic bacterial prostatitis, radical prostatectomy may cure both conditions.

Subtotal prostatectomy (transurethral, retropubic, suprapubic, or visual laser ablation) is the most common procedure for treating benign prostate disorders. These procedures remove periurethral adenomatous tissue, leaving the surgical capsule of the prostate. The observation that most bacteria appear to be located in the peripheral prostatic tissue may explain why subtotal prostatectomy cures only about a third of patients with well-documented chronic bacterial prostatitis.^{1,20,181} Therefore, transurethral or open surgical procedures for removal of prostatic adenomas are best reserved for patients who have symptoms of lower urinary tract obstruction that persist after sterilization of the midstream urine.

Occasional studies report higher cure rates using transurethral resection to remove infected prostatic calculi and periurethral adenoma in men with chronic bacterial prostatitis.^{182–184} “Radical” transurethral resection is necessary to remove all infected stones, because the peripheral zone of the prostate contains the greatest foci of infection and stones.^{10,177} The populations in most reports were defined poorly, and bacteriologic evaluation and follow-up were often inadequate to document the conclusion that 70–100% of patients were “cured.”

Rare patients with chronic bacterial prostatitis associated with other obstructive lesions, e.g., urethral stricture disease, may benefit from surgery combined with antimicrobial therapy. Before recommending surgery, it is essential to document the functional significance of such lesions by appropriate urodynamic and radiographic studies when the patient is not bacteriuric.

■ CATEGORY III. CP/CPPS

A wide variety of infectious and noninfectious causes have been implicated in the literature, but the etiology of this condition has been poorly defined. Men with recognized uropathogens respond to specific treatment, but therapy is empirical and ineffective for many patients. Fortunately, the quality of treatment studies has improved dramatically, reflecting the development of standard diagnostic and outcome criteria.

Clinical presentation

CP/CPPS represents the largest category of patients presenting with prostatitis, accounting for more than 90% of patients evaluated.^{185,186} These patients have no history of bacteriuria and lack objective evidence of bacterial infection of their prostatic secretions on careful lower urinary tract localization studies (Table 61-4).^{12,187,188} Until recently, the characteristic symptoms were defined poorly.¹¹⁸ However, a number of investigators have confirmed the observation that pelvic pain complaints represent the most characteristic symptoms, often with prominent voiding symptoms and sexual dysfunction.¹¹⁸ These observations led to development of the National Institutes of Health Chronic Prostatitis Symptoms Index (NIH-CPSI) (Table 61-1).⁷⁸ This instrument has now been validated in multiple languages and populations.^{79–82,92} Of the nine items in the index, four concern pain or discomfort (items 1–4), three concern urinary symptoms (items 4 and 6), two concern the impact of symptoms (items 7 and 8), and one concerns quality of life (item 9). The index can be scored as a total score (maximum score of 43). Scores can also be obtained in each of three domains: pain domain (items 1–4, maximum score of 21), urinary symptoms domain (items 5 and 6, maximum score of 10), and the quality-of-life domain (items 7–9, maximum score of 12). At this time, the precise NIH-CPSI cut-points for diagnosis and the appropriate outcome for clinical trials remain the subjects of active investigation.

Sickness impact

Standardized interviews and psychological testing showed that many CP/CPPS patients met objective criteria for depression.¹⁸⁹ One study compared age- and education-matched men with chronic low back pain to patients with CP/CPPS.¹⁹⁰ Subjects were evaluated by the same psychologist with standardized interviews plus Minnesota Multiphasic Personality Inventory testing. Prostatitis patients were employed but reported that

symptoms interfered greatly with their sexual and romantic relationships. In contrast, back pain patients reported that their pain interfered primarily with work; most had long-term marital relationships, whereas few prostatitis patients did. Half of the CP/CPPS patients met criteria for major depression, but back pain patients were more somatically focused, depressed, and anxious. Next, 39 CP/CPPS patients were evaluated using the sickness impact profile and several symptom measures.¹⁹¹ Multiple regression analyses showed that pain was the only physical symptom that significantly contributed toward sickness impact. The sickness impact profile score of CP/CPPS patients was within the range of patients suffering from myocardial infarction, angina, or Crohn's disease. These findings were confirmed in the NIH Chronic Prostatitis Clinical Research Network cohort study.¹⁹²

Etiology

The etiology of CP/CPPS is unclear for most patients. Many workers have examined microbiologic, urodynamic, and psychological aspects.^{1,3,7} However, no study has been completely satisfactory with careful definition of the disease, adequate microbiologic evaluation, and psychological assessment. The generally accepted symptoms of CP/CPPS (Table 61-1) overlap typical symptoms associated with conditions such as persistent and/or recurrent urethritis. Half of participants in some important prostatitis studies had urethral leukocytes, but these studies did not evaluate accepted urethral pathogens.^{115,117,193–195} The evidence for various proposed causes is summarized below, emphasizing genitourinary infection, the major focus of this text. We also consider the other prominent etiological theories.

Genitourinary tract infection

Several observations provide empirical support for the concept that genitourinary tract infection may be important in the etiology of CP/CPPS. Patients often relate the onset of their condition to sexual activity, commonly to an episode of acute urethritis.^{8,117,186} Antimicrobial therapy often results in transient relief of symptoms. Based on these observations, standard clinical practice is to use multiple courses of antibacterial therapy, hoping that patients will experience lasting relief.^{8,117,186} In addition, varied microorganisms, especially bacteria, have been implicated in CP/CPPS. The standard classification of prostatitis syndromes considers these agents as potential causes of CP/CPPS (category III) rather than acute bacterial prostatitis (category I) or chronic bacterial prostatitis (category II), because these patients do not have bacteriuria (urinary tract infection).

Chlamydia trachomatis. *C. trachomatis* is the most controversial infectious organism implicated in prostatitis. Mårdh and Colleen¹⁹⁶ obtained urethral specimens for culture of *Neisseria gonorrhoeae*, *T. vaginalis*, *Ureaplasma urealyticum*,

Mycoplasma hominis, *C. albicans*, anaerobic bacteria, and some viruses from 78 men with “nonacute prostatitis” and from 20 normal men. There were no significant differences between the cases and controls. One-third of the men with prostatitis had antibodies to *C. trachomatis*, compared with 3% of controls. Tetracycline treatment was superior to placebo in eliminating symptoms. However, in follow-up studies employing cultures and serology, these workers could not implicate *C. trachomatis* as the cause of idiopathic “prostatitis.”^{197–200} The authors concluded that chlamydiae were not important agents in “chronic prostatitis.” Similarly, we could not culture *C. trachomatis* from the urethras of men with nonbacterial prostatitis or prostatodynia,²⁰¹ nor did we demonstrate a serologic or local immune response to *C. trachomatis* in a smaller number of such patients. Doble and associates evaluated 60 men with the diagnosis of “chronic abacterial prostatitis,” using transrectal prostatic ultrasound with transperineal biopsy of abnormal areas.²⁰² Chlamydiae were not cultured from the prostatic tissue of any patient nor were they detected by immunofluorescence. In addition, no subject had serum antibody titers against *C. trachomatis*.

In contrast, Bruce et al.²⁰³ examined early-morning urine, prostatic fluid, or semen from 70 men with “subacute or Chronic Prostatitis.” Of these 70 men, 39 (56%) were infected with *C. trachomatis*. Criticism was directed against the microbiologic methods in this study and the high rate of positive chlamydial cultures in the control groups, i.e., nine (17%) of 54 men undergoing elective vasectomy had cultures positive for *C. trachomatis*.²⁰⁴ In a follow-up study, Bruce and Reid²⁰⁵ evaluated 55 men with “prostatitis,” including 31 “believed to have chlamydial prostatitis.” Only six cases met strict criteria for chlamydial prostatitis, based on identification of the organisms by culture or immunofluorescence techniques. Japanese investigators identified *C. trachomatis* in the urethras of 20% of men with prostatitis.²⁰⁶ Other investigators reached similar conclusions.^{207–209}

In support of a potential etiological role, Poletti and associates isolated *C. trachomatis* from prostate cells obtained by transrectal aspiration biopsy of men with “nonacute abacterial prostatitis.”²¹⁰ Abdelatif et al. evaluated transurethral prostate specimens with histologic evidence of chronic abacterial prostatitis using *in situ* hybridization.²¹¹ Intracellular chlamydiae were detected in seven (30%) of 23 cases. Shurbaji and associates also identified *C. trachomatis* in paraffin-embedded sections from five (31%) of 16 men with histological evidence of prostatitis, but in none of 19 cases of prostatic hyperplasia without significant inflammation.²¹² Kobayashi and Araki found peroxidase–antiperoxidase staining for chlamydiae in prostate biopsy tissue following therapy.²¹³ These studies suggest that chlamydiae may invade the prostate that chlamydial antigen may persist in the prostate after treatment and that presence of such antigen might be related to prostatitis.

Important criticisms of previous studies include absent or inappropriate controls, that urethral specimens may not reflect prostatic infection, and that prostate tissue and secretions inhibit culture methods for *C. trachomatis* and other microorganisms. Other reservations are that direct methods (such as microscopy, immunofluorescence, or *in situ* hybridization) may be insensitive for identification of defective organisms or organisms present in small numbers. Demonstration of chlamydial DNA and RNA by PCR in culture-negative cases of trachoma (a chronic eye disease caused by *C. trachomatis*) suggests that “Live Chlamydiae may remain at a site of infection and produce inflammation beyond the time at which microbial techniques are able to detect them.”²¹⁴ Similar events may occur in chronic prostatitis. Another problem is that biopsy studies sampled abnormal areas only. Thus, the precise role of *C. trachomatis* in nonbacterial prostatitis deserves further study.

Ureaplasma urealyticum. Weidner and associates²¹⁵ suggested that *U. urealyticum* may be associated with the development of “chronic prostatitis.” In a study of >700 patients, high concentrations of *U. urealyticum* ($>10^3$ /mL) in prostatic fluid, semen, or urine obtained after prostatic massage were associated with clinical signs and symptoms of “prostatitis.” A recent study identified “significant” concentrations of *U. urealyticum* in 18 (13%) of 143 men with prostatitis.²¹⁶ Treatment with either ofloxacin or minocycline resulted in clearance of the organisms in all cases and resolution of symptoms in 10 patients (71%). Isaacs cultured *U. urealyticum* at concentrations $>10^3$ ccu/mL from prostatic secretions of 11 (8%) of 131 men in study with chronic nonbacterial prostatitis without other organisms, suggesting an etiological role.²¹⁷ Other investigators, however, have been unable to implicate the genital mycoplasmas in nonbacterial prostatitis.^{181,196} Additional studies employing other, carefully defined patient populations and immunologic and/or molecular diagnostic techniques and methods for identification of multiple pathogens would be useful to assess the purported role of *U. urealyticum* in prostatitis syndromes.

T. vaginalis. It has been proposed as one cause of varied urological conditions. Studies outlined in the chapter on trichomoniasis suggest that *T. vaginalis* is, indeed, pathogenic in the male lower genitourinary tract. The protozoa may cause nongonococcal nonchlamydial urethritis and persistent infection. We isolated *T. vaginalis* and *C. trachomatis* with comparable frequencies from the urethras of men with CP syndromes.⁸ *T. vaginalis* has been identified in urinary sediment, prostatic secretions, and prostatic parenchyma. In some studies, the prevalence of trichomoniasis has exceeded 85% among men with symptoms of prostatitis that persisted despite antibacterial therapy.^{218,219} These findings support previous reports of an association between *T. vaginalis* and prostatitis.^{218–223} Some suggest that the highest prevalence is in men with long-term symptoms and in those who have not

responded to standard antibacterial therapy.²¹⁹ However, the precise role of *T. vaginalis* as a cause of nonbacterial prostatitis remains undefined. Specific diagnosis is necessary because treatment of trichomoniasis requires antimicrobials seldom prescribed for urogenital infections in men.

Other microorganisms. Many other organisms are regarded as potential causes of prostatitis and urethritis syndromes, including viruses, fungi, and anaerobic and Gram-positive bacteria. In two Scandinavian studies, men with “chronic nonbacterial” prostatitis had prostate biopsies that were cultured for aerobic bacteria, anaerobic bacteria, and viruses.^{224,225} Neither study demonstrated an etiologic role for such pathogens.

Gram-positive aerobic bacteria are the most controversial of these proposed microbial causes of nonbacterial prostatitis. Although the significance of Gram-positive cocci has been debated for over 20 years, until recently the consensus was that these organisms are rarely, if ever, causative.^{7,20,102,226} Costerton and Nickel revived this debate by localizing coagulase-negative staphylococci to the prostates of three men with “prostatitis” that was refractory to antimicrobial treatment.¹⁴⁰ The bacteria were isolated in culture from prostate biopsies. Electron microscopy demonstrated, “sparse and focal microcolonies adherent to the prostatic ductal walls,” suggesting sequestration of resistant staphylococci within intraprostatic biofilms. In contrast, other investigators found that such organisms disappeared without treatment in all cases.²²⁷

In the preantibiotic era, *N. gonorrhoeae* was a recognized cause of prostatitis and the most common cause of prostatic abscess.²²⁸ However, gonococcal prostatitis has seldom been reported in the postantibiotic era. Two studies demonstrated antibody against *N. gonorrhoeae* in prostatic fluid of men whose cultures were negative.^{199,229} In contrast, other studies seldom identified *N. gonorrhoeae* as a cause of prostatitis.^{3,102,201}

Anaerobes were suggested as potentially important, but controlled studies showed no significant differences in anaerobic bacteriology between cases and controls.²²⁷ However, these studies employed outdated bacteriological methods. Of viruses that may be cultured from genitourinary sites, herpes viruses types 1 and^{2230–232} and cytomegalovirus^{233–235} are the most likely causes of prostatitis, based on anecdotal reports.

Molecular data

The studies described above used culture or antigen detection in samples such as urine, urethral swabs, and EPS. Interpretation of the findings is complicated, since these samples can acquire organisms during passage through the urethra. These considerations led us to evaluate the urethra, EPS, segmented urine specimens, and prostate biopsy tissue from CP/CPPS patients. Potential subjects were excluded if they had evidence of bacteriuria, bacterial prostatitis, or urethritis.²³⁶ Of the 135 subjects evaluated, 10 (8%) had positive PCR assays for *Mycoplasma genitalium* (four subjects), *C. trachomatis*

(three subjects), and *T. vaginalis* (two subjects), and one man positive for both *M. genitalium* and *C. trachomatis* (Table 61-2). These data fit with previous studies indicating that both *C. trachomatis*^{210–212} and *T. vaginalis* may be identified in prostate tissue.²²² To our knowledge, this is the first demonstration of *M. genitalium* in prostate tissue. These findings suggest that *C. trachomatis*, *T. vaginalis*, and *M. genitalium* may be associated with some cases of CP/CPPS, even among men who have no evidence of urethritis and men who have negative urethral cultures. Tetracycline-resistance encoding sequences were detected in 25% of subjects, and bacterial ribosomal RNA-encoding sequences (16S rRNAs) were detected in 77% of subjects tested. There was a strong correlation between inflammation in the EPS and detection of 16S rRNA in prostatic tissue ($P < 0.001$).

Other investigators confirmed that 16S rRNAs may be found in prostate biopsies from patients with prostate disease,²³⁷ but not from prostate biopsies from healthy organ donors.²³⁸ DNA cloning and sequencing indicated that prostate tissue from patients with CP/CPPS harbored multiple sources of 16S rRNA-encoding DNA. “Real-time” PCR assays suggest that a minority of patients have 16S rRNA high levels, consistent with active infection.^{239,240} These studies should provide important insights into the causes of the CP/CPPS and may elucidate optimal clinical evaluation and treatment in patients. While it is impossible to determine cause and effect using a case-control design, these findings suggest that fastidious or noncultivable microorganisms might be important in inflammatory CP/CPPS.

Noninfectious causes

While several mechanisms have been proposed to be involved in the pathogenesis of CP/CPPS, there is currently no consensus. In addition to infection, neuromuscular dysfunction affecting voiding and/or ejaculation, immunological dysfunction, interstitial cystitis, and chronic pain have received considerable attention as potential etiological factors. Although these factors are likely important in individual patients, the precise proportion of cases related to these causes remains poorly defined and controversial. In part, the apparently contradictory and confusing literature appears to be related to previous treatment and the tertiary referral patterns of many patients enrolled in clinical studies.

Neuromuscular dysfunction and abnormal voiding

Ghobish et al. compared 238 uroflow studies from CP/CPPS patients to 71 studies from age-matched controls without lower urinary tract problems.²⁴¹ Most patients had varied urinary flow disorders. Some authors suggest that symptoms of CP/CPPS may reflect pelvic sidewall tenderness due to tension myalgia.^{242–244} Persson and associates found increased concentrations of creatinine, urate, and leukocytes in EPS from 56

CP/CPPS patients.²⁴⁵ They suggested that these findings most likely resulted from urinary reflux into the prostatic ducts. Hruz et al. found that 29 of 48 (60%) patients with refractory CPPS had significant bladder neck hypertrophy despite the absence of obstruction.²⁴⁶ Similarly, Kaplan et al. described 43 men, 23–50-years-old, with chronic voiding dysfunction secondary to pseudodyssynergia who were misdiagnosed as having CP/CPPS and recommended routine videourodynamic evaluation.²⁴⁷ In contrast, Mayo and associates found that only three (3%) of 123 CP/CPPS patients had urodynamic evidence of obstruction (definite in two [1.6%] and equivocal in one [0.8%]).²⁴⁸

In summary, the precise role of urodynamic and neuromuscular abnormalities remains controversial. If primary voiding or other neuromuscular dysfunction proves important in a substantial proportion of patients, then facilitate development of better diagnostic methods and specific therapies would prove beneficial for patients with CP/CPPS.

Immunological dysfunction

A wide range of immunological disorders has been associated with CP/CPPS, as outlined above in the section on host defenses. Abnormal host responses have also been related to DNA polymorphisms, such as cytokine production and/or regulation.^{54,249} Other data support the possibility that autoimmune mechanisms may be important in the pathogenesis of CP/CPPS. Several workers have investigated animal models of autoimmune prostatitis.^{250–252} For example, Pacheco-Rupil et al. reported that rats immunized with a mixed organ homogenate of ventral, dorsal, and lateral prostate, and coagulating glands developed a specific cell-mediated response with CD4⁺ and CD8⁺ T-cell infiltration of prostate lesions.²⁵² Ponniah and associates compared 14 patients with CP/CPPS to 12 normal volunteers, using recall proliferation assays with purified seminal plasma proteins as antigens.⁶¹ Five patients showed a greater than twofold increase in proliferative response to prostate-specific antigen, while no response was seen in the controls. These investigators concluded that prostate-specific antigen may represent a candidate antigen and a target for immunotherapy.⁶¹ In a subsequent study, this group compared 11 patients with granulomatous prostatitis to 540 controls.⁵⁹ Six (75%) of eight white patients were HLA-DR15 positive compared to 127 (28%) of 451 white controls, and one (33%) of three black American patients was HLA-DR15 positive compared to 23 (26%) of 89 black controls ($P = 0.0086$), consistent with an autoimmune etiology.⁵⁹

Interstitial cystitis

The term “interstitial cystitis” is used to describe an idiopathic bladder pain syndrome that is most commonly diagnosed in women. Many etiologies have been proposed, including mast cell activation, defects in the urothelial glycosaminoglycan

coating, autoimmune disease, toxic agents, neuropathic-mediated pain, presence of antiproliferative factor activity, or decreased levels of heparin-binding epidermal growth factor-like growth factor.^{253–256} None of these hypotheses is generally accepted and results of therapy are generally poor.

Because the symptoms of interstitial cystitis and CP/CPPS overlap, one hypothesis is that these syndromes should be combined.^{257–261} A proportion of CP/CPPS have been reported to have positive findings with various tests proposed for diagnosis for interstitial cystitis, including: cystoscopy with hydrodistension,^{262,263} the potassium sensitivity test,^{257,259} and various biomarkers.²⁶⁴ The clinical implication is that diagnosis of interstitial cystitis in patients presenting with symptoms of CP/CPPS would facilitate effective therapy if there were a proven therapy for interstitial cystitis.

Neuropathic pain

A new theory is that CP/CPPS patients may have various initiating causes but that, once established, this syndrome represents a chronic pain syndrome.^{51,265} Pain might arise from neurogenic inflammation in the peripheral or central nervous systems. Levels of nerve growth factor and cytokines that regulate inflammation may correlate with pain severity in CP/CPPS.⁵³ Nerve growth factor is a neurotrophin that plays a role regulation of nociceptive nerves by mediating and amplifying neurogenic inflammation. The clinical implication is that application of strategies directed at management of chronic pain might provide more benefit to patients than therapies directed at the underlying etiology. This remains an area of active investigation.^{51,265}

Differential diagnosis

The CP/CPPS case definition for clinical studies contains a number of important exclusion criteria.^{117,118,186,193,266} The exclusion criteria include duration <3 months, lower genitourinary tract cancer (e.g., transitional cell carcinoma, carcinoma in situ, and prostate cancer), active urinary stone disease, active genitourinary tract infection (e.g., bacteriuria genitourinary tuberculosis), gastrointestinal disorders (e.g., inflammatory bowel disease and perirectal disease, such as fissure or fistula), radiation cystitis, chemical cystitis (i.e., postchemotherapy), active urethritis, acute epididymitis, acute orchitis, functionally significant urethral stricture, or neurological disease affecting the bladder.¹²

Of the CP/CPPS exclusion criteria, two merit special attention: transitional cell carcinoma and prostate carcinoma. Patients presenting with symptoms of prostatitis and irritative voiding symptoms, hematuria, or history of industrial exposure, or, perhaps, extensive tobacco use may merit additional evaluation for transitional cell carcinoma or carcinoma in situ. Appropriate studies include urinalysis and urinary cytology with cystoscopy for selected patients.^{1,254,267} Patients with risk

factors for prostate cancer may also merit prostate biopsy. These risk factors include older age, a strong family history of prostate cancer, an abnormal rectal examination, or elevated prostate-specific antigen level.

The differential diagnosis of CP/CPPS also includes interstitial cystitis, a poorly understood pelvic pain syndrome that is associated with increased urinary frequency and urgency. As considered above, there some overlap between this syndrome and CP/CPPS. The precise amount of overlap and relationship between these two conditions is currently the subject of considerable debate. Thus, for selected patients, it may be reasonable to obtain urine specimens for cytology and to perform careful endoscopic examination under anesthesia (including bladder evaluation after hydrodistension), as well as to procure appropriate bladder specimens for histological evaluation.

Treatment

Therapy is unsatisfactory for most men with CP/CPPS.²⁶⁸ Patients typically receive antibiotics, alpha-blockers, anti-inflammatory drugs, and other treatments.

Antimicrobial drugs

Antimicrobial drugs represent the first-line treatment (Table 61-5).^{3,8} Patients with recognized uropathogens respond to specific therapy. However, few men receive an accurate diagnosis because lower urinary tract localization procedures and detection of fastidious organisms prove difficult in most clinical settings. For men without evidence of infection by recognized pathogens, antimicrobial treatment often results in temporary resolution. However, symptoms frequently return following treatment. Patients typically receive multiple courses of empirical antimicrobial therapy.^{8,186} Patients and their physicians often became frustrated following multiple courses of unsuccessful empirical therapy.

To date, few studies have evaluated this clinical approach, primarily in heavily pretreated, referral patients. One series evaluated the effect of 12 weeks of ofloxacin therapy in a nonblinded series of 102 referral patients, presenting with either chronic bacterial prostatitis or with CP/CPPS.²⁶⁹ Of the patients, 57% believed that they had moderate-to-marked improvement and had significant improvement in the NIH-CPSI. Culture and EPS leukocyte count did not predict response. Subsequently, this group completed a multicenter trial of 6 weeks of levofloxacin therapy compared with placebo for 80 patients with CP/CPPS.²⁷⁰ These referral patients had an average symptom duration of 6.5 years. Both groups experienced progressive improvement in symptoms as measured by the NIH-CPSI, but there was no difference in response at the end of the treatment (6 weeks) or at the end of the follow-up visits (12 weeks).

The NIH Chronic Prostatitis Clinical Research Network evaluated a heavily pretreated population of 179 patients.¹⁹³ The average duration of CP/CPPS symptoms was 6.2 years. Most participants had failed prior treatment with both antibiotics

and alpha-blockers.¹⁸⁶ This multicenter, randomized, double-blind trial employed a 2 × 2 factorial design to compare 6 weeks of therapy with ciprofloxacin, tamsulosin, both drugs, or placebo in tertiary-care settings. NIH-CPSI total scores decreased modestly in all groups, and neither therapy provided statistically significant benefit.

In summary, antimicrobial therapy remains the first-line treatment for CP/CPPS. Documentation of a specific pathogen is valuable for selecting specific therapy. However, it appears that repeated courses of empirical therapy in the absence of a recognized pathogen provide minimal benefit, particularly for heavily pretreated, tertiary referral populations.

Alpha-blockers

The best rationale for nonantimicrobial therapy supports use of alpha-adrenergic blockade to treat the neuromuscular dysfunction that some workers describe with CP/CPPS.^{6,271,272} Complaints of urinary hesitancy, poor or intermittent stream, or ejaculatory dysfunction may be manifestations of functional neuromuscular abnormalities. Small clinical series suggested that patients benefit from treatment with less-selective alpha-blocking agents, such as phenoxybenzamine,¹ phentolamine,⁶ or terazosin.²⁷³

Three randomized controlled clinical trials reported variable results. The Chronic Prostatitis Research Network Study described above found that 6 weeks of tamsulosin, a subtype-specific alpha-1 blocker, was not significantly better than placebo in their heavily pretreated referral population.¹⁸⁶ In contrast, Mehik and associates demonstrated some benefit from alfuzosin, a “uroselective” alpha-1 blocker. They compared alfuzosin with placebo and standard therapy in 66 CP/CPPS patients.²⁷⁴ After 6 months of active therapy, the alfuzosin group had had statistically significant decreases in total and pain NIH-CPSI scores, compared with the placebo and control/standard groups. Of the 17 patients in the alfuzosin group, 11 (65%) had a >33% improvement in the mean NIH-CPSI total score, compared with 24% and 32% of the placebo and control/standard groups, respectively ($P = 0.02$). Unfortunately, at 12 months (6 months after treatment was discontinued), symptom scores deteriorated, and there was no significant difference between the treatment groups.

Cheah and associates evaluated 86 newly diagnosed patients who had not received alpha-blockers previously.²⁷⁵ Subjects were randomized to receive terazosin, a non-subtype-selective alpha-1 blocker, or placebo for 14 weeks. Terazosin-treated patients had statistically greater reductions in NIH-CPSI total score and individual domain scores. There was no difference in urinary flow rate or postvoid residual between responders and nonresponders.

In summary, alpha-blocker therapy appears beneficial for patients with CP/CPPS, especially newly diagnosed and/or alpha-blocker naïve patients. The ideal agent and duration of therapy remain to be defined, but less selective alpha-1

blockers and therapy for 14 weeks or longer appear to be better than less selective agents or shorter duration of treatment.

Other therapies

Clinical studies suggest that a number of other drugs and treatments might benefit patients with CP/CPSP. Recommended drugs include anti-inflammatory agents such as rofecoxib to decrease prostate inflammation,²⁷⁶ 5-alpha reductase inhibitors such as finasteride to decrease prostate size,^{277,278} therapy for interstitial cystitis such as pentosan polysulfate,^{279,280} allopurinol to treat high EPS urate levels due to urinary reflux into the prostate ducts,^{281–284} muscle relaxants to reduce muscle tone, and anticholinergics.^{1,20,182,183,244} Many phytotherapeutic agents have been recommended, based on anecdotal experience and small series,^{285,286} such as pollen extract (Cernilton),²⁸⁷ saw palmetto,²⁷⁷ and quercetin.^{288–290}

Recommended procedures include sitz baths, prostate massage,^{111,291} acupuncture,^{265,292} physiotherapy, behavioral therapy, and bladder training biofeedback for pelvic floor myalgia.^{1,20,182,183,243,244} Case series recommend “multimodal therapy” with simultaneous use of multiple approaches combining antibiotics, prostatic massage, anti-inflammatory phytotherapy, alpha-blockers, and neuromuscular agents.^{293–295} Some clinicians recommend increased frequency of ejaculation to relieve “congestion.” Other physicians recommend abstinence from ejaculation, alcohol, coffee, tea, spicy foods, etc. There is little definitive evidence that any of these treatments affects the natural history of CP/CPSP.

Patients routinely undergo a wide variety of invasive diagnostic procedures, such as cystoscopy, transrectal ultrasonography, excretory urography, other imaging tests, urodynamic studies, and biopsies.^{162,272,296} The recent literature contains many reports of surgical procedures to treat men with CP and related syndromes. These operations include transurethral and “subtotal resection” of the prostate,^{162,182,183,297} balloon dilation of the prostate,²⁹⁸ hyperthermia,^{299–303} endourethral electrostimulation and laser radiation,^{304,305} and even radical prostatectomy.^{306,307} None of these small series includes adequate control groups and sufficient microbiological and clinical data. Although such procedures might be effective in certain, highly selected cases, our experience includes many men who failed surgical therapy.

■ CATEGORY IV. ASYMPTOMATIC INFLAMMATORY PROSTATITIS

The consensus classification of prostatitis syndromes includes a category for patients who have no genitourinary tract symptoms.¹²

Clinical presentation

Patients with category IV prostatitis have documented inflammation but have none of the usual symptoms associated

with other prostatitis syndromes. Diagnosis occurs during evaluation for other conditions such as evaluation of prostate tissue obtained for other clinical indications or during evaluation of patients presenting with infertility.

Inflammatory infiltrates are commonly noted during evaluation of prostate tissue removed for treatment of lower urinary tract symptoms associated with BPH and surgical treatment of prostate cancer.^{62,308,309} These observations have led some investigators to suggest that prostatic inflammation might play a role in the development of both BPH and prostate cancer.^{64,65,95,96,98} In addition, patients with elevated prostate-specific antigen levels routinely undergo prostate biopsy for evaluation of possible prostate cancer.^{310–312}

The most common benign pathologic diagnosis is “prostatitis,” based on the histologic finding of inflammatory infiltrates in the prostatic tissue. Many patients with such inflammatory prostate tissue infiltrates have no history of prostatitis symptoms, placing them in the asymptomatic category (Table 61-4).

Inflammation may be diagnosed among men undergoing evaluation for infertility (reviewed in Ref. 116). Many of these men have no genitourinary tract symptoms. On semen analysis, increased numbers of “round cells” may prompt a diagnosis of prostatitis. Other terms used in the infertility literature include “asymptomatic male genital tract infection,” “male accessory gland infection,” “prostatoseminal vesiculitis,” “leukocytospermia,” and “pyospermia.” The consensus classification includes such patients in category IV, or asymptomatic inflammatory prostatitis.

Treatment

Some clinicians recommend antimicrobial and/or anti-inflammatory therapy for asymptomatic patients with elevated prostate-specific antigen levels and inflammation noted on prostate biopsy.^{313–316} These recommendations are based on the observations that acute bacterial prostatitis and exacerbations of chronic bacterial prostatitis are associated with elevations of both serum prostate-specific antigen and prostatic acid phosphatase. Whether antimicrobial therapy is beneficial for asymptomatic patients with histologic evidence of prostatitis remains uncertain. The current consensus is that antimicrobial therapy is not indicated for asymptomatic patients (Table 61-5).³¹⁷

Similarly, some infertility specialists recommend antimicrobial therapy for asymptomatic men with seminal fluid inflammation, but the proportion of these patients who have active genital tract infections is poorly defined.^{116,318} Further, seminal fluid inflammation has been shown to resolve in many men over time, with frequent ejaculation only.³¹⁹ Thus, it would appear prudent to diagnose a specific genitourinary tract pathogen before recommending antimicrobial therapy for asymptomatic men presenting for infertility evaluation.

Complications

Animal studies²⁵⁸ and data summarized above suggest that chronic prostatic inflammation may promote development of both BPH and prostate cancer.^{68,95,320} Other investigators have proposed that asymptomatic prostatic inflammation represents a treatable cause of serum prostate-specific antigen elevation and that therapy with antibiotics and/or anti-inflammatory agents may reduce unnecessary biopsy rates.³¹⁶ Confirmation of these potential associations would support efforts to diagnose and treat both symptomatic and asymptomatic prostatitis syndromes. However, treatment of asymptomatic prostatic inflammation is associated with potential adverse outcomes and has not been proven to change the natural history of any prostate disorder.

■ GRANULOMATOUS PROSTATITIS

Most men with prostatitis syndromes may be classified into the four categories described above. However, granulomatous prostatitis is distinct from the four usual categories. Diagnosis of these unusual patients is important because specific therapy may be necessary to resolve the infectious causes of granulomatous prostatitis.

Clinical presentation

Granulomatous prostatitis is a characteristic reaction of the prostate to varied insults. Patients may present with findings suggesting prostate cancer on rectal examination.³²¹ Other men present with systemic symptoms or lower urinary tract obstruction due to prostatic enlargement. Biopsy or examination of tissue removed at surgery is often necessary for diagnosis. Thus, granulomatous prostatitis is a histologic diagnosis that does not correspond to a discrete clinical syndrome.

Histology

On gross examination, the prostate appears indurated, and, on rectal examination, it is frequently nodular. The histologic pattern is that of a granulomatous reaction with lipid-laden histiocytes, plasma cells, and scattered giant cells. A prominent eosinophilic infiltrate is apparent in some cases. Recent reports suggest that the histological findings range from a localized appearance, resembling rheumatoid nodules, often associated with a history of previous transurethral resection, to a more diffuse appearance, associated with systemic illness or idiopathic etiology.^{322,323} Specific stains or cultures may be necessary to make an etiologic diagnosis.

Etiology

Granulomatous prostatitis is arbitrarily classified as “specific,” when associated with particular granulomatous infections,

or as “nonspecific,” in other cases. Recognized causes of non-specific granulomatous prostatitis include acute bacterial prostatitis, prostatic surgery, and disorders associated with vasculitis.

Nonspecific granulomatous prostatitis. In many cases, granulomatous prostatitis follows an episode of acute bacterial prostatitis or previous prostatic surgery.^{1,137} Nonspecific granulomatous prostatitis occurs in two forms: a noneosinophilic variety and an eosinophilic variety. Although neither variety is seen frequently in clinical practice (the eosinophilic variety is especially rare), both types are important clinically, because they may be confused with prostatic carcinoma.

Some authors suggest that granulomatous prostatitis represents a tissue response of the foreign body type to extravasated prostatic fluid.¹³⁷ Acute signs and symptoms of bladder outlet obstruction associated with an enlarged, firm prostate that feels malignant characterize the clinical presentation. Fever and irritative voiding symptoms may occur.

Eosinophilic granulomatous prostatitis, associated with fibrinoid necrosis and generalized vasculitis, may present as a serious systemic illness.³²⁴ Because it occurs almost exclusively in patients with allergies, especially asthmatics, this entity is also known as “allergic granuloma of the prostate.”²²⁶ Granulomatous prostatitis has also been associated with other rheumatoid disorders, particularly Wegener’s granulomatosis.^{325–328}

Specific granulomatous prostatitis. There are a number of specific infectious causes of granulomatous reaction by the prostate. Tuberculous prostatitis is usually secondary to tuberculosis elsewhere in the genital tract.^{329,330} Most patients have no symptoms referable to prostatic infection. On biopsy, the granulomas frequently contain typical Langhans’ giant cells and may be associated with caseous necrosis. Such infections are caused most often by *Mycobacterium tuberculosis* but have also been reported with atypical mycobacteria.^{331,332} A similar histological picture may be noted following intravesical BCG therapy for transitional cell carcinoma.^{333–336}

With many of the deep mycoses, mycotic prostatitis may be secondary to systemic involvement.^{337,338} Most reported cases have been associated with blastomycosis,^{337,339} coccidioidomycosis,^{340–343} and cryptococcosis.^{344,345} However, histoplasmosis and paracoccidioidomycosis also occasionally involve the prostate.^{337,346} Cases of prostatitis due to candidiasis or aspergillosis have also been described.^{347–349} Usually, mycotic prostatitis is part of a systemic hematogenous dissemination. This process may involve any organ of the genitourinary tract. Mycotic involvement of the prostate is probably more common than is generally appreciated, since such involvement is frequently asymptomatic and the prostate is often not specifically evaluated in autopsy protocols.³³⁷

Other unusual infectious causes of granulomatous prostatitis include actinomycosis, candidiasis, and syphilis

(F. Mantz, personal communication).³⁵⁰ Cases of granulomatous prostatitis have also been associated with brucellosis³⁵¹ and can be sequelae of sacral herpes zoster.³⁵² Some reports suggest that AIDS and HIV infection may be associated with an increased risk of granulomatous prostatitis³⁵³ and that the etiology may include pathogens such as *Mycobacterium avium complex*.³⁵⁴

Diagnosis and treatment

Granulomatous prostatitis is perhaps the most important in the differential diagnosis of an indurated, firm, or nodular prostate. Frequently, the rectal examination of such patients raises the suspicion of prostatic carcinoma. Other causes of a nodular prostate include prostatic infarction, nodular BPH, or a prostatic calculus. Biopsy of the prostate may be necessary for diagnosis. Use of appropriate stains and cultures to detect specific etiologic agents is important in cases where granulomatous prostatitis is a consideration.

Treatment of patients with granulomatous prostatitis includes appropriate and specific treatment of the primary disease. A few patients have symptoms directly referable to the granulomatous reaction in the prostate. Such men usually complain of obstructive voiding symptoms. In most cases, the symptoms resolve with systemic therapy. Patients with urinary retention may be managed initially by percutaneous placement of a suprapubic cystostomy tube. Prostatectomy may be necessary if symptoms persist after an appropriate course of antimicrobial therapy.

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PART 11

Management of Dermatologic and Extragenital Manifestations of STD and HIV Infection

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Generalized Cutaneous Manifestations of STD and HIV Infection: Typical Presentations, Differential Diagnosis, and Management

Roy Colven

INTRODUCTION

Generalized skin lesions in any patient can perplex both the patient and the medical practitioner. Evaluating generalized skin lesions in a patient who has a sexually transmitted disease (STD) or human immunodeficiency virus (HIV) infection can present special problems. For example, the STD may be associated with, but not necessarily a cause of, the generalized rash. Patients infected with HIV may present with unique dermatoses, unusual infections, and atypical manifestations of common skin diseases. Among HIV-infected individuals, some type of skin disorder will develop in at least 80%.¹ Certain common skin conditions—including herpes zoster, severe seborrheic dermatitis, persistent staphylococcal folliculitis, and generalized pruritus—occur with increased frequency in HIV-infected patients and may provide the first clue that an individual is HIV-infected.^{2,3}

The first goal of this chapter is to outline a practical approach to the STD- and/or HIV-infected patient who presents with generalized skin disease (Fig. 62-1). Particularly important aspects of this approach are (1) to attempt to identify the primary lesion in a generalized skin condition, (2) to recognize any specific features of or patterns created by the primary lesion(s), and (3) to determine the distribution of the rash on the body surface. With this approach, the practitioner can usually generate a differential diagnosis. Evidence obtained from history and laboratory tests such as potassium hydroxide preparation or Gram's stain can then be applied to narrow the differential diagnosis. If necessary, a skin biopsy can be easily performed to add more specific information.

The second goal of this chapter is to familiarize the reader with the typical as well as the atypical presentations of a number of STD- and/or HIV-related generalized cutaneous manifestations. In addition, therapy of selected conditions will be discussed.

APPROACH TO A GENERALIZED SKIN CONDITION

■ GENERAL APPEARANCE

One's first glance at a patient often consciously or unconsciously starts the dermatologic assessment. Is the patient generally ill or overall well appearing? Is the patient obviously symptomatic with itching? Is there evidence of the skin condition on the face or scalp? Does the patient cover skin lesions with clothing or makeup? Does the patient have generalized edema? Vital signs, including the presence or absence of fever, are a critical part of this initial assessment. In order to examine the skin thoroughly, have the patient undress and put on a gown, thus allowing adequate exposure of the skin. One also needs good lighting, preferably natural lighting through a window to the outdoors.

The patient's normal skin pigmentation will influence the color of skin lesions. Erythema in darkly pigmented skin appears differently, and is often more subtle than in lighter skin.

Other factors to consider in this early assessment of a generalized skin condition are as follows:

- Is the condition acute, chronic, or in between?
- Is the patient known to be immunocompromised?
- How are the lesions distributed on the body?
- What is the primary lesion that best represents the condition?

This last query is discussed further and is the basis for organization in the remainder of the chapter.

■ PRIMARY SKIN LESIONS

A "primary lesion" refers to the initial stage in the evolution of a skin lesion. Identifying the primary lesion in a patient with a generalized skin condition provides critical information in

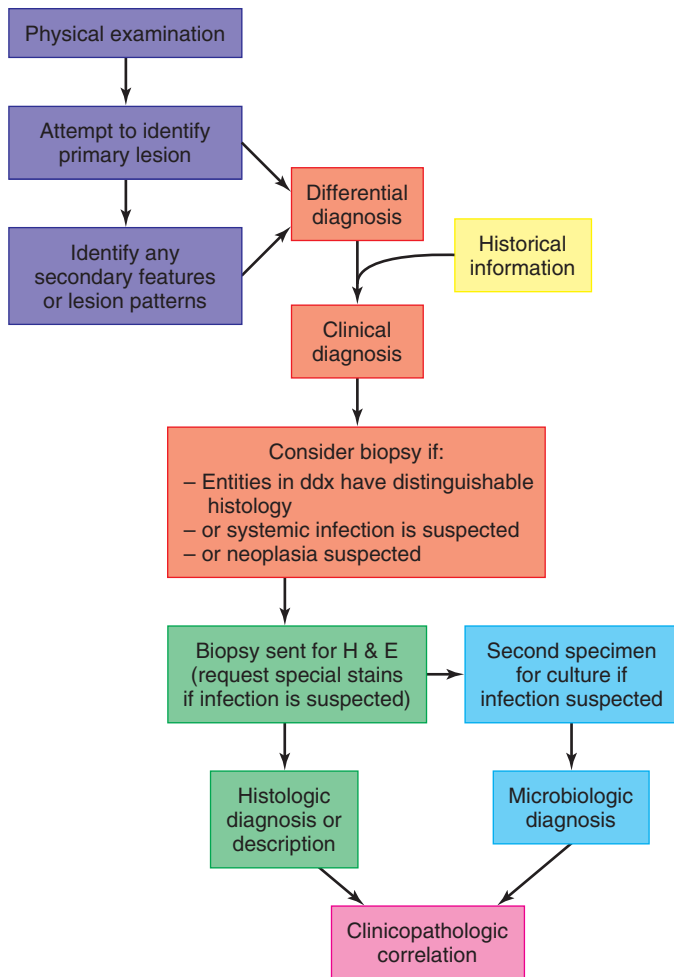


FIGURE 62-1. Approach to a patient with generalized rash.

making an accurate dermatologic diagnosis. Moreover, characterizing the appearance of the primary lesion directs the practitioner to a category of conditions based on lesion morphology. “Secondary lesions” refer to skin lesions altered, either naturally over time or by outside forces, to the extent that the primary morphology becomes obscured. For example, a patient with pruritic papules (primary lesions) may intensely scratch these lesions and turn them into erosions (secondary lesions), likely misleading the practitioner to formulate a differential diagnosis that does not include generalized papules. Alternatively, one should not assume the presentation of certain lesions, such as erosions, always represents secondary lesions. For example, the lesions could have been vesicles before the blister roof was either scratched away or naturally desquamated. Primary lesions are important in defining a generalized process and in communicating the appearance of a skin rash to another practitioner. A glossary of primary lesions is presented in (Table 62-1).

■ SECONDARY FEATURES AND LESION PATTERNS

Unfortunately, relying solely on the primary-lesion morphology is often not sufficient to diagnose skin conditions

Table 62-1. Definition of Primary Lesions

- **Macule:** a small (< 0.5–1 cm diameter) area of color change without surface elevation
- **Patch:** a larger macular area
- **Papule:** a small (< 0.5–1 cm diameter) solid elevation
- **Plaque:** a broad, solid elevation
- **Nodule:** a solid elevation distinguished from a papule by deeper penetration and larger diameter
- **Wheal:** a smooth-contoured, edematous elevation, which is often transient
- **Vesicle:** a small (< 0.5–1 cm diameter), clear fluid-filled blister
- **Bulla:** a larger, clear, fluid-filled blister
- **Pustule:** a pus-filled blister
- **Abscess:** a collection of pus in the dermis and deeper tissues, often manifested by tenderness, fluctuance, warmth, and surrounding induration
- **Cyst:** a dermal sac with soft or fluid contents manifested by a soft, fluctuant, smooth-contoured elevation
- **Erosion:** moist or crusted, usually superficially depressed, area of partial or complete denudation of epidermis that generally heals without scarring
- **Ulcer:** depression in the skin surface caused by destruction of the epidermis (and at least part of the dermis) that generally heals without scarring
- **Atrophy:** a thinning of intact epidermis, dermis, or subcutaneous fat often resulting in wrinkling, translucency, or depression of the skin surface

Other useful terms, though not considered primary skin lesions:

- **Crust:** dried serous or serosanguinous transudate
- **Eschar:** adherent, often black or gray product of coagulation necrosis of the dermis, typically found at the base of an ulcer
- **Exanthem:** a generalized macular and papular rash on cutaneous surfaces mostly associated with a viral illness
- **Enanthem:** a mucous membrane-limited erythematous eruption mostly associated with a viral illness

accurately. The differential diagnosis of a papular eruption, for example, is extensive; knowing this information is not necessarily helpful when applied to an individual patient. If one can initially classify subsets of papular conditions based on other prominent features, the differential diagnosis quickly narrows. In (Table 62-2), certain secondary features and lesion patterns are defined; these definitions can assist in further classifying cutaneous conditions. With the primary lesion and secondary features in mind, the clinician can better generate a differential diagnosis. (Table 62-3) outlines generalized STD- or HIV-related cutaneous conditions based on the conditions’ primary morphologies or

Table 62-2. Secondary Cutaneous Features Defined

- **Papulosquamous:** papules and plaques with prominent scale
- **Eczematous:** erythematous papules and plaques, often pruritic, with varying degrees of weeping, crust, and scale
- **Erythroderma:** < 90% total body surface area involvement with erythema, usually with some degree of scale
- **Xerosis:** generalized dry skin
- **Hyperkeratosis:** thickening of the stratum corneum producing visible scale
- **Ichthyosis:** flaking of skin with a distinct fish-scale pattern
- **Purpura:** dermal or subcutaneous bleeding producing a violaceous macule or patch

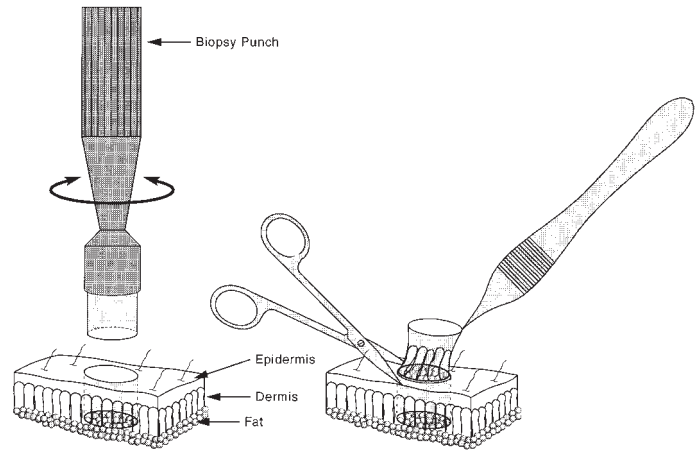


FIGURE 62-2. Technique of punch biopsy: After skin preparation and intra-dermal anesthesia, incises the skin with a twisting motion of a punch to the level of the subdermal fat. The specimen is then lifted carefully with toothed forceps, avoiding crushing, and the specimen is cut away from the fat using a fine scissors. A suture to close the wound is optional.

predominant lesion patterns/distributions. Note that diagnoses, such as secondary syphilis and scabies, appear in multiple categories. Also, exceptions to the categorization will occur because syphilis, particularly, can cause a wide range of skin lesions and patterns, and HIV can induce abnormal variations on common conditions and allow uncommon skin diseases, especially infections. Though (Table 62-3) distinguishes HIV- and STD-related conditions, this separation is arbitrary and is presented to help better organize one's differential diagnostic workup.

If the diagnosis cannot be established on clinical grounds, a skin biopsy often provides valuable information. Three- or four-mm punch biopsies sent for routine histology and/or culture can be performed with minimal discomfort (Fig. 62-2). Performing a biopsy of an early lesion generally gives the best diagnostic yield.

SELECTED CONDITIONS

■ MACULAR AND PAPULAR CONDITIONS

Exanthem of acute retroviral syndrome

During the period of viremia associated with primary HIV infection, a transient, erythematous macular and papular exanthem may appear (Fig. 62-3). Although the subtle nature of this rash has made it difficult to determine its true incidence, some investigators have estimated that as many as 75% of symptomatic acutely infected patients will develop this rash.⁴ Constitutional symptoms, namely fatigue, fever, and weight loss, as well as generalized lymphadenopathy and pharyngitis, often coexist with the rash, making this syndrome difficult to distinguish from acute mononucleosis caused by Epstein-Barr virus.⁵ In addition, patients may develop an enanthem.⁶ Both the exanthem and enanthem generally



FIGURE 62-3. Erythematous macular and papular exanthem in acute HIV infection. (Reproduced with permission from Handsfield HH. *Atlas of Sexually Transmitted Diseases*. New York: McGraw-Hill, 1992.)

resolve within 1 week. At this early stage, patients will have a negative HIV antibody test, but tests for viral replication, such as a plasma HIV RNA assay or a p24 antigen (in the setting of a negative antibody test), can confirm the diagnosis.

A similar rash and constellation of other symptoms and signs has occurred in HIV-infected patients who abruptly discontinue antiretroviral therapy.⁷⁻¹⁰ Usually this is in the setting of relatively high CD4 counts and undetectable viral loads while on therapy. The rapid rise in viremia and sudden drop in CD4 count simulates the primary viremia of acute retroviral syndrome, with the subsequent immune response resulting in a macular and papular rash, malaise, pharyngitis, and even CNS symptoms. The key to diagnosis is ruling out other potential pathogens, and restarting antiretroviral therapy if possible.

Table 62-3. Differential Diagnosis Based on Lesion Morphology or Secondary Features

Lesion Morphology of Pattern	Possible HIV-Related Infections or Dermatoses	Possible STD or STD-Related Dermatoses
Macules/small papules	Exanthem of primary HIV infection, morbilliform drug eruption, measles, scabies	Morbilliform drug eruption, roseolar syphilis, popular syphilis, ^a Jarisch-Herxheimer reaction, prodrome of hepatitis B virus, viral exanthems (other than HIV), erythema multiforme (associated with HSV infection), scabies
Larger papules/nodules	Eosinophilic folliculitis, molluscum contagiosum, bacillary angiomatosis, popular syphilis, deep mycoses (disseminated cryptococcosis, histoplasmosis, coccidioidomycosis), scabies, Kaposi's sarcoma, verrucae, papular eruption of HIV	Scabies, nodular syphilis
Wheals/urticaria	Drug hypersensitivity, idiopathic	Drug hypersensitivity, prodrome of hepatitis B virus, idiopathic
Vesicles/bullae/erosions/crusts	Disseminated VZV, HSV, impetigo contagiosa, bullous impetigo, ecthyma, erythema multiforme, toxic epidermolytic necrolysis, porphyria cutanea tarda	Erythema multiforme, VZV (dermatomal or disseminated)
Ulcers	HSV, VZV, cytomegalovirus, ecthyma, fixed drug eruption, deep mycoses	Rupoid syphilis (lues maligna)
Pustules: hair follicle-based not clearly hair follicle-based	Folliculitis (eosinophilic, staphylococcal, gram-negative, pityrosporum, demodex), acne Pustular psoriasis, Reiter's syndrome, disseminated HSV or VZV	Folliculitis (especially staphylococcal), acne Disseminated gonococcal infection, Reiter's syndrome (associated with chlamydial infection), pustular syphilis
Papules with scale (papulosquamous)	Seborrheic dermatitis, psoriasis, Reiter's syndrome, dermatophyte, scabies	Papulosquamous syphilis, Reiter's syndrome, pityriasis rosea, dermatophyte infection, seborrheic dermatitis
Eczematous	Seborrheic dermatitis, scabies, drug hypersensitivity, atopic dermatitis, dermatophyte	Scabies, atopic dermatitis, seborrheic dermatitis
Erythroderma	Seborrheic dermatitis, psoriasis, TEN, drug hypersensitivity	
Dry skin (xerosis), ichthyosiform	Ichthyosis, asteatosis, nutritional deficiencies, drug-related, atopic dermatitis	Atopic dermatitis
Purpura (including palpable purpura)	Kaposi's sarcoma, idiopathic thrombocytopenic purpura, vasculitis associated with hepatitis B or C virus	Disseminated gonococcal infection, vasculitic syphilis, vasculitis associated with hepatitis B or C virus
Pigmentary changes: hypo-/depigmentation	Postinflammatory hypopigmentation, vitiligo	Postinflammatory hypopigmentation with syphilis
hyperpigmentation	Postinflammatory hyperpigmentation, medication-related (zidovudine)	

^aFor any references to syphilis, assume the secondary stage unless otherwise specified.

Scabies

Scabies classically manifests as linear papules distributed in finger web spaces, flexor wrists, axillae, nipples, waistline, ankles, and genitals, but usually sparing the face and scalp (Figs. 62-4 and 62-5). The linear papules result from the burrowing of the adult mite into the epidermis (Fig. 62-6). Burrows, however, appear relatively infrequently compared with discrete papules, many of which are eroded from scratching (Fig. 62-7). In general, one should consider the diagnosis of scabies in any patient with a generalized pruritic rash. Though described here under the category of papular rash, scabies may appear eczematous or papulosquamous, depending on chronicity, presence of bacterial superinfection, and immune status of the patient. The diagnosis of scabies is covered in Chapter 46.

HIV-infected and other immunocompromised patients have an increased incidence of atypical manifestations of scabies, including face and scalp involvement, nodular lesions, and hyperkeratotic (often referred to as crusted or Norwegian) scabies (Fig. 62-8).¹¹ Because the diagnosis of scabies is often delayed in patients with atypical forms of the disease, community outbreaks and nosocomial infestations may result.¹²

The treatment of choice for most cases of scabies is a topical scabicide, such as permethrin 5% cream, applied from the neck down, left on overnight, and rinsed off in the morning. Most patients do not need a second application at a later time, as is common practice in the use of other scabicides. Patients with crusted scabies, however, require repeated total body (and head) applications. For those patients with crusted scabies who develop hyperkeratosis, adding ammonium lactate (12% lotion applied BID) can help to diminish the scale, though it may temporarily irritate

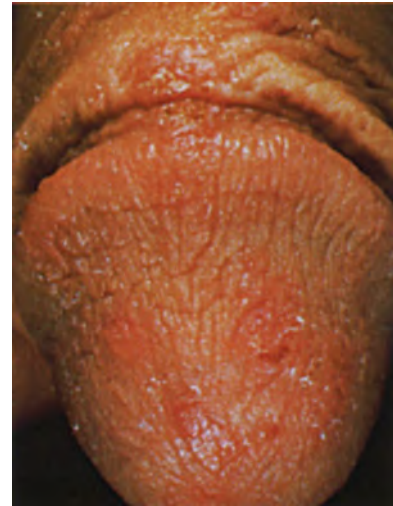


FIGURE 62-5. Scabies of the penis. Pyoderma of the penis is highly suggestive of scabies.

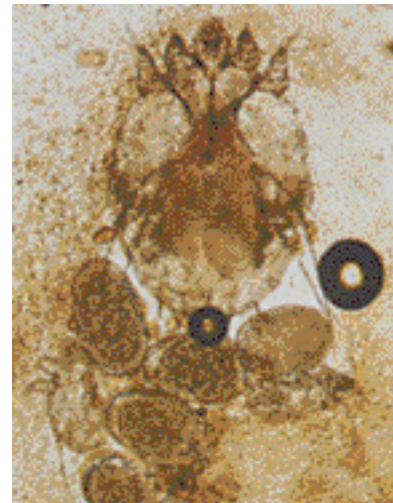


FIGURE 62-6. *Sarcoptes scabiei* mite with eggs in feces scraped from scabetic burrow.



FIGURE 62-4. Intradermal burrow of scabies demonstrated by coating the skin with ink, then wiping away surface ink, leaving the intradermal burrow filled with ink.



FIGURE 62-7. Grouped excoriations due to scabies on the lower buttocks, simulating dermatitis herpetiformis.



FIGURE 62-8. Hyperkeratotic scabies involving the scalp and face.

the skin. The use of single-dose oral ivermectin, 200 $\mu\text{g}/\text{kg}$, has shown promising results, including patients with crusted scabies.¹³

Macular and papular secondary syphilis

An array of generalized rashes can develop in patients with secondary syphilis, including the macular (roseola-like) and papular variants. The macular lesions often appear as faint, pale, pink macules that do not have scale. Papular secondary syphilis occurs more frequently than the macular form, and probably represents an evolution from undetected macular lesions. The papular lesions are typically distributed on the face, flexural folds, and trunk. Involvement of the palms and soles is characteristic, with lesions often appearing brown-red in this location (Figs. 62-9 and 62-10). Several variants of papular syphilis have been described. Annular lesions, more commonly seen on the faces of blacks with secondary syphilis, can resemble sarcoidosis or tinea. Corymbose (“flat-topped flower bouquet”) lesions appear as a central large papule or nodule surrounded by small satellite papules. Papulosquamous secondary syphilis is discussed later in this chapter. Later in the course of secondary syphilis, papules may occur at certain sites, such as the corners of the mouth (“split papules”), angles of the nose, and body folds. Patchy, “moth-eaten,” nonscarring alopecia commonly manifests in secondary syphilis (Fig. 62-11). With all forms of secondary syphilis, patients develop varying degrees of generalized lymphadenopathy.



FIGURE 62-9. Secondary syphilitic rash of the palm and sole.



FIGURE 62-10. Secondary syphilitic rash of palm.

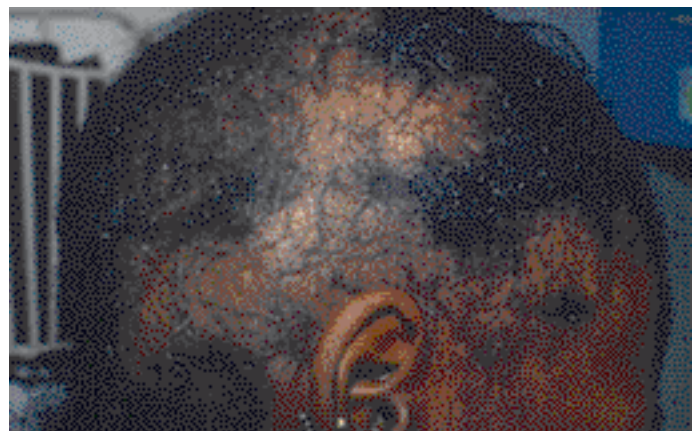


FIGURE 62-11. Patchy alopecia of secondary syphilis.

Jarisch–Herxheimer reaction

Two to eight hours after starting antimicrobial therapy for secondary syphilis, a febrile Jarisch–Herxheimer reaction

associated with malaise, headache, tender adenopathy, pharyngitis, and leukocytosis can occur and will alarm the unprepared patient and the unsuspecting practitioner. During this reaction, the existing rash may become more prominent, or a previously unrecognized rash of secondary syphilis may appear. The incidence of the Jarisch–Herxheimer reaction is approximately 95% in patients with seropositive primary syphilis or secondary syphilis. The incidence decreases in late secondary syphilis, and is frequently absent in latent syphilis.¹⁴ This reaction is considered a therapy-associated response, but not a drug hypersensitivity reaction. The precise mechanism remains unknown (see Chapter 35),¹⁵ though it seems to involve increased levels of tumor necrosis factor- α .¹⁶ The sudden onset and associated systemic symptoms distinguish the Jarisch–Herxheimer reaction from most drug-associated eruptions, including the generalized morbilliform rash (see below) observed with penicillin hypersensitivity. Although the anaphylactic, urticarial reaction to penicillin has a rapid onset, one can easily distinguish it from the Jarisch–Herxheimer reaction on the basis of lesion morphology (a wheal in the case of urticaria). A similar Jarisch–Herxheimer reaction has been observed with the treatment of other infections, including Lyme disease and relapsing fever.

Drug hypersensitivity

Although cutaneous reactions to drugs can take many forms, the most common reaction is the generalized macular and papular eruption. Many authors have referred to this reaction as a “maculopapular” or “morbilliform” rash. Neither of these terms, however, is optimal—the former because true “maculopapules” do not exist and the latter because many medical providers in Western countries have little experience diagnosing the “morbilliform” rash associated with measles. A generalized macular and/or papular drug hypersensitivity rash often begins on the trunk and spreads peripherally (Fig. 62-12). Individual edematous and erythematous macules and papules will commonly coalesce and sometimes appear urticarial. Although this type of drug reaction most commonly appears within the first two weeks of introducing a new drug, it can occur after long term use. Patients often complain of pruritus, but much less frequently of fever or other constitutional symptoms. One example of this systemic involvement is seen in the drug hypersensitivity *syndrome*, now termed *drug reaction with eosinophilia and systemic symptoms* (DRESS). DRESS typically occurs three or more weeks after initiation of the culprit medication, and in addition to an intense erythematous papular rash that often involves 75% or more of the body surface, the patient also experiences fever, malaise, leukocytosis (or sometimes leukopenia) and eosinophilia. Various internal organ involvement, such as hepatitis, nephritis, and pneumonitis may also occur.

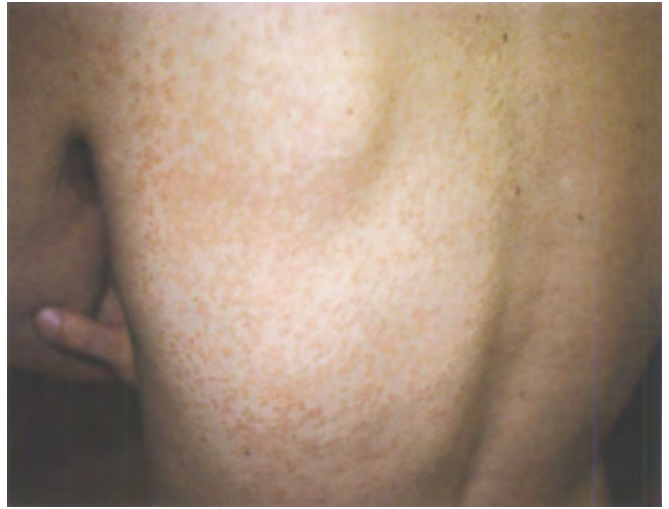


FIGURE 62-12. Generalized maculopapular rash due to drug hypersensitivity.

Common culprit drugs causing DRESS include sulfonamides, allopurinol, and aromatic anticonvulsants. Among the latter, cross-reactivity between phenytoin, phenobarbital, and carbamazepine is the rule. Authors have reported cases of DRESS from antiretroviral medications, particularly nevirapine and abacavir.^{17,18}

Some drug hypersensitivity eruptions are photodistributed; that is, they appear predominantly in ultraviolet (UV) light-exposed skin. Photosensitivity due to medications is divided into phototoxic and photoallergic reactions. Phototoxic reactions, which account for most photosensitive drug reactions, typically present as an exaggerated sunburn within hours of UV light exposure and do not require prior exposure to the culprit drug. Photoallergic reactions are uncommon and present approximately 48 hours after UV light exposure. Photosensitizing drugs commonly used to treat STDs or HIV-related disorders include doxycycline (phototoxic) and trimethoprim-sulfamethoxazole (phototoxic or photoallergic).

Human immunodeficiency virus-infected individuals when compared with HIV-negative persons, develop cutaneous manifestations of adverse drug reactions with increased frequency, even when controlling the rate of usage of certain drugs, such as sulfonamides.¹ Moreover, the risk of drug hypersensitivity increases with advanced immune-system dysfunction. Proposed mechanisms for this apparent increased susceptibility to adverse drug reactions include enhanced T-cell susceptibility and/or decreased hepatic metabolism of drugs secondary to glutathione deficiency.¹⁹

The approach to a patient with a suspected drug-hypersensitivity reaction depends on the severity of the reaction, the need to continue the suspected drug, and the question of whether an equally effective alternative exists or not. In HIV-infected patients, approximately one-third of sulfonamide-induced hypersensitivity eruptions (not DRESS) spontaneously resolve, and allow continued use for long-term

Pneumocystis carinii pneumonia prophylaxis.²⁰ Symptomatic treatment with antihistamines and topical steroids can help relieve symptoms during the acute reaction. Close observation is recommended, however, because more severe reactions, such as DRESS, Stevens–Johnson syndrome, or toxic epidermal necrolysis (see below), may ensue. Short courses of systemic steroids are occasionally needed with severe reactions, including DRESS; these severe reactions generally mandate stopping the suspected medication.

Erythema multiforme/Stevens–Johnson syndrome/toxic epidermal necrolysis

Erythema multiforme (EM) refers to an epithelial vascular reaction pattern, and is traditionally considered to represent a spectrum of disorders. Erythema multiforme minor typically present as acraly-predominant papules that evolve to form classic target lesions, though atypical targets and urticarial plaques without targets sometimes form. Vesicles or bullae may develop within the center of these lesions (Fig. 62-13), which is surrounded by a zone of pallor that is further circumscribed by a ring of erythema creating the characteristic target pattern. Patients with EM “minor” generally do not have constitutional symptoms or mucosal involvement. Investigators have identified herpes simplex virus (HSV) infection, both genital and orolabial (including asymptomatic infection), as a precipitating event in some of the cases of EM minor. In addition, recurrent EM minor can occur with recurrent herpetic outbreaks.

Although most authors have traditionally equated EM “major” (or EM with mucositis) with Stevens–Johnson syndrome, recent investigation indicates that these two disorders may be distinct. Stevens–Johnson syndrome is characterized by a sudden onset of fever, constitutional symptoms, rash, and mucosal erosions. The cutaneous lesions appear as erythematous or purpuric macules, sometimes with superficial vesicles or erosions, that tend to generalize with truncal predominance. Mucosal involvement includes oral, ocular, or

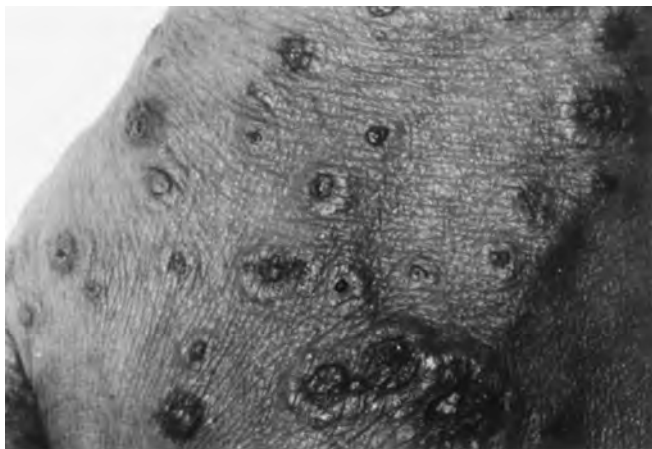


FIGURE 62-13. Typical target lesions in erythema multiforme on the wrist and hand. These lesions have central vesicles.

genital sites. Severe mucositis associated with acrally predominant target lesions is better termed as EM major.²¹ Investigators have attempted to distinguish Stevens–Johnson syndrome histologically from EM major, with more epidermal necrosis favoring Stevens–Johnson syndrome and more dermal inflammation suggesting EM major.²² Most cases of Stevens–Johnson syndrome are drug related, with sulfonamides and anticonvulsants most often incriminated, whereas most cases of EM major are HSV-related.²³

Toxic epidermal necrolysis (TEN or Lyell’s syndrome), conventionally considered to represent the most severe end of the EM spectrum, is characterized by the onset of painful erythroderma, followed by widespread sloughing of the epidermis (Fig. 62-14). Mortality is approximately 20%, though it varies widely depending on the population studied. The cause of toxic epidermal necrolysis is almost exclusively drugs, most of the culprits being the same as in Stevens–Johnson syndrome. An increased incidence of toxic epidermal necrolysis possibly exists among those with HIV infection,²⁴ but this may simply represent an increased use of medications, such as sulfonamides, known to cause toxic epidermal necrolysis. As with DRESS, an increasing number of reports implicate various antiretroviral agents in causing TEN.²⁵

■ GENERALIZED PAPULES AND NODULES

Molluscum contagiosum

The papules of molluscum contagiosum caused by a pox virus are distinctive. The lesions are generally 2–5 mm in size, and may number from a few located on the face or genitals to numerous widely scattered lesions. They are flesh-colored to white-pink, domed, and centrally umbilicated (Fig. 62-15). Among HIV-infected individuals, the lesions tend to be more numerous and may be nodular (so-called “giant molluscum” if 1 cm or more) and disfiguring. Reports have described patients with disseminated cryptococcosis, coccidioidomycosis, or

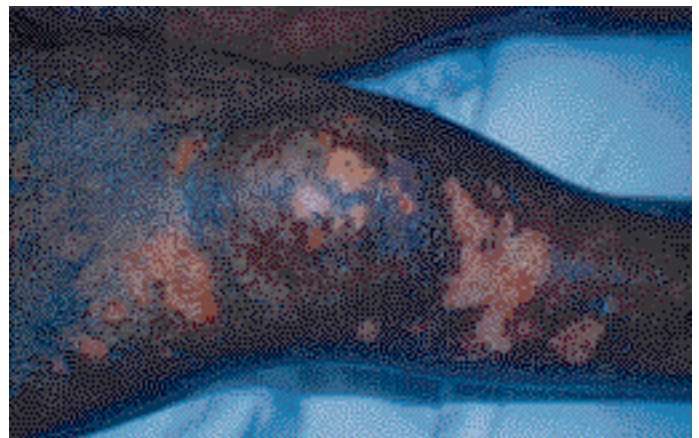


FIGURE 62-14. Toxic epidermal necrolysis due to trimethoprim-sulfamethoxazole. Initial confluent erythema progresses to epidermal sloughing.



FIGURE 62-15. Molluscum contagiosum of the lower abdomen and suprapubic area in a patient with coexisting genital molluscum lesions. Note central umbilication and pale salmon color.

Penicillium marneffei presenting with disseminated lesions that resemble molluscum contagiosum.^{26–28} Treatment options for patients with molluscum include cryotherapy, electrodesiccation, gentle curettage, topical tretinoin, and superficial chemical peeling. Generally, these therapies produce excellent cosmetic results. One report describes disfiguring molluscum contagiosum in an HIV-infected patient responding to combination antiretroviral therapy.²⁹ In the author's experience, molluscum contagiosum in HIV-infected patients generally responds well to effective antiretroviral therapy.

Kaposi's sarcoma

Kaposi's sarcoma lesions are usually easily recognized, especially in the setting of patients with confirmed or suspected HIV infection. The lesions typically appear as violaceous papules and nodules that can be single, few, or multiple and widely scattered (Figs. 62-16 and 62-17). Incipient lesions commonly appear macular and may resemble a bruise. With isolated skin involvement, Kaposi's sarcoma lesions generally produce no symptoms; if, however, the lesions progressively extend into the subcutaneous and lymphatic tissues, chronic lymphedema may form.

Bacillary angiomatosis

Bacillary angiomatosis (BA) was first described in 1983 in HIV-infected patients with fever and subcutaneous nodules.³⁰ Since then, BA has been observed most commonly in the skin as solitary or multiple vascular lesions that clinically resemble Kaposi's sarcoma. Involvement of the liver (peliosis hepatis), spleen, lymph nodes, bones, lungs, and central nervous system (CNS) have all been attributed to BA. The causative organisms, *Bartonella henselae* and *B. quintana*, have been isolated using special culture techniques and identified with polymerase chain reaction (PCR) techniques.^{31,32}

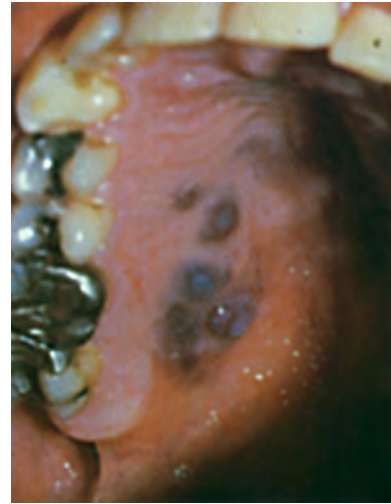


FIGURE 62-16. Kaposi's sarcoma in the palate as a manifestation of AIDS.

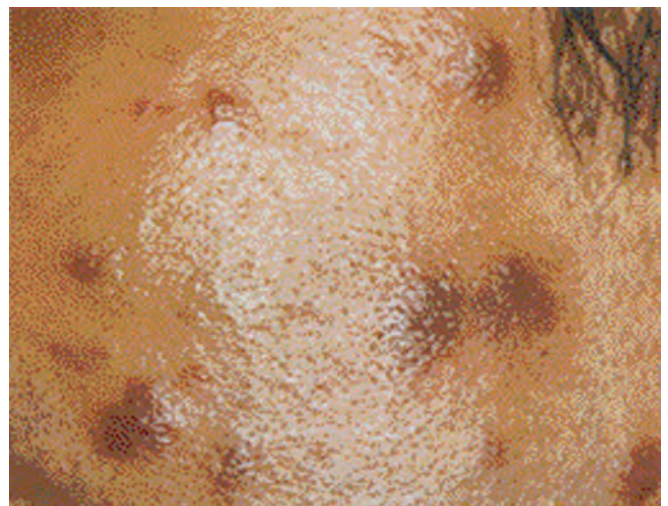


FIGURE 62-17. Kaposi's sarcoma on the face of a homosexually active man with AIDS.

Bartonella henselae is the most common cause of cat-scratch disease in immunocompetent patients.²³ Exposure to cats, especially kittens, is associated with a higher risk of contracting BA and cat-scratch disease.^{33,34}

Bacillary angiomatosis most often involves HIV-infected patients with advanced immunosuppression (CD4 count >100 cells/ μ l), though BA has rarely been reported in immunocompetent patients and organ transplant recipients.^{35,36} Perhaps due to prophylaxis for mycobacterial infection used in advanced stages of HIV infection, BA has become more rare than earlier in the AIDS pandemic. However, in some areas of the world where such prophylaxis is not widespread, BA appears to be quite prevalent.³⁷

The skin is the most commonly involved organ in BA, though the infection may present only with fever.³⁸ The lesions are red papules that progress to exophytic papules and nodules. These tend to be friable, and are surrounded by a collarette of scale, resembling pyogenic granulomas.

Subcutaneous lesions are flesh-colored, usually nontender, and mobile, similar to epidermoid cysts. Fever, night sweats, weight loss, and fatigue are common, though patients have variable degrees of constitutional illness.

Biopsy is very helpful, particularly when the clinical differential diagnosis includes Kaposi's sarcoma. Histologic appearance of BA lesions typically shows dermal vascular proliferation, with plump endothelial cells lining the vessels, as well as neutrophils aggregated around eosinophilic material.³⁹ With Warthin–Starry staining, innumerable black bacilli become evident. In some instances, cultures confirm the diagnosis. Treatment with erythromycin, 500 mg po qid, results in gradual improvement. Duration of therapy is not clear, though most recommend a minimum of 8 weeks of therapy for cutaneous lesions in HIV-infected patients.^{40,41}

Systemic mycoses in HIV

Although the lesion morphology may vary, the cutaneous lesions of disseminated cryptococcus, histoplasmosis, coccidioidomycosis, sporotrichosis, penicilliosis (due to *Penicillium marneffeii*), and others often appear as widely scattered papules or nodules, though other morphologies, such as mucocutaneous ulcers, cellulitic plaques, and pustules are also seen. Indeed, these papular and nodular lesions of disseminated fungal infections, especially cryptococcus, may resemble molluscum contagiosum.^{42,43} Patients infected with HIV who develop disseminated fungal infections have low CD4 counts, usually >100 cells/ μ l. Because primary cutaneous infections rarely occur with the systemic mycoses, the disseminated cutaneous lesions presumably arise from a noncutaneous focus, such as the lungs, and seed the skin from hematogenous spread. Other systemic mycoses that can rarely involve the skin in HIV-infected individuals include blastomycosis, primary cutaneous aspergillosis,⁴⁴ pneumocystosis, and paracoccidioidomycosis.⁴⁵

Cryptococcus neoformans is found worldwide and is a major cause of morbidity and mortality among AIDS patients, primarily through CNS infection. Dissemination to the skin occurs in approximately 6–10% of immunocompromised patients and can be the presenting sign of cryptococcosis (Fig. 62-18).^{42,46} The lesions often appear as flesh-colored papules and nodules, often with central umbilication resembling molluscum contagiosum. The lesions are most often located on the face and neck, though they can be found anywhere on the body. Less frequently, the lesions can present as ulcers of the skin or mucous membranes, cellulitic or violaceous plaques, palpable purpura, or Kaposi's sarcoma–like nodules.⁴² The diagnosis of any suspected disseminated fungal infection presenting in the skin is confirmed by performing a biopsy and sending the specimen for histology and culture. In disseminated cryptococcosis, the yeast cells are found in the dermis, often within a gelatinous



FIGURE 62-18. Cutaneous cryptococcosis presenting as an ulcer with a rolled border. A biopsy at the border sent for H & E and special stains for organisms and a second biopsy for culture is indicated here.

capsule. Special stains such as silver stain or mucicarmine will highlight the yeast cells or capsule, respectively.

One of the cornerstones in therapy of all of the disseminated mycoses, including cryptococcosis, in the HIV-infected patient is to enhance immune function by treating HIV with antiretroviral therapy. Specific initial therapy for HIV-infected patients with disseminated cryptococcal infection usually consists of amphotericin B. The addition of flucytosine helps to prevent relapse.⁴⁷ These patients generally require lifelong maintenance therapy with fluconazole, unless immune reconstitution with antiretroviral therapy intercedes.

Histoplasmosis is acquired in endemic areas by inhaling *Histoplasma capsulatum* microconidia or hyphae.⁴⁸ Disseminated infection can occur with primary exposure or by reactivating an old infection; the latter explains how cases occur outside of endemic areas. Skin lesions, with no site predilection, develop in approximately 11% of HIV-infected patients with disseminated histoplasmosis, and occurs more frequently than HIV-uninfected patients.^{49,50} An array of lesions have been reported, including diffuse erythematous macules and papules, keratotic or ulcerated papules and nodules, and pustules. Ulcers of the oral and, rarely, rectal mucosa have been described. Biopsy with special stains offers a rapid, though relatively insensitive, method of diagnosis. Culture of the skin with other diagnostic methods (blood or urine antigen detection and cultures of other tissues, e.g., bone marrow or respiratory secretions) will usually confirm the diagnosis.⁴⁷ Initial therapy consists of amphotericin B, followed by maintenance therapy with itraconazole capsules.⁵¹

Coccidioides immitis is endemic to the southwestern United States, northern Mexico, and Central America.^{45,47} Infection occurs after inhaling arthroconidia, with subsequent hematogenous dissemination of endospores. Skin lesions occur in approximately 5% of patients with disseminated infection. The primary lesion usually begins as a papule that evolves to a nodule, plaque, pustule, or ulcer. The lesions have

a predilection for the face and can resemble molluscum contagiosum. The oral cavity is spared. Biopsy for histology and culture is indicated when considering the diagnosis. Histologic examination shows large (30–60 μm) spherules filled with endospores. Cultures, DNA probes, and serologic testing also help confirm the diagnosis. Initial therapy is with amphotericin B for nonmeningeal disease, with or without an azole antifungal (fluconazole or itraconazole), or an azole for mild disease.⁴⁷

Disseminated sporotrichosis, though rarely reported, presents most commonly with skin lesions, including diffuse papules and nodules, in the setting of advanced HIV disease and other forms of immunosuppression.^{52,53} Other lesion morphologies include diffuse ulcers. Like the other disseminated fungi, skin biopsy for histology, and culture provides a convenient way to make this diagnosis. Amphotericin B and itraconazole have been the principal antifungals of choice.

Penicillium marneffei has emerged as an important fungal pathogen in HIV-infected individuals in Thailand, Vietnam, Myanmar, southern mainland China, Hong Kong, Taiwan, and India.^{54–57} The bamboo rat is the reservoir for this dimorphic, red pigment-producing fungus. Patients generally present with fever, cough, and a generalized skin eruption characterized by papules that have central necrosis or umbilication. These skin lesions have a predilection for the face, ears, upper trunk, and arms. Several reports have also described patients with genital and oral ulcers. Amphotericin B, followed by itraconazole, is the treatment of choice.

Paracoccidioides, due to *P. brasiliensis*, can present with protean manifestations, including fever, mucosal changes, adenopathy, and skin lesions. This fungus is endemic to areas of Central and South America and affects 10 million people. However, reports of infection in HIV-infected patients are relatively rare, perhaps owing to the use of prophylactic antibiotics for other opportunistic infections preventing productive infection with *P. brasiliensis* and the lack of geographical overlap between areas of *P. brasiliensis* endemicity and HIV-infected populations.⁴⁷

Cutaneous aspergillosis in HIV-infected patients has occurred as primary inoculation through the skin, especially at or near intravenous catheter sites or under occlusive dressings. It is frequently associated with neutropenia or malignancy. The infection leads to various lesion morphologies, including papular lesions that can resemble molluscum contagiosum. Interestingly, secondary cutaneous aspergillosis from disseminated infection has not been reported in HIV-infected patients.⁴⁴

Several case reports have described cutaneous pneumocystosis, including reports of widespread violaceous papules and nodules.⁵⁸ Moreover, direct extension of the organism from the eustachian tubes can produce polypoid papules of the external auditory canal.

Pruritic papular eruption and eosinophilic folliculitis of HIV

There is controversy about the existence of the pruritic papular eruption (PPE) of HIV as a distinct entity. As originally described, this condition consists of variably pruritic, waxing, and waning skin-colored papules distributed over the extremities, face, and trunk.^{59,60} Most authors have grouped the PPE eruption of HIV with various pruritic papular eruptions in HIV-infected patients, and refer to them collectively as “itchy red bump disease.”⁶¹ Some authors have postulated that the PPE represents an exaggerated response to insect bites⁶² or is a type of folliculitis,⁶³ despite the histologic lack of follicular involvement. When considered as a distinct condition, PPE is common in those who are HIV-infected, especially those with low CD4 counts.⁶⁴ Despite the controversy of its existence as a distinct entity and a perhaps waning prevalence in North America, the United Kingdom and Europe, providers in sub-Saharan Africa and Haiti regularly encounter this frustrating condition.⁶²

Eosinophilic folliculitis, discussed further below, is similar in its lesion morphology and somewhat overlapping distribution with that of PPE. Eosinophilic folliculitis is characterized by erythematous and edematous papules on the face, neck, upper trunk, and proximal upper extremities. Pustules are rare, and pruritus usually moderate to severe. Both PPE and eosinophilic folliculitis typically respond poorly to treatment with topical steroids, antihistamines, and most systemic antimicrobials. Ultraviolet light (UVB or psoralen with UVA) has been used with some success for PPE as well as for eosinophilic folliculitis.

■ LESIONS WITH VESICLES, EROSIONS, OR CRUSTS

Impetigo/ecthyma

Impetigo can manifest in one of the two forms: impetigo contagiosa or bullous impetigo (impetigo bullosa). Impetigo contagiosa is caused by *Staphylococcus aureus* or *Streptococcus pyogenes* (group A streptococci), though mixed infection with both of these organisms frequently occurs. Impetigo most often involves children, and the infection readily spreads via skin-to-skin contact. The primary lesion starts as a thin-roofed vesicle with an erythematous halo, though one typically sees the ruptured lesion as an erosion covered with a characteristic honey-colored crust. The lesions are painless, though often pruritic. In most instances, they involve the exposed skin of the face and extremities, but they may also complicate other skin diseases (secondary impetigo). In adults, secondary impetigo presents more commonly.

An analysis of trials of therapies for impetigo revealed that topical therapy, either mupirocin or fusidic acid, is more effective than systemic antibiotics in patients with localized impetigo.⁶⁵ In patients with more extensive disease, topical

therapy or treatment with an antistaphylococcal penicillin or first-generation cephalosporin effects resolution. Post-streptococcal glomerulonephritis is a rare but serious complication of streptococcal impetigo.

Bullous impetigo is caused by infection with specific phage types of *S. aureus* that produce within lesion an exfoliative toxin that leads to loss of cohesion of epidermal cells. This infection is common in infancy, but it also occurs among adults with poor hygiene, especially in hot, humid conditions. Lesions appear as flaccid, thin-roofed vesicles, and bullae, without an erythematous rim. They then become cloudy and pustular over 1–2 days, and rupture, leaving a dry, shiny, erythematous, varnish-like base. Lesions, typically pruritic, occur in the intertriginous areas of the axillae and groin. An oral antistaphylococcal antibiotic is preferred for this form of impetigo.

Ecthyma represents a deeper version of impetigo, with eventual formation of a superficial ulcer (Fig. 62-19). Group A streptococcus is most often the causative agent. The lesions are typically located on the lower extremities. Even with an appropriate extended course of antimicrobial therapy, the lesions heal slowly. Autoinoculation is common, and post-streptococcal glomerulonephritis develops with a frequency similar to that following impetigo contagiosa.

Disseminated vesicular viral infections

Disseminated herpes simplex virus (HSV) from hematogenous spread of the virus rarely occurs among HIV-infected patients, even those with advanced immunosuppression. Widespread HSV, known as eczema herpeticum, can occur in those with atopic dermatitis, or atopic-like dermatitis as seen with advanced HIV infection. Disseminated varicella-zoster virus (VZV) infection may occur concurrently with or following dermatomal zoster. The disseminated lesions resemble localized (dermatomal) disease—vesicles or pustules on an erythematous base (Fig. 62-20). Clinical appearance and a positive Tzanck preparation (for detection of multinucleated epithelial cells) help to make a presumptive

diagnosis of either disseminated HSV or VZV (Fig. 62-21) though it does not distinguish between the two viruses. A definitive diagnosis is best made using direct immunofluorescence and viral culture. If a patient presents with typical vesicles in a generalized distribution, the practitioner should presumptively treat for varicella-zoster virus until receiving results of direct immunofluorescence and viral culture tests.

Patients with advanced HIV disease may present with atypical ecthymatous or ulcerative varicella-zoster virus lesions (Fig. 62-22).^{66,67} These lesions often have a chronic course, even if the patient receives appropriate therapy for varicella-zoster virus infection. Disseminated herpetic infections generally warrant intravenous acyclovir in the immunosuppressed host. Oral acyclovir, valacyclovir, or famciclovir can be used for less severe infections. For confirmed



FIGURE 62-20. Dermatomal varicella-zoster virus infection.



FIGURE 62-19. Ecthyma. A deep erosion or superficial ulcer on an erythematous base is typical.

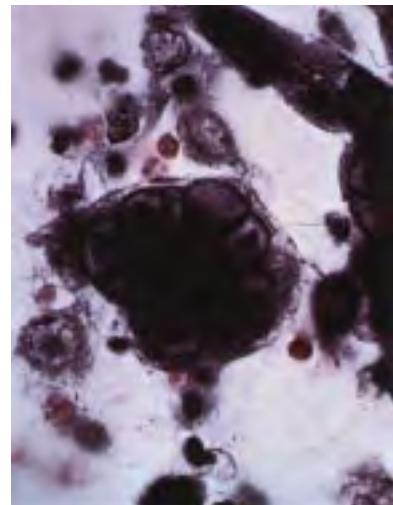


FIGURE 62-21. Wright-Giemsa stain of scrapings from a herpetic lesion (Tzanck smear) showing multinuclear giant cell and ground-glass appearance of nuclei with nuclear inclusions.



FIGURE 62-22. Chronic varicella-zoster infection in a child with AIDS. The lesions are difficult to distinguish from eczema.



FIGURE 62-23. Porphyria cutanea tarda in a male with HIV and hepatitis C virus infection. Note erosions and hypo- and hyperpigmentation over the dorsal aspects of his hands and forearms.

infections, failure to respond to the above warrants assessment for acyclovir-resistance.

Porphyria cutanea tarda

Porphyria cutanea tarda results from decreased activity of the hepatic enzyme uroporphyrinogen decarboxylase, either from acquired hepatic disease or from an inherited enzyme deficiency. This decreased enzyme activity leads to accumulation of intermediate substrates generated by heme synthesis, causing cutaneous photosensitivity and mechanical fragility. Skin lesions occur in sun-exposed areas or in areas incurring even trivial trauma, and include erosions, bullae, and hypo- and hyperpigmentation (Fig. 62-23). In addition, patients often develop facial hypertrichosis. Treatment consists of discontinuing all potential hepatotoxic agents, particularly ethanol, as well as having the patient undergo weekly phlebotomy to induce a mild iron deficiency anemia (a relative iron overload exacerbates the condition). Antimalarial medications are also used to treat porphyria cutanea tarda if phlebotomy does not lead to improvement or is contraindicated.

In recent years, investigators have increasingly recognized an association between porphyria cutanea tarda and viral infections, namely, hepatitis C virus⁶⁸ and HIV.⁶⁹ The association with HIV, however, may simply result from co-risk factors for acquiring hepatitis C virus.⁷⁰

■ FOLLICULITIS AND THE DIFFERENTIAL DIAGNOSIS OF PUSTULES

Folliculitis

Folliculitis refers to inflammation of the hair follicle and encompasses a number of disorders seen in STD patients and in HIV-infected individuals. A hair follicle–based pustule is the primary lesion that typifies this group of conditions. Folliculitis, however, can present as papules, sometimes with erosions and crusts, especially if itchy and excoriated. It can be difficult at times to determine whether a lesion is follicular, though clues include distribution in hair-bearing areas, regular spacing between lesions, and the presence of a hair shaft in the center of a pustule or papule.

Causes of folliculitis include infectious agents (*S. aureus*, gram-negative bacteria, pityrosporum, and demodex mites), chemical irritation (chloracne), or physical injury. Examples of physical injury include occlusion of the skin, friction (e.g., “razor burn”), and pseudofolliculitis. The latter is a problem particularly in blacks, in whom regrowth of tightly curled hair penetrates the nearby skin causing foreign-body inflammation. Other types of folliculitis that are of multifactorial or unclear cause include acne vulgaris, steroid acne, and eosinophilic folliculitis.

Staphylococcus aureus folliculitis typically presents in areas of high hair density such as the scalp, buttocks, groin, thighs, forearms, or beard. The lesions often arise as painful pustules enclosing a central hair. The pustule is surrounded by erythema that extends beyond the pustule. In patients who develop a cluster of staphylococcal follicular pustules, the involved area may become confluent indurated and very tender. In some instances, abscesses may form and require drainage. A Gram’s stain often reveals gram-positive cocci, either singly or in small clusters. If the patient has recently been hospitalized or recently taken antimicrobials, a culture with sensitivities would be indicated to exclude methicillin-resistant staphylococcus. An oral antistaphylococcal antibiotic will usually clear the condition. Bathing with soap and water and replacing the blade of the razor used for shaving may help to limit spread and decrease recurrences. In patients with recurrent staphylococcal folliculitis, eliminating nasal colonization with intranasal application of 2% mupirocin ointment (bid \times 5 days each month) may play an important role.⁷¹

In 1986, Soeprono first described HIV-associated eosinophilic folliculitis (EF),⁷² a disorder that resembles Ofuji’s eosinophilic pustular folliculitis.⁷³ When this HIV-related condition occurs, it virtually always involves those

with advanced stages of HIV disease (CD4 count less than 200 cells/μl). This disorder manifests as chronic pruritic, edematous papules distributed over the face, neck, and upper trunk. A preponderance of pustules should make one think of another diagnosis. Patients may have peripheral eosinophilia. Cultures from the lesions are negative, and this type of folliculitis responds poorly to antibacterials. Biopsy shows follicular inflammation with a predominance of eosinophils. Although difficult to treat, this condition sometimes responds to a combination of ultraviolet-B light therapy, high-potency topical steroids, and nonsedating antihistamines such as cetirizine (5–10 mg po qd). One study showed relatively favorable results with oral itraconazole (200–300 mg po qd).⁷⁴ After 1 month of itraconazole therapy, 17 of 28 patients had complete responses, and 4 patients had a partial response; at 6 months follow-up, 31% of patients had inactive disease, 13% required only topical steroids for control, and 56% remained on itraconazole with benefit (complete or partial control). Another report described the successful use of oral metronidazole (250 mg po tid × 3 weeks).⁷⁵ This report involved two patients who had lesions that contained gram-negative organisms that resembled *Leptotrichia buccalis*, a normal oral anaerobe. Aerobic and anaerobic cultures were negative, however. In the author's experience, metronidazole has been of little benefit for this condition.

Though eosinophilic folliculitis of HIV tends to affect those with CD4 counts less than 200 cells/μl, patients may experience EF after initiating antiretroviral therapy. Authors consider this a manifestation of immune reconstitution/inflammation syndrome.^{76,77}

Nonfollicular pustules

The differential diagnosis of pustules also includes nonfollicular conditions, such as pustular secondary syphilis, pustular psoriasis, and acute generalized exanthematous pustulosis (AGEP). If one observes generalized pustules on areas such as the palms, soles, or lips, one may safely assume a nonfollicular process. The pustular eruption of secondary syphilis is typically located on the face and trunk (Fig. 62-24). The lesions begin as erythematous papules that subsequently develop a central pustule and finally erode with an overlying crust. Darkfield microscopy of a sample taken from a lesion shows treponemes; serologic tests generally confirm the diagnosis. Pustular psoriasis is an unusual and often eruptive form of psoriasis that mainly involves the palms and soles, and may strongly resemble keratoderma blennorrhagicum (of Reiter's syndrome). Pustular psoriasis also includes a generalized form (von Zumbusch), which may follow tapering or cessation of systemic corticosteroids used to treat severe plaque-type psoriasis. A number of medications, including beta-lactam antibiotics, cause AGEP. In contrast to most other cutaneous drug hypersensitivity eruptions, AGEP



FIGURE 62-24. Pustular and macular lesions in secondary syphilis.

manifests within 2–3 days of drug exposure with high fever, red edematous skin with many tiny and superficial pustules. Distinction from acute pustular psoriasis can sometimes pose difficulty, though the temporal history of medication exposure supports AGEP. Discontinuation of the suspected drug, antipyretics, and topical steroids are usually enough to treat AGEP. Occasionally, one may need to use systemic steroids, thus eliciting an inciting medication history is crucial in distinguishing AGEP from pustular psoriasis.

Disseminated gonococcal infection initially appears as petechiae or palpable purpura, evolving to hemorrhagic pustules on an erythematous base (Figs. 62-25 to 62-27). The lesions are often tender, and typically they are few in number (>15) and acraly located, especially around the small joints. Cultures of material from the skin lesions of disseminated gonococcal infection are usually negative.

The natural evolution of many vesicular dermatoses includes a pustular stage. Thus, if one encounters a mixture of vesicular and pustular lesions, first consider the vesicular/bullous infectious diseases, such as varicella, disseminated HSV, and disseminated varicella-zoster virus.

■ PAPULOSQUAMOUS CONDITIONS

Seborrheic dermatitis

Seborrheic dermatitis presents as pruritic, erythematous, and scaly patches and plaques that involve the scalp (especially at the hairline), eyebrows, eyelash margins, nasal folds, beard area, and upper central trunk. The scale often appears greasy, particularly on the scalp and face. This condition is common, with 10–15% of the normal, healthy population afflicted.⁷⁸ Those afflicted will often recognize the condition as “dandruff” or “dry scalp”. Seborrheic dermatitis afflicts up to 80% of HIV-infected individuals, depending on whether examination or history is used to determine incidence. In one study,



FIGURE 62-25. Typical distribution of skin lesions in disseminated gonococcal infection. Usually 5–20 such lesions are apparent on the extremities, generally sparing the face and trunk.

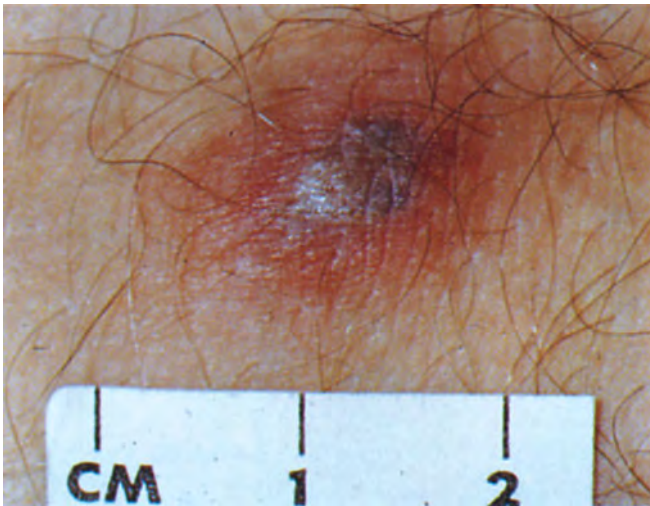


FIGURE 62-26. Hemorrhagic pustular lesion of disseminated gonococcal infection.



FIGURE 62-27. Crusted petechial lesion of disseminated gonococcal infection.



FIGURE 62-28. Sebopsoriasis. Erythematous papules and plaques with a greasy-appearing scale resembling seborrheic dermatitis.

53% of HIV-infected patients examined in a military-based study had seborrheic dermatitis.⁷⁹ Although most persons tend to have a waxing and waning course with seborrheic dermatitis, HIV-infected individuals generally have a more severe, persistent and recalcitrant condition, especially those with advanced stages of HIV disease.⁸⁰ Those patients treated with antiretroviral therapy enjoyed regression of the condition when compared to non-ARV-treated controls.⁸¹

The pertinent differential diagnosis includes psoriasis and dermatophytosis, the latter readily diagnosed by a positive potassium hydroxide preparation. When seborrheic dermatitis involves the axillae and groin, some authors prefer the term “sebopsoriasis” (Fig. 62-28).

The exact cause of seborrheic dermatitis remains unknown, but both enhance sensitivity to resident yeast on skin (*Malassezia species*) and overgrowth of this yeast within lesional skin appear to play an important role.⁸² For this reason, therapy usually consists of a topical steroid (hydrocortisone 1% cream or lotion) and an antifungal or anti-seborrheic (dandruff) shampoo, such as one containing zinc pyrithione, selenium sulfide, or coal tar derivatives. Topical ketoconazole cream has also been used with success. Those HIV-infected patients with severe seborrheic dermatitis, especially those with advanced immunosuppression, may require therapy with oral ketoconazole, 200 mg per day for 4 weeks. Limited published experience exists with itraconazole (200 mg per day for 7 days) and fluconazole for seborrheic dermatitis.

Psoriasis

Psoriasis is the prototype of papulosquamous (scaly papules and plaques) disease, and affects 1–2% of the general population. The common plaque variety, psoriasis vulgaris, develops as salmon-colored plaques that have a silvery scale, typically located on the extensor surface of the elbows and knees, as well as on the trunk. Patients often have scalp, gluteal fold, umbilical, genital, and nail involvement, but only rarely does psoriasis develop on the face. Patients typically have minimal or no

pruritus. One should always consider psoriasis in the differential diagnosis of a patient with scaly papules or plaques on the genitals. Lesions may appear in sites of skin trauma, such as linear plaques at sites of picking or scratching—the so-called Koebner phenomenon. Other forms of psoriasis exist, including guttate (droplike) psoriasis (Fig. 62-29). This form of psoriasis most often presents in young persons and may resemble papulosquamous secondary syphilis. An infection with *Streptococcus pyogenes* (group A streptococci), sometimes asymptomatic, often precipitates guttate psoriasis.

Although one study found a psoriasis prevalence of 5% among HIV-infected individuals,⁸³ most studies have not shown HIV-infected individuals to have an increased prevalence of psoriasis when compared with the general population. Individuals infected with HIV do have an increased prevalence of arthritis associated with psoriasis, however, correlating with the presence of HLA B27 and C7 antigens. Some authors have placed HIV-associated psoriasis and Reiter's syndrome along the same spectrum of disease.⁸⁴

The management of psoriasis is beyond the scope of this chapter, but therapy for HIV-related psoriasis has several unique aspects that warrant discussion. First, HIV-related psoriasis tends to respond to antiretroviral therapy. Although this was initially documented with zidovudine (AZT),⁸⁵ combination antiretrovirals produce similar responses. Second, despite initial reports of enhanced HIV replication and immune suppression caused by ultraviolet (UV) light treatment, subsequent studies have not found the use of UV-B or PUVA (psoralen with UVA) to accelerate HIV disease progression. Third, many systemic agents for psoriasis, such as methotrexate, azathioprine, and cyclosporine A, cause nonspecific or specific T-cell immunosuppression and should be avoided, until studies indicate otherwise. Lastly, the systemic retinoids, particularly acitretin, appear to help with moderate to severe psoriasis and do not exacerbate immunosuppression.



FIGURE 62-29. Droplike, or guttate, lesions of psoriasis. Such lesions are often seen with acute flares of the disease, often following streptococcal infection.

Reiter's syndrome (Reactive arthritis with mucocutaneous features)

Reiter's syndrome is a parainfectious reaction associated with urogenital infections (most often due to *C. trachomatis*) and enteric infections (*Shigella*, *Yersinia*, *Campylobacter*, and *Salmonella*) occurring in susceptible individuals, more often young men, with the HLA B27 genetic marker. The clinical syndrome is characterized by urethritis, conjunctivitis, and a seronegative spondyloarthritis. The cutaneous lesions keratoderma blennorrhagicum and circinate balanitis develop in 15% and 36% of patients, respectively (Figs. 62-30 and 62-31).⁸⁶ Mucocutaneous lesions may precede or follow the onset of extracutaneous illness (Fig. 62-32). The primary lesion of keratoderma blennorrhagicum begins as a dull red papule that rapidly forms a hyperkeratotic yellow surface. Lesions coalesce into plaques and may have a circinate collarette of scale. In some instances, pustular lesions form. Although keratoderma blennorrhagicum most often involves the soles of the feet, lesions may appear in other areas, such as the dorsa of the feet, legs, hands, fingers, nails, and scalp. Severe keratoderma blennorrhagicum can become generalized, especially in HIV-infected individuals; in this form, it resembles pustular psoriasis. On the penis, moist, red erosions merge to form circinate balanitis in the uncircumcised male; in the circumcised male, the lesions form hard crusts and plaques. Circinate vulvitis has been described.⁸⁷ Approximately 15% of patients with circinate balanitis have transient oral lesions, typically painless small vesicles that rapidly form superficial erosions or a patchy erythema. Reiter's syndrome often recurs without obvious relationship to new infections, although one should consider reinfection from untreated partners.

Dermatophytosis

Dermatophyte (tinea) infections typically manifest as a localized reaction on the feet, intertriginous areas, trunk,

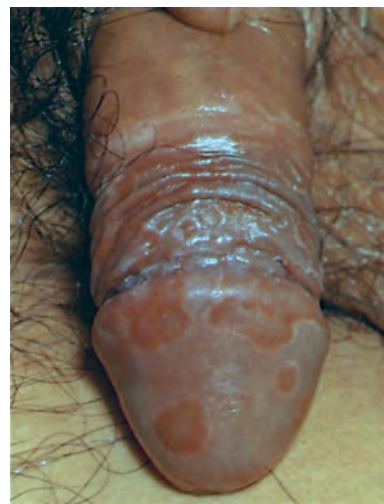


FIGURE 62-30. Circinate balanitis in Reiter's syndrome.



FIGURE 62-31. Keratoderma blenorrhagica in Reiter's syndrome.



FIGURE 62-32. Superficial ulcerations of the tongue in Reiter's syndrome.

scalp, or nails. The lesions generally appear annular with a relatively accentuated red, scaly edge (so-called “ring worm”). Infrequently, patients with tinea corporis present with a widespread rash, most often following use of topical steroids for misdiagnosed eczema (“tinea incognito”). The fungus most commonly responsible is *Trichophyton rubrum*. Scraping a lesion, especially at the accentuated edge and digesting the sample with potassium hydroxide sample usually confirms the diagnosis (Fig. 62-33). Sometimes a fungal culture is needed to confirm the diagnosis.

With localized dermatophyte infections, topical antifungals, such as 1% clotrimazole, 2% ketoconazole, 1% terbinafine, and others, are generally sufficient. When large surfaces are involved, systemic treatment, at least initially, may be warranted. The systemic azole antifungals (ketoconazole, itraconazole, and fluconazole), the allylamine terbinafine, and griseofulvin all have shown good efficacy.

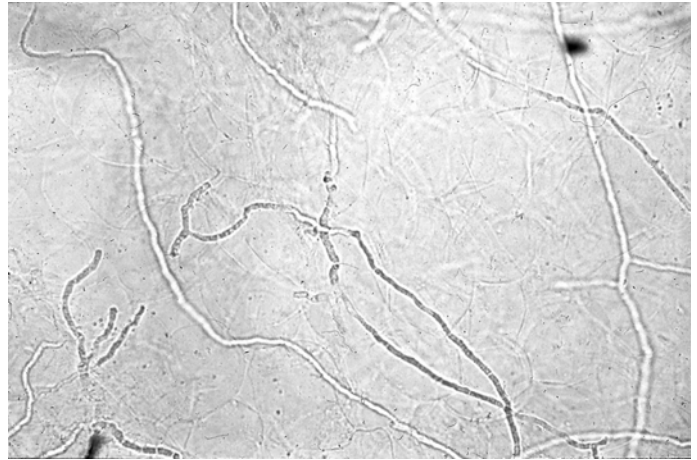


FIGURE 62-33. A potassium hydroxide preparation of scale from a patient with dermatophyte infection. Note abundant hyphae.

Patients infected with HIV tend to have more extensive dermatophytosis that can recur despite good initial response to therapy. Most of the time, one recognizes the lesions readily, but occasionally HIV-infected patients present with lesions that do not have the typical annular appearance. HIV-infected patients also more commonly acquire proximal subungual onychomycosis, an HIV-specific dermatophyte infection of the nails that is rare in individuals with intact immune systems.⁸⁸

Papulosquamous secondary syphilis

Patients with secondary syphilis often present with copper-colored papules and plaques with varying degrees of scale (Figs. 62-34 to 62-36). The lesions can mimic other papulosquamous dermatoses, namely psoriasis (Fig. 62-36), lichen planus, and pityriasis rosea. The color and generalized distribution (including the palms and soles) in a patient with generalized lymphadenopathy should cause one to suspect secondary syphilis.

Pityriasis rosea (PR) is morphologically similar to papulosquamous secondary syphilis but generally without lymphadenopathy or constitutional symptoms. Although the etiology is unknown, investigators suspect an infectious agent based on case-clustering and accounts of experimental transmission. Most cases occur in the winter months in persons 10–35 years of age. Human herpes types 6 and 7 have been implicated based on PCR assessment of patients with PR.⁸⁹

The first, and often the largest, lesion—referred to as the “herald patch”—usually appears on the thigh, upper arm, trunk, or neck. Initially, the lesion forms as an asymptomatic, well-defined, bright-red papule covered by a thin collarette of scale. After 5–15 days, crops of new lesions appear over a 7–10 day period. These lesions are oval, pale red with a dull, yellow-brown center; they are surrounded by a thin collarette of scale that points toward the center of the papule. The rash



FIGURE 62-34. Psoriasiform secondary syphilis.



FIGURE 62-35. Psoriasiform secondary syphilis.



FIGURE 62-36. Morphologically these lesions look like psoriasis. In fact, they are psoriasiform lesions of secondary syphilis.

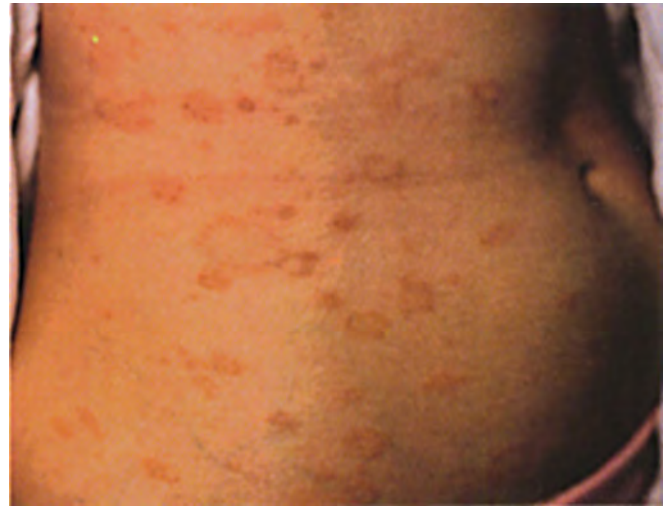


FIGURE 62-37. Characteristic lesions of pityriasis rosea.

is distributed over the trunk, upper arms, thighs, neck, and, infrequently, the face. On the posterior trunk, the long axes of the ovoid lesions follow the skin folds and give the typical “Christmas tree” appearance (Fig. 62-37). This pattern is inverted on the anterior trunk. The lesions typically persist for 3–4 weeks, though they may be present for 12 weeks or longer. Infrequently, patients develop an inverse form of pityriasis rosea, with lesions found in intertriginous areas as opposed to convex surfaces on the trunk. This variant may occur relatively more frequently in blacks than Caucasians. Patients with pityriasis rosea do not have constitutional symptoms, except for pruritus, usually mild to moderate, though occasionally severe. Topical triamcinolone, 0.1% cream or ointment applied twice daily, will relieve the symptoms of itching. The lesions fade after 3–6 weeks, and usually no other therapy is required. Ultraviolet light exposure is reported to hasten the resolution of PR.

■ PURPURA

Vasculitis

Vasculitis is a general term used to describe the inflammatory reaction to endothelial deposition of antigen–antibody complexes. The local inflammation and hemorrhage of cutaneous vasculitis produce the characteristic lesion of palpable purpura, a lesion that may progress to necrosis and ulceration. Lesions are commonly found first in areas of venous hypertension, most often the lower legs (Fig. 62-38). In addition to cutaneous lesions, patients with multisystemic vasculitis may have fever, arthralgias, gastrointestinal symptoms, and other constitutional manifestations. Vasculitis may develop as an acute disease with hemorrhagic, necrotic lesions that appear in crops and persist for 2–3 weeks; or as a more indolent disease in which purpura, erythematous macules, urticaria, and papules predominate and crops appear over months or years. Known associations with vasculitis



FIGURE 62-38. Purpuric papules and vesicles of vasculitis on the legs of a female intravenous drug user with the prodrome of hepatitis B.

include streptococcal and staphylococcal infection, prodromal hepatitis B, hepatitis C virus-associated mixed cryoglobulinemia, tuberculosis, persistent bacterial infection (such as dental abscess), certain drugs, malignancy, collagen vascular diseases, and pregnancy. It is important to exclude infectious causes before attempts are made to use corticosteroids or other immune suppressive agents.

In the prodromal stage of hepatitis B virus infection, patients can develop vasculitis and urticaria as well as macular and papular lesions. Hepatitis C virus (HCV) has been recognized as causing mixed cryoglobulinemia-associated vasculitis.^{90,91} This usually presents in the skin as palpable purpura, but livedo reticularis and urticaria have also been described. As opposed to the prodrome of hepatitis B, HCV-related vasculitis occurs during the course of active hepatitis. Rarely, patients with syphilis can develop cryoprecipitates that elicit a cutaneous vasculitis. Disseminated gonococcal infection, mentioned above in the section on nonfollicular pustules, often initially produces skin lesions that clinically and histologically suggest vasculitis.

■ PIGMENTARY CHANGES

Hyperpigmentation associated with HIV infection

Treatment with zidovudine (AZT) can cause nail and, less commonly, cutaneous hyperpigmentation, especially among blacks (Fig. 62-39). Clofazimine, which has sometimes been used to treat disseminated *Mycobacterium avium*-complex infection in AIDS patients, can produce generalized orange or red-brown hyperpigmentation. Generalized hyperpigmentation, apparently independent of zidovudine or clofazimine therapy, has also been reported in AIDS patients.⁹²

Postinflammatory pigment alteration

Postinflammatory hyperpigmentation or hypopigmentation presents during and following any inflammatory skin condition,



FIGURE 62-39. Hyperpigmentation associated with zidovudine (AZT) therapy.

for example, atopic dermatitis, drug eruptions, and syphilis. More darkly pigmented patients are at higher risk. Time following the inflammatory insult and treatment of the inciting condition constitutes the treatment of these common pigmentary alterations. Postinflammatory pigment change lasts longest on gravity dependent areas, especially the legs, and can take months to years to resolve completely.

CONCLUSION

This chapter has attempted to introduce the STD or HIV/AIDS healthcare provider to an approach for a patient presenting with a generalized cutaneous condition. Visual inspection of the skin, even before receiving any medical history, is the most important diagnostic tool. Identifying the primary lesion, any secondary features, and the distribution of the rash are the keys to generating a differential diagnosis. This cannot be carried out without a thorough skin exam, which requires good lighting and adequate exposure of the skin.

The array of conditions that can present in patients with STDs or infected with HIV is vast and is certainly not restricted to those conditions listed in (Table 62-3). One must remember that in HIV-infected patients, common conditions may present with atypical variations, and more than one condition presenting together is a common scenario. It is critical to discern whether an infectious agent is the cause for the rash, since treatment is often specific and delay in treatment may result in significant morbidity.

An interesting aspect of generalized dermatoses in STD-afflicted and HIV-infected patients is the significant proportion of noninfectious inflammatory cutaneous conditions. These include parainfectious phenomena such as HSV-related erythema multiforme, Chlamydia-induced Reiter's syndrome, guttate psoriasis associated with streptococcal disease, and vasculitis associated with hepatitis B or C.

In HIV-infected patients, the high frequency of inflammatory conditions such as drug hypersensitivity, seborrheic dermatitis, and eosinophilic folliculitis defies clear explanation and seems paradoxical within the simple paradigm of immunosuppression related to HIV infection. Perhaps immunodysregulation is a better term to explain the simultaneous risks of opportunistic infection and inflammatory skin conditions. Further investigation into these parainfectious phenomena and the “hyperimmune” conditions of HIV-related skin disease will be needed to elucidate their pathogenesis.

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Ronald C. Ballard

Genital ulcer adenopathy syndrome is a frequent presentation of sexually transmitted diseases (STDs), particularly in developing countries. The syndrome is usually caused by sexually acquired organisms gaining entry to the body via a breach in the epithelium of the genital skin or mucous membranes. Local multiplication of organisms, together with accompanying inflammatory reactions, results in the formation of open lesions. Under some circumstances, the regional lymph nodes may become involved leading to inguinal and/or femoral lymphadenopathy or ulceration. In cases of lymphogranuloma venereum (LGV), the reason for consultation may be the lymphadenopathy alone, owing to the transient nature of the initial lesion. There are a number of different causes of genital ulcer disease (GUD), and since the clinical presentation of each may be variable and the treatment for each different, genital ulcer adenopathy syndrome may create considerable diagnostic and management problems for clinicians. The relative importance of GUD and the need to provide prompt, effective treatment have increased as a result of the finding that these lesions are a major cofactor in the transmission of HIV.

EPIDEMIOLOGY

Epidemiological data on the genital ulcer adenopathy syndrome are incomplete, because diagnostic tests for all causes of the syndrome are usually not available at services where treatment is provided. Even when comprehensive services are available, notably during research projects, it is often not possible to determine the etiology of the disease in a significant proportion of cases, owing to lack of sensitivity of the laboratory tests used.¹⁻⁵ Of all causes of the syndrome, the recording of cases is probably the most complete for syphilis, owing to widespread use of serological screening tests and the recognition of the potential consequences of the disease if it is left untreated. However, overreporting of syphilis may frequently occur in some settings, since many patients presenting with proven nonsyphilitic lesions may prove seroreactive in tests for the disease.⁶

A total of 38,592 cases of genital ulceration were seen at Genitourinary Medicine Clinics in the UK during 2005. Of these, 35,451 (91.9%) were cases of genital herpes, 2,814 (7.3%) were classified as infectious syphilis, and the remaining 327 cases were chancroid, LGV, or donovanosis (0.8%).⁷ Unfortunately, genital herpes, LGV, and donovanosis are not reportable diseases in the United States and, therefore, comparable figures are not available. However, approximately 266,000 cases of genital herpes were seen in physicians' offices during the same year, while 8,724 cases of primary and secondary syphilis and 17 cases of chancroid were reported to the Centers for Disease Control and Prevention (CDC).⁸ In contrast, genital ulcerations are seen relatively more frequently at STD clinics and primary health-care facilities in developing countries. In sub-Saharan Africa and in Asia, genital ulcer disease may account for between 20% and 70% of STD clinic visits, whereas the comparable figure for Europe and North America is, at most, 5%.⁹ In the past, the etiology of genital ulceration showed considerable geographical variability, with genital herpes the most frequent cause in North America and Europe and genital ulcerations caused by bacteria predominating in most developing country settings. However, in the past few years, the patterns of infection in many developing country settings have changed dramatically, with genital herpes becoming the leading cause of ulceration.¹⁰ This may be due, in part, to the effective introduction of syndromic management for GUD resulting in a reduction in the relative prevalence of chancroid and syphilis and also to high rates of HIV infection with accompanying immunosuppression resulting in an increased rate of recurrence and severity of genital herpes. Despite these changes, chancroid remains a significant cause of GUD in sub-Saharan Africa—particularly in the south, Southeast Asia, India, South America, and the Caribbean. In North America, outbreaks of the disease have been associated with sex worker contact, particularly among minority populations.^{11,12}

Classical LGV and donovanosis appear to be restricted to geographical foci in tropical countries, with LGV being documented in sub-Saharan Africa, South America and the

Caribbean, the Indian subcontinent, and Southeast Asia, while donovanosis has largely been restricted to India, Papua New Guinea, Northern Australia, southern Africa, and Brazil. These diseases are occasionally diagnosed in North America and Europe largely as a result of importation from endemic areas. However, LGV has reemerged as a cause of severe proctocolitis and anorectal ulceration among MSM both in Europe and the United States even though classical genital ulceration adenopathy syndrome is rarely encountered in this population.^{13–14}

Overall, the proportion of STD patients with genital ulcerations and the causes of those ulcerations are probably dependent upon a number of factors, including geographical location, socioeconomic status, availability of diagnostic tests, sexual preference and practices, the relative importance of commercial sex in the spread of disease, the frequency of circumcision, and the prevalence of concomitant HIV infection.

Risk factors for genital ulceration inevitably vary according to etiology and population. The risk of acquisition of chancroid appears to be related to low socioeconomic status, geographic origin, commercial sex, and lack of circumcision.¹⁵ In contrast, in the United States and Western Europe the majority of cases of primary syphilis occur among MSM and among disadvantaged minority populations,¹⁶ while the disease has also reemerged as a significant public health problem among heterosexuals in many communities in Eastern Europe where sex work is often associated with illicit drug use.

Relatively recently, a considerable body of evidence has accumulated linking genital ulceration with increased transmission of HIV.^{17–19} These studies, conducted among MSM in the United States and among heterosexuals in many developing countries, indicate not only that the presence of genital ulcers significantly enhances susceptibility to HIV infection but also that the presence of genital ulcers in HIV-positive individuals results in increased transmission of the virus to others. Chancroid, in particular, was initially identified as a significant cofactor in the heterosexual transmission of HIV in Africa and Southeast Asia, with cofactor effects per sexual exposure being estimated as high as 10–50% for male-to-female transmission and 50–300% for female-to-male transmission in sub-Saharan Africa.²⁰ However, more recently, genital herpes has been implicated as a major cofactor enhancing HIV transmission, particularly in geographical regions with a mature HIV epidemic.^{21,22} As a result, prompt management and prevention of genital ulcer disease, including genital herpes, has been identified by the WHO as a priority within STD control programs aimed at reducing the incidence of HIV infection.²³

ETIOLOGY

The most frequent infectious causes of genital ulceration include herpes simplex virus (both HSV-1 and HSV-2), *Treponema pallidum*, *Haemophilus ducreyi*, the L-biotype of

Chlamydia trachomatis, and *Klebsiella* (previously *Calymmatobacterium*) *granulomatis*. In addition, *Phthirus pubis*–*Sarcoptes scabiei* pyoderma, *Trichomonas vaginalis*, *Entamoeba histolytica*, mixed nonsyphilitic spirochetes, and *Phthirus pubis* or *Sarcoptes scabiei* infestation with secondary bacterial infection may cause breaks in the genital epithelium. While *Neisseria gonorrhoeae* and non-L isolates of *C. trachomatis* may be detected in genital ulcerations, they may represent transient contamination or colonization of the site by urethral/cervical pathogens rather than a causal relationship. The differential diagnosis of infectious genital ulceration includes trauma, malignancy, fixed drug eruption, and Behçet's and Reiter's syndromes.

CLINICAL MANIFESTATIONS

Superficially, the textbook descriptions of the clinical features of the individual causes of genital ulcer adenopathy syndrome appear to be characteristic (Table 63-1). However, in practice, the clinical presentation of genital ulcerations often does not correspond to the classic description and even experienced clinicians can be easily misled.^{24–26} This situation is particularly evident in developing countries, where genital ulcerations are common and mixed infections are frequently encountered. In addition, other factors such as secondary bacterial infection; the local application of antiseptics, antibiotic, or corticosteroid creams; the systemic use of inappropriate or incomplete courses of antibiotics; and the influence of concomitant HIV infection with associated immunosuppression may all modify the clinical appearance of lesions¹² (Fig. 63-1).

In general, the incubation period for chancroid and genital herpes is short (less than 7 days) whereas it is usually longer for syphilis, LGV, and donovanosis. Unfortunately, estimated incubation periods can often be misleading owing to the failure



FIGURE 63-1. Multiple, superficial, secondarily infected lesions of genital herpes which mimic chancroid ulcerations in an HIV seropositive patient.

Table 63-1. Clinical Features of Genital Ulcers and Associated Lymphadenopathy

	Syphilis	Herpes	Chancroid	LGV	Donovanosis
Incubation period	9–90 d	2–7 d	1–14 d	3 d–6 wks	1–4 wks (up to 6 mo)
Primary lesions	Papule	Vesicle	Pustule	Papule, pustule, or vesicle	Papule
Number of lesions	Usually one	Multiple, may coalesce	Usually multiple, may coalesce	Usually one	Variable
Diameter	5–15 mm	1–2 mm	Variable	2–10 mm	Variable
Edges	Sharply demarcated, elevated, round, or oval	Erythematous	Undermined, ragged, irregular	Elevated, round, or oval	Elevated, irregular
Depth	Superficial or deep	Superficial	Excavated	Superficial or deep	Elevated
Base	Smooth, nonpurulent, relatively avascular	Serous, erythematous, nonvascular	Purulent, bleeds easily	Variable, nonvascular	Red, velvety, bleeds easily
Induration	Firm	None	Soft	Occasionally firm	Firm
Pain	Uncommon	Frequently tender	Usually very tender	Variable	Uncommon
Lymphadenopathy	Firm, nontender, bilateral	Firm, tender, often bilateral with initial episode	Tender, may suppurate, loculated, usually unilateral	Tender, may suppurate, loculated, usually unilateral	None, pseudobuboes

of patients to identify the correct source of the infection, especially when long incubation periods are involved.

Most genital ulcers in men are found on the prepuce (Fig. 63-2), near the frenulum, in the coronal sulcus, or on the penile shaft. In women, lesions may occur on the labia, on the vaginal walls and cervix, and on the inner thighs and fourchette. In both women and MSM, lesions may be found in the rectum and in the perianal region. Extragenital ulcers may be detected on the lips or in the throat as a result of orogenital contact. Classically, the lesions of primary syphilis and LGV are solitary; while those of chancroid, donovanosis, and genital herpes tend to be multiple, but these and other features are often atypical as a result of secondary bacterial infection and mixed etiologies.

Although the characteristics of primary ulcerations may be misleading when one is endeavoring to establish a definitive diagnosis on clinical grounds, features of the associated regional lymphadenopathy, when present, may be helpful in differentiating diseases. In both sexes, the lymphatic drainage of the external genitalia is primarily to the inguinal and to a lesser extent the femoral lymph nodes. However, the inner two-thirds of the vagina and cervix and the rectum drain to the deep pelvic

(sacral) and perirectal nodes. Inguinal/femoral lymphadenopathy may therefore be associated with genital ulcerations, which may be present either on the external genitalia or hidden within the vault of the vagina or in the urethra. Although there may be considerable overlap in the clinical characteristics of the lymphadenopathy, certain characteristics may aid the establishment of a diagnosis. Notably, the lymphadenopathy associated with primary syphilis is classically described as bilateral, discrete, rubbery, and painless, while the nodes associated with initial episodes of genital herpes are also bilateral but smaller and tender. In contrast, the lymphadenopathy associated with either chancroid or LGV is usually unilateral and painful and may frequently undergo suppuration to form inguinal abscesses, which may rupture²⁷ (Fig. 63-3). Involvement of both inguinal and femoral glands separated by the inguinal ligament results in the formation of the classic “groove sign,” which was previously considered pathognomonic for LGV (Fig. 63-4). However, many cases of chancroid may present with similar gland involvement (Fig. 63-5). Swellings in the groin associated with cases of donovanosis are not due to an adenitis; rather, they arise as a result of subcutaneous spread of the granulomas, resulting in pseudobubo formation.



FIGURE 63-2. Preputial and subpreputial lesions of chancroid with associated phimosis.



FIGURE 63-3. Inguinal ulceration following rupture of an inguinal bubo in a case of chancroid.

It should be noted that, particularly in developing countries, discrete, painful inguinal lymphadenopathy may be associated with nonsexually acquired lesions of the lower limbs, and that chronic nontender lymphadenopathy in the absence of genital ulceration or associated with a persistent lesion may be suggestive of genital or lymphatic malignancy.

COMPLICATIONS AND SEQUELAE

Complications arising from sexually acquired genital ulcers include secondary infection, particularly with anaerobic bacteria, which may result in the formation of destructive or phagedenic ulceration, phimosis (Fig. 63-3) or paraphimosis, and local edema. Successful treatment of both chancroid and donovanosis may result in the formation of scars which, if sited on the foreskin, may cause a permanent phimosis that could require circumcision. In contrast, the lesions of primary syphilis and genital herpes usually heal spontaneously with no scarring within 6 weeks and 1–3 weeks, respectively.



FIGURE 63-4. Classical “groove sign” of lymphogranuloma venereum.



FIGURE 63-5. Left inguinal and femoral lymphadenopathy separated by the inguinal ligament. *Haemophilus ducreyi* was isolated from a subpreputial lesion.

If left untreated, patients with primary syphilis may develop a secondary syphilitic rash and subsequently, following a long period of latency, the sequelae associated with tertiary disease. Unfortunately, the majority of patients with primary genital herpes develop recurrent disease which, although less severe than the initial episode, may have considerable psychological consequences. These recurrences may occur frequently and be severe, particularly in those patients coinfecting with HIV and who are severely immunosuppressed.

The most severe complications of chancroid and LGV are associated with lymph node involvement. Both chancroid and LGV may cause fluctuation and eventual ulceration of the inguinal and/or femoral glands, while autoinoculation of *H. ducreyi* may result in the formation of satellite chancroid

lesions both on the external genitalia and in the inguinal region.

In LGV, the genito-anorectal syndrome may result in pelvic and perirectal abscesses, rectal strictures, and fistulae. The chronic manifestations of LGV may result in scar formation resulting in blockage of the lymphatics draining the genitalia, causing severe edema. When the lymphatic edema is gross it is termed elephantiasis or esthiomene. A pseudo-elephantiasis also occurs in advanced cases of donovanosis when scarring results in occlusion of the lymphatics.

LABORATORY DIAGNOSIS OF GENITAL ULCER ADENOPATHY SYNDROME

Ideally, appropriate treatment of genital ulcer disease should be guided by the determination of the etiology of the genital ulcer, using all relevant laboratory tests available. In industrialized countries, where the majority of ulcerations are attributable to genital herpes or syphilis, these should include either darkfield microscopy, amplified molecular testing such as the polymerase chain reaction (PCR) or direct immunofluorescence staining of genital ulcer material for *T. pallidum*, culture, or PCR for herpes simplex virus or direct detection of HSV antigen with ELISA or direct immunofluorescence tests (DFA) and type-specific serological testing for HSV and for syphilis. In developing countries, where other causes of genital ulcer adenopathy syndrome are frequently encountered and establishment of a diagnosis on clinical grounds may be even more difficult, addition of tests for *H. ducreyi*, LGV infection, or *K. granulomatis* may be considered. However, in these situations laboratory facilities are usually either limited or not available. Under these circumstances

syndromic management principles should be applied which take into account the local patterns of disease. Even so, serological tests for syphilis should be performed in each case.

A summary of laboratory tests used for diagnosis of genital ulcer adenopathy syndrome is outlined in (Table 63-2). Specimens taken directly from the base of ulcerations should be obtained with small, sterile Dacron or cotton swabs following cleansing of the lesions with sterile saline. When small lesions are being sampled, care should be taken to overcome the inherent problems associated with reduction in sensitivity following multiple sampling. Specimens of ulcer exudate for darkfield microscopy or DFA for *T. pallidum* can be obtained by using a platinum scraper, loop, capillary tube, or glass coverslip following expression of exudate from a cleansed lesion. Specimens for herpes culture, PCR, or HSV antigen detection are best obtained following disruption of vesicles and collection of vesicle fluid. Swabs obtained from the bases of ulcerations are somewhat less sensitive for detection of HSV but are generally the specimens of choice for detection of *H. ducreyi* and *C. trachomatis* by culture or the use of molecular methods. Specimens of pus obtained from fluctuant lymph nodes should be obtained by aspiration of material with a wide-bore needle through healthy tissue in order to prevent fistula formation. Low rates of detection of both *H. ducreyi* and/or *C. trachomatis* should be anticipated from such specimens.

MICROSCOPY

Darkfield microscopy has traditionally been recognized as the most appropriate technique for establishing a definitive diagnosis in cases of primary or secondary syphilis.

Table 63-2. Laboratory Tests for the Diagnosis of Genital Ulcer Adenopathy Syndrome

	Syphilis	Herpes	Chancroid	LGV	Donovanosis
Microscopy	Darkfield or direct immunofluorescence	Tzanck. Preparation has low sensitivity	Gram-staining has low sensitivity and specificity	Not available	Giemsa- or Wright-stained tissue smears and sections
Culture	Not available except by rabbit testicular inoculation	Cell culture	Sensitive, selective media available	Cell culture	Cell culture (experimental)
Serology	RPR/VDRL, FTA-ABS, TPHA, TPPA, ELISA	Type-specific ELISA	Experimental	Complement fixation and indirect micro-IF test	Experimental
Molecular techniques	PCR (experimental)	PCR (experimental)	PCR (experimental)	PCR (experimental)	PCR (experimental)

Unfortunately, the technique has major shortcomings since it requires a microscope fitted with a darkfield condenser and considerable technical expertise to discriminate morphologically between *T. pallidum* and the saprophytic spirochetes that may colonize genital lesions. In addition, a balanoposthitis associated with a nontreponemal fusospirochetal infection has been described in tropical areas, which may result in high rates of false-positive readings using this technique. Under these circumstances, direct immunofluorescence staining of ulcer material may represent a more convenient alternative. Although inherently more specific, this technique requires a higher level of expertise, an immunofluorescence microscope, and expensive reagents.

Scrapings obtained from the bases of ulcers or smears made from vesicle fluid may be examined for HSV infection by using immunofluorescence or immunoperoxidase techniques or by microscopic examination of Tzanck preparations which is less sensitive and specific but which may reveal characteristic multinucleated giant cells.

Establishment of a diagnosis of donovanosis is usually dependent upon the demonstration of encapsulated intracytoplasmic Donovan bodies within mononuclear cells in Giemsa- or Wright-stained smears of ulcer exudate or in sections made from scrapings obtained from the edges of active lesions or from punch-biopsy material. In contrast, microscopic examination of gram-stained smears obtained from genital ulcers exhibits both poor sensitivity and poor specificity for *H. ducreyi*, since many nonchancroidal lesions are colonized by gram-negative rods. As a result, this technique cannot be recommended for diagnosis of chancroid even in resource-poor settings.

ISOLATION OF CAUSATIVE AGENTS

Viral isolation remains a frequent means of establishing a definitive diagnosis of genital herpes but is time-consuming and requires special expertise. The most frequently used cell lines are Vero cells and human diploid cells, such as MRC-5 cells, or human foreskin or lung fibroblasts. Depending on the amount of viable virus in the specimen, a characteristic cytopathic effect may be detected in cultures 1–7 days following inoculation.

Isolation of *H. ducreyi* has been the most frequent method used to establish a definitive diagnosis of chancroid. A number of solid, semiselective media have been developed which, when used either singly or in combination in biplates, have achieved sensitivities of approximately 80%. However, recovery of *H. ducreyi* from bubo aspirates is less efficient, with sensitivities of 40–50%.¹² Since direct plating of exudates onto freshly prepared medium is essential to achieve optimal isolation rates, few laboratories are able to maintain culture capability on an ongoing basis. A transport medium, which maintains the viability of *H. ducreyi* in swabs stored at 4°C

for up to 1 week, enables low volume laboratories to prepare fresh batches of isolation media following collection of the specimen.²⁸

Isolation of the L-serovars of *C. trachomatis* from primary ulcers, the urethra, the endocervix, rectal lesions, or bubo aspirates is a common means of confirming a diagnosis of LGV. However, non-LGV strains of *C. trachomatis* associated with concomitant urethral or cervical infection may contaminate ulcerations and give false-positive results. If the vast majority of cells are infected in a tissue culture monolayer and the intracellular inclusions are large 48 hours after inoculation, it is highly likely to be a case of LGV. Despite frequent textbook references, bubo aspirates are probably the least appropriate source of material for chlamydial isolation since few patients present with fluctuant glands. When patients do present, the organisms can rarely be demonstrated in bubo aspirates by culture, owing to the paucity of infectious organisms in bubo pus and the toxicity of this material for cell culture monolayers. Isolation of *K. granulomatis* from cases of donovanosis has been achieved by inoculation of material obtained from the bases of ulcerations onto monolayers of human monocytes²⁹ or HEp-2 cells.³⁰ However, these techniques have not been widely adopted for routine diagnosis of the disease.

SEROLOGICAL TESTS

Ideally, serological tests for syphilis should be performed routinely in all cases of STDs but particularly in cases of genital ulcer adenopathy syndrome. Cardiolipin (reagin) tests such as the rapid plasma reagin (RPR), or venereal disease research laboratory (VDRL) test may be negative when a patient initially presents with primary syphilis, since seroconversion may occur as late as 6 weeks after infection. The fluorescent treponemal antibody absorption (FTA-Abs) test becomes positive earlier than the reagin tests (after about 3 weeks), but care should be taken in the interpretation of a positive FTA-Abs test, since treponemal tests remain positive even after successful treatment of disease and may represent a previously treated episode. In areas where syphilis is common, patients presenting with nontreponemal ulcerations may also present with both reactive reagin and treponemal tests. These results may occur in cases that are the result of either concomitant untreated syphilis or a later stage of syphilis (of more than 2 years' duration) that was successfully treated.⁸ Quantitative RPR or VDRL tests should also be used as a baseline against which responses to treatment can subsequently be measured. In regions where syphilis is uncommon, it is necessary to confirm the results of positive cardiolipin tests by performing an FTA-Abs, *T. pallidum* hemagglutination assay (TPHA), *T. pallidum* passive particle agglutination assay (TPPA), or treponemal ELISA test, since false-positive reactions are frequently encountered. However, in regions where syphilis is commonly encountered the positive predictive value of the reagin (screening) tests is high, there are relatively few

false-positive reactions, and there is therefore little value in confirming the results with a more specific test.

Serological tests to detect type-specific antibody to glycoproteins G1 and G2 of herpes simplex virus can be used as an adjunct to the detection of HSV in lesions in the diagnosis of genital herpes to differentiate between primary and recurrent disease.³¹ However, when used alone, the results of type-specific serologic investigations may be misleading either because negative tests are often recorded in cases of primary disease or because patients may be seropositive for antibody to HSV-2, but the presenting lesion may be due to infection with another pathogen, or the presenting lesion may be caused by HSV-1. The use of commercially available tests that are not type-specific is not recommended.³²

The chlamydial complement-fixation test, which measures antibody to chlamydial group antigen, remains the most widely used serological test for diagnosis of LGV. Rising titers, or a single titer of $\geq 1/64$, usually have been considered diagnostic. A microimmunofluorescence (micro-IF) test that measures type-specific antibody to *C. trachomatis* has also been widely used, and broadly cross-reacting antibody titers of $\geq 1/256$ are frequently detected in cases of LGV.³³ Antibody to *H. ducreyi* may be detected in crude enzyme-linked immunoassays.³⁴ However, these tests are only useful for establishing lifetime exposure to the disease and are therefore only of value for epidemiological studies.

MOLECULAR TECHNIQUES FOR DIAGNOSIS

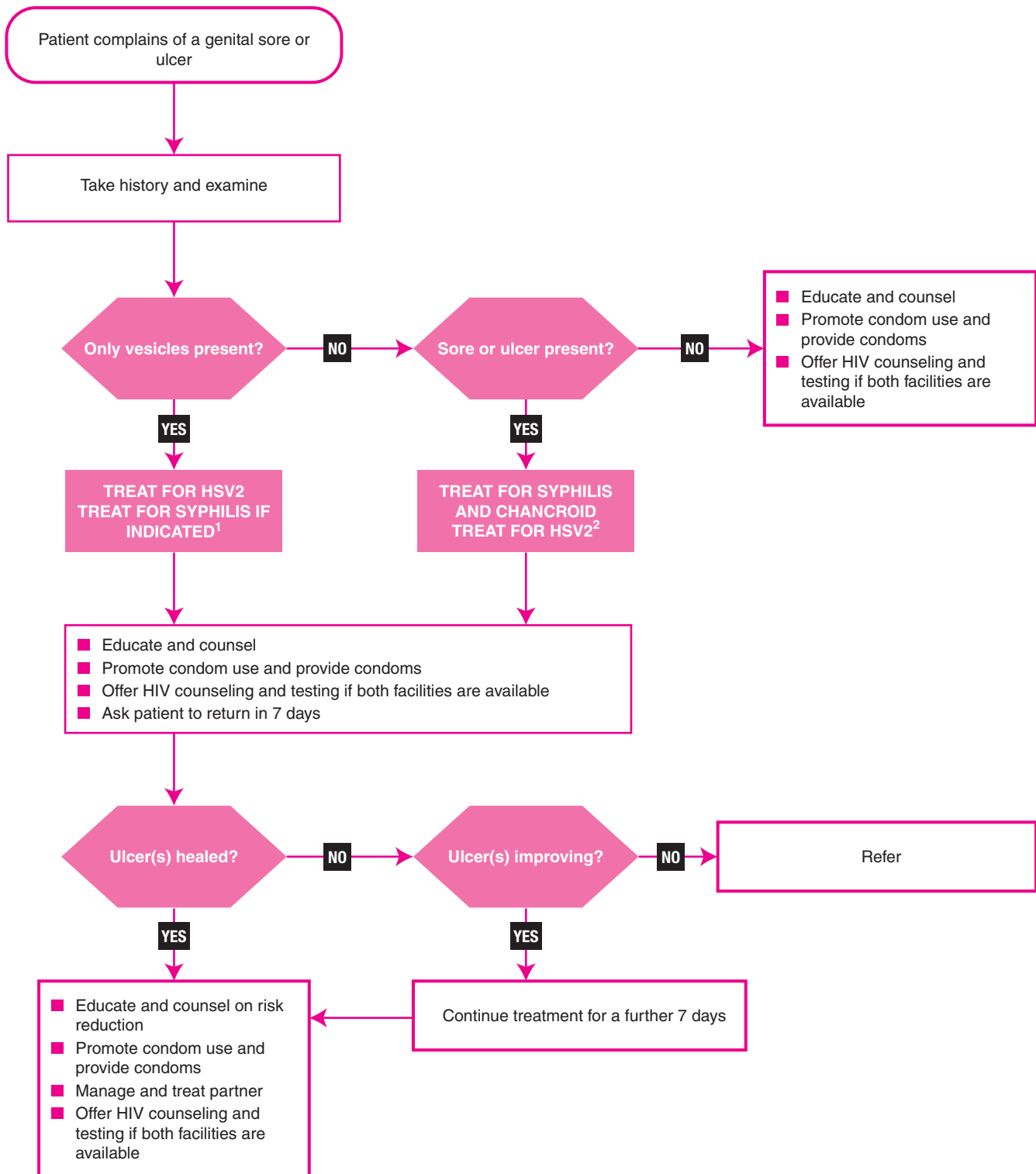
Although nucleic acid probes have been used to detect both HSV and *C. trachomatis* in clinical specimens, the development of amplified techniques such as the PCR has resulted in methods which are both sensitive and specific for the detection of agents associated with genital ulcer adenopathy syndrome. Separate PCR assays have been used to detect the presence of *T. pallidum*,³⁵ *H. ducreyi*,³⁶ and HSV³⁷ in clinical specimens, and a multiplex PCR (M-PCR) amplification assay has been described which is able to detect the presence of these three organisms in a single ulcer specimen.^{38,39} In addition, PCR tests for *K. granulomatis*⁴⁰ and tests that can differentiate between the *L. biovar* of *C. trachomatis* and the less invasive D-K strains^{41,42} have been developed. Collectively, these techniques represent a significant increase in the sensitivity of diagnostic testing for genital ulcer disease, which has resulted in fewer cases remaining unsolved. However, there is little chance that they will become commercially available in the foreseeable future.

MANAGEMENT

In an ideal situation, treatment for genital ulcer adenopathy syndrome should be initiated only after establishment of a definitive diagnosis by using appropriate laboratory investigations.

However, in order to provide effective treatment at the initial consultation, it is often necessary for clinicians to provide therapy which will cover the majority of causes of genital ulceration/bubo formation known to be prevalent in the target population. This often results in provision of treatment for more than one infection. This approach, known as syndromic management, is necessary because no single antimicrobial agent affords reliable treatment for all causes of the genital ulcer adenopathy syndrome. In addition, the reliability of clinical signs is questionable, mixed infections are common, laboratory support for clinical services is limited, and there are few tests for these infections that can be provided on-site. Syndromic management is recommended by the WHO, particularly for developing countries, and suitable flowcharts representing appropriate management algorithms need to be developed on the basis of the patterns of disease presenting in a particular geographical location.⁴³ Two examples of flowcharts, published by the WHO, the first for syndromic management of genital ulceration and the second for management of inguinal buboes, are shown in Figs. 63-6 and 63-7, respectively. It should be noted that these flowcharts should be validated by using the most sensitive laboratory tests available to establish the relative frequency of the different causes of the syndrome within a particular geographical setting.⁴⁴

Although all genital ulcers contain a mixed bacterial flora, it is usually not necessary to treat secondary infections in order to hasten healing. In cases that appear to be secondarily infected in developing country settings, some experts provide a nontreponemidal antimicrobial such as cotrimoxazole. Unfortunately, topical antiseptics or antiviral or antibacterial agents are often dispensed by pharmacies without prescription or are administered by traditional healers. These topical agents are not recommended. In addition, topical corticosteroids should not be applied directly to lesions. Patients with genital ulcer adenopathy syndrome should be managed by appropriately trained health professionals since potentially serious consequences may arise as a result of poor management. Ulcerations usually commence healing within 48 hours of initiation of appropriate therapy, but fluctuant buboes, which are usually associated with chancroid or LGV, should be aspirated through healthy tissue to prevent spontaneous ulceration. Repeated aspiration may be necessary because the suppuration process may continue even after initiation of effective antibiotic therapy. Although incision and drainage of suppurating glands may be indicated in an industrialized country setting, aspiration may be more appropriate for resource-poor settings to prevent scarring and delayed healing. Aspiration should be performed with a large-bore needle because the initial exudate may be thick and purulent, while subsequent aspirations performed after initiation of effective therapy may yield serous or serosanguineous exudates.



1 Indications for syphilis treatment:

- RPR positive; and
- Patient has not been treated for syphilis recently.

2 Treat for HSV2 where prevalence is 30% or higher, or adapt to local conditions.

FIGURE 63-6. WHO algorithm for syndromic management of genital ulcerations.⁴³

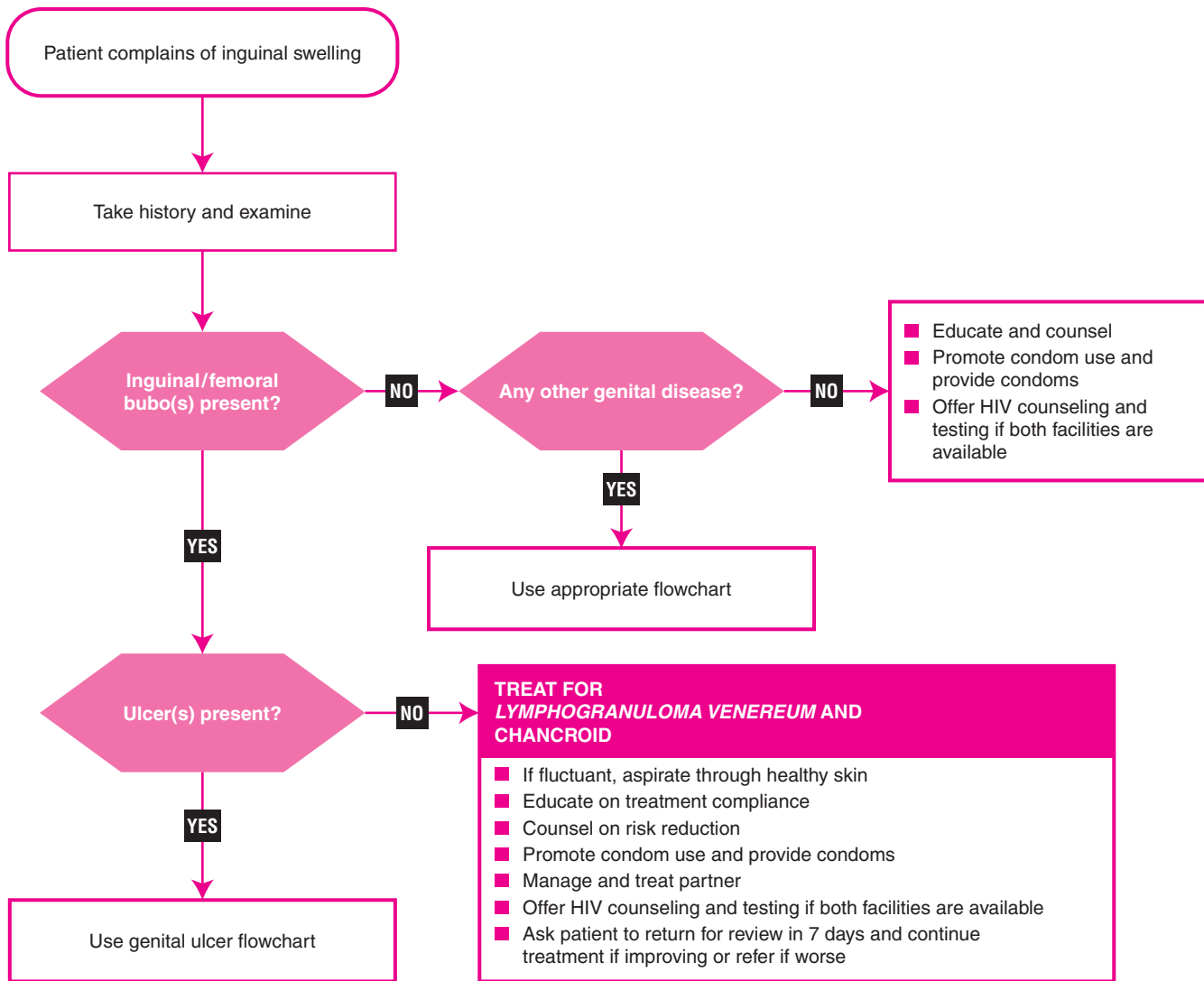


FIGURE 63-7. WHO algorithm for syndromic management of inguinal buboes.⁴³

The specific treatments for individual causes of genital ulcer adenopathy syndrome are discussed in the disease specific chapters elsewhere in this book and in treatment guidelines published by the WHO⁴³ and the Centers for Disease Control and Prevention.³² Antimicrobial resistance can be a cause of treatment failure in a minority of cases of syphilis where macrolide antibiotics are used to treat the disease, while treatment failure in cases of chancroid is usually associated with infection with multiresistant strains of *H. ducreyi*. Apparent treatment failure following antibiotic therapy may also occur as a result of mixed infection when one of the etiological agents is HSV.

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INTRODUCTION

The external genitalia are a common site for rashes, itching, and minor infections. This area is warm, moist, and occluded, and it is frequently exposed to irritating urine, feces, and vaginal secretions. In addition, concerns about hygiene and sexually transmitted diseases prompt some people to use overly vigorous cleaning regimens, deodorants, and specialized hygiene products. Abnormalities that, if they occurred elsewhere, would be considered trivial by the patient, suddenly become complicated due to both the local environment and psychological factors. Prompt recognition of the cause or causes of visible genital abnormalities or uncomfortable sensations not only minimizes the duration of pain or itching but also helps to avoid damage to self-esteem and sexual relationships.

Many physicians and patients assume that any genital abnormality is infectious. Although infectious processes certainly can affect the genitalia, there are many noninfectious causes of genital symptoms and abnormalities as well. It is often necessary to entertain a broad differential diagnosis. To assist with this process, we have organized this chapter by morphology. Some genital disease processes have more than one clinical presentation. Thus, some conditions are discussed several times.

RED PLAQUES AND PATCHES

The diseases in this section are characterized morphologically by large (generally >1.5 cm) areas of inflammation. Although these usually appear red, erythema is sometimes subtle and difficult to differentiate from the variable degree of normal background pinkness. Also, inflammation in black skin generally appears hyperpigmented rather than red. Whenever a patient complains of itching, burning, or pain, the skin is most likely inflamed, whether or not erythema is visible. In addition, normally scaly diseases such as eczema and psoriasis may lack visible scale owing to the damp nature of the skin in this area.

■ ECZEMA/NEURODERMATITIS

Eczema is an umbrella term often used to include atopic dermatitis, neurodermatitis, and lichen simplex chronicus, but the scope of the term is controversial. Lichen simplex chronicus is used here to describe a localized, lichenified eczema. Eczema is often called “the itch that rashes.” Patients initially experience pruritus that may be caused by a yeast infection, heat, moisture, or any other irritant. Scratching produces inflammation that heightens the sensation of itching. As itching worsens, scratching increases until finally an itch–scratch cycle takes on a life of its own, even though the initial precipitating event may have resolved.

The morphology of eczema is consistent with skin that has been scratched or rubbed. Therefore, linear or angular erosions produced by fingernails are common. There is usually surrounding, poorly demarcated erythema, with or without visible scale.

Lichenification, or thickening of the skin as a result of rubbing, is extremely common (Fig. 64-1). Lichenification, or thickening of the skin induced by rubbing, is usually detected by the accentuation of skin markings and thickened appearance of the skin. This can be difficult to appreciate over the scrotum and labia majora, where the skin normally can be thickened and rugated. When lichenification or significant inflammation occurs on the modified mucous membrane of the vulva, the skin frequently becomes white—a clue to subtle disease (Fig. 64-2).

In men, eczema occurs most often on the posterior scrotum and relatively often in the crural crease and upper, inner thigh. The penis is a less common location for this condition. In women, the labia majora as well as the modified mucous membranes of the vulva are often affected.

The treatment of eczema requires attention to several specific facets of the disease. The most common cause of a poor response to therapy is the failure to address all factors simultaneously.

First, inflammation and itching should be treated with a topical corticosteroid preparation. A high-potency medication such as clobetasol 0.05% (Temovate®) is often required.



FIGURE 64-1. Remarkable thickening of the scrotum with white areas of postinflammatory hypopigmentation are typical of neurodermatitis in black skin.



FIGURE 64-2. Excruciating pruritus was associated with the relatively subtle thickening of the right inner labium majus, manifested by slightly lighter color, mild thickening, and drier appearance than seen on the contralateral side. In addition, excoriations are visible and fissures with scale suggestive of bacterial or yeast superinfection.

Patients should be examined at least monthly to identify any early signs of adverse local effects, such as atrophy, and to decrease the potency or frequency of application of the topical corticosteroid when disease control is attained.

Second, any irritant should be discontinued. This begins with the appropriate choice of a vehicle for the corticosteroid. Creams contain alcohol, so that patients with significant inflammation and excoriation are often best treated with an ointment base. Other common irritants include overwashing, washing with harsh soaps, and the application of various borrowed and purchased medications. An extremely common irritant, especially in women, is secondary infection. This is most often caused by *Candida albicans*, but occasionally infection or colonization by *Staphylococcus aureus* or

Streptococcus spp. produces irritation. Often, treatment of the secondary infection requires ongoing, suppressive therapy until the skin disease and symptoms are controlled, because recurrent infections are extremely common in patients with eczema and in the setting of topical corticosteroid use.

Finally, scratching must be stopped. Daytime itching can be minimized by the cited measures but nighttime itching is often more severe. Sedation to produce deep sleep during the night can provide at least 8 hours of scratch-free time. This can be accomplished with oral diphenhydramine (Benadryl®) or hydroxyzine HCl (Atarax®), both at sedating doses of 25–100 mg. Some physicians prefer amitriptyline (Elavil®) at 10–100 mg because of the deeper and longer sleep induced.

Therapy should be continued until the patient looks and feels normal, although the potency of the corticosteroid can be decreased as the patient improves. Any remaining disease that is not treated will be scratched eventually, restarting the itch–scratch cycle. The patient should be warned that any future inflammation is also likely to induce itching and subsequent eczema.

■ IRRITANT CONTACT DERMATITIS

Inflammation produced by contact with irritating substances is a common problem. The patient usually describes irritation, soreness, stinging, or burning, although itching is present in some people. The most common irritants are soap and water, urine, feces, and infected or copious vaginal secretions. This mild chemical burn is manifested by erythema, sometimes with scale. More severe disease may exhibit edema, exudation, or even erosion (Fig. 64-3).

The treatment for irritant contact dermatitis consists primarily of the identification and the elimination of



FIGURE 64-3. This red, scaling and crusted plaque of irritant contact dermatitis was produced by washing the area several times a day with a disinfectant intended for cleaning floors.

irritants, which are sometimes surprisingly difficult. Patients must be asked specifically what they are using for any reason on their skin, including cleansing. Frequency is often important, because even clear water used multiple times daily serves as an irritant. In addition, a topical corticosteroid can hasten improvement.

■ ALLERGIC CONTACT DERMATITIS

An allergic contact dermatitis is a pruritic inflammatory eruption occurring in a previously sensitized patient in response to contact of the skin with a specific allergen. This condition usually occurs 1 or 2 days but sometimes up to 4 days following contact with the offending substance, unlike an irritant contact dermatitis, which occurs quickly.

An allergic contact dermatitis over the genitalia is usually indistinguishable morphologically from an irritant contact dermatitis and it often resembles eczema or neurodermatitis as well. This nonspecific picture is characterized by erythema, sometimes edema, and occasionally scale or desquamation (Fig. 64-4). With a very strong allergic response, vesicles can be present and erosions may be formed as vesicles break.

The most common causes of genital allergic contact dermatitis are ingredients in topical medications so that allergic contact dermatitis often complicates a preexisting process.¹ Topical antibiotics, anticandidal agents, local anesthetics, and even corticosteroids sometimes produce allergic contact dermatitis. Preservatives and stabilizers can also cause allergic reactions so that patch testing may be required to identify the specific allergen.

The treatment of allergic contact dermatitis includes the identification and elimination of the allergen. Topical corticosteroids, the elimination of irritants, and nighttime

sedation as described for eczema/neurodermatitis are also necessary for maximal and rapid improvement.

■ LICHEN PLANUS

Lichen planus is believed to be an autoimmune disease of cell-mediated immunity. Antigens recognized by Langerhans cells, epidermal antigen-presenting cells, may initiate the recruitment of activated lymphocytes, with epidermal damage likely produced by cytokines and cytotoxic T cells. This disease exhibits extremely variable morphology, which is partially dependent on location. Although lichen planus has been long recognized as a common condition on the penis, the frequency of erosive vulvovaginal disease has only been appreciated recently.^{2,3}

Patients with milder, papular disease generally report pruritus or no symptoms at all. Those with more severe, erosive disease generally describe pain, particularly with intercourse. These patients usually have associated mouth lesions.

On keratinized skin, such as the shaft of the penis, the circumcised glans, and the clinically hair-bearing portions of the genital area, lichen planus usually appears as well-demarcated, red or dusky, flat-topped papules (Fig. 64-5). Although lichen planus is a scaly disease, scale is often very subtle. Sometimes, the surface of the papules shows a lacy or fern-like pattern of fine, white striae, a pathognomonic sign when present.

When occurring on moist skin, such as the uncircumcised glans, or the clinically non-hair-bearing skin of the vulva, lichen planus is characterized by either white papules and plaques or erosions. Although the white lesions are occasionally well formed, sharply demarcated and uniformly hypopigmented papules or plaques, much more often these are irregular, reticulate striae (Fig. 64-6). Erosive lichen planus often appears as nonspecific, shallow erosions located

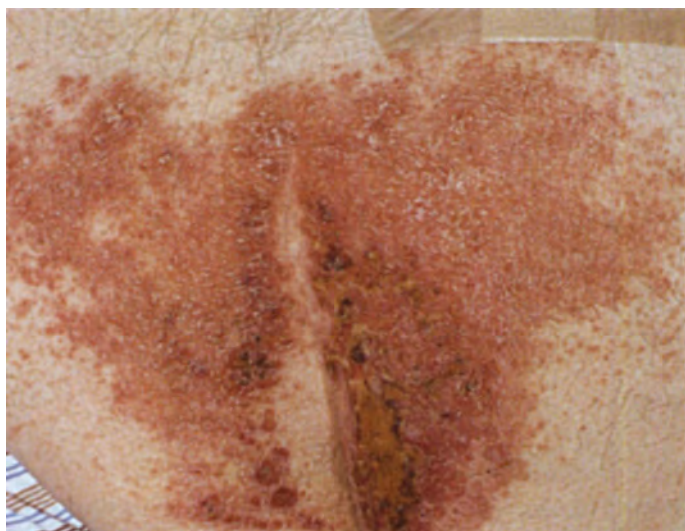


FIGURE 64-4. Erythema, exudation, and crusting are characteristics of allergic contact dermatitis in this patient who applied diphenhydramine (Benadryl) for itching. Positive results of patch testing, extreme pruritus, and time of onset are often more useful than morphology for differentiation from irritant contact dermatitis.



FIGURE 64-5. Two nondescript, red, scaling papules over the edge of the corona are characteristic of lichen planus but could also represent candida infection, psoriasis, or even scabies. An examination of other skin surfaces and the mouth may produce the diagnosis without a biopsy.



FIGURE 64-6. These white, branching striae are pathognomonic of lichen planus.



FIGURE 64-7. Endstage scarring with obliteration of the labia minora and clitoris, with remaining erosions of the vestibule (introitus) are characteristic of erosive lichen planus but can be seen also with late lichen sclerosis, cicatricial pemphigoid, pemphigus vulgaris, or any other intensely inflammatory, chronic vulvar disease. The diagnosis requires the identification of specific lesions elsewhere or a characteristic biopsy.

most often at the introitus and inner labia minora of women and on the glans penis of men (Fig. 64-7). Although a diagnosis based on the erosions alone is difficult, often specific white, lacy papules of lichen planus are found on examination, or less specific coexisting white epithelium is present. These white lesions usually yield a definitive diagnosis of lichen planus on biopsy.

The white lesions of lichen planus are occasionally confused with *Candida* infection, but negative fungal smears and lack of response to anticandidal therapy distinguish these two entities. Erosive disease differs from a syphilitic chancre by its indolent nature and the superficial morphology of the erosion of lichen planus as compared to the indurated ulcer of syphilis. Unlike most skin diseases that affect the genitalia,

lichen planus often affects other mucous membranes including the mouth and the vagina and may or may not cause symptoms. An examination of these areas can provide extremely valuable diagnostic information.

In the absence of erosions, genital lichen planus is usually treated satisfactorily with an ultra potent topical corticosteroid ointment (clobetasol propionate). Tacrolimus ointment (Protopic®) has also been shown to be effective in symptomatic patients without the risk of atrophy.⁴ However, local irritation is usually limiting. Lichen planus does not resolve with these therapies but symptoms abate and lesions improve. Most patients with lichen planus require chronic therapy, although some with milder, nonerosive disease do well with intermittent treatment. Very mild papular lichen planus may not produce future symptoms, and further therapy is not required. Resolution of nonerosive disease generally occurs over months or years. However, patients should be followed carefully until remission occurs, to evaluate the patient both for local corticosteroid side effects and for transformation of the disease into progressive, erosive, and scarring lichen planus.

The management of erosive lichen planus is extremely difficult and often unrewarding. Moderate erosive lichen planus can be treated with a topical ultra potent corticosteroid such as clobetasol propionate (with careful follow-up to monitor local side effects, including atrophy). More severe disease may require oral prednisone at 40–60 mg each morning to induce healing so that topical medication can then be substituted.

Erosive vulvar lichen planus is usually accompanied by vaginal disease. Scrupulous treatment of secondary vaginal, bacterial, and fungal infections in conjunction with hydrocortisone acetate 25 mg suppositories used at bedtime can improve many patients. Unless the patient is having regular intercourse, she should insert a small vaginal dilator daily to prevent the formation of vaginal synechiae.

Other medications that have been used for unresponsive lichen planus, although not supported by definitive clinical trials, include oral hydroxychloroquine, methotrexate, retinoids, mycophenolate mofetil (CellCept®), azathioprine, thalidomide, and cyclophosphamide, as well as topical and oral cyclosporine.^{5–7} In addition, etanercept (Enbrel®) has been used. Dapsone and griseofulvin have been used in the past with unimpressive results for vulvar lichen planus.

There is a risk of malignant transformation of lesions of lichen planus.⁸ One of the authors (Edwards) has cared for two patients with squamous cell carcinoma (SCC) associated with erosive lichen planus. Because of this risk, close, long-term follow-up of patients is recommended.^{9,10}

■ PLASMA CELL MUCOSITIS (ZONON'S)

Plasma cell balanitis and vulvitis are uncommon, medically insignificant inflammatory plaques that may represent a

variant of lichen planus. These lesions are located primarily over the glans penis or modified mucous membrane skin of the vulva. The plaques are red/rust, moist, well demarcated, and nonscaling. The diagnosis is made by clinical morphology and a biopsy that reveals a plasma cell infiltrate. Circumcision often improves or obliterates the lesion in men, and topical corticosteroids, retinoids, cyclosporine, and tacrolimus can be useful in others.^{11,12}

■ PSORIASIS

Psoriasis is a red, scaling skin disease that occurs as a result of hyperproliferation of the epidermis. This disease tends to occur preferentially in areas of irritation or skin injury, such as the elbows and knees. Warmth, perspiration, irritating urine, and friction often precipitate psoriasis in the genital area.

Psoriasis is manifested by red, sharply demarcated, scaling plaques that occur primarily over the hairbearing skin of the vulva and the glans and shaft of the penis, as well as the crural creases (Fig. 64-8). Because of the inherently moist nature of skin in the genital area, scale is often relatively inapparent as compared to the heavy, silvery scale of psoriasis in other locations. In addition, lesions are sometimes less well demarcated than in other areas.

Because the skin lesions of psoriasis in the genital area may not be classic for this disease, an examination of other areas of the body is warranted to make the diagnosis definitively. Most patients exhibit typical plaques on the elbows, knees, or scalp. Fingernails often show pitting or lifting of the nails from the nailbed, resembling a fungal infection.

Psoriasis is most often confused with eczema/lichen simplex chronicus, candidiasis, and tinea infection. Usually, the general body exam, and, when needed, microscopic smears to rule out fungus allow for the correct diagnosis.

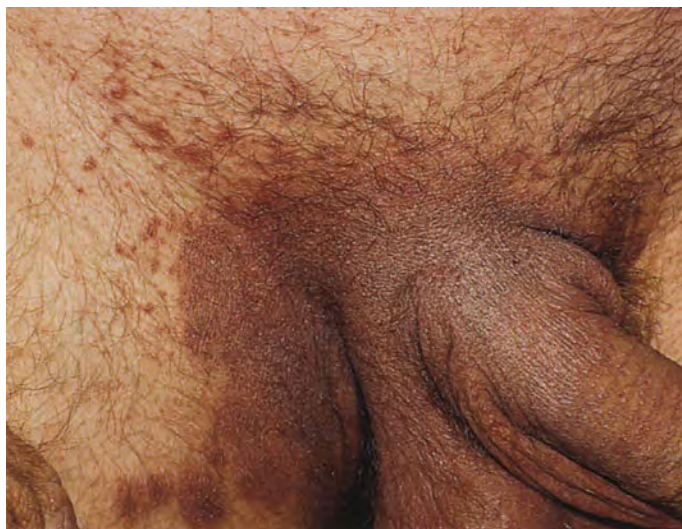


FIGURE 64-8. Psoriasis characterized by sharply demarcated, red, thickened plaques. Scale is present on the penis, although the classic heavy, silvery scale is often absent in the moist genital area.

The first-line treatment for genital psoriasis includes minimizing irritation and secondary infections and the application of topical corticosteroids. Low potency corticosteroids may not provide sufficient control. Patients with an inadequate response to hydrocortisone or triamcinolone can be treated with clobetasol propionate ointment, but careful follow-up to evaluate for atrophy is very important.

Because continuous use of topical corticosteroids can lead to tachyphylaxis, combination therapies are often used. Calcipotriene ointment (Dovonex®) is commonly used in rotation with topical corticosteroids. One method is to use clobetasol propionate ointment twice daily until clearance is achieved then maintain control with calcipotriene ointment twice daily on weekdays and clobetasol propionate ointment twice daily on weekends. More recently, tacrolimus ointment and pimecrolimus cream (Elidel®) have been reported to be effective for some patients with intertriginous psoriasis. Calcipotriene, tacrolimus, and pimecrolimus do not cause local atrophy but do have the common side effect of irritation.¹³⁻¹⁶

Patient education is crucial in treating psoriasis. Patients should be made aware that psoriasis is a chronic disease without a cure. Should psoriasis become widespread or severe, the more aggressive therapies, such as ultraviolet light, weekly methotrexate, oral retinoids, or newer biological medications instituted by a dermatologist usually improve the genital area as well.¹⁷

■ FUNGAL INFECTION

A classic and easily treatable cause of red plaques in the genital area is fungal disease.

Candida albicans, a yeast form, is the usual organism on the vulva or on the glans penis of uncircumcised men. *Dermatophyte fungi* (tinea cruris) produce the typical fungal infection over the proximal, medial thighs of men, and, less often, women.

Candida infection

Candida vulvitis can have several different morphologies (see also Chapter 45). Most often, there is simple, nonspecific erythema of the modified mucous membranes. Those with more severe or extensive disease, particularly obese women, may also have erythema and peeling of the hairbearing portion of their labia majora. Often, collarettes, a circular rim of scale, are found at the periphery of the involved skin. These represent very superficial pustules that have lost the blister roof. *Candida* vulvitis is regularly associated with *Candida* vaginitis unless the patient has treated her vagina without including the vulva. When occurring in men, *Candida* produces red papules or plaques over the glans of the uncircumcised penis or the crural crease. The shaft of the penis and the scrotum are generally spared since these areas are too dry to maintain a *Candida* infection.

The diagnosis of *Candida* is made on clinical grounds, generally with confirmation by a positive microscopic fungal preparation. In women, *Candida* can be confused (and sometimes coexist) with eczema, psoriasis, and lichen planus. *Candida* of the glans must be differentiated from psoriasis, lichen planus, and Bowen's disease. Therefore, any patient who does not respond to therapy should be referred to a dermatologist or undergo a skin biopsy.

Tinea cruris

Dermatophyte (tinea) fungal infections occur on drier, keratinized skin. Manifested by scaling, well-demarcated, red plaques located primarily over the inner thighs, tinea cruris is far more common in men (Fig. 64-9). The dermatophyte organism occasionally infects the stratum corneum of hair follicles, producing pustules or erythematous papules within the affected plaques. Unless the patient is immunosuppressed or using a topical corticosteroid on the area, a dermatophyte infection generally does not affect the scrotum or the penis.

Dermatophyte infections most closely resemble psoriasis, erythrasma, and eczema. *Tinea cruris* can be differentiated from these by a positive microscopic fungal preparation and the lack of psoriasis or eczema on other areas of the body.

The treatment of both *Candida* and dermatophyte infection can usually be achieved with topical antifungal agents. Azole creams such as miconazole, clotrimazole (both over the counter), ketoconazole, sulconazole, sertaconazole, and econazole treat both forms of fungus. However, nystatin is only effective against *Candida* and terbinafine (Lamisil®) is primarily used for dermatophyte infections. A very convenient therapy, a single dose of fluconazole 150 mg, clears most vulvovaginal *Candida* infections.



FIGURE 64-9. Red, scaling plaques with distinct margins and accentuation of disease at the borders are features of tinea cruris.

Oral therapy is required for patients with a dermatophyte infection and evidence of follicular involvement. Oral griseofulvin 500 mg twice a day until clearing occurs is usually sufficient for therapy but nausea, headache, and photodermatitis are common. Alternatively, but more expensive, are fluconazole 100 mg each day or 150 mg once weekly, or terbinafine 250 mg once daily until the skin clears.¹⁸ Recurrences of fungal infections are common, especially in a setting of fungal infection of toenails.

■ SQUAMOUS CELL CARCINOMA IN SITU

In squamous cell carcinoma in situ (SCCIS), the entire thickness of the epithelium is replaced by undifferentiated cells. Depending on the anatomic location of the lesion, the equivalent terminology of vulvar intraepithelial neoplasia III (VIN III), penile intraepithelial neoplasia III (PIN III), or anal intraepithelial neoplasia (AIN III) can be used. Because SCCIS presents clinically in several settings, with morphology characteristic of each setting, traditionally these entities were given different names (Bowen's disease, erythroplasia of Queyrat, bowenoid papulosis) despite each being SCCIS.

Bowen's disease

Classic Bowen's disease refers to SCCIS occurring in older patients, usually manifested by an erythematous or hyperpigmented, scaling, sharply demarcated plaque (Fig. 64-10). This can occur anywhere over the vulva, perineum, or inguinal crease. In men, an additional common site is the glans penis. This form of Bowen's disease sometimes resembles a fungal infection, lichen planus, psoriasis, or eczema.



FIGURE 64-10. This sharply marginated, red, scaling and hyperkeratotic plaque of Bowen's disease could easily be mistaken for psoriasis. However, the existence of a solitary plaque and a poor response to topical therapy should prompt a skin biopsy. Lesions may be more moist and less thickened, particularly on damp skin such as the modified mucous membranes and uncircumcised penis (erythroplasia of Queyrat).

Although most often an isolated finding, Bowen's disease is sometimes associated with urogenital malignancy.

Erythroplasia of Queyrat

Erythroplasia of Queyrat refers to SCCIS occurring over the glans of the penis. This disease presents as an inflammatory, moist plaque. Erythroplasia of Queyrat is believed to result from chronic irritation of smegma and retained secretions.

Bowenoid papulosis

When SCCIS occurs in younger patients, it is most often multifocal, occurring in the distribution and with general morphology similar to flat genital warts. Sometimes referred to as Bowenoid papulosis, these lesions are small, flat-topped, and either pink, pigmented, or sometimes skin-colored (Fig. 64-11). These lesions occur as a result of infection with specific types of human papillomaviruses (HPV). They are most easily confused with genital warts, pigmented nevi, or seborrheic keratoses. Although this form of SCCIS in immunocompetent patients is usually indolent, without progression into invasive and metastatic disease, associated lesions on the cervix and in the anus have a strong propensity for invasion and metastasis.

The diagnosis of SCCIS requires a high clinical suspicion and is confirmed by a skin biopsy. Management is by destruction or excision. However, any patient with areas of invasion should be managed by a gynecologic oncologist or a urologist.

■ EXTRAMAMMARY PAGET'S DISEASE

Extramammary Paget's disease is an epithelial malignancy suspected to be of apocrine gland origin that appears as red,



FIGURE 64-11. Bowenoid papulosis, a variant of squamous cell carcinoma in situ associated with human papillomavirus infection, resembles flat genital warts and may be pigmented, pink, or skin-colored.

scaling, or glistening plaques. Usually occurring in older patients, extramammary Paget's disease is most common over the perineum and hairbearing portion of the labia majora or scrotum. Morphologically, Paget's disease can be confused with SCCIS, eczema, tinea infection, or psoriasis. Diagnosis is by biopsy. Involved areas can be discontinuous, thus, many small sampling biopsies are often required to accurately map the extent of disease.

Extramammary Paget's disease in women has recently been divided into three types. Type 1 is primary cutaneous extramammary Paget's disease. This can be further subclassified as (1a) intraepithelial, (1b) intraepithelial with dermal invasion, and (1c) intraepithelial associated with an underlying cutaneous adenocarcinoma of the vulva. Type 2 extramammary Paget's disease is a manifestation of an often associated, adjacent primary anal, rectal, cervical, or other noncutaneous adenocarcinoma. Type 3 extramammary Paget's disease (pagetoid urothelial epidermal neoplasia or pseudoPaget's disease) is now considered a unique entity associated with neoplasms of the urinary tract.¹⁹

Because of the possibility of dermal invasion with metastases, underlying cutaneous adenocarcinoma or associated noncutaneous adenocarcinoma, management for all patients with extramammary Paget's disease includes an evaluation for associated malignancies, as well as local excision or Mohs micrographic surgery.²⁰ Recurrence is usual.

RED PAPULES AND NODULES

■ CHERRY ANGIOMAS AND ANGIOKERATOMAS

Cherry angiomas are small, bright red, sharply demarcated papules that are extremely common in older, white patients. Although most heavily distributed over the trunk, these can occur over the perineum as well. Angiokeratomas are similar in appearance but usually more purplish in color. Genetically predisposed patients may have uncountable numbers of these lesions over the labia majora or scrotum. Neither require therapy.

■ LICHEN PLANUS

Lichen planus, particularly over the penis, is often papular (see previous section and Fig. 64-6).

■ PYOGENIC GRANULOMAS

Pyogenic granulomas are inflammatory vascular tumors that may be spontaneous or may occur at a site of injury. Mucosal forms are most common in pregnant women. Pyogenic granulomas are pedunculated, erythematous, often glistening

tumors. Observation may be warranted in pregnancy as lesions may resolve spontaneously after delivery. Persistent or symptomatic lesions require surgical removal. Histologic confirmation is essential since amelanotic melanomas can occasionally mimic this benign tumor.

■ URETHRAL CARUNCLES

Urethral caruncles are red, polypoid, and benign growths at the urethral meatus in postmenopausal women. These are generally asymptomatic and require no therapy. However, larger lesions can be excised and submitted for biopsy to rule out malignant change.

■ URETHRAL PROLAPSE

Urethral prolapse occurs both in prepubertal children and in older women. This erythematous lesion is generally annular as the distal urethra is extruded circumferentially. When asymptomatic, this may require no therapy. Otherwise, surgical removal is sometimes required.

■ FOLLICULITIS/FURUNCULOSIS

Folliculitis is simply inflammation around a hair follicle. Furunculosis occurs when the inflammation increases to become a deeper, perifollicular abscess. These present as itchy or tender, erythematous papules and nodules on hair-bearing skin. The moist and occlude environment of the genital and inguinal areas is frequently affected. *Staphylococcus aureus* is a common inciting organism. Treatment includes washing with an antibacterial cleanser and using topical antibiotics (clindamycin or mupirocin). Recalcitrant cases may require oral antibiotics such as cephalexin or dicloxacillin, or as directed by culture. Warm compresses can provide relief in acute settings.

■ INFLAMED CYSTS

Cysts, including epidermal cysts, median raphe cysts, vestibular cysts, and Bartholin's duct cysts can sometimes become secondarily inflamed and appear red or cause tenderness. Although the inflammation is occasionally caused by infection (particularly with a Bartholin's abscess), most often the inflammation is due to friction or trauma.

Medical management can include a course of oral antibiotics for both the antibacterial and anti-inflammatory properties. Alternatively, or in conjunction, triamcinolone acetonide at a concentration of 5 mg per cc injected into the cyst can decrease inflammation easily and quickly. Surgical options include incision and drainage, and excision can be performed after inflammation has resolved. In Bartholin's duct cysts, a goal of management is to preserve gland function if possible. Insertion of a Word catheter or marsupialization, with a

course of antibiotics, is effective. Marsupialization should not be used to treat a Bartholin's gland abscess.

■ INFLAMED TUMORS

Normally skin-colored tumors can become secondarily inflamed. Basal cell carcinomas, squamous cell carcinomas, intradermal nevi, and genital warts are more common lesions that sometimes appear red either owing to local friction, trauma, or because of necrosis within a tumor that has outgrown its blood supply. The diagnosis of an inflamed tumor generally requires a biopsy.

■ HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa is a relatively common condition that represents cystic acne of the axillae and/or genital area. Unlike acne on the face, hidradenitis suppurativa does not generally remit after the teenage years.

This condition is manifested by comedones and nodules that represent apocrine pilosebaceous units with follicles distended by keratin and apocrine secretions. As these enlarge and rupture, nodules become very painful and red, occasionally draining to the surface with chronic sinus tract formation. The disease spans the spectrum from occasional, tender nodules to extensive, severe, deep scarring disease with frequent superinfection.

Most often confused with staphylococcal furuncles (boils), this diagnosis is made on the basis of its chronicity and location. First-line therapy consists of decreasing friction from obesity and tight clothing as well as regular use of an antimicrobial wash with or without topical clindamycin. Oral antibiotics administered chronically can be beneficial for mild to moderate disease, partially for their antibacterial effect in eradicating secondary infection, but primarily for their antiinflammatory effects. Tetracycline and erythromycin at 500 mg twice a day, doxycycline and minocycline at 100 mg twice a day, and clindamycin at 150 mg twice a day as used for acne are all somewhat effective. If organisms are being cultured, sensitivities can be used to guide antibiotic therapy. Unfortunately, more severe disease is rarely controlled with these regimens.

Several systemic treatments have shown some benefit including isotretinoin (Accutane®), finasteride (Propecia®) and antiandrogen therapy (ethinyl estradiol, cyproterone acetate, spironolactone). In case reports, infliximab (Remicade®) has been reported effective for hidradenitis suppurativa associated with inflammatory bowel disease.^{21,22} Although surgery is a treatment of choice for unresponsive axillary disease, the large area of apocrine glands over the genital area makes definitive surgery very difficult and sometimes mutilating. However, conservative excision of areas most troublesome is often very beneficial.

WHITE PATCHES AND PLAQUES

■ Lichen Sclerosus et Atrophicus

Lichen sclerosus (hypoplastic dystrophy) is a skin disease, probably of autoimmune origin, that preferentially affects the vulva and, less often, the penis and extragenital sites. The major symptoms are those of pruritus and eventual pain with more advanced disease. This disease occurs at all ages but is most often diagnosed in postmenopausal women.

Lichen sclerosus is most often characterized by well-demarcated, hypopigmented plaques of fragile skin. Usually, at least some areas of the skin show fine crinkling, and fragility is often manifested by purpura or erosions (Figs. 64-12 to 64-14). As lichen sclerosus progresses, scar-



FIGURE 64-12. The wrinkling of this white plaque covering the modified mucous membranes of the anterior vulva is an extremely useful finding that differentiates lichen sclerosus from vitiligo, the white lesions of lichen planus, and postinflammatory hypopigmentation.



FIGURE 64-13. Late lichen sclerosus displays the characteristic hypopigmentation and fine wrinkling in association with the loss of labia minora and clitoral hood to scarring.



FIGURE 64-14. Kraurosis vulvae consists of severe scarring of the vulvae and narrowing of the introitus due to lichen sclerosus. The erosions at the introitus were firm on palpation and proved to be squamous cell carcinoma.

ring occurs, resulting in resorption of the labia minora and scarring of the clitoral hood over the clitoris. Narrowing of the introitus occasionally occurs, resulting in the nonspecific, late appearance of kraurosis vulvae, characterized by resorption of normal vulvar architecture and constriction of the vaginal opening. Uncircumcised males generally experience phimosis as a presenting abnormality. Although lichen sclerosus was once believed to spontaneously resolve at puberty when occurring in children, chronic disease is recognized now as a common occurrence.

Complicating factors in patients, particularly women, include superimposed eczema from rubbing and scratching and secondary bacterial infection, particularly in prepubertal and postmenopausal women who normally have thin skin in this area. About 3–5% of women with uncontrolled lichen sclerosus eventually develop an associated squamous cell carcinoma. However, a recent study showed 9% of patients with symptomatic vulvar lichen sclerosus developing VIN III and 21% developing invasive squamous cell carcinoma.²³ Reports of penile squamous cell carcinoma arising in men with lichen sclerosus are rare. However, when cases of penile squamous cell carcinoma are retrospectively evaluated, just over half have either pathologic evidence or clinical history of lichen sclerosus.²⁴ Thus, the risk of squamous cell carcinoma needs to be communicated to both men and women at the time of diagnosis.

Lichen sclerosus is sometimes confused with vitiligo, but vitiligo consists of otherwise asymptomatic color change, with no texture change, scale, or scarring. Eczema can occasionally appear white owing to hydrated, thickened skin from scratching, and sometimes a biopsy is required for diagnosis. The clinician should also understand that endstage scarring can occur with several diseases, including mucous membrane pemphigoid and erosive lichen planus, so that late vulvar scarring cannot be ascribed automatically to lichen sclerosus.

The treatment for lichen sclerosus consists of twice daily topical application of an ultra-high potency corticosteroid ointment such as clobetasol propionate (Temovate®) until skin texture normalizes (2–4 months), with careful monthly examinations. Nighttime sedation and infection control are also important. Topical testosterone propionate is no longer considered a treatment option.²⁵

After lichen sclerosus has been controlled with a very potent corticosteroid, patients can be maintained with two or three times weekly applications. Patients should continue to receive twice yearly follow-up to monitor for continued disease control, local adverse reactions, and to evaluate for the development of squamous cell carcinoma.

■ POSTINFLAMMATORY HYPOPIGMENTATION

Some inflammatory diseases, particularly eczema, can produce secondary color change in the genital skin. Especially visible in normally dark-complexioned patients, light skin can result from damage to melanocytes both by inflammation and by the trauma of scratching (Fig. 64-2). Rarely, this white discoloration is sharply demarcated so that lichen sclerosus and vitiligo should be included in the differential diagnosis as well. The diagnosis is made by the setting and response to therapy, although sometimes a skin biopsy is necessary.

■ VITILIGO

The pathogenesis leading to an absence of epidermal melanocytes in patches of vitiligo is not known, but common theories include the autoimmune, antibody-mediated destruction, neurochemical eradication, and self-destruction by cytotoxic melanin precursors. The autoimmune hypothesis is most well supported by current data.²⁶ Occurring first around orifices and over extensor surfaces of joints, the genital area is sometimes affected early. Vitiligo is characterized by sharply demarcated patches of milk-white skin that have no evidence of texture change, inflammation, or scale.

At times, vitiligo can be difficult to distinguish from lichen sclerosus or postinflammatory hypopigmentation, particularly after the original inflammatory insult has resolved. The diagnosis can usually be made by an examination of other skin surfaces and by history. Therapy for vitiligo when occurring in the genital area is unnecessary although a mild topical corticosteroid occasionally induces some repigmentation.

■ ECZEMA/LICHEN SIMPLEX CHRONICUS

Thickened, lichenified eczema in moist areas often appears white owing to hydrated, hyperkeratotic skin (Fig. 64-3). Usually, the morphology is generally that of eczema (see the preceding discussion), which develops a whitish cast on thick, moist skin. Although the diagnosis can usually be made by the clinical appearance, a biopsy is occasionally required to differentiate between eczema superimposed on lichen scler-

osus and eczema that is white simply because of hydrated, hyperkeratotic skin.

■ LICHEN PLANUS

Papular lichen planus on moist skin often appears white. White striae, sometimes in association with dusky red papules or plaques are most common (Fig. 64-7). However, sometimes solid white epithelium occurs. (see discussion of lichen planus in the preceding section).

VESICULOBULLOUS/EROSIVE DISEASES

Ulcers are differentiated from erosions by their depth. Whereas erosions are simply lacking epithelium with most of the dermis intact, an ulcer extends well into, or, occasionally, even through the dermis.

Most blisters on thin, genital skin quickly lose their blister roof and appear as round erosions. This is especially true of the moist, modified mucous membrane skin of the vulva and the uncircumcised glans penis. The most common vesicular or erosive disease of the genitalia, herpes simplex virus infection, is discussed in Chapter 24.

■ EROSIIVE LICHEN PLANUS

A very common cause of nonspecific, chronic erosions, primarily over modified mucous membranes of the vulva and the vagina, is erosive lichen planus (see also discussion in the preceding section and Fig. 64-8). Most common, but not limited to middle-aged or older women, the primary symptom is one of irritation and dyspareunia, and sometimes itching. White epithelium or classic reticulate, white striae are occasionally present and provide clues to the diagnosis. More often, patients exhibit only introital erythema and erosions, frequently associated with a purulent vaginal discharge. These women usually have associated erosive, oral lichen planus that routinely affects the buccal mucosae and often involves the gingivae. Although erosive and scarring lichen planus occurs on the penis, especially the glans, this occurrence is much less common.

The diagnosis is made by the identification of classic associated lesions or by a biopsy of the edge of an erosion that includes some epithelial surface. Unfortunately, nondiagnostic biopsies are common.

The treatment of erosive genital lichen planus is discussed in the preceding section in this chapter.

■ MUCOUS MEMBRANE PEMPHIGOID (CICATRICIAL PEMPHIGOID)

Mucous membrane pemphigoid is an uncommon autoimmune blistering disease of older individuals that produces scarring, particularly of mucous membranes. This diagnosis

is relatively easy when nonmucous membrane surfaces are involved, because tense blisters are present and biopsies are generally diagnostic. However, the blistering nature is often not appreciated if only mucous membrane erosions are present. In addition, biopsies of these erosions are often non-diagnostic.

Mucous membrane pemphigoid of the genitalia is manifested by nonspecific erosions, skin fragility, and sometimes intact blisters over clinically hairbearing skin.²⁷ As time progresses, scarring ensues and the clinical picture can be nearly identical to the more common erosive lichen planus (Fig. 64-8). The labia minora are resorbed and the clitoris is buried under a scarred clitoral hood. Phimosis occurs in the uncircumcised male, and obvious scarring over the glans with loss of a sharp demarcation between the glans and shaft occurs in others. The severity of mucous membrane pemphigoid spans the spectrum from mild, chronic, nonspecific inflammation to rapidly progressive erosions, scarring, and blindness from eye involvement. The diagnosis of mucous membrane pemphigoid is made by the recognition and integration of multimucosal, scarring disease that includes the eyes, the mouth, and mucous membranes or modified mucous membranes of the genitalia. Disease is sometimes subtle so that a careful examination by an ophthalmologist may be required to identify conjunctival inflammation or scarring, and oral involvement may simply appear as mild gingivitis. The diagnosis can often be confirmed by routine biopsies from the edge of an erosion and an immunofluorescent biopsy from adjacent skin. If nonmucous membrane lesions are present, these usually are the easiest to biopsy and the most likely to yield a definitive diagnosis.

Initial therapy of mucous membrane pemphigoid is oral corticosteroids. Corticosteroid conspirator medications are often integrated for long-term suppression. There are small randomized controlled trials to support the use of dapsone in mild to moderate disease and cyclophosphamide in severe disease. Success has also been reported with sulfapyridine, minocycline, mycophenolate mofetil, and intravenous immunoglobulin.²⁸ Careful local care to control infections is crucial, and a vaginal dilator inserted once a day may help to prevent vaginal adhesions. Occasionally, a topical steroid adds some additional benefits to systemic therapy.

■ PEMPHIGUS VULGARIS

Pemphigus vulgaris is an autoimmune, superficially blistering disease that usually begins over mucous membranes, most often the posterior mouth. Most common in younger adults, this disease progresses to affect other mucous membranes, and, ultimately, nonmucous membrane skin. Because of the very superficial nature of the blister, tense bullae are rarely encountered, even over hair-bearing skin. Thinner, mucous membrane or modified mucous membrane skin dis-

plays erosions, and keratinized skin shows flaccid bullae and areas of denuded skin. Although pemphigus vulgaris does not usually scar when occurring on keratinized skin or in the mouth, long-standing pemphigus vulgaris can cause genital scarring, as described in the preceding section, for mucous membrane pemphigoid and lichen planus.

A routine skin biopsy from the edge of an erosion or the edge of a blister usually yields a diagnosis that can be confirmed with biopsy for direct immunofluorescence from adjacent skin.

Therapy consists of systemic corticosteroids. Immunosuppressant agents such as azathioprine and cyclophosphamide are often used as adjunctive, steroid-sparing medications. Again, local care and attention to infection as discussed for lichen planus can minimize scarring and maximize comfort for the patient.

There is an 80% mortality for pemphigus vulgaris when untreated. Although pemphigus vulgaris treated aggressively rarely causes death, the high doses of prednisone required for remission of the disease carry their own morbidity. After the disease is controlled, most patients can be maintained on medication that is slowly tapered to safer dosing schedules, and medication sometimes can be discontinued altogether.

■ IRRITANT/ALLERGIC CONTACT DERMATITIS

Contact dermatitis, either irritant or allergic, typically presents as inflamed, scaling plaques and was discussed in detail under red patches and plaques. However, with a very strong response, vesicles and erosions can occur.

■ FIXED DRUG ERUPTION

The fixed drug eruption is a peculiar and uncommon but characteristic disease that occurs in some patients in response to certain medications. Although the list of offending drugs is very long, the most common medications responsible include acetaminophen, barbiturates, nonsteroidal anti-inflammatory agents including salicylates, oral contraceptives, penicillins, tetracyclines, phenolphthalein, and sulfonamides.^{29,30}

One or a few blisters or erosions ranging from 1 to 3 cm appear within 1–2 days following ingestion of the offending medication. Subsequent exposure to the medication produces recurrence of lesions precisely at the same location and occasionally additional areas as well. Fixed drug eruptions of the genitalia preferentially affect the glans penis and non-hair-bearing skin of the vulva. On nonmucous membrane skin, lesions are very round edematous plaques or blisters, and, with recurrences, sharply demarcated, round patches of postinflammatory hyperpigmentation develop. On mucous membranes, lesions tend to be smaller and they may lack their characteristic round shape (Fig. 64-15). Because blisters



FIGURE 64-15. This nonspecific erosion due to a fixed drug eruption can be differentiated from ulcers caused by STD by its superficial nature and association with several other round, edematous plaques or blisters on keratinized skin, or oral lesions.

are so short-lived on mucosal surfaces, well-demarcated, red erosions are usual. Hyperpigmentation generally does not occur on these areas.

The diagnosis of a fixed drug eruption is made by the characteristic appearance of these lesions that occur recurrently in the same area in conjunction with a compatible history of medication use. The most common disease mistaken for a fixed drug eruption is a herpes simplex virus infection because of the recurrent nature of both diseases. However, herpes simplex virus infection normally shows small, coalescing erosions rather than fewer, large, discrete erosions. In addition, most patients with a fixed drug eruption have either oral or classic nonmucous membrane lesions as well as genital lesions.

The treatment for fixed drug eruption is avoidance of the medication.

■ ERYTHEMA MULTIFORME, STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS

Erythema multiforme is a hypersensitivity reaction that, when occurring as mucous membrane erosions, is produced by medication allergy or by hypersensitivity to recurrent herpes simplex virus infection. The classification scheme for these diseases is a subject of confusion and disagreement. For years, these three entities were considered to be a spectrum of the same disease, with erythema multiforme (EM) minor being the least inflammatory and rarely having mucous membrane involvement, and the more severe Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) having increasingly severe mucous membrane involvement. More recent distinctions have been made based on pathogenesis, causing further confusion, but ideally leading to a clearer classification scheme in time. Some now believe that all erythema multi-



FIGURE 64-16. Intense inflammation with resulting necrosis and loss of the epidermis, and exudation is characteristic of bullous erythema multiforme (Stevens-Johnson syndrome, toxic epidermal necrolysis).

forme minor is due to herpes simplex virus infection rather than triggered by other infections and medications as well. SJS and TEN are generally agreed to occur most often as a result of hypersensitivity to medication.³¹

Erythema multiforme is manifested by a range of severity and extent of skin lesions. Frequently, there are erythematous, usually target shaped red papules over the palms and soles. Sometimes, there are also erosions of the mucous membranes, particularly the oral mucosa. Treatment for erythema multiforme consists of addressing the trigger by treating or suppressing HSV infection using antiviral therapy. Prognosis is good, but recurrence is frequent.

SJS and TEN are hypersensitivity reactions as well but with different inciting factors and increased severity (Fig. 64-16). SJS and TEN are often caused by a drug but may be related to collagen vascular disease, HIV infection, or cancer.³¹ Although uncountable numbers of different medications have been reported in association with SJS and TEN, a more limited number have a clinically significant association. These include penicillins, cephalosporins, sulfas, phenytoin, carbamazepine, phenobarbital, hydrochlorothiazide, furosemide, procainamide, hydralazine, phenothiazines, allopurinol, nonsteroidal anti-inflammatory medications, and any related medications, particularly those containing a sulfa ring.

The lesions of SJS and TEN are much more extensive and can affect the modified mucous membranes of the vulva, vagina, and glans penis. Mucous membrane lesions can be severe and are associated with red, nonscaling papules with central blisters or large areas of coalescing bullae and erosions scattered over the entire skin surface. Morbidity is increased, and TEN has a mortality rate ranging from 30% to 50%. (Fig. 64-16).

Disease localized primarily to the genitalia and the mouth is most often confused with a herpes simplex virus infection

or fixed drug eruption. Very extensive disease is more suggestive of pemphigus vulgaris. The diagnosis is made by the setting, the abruptness of onset, and a confirmatory skin biopsy.

Treatment of SJS and TEN is controversial, but all agree that rapid diagnosis, discontinuation of any causative drug, and specialized, supportive care are most important. Immunosuppression by intravenous corticosteroids or cyclosporine or antiapoptotic measures in the form of intravenous immunoglobulin may minimize severity if instituted in the first 24–48 hours, but there are no randomized, prospective data.³² Continued use of intravenous corticosteroids, cyclosporine or immunoglobulin carries the risk of complications from systemic immunosuppression.³³

NONINFECTIOUS ULCERS

The primary consideration in a patient, who presents with a genital ulcer, is a possibility of a sexually transmitted disease, especially primary syphilis, chancroid, granuloma inguinale, or herpes simplex virus infection occurring in an immunosuppressed patient. Infectious ulcers are discussed in Chapter 63 and noninfectious causes of erosions are discussed in the immediately preceding section of this chapter. However, there are several noninfectious diseases that can produce genital ulcers.

■ APHTHOUS ULCERS

Aphthous ulcers (sometimes called canker sores) are mucous membrane ulcerations that are extremely common on the oral mucosa, but less common over the genitalia. Although patients with genital aphthae nearly always report oral disease as well, oral and genital lesions do not necessarily occur concurrently. Although oral aphthae are usually small, ranging from 1 to 2 mm, with an erythematous rim and a white fibrin base, genital aphthae are often larger and irregular. The base may be white, but deeper ulcerations may simply be red (Fig. 64-17). These are often quite painful and may heal with scarring. They are most common on the modified mucous membranes of the vulva and occasionally over the scrotum and penis.

When genital aphthae occurs in patients who have systemic signs of disease such as inflammatory eye disease, arthritis, meningoencephalitis, or pustular vasculitis, the diagnosis of Behçet's disease should be considered. Large aphthae alone do not constitute Behçet's syndrome. Patients with significant oral/genital aphthosis and gastrointestinal symptoms should be evaluated for inflammatory bowel disease, which can produce similar oral and genital ulcers.

Aphthae are diagnosed by appearance, the history of recurrent ulceration, and the exclusion of infectious and granulomatous causes, usually by skin biopsy.

Mild aphthae can be treated with a topical corticosteroid such as clobetasol propionate. For patients who have very



FIGURE 64-17. These aphthous ulcers show the characteristic larger size (as compared to oral lesions), peripheral red flare, and fibrin base. In the absence of a history of recurrence or oral aphthae, a biopsy may be required to rule out sexually transmitted causes.

occasional, painful disease, oral prednisone at 40–60 mg for 3–7 days usually induces prompt alleviation of pain and healing. The chronic administration of oral dapsone at 100–200 mg per day or colchicine beginning at 0.6 mg two or three times a day or are sometimes useful in suppressing frequent recurrences.

■ CROHN'S DISEASE

Crohn's disease, a granulomatous disease of the small bowel, sometimes produces perineal ulcers or fistulas. Less often, Crohn's disease can produce diffuse firm edema or linear ulceration and skin creases of the vulva.

Occasionally, this disease resembles hidradenitis suppurativa, which also produces sinus tracts, and in fact these diseases are sometimes seen together. The diagnosis of Crohn's disease is made by skin biopsy and the demonstration of intestinal disease. Therapy consists of oral corticosteroids, sulfones, mycophenolate mofetil, and biological response modifiers such as infliximab.

PIGMENTED LESIONS

■ PHYSIOLOGIC HYPERPIGMENTATION

Physiologic hyperpigmentation is noticeable primarily in patients who are naturally dark complexioned and as a response to some hormones, especially sex hormones. Women experience hyperpigmentation of the perianal skin and the edges of the labia minora. Less common in men, the hyperpigmentation primarily involves the scrotum and perianal skin. The diagnosis is by pattern and therapy is unnecessary.

■ BENIGN GENITAL LENTIGINOSIS (MELANOSIS)

Benign genital lentiginosis is an uncommon, idiopathic cutaneous abnormality consisting of irregular, variegate patches and macules of hyperpigmentation. Many clinicians believe that this often represents unusually striking postinflammatory hyperpigmentation, especially when associated with lichen sclerosus. This totally flat hyperpigmentation sometimes displays frightening irregularity of browns, tans, and black that mimic cutaneous melanoma. Most common over the glans and shaft of the penis and the modified mucous membranes of the vulva, a biopsy is required to differentiate this condition from malignant melanoma. Although this condition is felt to be benign despite its worrisome appearance, there is one report of melanoma of the bladder in a patient with genital lentiginosis so that at least occasional follow-up is recommended by some.

■ HYPERPIGMENTATION OF LICHEN SCLEROSUS

Patients with lichen sclerosus, particularly those with longstanding, treated lichen sclerosus, occasionally exhibit flat, irregular hyperpigmentation that requires biopsy to differentiate from melanoma and squamous cell carcinoma in situ. There have been recent reports of melanoma occurring in association with lichen sclerosus that may be more than coincidence.

Pigmented nevi

Pigmented nevi (moles) do not have a predisposition for the genital area but they are found often in that area by virtue of their ubiquitous occurrence. In addition, nevi that occur on the vulva, particularly during pregnancy, sometimes have an atypical appearance on biopsy, although this does not necessarily portend malignant transformation. A benign nevus is a macule or papule that is smaller than 7 mm in diameter, with regular, sharply demarcated borders, and homogeneous, brown pigmentation. Although many nevi exhibit some irregularity of shape or color, several atypical features or one extraordinarily abnormal finding should prompt the physician to refer the patient to a dermatologist or to biopsy the lesion. Otherwise, therapy is unnecessary although nevi can be excised if desired.

■ MALIGNANT MELANOMA

Cutaneous melanoma is a malignant tumor of melanocytes. Arising in a preexisting nevus or de novo, these lesions are not especially common in the genital area. However, melanomas located in this area are often diagnosed late with a grave prognosis. Melanoma can occur anywhere over the genital area, including the modified mucous membranes and even within the vagina.

Melanomas are usually greater than 7 mm in diameter with irregular and often poorly demarcated borders. The color is usually irregular and variegate. Most melanomas do not exhibit all of these clinical characteristics but generally several are present.

Diseases in the differential diagnosis of melanoma include pigmented nevi, pigmented genital warts, pigmented squamous cell carcinoma in situ, benign genital lentiginosis, and hyperpigmentation associated with lichen sclerosus. The diagnosis is confirmed by biopsy, and therapy consists of local excision with margins determined by the thickness of the tumor. Thin melanomas (those <0.86 mm thick) have a very good prognosis with most patients experiencing long-term, disease-free survival. However, as the lesions thicken, the risk of metastasis increases remarkably, and metastatic melanoma is an extraordinarily aggressive disease.

■ SQUAMOUS CELL CARCINOMA IN SITU

VIN III/PIN III can present as a hyperpigmented morphologic variants. These diseases are discussed in the preceding section covering red patches and plaques.

■ SEBORRHEIC KERATOSES

Seborrheic keratoses are benign tumors that do not exhibit a propensity for the genitalia but they are so common and sometimes so numerous that they may occur over this skin surface. Seborrheic keratoses are brown to skin-colored, keratotic, sharply demarcated, flat-topped papules. The firm, keratotic nature is sometimes not appreciated on the genitalia where the skin is damp. Seborrheic keratoses are most often confused with genital warts or nevi. At times, these require biopsy to differentiate from pigmented, intraepithelial neoplasms. Seborrheic keratoses have no malignant predisposition, and therapy is unnecessary. The lesions can be removed by liquid nitrogen therapy or light curettage.

SKIN-COLORED PAPULES

Genital warts, the most common skin-colored papules found in the genital area, are usually sexually transmitted and are discussed in Chapter 28. Most other skin-colored papules are medically trivial but nonetheless important to the patient.

■ PEARLY PENILE PAPULES

Pearly penile papules are common, skin-colored, monomorphous, dome-shaped papules or papillae arranged in rows around the edge of the corona (Fig. 64-18). These are most common in uncircumcised men. They are sometimes confused with genital warts, but the monomorphous nature and the arrangement in rows differentiate these from genital



FIGURE 64-18. Pearly penile papules are differentiated from genital warts by their regular, monomorphic appearance in rows around the edge of the corona and the dome-shaped rather than keratotic, acuminate tips to the papules.

warts, and virologic studies have shown no evidence of HPV.³⁴ These are asymptomatic and require no therapy.

■ VESTIBULAR (VULVAR) PAPILLOMATOSIS

Vestibular papillae are similar normal variants that occur over the modified mucous membrane of the introitus and medial labia minora. These tubular papillae are found in patches or lines that are bilaterally symmetrical. Like pearly penile papules, they are often mistaken for genital warts. However, these are very soft and monomorphic, and the papillae are discrete to the base, unlike genital warts that tend to be fused at the base.³⁵ In addition, the tips of the papillae are rounded rather than acuminate and keratotic. Although vestibular papillae often come to the patient's or physician's attention when vulvar itching or pain occur, these papillae are incidental findings present in about half of premenopausal women. They are asymptomatic and require no therapy.

■ FORDYCE SPOTS

Fordyce spots are enlarged sebaceous glands that occur primarily over the labia minora. Although usually subtle, at times these can be enlarged and may resemble small epidermal cysts or genital warts. However, Fordyce spots are usually monomorphic and slightly yellowish in color (Fig. 64-19). Enlarged pilosebaceous units are sometimes present on the shaft of the penis also. These are small, scattered, skin-colored papules 1–2 mm in size. These are most often noticed when a patient has genital warts and the physician has difficulty discerning whether these pilosebaceous units are normal irregularities in the skin or extremely small warts. They are asymptomatic and require no therapy.



FIGURE 64-19. Fordyce spots represent enlarged sebaceous glands located primarily over the inner aspect of the labia minora although they can be seen elsewhere, including the penis. Individual papules are lobular and white, yellowish, or skin colored.

■ CYSTS

Epidermal cysts

Cysts are common, benign tumors. Epidermal cysts (sometimes mistakenly called sebaceous cysts) are the most common. Although usually single or few in number, some patients exhibit large numbers of these firm, skin-colored to white, dermal nodules, particularly over the scrotum or the labia majora. These cysts generally represent hair follicles that have become plugged with keratin so that the proximal portion of the follicle has become distended with keratin and sebaceous material. Because pilosebaceous units are even found over the labia minora, epidermal cysts sometimes occur in this area. Epidermal cysts are usually asymptomatic and require no therapy. Surgical excision can be performed for those patients who wish removal.

Vestibular cysts

Vestibular cysts are skin-colored, slightly bluish, or slightly yellowish cysts found over the non-hair-bearing portion of the vulva. These are usually asymptomatic and unnoticed by the patient. They are dome-shaped without surface change.

Median raphe cysts

Median raphe cysts are innocuous, skin-colored, dome-shaped papules over the midline underside of the shaft of the penis.

Pilonodal cysts

Pilonidal cysts are small, dome-shaped papules most often located over the sacrum, coccyx, and near the clitoris. These can become inflamed and occasionally drain and develop a

sinus tract. Pilonidal cysts can be symptomatic and painful with chronic drainage. These may require excision.

■ SCLEROSING LYMPHANGITIS

Sclerosing lymphangitis consists of a firm, skin-colored cord located just proximal and parallel to the corona of the penis, sometimes encircling the shaft entirely. This asymptomatic, medically trivial, and self-resolving abnormality is believed to occur from trauma and friction.

■ PRURITUS

Genital pruritus is a common symptom. In predisposed, atopic patients, any inflammation or irritant can produce itching. Often, the physical examination shows a specific abnormality. However, genital skin is often normally pink, and scale can be masked by moisture so that sometimes the genitalia can appear amazingly normal in the face of significant inflammation. Any patient with pruritus should be examined specifically for the following causes of pruritus.

■ INFECTION

The most common cause of acute pruritus is an infection, particularly in women. The vagina should be carefully evaluated, especially for yeast infection. However, trichomoniasis and bacterial infection occasionally produce pruritus. Pinworms, found primarily in children, can cause itching.

■ ECZEMA/LICHEN SIMPLEX CHRONICUS

The most common cause of chronic itching is eczema. Erythema and lichenification can be extremely subtle so that in the absence of other abnormalities, the patient should be treated for eczema (see the preceding section).

■ OTHER SKIN DISEASE

Pruritus can occur with other skin diseases as well, especially lichen sclerosus, lichen planus, irritant contact dermatitis, and psoriasis.

■ NEUROPATHIC PRURITUS

Very occasionally, itching can occur in the absence of skin findings as a result of neuritis or neuralgia. This is a diagnosis of exclusion and is confirmed by successful treatment with medication for neuropathy, such as a tricyclic medication or gabapentin.

■ DEPRESSION AND ANXIETY

Finally, depression and anxiety occasionally cause and very often exacerbate itching. Psychological factors should be

recognized and addressed. Nighttime use of amitriptyline or doxepin sedates the patient, preventing awakening owing to pruritus, and provides antidepressant and anxiolytic effects.

GENITAL PAIN

■ VULVODYNIA/PENODYNIA AND SCROTODYNIA

Chronic genital pain can be caused by infections and skin disease but it can also be experienced with no clinical or laboratory abnormalities. Vulvodynia, scrotodynia, penodynia, and anodynia are defined as chronic burning, stinging, soreness, aching, or stabbing (not itching) in the absence of an objective etiology. Before diagnosing a chronic pain syndrome, infection, inflammatory skin disease, tumor, and neurologic disorders should be ruled out. Because of the rarity of scrotodynia, this entity is poorly understood and there is little published information regarding causes and therapy. Some experienced clinicians feel that scrotodynia is usually a manifestation of psychosexual dysfunction, whereas others believe that male genital pain syndromes are analogous to vulvodynia.

Although the vast majority of women with vulvar pain are extremely depressed and experience major disruption in their sexual functioning, vulvodynia is generally not believed to result primarily from psychosexual pathology. There are several known specific physical causes for vulvar burning, and directive therapy often produces major improvement in symptoms. Vulvodynia is often multifactorial.

Vaginal infections of any kind can sometimes produce secondary vulvar burning. Although *Candida albicans* usually produces itching, non-*albicans* *Candida* infections are more likely to produce burning and often they are treated inadequately with the usualazole therapies. Vulvar burning can also result from bacterial vaginitis, not to be confused with bacterial vaginosis. Vaginal secretions of bacterial vaginitis are purulent rather than noninflammatory with clue cells, as occurs with bacterial vaginosis.

Rarely, subtle skin disease produces vulvar irritation, soreness, and burning. Although eczema can be painful, this pain only occurs as a result of erosions from scratching, and the patient's primary complaint is one of pruritus. Very subtle lichen sclerosus sometimes produces pain, and erosive lichen planus is very often associated with pain. Occasionally, lichen planus can affect only the vagina, with irritating and superinfected vaginal secretions irritating the vulva secondarily. Desquamative inflammatory vaginitis, a noninfectious inflammatory vaginal dermatosis, can also produce irritating, purulent vaginal secretions that cause vulvar burning.

Skin malignancies, postherpetic neuralgia, spinal compression syndromes, or dental nerve entrapment can also cause genital pain.

When the above processes have been ruled out, vulvodynia, scrotodynia, penodynia, or anodynia can be diagnosed. Most believe these represent neuropathic pain syndromes and pelvic floor abnormalities.

In 2003, the International Society for the Study of Vulvovaginal Disease established recommended terminology and a classification scheme for vulvar pain.³⁶ Vulvodynia is defined as vulvar discomfort in the absence of an objective etiology. Vulvodynia is further classified by the location (generalized or migratory versus localized) and the nature of discomfort (spontaneous, provoked by touch, or mixed). There are two primary patterns of vulvodynia; generalized pain that is present with and without touch, and vestibulodynia (vulvar vestibulitis syndrome) that is localized to the vestibule and primarily provoked by touch. These patterns probably exist on a spectrum. Multiple therapies are used, either individually or in combination for the treatment of vulvodynia. These include sensitive skin care, topical therapies, oral medications, pelvic floor rehabilitation, local injections, and surgery.³⁷

Sensitive skin care simply emphasizes avoidance of irritants by cleansing the genital area with plain water and using mild soaps and shampoos on the rest of the body. Also, avoidance of unnecessary fragrances, medications, panty liners, and moisturizers can be important.

Topical therapies include plain petrolatum to improve barrier function and lidocaine ointment 5% or jelly 2% for symptom relief. Estrogen topically applied provides variable results.

Oral therapies include medications aimed at modulating both localized and generalized neuropathic pain. Amitriptyline, nortriptyline, desipramine, venlafaxine, and duloxetine at standard antidepressant doses have all been used effectively. Gabapentin (up to 3600 mg per day) is often useful, and pregabalin 150 mg each day is likely to prove beneficial in the future. For most of these medications, tapering from low to higher doses generally minimizes adverse reactions.

Pelvic floor rehabilitation is another therapy used for both localized and generalized vulvodynia. Physical therapy and exercises guided by surface electromyographic abnormalities can provide complementary benefits. This includes myofascial release, retraining of bowel, bladder, and pelvic floor muscles, ultrasound, electrical stimulation, and use of home vaginal dilators.

An occasional patient with very localized vulvodynia benefits from a local injection of corticosteroids, and there are reports of local interferon alpha being useful. Patients with vestibulodynia who are recalcitrant to the above measures usually respond well to a vestibulectomy, local excision of the painful area with advancement of the vaginal mucosa.

Scrotodynia and penodynia are much less common in vulvodynia and less well understood. There is little published information on these conditions. However, in one author's

experience (Edwards), tricyclic antidepressants, and gabapentin have proved useful.

Patients with chronic pain, particularly chronic genital pain, are uniformly depressed. Counseling and attention to depression and anxiety are extremely important and overall management, not to treat pain, but to help patients cope with both the pain and the psychosexual repercussions.

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Ocular Infections Associated with Sexually Transmitted Diseases and HIV/AIDS

William Lynn and Susan Lightman

INTRODUCTION

Sexually transmitted infections can present in a variety of ways, and many have the potential for ocular complications. All structures of the eye may be involved with severity ranging from minor irritation to rapidly progressive sight-threatening disease. Although many may have a minor problem and are not at risk of visual loss, patients who complain of visual disturbance or a red or painful eye are likely to have more serious disease, where delay in diagnosis and treatment could lead to serious visual loss. Such patients require prompt evaluation, including measurement of visual acuity and ocular examination. If there is any suggestion of intraocular inflammation, loss of visual acuity, or retinal involvement, then urgent specialist ophthalmological assessment is warranted. Ocular symptoms may be the presenting feature of an unsuspected sexually transmitted infection. In such cases, the patient is unlikely to be attending a genitourinary specialist, and it is essential that ophthalmologists and clinicians working in other fields, including primary care, are aware of the possibility of underlying sexually transmitted infection, when evaluating patients with eye signs.

Sexually transmitted pathogens may access the eye through a number of routes. Inoculation into the conjunctiva may occur directly through oculogenital contact or indirectly through autoinoculation with fingers, etc. Neonatal infection may be acquired transplacentally or during passage through the birth canal. Some pathogens, for example syphilis, may reach the retina by hematogenous dissemination. Underlying human immunodeficiency virus (HIV) infection may alter the presentation, including ocular manifestations, of some classical sexually transmitted infections. HIV may directly affect the eye, and if the patient is significantly immunocompromised, then the eye is vulnerable to other opportunistic infections.

Ocular inflammation may lead to permanent visual loss. It is, therefore, essential that clinicians treating patients with sexually transmitted infections and/or HIV/AIDS are aware of potential ocular manifestations and the appropriate clinical management.

GONORRHEA

Gonorrhea remains a serious threat to global public health and is one of the most commonly reported sexually transmitted infections in the United States, with 335,104 cases reported in 2003.¹ In the eye, the hallmark of gonococcal infection is a severe purulent conjunctivitis, but, as it is still relatively uncommon, diagnosis may be delayed. If not recognized and treated appropriately, permanent visual loss due to corneal scarring or perforation may occur.² *Neisseria gonorrhoeae* may be inoculated into the eye by direct oculogenital contact. More frequently this follows accidental self-inoculation, which occurs in approximately 1–2% of individuals with genital tract infection. Eye infection may be acquired in neonates from direct inoculation in the birth canal of an infected woman (see “Ophthalmia Neonatorum” section).³ Hematogenous dissemination of *N. gonorrhoeae* has not been reported to cause ocular disease, but, because disseminated infection can be fatal, hospitalization and treatment with intravenous antibiotics such as ceftriaxone sodium or cefotaxime sodium are required.⁴

Occasional, nonsexually transmitted cases of gonococcal conjunctivitis occur, and the diagnosis should be considered in a patient with purulent conjunctivitis, even in the absence of a possible sexual exposure. Cluster outbreaks of nonsexually transmitted gonococcal conjunctivitis have been reported. A survey of conjunctival isolates from six cases in Cuba were serogroup WI, penicillin producing, and showed the same antimicrobial susceptibility pattern and plasmid profile (2.6-3. 2-24.5).⁵ Four hundred and forty-seven cases of gonococcal conjunctivitis in Aboriginal communities, predominantly in Central and Western Australia, were identified, with chronic oropharyngeal carriage and spread of *N. gonorrhoeae* implicated.⁶ In another study in this group, 432 cases were identified—the highest attack rate being in the 0–4-year age group (86 per 1000), and the risk of conjunctivitis decreased with age. Isolates were predominantly IA serovars, but the trigger for nonsexually transmitted gonococcal conjunctivitis epidemics remains obscure.⁷



FIGURE 65-1. Gonococcal conjunctivitis with profuse purulent exudate.

Gonococcal conjunctivitis is characterized by a rapid onset of a red sore eye with an extremely profuse purulent discharge. In most cases of eye involvement, infection is limited to a unilateral or bilateral purulent conjunctivitis (Fig. 65-1). Cases of corneal involvement (keratitis) with thinning of the cornea⁸ or corneal necrosis requiring corneal grafting⁹ have been reported. Preseptal cellulitis (Fig. 65-2) causing swollen eyelids has also been reported.¹⁰ The incubation period of ocular infection is 3–19 days, and the urethral symptoms can precede the ocular symptoms by 1–3 weeks.¹¹ The diagnosis is made in someone with a relevant history and the characteristics of the ocular discharge and by taking samples of exudates and preferably conjunctival scrapings for Gram stain and laboratory culture.²

The outcome of gonococcal conjunctivitis is related to the severity of the disease at the start of adequate therapy.¹² To prevent serious ocular complications, the Centers for Disease Control and Prevention (CDC) recommend that all patients with gonococcal conjunctivitis are treated with parenterally administered antibiotics, for example ceftriaxone 1 g IM as a single dose.¹³ Initial therapy should be based on local resistance patterns, and it is essential to obtain material for culture and antibiotic sensitivity testing. Treatment with spectinomycin (2 g IM for 3 days) or norfloxacin 1200 mg orally for 3 consecutive days has been reported to be effective. However, recent reports of increasing resistance suggest that quinolones should not be used empirically to treat gonococcal infection.^{11,14,15} Topical antibiotics and saline lavage have been recommended as ancillary treatment but are not essential in treating adults or children with gonococcal conjunctivitis.¹⁶ There is some evidence that doxycycline may help to attenuate the destructive activity of collagenases released during corneal infection,¹⁷ but this is currently not recommended within clinical treatment guidelines.¹³



FIGURE 65-2. Preseptal cellulitis.

■ OPHTHALMIA NEONATORUM

Ophthalmia neonatorum is defined as conjunctivitis occurring in the first month of life. Many organisms can cause this including *N. gonorrhoeae*, *herpes simplex*, and *Chlamydia trachomatis* that may be acquired during passage through an infected birth canal.¹⁸ Neonatal infection with *C. pneumoniae* and *N. meningitidis* have also been reported.^{18,19} In the United States, *C. trachomatis* is the most common cause of neonatal conjunctivitis, although less common *N. gonorrhoeae* is the most significant pathogen, as it has the potential to cause severe ocular damage if not recognized and managed appropriately.¹³ Microbiological analysis is vital to confirm the infecting organism, particularly as neonatal infection with multidrug-resistant *N. gonorrhoeae* has been reported.²⁰ However, treatment must be started immediately and should not be delayed whilst awaiting cultures.

The risk of gonococcal ophthalmia in infants born to infected mothers may be up to 30%, and gonococcal ophthalmia, if untreated, may progress rapidly to corneal ulceration, perforation, and eventually blindness. Topical therapy alone is insufficient and systemic treatment should always be administered. U.S. guidelines recommend a single dose of 25–50 mg/kg (up to a maximum of 125 mg) of ceftriaxone for gonococcal ophthalmia.¹³ In a prospective study for treatment, 21 baby-mother pairs with culture-proven *N. gonorrhoeae* were treated with a single dose of ceftriaxone (62.5 mg for babies and 125 mg for mothers). *N. gonorrhoeae* was eradicated from all babies' eyes with no residual damage, as well as from the mothers' cervix.²¹

Recognition and treatment of gonorrhoeal infection during pregnancy may avoid infection of the baby during delivery, and various antibiotic regimes have been proposed. In a Cochrane review of two randomized trials involving 346 women, similar efficacy was found between amoxicillin plus probenecid compared with spectinomycin, amoxicillin plus probenecid compared with ceftriaxone, and ceftriaxone compared with cefixime, in achieving microbiological cure.²²

Ophthalmia neonatorum can be prevented by antenatal screening and treatment for gonococcal infection, as described

above. However, screening is not routine in many antenatal settings, and screening will not prevent neonatal infection due to other organisms. Therefore, in areas of high-prevalence consideration should be given to disinfection of the infant's conjunctivae at birth by (1) use of 1% aqueous silver nitrate solution into each conjunctival sac or (2) instillation of benzyl penicillin solution into the infant's eyes or (3) use of tetracycline 1% or erythromycin 0.5% eye ointment. The safety and efficacy of povidone-iodine ophthalmic solution to prevent ophthalmia neonatorum have been evaluated in 3117 infants in Kenya. The infants received one of the ophthalmic preparations: a drop of 1% silver nitrate ophthalmic solution or a 1-cm strip of 0.5% erythromycin ophthalmic ointment, or a drop of 2.5% povidone-iodine solution. Povidone-iodine was significantly more effective than silver nitrate and erythromycin in preventing infection,²³ and further studies have also shown this. No increased advantage was found by giving a second dose in the first postnatal day.²⁴

CHLAMYDIA TRACHOMATIS INFECTION

Chlamydia trachomatis is one of the most common sexually transmitted diseases in the world and the most frequently reported sexually transmitted infection in the United States.¹ Up to 75% of women and 50% of men infected with *Chlamydia* are asymptomatic, so many are unaware that they have the disease. The commonest eye problem associated with chlamydial infection is inclusion conjunctivitis.²⁵ This can affect adults following contact with infected genital secretions or neonates who become infected during passage through an infected birth canal. Nonsexually transmitted *C. trachomatis* infection of ocular secretions is the leading cause of preventable blindness worldwide—trachoma. Eye-seeking flies carry the chlamydial infection from person to person, and it is also spread by hands, towels, and bedding.

C. trachomatis isolates can be differentiated into serovars, based on antigenic variation of their major outer membrane proteins.²⁶ Serovars A–C are etiologic agents of trachoma,^{27,28} and serovars D–K cause the sexually transmitted genital infection. Serovars L1–3 cause lymphogranuloma venereum (LGV). Serovars A–K produce infections restricted to the mucosae, whereas the LGV serovars infect monocytes and disseminate to local draining lymph nodes.²⁸ A small number of genetic differences are responsible for the different behavior of the serovars.²⁹

■ ADULT INCLUSION CONJUNCTIVITIS

This is caused by the serovars D–K, and transmission is by genito-ocular contact or autoinoculation. In contrast to all the other serovars that show tissue specificity, serovars B and Ba have been isolated from the eye and genital tract and have been found in trachoma and sexually transmitted infection-associated



FIGURE 65-3. Inclusion conjunctivitis due to *C. trachomatis* in, **A**, an adult and, **B**, a neonate.

ocular disease. Inclusion conjunctivitis caused by the oculo-genital serovars results in chronic conjunctival inflammation of mild-to-moderate severity, usually without the cornea being involved. Fifty percent to 90% of adults with ocular infection also have concurrent detectable genital tract infection.³⁰ Symptoms of conjunctival infection are noticed usually by 2 weeks after infection. These are nonspecific and include a unilateral red eye with a gritty foreign body sensation, which later develops a mucopurulent discharge. Both eyes may become involved, if left untreated.²⁵ The diagnosis is made on clinical signs of a follicular-type conjunctivitis (particularly in the inferior tarsal conjunctiva) (Fig. 65-3). Occasionally, an enlarged preauricular lymph node may be present. The clinical diagnosis may be confirmed by staining conjunctival smears with a direct immunofluorescent antichlamydia monoclonal antibody. The pathogen can also be cultured, identified by Giemsa staining, or detected by nucleic acid amplification techniques.²⁵ The disease is usually self-limiting, even if left untreated, but may persist for months or

years in the absence of antibiotic therapy.²⁵ Treatment is aimed at eradicating the infection from the eye and the genital tract, and topical and systemic antibiotics are required. Systemic therapy is required according to local guidelines, for example azithromycin 1 g as a single dose or doxycycline 100 mg BID for 7 days.¹³ Erythromycin is a suitable alternative agent for pregnant women or children.¹³ In addition to systemic therapy, erythromycin or tetracycline ointment may be added.²⁵ All sexual partners should be treated to prevent reinfection.

■ NEONATAL INCLUSION CONJUNCTIVITIS

Neonates develop conjunctivitis usually within 2 weeks of exposure.³¹ Current U.S. guidelines recommend considering birth-related chlamydia in the differential diagnosis of all infants presenting with conjunctivitis within 30 days of birth.¹³ Signs include discharge, conjunctival injection, and lid swelling. The eye appearance differs to that in adults, with diffuse papillary conjunctivitis being seen in contrast to the follicles seen in the adult (Fig. 65-3). This is because neonates do not have lymphoid cells in their conjunctiva at birth but acquire them later. One or both eyes can be affected, and, as in adults, the cornea is largely uninvolved. Untreated infection can persist for months and cause chronic or recurrent disease.³² The infection needs to be rapidly distinguished from other causes of neonatal conjunctivitis such as gonococcal or herpetic infection, which require very different treatment strategies. If identified (using techniques as for adult ocular infection, see above) the organism should be treated locally and systemically, as the neonate may also have been infected in the respiratory or gastrointestinal tract. Treatment is with erythromycin antibiotic ointment for 1 week, in addition to erythromycin elixir for 2 weeks, or alternatively azithromycin is effective.^{13,33}

■ REITER'S SYNDROME

Reiter's syndrome is classically defined as a triad of arthritis, urethritis, and conjunctivitis.^{34,35} Although this triad can also follow gastrointestinal infection, many cases are triggered by infection with *C. trachomatis*.³⁶ Reiter's syndrome occurs in 1–3% of men following genital *C. trachomatis* infection,³⁷ and approximately 75–90% are positive for HLA B27.^{36,38,39}

Reiter's syndrome is a clinical diagnosis, and the systemic manifestations usually appear within 1 month of infection. Although the original description was of conjunctivitis, these patients can actually have a variety of ocular problems. Conjunctivitis is the most common and is seen in around 60–90%.⁴⁰ It usually occurs within a few weeks of the onset of the arthritis and urethritis.⁴¹ It is usually mild, symmetric, and bilateral with a mucopurulent discharge.³⁷ Cultures are



FIGURE 65-4. Anterior uveitis in Reiter's disease showing a diffusely red eye.

negative, and it typically resolves within 10 days without treatment.

Up to 37% of patients with Reiter's syndrome develop anterior uveitis, even if they have had conjunctivitis previously.³⁷ Uveitis is usually of acute onset, with redness (especially around the limbus) (Fig. 65-4), pain, and photophobia; 68% of cases are unilateral with bilateral involvement in 32%.⁴² Uveitis is more likely in those who are HLA B27+ and who have sacroiliitis.^{41,43,44} A hypopyon (visible pus in the anterior chamber) may occur, showing how dramatic the inflammatory response within the eye can be.^{45,46} Treatment is with topical corticosteroids to control the inflammation and mydriatics to control the ciliary spasm and to stop the iris sticking to the underlying lens during the inflammatory process due to the formation of posterior synechiae. Ocular inflammation may subside within 3 months, even if the patient is not treated but tends to recur after a variable length of time and may involve the other eye. Other reports include episcleritis, scleritis, keratitis, and posterior uveitis.^{37,41,47,48} Those with sight-threatening sequelae may require treatment with periocular corticosteroid injections, oral corticosteroids, and immunosuppressive agents. The ocular prognosis is usually good if the inflammation is adequately controlled.⁴² In all patients, the ocular inflammation is recurrent, with variable intervals between exacerbations, with some patients requiring treatment for many years.⁴²

Reiter's syndrome may be an indicator of other sexually transmitted infections and has been reported as the presenting manifestation of patients with HIV/AIDS.⁴⁹ Reiter's syndrome has been reported in between 1.7% and 11.2% of patients with HIV, and there is some evidence that it may be more difficult to treat in this group.⁴⁹ Approximately 70–80% of white HIV-positive patients with Reiter's syndrome are HLA B27 positive.⁵⁰ In a recent report, Reiter's syndrome, due to *C. trachomatis*, developed shortly after the introduction of

anti-HIV therapy, suggesting a possible role for immune reconstitution in disease presentation.⁵¹

SYPHILIS

The eye can be involved in both congenital (see below) and acquired syphilis, and all structures of the eye may be involved. Recently, a resurgence of syphilis in some countries, including the United States and UK, has been followed by a rise in reported cases of ocular involvement.⁵² Patients may present with an inflamed “red” eye or with visual loss in the context of known syphilis, but often the visual symptoms are the first manifestation of disease.^{53,54} Eye symptoms or signs can also present after antibiotic therapy has been commenced as part of a Jarisch-Herxheimer reaction.⁵⁵ The eyelid or periorbital structures may rarely be the site of a chancre from primary infection after direct genital contact with infected genital secretions.⁵⁶

Intraocular inflammation (uveitis) can occur at all stages of infection including primary infection⁵⁷ and may resolve spontaneously, but relapse is common. Several different types of uveitis may occur. Anterior uveitis is the most common and is nonspecific in type.⁵⁸ Patients with posterior uveitis may have vitritis, focal retinitis (Fig. 65-5), chorioretinitis,⁵³ periphlebitis, retinal hemorrhages, papillitis,⁵⁹ exudative retinal detachments,⁶⁰ neuroretinitis, and vascular occlusions.⁶¹ Visual loss can occur from any of these, and patients may present with paracentral scotomas and blind spot enlargement. Pupillary enlargement may be apparent in optic nerve disease, and small miotic pupils (Argyll Robertson pupils) that react to accommodation but fail to react to direct light are seen in tertiary syphilis. Healing of the retinal lesions results in full thickness loss and a salt and pepper fundal appearance (Fig. 65-6). Orbital involvement can also occur from gumma in the posterior fossa invading the eye through the superior orbital



FIGURE 65-5. Retinitis in syphilis.

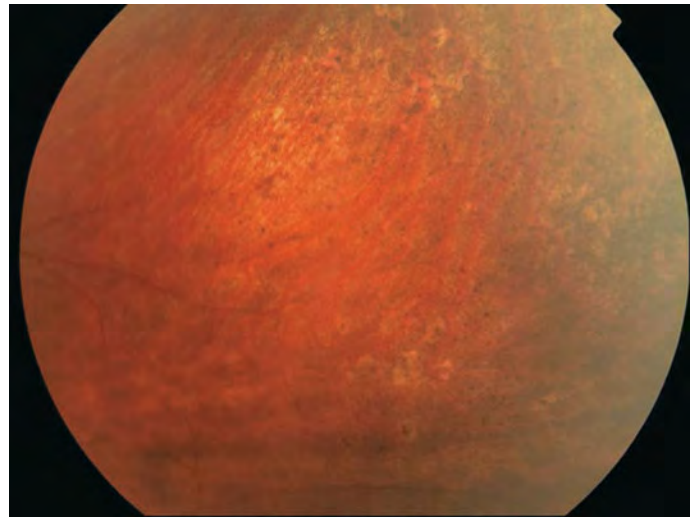


FIGURE 65-6. Salt and pepper appearance of the fundus occurring in healed syphilitic retinitis.

fissure.⁶² Intracranial involvement may result in papilledema and sixth nerve palsy.⁶³ Treatment with penicillin is usually very successful in eradicating the intraocular inflammation, but scarring may limit visual recovery. A Jarisch-Herxheimer reaction may occur in the eye with the initiation of treatment,⁵⁵ and corticosteroids are usually given to avoid further ocular damage, if this occurs. Topical steroids and mydriatics may be needed to control anterior uveitis. Most importantly, uveitis may persist or relapse after successful antimicrobial treatment of syphilis. Patients, therefore, require careful ophthalmological follow-up and may need further anti-inflammatory treatment.

Concomitant infection with HIV⁶⁴ alters the appearance of the uveitis so that it is more severe with more common involvement of the retina and optic nerve than anterior uveitis,⁶⁵ as well as a dense vitritis being seen.⁵⁴ In addition, the syphilis serology may also be negative.⁶⁶ At this stage, it may be associated with tertiary syphilis, and treatment will require neurosyphilis drug strategies.⁶⁷

■ CONGENITAL SYPHILIS AND THE EYE

This occurs when the mother contracts syphilis during pregnancy, and it passes across the placenta to the fetus.⁶⁸ The frequency of syphilitic involvement of the eye in early congenital syphilis is unknown. Occasionally, presentation is delayed until late childhood, with features of secondary or tertiary syphilis. Chorioretinitis, salt and pepper fundus, glaucoma, uveitis, keratitis, and chancres of the eyelid have all been described following congenital infection. Congenital glaucoma may also occur. Chorioretinitis rather than uveitis (as in the adult) is the more commonly diagnosed ocular problem in infancy, and the effect on vision depends on its location on the retina (Fig. 65-7). Interstitial keratitis is a common presentation in later life (Fig. 65-8) and can be

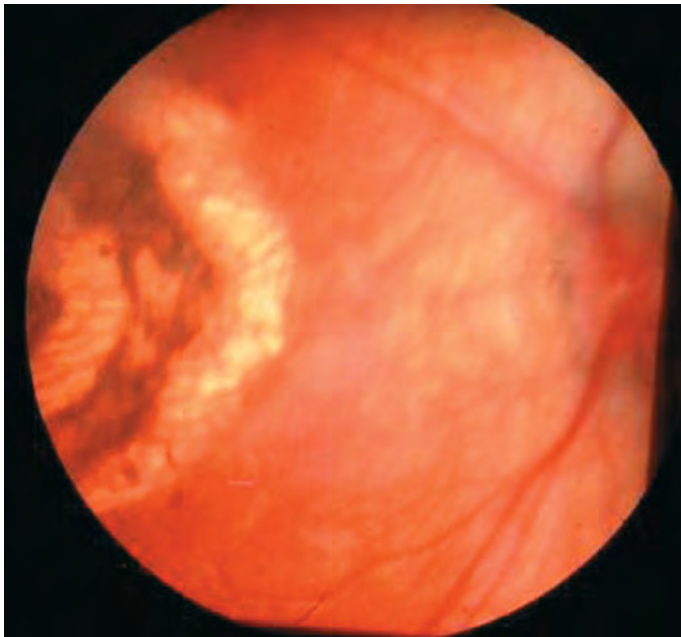


FIGURE 65-7. Chorioretinital scar in congenital syphilis.

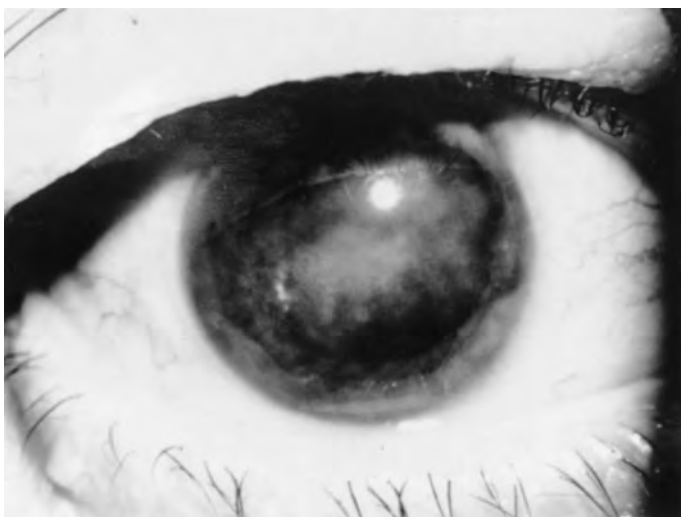


FIGURE 65-8. Interstitial keratitis in congenital syphilis.

prevented if the child is treated within the first 3 months of life. Interstitial keratitis presents with sore red eye(s), which are usually treated with topical steroids and cycloplegics. In one report, a child was successfully treated with oral cyclosporine 4 mg/kg/d, 6 days per week, and oral low-dose steroids suggesting involvement of the immune system.⁶⁹ Corneal grafting may be required to restore vision.⁷⁰

HERPES SIMPLEX VIRUS

The commonest ocular infection with the herpes simplex virus (HSV) is keratitis. This is due to reactivation of latent infection and is not associated with a sexually transmitted infection. Both HSV type 1 and HSV type 2 can involve the eye. A rarer but potentially devastating type of ocular infection

is acute retinal necrosis, which again is predominately reactivation of latent virus, either HSV 1 or HSV 2. Very occasionally, this occurs as a result of systemic dissemination.

Most people have been exposed to HSV, and their primary infection is subclinical. Even if clinically apparent, the lesions are self-limiting. In newborn infants, patients with eczema, or the immunocompromised patient, primary infection with HSV can become severe, disseminated, and life threatening.⁷¹ Neonatal infection is usually acquired from maternal genital herpes, which may be asymptomatic or unrecognized in 60–80% women. The greatest risk of neonatal infection occurs when the mother has primary genital herpes involving the cervix at delivery and the infant is premature. The use of instrumentation including scalp electrodes further increases the risk. More than 80% of neonates infected in this way will have typical herpetic lesions of the skin, eye, or mouth, and most of the remainder will be very sick with encephalitis, pneumonitis, and sepsis.⁷² The disease manifestations can occur days to weeks after delivery. The eyes first show conjunctival injection and swelling (chemosis), which is then accompanied/ followed by an outbreak of vesicles on the eyelids (Fig. 65-9). A purulent discharge is variably present. Trifluridine 1% solution should be instilled 2 hourly until the infection has resolved and intravenous acyclovir 500 mg/m² (or 10mg/kg) given 8 hourly for 10 days.⁷³

Much more rarely, HSV can be transmitted transplacentally, and disseminated infection of the fetus can occur. Many will die from this⁷⁴ or have congenital malformations. In the eye, this can include microphthalmia, chorioretinitis, optic neuritis, and cataracts,⁷⁵ all of which can result in severe visual loss. Persistent fetal vasculature in the eye has also been reported.⁷⁶ Patients who had neonatal HSV infection, particularly associated with encephalitis, have been reported to develop acute retinal necrosis in adult life, presumably from reactivation of latent infection.^{77,78}

Seventeen percent to 39% of patients with congenitally acquired HSV do not have skin lesions at presentation or during the course of the disease. This can make the diagnosis of HSV infection more difficult. A recent study has shown that no progress has been made in decreasing the interval between onset of symptoms and initiation of antiviral therapy since the early 1980s.⁷⁹ Of note in this study is that skin or conjunctival cultures were positive in 94% of patients, a much greater diagnostic yield than the culture of mouth/oropharyngeal swabs (48%) or 40% with CSF or brain biopsy. Treatment of the mother predelivery to prevent infection or recognition of vesicles present during labor so pre-emptive cesarean section can be undertaken and treatment with acyclovir started immediately are the best ways to prevent neonatal infection and its complications.

The International Herpes Management Forum (IHMF) has produced guidelines on the diagnosis, prevention, and effective management of neonatal herpes. They suggest that



FIGURE 65-9. Primary herpes simplex lesions on lids of neonate.

neonates with suspected HSV infection should be treated with intravenous acyclovir (20 mg/kg) every 8 hours for 21 days. If disease is localized to the skin, eyes, or mouth, treatment can be limited to 14 days.⁸⁰

PUBIC LICE (*PHTHIRUS PUBIS*)

The head louse does not involve the eyelashes despite the close proximity to the hairline. The crab louse, however, can live in body hair including pubic, axillary, and chest hair or the eye lashes.⁸¹ Eyelid involvement frequently causes symptoms of itching and burning, and the white eggs or egg cases are clearly visible to the naked eye (Fig. 65-10). The egg cases are made of chitin and are firmly attached to the eyelash. After a week, the eggs hatch into lice, which are transparent, firmly attached to the eyelash by thick claws, and not easily visible without magnification. Secondary infection, with associated preauricular lymphadenopathy, can occur at the sites of lice bites.⁸²

There are several treatment options, none of which are ideal.^{83,84} The eggs can be removed with forceps, but this is very time consuming. Alternatively, the lashes can be maximally trimmed to remove both eggs and lice, but they take some time to regrow and this is cosmetically unacceptable for many patients. The lice can be smothered with the application of a thick layer of ophthalmic ointment, but this does not kill the eggs. Ointment containing physostigmine is sometimes suggested, but, although effective in killing lice, the eggs are unaffected, necessitating repeat treatment for up to 14 days to kill lice emerging from the eggs.⁸⁵ One percent gamma-benzene hexachloride (Lindane) is effective if repeated 5–6 days later to catch newly hatched lice; however,



FIGURE 65-10. Lice eggs on eye lashes.

this solution may irritate the eyes.⁸² More recently, a 4% pilocarpine solution (usually used to control intraocular pressure) has been used to scrub the eyelashes twice daily for 4 days and successfully eradicated both lice and eggs.⁸⁶ Pilocarpine is thought to induce cholinergic toxicity of the nervous system of the louse. If pilocarpine gets onto the ocular surface it can cause temporary miosis and reduced vision from induced myopia, so it is very important to give clear instructions on its use.

The finding of lice in the eyelashes is often indicative of a generalized infestation, and other affected areas of the body must also be treated, usually with 1% permethrin cream or 1% gamma-benzene hexachloride shampoo, together with all bedding, clothing, and contacts.

HIV INFECTION

The era of HIV/AIDS has dramatically altered the clinical presentation of many infections, and this is also true of those that may affect the eye. Eye complications are seen at all stages of HIV infection and may be the first clue to unsuspected underlying infection with HIV. Eye involvement is uncommon at the time of seroconversion, although there are a few reports of HIV retinopathy presenting during seroconversion.⁸⁷ The type of eye involvement in HIV/AIDS depends on the level of immune function, particularly related to the CD4 count,^{88,89} and other systemic diseases/infections that may be present. Before the advent of effective antiretroviral therapy, blindness due to cytomegalovirus (CMV) retinitis was one of the most feared complications of AIDS. With effective anti-HIV treatment, CMV retinitis is much less common except in patients who present late in the course of the disease.^{90,91} However, CMV and other retinal infections such as those due to toxoplasmosis, herpes simplex, and herpes zoster still occur, and a thorough knowledge of their presentation and treatment is important. The eye may also be involved in an immune reconstitution reaction following initiation of antiretroviral therapy, resulting in inflammation within the eye.

Visual symptoms should always be taken very seriously in patients with HIV/AIDS, due to the potential for visual loss. Prompt, expert ophthalmological assessment is essential in any patient with reduced visual acuity, visual field defects, or a painful red eye. The diagnosis of most intraocular infections is clinically based on the appearance of the lesions and clinical features of the patient. It is ideal, therefore, that an ophthalmologist who is experienced in HIV-related eye disease is asked to evaluate patients. Where there is doubt as to the correct diagnosis, then intraocular fluid (especially vitreous) specimens can be obtained for PCR and culture. It is useful to consider the eye complications seen at different levels of immune function and then to consider specific pathogens.

Patients with a high CD4 lymphocyte count greater than 500 cells/ μL have a minimal or no risk of opportunistic infections, and many patients are asymptomatic. However, a number of inflammatory eye problems may be seen, possibly due to dysregulation of the immune system. The clinical spectrum includes allergic conjunctivitis, Sjogren's syndrome, Reiter's syndrome, uveitis, retinal vasculitis, HIV microvasculopathy, and optic neuropathy. HIV microvasculopathy rarely causes visual symptoms and causes hemorrhages, microaneurysms, and cotton wool spots, which come and go, occurring predominantly around the optic disc and macula (Fig. 65-11).

As the CD4 count falls (200–500 cells/ μL) and susceptibility to infection increases, the eye may start to be involved. Many infections seen at this stage are also seen in non-HIV-infected patients, but, in the context of moderate immunodeficiency, they tend to be more prevalent and persistent. Thus, eye problems should be considered part of the “symptomatic HIV” complex and, along with other clinical findings, might alert an astute clinician to the possibility of underlying immunodeficiency. Bacterial infections include conjunctivitis and blepharitis (infection of the eyelids). Syphilis may present with uveitis or necrotizing retinitis (see above). Molluscum contagiosum are common and can occur on the

eyelids. Molluscum, however, are rarely severe unless the CD4 count falls to less than 100 cells/ μL .

As the CD4 count falls below 200 cells/ μL , the patient becomes susceptible to a wide range of infections, including opportunistic infections, and also to malignant disease. The risk of ocular infection is particularly high as the CD4 count falls below 75 cells/mL. Ocular manifestations include retinitis (CMV, toxoplasmosis, HSV, and varicella zoster virus [VZV]), choroiditis (candida, pneumocystis, cryptococcosis, and TB), and tumors (Kaposi's sarcoma, lymphoma, and squamous cell carcinoma [SCC] of the conjunctiva).

■ CMV RETINITIS

Before antiretroviral therapy, up to 40% of patients with AIDS would develop invasive CMV infection, with retinitis accounting for 75–85% of CMV disease in these patients. The risk of CMV retinitis is particularly high, 20–40% with a CD4 cell count <50 cells/ μL .⁹² Anti-CMV drug therapy is not virocidal, and, therefore, in the absence of immune restoration, progression of CMV retinal destruction is inevitable, despite continuous treatment.^{93,94} The advent of effective antiretroviral therapy has seen a significant fall in both new cases of CMV retinitis and disease relapse.^{91,95,96}

CMV infection results in full-thickness retinal necrosis, which appears clinically as a white necrotic lesion with accompanied hemorrhages (Fig. 65-12). Although the diagnosis is usually established on clinical grounds, CMV can be confirmed by PCR of a vitreal aspirate, and where possible this is usually undertaken. In immunocompromised patients not on antiretroviral therapy, there is little or no intraocular inflammation, and the diagnosis is easy to make on the appearance. In contrast, patients on antiretroviral therapy in

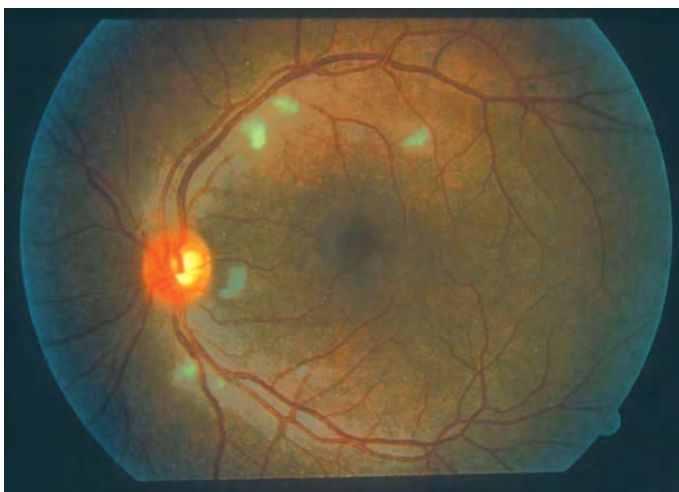


FIGURE 65-11. Cotton wool spots in HIV infection.

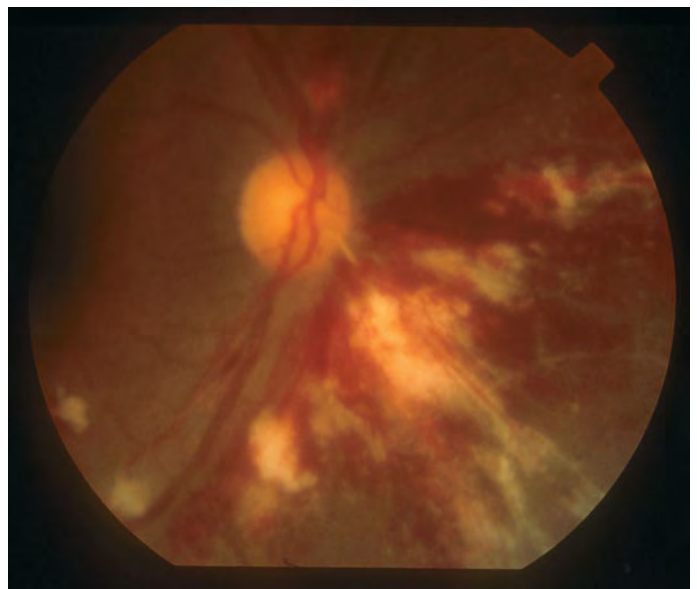


FIGURE 65-12. CMV retinitis.

whom immune reconstitution is occurring may exhibit a marked inflammatory response, which can induce vitritis and macular edema, resulting in further visual loss⁹⁷ and an atypical appearance that may be more typical of infection with HZV or HSV.

The best long-term management is the use of antiretroviral therapy to increase the CD4 cell count and thereby provide immunological control of CMV replication. However, with patients presenting with CMV retinitis and very low CD4 cell counts, this will take several months to achieve, and specific anti-CMV therapy is required to preserve vision. The therapeutic decision is based on the site of the retinal lesion (lesions close to the macula or optic nerve present a high risk of permanent visual loss), evidence of systemic infection, and whether the disease is unilateral or bilateral.⁹⁸ Ocular disease is better managed with intraocular treatment either with an intravitreal ganciclovir or foscarnet or with a ganciclovir implant that can release drug into the eye for up to 6–8 months (Fig. 65-13). Intraocular therapy is advised for all patients

with immediately sight-threatening disease. Patients with isolated peripheral lesions may be managed with systemic therapy alone and the eye monitored regularly. Systemic anti-CMV therapy is indicated for the majority of patients, to protect the uninfected eye and to treat/prevent disease elsewhere. For small peripheral lesions, some authorities would initiate antiretroviral therapy alone and monitor progress carefully. The risk of second eye involvement in patients with unilateral CMV retinitis is substantial in the months after initiation of antiretroviral therapy, and close monitoring is vital.⁹⁹ Even in the era of antiretroviral therapy, CMV disease as manifested by CMV retinitis and a detectable CMV viral load are associated with an increased risk of mortality, even after adjusting for demographic, treatment, immunologic, and HIV virologic factors.¹⁰⁰

Anti-CMV therapy is summarized in Table 65-1. Induction anti-CMV therapy may be with intravenous ganciclovir, intravenous foscarnet, or oral valganciclovir. Oral ganciclovir is inferior to valganciclovir for induction and should not be used. Maintenance therapy is best given with oral valganciclovir, although there are a number of alternative regimens (Table 65-1). Cidofovir is effective in CMV retinitis and may be considered where there are contraindications to other agents. Cidofovir may cause a uveitis, particularly in patients on antiretroviral therapy, and is less commonly used now.¹⁰¹⁻¹⁰³ Formiverson, a novel antisense drug, is approved for use in patients with CMV retinitis, is given as an intravitreal injection, and can be useful if drug resistance is a problem.¹⁰⁴ Discontinuation of all anti-CMV therapy is usually possible when the CD4 count rises to >150 cells/ μ L and is maintained for more than 3 months.^{98,105} CMV resistance may develop to all of the agents in current use due to specific mutations.^{106,107} Ganciclovir-resistant CMV (mutation in the UL97 or genes) is often cross resistant to cidofovir but generally remains susceptible to foscarnet. Routine monitoring of peripheral blood CMV viral load is of poor sensitivity in predicting CMV disease progression; however, a negative blood CMV viral load whilst on therapy has a high negative predictive value for CMV drug resistance.¹⁰⁸

The best timing for initiation of antiretroviral therapy in patients with CMV retinitis has not been determined. These patients all have low CD4 counts, and therefore, it is important to start therapy quite quickly. However, immune reconstitution vitritis in which there is a vigorous intraocular inflammatory response, can be very difficult to treat, as a good response to steroids may not occur.^{109,110} Thus, many clinicians will defer antiretroviral therapy for a short time (generally 2–4 weeks) to allow anti-CMV therapy to bring the retinitis under control first. For this reason, it is wise to evaluate high-risk patients (CD4 < 75 cells/ μ L) for ocular CMV prior to initiating HAART. Retinal detachment remains a problem in any eye infected with CMV, and the risk increases with increasing area of retinal destruction.¹¹¹ Damage to the

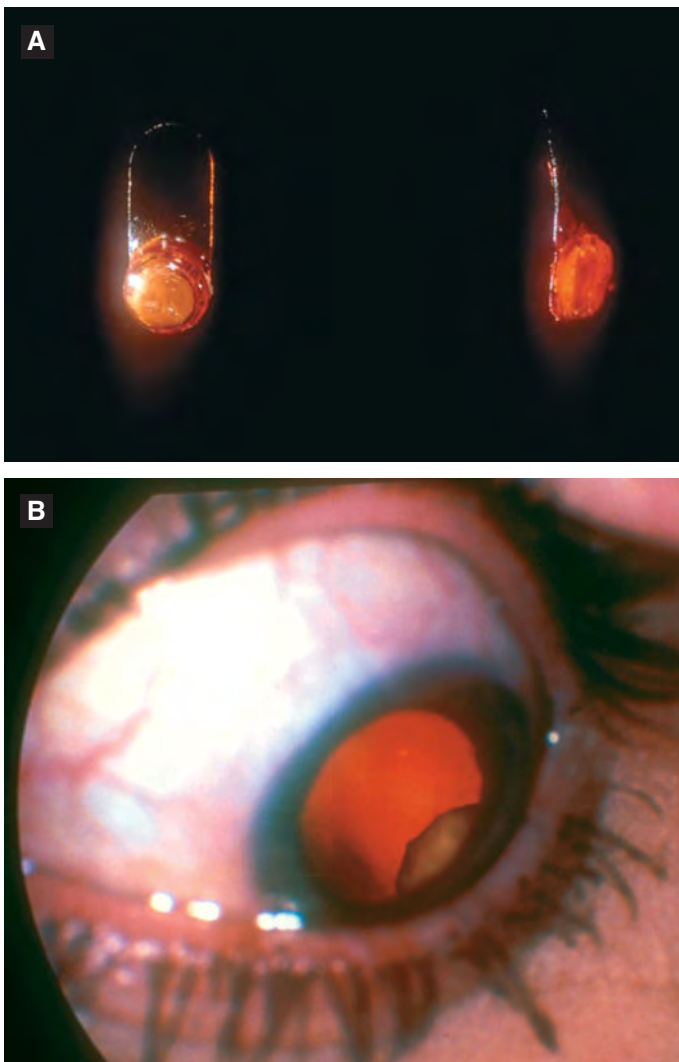


FIGURE 65-13. Ganciclovir implant, **A**, device and, **B**, in situ in eye.

Table 65-1. Drugs Available for the Treatment of CMV Retinitis

Drug	Mechanism	Induction ^a	Maintenance ^a	Intravitreal Dose	Adverse Effects
Ganciclovir—IV, oral and intravitreal use	Deoxyguanosine nucleoside analog inhibits CMV DNA polymerase	5 mg/kg q12h IV for 2–3 wk	5 mg/kg qd IV 1 g TID PO	2 mg weekly until disease controlled Ganciclovir implant lasts for up to 6 months	Anemia, leucopenia, and pancytopenia
Valganciclovir—oral only	Deoxyguanosine nucleoside analog inhibits CMV DNA polymerase	900 mg q12h PO for 2–3 wk	900mg qd	n/a	Anemia, leucopenia, and pancytopenia
Foscarnet—intravenous and intravitreal only	Pyrophosphate analog inhibits CMV DNA polymerase	90 mg/kg q12h IV for 2–3 wk—hydrate well	90 mg/kg/qd hydrate well	2.4 mg weekly until disease controlled	Renal toxicity in 20–60%, hypocalcemia, hypokalemia, convulsions, and genital ulceration
Cidofovir—intravenous only	Cytosine nucleotide analog inhibits CMV DNA polymerase	5 mg/kg IV weekly for 2–3 wk—(hydrate well + probenecid)	5 mg/kg IV every 2 weeks—(hydrate well + probenecid)	n/a	Renal toxicity, fanconi syndrome, ocular hypotony, and uveitis
Fomiverson—intravitreal only	Antisense oligonucleotide inhibits CMV mRNA	Intravitreal injection every 2 wk	Intravitreal injection every 4 weeks	165/330 µg	Increased intraocular pressure and blurred vision in 5%

^aGanciclovir, valganciclovir, and foscarnet require dose modification in patients with renal impairment.

retina may result in detachment long after the CMV retinitis has been controlled, and sudden loss of vision in a patient with previous CMV retinitis should always prompt an urgent review to exclude retinal detachment.

■ HERPES SIMPLEX VIRUS

Patients with and without HIV may suffer from recurrent HSV infection of the cornea (HSV keratitis). HSV keratitis may be difficult to treat in patients with HIV; recurrences are common and vision may be lost if the central part of the cornea is involved (Fig. 65-14). The diagnosis is usually established by examination with fluorescein instilled into the eye, demonstrating the typical appearance of a dendritic ulcer. Rarely is culture undertaken but may be useful in atypical cases. Management consists of topical antiviral agents and prompt treatment of recurrences. The most serious complication of HSV in the eye is acute retinal necrosis. Acute retinal necrosis (necrotizing retinitis) can lead to rapid visual

loss and may be caused by VZV or HSV (Fig. 65-15). Acute retinal necrosis generally occurs in patients with higher CD4 cell counts and can also occur in the immunocompetent host. The diagnosis is established on clinical grounds and confirmed by PCR of a vitreal aspirate. Therapy is with high-dose acyclovir given intravenously until control has been achieved, when treatment can be changed to oral acyclovir. The optimum duration of therapy has not been defined, and long-term maintenance treatment is sometimes required. Necrotizing retinitis can lead to retinal detachment and loss of vision.

■ VARICELLA ZOSTER VIRUS

VZV can affect the eye in a number of ways in patients with HIV. VZV involving the first division of the trigeminal nerve (herpes zoster ophthalmicus) can cause severe lid infection and necrosis and/or intraocular inflammation with marked vitritis obscuring the retina. VZV may cause acute retinal necrosis as

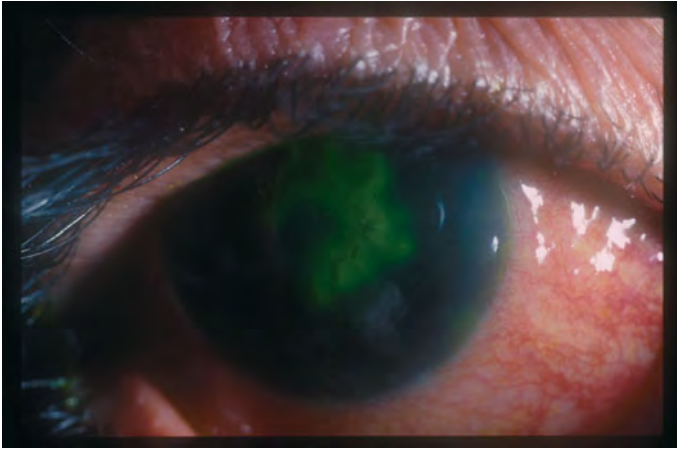


FIGURE 65-14. Herpes simplex keratitis in HIV infection.



FIGURE 65-16. Left herpes zoster ophthalmicus with sixth nerve palsy.

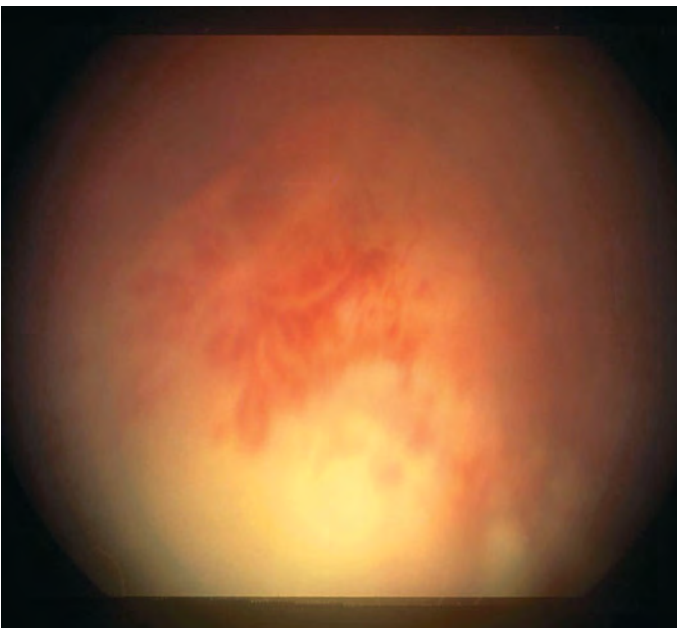


FIGURE 65-15. Acute retinal necrosis.

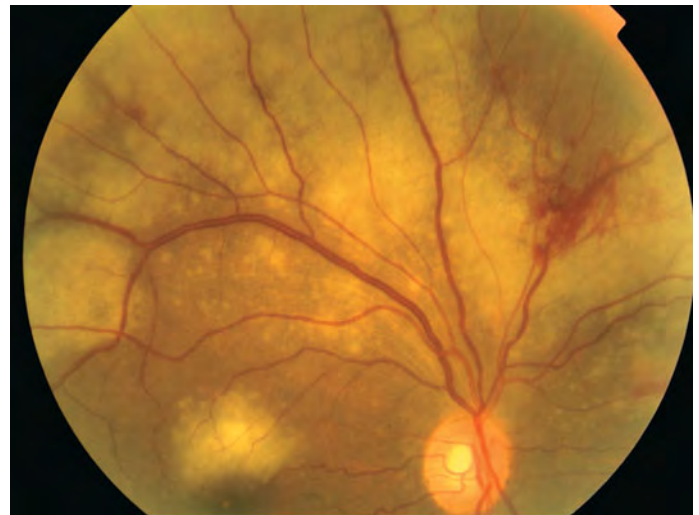


FIGURE 65-17. Progressive outer retinal necrosis.

above. In addition, cerebral vasculitis can occur and cranial nerve palsies such as VI (Fig. 65-16) and III may result.

In patients with very low CD4 counts, VZV can cause a fulminant outer retinal necrosis (previously known as progressive outer retinal necrosis or PORN but now called VZV retinitis) without vitritis in contrast to acute retinal necrosis, which is usually associated with marked intraocular inflammation. The retinitis starts as discrete lesions (Fig. 65-17), which rapidly coalesce and involve the central part of the retina. The disease is usually bilateral, with early involvement of the second eye when uninvolved at presentation. Severe visual loss and retinal detachment occur within weeks.^{112,113} VZV retinitis may, on occasion, be preceded by aseptic meningitis or retrobulbar optic neuritis.¹¹⁴ Patient may have a recent history of shingles, but frequently there is no sign of VZV elsewhere. Recommended systemic therapy is the

combination of high-dose intravenous acyclovir and foscarnet.⁹⁸ Intravitreal therapy is also frequently used and provides an opportunity to take samples for PCR. Treatment of retinal detachment requires intraocular surgery with vitrectomy and silicone oil tamponade, but the prognosis for vision is poor.

■ TOXOPLASMOSIS

Infection with *Toxoplasma gondii* is common worldwide, with a prevalence varying from 15% to 80%, depending on the population studied. Infection may be primary (positive IgM), reactivation of previous ocular infection (based on the finding of old chorioretinal scars), or metastatic from another part of the body.¹¹⁵ Toxoplasma retinitis in AIDS patients is most commonly due to reactivation of latent infection and may occur at any CD4 count, although it is uncommon at CD4

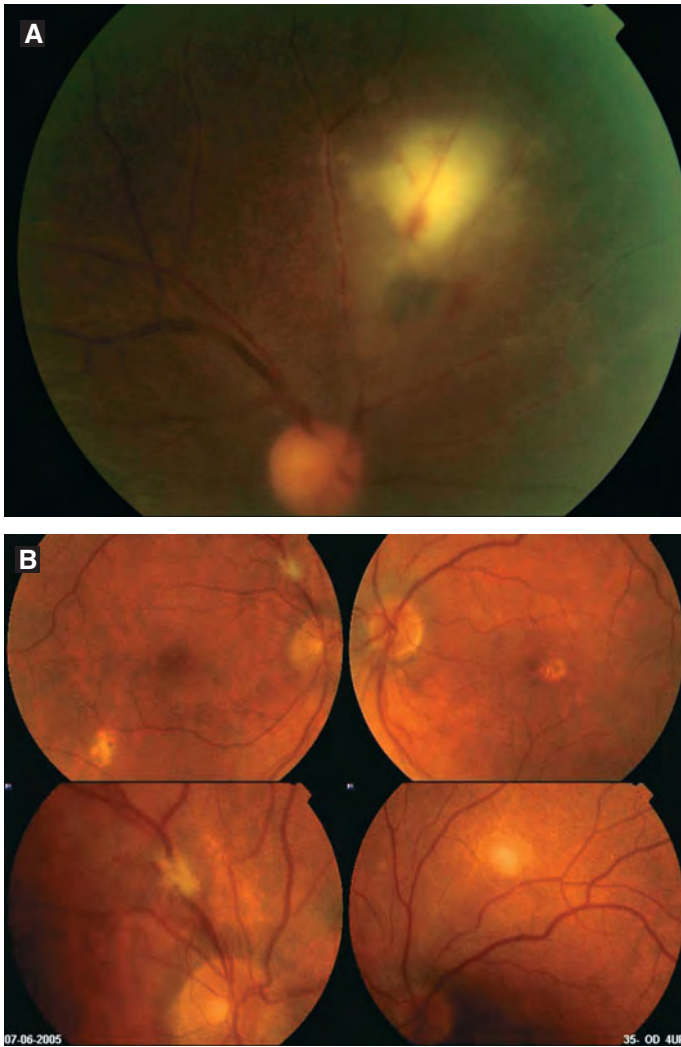


FIGURE 65-18. Toxoplasmic chorioretinitis: **A.** Single focus. **B.** Multiple active foci.

counts of above 150 CD4 cells/ μ L. All HIV-positive patients with a CD4 count of less than 200 cells/ μ L should be given prophylactic antibiotics to prevent pneumocystis carinii infection. Sulphonamide antibiotics such as trimethoprim-sulphamethoxazole (septrin and bactrim) used for this purpose also afford protection against toxoplasmosis.

The clinical appearance varies and may be a focal necrotizing retinitis or diffuse or multifocal lesions (Fig. 65-18). Inflammation with anterior uveitis and vitritis is usually present but is quite variable.¹¹⁶ Concomitant CNS toxoplasmosis is frequently present, and CT or MRI (more sensitive than CT) brain imaging should be performed (Fig. 65-19). Patients with cerebral lesions and raised intracranial pressure may have papilledema and/or cranial nerve palsies. Treatment of ocular toxoplasmosis follows the same regimen as that of CNS disease, as the drugs have good ocular penetration. Sulphadiazine plus pyrimethamine or clindamycin plus pyrimethamine are the preferred treatment.⁹⁸ Oral corticosteroids are not indicated for ocular toxoplasmosis

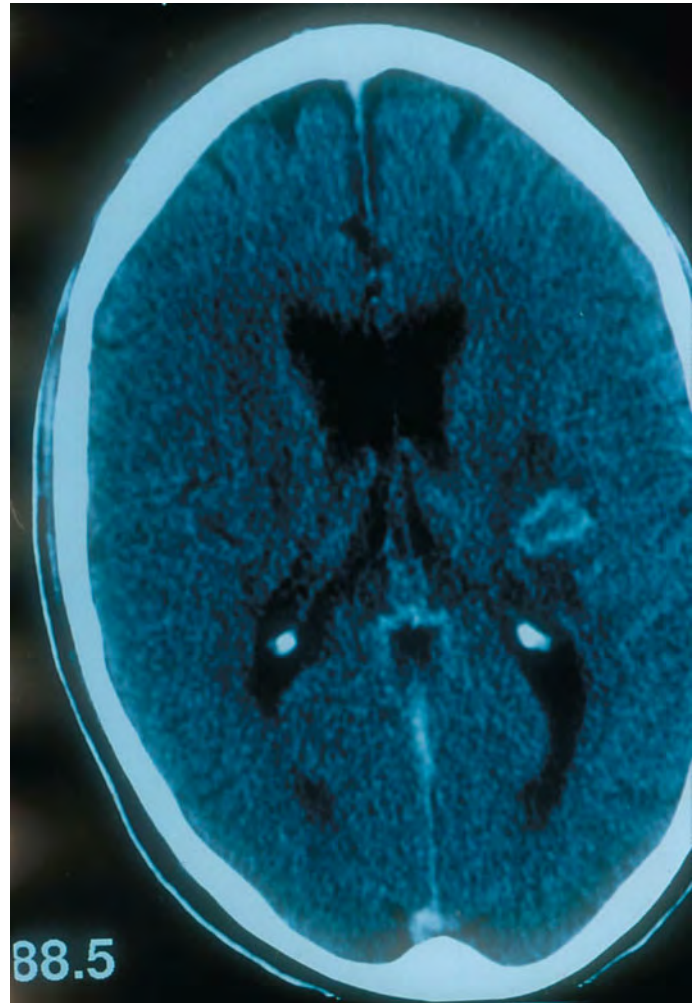


FIGURE 65-19. CT scan showing toxoplasma lesion in brain.

complicating HIV. Treatment duration will depend on the clinical response to therapy, with full-dose treatment generally being required for 4–6 weeks. All patients with ocular toxoplasmosis must receive secondary antimicrobial prophylaxis until the CD4 cell count is sustained for at least 6 months over 200 cells/ μ L.⁹⁸

■ PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease caused by the human neurotropic JC virus¹¹⁷ (Fig. 65-20). PML is characterized by progressive lysis of oligodendrocytes with demyelination. A rapid clinical course ensues with focal neurological deficits and a median time to death of 3.5 months without treatment. Prior to highly active antiretroviral therapy, there was no effective therapy. Since the advent of antiretroviral therapy, the prognosis for PML has much improved; however, a significant number of patients appear unresponsive to antiretrovirals, and some worsen because of the development of immune reconstitution disease.¹¹⁸ Eye involvement may occur in terms of eye movement disorders and visual field

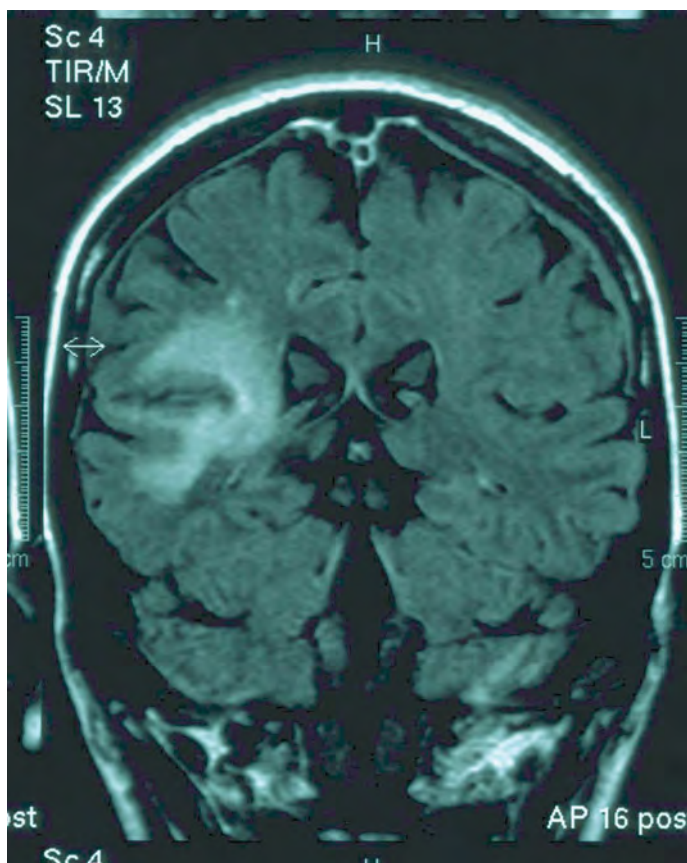


FIGURE 65-20. MRI brain scan showing lesions of PML which resulted in a homonymous hemianopia.

defects. JCV DNA has been detected in ocular tissue of AIDS patients at a significantly higher level than in eyes of nonimmunosuppressed patients, but the clinical significance of this is unknown.¹¹⁹

■ SYPHILITIC RETINITIS

Syphilis and AIDS are epidemiologically associated.⁶⁴ Syphilis is described in detail earlier in this chapter. Ocular involvement by syphilis in AIDS patients is more aggressive and includes necrotizing retinitis with vitritis, retinal vasculitis, serous retinal detachment, and neuroretinitis. The diagnosis is based on clinical presentation with positive serology. Treatment includes high-dose intravenous penicillin for 10–14 days.

■ INFECTIVE CHOROIDITIS

This is seen in patients with systemic infections and therefore indicates miliary spread. It can be seen in TB, fungal infection such as candidemia, bacterial sepsis, and *Pneumocystis jirovecii*.¹²⁰ Candidemia is rare in patients with HIV/AIDS unless there are additional factors such as neutropenia, intensive care treatment, or intravenous drug abuse.¹²¹ The widespread use of prophylaxis for *P. jirovecii* and the introduction of antiretroviral therapy have contributed to the dramatic fall in the incidence of *P. jirovecii* choroiditis. Choroidal lesions are usually found on routine



FIGURE 65-21. Pneumocystis choroiditis.

examination: one to several yellow-white lesions (Fig. 65-21), located mostly in the posterior pole and up to the equator. Visual function is not compromised, even if the lesion is under the fovea.

■ TUBERCULOSIS

In many countries, TB has become one of the commonest presenting opportunistic infections in patients with HIV.¹²² Tuberculosis can cause uveitis as well as choroidal granulomas, which may be single or multiple or may involve the optic nerve (Fig. 65-22).¹²³ The eye signs of tuberculosis are frequently overlooked and can provide an important clue to the diagnosis in the febrile patient. For example, in a recent report, 4/17 patients with HIV and TB were found to have ocular involvement (one uveitis and three retinal granulomas).¹²² In acute disseminated TB, 60% were found to have ocular involvement (83% choroidal tubercles and 16% retinal vasculitis), and detection of these lesions allowed a lead time of 12–72 hours, in which earlier appropriate therapy was started.¹²⁴ TB involving the eye should be treated with standard antituberculous therapy, as recommended for patients with HIV.⁹⁸

■ CRYPTOCOCCUS

Ocular involvement in cryptococcal meningitis, which is a life-threatening infection in AIDS patients, is mainly related to papilledema or optic neuropathy. Occasionally, there are multifocal choroidal lesions (Fig. 65-23) similar to *Pneumocystis jirovecii*, without anterior chamber or vitreal inflammation. The choroidal lesions respond to treatment, with optic nerve disease being the limiting factor for visual outcome.¹²⁵

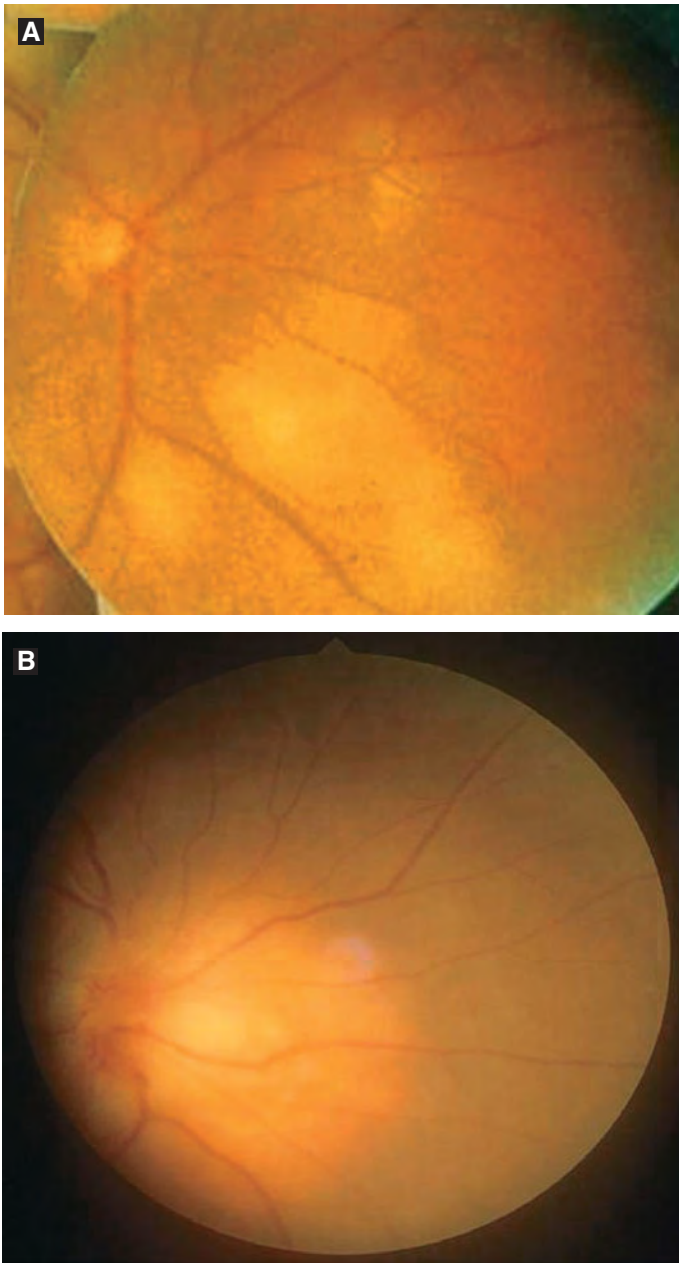


FIGURE 65-22. Tuberculosis, **A.**, in choroid and, **B.**, involving optic nerve.



FIGURE 65-23. Cryptococcal choroidal lesions.

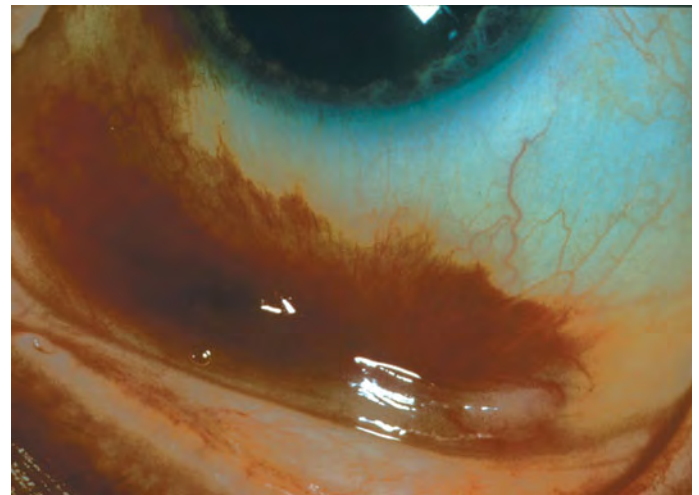


FIGURE 65-24. Kaposi's sarcoma.

MALIGNANCY ASSOCIATED WITH HIV

■ KAPOSI'S SARCOMA

Although this used to be fairly common in AIDS patients, its incidence has declined, as shown by Rutherford et al.¹²⁶ It has been strongly associated with human herpes virus type 8. The clinical appearance is of multicentric vascular red-purple nodules, which typically involve the skin. The ocular involvement includes the eyelids, the conjunctiva (Fig. 65-24),¹²⁷ and rarely the lacrimal sac and the orbit. Spontaneous regression has been documented following antiretroviral therapy, so deferral of treatment for a few months after commencement

of treatment is possible. Other treatment options include local excision, cryotherapy and focal irradiation, and intraleSIONAL injection.¹²⁸

■ LYMPHOMA

AIDS patients are at increased risk of developing non-Hodgkin's lymphoma as their life span increases and are particularly at risk when their CD4 count has fallen below 50 cells/ μ l at any stage. The lymphoma is mostly of a high-grade B-cell type and is associated with EBV infection. Historically, increased risk was observed in patients treated

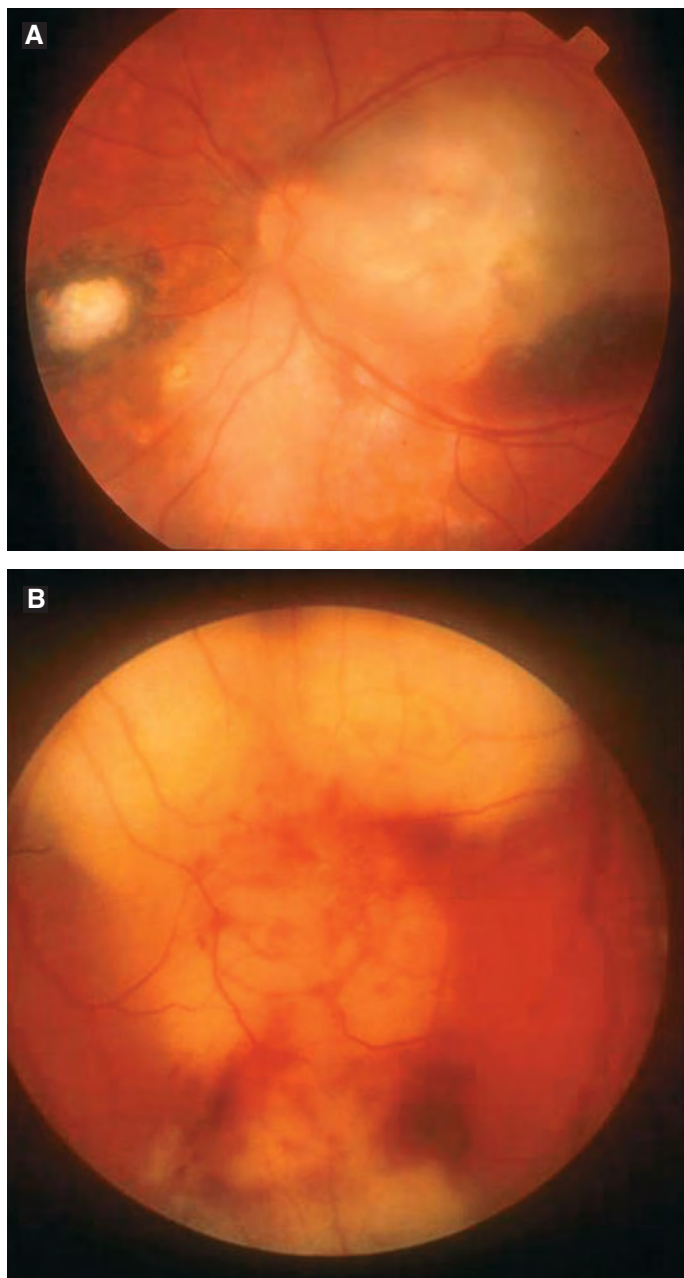


FIGURE 65-25. Lymphoma, **A**, intraocular with retinal involvement—note old inactive toxoplasma scar and, **B**, systemic with choroidal involvement.

with zidovudine (AZT), but this association has not been reported where zidovudine forms part of an antiretroviral regimen. The most common presentation in the eye is from a primary CNS lymphoma with ocular involvement, and less frequently from spread to the eye by systemic lymphoma. Intraocular involvement of CNS lymphoma involves the vitreous and retina and may resemble viral retinitis, in contrast to systemic lymphoma, which more commonly spreads to the choroid (Fig. 65-25) or presents as an orbital mass.^{129,130} Treatment of lymphoma includes chemotherapy, with intrathecal methotrexate for CNS involvement,¹³¹ and fractionated radiotherapy. Intravitreal

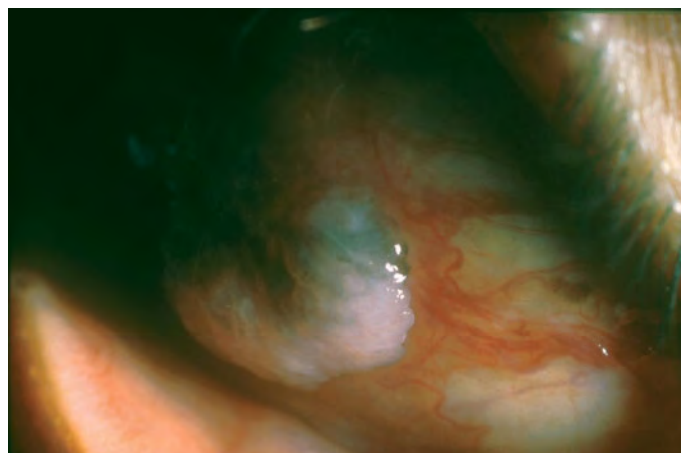


FIGURE 65-26. Squamous carcinoma of the conjunctiva.

methotrexate may be used for intraocular disease when recurrence occurs after radiotherapy, but in general the prognosis is poor.

■ SCC OF THE CONJUNCTIVA

SCC of the conjunctiva is associated with sun exposure and can occur in HIV-positive individuals (Fig. 65-26). It is rarely seen in Caucasians but is much more common in Africans. HIV and genus beta HPV types have been associated with SCC. A recent study did not confirm a specific association with SCC and HPV but suggested that infection with genera beta or gamma HPV types in conjunctiva is common, but not greatly enhanced by the presence of HIV.¹³² Metastatic SCC may occur and, as conjunctival SCC may be difficult to distinguish on clinical appearance alone, patients with a history of high ultraviolet-B radiation exposure should be given a low threshold for excision biopsy of suspicious lesions particularly.¹³³ Analysis of TP53 mutations confirmed at the molecular level the causal role of solar UV rays in the etiology of SCC of the conjunctiva and suggested that infection with epidermodysplasia verruciformis types of human papillomavirus may act as a cofactor to increase the sensitivity of conjunctiva cells to UV-induced mutagenesis.¹³⁴

■ DRUG-INDUCED EYE PROBLEMS

Patients with mycobacterium avium intracellulare infection may receive the drug rifabutin. Clarithromycin and fluconazole block the hepatic metabolism of rifabutin, and high levels of rifabutin may accumulate in the eye, resulting in a sudden profound loss of vision. The eye looks as if it is infected with bacteria with an intense inflammatory response that may include a hypopyon. This quickly quiets with topical steroids, rifabutin dose reduction, or discontinuation of the additional agents.¹³⁵

CONCLUSION

Sexually transmitted infections can involve the eyes in a variety of ways. A high index of suspicion and prompt investigation of visual symptoms are necessary to allow prompt diagnosis and treatment so as to avoid potentially sight-threatening complications. This is particularly true for patients with HIV/AIDS with very low CD4 lymphocyte counts who are at risk of severe ocular complications.

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Mark W. Russo and Ian Grimm

INTRODUCTION

Prior to the development of interferon therapy in the mid-1980s, no drug had shown efficacy in treating chronic viral hepatitis. Unmodified alpha interferons showed modest efficacy against hepatitis C. The addition of ribavirin and the development of pegylated interferons (peginterferon) were major breakthroughs in the treatment of hepatitis C. The addition of ribavirin to interferon increases response rates to therapy and pegylated interferons are not only associated with higher response rates; they are also more conveniently dosed at once weekly. Unfortunately, not all affected patients are candidates for therapy, and although there have been advances in therapy many patients fail to respond to treatment. More effective approaches to treatment of chronic hepatitis C with fewer side effects are clearly needed. Advances have also been made in the treatment of chronic hepatitis B with the development of peginterferon- α , oral nucleoside, and nucleotide analogs.

The short term goals of therapy for chronic viral hepatitis are to terminate viral replication and to prevent the progression of chronic hepatic inflammation to fibrosis. Approval of interferon- α therapy was based primarily on the drug's effect on intermediate markers of disease progression, such as serum aminotransferase levels and hepatic histology. In the current era, successful therapy for hepatitis C is defined as a sustained viral response (SVR) that is undetectable serum levels of virus 6 months after completing therapy. Data regarding long-term outcome measures such as morbidity and mortality from liver disease are emerging or under study. Results of antiviral therapy on hepatocellular carcinoma have been reported, and studies on the effect of antiviral therapy on the development of cirrhosis, liver failure, or death are underway.¹

This chapter summarizes current approaches to therapy in chronic viral hepatitis, focusing on peginterferon, oral nucleoside and nucleotide analogs for chronic hepatitis B, and peginterferon plus ribavirin for chronic hepatitis C. Because this is a rapidly evolving area, treatment recommendations are likely to change.

APPROACH TO THERAPY OF CHRONIC HEPATITIS

Chronic hepatitis is a syndrome defined by persistent necroinflammatory liver disease with viremia, typically lasting more than 6 months. In addition to the major viral causes, hepatitis B virus (HBV) and hepatitis C virus (HCV), a diverse group of nonviral causes of chronic hepatitis must be considered in the differential diagnosis, including alcohol abuse, nonalcoholic fatty liver disease, and drugs. It is possible that additional, yet unidentified, viral causes of chronic hepatitis exist. If so, these would account for only a small proportion of cases.

The histologic classification of chronic hepatitis has been revised to reflect advances in the understanding of the etiology and prognosis of chronic liver disease. Natural-history studies of HCV-infected patients have demonstrated that even a mild necroinflammatory lesion can eventually progress to cirrhosis.^{2,3} For this reason, older terms such as "chronic persistent" and "chronic active" hepatitis, which have prognostic implications, have been replaced with specific scales for grading necroinflammatory activity and for staging the degree of fibrosis present.⁴

The 6-month definition of chronicity, while arbitrary, allows a reasonable time for spontaneous resolution of a self-limited process. Spontaneous resolution of hepatitis B or C after 6 months of infection is rare. In practice, 20–30% of patients who test positive for the hepatitis C antibody do not have chronic hepatitis C.^{2,3} A positive anti-HCV may be a false positive result or indicate prior infection in a patient who has spontaneously cleared the virus. The chance of having chronic hepatitis C with a positive hepatitis C antibody is higher if a risk factor(s) for hepatitis C is identified, such as a history of intravenous drug use or blood transfusion. False positive anti-HCV is more common in patients without risk factors where there is a low prevalence of disease. Radioimmunoblot assays (RIBA) were commonly used before the availability of polymerase chain reaction (PCR) for hepatitis C RNA. RIBA is rarely used now that PCR is available. RIBA may be useful in distinguishing false positive from true positive ELISA tests in

patients who test antibody-positive with ELISA and have undetectable serum HCV RNA by PCR.

Acute hepatitis C is very rarely encountered because it is usually asymptomatic, and blood products are screened for antibodies to HCV. In contrast, patients with acute hepatitis B may seek medical attention because they are more likely to develop symptoms, such as malaise, nausea, or jaundice. Symptomatic exacerbations in patients with hepatitis B can be a harbinger of spontaneous seroconversion and subsequent termination of the replicative state. Therefore, a 6-month period of observation may be considered before recommending therapy for patients with well-compensated chronic hepatitis B. Exacerbations of chronic hepatitis B can usually be distinguished from acute hepatitis B by the absence of IgM anti-HBc in chronic infection. However, reactivation of chronic hepatitis B infection in patients with chronic infection can be associated with detectable serum IgM anti-HBc.

DIAGNOSIS

Chronic hepatitis is often discovered incidentally, with a positive serologic test during blood donation, during routine office visit, an employment or life insurance screening, or in patients with elevated serum aminotransferase levels. Symptoms are frequently absent, even with advanced liver

disease. Nonspecific complaints such as fatigue, weakness, or anorexia may occur, but these correlate poorly with the severity of the disease.

Correctly interpreting hepatitis B and C serology is essential in making an accurate diagnosis (Table 66-1). Serologic diagnosis of chronic hepatitis B or hepatitis C is usually straightforward, but not all patients with persistently elevated aminotransferases and HBsAg or anti-HCV in serum have chronic hepatitis. A patient may have a false-positive serologic test for anti-HCV or spontaneously cleared hepatitis C and remain positive for anti-HCV. A patient may be mistakenly diagnosed with chronic viral hepatitis when his or her aminotransferase elevations are due to another cause, such as nonalcoholic fatty liver disease or alcoholic liver disease. Because multiple potential causes of persistent liver inflammation or elevated serum aminotransferases can coexist, it is essential to arrive at a firm diagnosis before initiation of therapy. Thus, testing for virus in serum is essential using PCR. Hepatitis B DNA and hepatitis C RNA can be measured in serum using PCR, which is now widely available. The presence of hepatitis C RNA in the serum indicates chronic infection with hepatitis C, whereas the presence of hepatitis B DNA in the serum may indicate acute or chronic infection. It is the presence of hepatitis B surface antigen in the serum for more than 6 months that defines chronic infection with hepatitis B.

Table 66-1. Blood Tests for Hepatitis B and C

Test	Interpretation
Hepatitis B surface antigen	Either acute infection or chronic infection if present for >6 mo
Hepatitis B surface antibody	Indicates immunity
Hepatitis B e antigen	Indicates infectivity and replication
Hepatitis B e antibody	Usually indicates patient has low level of infectivity and replication unless patient has precore mutant virus
Hepatitis B core IgM antibody	Acute hepatitis B infection or reactivation of chronic hepatitis B
Hepatitis B core total antibody	Indicates prior infection
Hepatitis B DNA	Typically measured with PCR, if greater than 100,000 copies/mL patient should be considered for treatment
Hepatitis C antibody (ELISA)	Indicates prior infection or current infection or false-positive test
Hepatitis C RNA	Typically measured with PCR, any level indicates chronic infection and patients should be considered for treatment. An undetectable level indicates patient may have spontaneously cleared virus or false-positive antibody test
Hepatitis C genotype	6 genotypes. Genotype 1 most common in United States and most difficult to treat

IS A LIVER BIOPSY NECESSARY?

Previously, a liver biopsy had been considered essential before initiation of antiviral therapy. With the recent development of accurate and sensitive assays for the presence of viremia (HBV-DNA, HCV-RNA), however, recommendations on pretreatment biopsies are now individualized. A liver biopsy before initiation of therapy allows for histologic confirmation of chronic viral hepatitis and exclusion of other causes of liver inflammation. In addition, histologic grading and staging of hepatic inflammation and fibrosis are used to provide prognostic information and to establish the relative urgency for therapy. These benefits must be weighed against the costs and potential morbidity associated with the procedure. In general, liver biopsy is very safe and associated with very low rates of complications, such as bleeding.⁵ In patients with significant coagulopathy, such as hemophilia A, or coagulation defects associated with advanced liver disease, the risks of a biopsy may outweigh the potential benefits. In this situation, treatment without a biopsy may be appropriate. Commercially available blood tests are available that claim to correlate with the amount of fibrosis on liver biopsy.⁶ These blood tests for liver fibrosis have not replaced liver biopsy but may be a useful alternative in patients at high risk for complications from a liver biopsy.

The rationale behind performing a pretreatment liver biopsy may vary depending on the hepatitis virus involved and has evolved with the ability to measure virus in the serum.⁷ Liver biopsy may not be necessary with chronic hepatitis B because the decision to treat is not only based on the histologic severity of inflammation or stage of the disease. The presence of ongoing viral replication and alanine aminotransferase levels are important determinants for therapy.

In contrast, histologic criteria determined from liver biopsy may play a greater role in guiding therapeutic recommendations for patients with chronic hepatitis C, specifically patients with genotype 1. Patients with no fibrosis may defer treatment, but they should be made aware that individuals with mild chronic hepatitis are more likely to respond to treatment with pegylated interferon and ribavirin than patients with cirrhosis.⁸ Although response rates are lower in patients with cirrhosis, antiviral therapy can be effective in 20–30% of cirrhotic patients, and patients with advanced liver fibrosis may have the most to gain from therapy.⁹ A liver biopsy may not be necessary in patients with chronic hepatitis C who have genotype 2 or 3 because response rates are high and the biopsy may not change the decision to treat.

BIOLOGY OF INTERFERONS

There have been continued advances in the treatment of chronic HBV and HCV. Chronic HBV was initially treated with alpha interferons. The development of oral agents active

against HBV became a much more attractive alternative to IFN- α because they are associated with fewer side effects and do not require subcutaneous injection. IFN- α monotherapy was initially used to treat chronic HCV infection until the addition of ribavirin was shown to improve efficacy.

Interferons are a group of naturally occurring cytokines that are released in response to viral infections. After binding to specific cell surface receptors, they induce profound antiviral, antiproliferative, and immunomodulatory effects. The viral life cycle is inhibited at several phases, including cell entry, uncoating, RNA synthesis, and protein synthesis. Induction of HLA class I antigens on the liver cell membrane by IFN- α promotes lysis of infected hepatocytes by CD8⁺ cytolytic lymphocytes.¹⁰

Many natural and recombinant interferons have been studied for the treatment of viral hepatitis. IFN- α and IFN- β both bind to the same cell receptor and thus have similar effects. Natural interferons (lymphoblastoid IFN, leukocyte IFN) and recombinant products of one or more IFN- α genes (r-IFN α_{2a} , r-IFN α_{2b} , r-IFN α_{2c} , consensus interferon) all appear to have similar efficacy in clinical trials.¹⁰ Neutralizing antibodies to recombinant interferons may develop during therapy and lead to loss of efficacy. Patients with chronic hepatitis C who develop a relapse during treatment with r-IFN α_{2a} are typically found to have IFN- α binding antibodies. Switching these individuals to natural lymphoblastoid interferon has been reported to rapidly restore a complete response.¹¹ Others have failed to find a significant correlation between the presence of neutralizing antibodies and a loss of IFN- α efficacy.¹²

Adding a polyethylene glycol molecule to IFN- α prolongs the half life of the drug and the need for only once a week dosing. Increased exposure to IFN- α increases the efficacy of the drug in treating chronic hepatitis B or C.^{13–15} Two formulations of pegylated interferon are approved for the treatment of chronic hepatitis C: pegylated interferon alfa-2a (Pegasys, Roche Pharmaceuticals, Basel Switzerland) and pegylated interferon alfa-2b (Pegintron, Schering Plough, Hackensack, NJ). The polyethylene molecule attached to interferon alfa-2a is a 40 Kilodalton (kD) molecule and the polythene ethylene molecule attached to interferon alfa-2b is 12 kD. Both peginterferons are used in combination with ribavirin. There is a clinical trial underway comparing the two formulations of peginterferon in combination with ribavirin.

■ RIBAVIRIN

Ribavirin is a guanosine analog that has antiviral properties against hepatitis C. The antiviral mechanisms of ribavirin are unknown. Ribavirin is an inosine monophosphate dehydrogenase (IMPDH) inhibitor and one proposed mechanism of its antiviral action is that IMPDH is necessary for HCV viral

replication.¹⁶ Other proposed mechanisms of action include modulation of the host's Th1/Th2 response and impairment of viral entry or viral budding. Ribavirin should be used in combination with peginterferon if there are no contraindications to ribavirin because combination therapy is associated with higher response rates in monoinfected and coinfecting patients compared to interferon monotherapy.^{17,18}

THERAPY OF CHRONIC HEPATITIS B

■ INTRODUCTION

Chronic hepatitis B is a major cause of cirrhosis and hepatocellular carcinoma worldwide. Thirty to forty percent of patients with persistent liver inflammation will progress to cirrhosis.¹⁹ Progressive liver injury occurs most rapidly during the phase of active viral replication, marked by the presence in serum of hepatitis B e antigen (HBeAg) and HBV-DNA. Individuals with chronic hepatitis B may experience a spontaneous cessation of viral replication, which is followed by a histologic and biochemical remission of disease. Spontaneous clearance of HBV-DNA (by hybridization assay) and HBeAg from serum, with seroconversion to anti-HBe, occurs at a rate of 10–25% per year. Termination of viral replication is associated with a significant improvement in survival, even in patients with cirrhosis.^{20,21} IFN- α therapy appears to hasten the rate of loss of viral replication. As with spontaneous remissions, successful IFN- α therapy leads to the loss of markers of viral replication, followed by biochemical and histologic improvement. Therapy rarely results in the loss of hepatitis B surface antigenemia.

■ UNMODIFIED AND PEGYLATED INTERFERON- α

Therapy for chronic hepatitis B includes treatment with alfa-interferons or nucleoside analogs that inhibit hepatitis B DNA polymerase and viral replication (Table 66-2). A meta-analysis of 15 randomized controlled studies (837 patients) concluded that approximately one-third of patients treated with IFN- α have a favorable outcome, defined as a sustained disappearance of HBeAg and HBV-DNA from serum.²² Loss of these markers of viral replication occurred significantly more often in those receiving IFN- α than in controls (33% vs. 12% for loss of HBeAg, and 37% vs. 17% for the loss of HBV-DNA). The absolute difference for disappearance of markers of viral replication was about 20%, indicating that only one of five patients benefited from treatment. Higher IFN- α doses were more effective but they were also associated with more side effects.

Because pretreatment host characteristics associated with a response to IFN- α , such as a history of acute hepatitis, high alanine aminotransferase (ALT) levels, and low levels of HBV-DNA are the same characteristics associated with spontaneous seroconversion, it is conceivable that many individuals who

Table 66-2. Treatment for Hepatitis B

Treatment	Outcomes
Lamivudine 100 mg/d orally for 52 wks	Seroconversion ^a : 17% Undetectable HBV-DNA ^b : 44% Histologic response: 52% Resistance: 16%
Adefovir dipivoxil 10 mg/d orally for 52 wks	Seroconversion: 12% Undetectable HBV-DNA: 21% Histologic response: 53% Resistance: 0%
Entecavir 0.1 mg/d orally for 24 wks	Seroconversion: 13% Undetectable HBV-DNA: 26.5%
Pegylated interferon alfa-2b	Seroconversion: 29%
100 μ g SQ/wk for first 32 wks then 50 μ g/wk until end of treatment	Suppression of HBV-DNA: 32% (while on treatment) Histologic response: 22%

^aSeroconversion from hepatitis B e antigen to hepatitis B e antibody.

^bHBV-DNA measured using DNA hybridization assay, which is less sensitive than PCR.

“responded” to IFN- α would have had the same eventual outcome without therapy. After adjusting for the effect of pretreatment variables on IFN- α response rates, a meta-analysis of 10 European trials (751 patients) found that the effect of treatment was less than previously assumed.²³ The rate of disappearance of HBeAg in treated patients was increased but only by a factor of 1.76 compared to untreated patients.

Pegylated interferons are effective against hepatitis B. In 307 hepatitis B-eAg positive subjects randomized to pegylated interferon alfa-2b with or without lamivudine for 52 weeks, loss of e antigen occurred in 36% of subjects treated with peginterferon alfa-2b monotherapy.¹⁵ Subjects treated with peginterferon and lamivudine had a similar response rate at 35%. Interestingly, this is one of the first trials demonstrating differences in response by hepatitis B genotype, with the highest response rate seen in subjects infected with hepatitis B genotypes A or B.

Long-term outcomes following IFN- α therapy have been analyzed retrospectively in a cohort of 103 patients followed for a mean of 5 years after treatment.²⁴ Cumulative clearance of HBeAg was estimated to be 56% after 5 years in IFN- α treated patients compared to 28.1% in a nonrandomized group of controls. Six of the treated patients died of liver failure and two required liver transplantation; all eight had remained persistently positive for HBeAg. In contrast, none of the patients who lost HBeAg developed severe complications

of cirrhosis or required transplantation. Overall survival and survival without complications of cirrhosis were significantly greater in patients who lost HBeAg following therapy. These data strongly suggest that IFN- α therapy improves the outcome of patients with chronic hepatitis B, even in the presence of cirrhosis.

■ PATIENT SELECTION FOR INTERFERON- α THERAPY

The decision to treat a patient with chronic hepatitis B is generally straightforward. Virtually all patients with compensated liver function who have had persistent elevation of serum aminotransferases and ongoing HBV replication should be considered candidates for therapy. The risks of disease transmission and development of hepatocellular carcinoma in individuals with long-standing HBV infection provide a rationale for treatment regardless of the presence of symptoms or the degree of necroinflammatory activity on biopsy. Even patients with mild histologic liver injury are susceptible to spontaneous exacerbations and disease progression, and thus they should be treated. Carriers of hepatitis B surface antigen with persistently normal aminotransferase levels without replication are not currently treated. In the Western world, these individuals have an excellent prognosis and do not require therapy unless there is a reactivation of disease, but surface antigen carriers without replication are at increased risk for hepatocellular carcinoma compared to uninfected individuals.^{25,26} In general, patients with advanced cirrhosis or decompensated liver disease should not be treated with IFN- α but should be considered for treatment with an oral nucleoside or nucleotide inhibitor (see below).

■ PREDICTORS OF RESPONSE

Several patient characteristics correlate with the probability of success with IFN- α therapy in patients with chronic hepatitis B. Individuals with high aminotransferase levels, active liver disease, and relatively low levels of replicating virus in serum respond more frequently, presumably because these features are associated with a greater immune response to HBV infection.²⁷ Poorer results are seen in patients with disease acquired during early childhood and in patients from areas of the world where perinatal transmission is common. Individuals infected early in life with HBV appear to have immune tolerance to the virus, often associated with very high levels of viral replication but normal aminotransferases and minimal necroinflammatory activity on biopsy. Patients with this pattern, which is common where hepatitis B is endemic, rarely respond to IFN- α . Similarly, treatment of individuals who are immunocompromised is rarely successful.

Hepatitis B genotypes have been identified and associated with differences in disease progression and response to

treatment.²⁸ Genotypes A through G represent the different variants, with genotype A most common in the United States, genotype B most common in Western Europe, and genotype D most common in Africa. Genotype A is associated with greater response to treatment with pegylated interferon compared to the other genotypes.

■ PRESCRIBING INTERFERON- α FOR HEPATITIS B

Before the development of pegylated interferons, the unmodified alpha interferons were prescribed for patients with chronic hepatitis B. The recommended therapy consists of 5 million units of IFN- α daily, administered subcutaneously for 4 months. Alternatively, 10 MU of IFN- α can be administered 3 times weekly with equal efficacy. Larger doses appear to be marginally more effective, but they probably do not warrant the additional cost and side effects. Pretreatment with a tapering dose of corticosteroids is not recommended.

Pegylated interferons are the preferred form of interferon for the treatment of chronic hepatitis B because they are administered once weekly. Pegylated interferon alfa-2b is administered at 1.5 $\mu\text{g}/\text{kg}$ for 32 weeks with lamivudine 100 mg/day for 52 weeks. A 48-week course of pegylated interferon alfa-2a 180 μg subcutaneously weekly was associated with 32% rate of hepatitis B e antibody seroconversion.²⁹ The addition of lamivudine to pegylated interferon alfa-2a did not provide any additional benefit.

■ PATTERNS OF RESPONSE TO INTERFERON- α THERAPY

An exacerbation of liver disease, with increases in serum aminotransferases to more than twice the baseline level, may occur during the second or third month of therapy. This flare-up is seen in 25% of patients treated with pegylated interferon.³⁰ Fifty-eight percent of patients with flares due to medication respond to treatment compared to 20% of patients with flares due to virus. It is believed that the flare in aminotransferases indicates lysis of infected hepatocytes by an activated immune system, and it often precedes loss of HBV-DNA. Typically, this “seroconversion hepatitis” is asymptomatic. It should be regarded as a favorable sign and should not prompt discontinuation of therapy unless significant hepatic dysfunction occurs. Following the loss of HBV-DNA from serum (by hybridization assay), most responders have a clearance of HBeAg, seroconversion to anti-HBeAb, and eventual improvement in liver histology. All of these endpoints occur in 80–90% of responders, though loss of HBeAg may be delayed for several months following discontinuation of IFN- α . Retreatment of nonresponders is rarely effective. Only about 7% of responders lose HBsAg from serum in the first year after therapy with peginterferon alpha-2b.^{15,31} In a long-term follow-up study in the United States, however, 65% of patients who lost HBeAg eventually lost HBsAg a mean of

3 years later.^{15,32} In endemic areas, rates of loss of HBsAg have been much lower.^{33,34}

IFN- α responders may not have a durable remission of liver disease. Relapse may occur in 13–16% of patients, typically in the first year following therapy.³⁴ As long as HBsAg persists in serum, minute quantities of HBV-DNA are usually also detectable by the PCR. Following the disappearance of both HBsAg and HBV-DNA by PCR from serum, HBV-DNA may still be detectable in liver and in peripheral blood mononuclear cells. Thus, a potential for late relapse remains, especially in the setting of immunosuppression or chemotherapy. Reactivation of hepatitis B may occur with chemotherapy or immunosuppression leading to symptoms similar to severe acute hepatitis. Prophylaxis with oral nucleoside analog therapy should be strongly considered in patients with chronic hepatitis B who are about to receive chemotherapy, even if the patient appears to be in virological remission.

■ SPECIAL PATIENT CATEGORIES

Hepatitis B cirrhosis

Most studies of IFN- α for chronic hepatitis B have excluded patients with evidence of advanced cirrhosis, such as jaundice, hepatic synthetic dysfunction, ascites, encephalopathy, or variceal hemorrhage. Prescribing IFN- α for individuals with marginal liver function is hazardous, because flares in liver enzymes during seroconversion can lead to decompensation and liver failure. Furthermore, these patients are susceptible to life-threatening infections and intolerable IFN- α side effects. These patients should generally be managed by experienced hepatologists at centers providing liver transplantation. Nonetheless, some Child's class A and B cirrhotics have been successfully treated with low-dose IFN- α , resulting in stabilization of disease.^{35,36} Lamivudine and adefovir appear to be well tolerated in decompensated cirrhosis and are safer alternatives.^{37,38}

■ PRECORE MUTANTS AND DELTA HEPATITIS

The absence of detectable HBeAg in a patient who has high levels of serum HBV-DNA suggests the presence of a precore mutant, an HBV strain with a mutation in the upstream HBeAg reading frame that blocks the synthesis of the envelope protein. These strains, which are often associated with severe liver disease, are prevalent in Mediterranean countries and are becoming more common in the United States. Patients with precore mutants may have higher response rates to IFN- α compared to patients with wild type hepatitis B.^{39,40} Treatment of patients superinfected with the hepatitis delta virus (HDV) with high doses of IFN- α may lead to a gradual normalization

of aminotransferase levels in up to one-half of treated patients.^{41,42} With cessation of therapy, however, relapse is also frequent. Nonetheless, IFN- α therapy or an oral agent is generally advocated for delta hepatitis, as it is often rapidly progressive without therapy.

■ HUMAN IMMUNODEFICIENCY VIRUS COINFECTION

Because HBV and the HIV share routes of transmission, coinfection with both viruses may occur in as many as 10% of HIV-infected individuals. Response to IFN- α is possible if CD4 counts are well preserved, but unfortunately, a high level of HBV replication is common in the setting of immunosuppression, and responses to IFN- α are generally poor. Although HIV infected patients with chronic hepatitis B have lower response rates to interferon, treated patients have a reduced risk for progressing to cirrhosis.⁴³

Administration of lamivudine at doses of 300–600 mg daily as therapy for HIV infection markedly suppresses serum HBV-DNA to undetectable levels. During continued therapy for up to 1 year, breakthrough of viral replication appears uncommon. Mean ALT levels decline significantly, but the effect on disease progression has not been determined.⁴⁴ Thus, lamivudine should be considered in HIV antiviral therapy for individuals coinfecting with HBV, but patients with hepatitis B coinfecting with HIV have lower response rates to treatment and higher rates of resistance to lamivudine on long-term therapy.^{45,46} Tenofovir and emtricitabine have activity against hepatitis B and HIV and are alternatives to lamivudine that should be considered as part of the treatment regimen in patients coinfecting with HIV and hepatitis B.^{47,48}

■ ORAL NUCLEOSIDE AND NUCLEOTIDE ANALOGS FOR CHRONIC HEPATITIS B

Over the last several years, there has been development of oral nucleoside analogs that inhibit hepatitis B replication by inhibiting hepatitis B DNA polymerase (Table 66-2). Progress in the development of animal models and cell culture systems for studying HBV replication has facilitated the identification of nucleoside analogs with activity against hepatitis B. Lamivudine (3-thiacytidine) is a potent inhibitor of HBV replication that causes termination of the nascent proviral DNA chain. Lamivudine is effective in reducing serum levels of hepatitis B DNA initially in almost all patients. Seroconversion from hepatitis B e antigen to antibody occurs in 15–20% of patients, and histologic improvement is seen in 50% of treated patients, but relapse and resistance to lamivudine occurs in 16% of patients at 1 year and 40% on 3 years of therapy.^{49,50} The mutation associated with lamivudine is frequently due to a mutation in the HBV-DNA polymerase termed the YMDD variant.

In a 52-week randomized clinical trial of patients with chronic hepatitis B, 17% of subjects on lamivudine and 6% of subjects treated with placebo seroconverted to hepatitis B e antibody.⁵⁰

HBV-DNA rapidly becomes undetectable in serum but it rebounds promptly after discontinuation of the drug. Patients need to be aware that discontinuation of therapy may result in reactivation and flare of symptomatic hepatitis. Therefore, therapy with oral nucleoside analogs may need to be indefinite in patients who do not seroconvert to anti-HBe.

Famciclovir is a nucleoside analog developed to treat herpesviruses that also have activity against HBV. However, with the development of more effective agents it has virtually no role in the treatment of hepatitis B.

Adefovir dipivoxil is a nucleotide analog approved by the FDA for the treatment of chronic hepatitis B infection that inhibits hepatitis B replication. Initially there was concern of nephrotoxicity associated with adefovir prescribed in patients with HIV, but at lower doses used in hepatitis B nephrotoxicity is rare. Adefovir has been shown to be effective against hepatitis B eAg positive and eAg negative patients.^{51,52} At 10 mg/day histologic improvement and hepatitis B eAg seroconversion have been reported in 52% and 12% of subjects, respectively. Although resistance to adefovir has been reported, it is much less common than resistance to lamivudine.

Entecavir is the most recently FDA approved oral agent for chronic hepatitis B infection; it is effective at reducing serum hepatitis B DNA, and is well tolerated. Entecavir achieved viral suppression in 83.7% of treated patients compared to 57.5% of patients treated with lamivudine.⁵³ Seroconversion of hepatitis B eAg with entecavir is rare.

The strengths and limitations of interferons compared to nucleoside and nucleotide analogs are related to side effects, resistance, and duration of therapy (Table 66-2). It is likely that therapy for hepatitis B will evolve to combination therapy analogous to the approach used in HIV infection.

■ SUMMARY

Treatment of chronic hepatitis B has advanced substantially in recent years. Peginterferon should be considered initially for patients with chronic hepatitis B and replication because of higher seroconversion rates, lower resistance, and a finite duration of therapy compared with oral agents. However, patients may have contraindications to interferon or elect for therapy with fewer side effects. The development of safe and effective oral nucleoside and nucleotide analogs that can chronically suppress HBV replication represents a major milestone in HBV therapy. Therapy for chronic hepatitis B is evolving to combination nucleoside therapy in order to minimize resistance. The role of hepatitis B genotypes is likely to be an important factor in guiding treatment.

THErapy FOR CHRONIC HEPATITIS C

■ INTRODUCTION

In contrast to hepatitis B, there are fewer treatment strategies for hepatitis C. IFN- α or pegylated alfa interferons alone or in combination with ribavirin are the only FDA approved therapy. SVR, defined as undetectable serum hepatitis C RNA by PCR, is the goal of therapy and thought to represent a cure. Marked improvements in SVR rates have occurred over the past decade, with rates of less than 10% seen with interferon monotherapy to rates of 50% with pegylated interferon and ribavirin combination therapy. Selection of candidates for treatment is individualized. Clinicians differ in their views regarding PEG-IFN- α and ribavirin therapy and patients vary in their willingness to receive it. Frequently the decision for treatment is based on the amount of fibrosis on liver biopsy and the hepatitis C genotype.

■ PEGYLATED (PEG) INTERFERON- α AND RIBAVIRIN

Pegylated interferons have largely replaced unmodified interferons for the treatment of hepatitis C. Pegylated interferon with ribavirin has greater efficacy against hepatitis C compared to interferon and ribavirin, specifically in patients infected with genotype 1 (Table 66-3). SVR rates in genotype 1 patients treated with unmodified interferon or peginterferon plus ribavirin increased from 36% to 46% in the pegylated interferon alfa-2a trial and 34–42% in the pegylated interferon alfa-2b trial.^{13,14} An improvement in SVR rates was seen in genotype 2 or 3 infected patients treated with pegylated interferon alfa-2a plus ribavirin compared to unmodified interferon alfa-2a plus ribavirin but not with pegylated interferon alfa-2b plus ribavirin. A clinical trial comparing pegylated interferon alfa-2a to pegylated interferon alfa-2b is currently underway.

■ PREDICTORS OF RESPONSE

Several pretreatment host factors are associated with increased rates of response to IFN- α therapy. Hepatitis C genotype is the strongest predictor of SVR. HCV genotypes 2 or 3, younger age, female gender, lower serum HCV-RNA levels, shorter duration of infection, milder histologic lesions, and smaller body weight are positive prognostic indicators, whereas high hepatic iron concentration, HCV genotypes 1a or 1b, and cirrhosis are negative indicators.^{54–56} Of these variables, viral genotype is the strongest independent predictor of sustained response. Viral genotypes 1a and 1b, which together account for more than 70% of infected patients in the United States, show sustained response rates of 42–46%, whereas rates for genotypes 2 and 3 are approximately 60–80%.^{13,14}

Table 66-3. Sustained Response Rates to Pegylated Interferon and Ribavirin in Monoinfected and Coinfected Patients

Regimen	Sustained Response Rate by Genotype	Dose and Duration
Pegylated interferon alfa-2a + ribavirin ¹³	Genotype 1: 46%	Peginterferon alfa-2a 180 µg SQ q wk + ribavirin 1000–1200 mg/d for 48 wks
	Genotypes 2 and 3: 76%	Peginterferon alfa-2a 180 µg SQ q wk + ribavirin 800 mg/d for 24 wks
Pegylated interferon alfa-2b + ribavirin ¹⁴	Genotype 1: 42%	Peginterferon alfa-2b 1.5 µg/kg SQ q wk + ribavirin 800 mg/d for 48 wks
	Genotypes 2 and 3: 82%	Peginterferon alfa-2b 1.5 µg/kg SQ q wk + ribavirin 800 mg/d for 24 wks
Studies in Patients with HIV and Hepatitis C		
Pegylated interferon alfa-2a + ribavirin ⁷³	Genotype 1: 29%	Peginterferon alfa-2a 180 µg SQ q wk plus ribavirin 400 mg po bid for 48 wks for all genotypes
	Genotypes 2 and 3: 62%	
Pegylated interferon alfa-2a + ribavirin ⁷²	Genotype 1: 14% Nongenotype 1: 73%	Peginterferon alfa-2a 180 µg weekly + ribavirin 600 mg QD for 4 wks then 800 mg/d for 4 wks then 1000 mg/d until completion of study

Thus, viral genotype is useful in deciding to proceed with therapy. A lower threshold may be used to initiate therapy in patients infected with genotype 2 or 3, not only because sustained response rates are higher but also because the recommended duration of therapy is 24 weeks compared to up to 48 weeks for genotype 1 infected patients.

■ PATTERNS OF RESPONSE TO PEGYLATED INTERFERON- α THERAPY

One of the most important predictors of response to treatment with antiviral therapy is the early virologic response (EVR). EVR is defined as undetectable or a 2-log or greater decline in hepatitis C RNA by PCR at week 12 of therapy as compared to baseline. Patients treated with peginterferon plus ribavirin, who achieve an EVR, have an SVR rate of 63–90%,⁵⁷ whereas patients who do not achieve an EVR will rarely achieve an SVR. Of genotype 1 patients who achieve an EVR, 63% reached an SVR. Of the genotype 2 or 3 patients who achieve an EVR, 86% reach SVR.⁵⁷

Biochemical response to antiviral therapy was previously monitored by following serial ALT levels. Patients who respond to therapy with IFN- α typically develop a decline in serum aminotransferases and HCV-RNA levels. Most responders to antiviral therapy have normalization of ALT levels by 8–12 weeks of therapy.⁵⁸ Unlike with HBV, an increase in aminotransferase levels shortly after initiation of IFN- α is not characteristic of HCV treatment. Such a response should lead to discontinuation of therapy and a search for evidence of autoimmune hepatitis. Failure to attain

complete normalization of aminotransferase levels is usually associated with persistence of viremia. Similarly, an elevation of serum aminotransferase levels following an initial normalization indicates a resurgence of viremia. However, the role of ALT in following patients for a virologic response is limited, especially with the widespread availability of PCR assays for measuring HCV-RNA.

Biochemical remission of hepatitis during IFN- α therapy may correlate with histologic improvement, characterized by a reduction in lobular and periportal inflammation. However, sustained normalization of ALT levels during therapy does not always indicate a virologic remission, as evidenced by the high relapse rate following discontinuation of IFN- α .⁵⁹ Even individuals with persistently normal aminotransferase levels following IFN- α are at risk for late relapse. Up to one-fourth of such patients ultimately relapse.⁶⁰

The goal of therapy is to reduce mortality from hepatitis C associated deaths, specifically end stage liver disease and complications from portal hypertension and hepatocellular carcinoma. However, because favorable outcomes from these end points would take decades to demonstrate, eradicating hepatitis C viremia is the end point used in clinical trials. Compelling data have emerged demonstrating that sustained viral responders and even patients treated with interferon who are nonresponders have a significantly lower risk of hepatocellular carcinoma compared to infected, untreated patients.⁶¹

SVR, defined as undetectable HCV-RNA by PCR 6 months after completion of therapy is defined as a cure and seems to be durable. Late relapse, after SVR is achieved, occurs in 5%

of patients 5 years later and 1% of patients with SVR followed for more than 5 years.⁶²

■ PATIENT SELECTION FOR (PEG) INTERFERON- α THERAPY

Consideration of IFN- α therapy is appropriate in all patients with evidence of active HCV infection. Individuals with normal aminotransferase levels may have significant liver fibrosis and should be considered for therapy.⁶³ The decision to initiate therapy should be based on a candid discussion with the patient regarding the natural history of his or her disease, as well as the risks, contraindications, and benefits of IFN- α therapy. In addition to viral load and genotype, the patient's age, medical condition, psychiatric history, and the stage of fibrosis on biopsy are important. Symptoms of chronic hepatitis do not correlate with disease severity or prognosis and should not be used as a guide to treatment.

Patients with cirrhosis on liver biopsy have lower response rates compared to patients with mild liver fibrosis, although they may have the most to gain from therapy. Those with well-compensated cirrhosis should be considered for antiviral therapy because they may respond to treatment.⁹ Young patients have the most potential life-years at stake, and treatment of this subgroup of patients may be most cost-effective.⁶⁴ Consideration of liver transplantation should not be postponed in favor of IFN- α therapy in cirrhotic patient with decompensation.

■ INITIATION OF PEGINTERFERON- α AND RIBAVIRIN THERAPY

Contraindications

Psychiatric symptoms are among the most frequently encountered side effects and uncontrolled depression or suicidal ideation are contraindications to therapy.⁶⁵ Patients with decompensated cirrhosis may develop serious complications with therapy and should not be treated outside of a clinical trial. Patients with hepatitis C on methadone maintenance therapy have been effectively treated with interferon based therapy and should be considered as potential treatment candidates.⁶⁶

■ PEGINTERFERON- α AND RIBAVIRIN SIDE EFFECTS

Side effects of IFN- α therapy occur frequently, but most symptoms are tolerable (Table 66-4). Adverse effects are typically dose-dependent and abate rapidly with reductions in dose or with temporary discontinuation. Only about 5–10% of patients need to stop PEG-IFN- α entirely.^{13,14} Early side effects include fatigue, fever, chills, myalgias, and arthralgias. These flu-like symptoms occur almost universally after the first few doses but administration at bedtime and

use of acetaminophen or ibuprofen help alleviate these effects. Fatigue and irritability may continue throughout therapy. Dose reduction or discontinuation should be considered for significant neuropsychiatric side effects or for symptoms that interfere with the patient's lifestyle. Bone marrow suppression and bacterial infections are potentially life threatening but are rare. Autoimmune thyroid disease develops in about 1–5% of patients and may be irreversible despite discontinuation of IFN- α .⁶⁵ Patients already taking thyroid medication may require adjustments in their dosage. Injection site reactions with erythema and mild tenderness are more common with peginterferons compared to unmodified interferons but rarely require discontinuation or dose modification.

■ MONITORING PEGINTERFERON- α AND RIBAVIRIN THERAPY

Regular follow-up visits are recommended to monitor for side effects and to obtain complete blood counts with differential

Table 66-4. Side Effects of Pegylated Interferons and Ribavirin

Constitutional

- Fever
- Myalgias
- Headache
- Weakness
- Fatigue

Psychiatric

- Anxiety
- Depression
- Insomnia
- Emotionally labile

Hematologic

- Neutropenia
- Hemolytic anemia (ribavirin)
- Thrombocytopenia

Endocrine

- Hypo or hyperthyroidism
- Hyperglycemia in diabetics

Other

- Teratogen (ribavirin)
- Retinopathy (peginterferon)
- Intractable cough
- Rash

and liver tests. Visits are typically scheduled after the first and second weeks of therapy and monthly thereafter. During the first 4 weeks, complete blood counts are obtained weekly or every 2 weeks to monitor for neutropenia. Dose reduction should be considered for platelet counts below 50,000/mL or granulocyte counts below 750/mL. For platelets less than 30,000/mL or granulocytes below 500/mL, treatment should be interrupted until counts return to their baseline levels. Thyroid-stimulating hormone (TSH) levels should be checked at baseline and every 3–6 months on therapy.

Ribavirin

Hemolytic anemia with a 2–4 g/dL decrease in hemoglobin typically occurs after the first 3–6 weeks of therapy. Erythropoietin has been used to help maintain hemoglobin levels and improve quality of life in patients who become anemic while on therapy.⁶⁷ Ribavirin is a teratogen. Therefore, two forms of contraception should be used by sexually active patients. Chronic cough or rash are infrequently seen with interferon or ribavirin but if they do occur and are persistent then the dose of each medication needs to be decreased or discontinued if symptoms persist.

■ PRESCRIBING PEGYLATED INTERFERON- α FOR HEPATITIS C

The most effective FDA-approved regimen of antiviral therapy for HCV is pegylated interferon alfa-2a 180 μ g weekly subcutaneously plus ribavirin or pegylated interferon alfa-2b 1.5 μ g/kg weekly subcutaneously plus ribavirin. The dose of ribavirin is 800–1200 mg/day in divided doses depending upon body weight and genotype. Patients with genotype 1 are treated with 1000–1200 mg/day of ribavirin. Genotype 2 or 3 infected patients are treated with 800 mg/day of ribavirin. Therapy is for up to 48 weeks for genotype 1 patients and 24 weeks for genotype 2 or 3 patients. Patients infected with genotype 1 are monitored with HCV-RNA by PCR every 12 weeks for the first 24 weeks of therapy. Patients with an EVR at week 12 continue therapy, and patients with undetectable serum HCV-RNA at week 24 of therapy complete 48 weeks of treatment. Patients with detectable serum virus at week 24 of therapy discontinue treatment. Increasing the dose of interferon is not justified in individuals who have failed to demonstrate a response at 12 weeks of therapy because it is not associated with increased efficacy in initial nonresponders and higher doses are associated with increased toxicity.⁶⁸ Patients infected with genotype 2 or 3 are treated for 24 weeks, and currently EVR is not used to guide therapy although 4-week viral load identifies patients who are most likely to respond to therapy.⁶⁹

The treatment of patients who did not respond or relapse after treatment with IFN- α monotherapy, IFN- α plus ribavirin, or PEG-IFN- α plus ribavirin has been dis-

appointing. Retreatment of relapsers to IFN monotherapy or combination therapy with peginterferon plus ribavirin may be justified in some patients who are motivated for retreatment who did not experience serious side effects. Retreatment of nonresponders to interferon monotherapy, interferon/ribavirin, or peginterferon/ribavirin is associated with low response rates and is generally not justified.⁷⁰

COINFECTION WITH HIV OR HBV

Hepatitis C is more aggressive and more difficult to treat in patients coinfecting with HIV. It appears that concurrent HIV disease portends a more aggressive course, especially in those with declining CD4 counts, as evidenced by cohort studies of both IV drug abusers and hemophiliacs.⁷¹ Additionally, patients with HCV and HIV have significantly higher viral loads than those with HCV alone.⁷²

Clinical trials in patients coinfecting with HCV and HIV comparing peginterferon alfa-2a plus ribavirin to interferon alfa-2a plus ribavirin demonstrate significantly higher SVR rates with the peginterferon regimen (Table 66-3).^{72,73} In patients infected with genotype 1, the peginterferon/ribavirin regimen results in an SVR of 14–29% compared to 7% with the interferon/ribavirin regimen.^{72,73} However, sustained response rates are lower than those reported in patients with HCV alone.

CD4 counts may drop by approximately 100 cells/cc during therapy. After discontinuation of peginterferon and ribavirin, CD4 counts return to baseline. There is no appreciable effect of peginterferon and ribavirin on HIV viral loads or HIV disease progression.

Concomitant HCV infection occurs rarely in patients with chronic active hepatitis B, and liver disease may be more severe in coinfecting individuals than those infected with a single virus.⁷⁴ Coinfection may lead to the suppression of one virus such that replication of the suppressed virus cannot be detected. Both HCV and HBV viral loads should be measured before therapy in the coinfecting patient. Because pegylated interferon is effective against both hepatitis B and hepatitis C, peginterferon should be considered in combination with ribavirin in coinfecting individuals if there are no contraindications to therapy.

ACUTE HEPATITIS C INFECTION

Patients who develop acute hepatitis C and do not spontaneously clear the virus should be strongly considered for therapy. A compelling study of 44 patients with acute hepatitis C who were treated with standard IFN- α reported that 43 patients cleared virus with therapy.⁷⁵ Patients were treated with IFN- α 5 MU subcutaneously daily for 4 weeks followed by 3 times a week for 20 weeks. Based on these data treatment of acute hepatitis C infection with IFN- α is recommended.

OTHER APPROACHES TO TREATING HEPATITIS C

A variety of agents have been tested for use in HCV, either alone or in combination with IFN- α , including corticosteroids, nonsteroidal antiinflammatory drugs (NSAIDs), acyclovir, ursodeoxycholic acid, thymosin, phlebotomy, and ribavirin monotherapy.^{76–82} Although some of these drugs have shown promise in initial trials, none has emerged as a viable single-agent treatment strategy for HCV. The structure of the HCV protease enzyme has been elucidated.^{83,84} However, trials of protease inhibitors have been discouraging thus far due to the emergence of rapid resistance or associated toxicity.^{85,86} Development of more specific anti-HCV chemotherapeutic agents is anxiously awaited. Phase I and II trials of inhibitors of the HCV protease are underway. The recent development of a transfected cell culture system with genotype 1a hepatitis C should facilitate the development of new drugs and a vaccine.⁸⁷

SUMMARY

Standard or pegylated IFN- α with ribavirin is currently the only approved treatment for chronic hepatitis C infection. Advancements in antiviral therapy over the past decade have increased response rates from 10% to 50%. However, there is a need for more effective, less toxic therapy.

Treatment of chronic hepatitis C before the development of significant fibrosis is probably necessary if the natural history of this condition is to be altered. Patient selection and treatment strategies continue to evolve as additional data become available. The ultimate goal is to develop a vaccine with the potential to eliminate the disease. An effective vaccine exists for hepatitis B and widespread administration of the vaccine has led to reduced rates of hepatocellular carcinoma in Taiwan.⁸⁸ The development of an effective vaccine against hepatitis C has been challenging. Whereas the focus of current clinical research is on combination therapies, major therapeutic advances will probably require development of novel antiviral compounds against enzymes involved in hepatitis C replication.

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Peter A. Rice and H. Hunter Handsfield

INTRODUCTION

Acute arthritis is a common clinical problem, and in some settings disseminated gonococcal infection (DGI) and sexually related reactive arthritis together may account for more than one-half of all new cases of acute nontraumatic arthritis in sexually active young adults.^{1,2} The association of acute arthritis with urethritis in men had been recognized repeatedly from antiquity to the eighteenth century. Gonococcal arthritis and sexually acquired nongonococcal arthritis were characterized as distinct entities after that in the nineteenth and early twentieth centuries. The patient described by Hans Reiter in 1916³ was one of several such cases⁴ that had been reported by then. Owing to revelations of Reiter's human rights record,^{5,6} recently the term reactive arthritis has been adopted to describe variations of the syndrome that had borne his name.

Reactive arthritis is the general term for inflammatory arthritis that follows a localized infection with a number of pathogens, which usually involves a mucosal surface.^{7,8} Reactive arthritis is an immune-mediated aseptic synovitis that may be associated with extra-articular manifestations and affects patients with a specific genetic predisposition. The term reactive arthritis encompasses the disorders commonly referred to as sexually acquired reactive arthritis, reactive spondyloarthropathy, reactive uroarthritis, postgonococcal arthritis, and postdysenteric arthropathy.^{2,7,8} The reactive arthritides occur predominantly in persons of the HLA-B27 haplotype, particularly in whites.

Other sexually transmitted diseases (STDs) associated with acute arthritis include syphilis, lymphogranuloma venereum (LGV), hepatitis B virus (HBV) infection, HIV infection and, rarely, genital herpes, cytomegalovirus, and genital mycoplasma infections. Arthritis may also result from allergic reactions to drugs used in the treatment of sexually transmitted infections.

DISSEMINATED GONOCOCCAL INFECTION

■ ETIOLOGY AND PATHOGENESIS

Neisseria gonorrhoeae is the most commonly recognized sexually transmitted pathogen that causes infective arthritis, and in parts of the United States and Scandinavia it may have been the most common of all causes of infective arthritis during the 1970s and 1980s.^{1,2,9,10} Septic or purulent monoarticular or oligoarticular gonococcal arthritis is often associated with positive synovial fluid cultures for *N. gonorrhoeae*. This form of the disease accounts for less than 50% of cases of disseminated gonococcal infection (DGI), and most patients present with polyarthralgias and tenosynovitis and experience clinical courses that may resolve spontaneously. Although these features might suggest an immunologic pathogenesis,^{11,12} several lines of evidence indicate that this form of DGI, in fact, results from direct synovial or periarticular infection: (1) Gonococcemia is commonly documented; positive blood cultures may occur in up to 50% of patients with tenosynovitis accompanied by polyarthralgias who are examined within 2 days of onset, giving rise to the possibility that the synovium and periarticular tissues may be seeded early in the disease.^{1,10,13–16} (2) Other common systemic manifestations of DGI, including skin and visceral lesions, are more likely due to localized infections at these sites.^{10,11,16–19} (3) *N. gonorrhoeae* is occasionally identified histologically or by immunochemical methods in apparently sterile synovial fluid and periarticular tissues of patients with DGI or in skin lesions.^{16,17} (4) Antimicrobial therapy is often followed by rapid clinical resolution (within 48 hours) of polyarthralgias, consistent with a direct therapeutic effect.^{10,13,14,16,20–23} (5) Finally, attempts to identify circulating immune complexes in patients with DGI have yielded conflicting results. Reduction of complement (presumed to be due to consumption) to subnormal levels is uncommon, although modest decreases in complement may be frequent.^{10,24–26} Nonetheless, the question

of pathogenesis is still not settled, and immune-complex deposition or other immunologic mechanisms may play pathogenic roles in some patients. For example, it has been hypothesized that immune-complex synovitis early in the course of DGI may predispose to later entry of circulating gonococci into the joint space.²⁷ Alternatively, gonococcal cell wall constituents, such as lipooligosaccharide or peptidoglycan fragments, may circulate from the site of a mucosal infection to initiate arthritis in the absence of viable gonococci.²⁸ Host factors and characteristics of *N. gonorrhoeae* that predispose to dissemination are discussed in Chapter 34.

■ EPIDEMIOLOGY

The risk of acquiring DGI in patients with gonorrhea had been estimated to be 0.5–3.0% in the 1970s, depending principally on the regional prevalence of specific strains of *N. gonorrhoeae* that possessed features that enabled them to disseminate,^{10,16,17} as discussed in Chapters 34 and 35. These strains were endemic in the northwestern United States and Scandinavia at that time, where DGI apparently occurred in up to 3% of patients with gonorrhea.²⁹ It is likely that the rate of DGI now is substantially lower at least in part because today such strains are not so prevalent. In the preantibiotic era, DGI was documented primarily in men,³⁰ but studies in the 1960s and 1970s reported a female predominance of 78–97%.^{10,13–16,29,31} A potential explanation for this change may have been a past misdiagnosis of reactive arthritis, which until recently was believed to be uncommon in women. Dissemination of *N. gonorrhoeae* in women may be most probable during menses. Possible explanations include hormonal factors and a more alkaline pH of genital secretions at the time of menses,³² conditions which are permissive to the growth of *N. gonorrhoeae*, and phenotypes of gonococci that may disseminate more readily.³³ Gonococcal dissemination appears to be uncommon in homosexually active men, perhaps because strains of *N. gonorrhoeae* that cause anorectal infection typically lack the features usually associated with DGI strains (Chapter 35).^{34,35}

■ CLINICAL AND LABORATORY MANIFESTATIONS

The musculoskeletal manifestations of DGI are prominent and sometimes have been classified into two stages: a bacteremic stage and a joint-localized stage with suppurative arthritis. Although some cases apparently evolve sequentially from a bacteremic phase characterized by polyarticular involvement and dermatitis to a later oligoarticular stage often with overt septic arthritis,^{1,13,16} an obvious progression from one stage to the other usually is not evident.¹⁰ Whereas a single, hot, swollen joint is characteristic of gonococcal septic arthritis, skin lesions, tenosynovitis, and polyarthralgias are more typical of the bacteremic stage of DGI (Table 67-1).

Table 67-1. Differential Features of Gonococcal and Nongonococcal Bacterial Arthritis

Gonococcal Arthritis	Nongonococcal Bacterial Arthritis
Usually healthy, young adults	Often compromised host, often very young or aged
Tenosynovitis often	No tenosynovitis
Polyarthritis common	Monoarthritis common
Skin lesions in two-thirds	No associated dermatitis
Wrists and small joints common	Large joints predominate
Migratory polyarthralgias	No prodromal joint symptoms
Synovial-fluid cultures usually negative	Synovial-fluid cultures usually positive
Blood cultures rarely positive, except in prodromal phase patients	Blood cultures positive in 50% of patients
Rapid and complete response to antibiotics; synovial-fluid drainage usually unnecessary	Slower response to antibiotics; synovial-fluid drainage important

Painful joints usually include the knees, elbows, and the more distal joints; the axial skeleton is usually spared. About 75% of patients with polyarticular involvement or bacteremia typically have 5 to 40 lesions, including papules, sometimes macules and pustules, often with a hemorrhagic component. Most lesions are painless and are usually unrecognized, except at pressure points or in tightly bound skin, such as the fingertips (Fig. 67-1). Skin lesions appear predominantly on the extremities, sometimes on the trunk and infrequently on the face. Papules or small macules are the most common lesions, followed by pustules; occasionally skin lesions resemble vasculitis. However, all forms of skin lesions have been associated with DGI, including vesicles and bullae (Fig. 67-1) and other lesions that are usually not directly involved with infection such as erythema nodosum or erythema multiforme and urticaria. *N. gonorrhoeae* usually cannot be recovered from skin lesions by culture and lesions sometimes may appear after appropriate antibiotic therapy has been started. Nevertheless, directly cutaneous inoculation as the result of bacteremia is implied as the usual pathogenesis by the frequent ability to identify gonococci in skin lesions by polyclonal fluorescent antibody.¹⁸

Suppurative gonococcal arthritis usually involves one or two joints; the knees, wrists, ankles, and elbows are involved in decreasing order of frequency. Most patients who present with gonococcal suppurative arthritis do so without prior

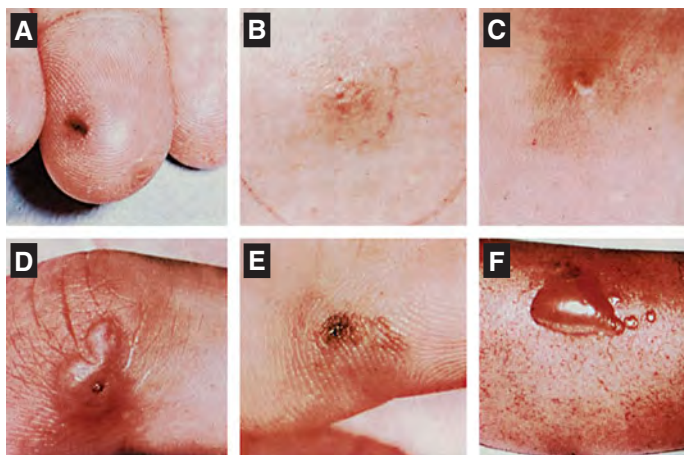


FIGURE 67-1. Characteristic skin lesions of gonococcal bacteremia in various stages of evolution from patients with proved gonococcal bacteremia. **A.** Very early petechia on finger. **B.** Early papular lesion, 7 mm in diameter, on lower leg. **C.** Pustule with central eschar resulting from early petechial lesion. **D.** Pustular lesion on finger. **E.** Mature lesion with central necrosis (black) on hemorrhagic base. **F.** Bullae on anterior tibial surface. (Reprinted with permission from Holmes KK et al. Disseminated gonococcal infection. *Ann Intern Med* 1971; 74: 979.)



FIGURE 67-2. Gonococcal arthritis: dactylitis secondary to gonococcal bacteremia. (Reprinted with permission from HS Lambert et al: *Slide Atlas of Infectious Diseases: Disseminated Infections*. 1982, Fig. 10.46 [Slide 46].)

polyarthralgias or skin lesions. In the absence of symptomatic genital infection, this form of the disease cannot be distinguished from septic arthritis caused by other pathogens. Other joints, such as the sternoclavicular and temporomandibular joints and the small joints of the hands (Fig. 67-2) or feet are occasionally involved. Rarely, direct extension of an infection results in osteomyelitis.²⁰ Synovial fluid leukocyte counts are similar in gonococcal suppurative arthritis compared with septic arthritides caused by other bacteria, typically with 40,000–60,000 cells/mm³, with >80% polymorphonuclear leukocytes.³⁶ Synovial fluid analysis and tests for *N. gonorrhoeae* (ideally, using both culture and DNA amplification) are important in identifying patients with gonococcal septic arthritis.

The concept of sequential clinical stages in DGI has been controversial. Several investigators^{1,13,16} believed that an initial bacteremic phase, typically with polyarticular tenosynovitis and arthralgias accompanied by skin lesions (“arthritis-dermatitis syndrome”²⁹), was followed by a localization of infection in the form of purulent arthritis in one or two joints as bacteremia resolved. Others, however, concluded that there may be too much overlap in these manifestations, and that too many patients presented with septic arthritis as the initial manifestation, to be consistently explained by such a temporal sequence.¹⁰ Although skin lesions are common in patients with tenosynovitis (80%), these may also be found in up to 30% of those with purulent arthritis. Most probably, there is a clinical and pathogenetic continuum of DGI, during which signs of sepsis (fever accompanied by tenosynovitis and skin lesions) may be more prominent earlier in the disease. In addition, some patients have polyarthralgias that resolve spontaneously, and others present with monoarticular septic or purulent arthritis without preceding polyarthralgias or skin lesions. It is also interesting to speculate that geographic differences in the distribution of gonococci with selected genotypic or phenotypic characteristics might have influenced the observations made in the northwestern United States and Scandinavia^{1,13,16} compared with the northeastern United States.¹⁰ Whatever the explanations, it is clear that such clinical progression is by no means universal and may be the exception.

The variable descriptions of the musculoskeletal manifestations in DGI, e.g., the proportions of cases reported to present with tenosynovitis, polyarthralgias without objective inflammatory signs or overt suppurative arthritis, may also be related to differences in the definitions employed by different authors. For example, a common criterion for arthritis requires the demonstration of purulent synovial fluid defined by >25,000 leukocytes/mm³. Using this definition, suppurative arthritis may be less common than tenosynovitis accompanied by arthralgias.¹⁰ Therefore, it remains unclear whether the increased frequency of tenosynovitis is related to a true change in the clinical manifestations or whether it results from a greater appreciation and definition of tenosynovitis instead of classifying all joint inflammation as arthritis. In the preantibiotic era, suppurative arthritis, confirmed by joint aspiration, was reported often; tenosynovitis was reported less frequently.³⁰ Inflamed tendons (tenosynovitis Fig. 67-3) usually cross multiple joints, especially the wrists, fingers, toes, and ankles. The differential diagnosis of the bacteremic stage of DGI includes reactive arthritis, acute rheumatoid arthritis, sarcoidosis, erythema nodosum, drug-induced arthritis, and viral infections (e.g. Hepatitis B and acute HIV infection). The distribution of joint symptoms in reactive arthritis, perhaps the most common differential diagnosis, differs from DGI (Fig. 67-4) as do the skin and genital manifestations.^{37,38}



FIGURE 67-3. Gonococcal tenosynovitis of the left thumb secondary to gonococcal bacteremia. Note erythema and swelling of thenar eminence. (Reprinted with permission from HS Lambert et al: *Slide Atlas of Infectious Diseases: Disseminated Infections*. 1982, Fig. 10.44 [Slide 44].)

Gonococcal endocarditis, rare today,^{39,40} was relatively common in the preantibiotic era, causing about one-quarter of reported cases of endocarditis.^{41,42} Whether this change simply reflects more effective early diagnosis and treatment of DGI or other factors is unknown. Central nervous system infections including meningitis⁴³ and epidural abscess⁴⁴ are also rare. There have been a few reports of a presumed immune-mediated glomerulonephritis secondary to DGI.⁴⁰ Mild hepatitis has been reported in up to 50% of patients with DGI but usually it is not clinically apparent.^{16,45}

Patients in the bacteremic stage of DGI have higher temperatures than those with suppurative arthritis and may have shaking chills, but up to 40% of patients with DGI are reportedly afebrile.^{1,10,12} Most DGI patients deny local genitourinary, rectal, or pharyngeal symptoms, even though genital, anorectal, or pharyngeal gonococcal infection can be identified in 70–80% of patients with DGI or in their sex partners. In a series assembled in Seattle, *N. gonorrhoeae* was identified by culture or by antigen detection using a direct fluorescent antibody test on blood, synovial fluid, or skin lesions in 52 of 102 (51%) subjects with DGI¹; in Boston 23 (47%) of 49 patients were so identified.¹⁰ This observation is at least partly explained by the association of

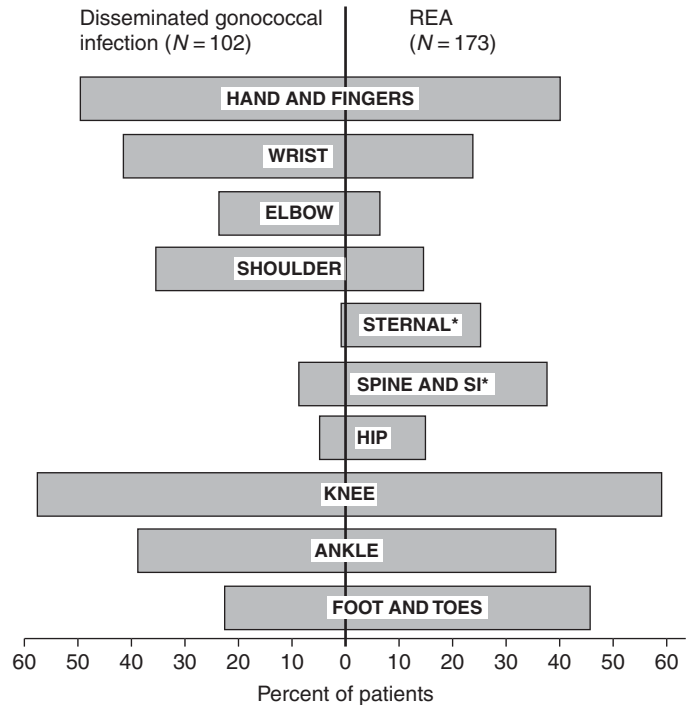


FIGURE 67-4. Distributions of joints with arthritis in 102 patients with DGI¹ and 173 patients with reactive arthritis (REA).³⁷ *Sternal" includes the sternoclavicular joints. *SI denotes the sacroiliac joint. (Reprinted with permission from Kousa M et al. Frequent association of chlamydial infection with Reiter's syndrome. *Sex Transm Dis* 1978; 5: 57.)

selected genotypic and phenotypic characteristics of different strains of *N. gonorrhoeae* with the propensity to cause subclinical mucosal infections, to resist nonimmune serum bactericidal activity, and to cause bacteremia (Chapter 34).

REACTIVE ARTHRITIS SYNDROME

ETIOLOGY AND PATHOGENESIS

The pathogenesis of reactive arthritis is multifactorial and not fully understood. A preceding infection, usually of a mucosal surface, likely serves as a trigger in a genetically predisposed host, and the syndrome may then persist or recur despite eradication of the initial infection.^{2,7,8} Infectious agents that have been implicated include *Chlamydia trachomatis*, *Shigella flexneri*, *Salmonella* spp., *Yersinia enterocolitica*, and *Campylobacter* spp., perhaps *N. gonorrhoeae*, the genital mycoplasmas or other organisms. In several studies, genital *C. trachomatis* infection has been documented in approximately 50% of men with sexually acquired reactive arthritis.^{7,8,37,46} Antichlamydial antibody is common in these patients, usually in higher titer than in patients with uncomplicated chlamydial infection.^{7,46} Enhanced cellular immunity against *C. trachomatis* is also present, as evidenced by increases in lymphocyte-transformation responses to chlamydial antigen.⁴⁶

A few reports have documented the occurrence of reactive arthritis after successful treatment of gonorrhea.^{1,3,47-50} Often associated with postgonococcal urethritis, reactive arthritis is distinct from DGI and may be involved in a syndrome that is accompanied or followed by conjunctivitis or mucocutaneous lesions. Although simultaneous genital infection with *C. trachomatis* may occur in 10–40% of heterosexual patients with gonorrhea, chlamydial infection has not been sought in most reported cases of postgonococcal arthritis. In one report, three patients who developed the typical reactive arthritis syndrome following gonococcal urethritis lacked both culture and serologic evidence of chlamydial infection. Thus, *N. gonorrhoeae* itself may initiate some cases of reactive arthritis.

The failure to demonstrate an immune response to *C. trachomatis* in one-fourth of patients or to isolate any sexually transmitted pathogen from urethral specimens of one-third to one-half of those who had sexually acquired the reactive arthritis syndrome^{37,46} suggests that other infectious agents may sometimes cause urethritis. In some cases of reactive arthritis, urethritis may be noninfective. For example, urethritis occurs in many patients with the enteric form of the disease,^{7,51-53} and recurrence of urethritis may be a part of the late exacerbation of reactive arthritis in the absence of recent sexual exposure.³

How inflammation at a mucosal surface initiates a sustained systemic illness is not completely understood. A commonly accepted hypothesis is that genetically susceptible individuals, particularly those who express certain subtypes of the major histocompatibility-complex class 1 molecule HLA-B27, may develop exaggerated or aberrant immune responses that result in the inflammatory manifestations of reactive arthritis.^{7,53,54} The HLA-B27 haplotype is found in 70–80% of white patients with reactive arthritis,^{46,51,55,56} compared with 6–8% of whites in the general population. In African American patients with reactive arthritis, the reported prevalence of HLA-B27 has varied from 15–75%,⁵⁷⁻⁵⁹ compared with about 2% in African Americans in the general population.⁶⁰ In one small study, 7 of 10 HLA-B27-negative patients with reactive arthritis possessed other HLA antigens that cross-reacted with B27, such as B7, BW22, and BW42.⁵⁷

It has been suggested^{8,57} that HLA-B27, and perhaps cross-reacting antigens, induce recognition of B27 as a foreign antigen,^{61,62} resulting in a self-perpetuating autoimmune process.⁶³ Alternatively, HLA-B27 or related antigens may present bacterial antigenic peptides to disease-causing CD8-positive cytotoxic T lymphocytes.⁶⁴⁻⁶⁶ Another hypothesis suggests that the HLA-B27 antigen itself may be immunologically cross-reactive with certain bacterial proteins.^{67,68} Several such proteins have been identified⁶⁸⁻⁷⁰ (although not in *C. trachomatis*), and perhaps a search of the human and the chlamydial genomes would reveal homologous sequences

encoding for similar proteins. The term heat shock protein (hsp) refers to a family of peptides with considerable homology among bacteria, including *C. trachomatis*. These proteins may incite T-cell-mediated immunopathogenic responses involving local sites (e.g., endometrium and pelvic adnexa) as well as distal sites (e.g., the joints in reactive arthritis). The gene for *hsp60* of *Mycobacterium tuberculosis*, which shares homology with hsp expressed by *C. trachomatis*, when transfected into an HLA-B27 cell line, resulted in the generation of peptide complexes that were shown to be recognized preferentially by antibodies present in HLA-B27-positive reactive patients with arthritis.⁷¹

The HLA-B27 haplotype is not the only determinant of disease expression because no more than 25% of HLA-B27-positive individuals with nongonococcal urethritis (NGU) or shigellosis develop reactive arthritis. However, the initial manifestations of reactive arthritis may be more severe and the natural course more aggressive in persons with the HLA-B27 haplotype than in those without it.^{7,72} Experimental studies have directly implicated the B27 antigen in the disease process. Transgenic rats that overexpress the B27 gene spontaneously develop a disease characterized by diarrhea that is followed by arthritis. Clinical manifestations begin earlier in male rats than in females and are accompanied by genital inflammation.⁷³ Histopathologic examination has shown enthesitis (inflammation at tendon insertion sites) and anterior uveitis.⁷³ Adoptive transfer of bone marrow cells from transgenic rats to normal rats also transfers the disease. The disease cannot be reproduced in this model using athymic (nude) mice,⁷⁴ showing that T lymphocytes (probably CD8-bearing cytotoxic T cells) are critical to its pathogenesis.

Data also suggest that *C. trachomatis* may be directly involved in the pathogenesis of synovitis. The organism can be delivered to the joints from the genital tract via circulating monocytes⁷⁵; monocytes/macrophages are the host cells for *C. trachomatis* during prolonged infection of synovial tissues. Persistence in these cells occurs when the organisms are metabolically active but morphologically aberrant.^{76,77} *C. trachomatis* can enter the persistent state 48 hours after infection of normal human peripheral monocytes, thereupon altering expression of several important genes, including increasing transcription of Chlamydia *hsp60*-encoding genes.⁷⁸⁻⁸⁰ Acute arthritis develops after 1 week or more following genital infection,⁸¹ suggesting that the organism is already in the persistent state when it reaches the joint and that reactive arthritis, even acutely, is elicited by persistent, rather than actively growing, organisms. This observation further suggests that the immunogenic hsp60 protein produced by persistent Chlamydiae is largely responsible for eliciting synovial inflammation in both the acute as well as the relapsing forms of reactive arthritis.

Antimicrobial therapy, though often used, has not generally been clinically beneficial in treating the articular

manifestations in most patients with reactive arthritis that has flared long after the initial infection.⁸² Nevertheless, prompt antimicrobial therapy of chlamydial infection may help prevent reactive arthritis, as suggested by a retrospective review of 224 patients with sexually acquired urethritis or cervicitis.⁸³ In that study, 68 patients were treated for presumed chlamydial infection with tetracycline or erythromycin; acute reactive arthritis developed in 7 (10%) of these patients. The other 156 patients had gonorrhea, or they had no identified pathogen, and were untreated or received only penicillin therapy; 57 (37%) of these patients developed reactive arthritis ($p < 0.001$).⁸³

■ OTHER IMMUNOLOGIC STUDIES IN REACTIVE ARTHRITIS

Many immunologic phenomena have been associated with reactive arthritis, but their importance and pathogenic roles have not yet been well established. Synovial fluid lymphocytes from patients with reactive arthritis may be more reactive than peripheral blood lymphocytes from the same patients when incubated with a variety of potential triggering agents, particularly *C. trachomatis*, or with a number of enteric organisms, *N. gonorrhoeae*, or *Ureaplasma urealyticum*.^{84,85} The ratio of T to B lymphocytes is higher in synovial fluid from patients with reactive arthritis than in synovial fluid from normal controls.⁸⁶ The blastogenic response of circulating lymphocytes to *C. trachomatis*⁴⁶ or *Y. enterocolitica*⁸⁷ in reactive arthritis associated with these pathogens is elevated relative to the response in patients who have chlamydial or yersinial infections without reactive arthritis. CD4-bearing (helper-inducer) lymphocytes outnumber CD8-positive (suppressor-cytotoxic) lymphocytes in the synovial fluid of patients with reactive arthritis, even though stimulation of CD8-positive cytotoxic-cell populations results from antigen presentation by, for example, HLA-B27 class I molecules. Further evidence favoring a pathogenic role of CD8-positive cytotoxic cells is represented by the occurrence of reactive arthritis in AIDS patients who have profound depletion of CD4-positive lymphocytes.⁸⁸ These observations are concordant with those in the athymic (nude) mouse model⁷⁴ and suggest that an intact helper-inducer CD4 system may not be central to the pathogenesis of reactive arthritis.

Immune complexes of the IgG class are present in the blood of up to 76% of patients with reactive arthritis,⁸⁹ and synovial biopsies often reveal exudative synovitis with interstitial and intracellular deposits of IgG, IgA, and the third component of complement (C3).^{90,91} Nonetheless, the clinical features of the arthropathy and the usual absence of glomerulonephritis, vasculitis, and other manifestations of immune-complex deposition suggest that

this mechanism also may not be central to the pathogenesis of this disease.

■ EPIDEMIOLOGY

Epidemiologically, reactive arthritis is characterized by an endemic form, usually sexually acquired, and a less common epidemic form, most often associated with enteric infection. Although endemic reactive arthritis commonly follows sexual contact with a new partner, clear evidence of sexual transmission of individual cases has been uncommon. One report⁹² described the simultaneous occurrence of NGU and reactive arthritis in two HLA-B27-positive men after both had intercourse with the same woman. The enteric form of reactive arthritis typically follows shigellosis,^{2,7,8,53,93} salmonellosis,^{94,95} yersiniosis,^{96–98} or infection with *Campylobacter* spp.⁹⁹ Although sexual transmission of enteric reactive arthritis has not been reported, such cases are likely to have occurred, perhaps especially in men who have sex with men (Chapter 68).

The incidence and prevalence of reactive arthritis is uncertain and may vary geographically.^{2,7,72} In one series reported more than 30 years ago,¹ the diagnosis was made in 16 (11%) of 151 consecutively hospitalized adults with acute nontraumatic arthritis, second in frequency only to DGI as a cause of arthritis (Fig. 67-5). Septic arthritis related to injection drug use has become much more frequent in the past three decades and undoubtedly is now among the most common causes of acute arthritis in young adults. Because a corresponding decrease in DGI cases has occurred during this period, reactive arthritis may now be the most common cause of acute arthritis in young persons who are not injection drug users. The overall risk of acquiring reactive arthritis has been estimated to be 1–3% among men with sexually acquired NGU^{100,101} and among patients with acute shigellosis,⁵⁰ rising to as high as 20–37% for individuals with the HLA-B27 haplotype.^{52,82,101}

Although enterically acquired reactive arthritis may occur in children (in whom infectious diarrhea is most common), most patients are adults. The modal age of patients with sexually acquired reactive arthritis is in the fourth decade, compared with the third decade for patients with DGI and most other STDs. This may be partly because some series have included patients whose reactive arthritis was not sexually acquired or patients with recurrent disease. In most series, 80–90% of patients with reactive arthritis have been whites, and most of the remainder have been African Americans.^{8,58,59,100} Differences in racial susceptibility remain poorly defined because many studies do not report the racial compositions of the patients studied. It is likely that African Americans are less susceptible, however, in part because they have a lower prevalence of the HLA-B27 haplotype than whites.

Enteric reactive arthritis has been recognized to affect women somewhat less frequently than men, with reported

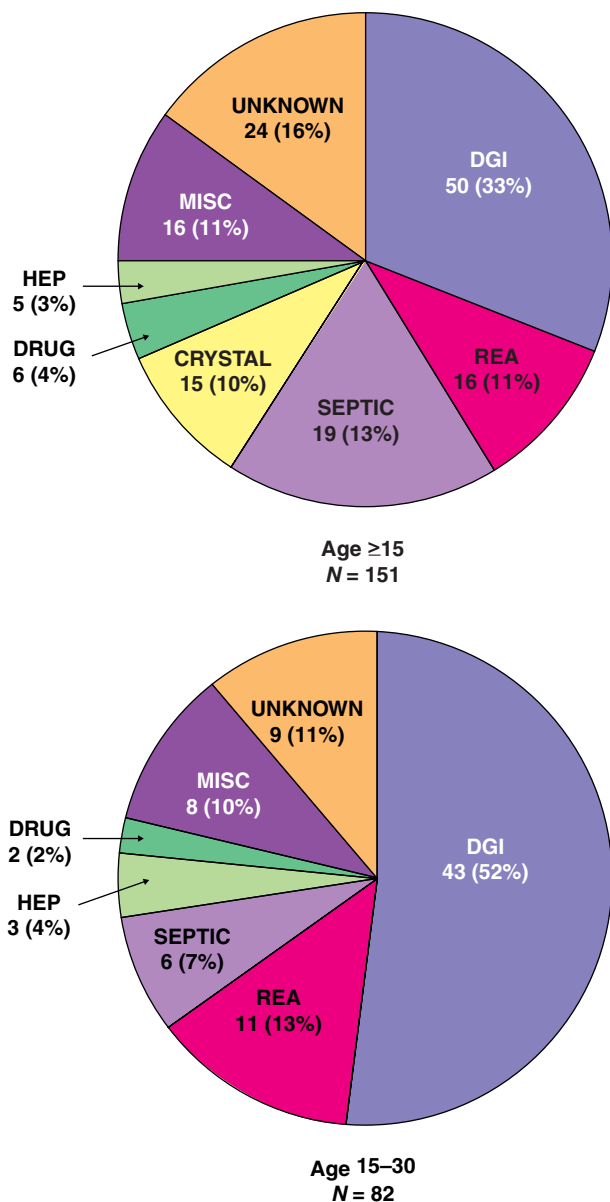


FIGURE 67-5. Diagnosis in 151 consecutive adults (age >15 years) hospitalized in Seattle because of acute, nontraumatic arthritis of <14 days duration. REA (reactive arthritis) includes postgonococcal arthritis; DRUG denotes drug-induced arthritis; HEP denotes hepatitis B infection (From Handsfield HH. Disseminated gonococcal infection. *Clin Obstet Gynecol* 1975; 18: 131.).

male-to-female ratios that vary from 1:1 to 10:1.⁷ Many series of patients with reactive arthritis have been drawn predominantly from male populations (e.g., from military installations, ships' companies, and military or veterans' hospitals). By contrast, few women have been included in most series of sexually acquired reactive arthritis; in one example, women accounted for only 20 (3.6%) of 557 cases.⁷ In another series, however, 13 (52%) of 25 patients with reactive arthritis were women.¹⁰² Clinical presentations of reactive arthritis described in 29 women, as well as their HLA haplotypes and their clinical courses, were reported to be similar to those in men.¹⁰³ Nonspecific rheumatic complaints and overt reactive arthritis

have also been documented in women with histories of salpingitis, gonorrhea, bacterial urinary-tract infection, and trichomoniasis.¹⁰⁴ A high prevalence of musculoskeletal disorders in the sexual partners of men with reactive arthritis was found, and an association of salpingitis with radiologic evidence of sacroiliitis has been reported.^{7,105} These observations suggest that reactive arthritis may be more frequent in women than commonly realized, and that it may be sexually acquired.¹⁰⁶

CLINICAL AND LABORATORY MANIFESTATIONS

The clinical manifestations of reactive arthritis may be accompanied by urethritis and perhaps cervicitis, conjunctivitis, and mucocutaneous inflammatory lesions. Although it is uncommon for all of these manifestations to be observed at the time of presentation, most patients eventually develop all four features, especially if they are HLA-B27-positive.^{51,56,107} Estimated frequencies of these manifestations at presentation and during follow-up are shown in Table 67-2. The articular, mucocutaneous, and ocular manifestations usually follow onset of urethritis or diarrhea by 1–4 weeks, although delays of several months may be seen.^{7,51,53,55} The American College of Rheumatology (ACR) and the Third International Workshop on Reactive Arthritis¹⁰⁸ have established criteria for the diagnosis of reactive arthritis (Tables 67-3 and 67-4). The Third International Workshop proposed that the criteria should include specific clinical features, such as oligoarthritis or asymmetric arthritis of the lower limb, with or without inflammation of tendons or the sacroiliac joint, plus evidence of gastrointestinal or genitourinary infection within the past 4 weeks with known reactive arthritis-inducing organisms. The ACR criteria require the presence of peripheral arthritis occurring in association with urethritis (men) or cervicitis (women), or with conjunctivitis.¹⁰⁹

Urogenital inflammation

Patients with sexually acquired reactive arthritis frequently give histories of recent sexual contact with a new partner, followed by the development of urethritis that is indistinguishable from uncomplicated NGU.^{51,55} Gonococcal urethritis has been reported in up to 20% of patients, but concomitant chlamydial infection has not always been excluded. Furthermore, culture and other tests for *C. trachomatis* may miss infections,^{5,110} and increasingly, studies of reactive arthritis using more sensitive nucleic acid amplification tests of joint fluids and synovial tissues are reporting the presence of Chlamydia.¹¹¹⁻¹¹⁴ Some studies suggested that many patients with reactive arthritis had had nonbacterial prostatitis,^{49,51,115,116} but prostatitis was not always clearly differentiated from urethritis, cystitis, or other forms of lower urogenital tract inflammation.

Urethritis occurs in up to 90% of patients with enteric reactive arthritis^{51,52,96,99} and has been documented in children¹¹⁷

Table 67-2. Frequencies of Clinical Manifestations in Patients with Reactive Arthritis Syndrome

	Percent of Patients	
	Initial Attack ^a	Entire Course ^b
Urogenital Inflammation		
Urethritis (criteria not specified)	85	87
Cervicitis (criteria not specified)	71	NA
Arthritis		
Monoarticular	14	3
Polyarticular	81	86
Arthralgia only	0	9
Sacroiliitis or back pain	49	21
Heel pain	40	Not recorded
Tendinitis or tenosynovitis	25	25
Fusiform dactylitis	17	Not recorded
Ocular involvement		
Conjunctivitis	57	50
Uveitis	0	12
Mucocutaneous involvement		
Balanitis/vulvovaginitis	39	69
Stomatitis	31	17
Keratoderma blennorrhagica	21	18
Nail changes	9	16
Other		
Cardiac	0	9
Neurologic	1	2
Diarrhea	14	12

^aData from Wilkens RF et al. Reiter's syndrome: Evaluation of preliminary criteria for definite disease. *Arthritis Rheum* 1981; 24: 844. (N = 83).

^bData from Kousa M. Clinical observations on Reiter's disease with special reference to the venereal and nonvenereal aetiology: A follow-up study. *Acta Dermato Venereol (Stockh)* 1978; 58(Suppl 81): 1. (N = 173).

Table 67-3. American College of Rheumatology (ACR) Criteria for Reactive Arthritis Syndrome

- Arthritis for greater than 1 month and urethritis (cervicitis) ± conjunctivitis
- Arthritis for greater than 1 month and bilateral conjunctivitis ± urethritis (cervicitis)
- Acute episode of arthritis and conjunctivitis occurring together

Adapted from the *ACR Slide Collection on the Rheumatic Diseases*, 3rd edn. American College of Rheumatology, 2004.

Table 67-4. Third International Workshop on Reactive Arthritis (REA),^a 1995

Peripheral arthritis:
predominantly lower limb asymmetric oligoarthritis ± tendonitis/sacroiliitis
plus
Evidence of a preceding infection:
diarrhea or urethritis (cervicitis) in the prior 4 weeks with a known REA producing organism

^aOther causes of monoarthritis or oligoarthritis excluded.

Adapted from Kingsley G, Seiper J. Third International Workshop on Reactive Arthritis, 23-62 September 1995, Berlin, Germany. *Ann Rheum Dis* 1996; 55: 564

and in sexually inactive adults with enteric reactive arthritis, observations that imply an immunologic pathogenesis of urethritis. Therefore, genital inflammation in reactive arthritis should not always be assumed to be sexually acquired,^{7,8} especially when reactive arthritis follows infectious diarrhea. Nevertheless, the possibility of sexual acquisition should be explored even in these cases, and patients' sexual partners should be examined. Symptoms or signs of urethritis or pyuria have been documented in 30% of women with reactive arthritis^{102,103} but standardized criteria for lower genital tract inflammation often were not used (Chapter 55). A number of studies^{7,104-106} suggest that cervicitis, urethritis, cystitis, and salpingitis may all be important, but the spectrum of urogenital inflammation in women with reactive arthritis remains undefined.

Arthritis

A wide range of articular disease occurs. Asymmetric polyarticular synovitis and tendinitis are often seen initially, followed by persistence of signs and symptoms usually referable to a few joints. Arthritis typically begins in the distal weight-bearing joints (knees, ankles, feet), often with knee effusions and fusiform dactylitis ("sausage digits") (Fig. 67-6). Chlamydial reactive arthritis, which more often encompasses a monoarticular or oligoarticular clinical picture with predominant distal extremity involvement, may differ from nonchlamydial disease, where more joints are involved, usually in the upper extremities.¹¹⁸ Sacroiliitis is common in reactive arthritis, occurring in up to 10% of cases acutely and in higher proportions of those with chronic relapsing reactive arthritis; often it is detected as asymmetric subclinical radiographic abnormalities (Fig. 67-7), especially in sexually acquired cases.^{7,51,118,119} Tendon-insertion sites (entheses) are common sites of inflammation, the basis for the rheumatologic classification of reactive arthritis as an enthesopathy.^{72,120}



FIGURE 67-6. Reactive arthritis (REA): severe chronic swelling of the metacarpalphalangeal and interphalangeal joints, part of the widespread involvement of joints which may occur. (Reprinted with permission from HS Lambert et al: *Slide Atlas of Infectious Diseases: Sexually Transmitted Diseases*. 1982, Fig. 9.12 [Slide 12].)

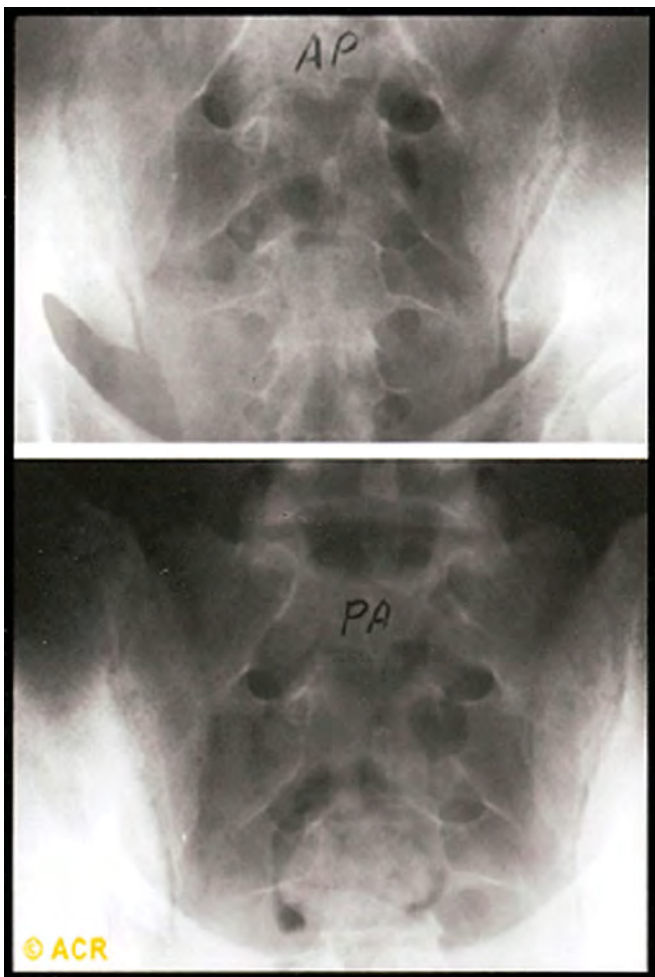


FIGURE 67-7. Reactive arthritis (REA); sacroiliitis: Sacroiliac joints are shown in Ferguson (top view) and posteroanterior projections (bottom). Moderate narrowing and sclerosis appear on adjacent margins of the middle third of the sacroiliac joint on the left; the sacroiliac joint on the right is relatively normal. Asymmetry is more common in reactive arthritis and psoriatic spondylitis than in idiopathic ankylosing spondylitis. (From Berens DL. Roentgen features of ankylosing spondylitis. *Clin Orthop Relat Res* 1971; 74: 20–33.)

Common enthesopathic sites include the insertion of the Achilles tendon and the plantar fascia. In contrast to ankylosing spondylitis and other spondyloarthropathies, spinal involvement is uncommon in reactive arthritis. Radiographic evidence of sacroiliitis has been reported in association with chronic prostatitis¹¹⁵ and salpingitis^{105,106} without other manifestations of reactive arthritis; it remains to be determined whether this represents a variant of reactive arthritis.

Mucocutaneous manifestations

Mucocutaneous lesions are common in sexually acquired reactive arthritis and in disease following shigellosis, but reportedly they are uncommon in reactive arthritis associated with *Salmonella*, *Campylobacter*, or *Yersinia* infections.⁷ These lesions are usually painless and are easily overlooked. Circinate balanitis is the most common cutaneous manifestation, typically occurring in 20–40%⁷ and perhaps up to 85%⁵¹ of men with sexually acquired reactive arthritis. In uncircumcised men, circinate balanitis typically appears as a painless, serpiginous, “geographic” dermatitis of the glans penis (Fig. 67-8) and is diagnostic of reactive arthritis. In circumcised men, circinate balanitis often takes the form of hyperkeratotic papules that, except for their location, closely resemble the other characteristic skin lesion, keratoderma blennorrhagica (Fig. 67-9). Erosive vulvitis, perhaps the female equivalent of circinate balanitis, has been documented in some women with reactive arthritis.¹¹⁹

Lesions of keratoderma blennorrhagica can begin as erythematous macules that gradually thicken and enlarge to form hyperkeratotic papules and plaques, sometimes with red halos and occasionally with central clearing. The lesions of keratoderma blennorrhagica resemble those of psoriasis both clinically and histologically, and some well-documented cases of reactive arthritis have evolved to become clinically indistinguishable from chronic psoriatic arthritis.^{7,8,72,121,122} Keratoderma blennorrhagica most commonly involves the



FIGURE 67-8. Circinate balanitis in reactive arthritis (REA).



FIGURE 67-9. Keratoderma blennorrhagica in reactive arthritis (REA). (Reprinted with permission from JS Bingham: *Sexually Transmitted Diseases: An Essential Slide Collection*. 1984, Fig. 13 [Slide 13].)

plantar surfaces of the feet (Fig. 67-9) and occasionally the palms of the hands, but it may occur anywhere. Cutaneous manifestations have been reported to be more common (up to 20%) in patients with sexually acquired reactive arthritis than in those with the enteric form.⁷

In up to 30% of patients with reactive arthritis, especially those with sexually acquired form, shallow, painless ulcers occur on the palate, tongue, buccal mucosa, lips, tonsillar pillars, or pharynx (Fig. 67-10).^{56,123} The nails are involved in up to 15% of patients, manifested by thickening and brown-yellow discoloration due to subungual hyperkeratosis.^{2,3,37,51,56} Erythema nodosum occasionally occurs in reactive arthritis following yersiniosis but seems to be rare in other forms of the disease.⁷

Ocular inflammation

Ocular manifestations occur in up to half of patients with acute sexually acquired reactive arthritis and in up to 90% of cases following shigellosis.⁷ Conjunctivitis, often sufficiently



FIGURE 67-10. Superficial ulcerations of the tongue in reactive arthritis (REA).

mild to escape detection in a cursory examination, is the most common ocular manifestation.^{37,51,56} Iritis or more extensive uveitis ultimately develops in up to 10% of patients,^{2,7,51,56} although these are uncommon at presentation.

OTHER SYSTEMIC MANIFESTATIONS

Acute reactive arthritis is often accompanied by malaise, fever, anorexia, and weight loss. Transient and usually benign electrocardiographic abnormalities, including atrioventricular conduction disturbances, ST-segment elevations or depression, or nonspecific T-wave changes, occur in 9–30% of acute episodes.^{51,124} Complete heart block, myocarditis, pericarditis, acute aortitis with aortic-valve incompetence, and heart failure are rare but well-documented sequelae, especially in sexually acquired cases.^{125,126} Rare complications, each occurring in fewer than 1% of patients, include peripheral neuropathy, hemiplegia, meningoencephalitis, generalized lymphadenopathy, pleuritis, pneumonitis, thrombophlebitis, and amyloidosis.^{2,51}

Laboratory features

Several laboratory abnormalities are common although not specific. The erythrocyte sedimentation rate is typically elevated, exceeding 50 mm/hour in nearly one-half of patients,⁵¹ but the degree of elevation does not correlate with the severity of clinical manifestations. Leukocytosis, with up to 20,000 leukocytes/mm³, and mild anemia are common. Antinuclear antibodies, rheumatoid factor, cryoglobulins, or circulating immune complexes are occasionally present.^{2,7,51} C-reactive protein (CRP) is usually elevated during the acute phase; in one study patients with chlamydial reactive arthritis had lower CRPs than patients with nonchlamydial reactive arthritis.¹¹⁸

Synovial fluid analysis is seldom specific. The results often mimic those of septic arthritis. Leukocyte counts range from 500 to >50,000 cells/mm³ and are >20,000/mm³ in about

50% of patients; differential counts usually demonstrate >90% neutrophils. Decreased viscosity, normal or elevated complement levels, decreased ratio of synovial fluid to serum complement concentration,⁹⁰ and elevated protein levels are common. Synovial fluid glucose levels are usually normal.

Clinical course

Most initial episodes of acute reactive arthritis resolve completely over 2–6 months, but recovery may be delayed for more than 1 year in up to 35% of patients and indefinitely in a few cases.^{7,51} Subsequently, the annual risk of recurrent acute episodes has been estimated at about 15%.^{7,51,100} Recurrences may be manifested by any of the clinical features alone or in combination. In one series of 122 patients followed for a mean of 5.6 years, arthritis persisted or recurred in 83%, urethritis or cervicitis in 42%, ocular disease in 31%, circinate balanitis in 29%, and other mucocutaneous lesions in about 25%.⁵⁵ The severity of functional impairment caused by chronic or relapsing reactive arthritis is variable. In one study, 34% of patients had sustained disease activity; almost 16% required a change of job, and 11% were disabled for further employment.⁵⁵ Other investigators have reported similar rates of persistence or recurrence but with substantially less functional impairment.¹²⁷ Death from reactive arthritis is rare, occurring primarily as the result of aortic valve incompetence,^{125,126} amyloidosis,¹²⁸ or complications of drug therapy.⁵¹

HEPATITIS B VIRUS INFECTION

The occurrence of articular symptoms early in the course of viral hepatitis was first reported by Robert Graves in 1843 and was “rediscovered” in the 1970s.^{129–134} Although HBV may invade the synovium,¹³⁰ several studies have confirmed the pathogenic role of immune-complex deposition in this syndrome. For example, complement levels are low in serum and synovial fluid during active joint inflammation and return to normal as the arthritis abates. Peak serum hepatitis B surface antigen (HBsAg) titers, synovial-membrane and fluid viral antigen, and cryoprecipitates containing HBsAg, complement components, IgA and complement-fixing IgG antibodies, all have been detected during acute arthritis.^{131–133}

Generalized arthralgias occur in up to 50% of patients during the prodrome of hepatitis B. Ten to twenty percent of patients have overt polyarthralgias or polyarthritis, usually with symmetric involvement of the hands, knees, ankles, shoulders, wrists, and feet.^{129–134} A urticarial rash, usually involving the lower extremities, occurs in about 25% of patients with arthralgias and in 50% of those with overt arthritis. Vasculitis is not associated with acute hepatitis B infection but can be seen in the chronic form of the disease

after the development of polyarteritis nodosa. The acute clinical syndrome closely parallels classical descriptions of serum sickness.¹² The onset of overt hepatitis usually coincides with resolution of the musculoskeletal and cutaneous manifestations. Because many patients with hepatitis B are anicteric, laboratory assessment of hepatic function and laboratory tests for HBV infection are indicated for all patients with acute polyarthritis or other manifestations consistent with immune-complex disease, regardless of the presence or absence of jaundice or hepatomegaly.¹³⁴

SYPHILIS

A small minority (probably 1%) of patients with secondary syphilis have overt osseous or synovial involvement.¹³⁵ Acute periostitis, sometimes mimicking acute arthritis, is the most common of these lesions but some cases of true arthritis result from synovial invasion by *Treponema pallidum*, as demonstrated by darkfield examination.¹³⁶ Indirect immunologic mechanisms may be involved in some cases; complement consumption, circulating immune complexes, and immune-complex glomerulonephritis all have been documented in patients with primary, secondary, and congenital syphilis.^{12,137} In late syphilis, acute or chronic arthritis is usually the result of direct spread of infection into the synovial space from adjacent osteomyelitis or periostitis.¹³⁵ The Charcot joint is believed to be traumatic in origin, the indirect result of syphilitic neuropathy and, perhaps, microvascular disease.^{135,138,139} Neuropathic joints almost always involve the lower extremities, although multiple neuropathic joints in the upper limbs and spine were documented in one patient whose occupation required heavy use of the upper body.¹³⁹ A case of vertebral syphilitic osteitis in an adult has also been reported.¹⁴⁰

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum (LGV) occasionally has been associated with a syndrome that resembles serum sickness, including polyarthritis, rash, cryoglobulinemia, and circulating rheumatoid factor.^{141–144} It is uncertain whether direct synovial infection occurs; *C. trachomatis* antigen may have been demonstrated in synovial fluid of patients with LGV,¹⁴¹ but specific identification of LGV strains in synovial fluid has not been reported.

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Rheumatic manifestations occur with modest frequency in persons with AIDS and earlier stages of infection with HIV.^{145,146} Table 67-5 lists the most common conditions seen in these patients. Typical and limited forms of reactive

Table 67-5. Rheumatic Manifestations Associated with HIV Infections

- Reactive arthritis syndrome and spondyloarthritis
- HIV-associated arthropathy
- Psoriatic arthritis
- Lupus-like syndrome
- Myositis
- Nonspecific arthralgia
- Septic arthritis-bursitis

arthritis may be common; these have been documented both in HLA-B27-positive and -negative persons with AIDS.^{147–149} In particular, seronegative spondyloarthritis occurs in patients with advanced AIDS. This condition develops in the face of depletion of CD4-positive lymphocytes, indirectly emphasizing the possible role of CD8-positive cytotoxic T cells and their interaction with HLA-B27.⁸⁸ Most AIDS patients with reactive arthritis exhibit a syndrome that lacks conjunctivitis and urethritis. Asymmetric oligoarthritis is usual, accompanied by enthesitis. Extra-articular features may include circinate balanitis, keratoderma blennorrhagica, and uveitis. In those who develop sacroiliitis or spondylitis, 70% are HLA-B27-positive.^{146,149} The prevalence of rheumatologic manifestations thought to be reactive arthritis in HIV-infected persons varies in different reports and in different demographic groups, however, and it remains a matter of some disagreement. Reactive arthritis has been reported to range from 0.1% to 11% in prevalence. In one prospective study, the prevalence of reactive arthritis was low at the onset of the study (0.5%), and the incidence over the next 5 years was no different in HIV patients compared to an HIV-negative matched cohort.¹⁵⁰

Patients with other HIV-associated arthropathies often present with oligoarticular or polyarticular asymmetric arthritis without extra-articular manifestations. These arthropathies may resemble those of reactive arthritis, rheumatoid arthritis, or psoriatic arthritis. These patients, who are usually men, are often HLA-B27-negative. Significant clinical improvement may occur in response to antiretroviral therapy. In HIV-infected women, the rheumatologic manifestations seem to be less frequent and clinically different than in men. Raynaud's phenomenon and livedo reticularis are the most common features in women, followed by vasculitis, lupus-like syndromes, and myositis.¹⁵¹ The association of psoriasis and psoriatic arthritis with AIDS has also been well recognized.^{152,153} The skin condition may precede AIDS or it may occur at any of its stages, and it may worsen as immunodeficiency progresses.

OTHER STDs ASSOCIATED WITH ARTHROPATHY

Mycoplasma hominis has rarely caused septic arthritis, often in association with postpartum fever and bacteremia.^{154–156} *U. urealyticum* is an occasional cause of acute monoarticular or polyarticular septic arthritis in patients with hypogammaglobulinemia.^{157–160} Herpes simplex virus, Epstein-Barr virus, and cytomegalovirus infections are rarely associated with acute monoarticular arthritis that results from direct synovial infection. However, these infections are more commonly associated with polyarthritis, probably related to circulating immune complexes.^{161–165} Acute arthritis is a major manifestation of chronic meningococemia and may also occur during or following acute meningococemia, which may rarely be transmitted sexually¹⁶⁶; the clinical picture may mimic that of DGI.^{166–170} In addition, acute noninfective arthritis occasionally follows meningococemia. This syndrome is not associated with the HLA-B27 haplotype and probably results from immune-complex deposition. Finally, antimicrobial therapy of STDs occasionally causes allergic reactions manifested by serum sickness-like illnesses with dermatitis, arthralgias, or arthritis-associated with high concentrations of circulating immune complexes.¹²

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute arthritis is broad, but many cases are related to sexually transmitted infections. Fig. 67-5 shows the diagnoses for 151 consecutive adults (age >15 years) who were hospitalized in the 1970s for acute, non-traumatic arthritis or tenosynovitis of 14 days duration.¹ DGI was documented by isolation of *N. gonorrhoeae* from 38 patients (25%) and was suspected on the basis of clinical features and response to antibiotic therapy in 12 others (8%). Sixteen patients (11%) had reactive arthritis, including postgonococcal arthritis; none of these had symptoms or signs of enteritis. None of five patients who had arthritis associated with acute HBV infection gave histories of drug injection use, and arthritis in two of six patients was attributed to reactions to antimicrobial agents used to treat gonorrhea. Thus, 73 (48%) of the patients in this series had arthritis that was directly or indirectly related to an STD. Among the subset of 82 patients who were 15–30 years of age, 43 (52%) had DGI and 58 (71%) were related to sexually transmissible infections. In recent years, however, the decreasing incidence of gonorrhea and the marked decline in prevalence of gonococcal strains that are likely to disseminate have reduced the frequency of DGI in many geographic areas. Nevertheless, in most settings the proportion of acute arthropathy that is directly or indirectly due to an STD undoubtedly remains high. Sexually active younger persons (e.g., ≤40 years) in particular who present with new onset of unexplained

arthralgia or arthritis should routinely be evaluated for common STDs. Infection with HIV should also be considered in persons who present with otherwise unexplained acute arthritis.

Reactive arthritis and DGI probably remain the two most common causes of sexually acquired arthritis and either may present with a combination of arthropathy, genitourinary inflammation, dermatitis, and conjunctivitis or iritis. Sometimes this poses a diagnostic dilemma, but in most cases, the correct diagnosis can be made readily using clinical criteria. The two syndromes can usually be differentiated from one another by their characteristic mucocutaneous lesions, if present. Several surveys have documented differing predilections of reactive arthritis and DGI for various joints or groups of joints, but the overlap in affected joints is considerable (Fig. 67-4) so that the pattern of joints involved is nonspecific. The exceptions are sacroiliitis, typical fusiform dactylitis (Fig. 67-6), or calcaneal enthesopathy, which are common in reactive arthritis and have not apparently been observed in patients with DGI.^{51,120} Tenosynovitis is often considered evidence for DGI, but it may also be the sole feature in reactive arthritis and does not reliably distinguish DGI from reactive arthritis or other acute arthritides. The presence of NGU, conjunctivitis, or radiographically confirmed sacroiliitis almost always indicates reactive arthritis rather than DGI.

Genital, anorectal, or pharyngeal gonococcal infection can be identified in 70–80% of patients with DGI or in their sex partners, but it has also been documented in up to 20% of patients with the initial presentation of reactive arthritis.⁵¹ These proportions might be higher with more sensitive DNA amplification tests, but no data have been reported. All potential mucosal sites of infection should be tested for gonococcal and chlamydial infection, regardless of the presence or absence of local symptoms. *N. gonorrhoeae* was identified by culture or by the direct polyclonal fluorescent antibody test in blood, synovial fluid, or skin lesions of 52 (51%) of 102 patients with DGI in a Seattle series and in 23 (47%) of 49 patients studied in Boston.¹⁰ Recent sex partners should also be examined; DGI is sometimes confirmed bacteriologically only by detection of gonorrhea in a partner.^{1,171} Similarly, *C. trachomatis* should be sought in patients with reactive arthritis and their sex partners.

Synovial-fluid analysis and tests for *N. gonorrhoeae* (ideally, both culture and DNA amplification) are important in distinguishing patients with crystal-induced arthritis from those with gonococcal septic arthritis. Other forms of septic arthritis should also be sought routinely with specific tests for other bacteria. Synovial fluid leukocyte and differential counts are useful in establishing the presence of inflammation but do not establish its cause. Protein, glucose, and complement levels provide nonspecific but sometimes useful information. Radiographs of peripheral joints, tests for serum uric acid levels, C-reactive protein, an erythrocyte sedimentation rate

and assays for rheumatoid factor, antinuclear antibodies, complement levels, and circulating immune complexes usually are not indicated as routine tests in acute arthritis, although they may be diagnostic in selected clinical settings. It has been argued that HLA typing is not diagnostically useful¹⁷² because the diagnosis of reactive arthritis is more reliably based on clinical criteria and because the results of typing seldom affect therapy. On the other hand, a positive test may solidify an otherwise equivocal diagnosis of reactive arthritis.¹⁷³

The diagnosis of DGI is unequivocal if *N. gonorrhoeae* is identified in blood, synovial fluid, a skin lesion, or cerebrospinal fluid. The diagnosis is also secure if a mucosal gonococcal infection is documented in the presence of a typical clinical syndrome that responds promptly to appropriate antimicrobial therapy,^{1,22} especially if other causes of acute arthropathy are excluded. The presence of gonorrhea in a sex partner also supports the diagnosis.

As indicated above, the ACR defines reactive arthritis as an episode of peripheral arthritis of >4 weeks duration occurring in association with urethritis or cervicitis or occurring simultaneously with conjunctivitis.⁵⁶ These criteria will accurately classify the majority of patients with sexually acquired reactive arthritis. The occurrence of ocular inflammation or the typical mucocutaneous lesions, documentation of the HLA-B27 haplotype, and clinical or radiologic evidence of sacroiliitis helps to confirm the diagnosis. The pattern of joint involvement and other clinical and laboratory features can help distinguish the reactive arthritides from rheumatoid arthritis and arthropathies due to immune-complex deposition.

Although most cases of DGI and reactive arthritis can be diagnosed by the above criteria, neither set of criteria is completely satisfactory for the initial evaluation of patients presenting with acute arthritis. The criteria for DGI require up to several days to obtain microbiologic results, and those for reactive arthritis may require a month or more of clinical observation. The algorithm illustrated in Fig. 67-11 represents a diagnostic approach to reach a tentative diagnosis at the time of presentation of a sexually active patient with acute arthritis. The algorithm represents the logic used in analyzing the results of the initial clinical and laboratory examinations, not necessarily a procedural sequence. For example, evaluation for genital inflammation is indicated for all patients, regardless of whether a probable diagnosis is reached before the relevant branching point.

Examination for crystals by polarizing microscopy and for bacteria by Gram's stain should be performed on synovial fluid taken from patients with arthritis; occasionally these will lead to an immediate diagnosis. If no synovial fluid is available or its analysis is nondiagnostic, the results of a careful examination of the skin may be helpful. The presence of typical papular, pustular, or hemorrhagic lesions (Fig. 67-1) in various stages of evolution, located primarily on the

Sexually Active Patient with Acute Nontraumatic Arthritis

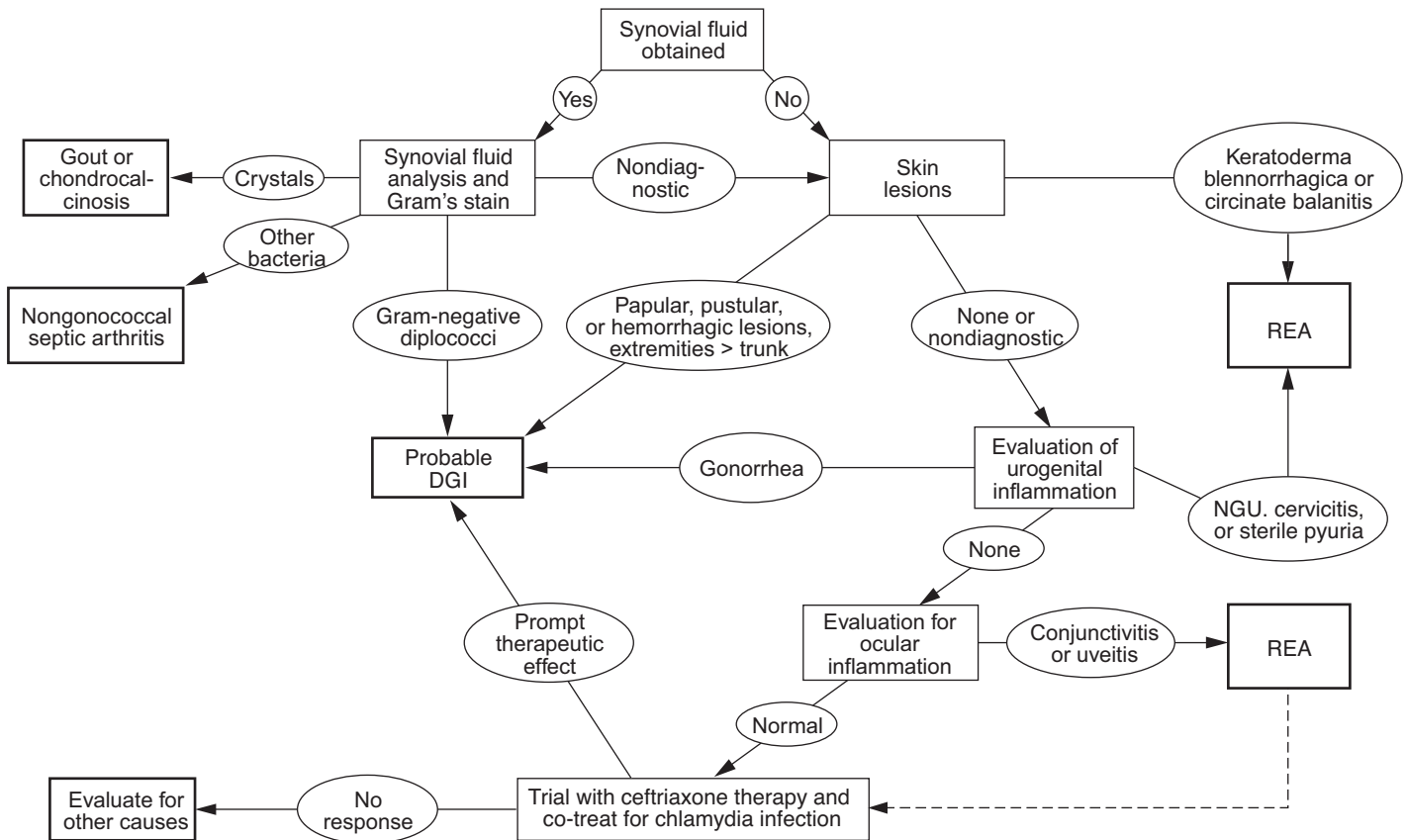


FIGURE 67-11. Algorithm for the presumptive diagnosis of acute nontraumatic arthritis in sexually active patients.

extremities, is strong evidence of DGI. On the other hand, circinate balanitis (Fig-67-8) or keratoderma blennorrhagica (Fig.67-9) in patient with acute arthralgias or arthritis are diagnostic of the reactive arthritis syndrome. In the absence of typical skin lesions, the results of the evaluation for genital inflammation may provide additional support in establishing a diagnosis. Gonococcal urethritis or cervicitis, identified by the presence of intracellular gram-negative diplococci, supports a tentative diagnosis of DGI in these patients; the presence of NGU or other nongonococcal genital tract inflammation implies reactive arthritis. For patients who lack both diagnostic mucocutaneous lesions and urogenital inflammation, conjunctivitis or uveitis may accompany reactive arthritis, although the diagnosis may remain uncertain if ocular inflammation is not present. Regardless of the preliminary diagnosis, it is essential to obtain cultures or other sensitive and specific tests (e.g., nucleic acid amplification tests for *C. trachomatis* and *N. gonorrhoeae*) from the cervix, urethra, and rectum and, in addition, specimens from the pharynx, blood, and synovial fluid for *N. gonorrhoeae*. Other potentially useful tests, not presented in the algorithm, include HLA typing, tests for HIV and HBV infection, and radiographic imaging of the sacroiliac joints.

In some cases, a trial of antibiotic therapy is warranted. Antibiotic-responsive, culture-negative acute arthritis in a sexually active young person may be due to DGI, although probably less frequently than found in older case series when DGI was more common than it is today. Failure of response to treatment at this point necessitates further evaluation for an acute presentation of a connective tissue disorders such as rheumatoid arthritis or systemic lupus erythematosus. Blood cultures must be obtained before the therapeutic trial not only to detect gonococcemia but also to help exclude other septic arthritides and infective endocarditis as a cause of arthritis. If monoarticular arthritis persists during continued observation, synovial biopsy may be required to exclude tuberculosis, fungal infection, or a synovial tumor.

MANAGEMENT

The treatment of DGI is discussed in Chapter 35. Ceftriaxone is the mainstay of antibiotic therapy. DGI may require higher dosages of antibiotics and longer durations of therapy. Hospitalization is indicated when the diagnosis is uncertain, the patient has localized joint disease that requires aspiration, or the patient cannot be relied upon to comply with treatment.

Closed drainage of purulent effusions should be performed once or twice, which is all that is usually necessary. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be indicated to alleviate pain and are often useful to prevent recurrent joint effusions. Open drainage of suppurative joints is rarely necessary^{1,22} but may be needed for joints that are difficult to drain percutaneously, such as the hip.¹⁰ All persons who experience more than one episode of DGI should be evaluated for complement deficiency.

In reactive arthritis, NGU or cervicitis should be treated, usually with doxycycline or azithromycin, as described in Chapter 32. Similarly, antimicrobial therapy may be indicated for infectious enteritis, depending in part on the specific microbial etiology. In most cases, treatment of the triggering infection after the signs and symptoms of reactive arthritis have appeared is unlikely to affect the course of established arthritis, mucocutaneous lesions, or ocular manifestations; the mainstay of treatment is administration of NSAIDs, which are used for control of the articular symptoms of reactive arthritis but do not shorten the course or diminish the extent of disease. Therapeutic trials with different NSAIDs and at different doses may be necessary to balance efficacy and tolerance in individual patients. Corticosteroids do not benefit axial symptoms but may provide short-term relief for peripheral joints particularly when they are injected into the joint(s).¹⁷⁶ Corticosteroids may be useful to treat certain of the extra-articular manifestations such as iritis; topical applications of corticosteroids may be useful for circinate balanitis and keratoderma blenorrhagica.^{174,175} For recalcitrant cases that resist treatment with these drugs, treatment with disease-modifying antirheumatic drugs may be attempted. Sulfasalazine is effective for limited time in some cases, particularly in the treatment of peripheral joints. Methotrexate or other immunosuppressive agents (e.g., azathioprine and cyclosporine) have also been advocated to shorten the duration of symptoms.^{109,175} Treatment with biological tumor necrosis factor antagonists, such as infliximab or etanercept might have promise for the treatment of reactive arthritis in view of their documented efficacy against psoriatic arthritis and other spondyloarthropathies. On theoretical grounds, however, patients with reactive arthritis have lower levels of circulating TNF alpha than patients with other types of spondyloarthropathies^{176,177} (although higher than in normal volunteers¹⁷⁸), and inhibition of this cytokine may not provide the same level of benefit. No control trials have been reported, but a small open label study and case reports have suggested clinical benefit.^{179,180} Most cases of reactive arthritis should be managed in consultation with a rheumatologist.

Arthritis due to HBV infection is self-limited and usually does not require drug therapy, although symptoms may be ameliorated by transient use of aspirin or other nonsteroidal antiinflammatory drugs. Patients with arthritis due to syphilis, LGV, or other sexually transmitted infections

should be treated with standard antibiotic regimens. Arthritis associated with HIV is best managed symptomatically with NSAIDs and may also respond to antiretroviral therapy.

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Anne M. Rompalo and Thomas C. Quinn

Sexually transmitted intestinal syndromes involve a wide variety of pathogens infecting multiple sites of the gastrointestinal tract. Infections of the anus and rectum are frequently sexually transmitted and occur primarily in men who have sex with men (MSM) and heterosexual women who engage in anorectal intercourse. STD pathogens such as syphilis, gonorrhea, condyloma acuminata, lymphogranuloma venereum (LGV), granuloma inguinale (donovanosis), herpes simplex virus (HSV), and non-LGV strains of *Chlamydia trachomatis* have been recognized as causing anorectal infection¹⁻⁶ (see Fig. 68-1). In addition, infections with pathogens that have traditionally been associated with food or waterborne acquisition or with foreign travel (for example, *Giardia lamblia*, *Entamoeba histolytica*, *Campylobacter*, *Shigella*, and hepatitis A) are known to occur via sexual transmission.

Over the past several years, the array of sexually transmitted intestinal disorders has become even more complex, with the recognition of opportunistic infections within the

gastrointestinal tract of patients with acquired immunodeficiency syndrome (AIDS).⁷⁻⁹ Prominent among these infections are *Candida*, *Microsporidia*, *Cryptosporidium*, *Isospora*, *Cyclospora*, *Mycobacterium avium* complex (MAC), and cytomegalovirus (CMV).¹⁰⁻¹² This diverse array of sexually transmitted infections responsible for intestinal disease remains a challenge to the clinician.

DEFINITIONS

Depending on the pathogen and the location of the infection, symptoms and clinical manifestations vary widely. The normal anorectal anatomy is illustrated in Figs. 68-2 and 68-3. The perianal area up to the anal verge is lined by keratinized, stratified squamous dermal epithelium. Thus, perianal lesions caused by syphilis, HSV, granuloma inguinale, chancroid, and condyloma acuminata generally resemble the corresponding lesions as they appear elsewhere in the genital area. The anal canal, which extends 2 cm from the anal verge internally to the anorectal (pectinate or dentate) line, is lined by epithelium which gradually changes from stratified squamous to stratified cuboidal epithelium and is supplied with one of the richest networks of sensory nerve endings in the body. Infection of this area is commonly very painful and results in constipation and tenesmus (ineffectual straining to defecate) due to spasm of the anal sphincter muscle. The external hemorrhoidal venous plexus surrounds the anal verge.

At the anorectal line, the separation of the anal canal from the rectum is indicated by the longitudinal folds called the columns of Morgagni. The internal hemorrhoidal venous plexus occurs at the level of the columns of Morgagni. In this area, the epithelium consists of transitional cuboidal cells, mucus-producing columnar cells, and blind-end crypts.

From the anorectal line cephalad is the rectum, which is lined by columnar epithelium. The term proctitis refers to inflammation of the rectal mucosa. Symptoms include constipation, tenesmus, rectal discomfort or pain, hematochezia (passage of bloody stools), and a mucopurulent rectal discharge which is occasionally misinterpreted by the patient as diarrhea.

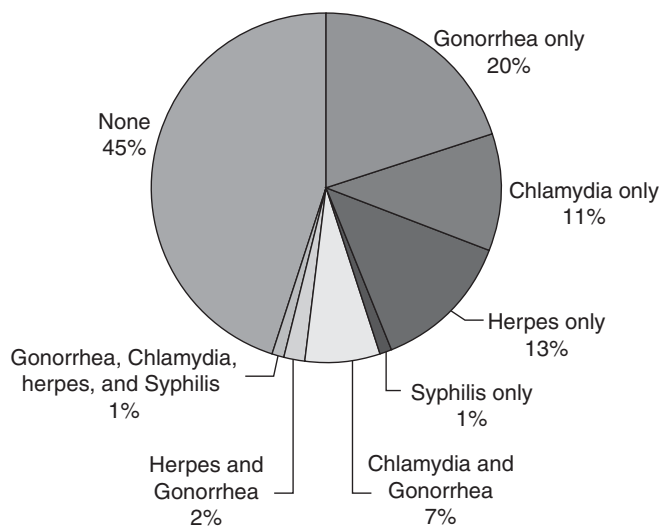


FIGURE 68-1. Frequency of diagnosis of sexually transmitted diseases in male patients with proctitis ($n = 101$), San Francisco City Clinic, 2001–2002. Data are percent of patients. (From Klausner JD, Kohn R, Kent C. Etiology of clinical proctitis among men who have sex with men. *Clin Infect Dis* 2004; 38: 300.)

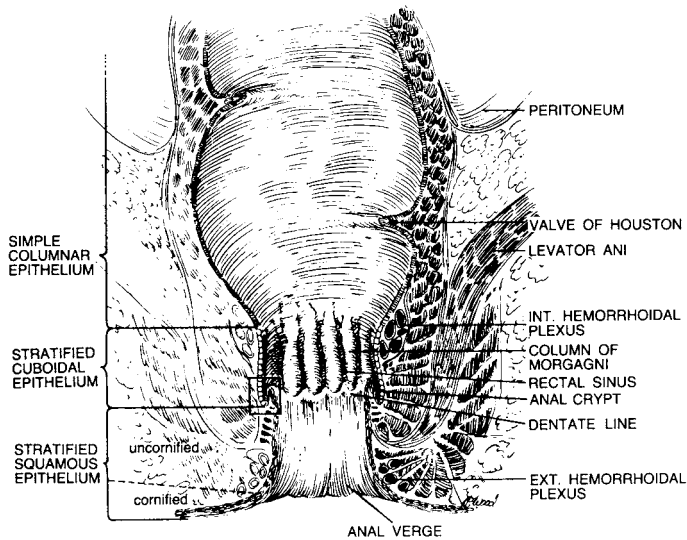


FIGURE 68-2. Diagram of the rectum and anal canal, showing normal anal and rectal structures with the types of epithelium lining the anus and rectum. The box outlining the anal crypt is enlarged in Fig. 68-3.

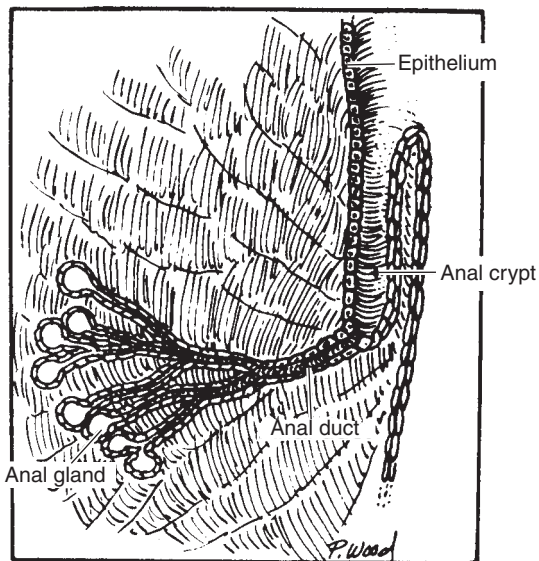


FIGURE 68-3. Diagrammatic representation of the anal crypt. The anal crypts are located along the dentate line and consist of anal ducts which penetrate into muscle. These ducts are lined by both stratified squamous and mucus-secreting cells.

Although stretching of rectal tissue causes pain, the area is insensitive to other direct stimuli such as a rectal biopsy. Hence, infections which involve the rectum but spare the anus are relatively painless. Sigmoidoscopic findings may range from normal mucosa with only mucous present to diffuse inflammation of the mucosa with friability or discrete ulcerations. If these sigmoidoscopic findings are limited to the rectum and further passage of the sigmoidoscope reveals normal mucosa above 15 cm, the condition is properly termed proctitis; if the mucosa is abnormal as high as the sigmoidoscope is passed, the condition probably represents

proctocolitis, which could be confirmed by colonoscopy. Proctitis and proctocolitis generally have different infectious etiologies. Rectal biopsy provides histologic confirmation of proctitis, and findings may reveal nonspecific inflammation or changes highly suggestive of certain infections such as LGV, HSV, or syphilis.¹³

Enteritis is an inflammatory illness of the duodenum, jejunum, and/or ileum. Sigmoidoscopy shows no abnormalities. Infectious enteritis is usually contracted either by ingestion of pathogens present in feces, contaminated water or food, or by certain sexual practices or other forms of human contact which result in fecal ingestion. Symptoms of enteritis consist of diarrhea, abdominal pain, bloating, cramps, and nausea. Additional symptoms may include flatulence, urgency, a mucous rectal discharge, and in severe cases melena. Systemic manifestations such as fever, volume depletion with orthostatic hypotension, acidosis, hypokalemia, malabsorption syndrome, weight loss, and myalgias may also be present. The presence of fecal leukocytes, as determined by Gram stain or methylene blue stain of stool or rectal swabs, usually implicates an invasive inflammatory process but does not differentiate between various sites of involvement of the intestinal tract.

Esophagitis is an inflammatory process of the esophagus which may or may not extend to involve the oral cavity. Infections of the esophagus are most commonly seen in immunocompromised individuals in whom opportunistic pathogens such as *Candida albicans*, CMV, and HSV infections proliferate and induce ulcerations. Symptoms of esophagitis typically consist of dysphagia and odynophagia. Esophograms may reveal irregularity of the mucosa, dilatation, and abnormal motility, and endoscopy frequently reveals either ulcerations or cottage-cheese exudates, depending upon the infecting organism.

ETIOLOGY AND EPIDEMIOLOGY

Microorganisms not requiring an intermediate host may be transmitted by the oral–anal or genital–anal routes.¹⁴ Those pathogens that may cause gastrointestinal illness and have been proven to be or have the potential to be sexually transmitted are shown in Table 68-1. Those enteric pathogens that are infectious at low inoculums, such as *Shigella* (10–100 organisms), *Giardia lamblia* (10–100 cysts), and *E. histolytica* (10–100 cysts), all occur commonly in men who have sex with men (MSM) and are thought to be sexually transmitted through oral–anal sex. Hepatitis A virus appears to be transmitted by oral–anal sex as well.¹⁵

Sexual transmission of enteric pathogens that are shed in feces may be attributable to ingestion of feces during anilingus or during fellatio of a fecally contaminated penis or to direct intrarectal inoculation of organisms by a fecally contaminated penis. Anorectal infection with conventional STD

Table 68-1. Sexually Transmissible Causes of Intestinal or Anal Infections in Homosexual Men

Bacterial pathogens

*Neisseria gonorrhoeae**Neisseria meningitidis**Chlamydia trachomatis**Haemophilus ducreyi**Calymmatobacterium granulomatis*

Treponema pallidum

Group A $\geq\beta$ T-hemolytic streptococci

Enteric bacterial pathogens

Shigella sp.*Salmonella* sp.*Campylobacter* sp.

Fungus

Candida albicans

Protozoa

*Giardia lamblia**Entamoeba histolytica**Dientamoeba fragilis**Cryptosporidium* sp.^a*Isospora belli*^aMicrosporidia^aCyclospora^a

"Nonpathogenic" protozoans Helminths

*Enterobius vermicularis**Strongyloides stercoralis*

Viruses

Herpes simplex virus

Cytomegalovirus^aAdenovirus^a

Human papilloma virus

Human immunodeficiency virus

Hepatitis A and B viruses

^aCommonly seen in HIV-infected homosexual men; not necessarily sexually transmitted.

pathogens in men is caused by rectal intercourse. Fomite transmission may occur with the shared use of unsterile equipment for rectal douching and colonic irrigation, or with use of fecally contaminated sex toys. An outbreak of amebiasis has been traced to use of unsterile equipment for colonic irrigation.¹⁶

In the pre-AIDS era, the role of homosexual transmission of certain enteric infections was recognized with increasing frequency.¹⁷ For example, in San Francisco between 1975 and 1977 the reported cases of amebiasis, shigellosis, hepatitis A, and hepatitis B showed a marked predominance in males between the ages of 20 and 39. Many of these individuals acknowledged MSM contact, including anilingus and fellatio. Fecal cultures of male sexual contacts of men with *Shigella* infection revealed that their contacts were often asymptomatic carriers of *Shigella* of the same serotype. Similarly, several men with *Salmonella* infection reported sexual relations with men who were asymptomatic carriers of the same serotype.¹⁸ A marked predominance of men in this age group was reported for these infections in other parts of the United States as well.^{19–23}

In the post-AIDS era, the incidence of acute, sexually transmitted proctitis and proctocolitis initially decreased steadily until the 1990s, but over the past 5 years sexually transmitted gastrointestinal infections have begun to increase worldwide. For example, the US rates of rectal gonococcal infections decreased dramatically, particularly among MSM from 1985 to 1995, but according to the Centers for Disease Control and Prevention's (CDC) MSM Prevalence Monitoring Project, median gonorrhea positivity rates have increased between 1999 and 2003 from 13.7% to 15.3%.²⁴ Gonorrhea positivity was higher in HIV-positive MSM compared with MSM who were HIV-negative or in those with unknown HIV status: 17.8% versus 12.1%. Recent resurgence in syphilis among MSM has been reported in Western Europe and the United States, with an HIV coinfection rate ranging from 20% in Ireland to nearly 60% in Belgium.^{25,26} In 2004, hepatitis A outbreaks as well as LGV outbreaks among MSM have been reported from several countries.^{27,28} High levels of concurrent STDs have been reported as common among the recent LGV cases. Current surveys report that safer sexual guidelines are not being followed, particularly in the practice of anal intercourse.^{27,28} Other recent reports of sexual behavior among homosexual and heterosexual adolescents, illicit drug users, and heterosexual adults suggest that unprotected anal intercourse is quite common.^{27–30}

Heterosexuals could also be at risk for acquiring enteric infections by anilingus, and women can acquire anorectal STD by anal intercourse.³¹ However, sexually transmitted anorectal infections with *Neisseria gonorrhoeae*, *C. trachomatis*, HSV, and human papillomavirus in women

may also result from contiguous spread of infection from the genitalia.

There are very few reports on the prevalence of anorectal infection with the infectious agents named above in patients seen in the STD clinic setting. In a study of 260 MSM with anorectal symptoms, specific infections, including gonorrhea, syphilis, hepatitis, amebiasis, *Shigella*, and LGV, were present in only 21% of the patients.¹⁷ The remainder had condylomata acuminata, hemorrhoids, “nonspecific proctitis,” and a variety of rectal conditions such as polyps, fissures, fistulas, perirectal abscesses, ulcers, and foreign bodies. However, in a more detailed microbiologic study of 194 MSM presenting to an STD clinic in the pre-AIDS era with anorectal and/or intestinal symptoms, specific anorectal or enteric infections with one or more pathogens were demonstrated in 80%.³² In comparison, significantly fewer MSM without such symptoms who were seen in the same clinic were found to be infected with these pathogens. The prevalence of specific infections in each group is shown in [Table 68-2](#).

The same study examined the association of specific pathogens with specific symptoms and signs ([Table 68-3](#)). Prominent pathogens in patients with symptoms and signs of proctitis were *N. gonorrhoeae*, HSV, *C. trachomatis* (non-LGV), and *Treponema pallidum*. The only pathogen

associated with symptoms and signs of enteritis was *Giardia lamblia*. *Campylobacter* species, *C. trachomatis* (LGV), and *Shigella flexneri* were associated with evidence of proctocolitis. In this study, 22% of symptomatic patients had multiple infections (see [Table 68-2](#)). For example, 48% of patients with anorectal gonorrhea were also found to have one or more additional pathogens present, and four or more pathogens were found in several patients. In the absence of a history of foreign travel, the demonstration of infections with multiple enteric pathogens, including “nonpathogenic” protozoa, should suggest sexual transmission. Histories of homosexual behavior have been recorded in other community outbreaks of shigellosis, giardiasis, and amebiasis.^{21,22,33–35}

In the post-AIDS era, reports of sexually transmitted proctitis and proctocolitis declined markedly, but within the past several years this trend has reversed.³⁶ A retrospective review of cases of clinical proctitis as documented in medical records of men presenting to the San Francisco municipal STD clinic with symptoms of rectal pain, itching, tenesmus, rectal bleeding or discharge was conducted between January 2001 and December 2002. Gonorrhea and chlamydia infections diagnosed using nucleic acid amplification tests (NAATs) were the most common STDs identified, followed by herpes and syphilis.³⁷ Although this is the most recent evaluation published, no other pathogens were tested.

Table 68-2. Infectious Pathogens Identified in 194 Homosexual Men With and Without Anorectal or Intestinal Symptoms

Anorectal and Intestinal Pathogens ^a	Symptomatic group, % (N = 119)	Asymptomatic group, % (N = 75)
<i>Neisseria gonorrhoeae</i>	31*	23
Herpes simplex virus	19*	4
<i>Chlamydia trachomatis</i>	10	5
<i>Treponema pallidum</i>	5	1
<i>Entamoeba histolytica</i>	29	25
<i>Giardia lamblia</i>	14	4
<i>Campylobacter jejuni/C. fetus fetus</i>	7	3
<i>Shigella flexneri</i>	3	1
<i>Clostridium difficile</i> cytotoxin	3	1
Enterovirus (Echovirus 11)	3	1
Patients with any of the above pathogens	80*	39
Patients with more than one of the above pathogens	22*	4

^aOther infectious agents identified were campylobacterlike organisms, nonpathogenic protozoans, *Candida albicans*, *Neisseria meningitidis*, *Ureaplasma urealyticum*, and *Mycoplasma hominis*.

* $p < .05$

Source: TC Quinn et al.²⁵

Table 68-3. Microbial and Symptomatic Correlates of Proctitis, Proctocolitis, and Enteritis Among 65 Homosexual Men with Intestinal Symptoms Who Underwent Sigmoidoscopy to a Distance Above 15 cm

	Proctitis: Sigmoidoscopic Findings Abnormal Only Below 15 cm (N = 41)	Proctocolitis: Sigmoidoscopic Findings Abnormal Beyond 15 cm (N = 15)	Enteritis: Sigmoidoscopic Findings Normal (N = 9)
Sexually transmitted rectal pathogens:			
<i>Neisseria gonorrhoeae</i>	12	0	2
Herpes simplex virus	13	1	0
<i>Chlamydia trachomatis</i> (non-LGV)	8	1	0
<i>Treponema pallidum</i>	6	0	0
Total with any rectal pathogens	33*	2	2
Infectious causes of colitis:			
<i>Campylobacter jejuni/C. fetus fetus</i>	3	4	0
<i>Shigella flexneri</i>	0	2	0
<i>Chlamydia trachomatis</i> (LGV)	0	3	0
<i>Entamoeba histolytica</i>	5(26)*	4(11)	1(8)
<i>Clostridium difficile</i> cytotoxin	1	1	0
Total with any colitis pathogen	8	9	1
Infectious causes of inflammation limited to small intestine:			
<i>Giardia lamblia</i>	2(26)	2(11)	4(8)
Any three of the following four symptoms present: diarrhea, abdominal pain, bloating, nausea	3	8	9*
Any three of the following four symptoms present: constipation, rectal discharge, anorectal pain, tenesmus	38*	7	0

*Figures in parentheses indicate the number of patients who submitted stools for examination for ova and parasites.

* $p < .05$, by multiple logistic regression analysis.

Source: TC Quinn et al.²⁵

IMPACT OF HIV ON SEXUALLY TRANSMITTED INTESTINAL INFECTIONS

Many studies have documented the interaction of HIV with other STDs. HIV transmission has been associated with a history of syphilis and HSV infections, antibodies to HSV-2³⁸⁻⁴¹ and *T. pallidum*,^{42,43} anal warts,⁴⁴ *C. trachomatis*⁴⁵ and *N. gonorrhoeae* genital infection,⁴⁶ and rectal gonorrhea.⁴⁷ Law et al. demonstrated an independent association between HIV seropositivity and histologically diagnosed proctitis in MSM.⁴⁸ Although the association between HIV and other STDs is clear, methodological variables have made it difficult

to determine whether these infections truly facilitate HIV infection or serve as markers for other risk factors such as unprotected anal intercourse which have a significant impact on HIV transmission.⁴⁹

Evidence is accumulating from in vitro data that STD pathogens may directly facilitate HIV transmission. Activation of HIV-1 from latency by coinfection with HSV-2 has been demonstrated. Recently, Ho et al. showed that neutrophils from HIV-seronegative donors induced HIV-1 replication in chronically infected mononuclear cells in the presence of *C. trachomatis*.⁵⁰ Additionally, Moss et al. have shown that successful treatment of gonococcal urethritis is associated with a

twofold reduction in urethral HIV-1 DNA, indicating that treatment of other STDs may decrease HIV-1 transmission.⁵¹

Other STDs may act as cofactors for HIV-1 transmission, and HIV infection may alter the clinical course of a variety of sexually transmitted gastrointestinal syndromes. Anorectal infections appear to have a more aggressive course in HIV-infected patients. Several studies have demonstrated failure of chancroid ulcers to respond to standard therapy,^{52,53} more aggressive course of HSV-2 ulcers with development of giant ulcers,⁵⁴ more rapid progression to neurosyphilis,⁵⁵ atypical clinical and serologic response to syphilis,^{56–58} failure to respond to standard syphilitic therapy,^{59,60} and increased rates of anal intraepithelial neoplasia (AIN) in patients coinfecting with HPV and HIV-1.^{61–64}

Several recent reports of HIV-infected patients referred to colorectal surgery clinics for anorectal diseases from 1983 to 1995 confirm the findings by Quinn et al.^{32,65–68} The majority of these patients were MSM with AIDS. Approximately 63% of these patients had more than one lesion on presentation and 20% had more than one pathogen identified.^{65,66} The authors describe a wide variety of anorectal lesions, including ulcers, condylomas, fissures, fistulas, and abscesses. The most common etiologies were condylomas and CMV and HSV-2 ulcerations. Idiopathic anorectal ulcerations have also been described, usually in patients with CD4 counts of less than 20/mm³. No etiology for the lesions was found after routine microbiologic, sigmoidoscopic, and histological examination. These ulcerations appear less responsive to steroid therapy than was previously reported for idiopathic esophageal ulcers.⁶⁹

The gastrointestinal tract appears to be a major target organ in HIV infection.^{70,71} In MSM the intestinal tract is a primary site of inoculation. Many reports have been recently published documenting intestinal pathology in HIV-infected patients, and the subject has been well reviewed by Smith.⁷² HIV-infected mononuclear cells are found throughout the gastrointestinal tract, and in situ hybridization has detected HIV RNA in presumably neuroendocrine cells from the rectum, duodenum, and esophagus.^{73,74} HIV infection is associated with villus atrophy, with or without crypt hyperplasia, decreased villus surface, dysmotility, decreased level of brush border enzymes, gastric acid secretory failure, and bacterial overgrowth.^{72,75} It is believed that this is the pathogenesis of the chronic, nonbloody diarrhea with weight loss and malabsorption seen in some AIDS patients without detectable pathogens, which has been termed AIDS enteropathy.⁷²

Recent studies indicate that a pathogen is identified in 50–85% of patients with HIV-associated diarrhea.^{76–80} Limited studies evaluating the microbiology of HIV-associated gastrointestinal disease found oral–esophageal candidiasis was evident in 80% of the cases, cryptosporidiosis in 30%, *Isospora* in 10%, and *E. histolytica*, *Strongyloides stercoralis*, *G. lamblia*, *Salmonella*, *Mycobacterium*, and CMV infections in

approximately 5–10% of patients.^{80–82} Evidence of CMV infection of the gastrointestinal tract by culture of biopsy is evident in 30–50% of AIDS patients.^{79,80} Recent studies have suggested that in addition to CMV, other viruses such as adenovirus, astrovirus, and picornavirus may play an etiologic role in diarrhea in HIV-infected patients.^{83–85} Janoff et al. identified adenovirus in 5 of 67 (7.4%) of infected patients with diarrhea compared with none of 10 AIDS patients without diarrhea.⁸³ Grohmann et al. identified astroviruses and picornaviruses in 35% of HIV-infected patients with diarrhea compared with 12% without diarrhea ($p < 0.001$).⁸⁴ Greenson et al. found that microsporidia and MAC are the pathogens most commonly identified following extensive evaluation for occult enteric infection in patients with AIDS.⁷⁷ Kotler et al. found that 62% (27 of 43) of AIDS patients with chronic diarrhea of over 1-month duration had partial villus atrophy with or without crypt hyperplasia on jejunal biopsy.⁸⁶ Seventy percent of these patients (19 of 27) had cryptosporidia or microsporidia identified. The villus architecture was normal in most of the AIDS patients without parasitic infection, even if they had other pathogens such as CMV, bacterial enteritis, or mycobacteria. Extensive *M. avium*–complex (MAC) infection was associated with villus atrophy. Malabsorption, as demonstrated by abnormal d-xylose and C14-glycerol-tripalmitin absorption, is likely due to this derangement of the villus architecture. In addition to protozoan parasites, MAC, and HIV-1, chronic bacterial enteropathy due to adherent bacteria alone may produce these symptoms in up to 17% of AIDS patients.^{86,87}

The prevalence of gastrointestinal symptoms varies with the stage of disease as well as the population at risk for HIV infection. In developed countries, 40–50% of MSM with AIDS have a history of a clinical prodrome characterized by progressive weight loss of >10% of body weight and diarrhea of unexplained origin, while this clinical presentation is much less frequent among intravenous drug users, transfusion recipients, hemophiliacs, and heterosexual partners of other groups at risk for AIDS. In developing countries, gastrointestinal symptoms are observed in over 80% of AIDS patients, perhaps reflecting a greater exposure and susceptibility to gastrointestinal pathogens common to the specific geographic location, as well as less antibiotic therapy.^{81,88,89} Because of the frequency of gastrointestinal complaints in many of these patients, AIDS has been commonly referred to as “slim disease” in many developing countries.

RECTAL GONORRHEA

Klein et al. reviewed the literature on gonococcal infection in women from 1966 to 1977. Rectal gonorrhea was documented in 26–63% (mean 44%) of women with gonorrhea and in 0–20% (mean 4%) the rectum was the only site from which

the organism was isolated.⁹⁰ Rectal gonococcal infection in women may be attributable to receptive rectal intercourse.^{91,92} Historically, in most cases of rectal gonorrhea among women there is no history of rectal intercourse,^{93,94} and the infection is thought to have resulted from contiguous spread of infected secretions from the vagina. However, US survey and other data suggest that, in terms of absolute numbers, approximately seven times more women than MSM engage in unprotected receptive anal intercourse,⁹⁵ and clinicians should query regarding specific sexual acts in order to appropriately direct testing. The clinical manifestations of rectal gonococcal infection in women, therefore, have not been well defined.

The prevalence of rectal infection in MSM attending bath-houses in the pre-AIDS era was between 6% and 8%, and among MSM seen at STD clinics it was between 13% and 45%.^{90,94,95–97} Although prevalence declined steadily during the 1980s, resurgence of rectal gonorrhea has been noted among MSM in several countries as well as in many US cities since the mid-1990s.^{98–102} For example, increases in rectal gonorrhea, unprotected receptive anal intercourse, and multiple, anonymous sexual partners among MSM have been reported in a 12-year trend analysis at the Denver Metro Health Clinic.¹⁰³ In previous studies, the rectum was more commonly found to be infected than the pharynx or urethra,^{104,105} however, recent studies using nucleic acid amplification testing at all exposed sites report high rates of gonorrhea at all sites.^{106,107} Those men identified as sexual contacts for MSM with gonococcal urethritis are usually found to have asymptomatic rectal gonorrhea.¹⁰⁸ However, in MSM who have not been named as gonorrhea contacts and who attend an STD clinic, rectal gonorrhea is more often symptomatic.¹⁰⁹ In 2002, a survey of 564 MSM presenting to the San Francisco City Clinic was conducted before rectal gonococcal culture results were known. Rectal signs and symptoms were determined by clinicians at the time of screening and were defined as rectal discharge, anal fissures, and/or pus identified on anoscopy. Of the 564 men screened, 40 (7.1%) had rectal gonorrhea and 12 of the 40 (20%) had symptoms.¹¹⁰ Behavioral risks for rectal gonorrhea varied significantly by HIV serostatus. HIV-infected MSM engaging in anonymous sex were at highest risk for rectal gonorrhea. Drug use during anal sex was the strongest risk factor for rectal gonorrhea infection among HIV-negative or unknown HIV status MSM. Thus, asymptomatic infection of the rectum constitutes the main reservoir of gonococcal infection in MSM, and screening based on exposure is warranted for both HIV-infected and uninfected individuals as recommended by the US Department of Health and Human Services and the CDC.¹¹¹

Symptoms, when present, develop 5–7 days after exposure. They are usually mild and include constipation, anorectal discomfort, tenesmus, and a mucopurulent rectal discharge which may cause secondary skin irritation resulting in rectal

itching and perirectal erythema.³ Occasionally, the patient may only notice strands of mucus on his stool or small amounts of blood commonly mistaken for hemorrhoidal bleeding. The relatively high rates of asymptomatic infection and coinfection suggest that isolation of *N. gonorrhoeae* from a homosexual man with anorectal symptoms does not prove causation. Although asymptomatic or mild local disease is common, complications such as fistulas, abscesses, strictures, and disseminated gonococcal infection (DGI) may occur. DGI is typically associated with isolation of arginine, hypoxanthine, and uracil (AHU)—auxotypes, and patients with terminal complement component deficiency are at increased risk.^{112,113}

There is also evidence that specific gonococcal strains may cause preferential infection of the rectum. Compared with heterosexuals, MSM are more likely to be infected with strains with the *mtr* mutation, which confers antibiotic susceptibility and is associated with decreased membrane permeability.¹¹⁴ These traits are believed to enhance the ability of this strain to survive in the rectum. A study from the United Kingdom evaluated gonococcal isolates from 383 episodes of infections in women and found one serovar, Bajk, isolated with significantly higher frequency in rectal (27%) than genital (17%) infections.¹¹⁵ In a study of gonococcal infections among MSM in Seattle, utilizing serovar and auxotyping strain typing, Proto/IB-1, Proto/IB-2, and Proto/IB-3 accounted for 70% of anorectal infections among MSM, whereas these same auxotype/serovar classes accounted for only 40% of urogenital gonococcal infections.¹¹⁶ In this same study, the proportion of anorectal isolates that was erythromycin-resistant (48%) was higher than urogenital isolates from men and women (15%).

Findings of rectal gonorrhea during proctoscopy are non-specific and limited to the distal rectum.^{117–119} The most frequent finding is the presence of mucous in the rectum. The rectal mucosa may appear completely normal or demonstrate generalized erythema with localized areas of easily induced bleeding primarily near the anorectal junction. Histologically, abnormal findings are especially prominent at the anorectal junction around the anal crypts and columns of Morgagni.^{117,120} However, only limited histologic studies of gonococcal infection of the distal rectum have been conducted because of the hazards of biopsy of this area with its surrounding venous hemorrhoidal plexus. With gonococcal infection there is patchy disorganization and derangement of these mucus-secreting cells, vascular engorgement, and an infiltration of neutrophils, plasma cells, and lymphocytes throughout the lamina propria.^{117,118} These findings are not pathognomonic and concomitant rectal infection with another pathogen may alter the proctoscopic and histopathologic findings.

Although NAATs are quickly replacing traditional diagnostic methods, diagnosis of rectal gonorrhea is usually made by Gram stain and culture of material obtained by swabbing the

epithelial mucosa of the distal rectal area. In men with anorectal symptoms, the anoscope should be used to examine the rectum and obtain exudate for culture and gram staining. In a study of men with symptomatic rectal gonorrhea,¹²¹ the sensitivity of the Gram stain of rectal exudate for identification of gonococci was 79% when obtained through an anoscope versus 53% for blindly inserted swabs. A positive smear showing intracellular Gram-negative diplococci is usually reliable when the smear has been taken and analyzed properly, and therapy can be instituted while awaiting culture results. In men without anorectal symptoms, a sterile cotton swab can be inserted blindly 2–3 cm into the rectum. Cultures performed on material obtained in this way appear to be as sensitive as cultures performed on material obtained by anoscope.¹²²

The actual sensitivity of a single rectal culture for gonorrhea is unknown and probably is no greater than the estimated 80% sensitivity of a single endocervical culture in women. Quinn et al. noted that the Gram stain missed 7 of 52 (14%) culture-positive infections in MSM. Selective media used to isolate *N. gonorrhoeae* contain antimicrobials active against other bacteria (for example, vancomycin and colistin). Since none of these antimicrobials inhibits swarming *Proteus* species, which are often present in feces, trimethoprim is commonly added to inhibit *Proteus* in selective media used for rectal cultures.¹²³

DNA detection assays are now widely available for detection of gonorrhea in urogenital specimens and are being studied for rectal specimens.^{124–129} A recent study compared ligase chain reaction (LCR) with culture for detecting rectal and pharyngeal gonorrhea in MSM attending a genitourinary medicine clinic in London (ref-comment A19). Duplicate rectal samples were obtained from 227 MSM and the results of LCR and culture were concordant in 219 samples (96.5%). The prevalence of rectal gonorrhea by LCR and culture was 7.0% (16/227) and 4.0% (9/227), respectively. The specificity of rectal LCR was 99.5%.¹²⁶

Quinolone-resistant *N. gonorrhoeae* (QRNG) continues to spread. QRNG is now common in parts of Europe, the Middle East, Asia, and the Pacific. In the United States, QRNG has become increasingly common with reports starting in California and Hawaii.¹³⁰ According to 2006 data from the U.S. Gonococcal Isolates Surveillance Project (GISP) QRNG has continued to increase among heterosexual males as well as MSM and is present in all regions of the country.¹³¹ Therefore, quinolones should not be used for the treatment of gonorrhea among MSM, regardless of site of infection. Current STD treatment guidelines recommended therapy for urogenital gonococcal infection include a single 125 mg intramuscular injection of ceftriaxone which cures 98.9% of uncomplicated urogenital and anorectal infections,¹³¹ or cefixime in a single 400 mg oral dose cures, which cures 97.4% of uncomplicated infections. Cotreatment for chlamydial infection should always be given, if it has not been ruled out by appropriate testing.

Empiric treatment for acute proctitis/proctocolitis syndromes is ceftriaxone 125 mg IM plus doxycycline 100 mg PO twice a day for 7 days.¹³² This regimen offers coverage for the most common sexually transmitted pathogens that cause these symptoms (Table 68-1) and is especially effective against gonorrhea, Chlamydia, and incubating syphilis.

ANORECTAL HERPES SIMPLEX VIRUS INFECTION

Although genital herpes infection is well recognized, and HSV is second only to *N. gonorrhoeae* in frequency of association with proctitis in MSM, there have been few descriptions of anorectal herpetic infections.^{133–139} Clinical description of anal herpes was recorded in 1736 by Astruc, physician to the king of France.¹³⁶ He stated, “[It is] observed in catamites and pathics, if they contract foul ulcers in the anus by the unnatural use of venery; from these ulcers they are tormented by a grievous inflammation upon the extremity of the rectum...hence the evacuation of the faeces becomes difficult and painful.” In one study, 236 MSM with anorectal herpes were seen in one genitourinary medicine clinic in England over a 2-year period.⁵ In two Seattle studies, HSV was cultured from the anorectal area of 32% and 20% of MSM with anorectal symptoms.^{140,141} Limited data are available on the risk of HSV anorectal infection in women. Koutsky et al. recently found serologic or virologic evidence of HSV-2 infection in 47% of 779 women seen at a Seattle STD clinic.¹³⁸ HSV-2 was isolated from the anus or rectum of 26 women (3%). In this study, a history of anorectal intercourse was not more common in women with anorectal HSV than in women with genital HSV infection or no infection. Anorectal herpes is usually acquired by anal intercourse, although oral–anal contact with an individual who has HSV type 1 (HSV-1) infection of the mouth or lips presumably could lead to anorectal infection with HSV-1. In the Seattle studies, 37 of 39 isolates from the rectum were HSV type 2 (HSV-2) and the remaining two isolates were HSV-1.^{3,140}

The complete clinical spectrum of anorectal herpes ranges from asymptomatic shedding to ulcerative proctitis. Clinically, herpes infection may involve the perianal area, the anal canal, and/or the rectum. While symptoms are quite prominent in some cases, many individuals may be totally asymptomatic.¹³⁹ In one study, HSV was isolated from the anal canal of 3 of 75 asymptomatic MSM.³ In a more recent study of HSV-2 seropositive, HIV-negative MSM, 30 men collected daily HSV culture samples from genital, perianal, and oral areas for 100 days and maintained diaries of signs and symptoms.¹⁴⁰ Sixteen men shed HSV-2 (53%) and 9 of 16 (56%) who were HSV-1 seropositive shed HSV-1. HSV-2 shedding was predominantly perianal (83%), while HSV-1 shedding was primarily oral. Thus, asymptomatic anorectal HSV shedding may contribute to transmission of the infection to other individuals.

When symptomatic, anorectal HSV infections may be characterized by severe, often debilitating, anal pain, present in 94% of patients in one study.¹³⁷ Constipation, a nonspecific manifestation of proctitis, is usually present. The occurrence of constipation, anorectal pain, and urinary retention in a homosexual man strongly suggests herpetic proctitis.^{137,139} Samarasinghe et al.⁵ described 11 patients with herpetic proctitis, all of whom developed urinary difficulty of varying severity associated with sacral paresthesias, neuralgia, and impotence. Such symptoms are uncommon with HSV infection of the genitalia, which leads to latent infection of the S2 and S3 dorsal root ganglia. Urinary retention, constipation, and impotence in anorectal herpes are suggestive of a sacral radiculopathy, perhaps due to infection of lower-level sacral nerves and dorsal root ganglia; alternatively, urinary retention and constipation could be ascribed to a pain-induced reflex spasm of the anal and vesical sphincters caused by the severe anorectal pain associated with the syndrome. The dermatomic distribution of sacral dysesthesia or neuralgia has not been well characterized or compared in genital versus anorectal herpes.

Other symptoms of anorectal herpes include tenesmus, hematochezia, and rectal discharge. Constitutional symptoms such as fever, chills, malaise, and headache are common with primary anorectal HSV infection. Tender inguinal lymphadenopathy occurs in nearly one-half of men with primary anorectal herpes. Although initial attacks of genital herpes differ clinically from recurrent attacks (see Chapter 21), initial and recurrent attacks of anorectal herpes have not yet been carefully compared. However, clinical experience suggests that recurrent anorectal attacks are often mild, of shorter duration, and rarely associated with constitutional symptoms. The presence of concomitant HIV-1 infection can adversely affect the clinical course of HSV proctitis. Unlike immunocompetent hosts, who have spontaneous resolution of lesions, in the absence of treatment HIV-infected patients tend to develop chronic progressive disease leading to large, destructive perianal ulcers.¹⁴¹ Chronic mucocutaneous HSV with positive HIV serology is diagnostic of AIDS.¹⁴¹

Clinically, many infected individuals will not have any visible ulcerative perianal lesions but instead will present with ulcerative findings deep in the anal canal or involving the rectal mucosa.^{3,137} Quinn et al. noted only 4 of 15 (27%) patients with anorectal herpes had visible perirectal lesions.³ When present externally, the initial lesion is a small vesicle or cluster of vesicles, each surrounded by a red areola. The vesicles soon rupture and may become confluent, particularly near or in the anal canal. With HSV infection of the rectum, the lower 10 centimeters of the rectum may appear edematous, with discrete focal vesicular or ulcerative lesions occasionally present (see Figs. 68-4 and 68-5). HSV proctitis is more likely than other causes of proctitis to cause diffuse friability, primarily involving the distal 10 cm of the rectal mucosa. The rectal



FIGURE 68-4. Short-bundle sigmoidoscopic view of the distal rectum in a patient with early primary anorectal herpes, showing intact vesiculopulsules.

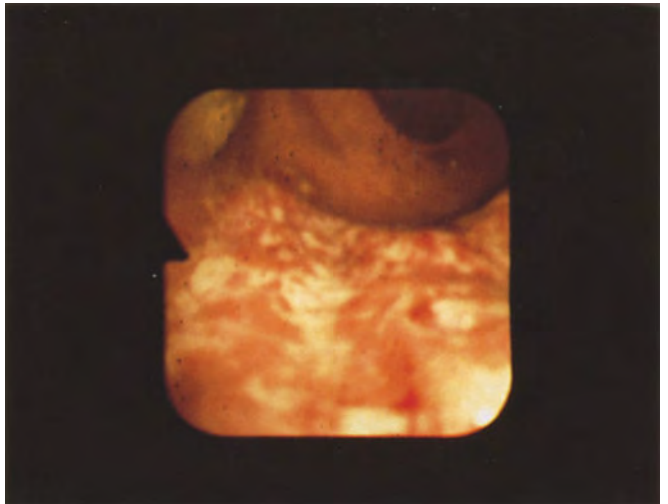


FIGURE 68-5. Short-bundle sigmoidoscopic view of primary anorectal herpes showing patchy bleeding and exudate extending up to 8 cm, with normal rectal mucosa above.

mucosa is characteristically normal above this level, although occasionally involvement may occur above 10 cm. Histologic examination of rectal biopsies reveals acute nonspecific inflammation with focal ulcerative changes. The histologic findings which are characteristic of rectal herpes, though not found in all cases, are perivascular mononuclear cell infiltration, intranuclear inclusion bodies, and extensive nuclear debris (Fig. 68-6); multinucleated cells can also be seen occasionally but are not uniquely associated with this infection. Other rectal infections are commonly associated with HSV infection and may cause a more diffuse proctitis.

The clinical diagnosis of genital herpes is both insensitive and nonspecific. Diagnosis of anorectal herpes should be suspected on the basis of proctitis with focal ulcerative changes of the distal rectum in a patient with severe anal pain, constipation, inguinal adenopathy, constitutional symptoms, and

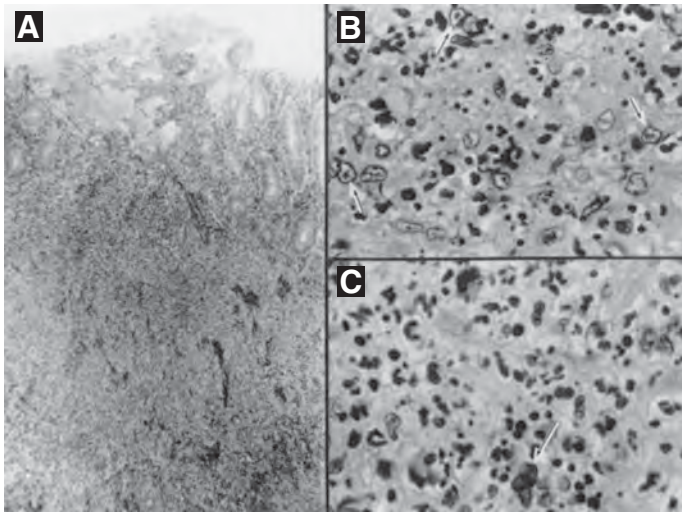


FIGURE 68-6. Herpetic proctitis. **A.** An ulceration and intense acute inflammation are present in the rectal mucosa. H&E stain, $\times 102$ magnification. **B.** Within this area of inflammation, intranuclear inclusions can be identified, which are consistent with HSV infection (arrow). H&E stain, $\times 1360$ magnification. **C.** Multinucleated cells with a ground-glass appearance (arrow), a finding typical for HSV. H&E stain, $\times 1360$ magnification. (Courtesy of M. Schuffler.)

urinary retention. Cultures of external lesions, of rectal swabs, or of rectal biopsy are confirmatory. Immunofluorescent staining of tissue biopsy is also useful. Polymerase chain reaction (PCR) assays for HSV DNA are very sensitive and can be used instead of viral culture with viral typing. Commercially available enzyme immunoassays (EIAs) do not distinguish well between antibody subtypes.¹⁴² Accurate type-specific assays for HSV antibodies must be based on the HSV-specific glycoprotein G2 for the diagnosis of infection with HSV-2 and glycoprotein G1 for diagnosis of infection with HSV-1. Recently, FDA-approved, gG-based type-specific assays have been shown to be highly specific and accurate for detection of these antibodies.¹⁴³ Isolation of HSV is the most specific means of confirming a first episode of infection, but detection of HSV-2-specific antibody is the most sensitive way to confirm symptomatic reactivation and to detect asymptomatic infection.¹³⁸

The clinical course of an initial attack of anorectal herpesvirus infection is self-limited, but manifestations may last for 2–3 weeks. Secondary bacterial superinfections, which are uncommon in genital herpes, may be more common in anorectal herpes, although this has not been determined. Treatment includes analgesics and sitz baths, and one study suggests that oral acyclovir may be efficacious in shortening the duration of symptoms and viral shedding of anorectal herpes.¹⁴⁴ Initial cases of infection should receive acyclovir orally 400 mg five times per day for 10 days. The newer antiviral agents famciclovir and valacyclovir have been used for genital HSV infection and may be efficacious for anorectal infection, although they have not been studied for this specific indication (see Chapter 21). Acyclovir 400–800 mg orally twice to three times daily, famciclovir 500 mg orally

twice daily, or valacyclovir 1 gram daily or 500 mg orally twice daily have been recommended for daily suppressive therapy in HIV-infected persons. While antiretroviral therapy reduces the severity and frequency of symptomatic genital herpes, frequent subclinical shedding still occurs. Subclinical mucosal HSV is associated with higher loads of mucosal HIV^{146,147} and HIV-infected persons are likely to be contagious for HSV. As HIV-infected persons are evaluated on entry to care, type-specific serologies should be offered during initial staging and suppressive antiviral therapy considered. In AIDS patients with severe mucocutaneous herpes, 5–10 mg/kg of intravenous acyclovir should be administered every 8 hours until clinical resolution is attained. The patient may then be placed on oral antiherpetic therapy for suppression of recurrences, as these are more frequent and severe in AIDS patients.¹³³ If lesions persist or recur in a patient receiving HSV antiviral treatment, HSV resistance should be suspected and a viral isolate obtained for sensitivity testing. If resistant to acyclovir, foscarnet, 40 mg/kg body weight IV every 8 hours is often effective. Topical cidofovir gel 1% applied to the lesions once daily for 5 consecutive days may also be effective, but this preparation is not commercially available and must be compounded at a pharmacy.¹⁴⁵

ANORECTAL SYPHILIS

As with other STDs, the incidence of syphilis appears to be increasing among MSM in industrialized countries.^{148–154} Although the rate of primary and secondary syphilis reported in the United States decreased during the 1990s and in 2000 was the lowest since 1941, in the years from 2000 to 2004 primary and secondary syphilis cases increased and this increase was observed primarily among men.^{149,152,154}

T. pallidum is commonly seen in its earliest infectious stages, with the primary anorectal lesion appearing 2–6 weeks after exposure by rectal intercourse. However, clinicians often fail to recognize anorectal chancres. Consequently, early syphilis in MSM is diagnosed in the secondary or early latent stage much more often than in the primary stage. It is not certain what proportion of anorectal chancres is asymptomatic. Careful perianal examination can reveal unsuspected perianal chancres, while digital rectal examination and anoscopy may be required to detect asymptomatic chancres higher in the anal canal or rectum. The variable appearance of the lesion accounts for the high rate of misdiagnosis. When anorectal syphilis causes symptoms, it is commonly misdiagnosed as a traumatic lesion, fissure, or hemorrhoiditis.¹⁵⁵

Anorectal chancres due to syphilis have been recognized at least since the early 1900s. In 1925, Martin and Kallet found 20 patients (6.7%) with anorectal chancres among 300 proctologic cases.¹⁵⁶ Over the next 20–30 years there were several reports which stated that anorectal chancres represented

0–15% of extragenital chancres.^{157,158} However, as STD clinicians have more frequently examined the anal area for chancres, the proportion of chancres found to involve the anorectal area has also increased.

As previously mentioned, symptoms are commonly absent in the primary stage of anorectal syphilis, but when symptoms are present they include mild anal pain or discomfort, constipation, rectal bleeding, and occasionally a rectal discharge. Primary anorectal syphilis may appear as single or multiple eccentrically placed or mirror image (“kissing chancres”) perianal ulcers.¹⁵⁹ It can also present as ulcerated masses, typically located on the anterior wall of the rectum.¹⁶⁰ Inguinal adenopathy with rubbery, nonsuppurative painless nodes may be associated with anorectal syphilis and helps distinguish it from fissures. Within the rectum, secondary syphilis may cause discrete polyps,^{161,162} smooth lobulated masses,^{163,164} mucosal ulcerations, and nonspecific mucosal erythema or bleeding, as well as submucosal irregularities with rubbery nodes which may be confused with lymphoma.^{164,165} Syphilitic inflammation of the gastrointestinal tract is usually limited to the distal 15 cm but may be as high as 20 cm with secondary syphilis.

In secondary syphilis, condylomata lata may be found near or within the anal canal. These are smooth warty masses and must be differentiated from the more highly keratinized condylomata acuminata. Condylomata lata are often pruritic and produce a foul discharge, which is highly infectious. The term condyloma latum has generally been limited to morphologically characteristic lesions involving stratified squamous epithelium, and we therefore do not use the term to include lesions of the columnar epithelial mucosa of the rectum. It is probable that secondary syphilis frequently involves the gastrointestinal tract, particularly the stomach. Constitutional symptoms, skin rash, and mucous patches can also occur. The lesions of primary and secondary syphilis may also coexist.^{165,166}

Late syphilis may uncommonly involve the gastrointestinal tract, and the involvement can range from infiltrative, constrictive, or polypoid masses within the stomach to lesions of the lower bowel.^{167,168} Anal sphincter paralysis and severe anal pain may develop with tabes dorsalis. Most past descriptions of gastrointestinal syphilis should be interpreted cautiously, since many of these lesions were ascribed to syphilis solely on the basis of serology, clinical responses to therapy, and compatible histology. Only a few reports have demonstrated *T. pallidum* in gastrointestinal lesions by silver stain or indirect immunofluorescence.^{168–172}

Diagnosis of anorectal syphilis is based on serology, perirectal and digital rectal examination, and anoscopy. Detection of motile treponemes by darkfield examination is useful for evaluation of perianal and anal lesions but may be less specific for rectal lesions, since nonpathogenic treponemes can be found in the intestine. However, the number

of species of nonpathogenic treponemes which have been described is greater in the mouth than in the intestine.¹⁶⁹ Additionally, since 10^5 treponemes/mL are required for visualization, a negative test does not rule out the diagnosis. Immunohistochemical stains of exudate from lesions may be useful in darkfield-negative specimens.¹⁷⁰ Biopsies of any rectal lesions or masses should be processed for silver staining, as well as routine histology, if syphilis is suspected. Although Nazemi et al.¹⁶² described a case of syphilitic proctitis by demonstrating a spirochete on silver stain of a rectal biopsy, some investigators believe that silver stains are unreliable and recommend identification of *T. pallidum* by immunofluorescence using anti-*T. pallidum* antisera.^{166,169} Figure 68-7 illustrates a positive immunofluorescent stain for *T. pallidum* in a rectal mass lesion found in a homosexual man who had secondary syphilis associated with anorectal pain and discharge.

In addition, the histopathology of anorectal syphilitic lesions is also quite characteristic. As shown in Fig. 68-8, a hematoxylin and eosin preparation of the same tissue shown in Fig. 68-7 demonstrates at low magnification a uniform infiltrate of mononuclear cells throughout the submucosa and lamina propria. At higher magnification these are seen to be predominantly plasma cells, lymphocytes, and histiocytes. This degree of plasma cell infiltration is characteristic of gummas, syphilitic gastritis, condylomata lata, and syphilitic chancres.^{166,170} Presumably, this intense plasma cell infiltrate in early syphilis represents an immune response to the large number of treponemes demonstrated throughout the tissue

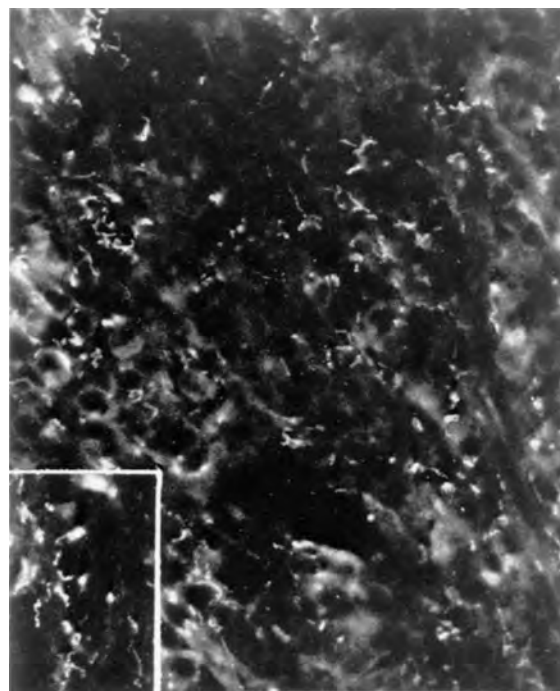


FIGURE 68-7. Immunofluorescent staining for *Treponema pallidum* reveals numerous brightly stained organisms scattered throughout the mucosa and submucosa of a rectal biopsy from a patient with a rectal mass and secondary syphilis. (Courtesy of S. Lukehart.)

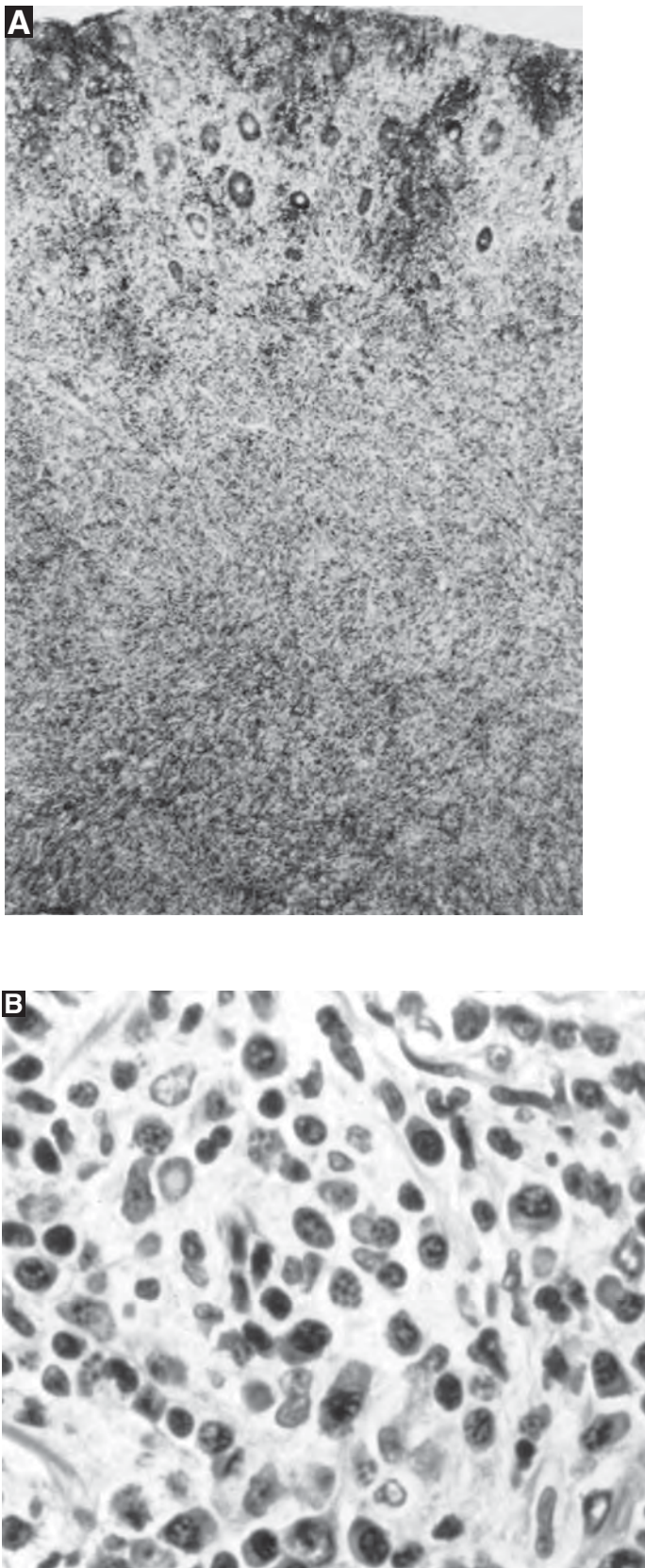


FIGURE 68-8. Biopsy of a rectal mass from a patient with secondary syphilis. **A.** An extensive uniform cellular infiltrate has replaced the submucosa and lamina propria and has disrupted the muscularis mucosa. **B.** The infiltrate consists of plasma cells, histiocytes, and lymphocytes.

by immunofluorescent antibody staining.^{171,172} These lesions often show an obliterative endarteritis with capillary proliferation and occasionally granulomas and crypt abscesses.^{13,58}

Serologic diagnosis of syphilis is based on presence of antibodies to nontreponemal and treponemal antigens. A positive VDRL or RPR must be corroborated by a positive test specific for antibody to *T. pallidum* antigens, such as the fluorescent treponemal antibody absorption (FTA-ABS) test or the *T. pallidum* particle agglutination (TP-PA). Treponemal antibody titers do not correlate with disease activity and usually remain positive after the infection. The VDRL test detects approximately 50–85% of cases of primary syphilis, 100% of cases of secondary syphilis, and 85–100% of cases of tertiary syphilis. The FTA-ABS is the first serologic test to become positive and is present in 70–90% of patients with a chancre. This test is generally 100% sensitive in secondary and tertiary syphilis. The specificity of the VDRL varies with the population tested and is higher in healthy than in sick persons.¹⁷²

Concomitant HIV-1 infection may alter the serologic manifestations of syphilis. There has been delayed or absent serologic test reactivity in patients infected with HIV-1 and proven secondary syphilis, particularly at a later stage of HIV infection.^{56,57} Higher VDRL titers in patients with earlier-stage infection and secondary syphilis have also been noted.⁵⁸ Biological false-positive tests, VDRL- or RPR-positive, and FTA-ABS- or MHATP-negative, which occur in a wide variety of infectious and noninfectious conditions, have been associated with HIV-1 infection.^{173,174}

The differential diagnosis of anorectal syphilis includes ulcers due to HSV infection, chancroid, granuloma inguinale, LGV, trauma, and malignancy. Syphilitic lesions may be commonly misdiagnosed as anal fissures, fistulas, hemorrhoids, traumatic lesions, rectal polyps, condylomata acuminata, and even rectal carcinoma.^{160–162} Indeed, there have been several reports of patients who underwent surgery for removal of lesions which were initially thought to be malignant but were later diagnosed as syphilitic lesions.¹⁷⁵

Treatment for early syphilis is discussed in Chapter 35. Benzathine penicillin, in a single dose of 2.4 million units IM, remains the treatment of choice for early syphilis. Penicillin-allergic patients may be treated with a 14-day course of doxycycline, 100 mg orally given twice daily, or tetracycline 500 mg four times daily. A single 2-g oral dose of azithromycin was reported effective in treating syphilis in a Tanzanian study, but recent reports of azithromycin-resistant *T. pallidum* among MSM in North America and Dublin have prompted caution and close follow-up of persons receiving this therapeutic option.¹⁷⁶ All patients should be offered HIV testing. All sexual contacts should be screened and treated.

Although the standard regimen for early syphilis may be adequate for some patients coinfecting with syphilis and HIV-1, several reports have documented poor response to standard therapy in this setting.^{177,178} Following treatment, the serologic

titer may decrease more slowly in some HIV-infected patients.^{179,180} These patients should have repeat serologic testing 3, 6, 9, 12, and 24 months after treatment to evaluate for response to therapy. Examination of CSF fluid is indicated in patients with neurological symptoms or if there is a rise or a less than fourfold decrease in the serologic titer within 6–12 following treatment.¹⁸¹

C. TRACHOMATIS PROCTITIS

Several studies in the pre-HIV era demonstrated prevalences of 4–8% for anorectal *C. trachomatis* infection in men and 5–21% for anorectal infections in women.^{182–186} Rates were higher for patients with symptoms of proctitis than for asymptomatic patients. In women with anorectal *C. trachomatis* infection, rectal intercourse was associated with the presence of symptoms. Most studies describing the clinical manifestations of chlamydial proctitis have been conducted among MSM, and in the pre-AIDS era, *C. trachomatis* was responsible for up to 15% of proctitis cases seen in MSM. In a recent study of the etiology of clinical proctitis among MSM, 19% of 101 patients had chlamydial proctitis.³⁷ Barnes et al. compared serovars causing anorectal infection in homosexual and bisexual men with those causing cervical infections in heterosexual women in the same STD clinic.¹⁸⁷ They found D/D' in 53% of rectal and 18% of cervical isolates, while serovar E was found in 32% of cervical and 6% of rectal isolates.¹⁸⁷ The highly significant difference in isolates from the two sites may be attributed to limited transmission between the two populations or to a decreased capability of certain serovars of surviving at one or the other mucosal site. Since the clinical manifestations and histopathology of *C. trachomatis* rectal infections differ according to the infecting immunotype, these will be discussed separately.

Rectal infections with LGV immunotypes of *C. trachomatis* have been recognized since 1936.¹⁸⁸ Infections with the LGV biovar of *C. trachomatis* are endemic in East and West Africa, South America, and the Caribbean, but they have been seen only sporadically in the United States and Europe and more often in MSM than in heterosexual men or in women until recently. In 2003, a cluster of LGV cases among MSM was reported in Rotterdam, the Netherlands,¹⁸⁹ and since then there have been numerous reports or similar outbreaks in large cities in Western Europe, Australia, and the United States. Initially referred to as the anorectal syndrome of LGV, rectal involvement was generally believed to be a late, or secondary, manifestation of a genital infection. Secondary anorectal involvement does occur: After contact with an infected individual, a transient papule or ulcer sometimes appears on the genitalia, followed by systemic symptoms and prominent inguinal adenopathy; without treatment, the infection progresses to destructive granulomatous lesions of the lymph nodes and lower intestinal tract, which progresses to the formation of

fistulas, strictures, and perianal abscesses and fistulas. The rectal strictures often form 2–5 cm above the anocutaneous margin, where there is a rich supply of lymphatics. Obstruction of lymphatic and venous drainage may cause perianal outgrowth of lymphatic tissue similar to hemorrhoids, called lymphorrhoids or perianal condylomas.¹⁹⁰

Primary anal or rectal infections have been described in women and MSM who practice anal intercourse. In these infections, rectal involvement is initially characterized by severe anorectal pain, a bloody mucopurulent discharge, and tenesmus. Inguinal adenopathy, which is characteristic of genital LGV, is often present. A study by Bauwens et al. suggests that the severity of infections may be associated with specific serovars and that infections with the L1 serovar may be less severe than those caused by L2.¹⁹¹ However, a recent case-control study comparing the clinical characteristics of 87 MSM who had LGV to 377 MSM who had non-LGV anorectal chlamydia and 2677 MSM who did not have anorectal chlamydia found that a small number of patients with LGV presented with self-reported anorectal problems, with only 4 reporting anorectal pain or discharge.¹⁹² Proctoscopic signs of proctitis, enlarged inguinal lymph nodes, and the presence of >1 anorectal ulcer upon examination were significant predictors of LGV infection, irrespective of the control group used. In addition, the number of white blood cells in the Gram-stained anorectal smear specimen was a significant predictor of LGV anorectal infection.

In both primary and secondary anorectal LGV, sigmoidoscopy reveals diffuse friability with discrete ulcerations in the rectum that occasionally extend to the descending colon.^{193,194} Strictures and fistulas may become prominent and can be easily misdiagnosed clinically as Crohn's disease or carcinoma.^{190,195} Histologically, rectal LGV may also be confused with Crohn's disease. Commonly, there is diffuse inflammation throughout the mucosa and submucosa, with plasma cells, neutrophils, and eosinophils, as well as giant cells, crypt abscesses, and granulomas (Fig. 68-9). Due to

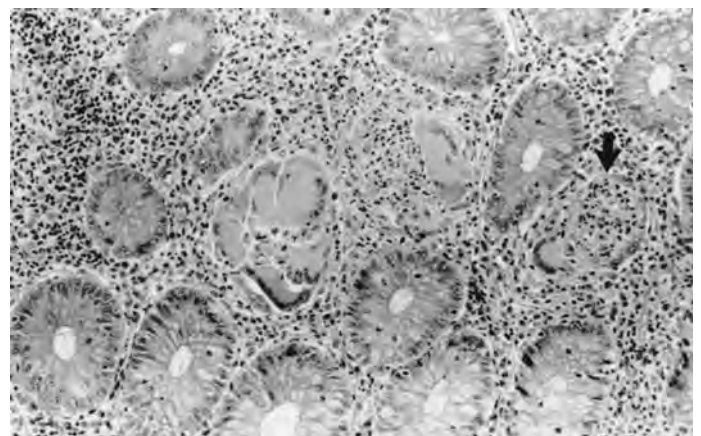


FIGURE 68-9. Rectal biopsy of a patient with rectal LGV (*C. trachomatis*, LGV-2 immunotype). There is diffuse inflammation throughout the mucosa and submucosa. Giant cells, crypt abscesses (arrow), and granulomas are present.

these similarities, Crohn¹⁹⁶ and others^{197,198} speculated about a possible relationship between the two disorders. Schuller et al.¹⁹⁹ later demonstrated antibody to LGV strains in over 70% of patients with Crohn's disease and in less than 2% of healthy controls. At least three subsequent studies have failed to document such a relationship.^{200–202} However, in our own analyses of rectal biopsies from MSM with proctitis, histopathologic findings were interpreted as consistent with Crohn's disease in two of three men from whom LGV immunotypes of *C. trachomatis* were isolated.⁴ From these data, it appears that LGV infection should be suspected and ruled out in MSM with unexplained proctitis.

The non-LGV immunotypes of *C. trachomatis* are less invasive than LGV and can cause a mild proctitis characterized by rectal discharge, tenesmus, and anorectal pain.³ Anal lesions have not been described. Many infected individuals may be asymptomatic and can be diagnosed only by routine culturing. Data from Dean et al. suggests that serovar F may be associated with more severe female genital infections than serovar E.²⁰³ This association of specific serovars and severity of infection has not been seen with non-LGV *C. trachomatis* anorectal infections. Even in asymptomatic cases, abnormal numbers of fecal leukocytes are usually present. Sigmoidoscopy may be normal or may reveal mild inflammatory changes with small erosions or follicles in the lower 10 cm of the rectum. Histology of rectal biopsies generally shows anal crypts and prominent follicles, as well as a neutrophilic infiltration of the lamina propria.

Diagnosis of chlamydial proctitis is best made by isolation of *C. trachomatis* from the rectum, together with response to appropriate therapy. Direct fluorescent antibody staining of rectal secretions using monoclonal antibodies can also be used to make the diagnosis.²⁰⁴ Rompalo et al. used the direct fluorescent antibody technique to evaluate rectal swab samples for *C. trachomatis* and found a 90% sensitivity and 100% specificity for DFA compared with culture.²⁰⁴ EIAs for chlamydial antigens have been attempted on rectal samples but give high false-positivity rates due to cross-reacting antigens on other fecal bacteria.²⁰⁵ NAATs testing has been used with good reported sensitivity and specificity, but is not currently FDA approved for rectal specimens.^{206,207} Serology is considered useful for the diagnosis of LGV and a complement-fixation titer of greater than 1:64 is considered suggestive of LGV infection.^{208–211} Specificity of microimmunofluorescent antibody titers, however, has been questioned recently and requires further study. Serology for the diagnosis of non-LGV rectal chlamydial infection has been less useful, often confusing, and not commonly used. The CDC LGV Project has specific instructions for specimen collection and transport for LGV testing at the CDC and the procedure is available on the web.²⁰⁸

Doxycycline, or azithromycin, are the drugs of choice for infection with *C. trachomatis*. Doxycycline 100 mg twice daily

for 7–10 days may be used; azithromycin 1 g as a single dose is effective for urethritis and cervicitis and has been recommended for uncomplicated rectal infections.^{212,213} Patients should be followed carefully with repeat sigmoidoscopy, particularly when there is any question about the differential diagnosis of LGV versus inflammatory bowel disease. Therapy for LGV is discussed in Chapter 30.

PROCTOCOLITIS AND ENTERITIS DUE TO ENTERIC PATHOGENS

Epidemiologic and anecdotal reports have suggested the sexual transmission of several enteric pathogens, including *Shigella*, *Salmonella*, and *Campylobacter jejuni*.^{214–217} Since these organisms are described in depth in Chapter 41, we will only briefly review some of the clinical and epidemiologic data concerning the role of these pathogens in MSM with symptoms and signs of enteritis or proctocolitis.

Although bacterial enteric infections account for fewer than 5% of opportunistic infections in AIDS patients in developed countries, these infections are significantly more common in AIDS patients than in similar patients without AIDS. In developing countries, persistent diarrhea of greater than 7 days has been reported to affect up to 95% of AIDS patients.²¹⁸ Further, these infections tend to be more prolonged in AIDS patients and are associated with more frequent recurrences, more frequent bacteremia, and more antibiotic resistance than in non-AIDS patients. Diarrhea in the setting of HIV infection can have many causes. It may be a consequence of HIV infection directly and it is likely that the gastric hypoacidity which develops with AIDS predisposes to bacterial overgrowth and opportunistic enteric infections.²¹⁴ Diarrhea in HIV-infected patients on highly active antiretroviral therapy (HAART) may also be a drug sideeffect, especially with the use of protease inhibitors.²¹⁹

Although several species of *Shigella* are responsible for human disease, *S. sonnei* and *S. flexneri* account for most infections in the United States. Since *Shigella* is highly infectious, transmission of the organism can occur rapidly and is commonly seen in children and travelers, in people in mental or penal institutions, and in populations where localized outbreaks are traced to contaminated food or water. The sexual transmission of *Shigella* was recognized in 1972, when reports from San Francisco and later from Seattle and New York documented that 30–70% of patients with *Shigella* were MSM.^{215,220} Contact tracing demonstrated recovery of the same serotype from sexual partners, and no contaminated food or water source could be shown to be common to any of the cases.

Shigellosis presents with an abrupt onset of diarrhea, fever, nausea, and cramps. The diarrhea is usually watery but may contain mucus or blood. The infection may be complicated by the development of toxic megacolon. Sigmoidoscopy usually reveals an inflamed mucosa with friability not limited to

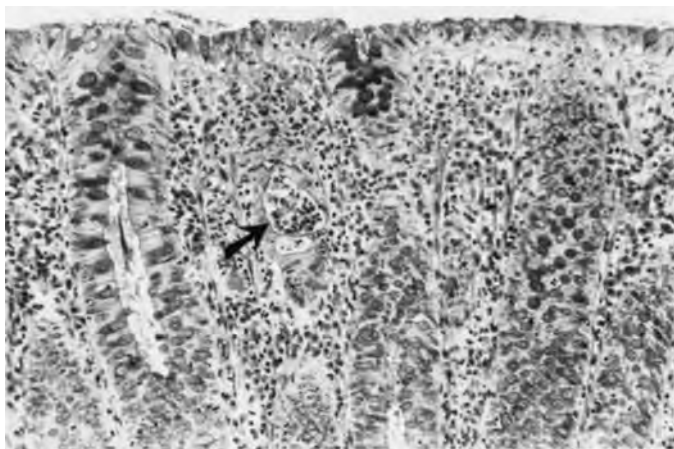


FIGURE 68-10. *Campylobacter* colitis. The colonic mucosa is acutely inflamed, with polymorphonuclear leukocytes in the epithelium and lamina propria. A crypt abscess is also present (arrow). These findings are not specific for *Campylobacter* and may be found in the acute colitis caused by other invasive pathogens. H&E stain, $\times 340$ magnification. (Courtesy of M. Schuffler.)

the distal rectum, and histologic examination shows diffuse inflammation, with bacteria scattered through the submucosa and muscularis mucosa (Fig. 68-10). Diagnosis is made by culturing the organisms from the stool on selective media. Treatment is usually supportive, and antimotility agents should be avoided, but antibiotics are generally recommended to prevent complications in immunocompromised patients. Due to widespread development of resistance, selection of antibiotics should be based on regional antibiotic sensitivities. Ciprofloxacin 500 mg orally twice daily for 7 days is usually effective. As recurrences are common, antibiotic resistance may develop.²¹⁴ Repeat cultures of stool and blood are necessary to monitor response to therapy. Since asymptomatic carriers of *Shigella* exist, contact tracing is an important public health measure. Studies are needed on the value of tracing sexual contacts of MSM with shigellosis. Recent guidelines for treating opportunistic infections among HIV-infected persons recommend that household contacts of HIV-1-infected persons who have shigellosis should be evaluated for persistent asymptomatic carriage of either organism so that strict hygienic measures or antimicrobial therapy can be instituted and recurrent transmission to the HIV-1-infected person can be prevented.²²¹

Campylobacter jejuni is one of the most commonly isolated bacterial agents from patients with acute diarrhea in the United States. In a survey of AIDS cases in Los Angeles from 1983 to 1987, *Campylobacter* was reported in 29 of 4433 (0.7%) AIDS cases. There was a 39-fold increased annual incidence in AIDS patients compared with other men aged 15–55 years.²²² It is believed that the 5 or 6 per 100,000 population rate reported to the CDC significantly underestimates the true incidence of 1000 per 100,000 per year.²²³ The underestimation is likely due to frequent asymptomatic infections and underutilization of

the appropriate culture techniques. This pathogen is generally acquired by ingestion of contaminated water or food, particularly chicken and unpasteurized milk, or by close contact with infected animals.^{224,225} Infection rates peak in the late summer and early fall. This is a significantly less infectious organism than *Shigella*, as 800×10^6 organisms are needed for infection in 10–50% of patients.

Sexual transmission has been documented in animals and was suspected in early reported cases of human abortion,^{226,227} and a few reports have recently addressed the possible sexual transmission of *Campylobacter* in humans.^{227–231} *Campylobacter* species or “atypical” campylobacter organisms have been recovered from the stools of 24% of symptomatic MSM and 10% of asymptomatic MSM.²⁵ In a subsequent study performed in 1986 in Baltimore, *Campylobacter* species were isolated from 4% of asymptomatic MSM, from 20% of MSM with intestinal symptoms, and from 9% of MSM with AIDS.²²⁸ The most frequent isolates were *C. jejuni*, followed by campylobacter-like organisms.

These studies have clearly documented the frequent occurrence of “atypical” campylobacter organisms in MSM. In the AIDS era, “atypical” campylobacter organisms have been recovered less often from rectal or stool cultures of MSM with diarrhea (Table 68-4) but have caused bacteremic illness in AIDS patients.²²⁹ Although 99% of reported *Campylobacter* isolates in the United States are *C. jejuni*, there is a growing list of atypical *Campylobacter* and related species which have been shown to cause diarrheal syndromes. These include *C. coli*, *C. upsaliensis*, *C. lari*, *Arcobacter cryaerophilus*, and *A. butzleri*, *Helicobacter fennelliae*, and *H. cinaedi* (previously classified as *Campylobacter* species) have been associated with chronic mild diarrhea and proctitis in MSM.^{229–231} Although blood culture systems will generally grow these organisms, routine stool cultures performed by most laboratories will fail to identify these more fastidious *Campylobacter* species. Even when isolated from asymptomatic MSM these organisms are significantly correlated with the presence of neutrophils in rectal secretions, which suggests clinical disease.

Clinically, *C. jejuni* produces an acute diarrheal illness of several days duration, with fever, chills, myalgias, and abdominal pain. Gastrointestinal infections may mimic inflammatory bowel disease or acute appendicitis and may be complicated by pseudomembranous colitis, gastrointestinal hemorrhage, toxic megacolon, cholecystitis, and pancreatitis. Postinfectious complications include reactive arthritis²³² and Guillain-Barré syndrome.²³³ Although the infection usually involves the small intestine, involvement of the colon and rectum has also been described.^{234–236} The sigmoidoscopic and rectal biopsy findings are nonspecific and similar to those described for shigellosis (see Fig. 68-10). Fecal leukocytes are uniformly present and diagnosis is confirmed by isolating the organisms from the stool by culture on selective media in a microaerophilic atmosphere.²²⁴

Table 68-4. Comparison of Gastrointestinal Infections Among Homosexual Men Attending the Seattle STD Clinic in Two Time Periods

% of patients positive for each pathogen ^a	1980–1981 (n = 119)	1983–1984 (n = 184)	p value
<i>Neisseria gonorrhoeae</i>	31	14	p = .0003
HSV	19	30	p = .05
<i>Chlamydia trachomatis</i>	10	14	NS
<i>Treponema pallidum</i>	5	6	NS
<i>Entamoeba histolytica</i>	29	15	p = .02
<i>Giardia lamblia</i>	14	7	p = .07
<i>Campylobacter jejuni</i>	7	7	NS
Campylobacterlike organisms	18	7	p = .005
Shigella	3	5	NS
Any pathogen	80	66	p = .02
≥ 2 pathogens	22	19	NS
HIV seroprevalence	14	58	p < .001

^aData from TC Quinn et al.²⁵ and WE Stamm (personal communication).

Although the need for antimicrobial therapy has not been fully established in human *Campylobacter* infection of the intestinal tract, treatment with azithromycin 500 mg daily for 3 days or erythromycin 500 mg four times daily for 1 week has been recommended for severely symptomatic cases and for immunocompromised patients.²²⁵ Antimicrobial therapy started within the first 3 days of the illness reduces the duration of excretion of the organism in the stool. A cluster of erythromycin- and ciprofloxacin-resistant *Campylobacter jejuni* subsp. *jejuni* was recently reported among MSM from 1999 to 2001 in Quebec²³⁷ and ciprofloxacin- and azithromycin-resistant isolates from Thailand have recently been described.²³⁸ Bacteremia and recurrent diarrhea following specific therapy have been reported.

There are several species of salmonella with more than 2000 different serotypes that cause a variety of clinical entities in humans. There is an estimated 20-fold increased incidence of salmonellosis in AIDS patients.²³⁹ These infections, which are primarily due to *S. typhimurium* and *S. enteritidis*, are often more severe and more frequently associated with bacteremia and relapse despite therapy in AIDS patients. *Salmonella* bacteremia in an HIV-infected individual is diagnostic of AIDS. Only anecdotal reports have commented on the possible sexual transmission of *Salmonella*; in one report,²⁴⁰ *S. typhi* was recovered from the stools of MSM and the same serotype was recovered from asymptomatic sexual partners with whom no housing, food, or water was shared. These organisms can survive in the environment for up to 30 months; therefore, fomite transmission may occur.²⁴⁰ It appears that these organisms have different capabilities for

invasiveness in different populations. A review of salmonellosis in New York City found that *S. enteritidis* was more competent in causing septicemia and less competent in causing gastroenteritis than *S. typhimurium* in HIV-infected patients, the reverse was true for HIV-uninfected patients.²⁴¹

Diagnosis is made by culturing the organisms from the stool on selective media. Treatment must be individualized, depending on severity of symptoms and antibiotic sensitivity of the isolate. For AIDS patients with bacteremia, ciprofloxacin 750 mg twice daily for 14–30 days is generally recommended.²⁴² As with all enteric pathogens, resistant strain are always a concern and recently three cases of community-acquired *Salmonella* bacteremia were reported with resistance to quinolones and extended-spectrum cephalosporin resistance.²⁴⁵

As additional important feature of *Salmonella* bacteremia among patients with AIDS is its propensity to relapse. The rate of recurrent bacteremia is approximately 45% unless chronic suppressive therapy is administered.²²¹ If relapse occurs, ciprofloxacin 500 mg twice daily is given indefinitely. Isolates sensitive to ampicillin and trimethoprim-sulfamethoxazole may be treated with these drugs. In immunocompetent patients with mild illness, supportive therapy without antibiotics is appropriate. Since asymptomatic carriers are common and may be employed as food handlers in public establishments (as were the reported cases), tracing of sexual partners of infected individuals is particularly important. Household contacts of HIV-1-infected persons who have salmonellosis or shigellosis should be evaluated for persistent asymptomatic carriage of either

organism so that strict hygienic measures or antimicrobial therapy can be instituted and recurrent transmission to the HIV-1-infected person can be prevented.²²¹

Recent reports suggest that enteroadherent bacteria may produce a chronic diarrheal syndrome in AIDS patients.²⁴³ In one review these organisms were found in 17% of AIDS patients evaluated for chronic diarrhea in a 1-year period.²⁴⁴ Typically, these patients have less than 100 CD4 cells/mm³ and present with diarrhea with malabsorption and weight loss. The right colon is most commonly involved. Histologically, three types of adherence patterns have been described: bacteria intercalated between microvilli, aggregates of bacteria loosely attached to damaged epithelium, and attaching and effacing lesions.^{244,245} Cultures of biopsy samples have yielded *E. coli* in 67% of cases.²⁴⁴ These infections have been described in MSM with AIDS, but the mechanism of transmission is not certain.

PARASITIC INFECTIONS

Although reports of cutaneous amebiasis of the penis, vulva, and cervix suggested sexual transmission of amebiasis,^{246–248} it has only been within the last two decades that sexual transmission of certain parasitic infections has been fully appreciated.^{21,22} In 1972, it was suggested that *Giardia lamblia*, *Iodamoeba bütschlii*, *Dientamoeba fragilis*, and *Enterobius vermicularis* were sexually transmitted among homosexuals.^{249–252} In two separate surveys in New York City, the prevalence of infection with giardiasis and/or amebiasis was between 30% and 40% in selected MSM.^{21,22} The presence of infection correlated better with a history of anilingus than with travel history.²¹ In Seattle, 25% of MSM we have studied with anorectal or intestinal symptoms have had either *Giardia*, *E. histolytica*, or both present in their stools.²⁵ *G. lamblia* was associated with symptoms of enteritis, while *E. histolytica* was equally common in symptomatic and asymptomatic men. In addition, mixed infections with a variety of intestinal parasites, including other protozoans and nematodes, have also been described in MSM.^{249–253} More recently, Peters et al. found that 48.5% (33 of 274) of MSM with symptomatic diarrhea in a community-based clinic in Chicago had at least one intestinal protozoan.²⁵⁴ *E. histolytica* and *G. lamblia* were isolated from 26% to 8%, respectively, of these men and represented 53% and 16%, respectively, of positive isolates. Other parasites frequently isolated in this study were *E. nana* (39%), *E. coli* (14%), and *E. hartmanni* (9%). *D. fragilis*, *I. bütschlii*, *Chilomastix mesnili*, cryptosporidia, and *Isospora* were isolated in less than 1% of patients.

The etiologic agent of amebiasis is *E. histolytica*. *E. dispar* is a recently distinguished morphologically similar but nonpathogenic species and together, it is estimated that these two species infect 10% of the world's population.²⁵⁵ High rates of infection occur in India, Africa, the Far East, and South and

Central America; in the United States, the prevalence is approximately 4%.²⁵⁶ Although *E. histolytica* is primarily a waterborne agent, sexual transmission may be responsible for its high prevalence in MSM. In 1977, 40% of all reported cases of amebiasis in the United States were from New York City. Eighty percent of these cases were located in Manhattan, and its large male homosexual community had the highest morbidity rate.²³ Similarly, in San Francisco, 89% of the reported cases of amebiasis were in males 20–39 years of age.¹ In a retrospective review of records of patients with *E. histolytica* infection seen at New York Hospital, Schmerin et al.²⁷ noted that 20 of 20 men who had not traveled were homosexual, while only 2 of 30 men who had traveled were homosexual. More recent studies have identified *E. histolytica* in 21–32% of selected MSM populations in North America and in 12% of MSM in the United Kingdom.^{257–259} Among HIV-infected patients in the United States, the incidence of diagnosed *E. histolytica* is low (13.5 cases per 10,000 person-years) with the diagnosis most common among MSM.²⁵⁵

The majority of infections is asymptomatic and only 10% of those infected develop invasive disease with amebic dysentery or liver abscess. There has been considerable recent debate about whether, in most cases, *E. histolytica* actually causes illness in MSM who are positive by stool wet-mount examination.^{260–261} The prevalence of *E. histolytica* is approximately equal in symptomatic and asymptomatic groups of MSM,²⁵ and many of those who are symptomatic have other pathogens in addition to *E. histolytica*. Additionally, AIDS patients do not seem to be at increased risk of invasive amebiasis.²⁶²

E. histolytica trophozoites have recently been divided into pathogenic and nonpathogenic zymodeme types using isoenzyme patterns. Most *E. histolytica* strains isolated from MSM are the nonpathogenic *E. dispar*, which are not usually associated with gastrointestinal symptoms, invasive disease,^{258,261,263} or a serologic response.²⁶⁴ Conversion from nonpathogenic to pathogenic zymodemes has been reported in culture but has not been seen in serial isolates from infected patients.²⁶⁵ Pathogenicity of *E. histolytica* strains has been recently linked to the presence of a galactose-inhibitable adherence protein. An ELISA which detects this antigen in serum and feces may be useful in distinguishing pathogenic and nonpathogenic strains.²⁶⁷ The high rate of occurrence of asymptomatic infection facilitates transmission of infection within the MSM community, as inadvertent transmission occurs from patients unaware of their infection.

When present, symptoms may vary from mild diarrhea to fulminant bloody dysentery. Extension of the infection to the liver, lung, or brain occurs rarely. Amebic proctocolitis causes diffuse inflammation and ulceration of the distal colon, often clinically indistinguishable from inflammatory bowel disease, shigellosis, *Campylobacter jejuni* infection, or *Yersinia enterocolitidis*.^{268,269} These symptoms may wax and wane for weeks to

months. Fulminant dysentery is uncommon and is associated with steroid use.²⁷⁰ Amebomas, which are chronic localized amebic infections, may present as painful abdominal masses. They are usually located in the cecum and descending colon.²⁵⁶ Complications of amebic colitis include peritonitis; hemorrhage; strictures of the anus, rectum, and sigmoid; and painful perianal ulcerations which are due to contiguous spread of intestinal infection.

Diagnosis is based on the demonstration of *E. histolytica* in the stool, in a wet mount of a swab, or in a biopsy of rectal mucosal lesions. Occasionally, multiple fresh stool examinations are necessary to demonstrate the cysts or trophozoites of *E. histolytica*. Barium, laxatives, antibiotics, and enemas should be avoided at the time of sample collection. Samples not evaluated immediately should be fixed with polyvinyl alcohol or refrigerated, to avoid disintegration of trophozoites. Sensitivity of stool examination can be increased with concentration techniques and with trichrome and iron hematoxylin stains.²⁵⁶ Definitive diagnosis of amebic colitis is by colonoscopy with scraping or biopsy of the ulcer edge; however, there is a risk of perforation. Serology (indirect hemagglutination) is useful in acute amebic colitis because it is positive in 82–98% of infected patients.²⁵⁶ Indirect hemagglutination tests may remain positive for years following infection.²⁷⁰ Agar gel diffusion, counterimmunoelectrophoresis, and EIA techniques are quite sensitive (87–95% for proctocolitis, 95–100% for amebic liver abscess) and have the benefit of becoming negative 6–12 months following infection.²⁷⁰ Newer diagnostic methods are also being tested. A single-round PCR assay was developed for detection and differential diagnosis of the three *Entamoeba* species found in humans, *E. moshkovskii*, *E. histolytica*, and *E. dispar*, that are morphologically identical as both cysts and trophozoites.²⁷¹ Point-of-care tests for rapid diagnosis of amebiasis are also being developed. In Bangladesh and Vietnam, a novel and simple-to-use *E. histolytica* rapid antigen test had 97% sensitivity and 100% specificity when compared to a standard ELISA antigen detection method, and a rapid antibody test had 89–100% sensitivity and 89–95% specificity.²⁷²

Treatment for amebiasis is discussed further in Chapter 44. Asymptomatic carriage of the organisms should be treated to prevent continued infection with a possible pathogenic strain and to prevent continued transmission of the infection. At present, three luminal amebicides are available to treat this type of infection. Iodoquinol 650 mg orally three times daily for 20 days is the regimen of choice.²⁷³ Paromomycin 25–30 mg/kg/day in three doses for 7 days and diloxanide furoate 500 mg three times per day for 10 days are additional options.²⁷⁴ Diloxanide furoate is presently available only from the CDC. Invasive intestinal disease should be treated with metronidazole 750 mg three times daily for 10 days.²⁷³ This drug is well absorbed and does not eradicate organisms in the intestinal lumen, so iodoquinol 650 mg three times daily for

20 days should be given subsequently. Dehydroemetine 1.5 mg/kg/day (maximum 90 mg/day) IM, plus tetracycline 500 mg 4 times daily up to 5 days, may be used as an alternate regimen, followed by iodoquinol.

Giardia lamblia, another frequent waterborne disease, also appears to be sexually transmitted through oral–anal contact. In a review of giardiasis in men seen at New York Hospital, 19 (22%) had not traveled recently, and all were homosexual.²⁷⁵ In 1977, Meyers et al. documented giardiasis in 6 of 8 MSM who were sexual partners.²⁸ Giardiasis is typically an infection of the small intestine, although it is often found in association with amebiasis. Symptoms of giardiasis include diarrhea, abdominal cramps, bloating, and nausea. Multiple stool examinations are necessary to document infection with *G. lamblia*. *Giardia* antigen detection by immunofluorescence ELISAs, nonenzymatic immunoassays, and direct fluorescence antibody tests are becoming the standard diagnostic tests in the United States. Sensitivities of these tests range from 85% to 96% compared with microscopy with specificities in the 98–100% range. Other option, when stool examination has been negative, include sampling of jejunal mucus by the Enterotest²⁷⁶ or small bowel biopsy so as to confirm the diagnosis.

Metronidazole 250–500 mg three times a day for 7 days is presently recommended in the United States but is associated with a 10–20% failure rate.^{273,277} Tinidazole, another 5-nitroimidazole, is considered by some authorities as first-line therapy since it is given as a 2-g single dose and may be more effective.²⁷⁷ Paromomycin 500 mg orally three times daily or furazolidone 100 mg four times daily for 7–10 days may also be used as an alternative.²⁷⁸ Quinacrine hydrochloride, previously used to treat giardiasis, is no longer available in the United States. Nitazoxanide has been approved for the treatment of giardiasis and cryptosporidiosis. When given at a dose of 500 mg twice a day for 3 days, it has a 71% reported parasitologic cure rate.²⁷⁸ Follow-up stool examinations are particularly important in management of *G. lamblia* and *E. histolytica* infection. Examination of sex partners of MSM may be important in reducing the reservoir of infection in the community; asymptomatic cyst passers should be treated.

Several reports have commented on the identification of *Enterobius vermicularis*, or pinworms, in MSM,^{252,278} although this infection is commonly found in children. Adult pinworm infection is usually acquired by contact with an infected child or by sexual transmission via anilingus. Ova are deposited by the adult worm in the perianal area and are infective for several hours. Pruritus ani is a common symptom. Diagnosis is made by demonstrating the ova, collected on cellophane tape from the anal area. Ova are rarely seen in stool examinations. Mebendazole 100 mg, pyrantel pamoate 11 mg/kg orally, or albendazole 400 mg—all as a single dose, then repeated once after 2 weeks, are usually effective and well tolerated.²⁷³

Although many helminth infections cannot be transmitted person to person because of their particular life cycle, *Strongyloides stercoralis* could be transmitted sexually, since the infective filariform larvae are often found in the feces. However, there has been no published evidence as yet that this infection has been sexually transmitted.

Intestinal infection with three protozoan parasites—cryptosporidium, *Isospora*, and microsporidium—has been identified in MSM with AIDS.^{279–281} Although there has been no documentation of sexual transmission of these parasites, this mode of transmission is highly suspectable due to the relatively high frequency in MSM compared to other select populations with AIDS.

Cryptosporidium is a tiny protozoan parasite that primarily inhabits the microvillus region of epithelial cells. This parasite has been known to cause diarrhea in various animals, especially calves and other domestic animals.²⁸² In 1976, the first human infection with cryptosporidium was reported, and until 1983 this pathogen was identified only in immunosuppressed patients.^{283,284} In 1983, however, investigators reported identification of this parasite in immunocompetent persons exposed to infected calves.²⁸⁵ The prevalence of infection by stool samples is approximately 1–3% in Europe and North America; however, serology suggests that 32–58% of European and North American adults may be infected. The prevalence is significantly higher (5–10%) in Asia and Africa.^{286,287} Worldwide the organism can be isolated from the stool of 10–20% of patients with AIDS-associated diarrhea.²⁸⁷ In developed countries that have good sanitation and where HAART is available, cryptosporidiosis occurs at an incidence rate of <1 per 100 person-years among persons with AIDS.

Isospora belli is endemic in Africa, Asia, South America, and the Caribbean. The organism is isolated from 8% to 20% of Haitian and African AIDS patients; however, it has been associated with only 0.2% of cases of diarrhea in AIDS patients in the United States.²⁸⁸ It is possible that *Isospora* is less frequently seen in the United States because drugs used for prophylaxis of *Pneumocystis carinii* and *Toxoplasma* are also effective against this organism.

Cryptosporidial infection may cause asymptomatic, transient, chronic, or fulminant infection.²⁸⁷ The majority of immunocompetent patients develop profuse diarrhea with abdominal cramps, which is self-limited and subsides in 7–10 days. *Isospora* also can cause a self-limited diarrhea in immunocompetent hosts. Chronic, severe infection is associated with CD4 counts of less than 100 cells/mm³.²⁸⁹ In AIDS patients, both infections can produce an illness characterized by intermittent episodes of abdominal cramps, bloating, and nausea in association with either steatorrhea or a profuse secretory diarrhea. Weight loss is usually profound and the infection is unresponsive to any therapeutic attempts to eradicate it or to sustain nutritional status.^{279,280} In addition

to AIDS, IgA deficiency is an additional risk factor for severe cryptosporidial diarrhea.²⁹⁰

Diagnosis of either *Cryptosporidium* or *Isospora* can be rapidly established by a modified acid-fast stain or auramine stain of the stool or by concentration and identification of the organisms by the sugar-flotation method.²⁹¹ The large size of *Isospora* cysts helps differentiate them from the smaller *Cryptosporidium* cysts (4–5 μ m). A commercially available fluorescein monoclonal antibody assay increases the sensitivity for detection of cryptosporidia.²⁹² Intestinal biopsies are also useful in confirming the diagnosis. Primarily, parasites of the small bowel, *Cryptosporidium* or *Isospora*, can be present throughout the small bowel, colon, or both in AIDS. Mucosal biopsies usually reveal the organisms clustered on the surface epithelial cells of the villi with little or no mucosal destruction, ulceration, or inflammation. Consequently, fecal white blood cells are rarely seen in these protozoal infections as they are in infection with enteric bacteria. Improved diagnostic techniques will provide useful information on the epidemiology of these infections in MSM populations and other populations at risk for infection.

Treatment of *Cryptosporidium* or *Isospora* infections in immunocompetent patients with self-limited diarrhea is rarely required. ART with immune restoration is associated with complete resolution of cryptosporidiosis in HIV-infected patients, and all patients with cryptosporidiosis should be offered ART as part of the initial management of their infection.²²¹ Despite numerous attempts to treat symptomatic infection in immunocompromised individuals, no drugs have been shown to be fully efficacious. In limited studies, the antiprotozoal drug spirinomycin was reported to be effective in several AIDS patients with cryptosporidiosis,²⁹³ but subsequent studies have not confirmed this finding. Paromomycin, a nonabsorbable aminoglycoside, given as a dose of 500 mg four times daily for 14–28 days may improve symptoms; the response rate varies from 30% to 70%.^{292,294,295} Relapses are common, with long-term success rates of only 33%. Current efficacy data do not support a recommendation for paromomycin's use.²²¹ Nitazoxanide has documented increased cure rates compared with controls with HIV-infected patients with CD4⁺ T lymphocyte counts >50 cells/L, but not in those with lower counts.²⁹⁶ *Isospora* infection does respond to antifolates, but the organism is rarely eradicated, and relapse occurs in 50% of treated AIDS patients. The treatment of choice is trimethoprim (160 mg) and sulfamethoxazole (800 mg) (Bactrim DS), given four times a day for 10 days.²⁹⁷ Doses of two tablets twice daily for 2 days is as effective and better tolerated. No effective alternative treatment is available for those patients who cannot tolerate sulfonamides, although pyrimethamine 50–75 mg daily with folinic acid for acute infection appears comparable to treatment with trimethoprim and sulfamethoxazole.²⁹⁸ ART is recommended as part

of the treatment since immune restoration is associated with more rapid symptom resolution and less relapse.

Like cryptosporidia and *Isoospora*, *Cyclospora cayetanesis* is a cause of chronic diarrhea in immunocompetent and immunocompromised hosts. Previously called cyanobacterium-like body (CLB), blue-green alga, and “Big Crypto,” this organism is found worldwide.^{288,299,300} The epidemiology of this infection is not fully elucidated; however, in the United States it has been identified as a cause of traveler’s diarrhea³⁰¹ and has been associated with outbreaks due to ingestion of unwashed raspberries.³⁰⁵ Evaluation of stool samples from patients with diarrhea in Chicago and Massachusetts found a prevalence of *Cyclospora* of 0.3–0.5%, similar to that of *Isoospora*.^{299,303} Pape et al. found cyclospora to be the cause of diarrhea in 11% of 450 HIV-infected Haitians but in no HIV-uninfected patients with diarrhea.³⁰⁴ The clinical syndrome of watery nonbloody diarrhea is indistinguishable from cryptosporidiosis and isosporosis.

The diagnosis of *Cyclospora* infection can be made by identification of the 8- to 10- μ m nonrefractile oocysts in fresh or preserved stool samples. The oocysts have variable acid-fast staining and with UV epifluorescence they autofluoresce as neon blue circles. Bactrim DS four times daily for 10 days followed by suppressive therapy three times per week usually produces symptomatic improvement in AIDS patients.³⁰⁴

Microsporidia are obligate intracellular protozoa, and before AIDS only 10 cases of human infection had been documented. Since 1981 several hundred cases have been reported, most since 1991.^{305,306} As with other protozoal infections, the incidence of microsporidiosis has declined dramatically with the widespread use of effective ART. Two species of microsporidia are associated with diarrhea in HIV-infected patients: *Enterocytozoon bieneusi* and *Encephalitozoon (Septata) intestinalis*.^{306,307} The mode of transmission of these organisms is not known; however, they are ubiquitous organisms and are likely zoonotic and/or waterborne in origin. They have been identified as a cause of diarrhea in MSM, and the majority of cases of infections are in adult males, suggesting sexual transmission.

Microsporidia cause a spectrum of disease from asymptomatic infection to severe diarrhea and malabsorption.³⁰⁸ Rabeneck et al. recently identified *E. bieneusi* in the intestinal epithelial cells of HIV-infected patients without diarrhea. Self-limited diarrhea occurs in patients without severe immunodeficiency, and chronic watery diarrhea with malabsorption occurs with severe immunodeficiency when the CD4⁺ T lymphocyte count is <100 cells/ μ L.^{309,310}

The diagnosis can be made by identification of the small (1–2 μ m) spores in stool and duodenal fluid by light or electron microscopy. The organisms are well visualized by light microscopy with chromotrope staining.³¹¹ Light- or electron-microscopic examination of semithin plastic sections of biopsy samples from the duodenum and jejunum demonstrates infection confined to enterocytes covering the villi, along

with villous atrophy and cell degeneration. Electron microscopy is required for species identification or by PCR using species- or genus-specific primers.³¹²

At present, there is no reliably effective therapy for microsporidial infection and the best approach to resolution of symptoms is immune restoration. Albendazole has been curative in some cases of infection with *Encephalocytozoon* and disseminated *Septata*.³¹³ Albendazole treatment of *E. bieneusi* may alleviate symptoms, but it does not seem to eradicate the organism and is associated with a high rate of relapse.³¹⁴ Oral fumagillin (60 mg/day) is a water insoluble antibiotic made by *Aspergillus fumigatus* which may have promise, and nitazoxanide might resolve chronic diarrhea caused by *E. bieneusi*.^{315,316} Symptomatic treatment with antidiarrheal agents such as lomotil, loperamide, octreotide, and nutritional supplements is helpful in refractory cases.³¹⁷

CONDYLOMATA ACUMINATA

Anal warts due to human papillomaviruses are common in individuals who practice anal intercourse.³¹⁸ In one series of 260 MSM seen by proctologists, 134 (51.5%) had anal warts.¹⁷ Warts due to papillomaviruses may occur anywhere in the anal or genital area but are particularly common in the anus in MSM. Of those individuals with warts in the study just cited, 6% had them in the perianal area, 10.5% had them only in the anal canal, and 83.5% had them in both areas. These warts rarely, if ever, extend beyond the pectinate line into the rectum. Perianal condylomata acuminata appear as raised pink-to-brown papules, usually in clusters, and occasionally as large cauliflower-like masses. Patients immunocompromised due to malignancy or HIV infection are more likely to have frequent recurrences of extensive lesions which are recalcitrant to therapy.³¹⁹

Diagnostically, warts should be differentiated from squamous cell carcinoma and from condylomata lata, the moist, flat papules of secondary syphilis. These may be diagnosed by a reactive serology for syphilis and by a dark field demonstrating spirochetes in the lesions. Papanicolaou smears of mucosal lesions for dyskeratosis and koilocytes is less sensitive than DNA detection techniques such as dot blot and in situ hybridization.^{320,321} These assays are less specific than Southern blot hybridization. Formal guidelines recommending anal Pap smear screening have not been adopted. If uncertainty exists about the etiology of visible lesions or the presence of high-grade dysplasia or malignancy prevails, biopsy should be performed.

Therapy of genital warts is discussed in Chapter 25. Topical podophyllin (20% solution), commonly used for genital warts, is also effective in some cases of perianal warts; however, it can cause burns with subsequent stenosis when used intranally. A 0.5% podophyllin solution (podofilox) or a 0.5% gel is effective and has the benefit of being able to be applied by

the patient.³²² Imiquimod in a 5% cream formulation can be self-applied to lesions at bedtime and removed in the morning by washing. It is applied on three nonconsecutive nights per day up to 16 weeks. Cryotherapy with liquid nitrogen clears up to 90% of treated warts. Laser-beam therapy and surgical excision have been used in refractory cases. Interferons alpha, beta, and gamma have been successfully used,^{323–325} but are not generally recommended because of high cost and administration difficulty.

There has been a recent increase in the number of cases of AIN in MSM and a growing body of evidence to support the role of HPV in this malignancy. HPV types 16 and 18 have been found in 56% and 5%, respectively, of anal cancers.³²⁶ Additionally, there appears to be an increased incidence of HPV infection and AIN in HIV-infected individuals. High-grade intraepithelial neoplasia has been found in 0.5–5.4% of HIV-seronegative MSM compared with 4–15.2% of HIV-seropositive men.³²⁷ Risk of high-grade AIN was associated with HPV types 16 and 18 in both HIV-seronegative and seropositive men and was 2.9-fold higher for HIV-seropositive men with fewer than 500 CD4 cells/mm³, compared with men with more than 500 CD4 cells/mm³.³²⁸ Although data are limited, effective ART does not appear to substantially influence the short-term natural history of AIN.

MYCOBACTERIAL INFECTIONS

MAC is a group of “atypical” mycobacteria that has been identified in severely immunocompromised patients, including MSM with AIDS.¹⁰ Ninety-eight percent of these isolates are *M. avium* (usually serovars 1, 4, and 8); the remainder include *M. intracellulare*. The gastrointestinal tract and lymph nodes appear to be the most common organs infected by this organism. Infections of the intestinal tract are usually part of disseminated infection which presents with fever, night sweats, abdominal pain, watery diarrhea, steatorrhea, and malabsorption. Both the clinical and the radiographic features of this disease may mimic Whipple’s disease.³²⁹ The major risk factor for this disease is severe immunocompromise, with less than 75 CD4 lymphocytes/mm³ or previous opportunistic infection, especially CMV disease.³²⁹

It has been postulated that the gastrointestinal symptoms of MAC infection are due to defective macrophage processing of the MAC pathogens, which leads to accumulation of macrophages and secondary malabsorption, as seen in Whipple’s disease. The defective T-cell activation of macrophages has been proposed as a mechanism in the pathogenesis of Whipple’s disease, an immunologic defect which is also characterized by depression of T-cell function.^{329,330} The characteristic findings seen in MAC infection of AIDS patients, such as severe lymphopenia and anemia,

reduction of circulating helper-T cells, skin test anergy, and polyclonal hypergammaglobulinemia, are not classically seen in Whipple’s disease.

The diagnosis of MAC infection is based on stool culture, acid-fast staining of the organism in the stool, and histologic examination of small bowel biopsy specimens. Although some patients are asymptomatic excretors of MAC, histologic evidence of gastrointestinal involvement is indicative of disseminated infection. Fine, white mucosal nodules noted on endoscopy are highly suggestive of MAC disease.³³¹ The main histologic features on small bowel biopsy include increased numbers of macrophages filled with PAS-positive and acid-fast bacilli within the lamina propria, villous atrophy, and exudative enteropathy.³²⁹ Blood and bone marrow cultures are positive in 85–90% of patients with gastrointestinal involvement. Blood cultures using the lysis centrifugation techniques for mycobacterial organisms are frequently positive in AIDS patients with disseminated MAC.³³¹

The following combination drug regimes have been found to decrease bacteremia and improve symptoms: Clarithromycin 500 mg twice daily and ethambutol 15–25 mg/kg/day with or without ciprofloxacin 750 mg twice daily and rifabutin 300 mg daily, or azithromycin 500–600 mg daily and ethambutol 15–25 mg/kg/day with or without ciprofloxacin 750 mg twice daily and rifabutin 300 mg daily. Prophylaxis with clarithromycin 500 mg twice daily, azithromycin 1200 mg weekly, or possibly rifabutin 300 mg daily for AIDS patients with less than 50 CD4 lymphocytes/mm³ is recommended to decrease the frequency of disseminated disease and improve survival.^{332–334}

CYTOMEGALOVIRUS INFECTION

Gastrointestinal CMV disease may be sexually transmitted and can occur in immunocompromised and immunocompetent patients, involving any area from mouth to anus. Several case reports have described CMV proctitis or proctocolitis following sexual intercourse and as part of a primary CMV infection.^{335–338} Gastrointestinal symptoms of CMV disease have been reported in 2–16% of organ transplant recipients, but AIDS patients with advanced immunosuppression, typically those with CD4⁺ T lymphocyte counts <50 cells/μL, are at risk of developing CMV disease.³³⁹ This is usually due to reactivation of latent infection, but a few cases may be due to primary infection or reinfection. In one autopsy series before potent ART, gastrointestinal CMV was identified in 90% of AIDS patients, and in AIDS patients with intestinal symptoms CMV has been identified—in stool cultures or in rectal or intestinal biopsy samples at autopsy—in up to 50%.^{7,12} CMV infection of the gastrointestinal tract may be associated with esophagitis, esophageal ulcerations, enteritis, colitis, or proctitis.

CMV most often presents as a diffuse colitis associated with fever, abdominal pain, anorexia, and watery or bloody

diarrhea.^{340–342} Occasionally, patients with CMV intestinal symptoms may present clinically with a solitary intestinal ulcer, occasionally resulting in toxic dilatation and rarely in intestinal perforation.³⁴³ Barium enema may show a picture of segmental colitis or pancolitis.³⁴⁴ Sigmoidoscopy or colonoscopy frequently shows erythema, ulceration, or occasionally plaques, nodules, polyps, or violaceous lesions resembling Kaposi's sarcoma. Biopsy of these lesions reveals CMV vasculitis giant cells with large pleomorphic nuclei containing basophilic intranuclear CMV inclusions; these are usually endothelial cells and fibroblasts. Biopsy also shows acute hemorrhage and inflammation in the lamina propria. The presence of intranuclear inclusion bodies suggests that CMV is present in the tissue, but its role in disease pathogenesis remains unclear, since its presence is documented in both inflamed and noninflamed tissue. Marked involvement of endothelial cells can be associated with frank vasculitis and secondary mucosal ischemic changes.

Diagnosis of CMV infection is confirmed by histologic demonstration of intranuclear inclusion bodies or by viral cultures or immunofluorescent stain of intestinal biopsies.³⁴⁵ Abnormal cytopathology is more likely than isolation of the virus in culture to correlate with significant disease. Systemic CMV can be determined by viral culture of the white blood cell buffy coat or urine.³⁴⁴ New techniques using labeled nucleic acid probes and PCR have been effective in detecting CMV in tissue and other specimens; however, detection of the organism by PCR does not distinguish infection from disease.^{346,347}

Therapy for CMV disease has been best evaluated for CMV retinitis. Treatment with ganciclovir, foscarnet, and cidofovir has been effective in suppressing viral replication with subsequent negative cultures and stabilization of clinical disease, but relapses are common after therapy is discontinued.³⁴⁸ Symptomatic improvement has been reported in 93–100% of solid organ transplant recipients with CMV gastrointestinal disease treated with ganciclovir. In AIDS patients, ganciclovir treatment of CMV esophageal ulcers produces improved symptoms in 75%; therapy for CMV colitis appears to be less effective.³⁵ Nelson et al. noted that while 15 of 18 (83%) patients with esophageal disease treated with foscarnet had complete response, only 11 of 18 (61%) patients with colitis had a complete response.³⁴⁹ Pancytopenia is the major toxicity of ganciclovir; it may be alleviated with granulocyte colony-stimulating factor and erythropoietin. Nephrotoxicity is the major side effect of foscarnet and cidofovir.³⁴⁸ Foscarnet also causes significant electrolyte wasting and may produce seizures. Without treatment and with continued immunosuppression, CMV may result in intestinal complications such as intestinal perforation, toxic megacolon, and acalculous gangrenous colitis.^{346–347} Oral ganciclovir 1 g three times daily may be effective in reducing the risk of CMV disease.³⁵⁰ Chronic maintenance therapy is not routinely recommended for gastrointestinal disease but may be considered if relapses occur.

INTESTINAL SPIROCHETOSIS

Spirochetes other than *T. pallidum* were documented in the human intestinal tract as early as the nineteenth century. In humans, *Brachyspira aalborgi* and *Brachyspira pilosicoli* predominate. However, the pathologic and clinical significance of this condition remains unclear.^{351–354} McMillian and Lee reported the identification of intestinal spirochetes on biopsies of 36 of 100 MSM.³⁵⁵ There was no attempt to correlate symptoms with the presence or absence of spirochetes, and a comprehensive search for other pathogens in these patients was not carried out. Surawicz et al. diagnosed intestinal spirochetosis in 15% of MSM and no heterosexual men. Rectal spirochetosis was not associated with other histopathologic abnormalities or symptoms.³⁵³ Law et al. diagnosed rectal spirochetosis in 39% of healthy unselected MSM attending an STD clinic. Rectal spirochetosis was associated with a history of oral–anal contact (OR 3.45), detection of three to five different nonpathogenic protozoans in feces (OR 11.7), and positive HIV-1 serology (OR 4.48).^{354,355}

The association of intestinal spirochetosis with symptomatic disease remains largely anecdotal. Usually, gastrointestinal symptoms are attributed to intestinal spirochetosis if no other cause can be identified. Kostman et al. described two AIDS patients with diffuse colitis who on histopathology had spirochetes overlying abnormal mucosa.³⁵⁶ No other pathogen was identified. Both patients responded to metronidazole therapy. Gebbers et al. also reported on two patients with mild intestinal symptoms in whom rectal spirochetosis was the only abnormality diagnosed.³⁵⁷ Their histopathologic findings, as with the previous study, indicated invasion of the organism, with spirochetes within epithelial cells and subepithelial macrophages. They also found numerous partially degranulated mast cells and an increased proportion of IgE plasma cells, all suggesting an immune response to the infection. Antibiotic therapy was associated with clearance of the organisms and symptomatic improvement.³⁵⁷ Additional studies have identified intestinal spirochetosis by biopsy in 28 of 100 symptomatic MSM¹³ and by culture in 13 (39%) of 33 symptomatic, and 33 (16%) of 203 asymptomatic men.⁷⁰ Identification of spirochetes by culture was more commonly associated with symptoms of diarrhea than with symptoms of proctitis. Although these data are not definitive, they suggest that intestinal spirochetosis is more prevalent in MSM and that it may be associated with diarrhea.

Intestinal spirochetosis is readily diagnosed histologically by the presence of a prominent hematoxyphilic band adjacent to the luminal surface of mucosal epithelial cells.¹³ Morphologically distinct from *T. pallidum*, intestinal spirochetes can be demonstrated by darkfield microscopy of fresh material or cultured anaerobically in selected medium. Serological tests for syphilis (VDRL and RPR) are negative.

Since the clinical significance of human intestinal spirochetosis remains in question, the treatment is controversial. No controlled trials have been undertaken to examine the efficacy of antibiotics and whether eradication of the spirochetes leads to resolution of symptoms. Anecdotal reports suggest that treatment with metronidazole 400 mg three times daily for 10 days is effective in eliminating spirochetes and may afford some symptomatic relief. Consequently, until adequate clinical antibiotic studies are performed, metronidazole should be recommended for the treatment of symptomatic human intestinal spirochetosis following the exclusion of other known pathogens. Treatment is not recommended for asymptomatic intestinal spirochetosis.

OTHER PERIANAL SEXUALLY TRANSMITTED DISEASES

Donovanosis (or granuloma inguinale) is a chronic ulcerative disease which generally involves the skin and subcutaneous tissue of the genital, inguinal, and anal regions. Described in Chapter 39, donovanosis is believed to be caused by *Calymmatobacterium granulomatis*, a bacterium which multiplies within tissue histocytes and monocytes.

Donovanosis is rare in industrialized countries but relatively common in tropical and subtropical countries such as New Guinea, India, central Australia, and the Caribbean. The disease occurs more often in males than in females, and it is more common in homosexual than in heterosexual men. Although donovanosis is probably sexually transmitted, the exact mechanism of transmission is still debated. Perianal lesions occur predominantly among those who practice anal intercourse,^{358,359} although the disease can also spread contiguously from the genital area to the anal region. Very little is known concerning involvement of the rectum or gastrointestinal tract. Within the perianal and anal area, the infection starts as a small, commonly pruritic, papule and later ulcerates to form a granulomatous beefy-red ulcer. Opposing (kissing) lesions are common. Lesions can become hypertrophic, at which point they are similar in appearance to condylomata lata. Most of the lesions are painless. Lesions that are located in the anal canal may be associated with rectal bleeding, and they may lead to stenosis of the anal canal.

Diagnosis is based on demonstrating the intracellular organisms (Donovan bodies) on Giemsa-stained impression smears or sections of biopsies from a lesion. Treatment consists of doxycycline 100 mg twice daily for 10 days or longer.

Chancroid occasionally causes perianal lesions in women and MSM. Although anorectal chancroid has not been well studied, it is likely that the painful lesions produced by *Haemophilus ducreyi* would most closely resemble herpetic lesions in the anorectal area, as they do in the genital tract. Diagnosis and therapy of anorectal chancroid are analogous

to the management of genital chancroid (discussed in Chapter 38).

ANORECTAL TRAUMA AND FOREIGN OBJECTS

Complications of anal intercourse include prolapsed hemorrhoids, fissures, rectal ulcers, tears, and foreign bodies.¹⁹ Rectal tears, and occasionally rectal perforation, may be caused by rectal intercourse, by insertion of a closed fist and part of the forearm into the rectum, or by insertion of foreign bodies.^{360,361} Typically, patients with anorectal trauma present with the acute onset of rectal bleeding, or with signs of an “acute abdomen” if rectal perforation has occurred above the peritoneal reflection. Medical attention may be sought because the patient is unable to remove a foreign object. Retained foreign bodies have included vibrators, rubber phalluslike devices, bananas, bottles, apples, billiard balls, light bulbs, a Bermuda onion, and a variety of other unusual objects.³⁶¹

Management of such cases is based on the clinical history, evidence of an acute abdomen, the degree of rectal trauma, and the type of retained object. If an object is present, digital and radiographic examination should confirm the position of the object. The object may be removed through a proctoscope with biopsy forceps, snare, or Foley catheter. Occasionally, local or general anesthesia may be required to remove a foreign body manually or with obstetric forceps.³⁶¹

DIFFERENTIAL DIAGNOSIS

Many agents that infect the gut in MSM cause similar pathology, and differentiation as to the causative agent is sometimes possible only by laboratory tests. Further, infection with several pathogens is not uncommon and overlapping symptoms make differentiation on clinical grounds even more difficult. However, characteristic features of some infections are helpful in narrowing the diagnostic possibilities. It seems apparent that the majority of MSM with anorectal symptoms who consult an STD clinic have a specific infection, and diagnoses such as “idiopathic rectal ulcer,” “nonspecific proctitis,” or “trauma” are usually unwarranted unless specific infections are excluded. In general, it is clear that in MSM proctitis or discrete ulcerative lesions of the rectum are usually caused by conventional STD agents such as *N. gonorrhoeae*, *C. trachomatis*, HSV, and *T. pallidum* and are probably acquired by receptive rectal intercourse. Infections associated with proctocolitis are caused by enteric pathogens such as *E. histolytica*, *C. jejuni*, *Salmonella*, and *Shigella*, which may be acquired most often among MSM by anilingus. Symptoms of enteritis, without sigmoidoscopic evidence of proctocolitis, are most often attributable to *G. lamblia* infection in homosexually active men.²⁷

In immunocompromised MSM with HIV infection, additional organisms should be considered, such as cryptosporidia, microsporidia, *Isospora*, *Cyclospora*, MAC, and CMV, in addition to HIV-1. In these immunosuppressed patients, esophagitis may develop secondary to *Candida*, HSV, and CMV.

The constellation of fever, severe anorectal pain, constipation, urinary retention, and sacral neuralgias in a patient with ulcerative rectal mucosa strongly suggests HSV infection. The presence of nonpainful anorectal ulcers, rectal polyps, or nonspecific anorectal symptoms in a patient with a rash should suggest the possibility of anorectal syphilis. LGV proctitis or proctocolitis should be considered in MSM who have severe anorectal symptoms such as hematochezia, rectal discharge, diarrhea, and fever and who may have severe ulcerative rectal mucosa with granulomas present on rectal biopsy. LGV should also be considered in MSM who are suspected to have Crohn's disease of the rectum. Since *N. gonorrhoeae* and non-LGV *C. trachomatis* cause nonspecific anorectal symptoms without symptoms of enteritis and result in nonspecific pathology of the lower rectum, these pathogens should be considered in most individuals who present with anorectal symptoms, have only mild proctitis on sigmoidoscopy, and acknowledge receptive anorectal intercourse.

Campylobacter, *Salmonella*, and *Shigella* should be suspected in those individuals with a history of acute diarrhea associated with bloody stools and fecal leukocytes, especially if sigmoidoscopic findings are not limited to the distal rectum and if stools are negative for ova and parasites. *Giardia* infection will more often cause diarrhea which is more chronic and nonbloody and is associated with nausea and bloating. *E. histolytica* infection presents with symptoms ranging from acute bloody diarrhea to chronic diarrhea with intermittent exacerbations.

A heavy concentration of *Candida albicans* in stool has been associated with pruritus ani or rectal itching in MSM in our studies, and topical and oral therapy with appropriate antifungal agents may be beneficial in such patients. The presence of perianal dermatitis with or without pustulae may suggest anorectal candidiasis. However, perianal erythema extending over an area of several centimeters in diameter is commonly associated with rectal discharge caused by a variety of agents and is not specific for anorectal candidiasis. When symptoms of proctitis or enteritis occur during or after antimicrobial therapy, *C. albicans* infection or pseudomembranous enterocolitis with *Clostridium difficile* infection should be considered.

When the patient is known to be immunocompromised secondary to HIV infection or AIDS, a more extensive evaluation for opportunistic infections should be undertaken. *Candida*, HSV, and CMV should be evaluated in those patients with symptoms of esophagitis. Intestinal protozoans such as cryptosporidia, *Isospora*, and microsporidia, as well as

MAC and CMV, should be considered in those immunocompromised patients presenting with a diarrheal illness of a chronic nature (longer than 2–3 weeks).

If no infectious etiology is demonstrated despite appropriate tests and a trial of antimicrobial therapy (see below) has no effect, then idiopathic inflammatory bowel disease, such as ulcerative colitis or Crohn's disease, or HIV-1 infection of the intestine should be considered. Because of clinical similarities between enteric infections (a common problem) and inflammatory bowel disease (much less common), all appropriate infectious agents should be ruled out before a diagnosis of inflammatory bowel disease is made. Additional noninfectious conditions that could be confused with enteric infections include radiation colitis, chemically induced colitis (due to drugs, gold therapy, soaps, lubricants, or other chemicals), and neoplasm.

MANAGEMENT

The large number of infectious agents that cause enteric and anorectal infections in MSM necessitate a systematic approach to the management of these conditions. The medical history should attempt to differentiate among proctitis, proctocolitis, and enteritis and should assess the constellations of symptoms that suggest one or another likely infectious etiology. The history should also investigate types of sexual practices and possible exposure to the pathogens known to cause proctitis, proctocolitis, or enteritis. Examination should include inspection of the anus, digital rectal examination, and anoscopy (avoiding or minimizing use of bacteriostatic lubricants, which might interfere with microbiologic studies) to identify general mucosal abnormalities. Such abnormalities, including easily induced bleeding and exudate and discrete polyps, ulcerations, or fissures, should be cultured and biopsied if appropriate. Anal warts are frequently detected, but if proctitis is present, therapy of these warts should usually be deferred until the proctitis is resolved.

Initial laboratory tests should include a Gram stain of any rectal exudate obtained with the use of an anoscope; if no exudate is seen, material should be obtained for the Gram stain from the rectal mucosa or from any abnormal appearing stool. The demonstration of leukocytes provides objective evidence for the presence of an infectious or inflammatory disease. Until NAATs are approved for rectal specimens, cultures for *N. gonorrhoeae* should be obtained from the rectum, urethra (if NAAT is not done), and pharynx, and if possible a rectal culture for *C. trachomatis* should be performed. A serologic test for syphilis should be performed in all cases. If any external ulcers, rectal mucosal lesions, or suspected condylomata lata are seen, darkfield examination of these lesions and a rapid plasma reagin test should be performed in the clinic. HSV cultures should be performed if ulcerative lesions are

present. If proctocolitis is likely on the basis of either symptoms or sigmoidoscopic examination, then additional cultures for *Campylobacter*, *Salmonella*, and *Shigella* and stool examination for *E. histolytica* are indicated.

If symptoms and signs suggest enteritis rather than proctitis or proctocolitis, stool should be cultured for *Campylobacter* and examined (in addition to jejunal aspirate, perhaps) for *Giardia*, cryptosporidia, *Isospora*, mycobacteria, and microsporidia. Additionally, endoscopy and biopsy can aid in diagnosis of HIV, microsporidia, CMV, and MAC enteropathy. Cultures for *Salmonella*, *Yersinia*, and *V. parahemolyticus* and attempts to demonstrate *C. difficile* toxin or enterotoxigenic *E. coli* are sometimes indicated in MSM, as in heterosexual men and women, although these agents have not been found with greater frequency in MSM.

If a diagnosis of gonorrhea is initially made by a positive Gram stain, or if syphilis is confirmed by darkfield examination or rapid plasma reagin serology, appropriate treatment should be instituted promptly. Similarly, anyone with sexual contact with a person with known gonorrhea, syphilis, or chlamydial infection should be treated appropriately on an epidemiologic basis after complete physical examination, while results of cultures for *N. gonorrhoeae* and serology for syphilis are pending. A presumptive diagnosis of HSV can often be made initially on clinical appearance alone or by history, but laboratory confirmation of suspected herpetic lesions is always desirable unless the clinical appearance of vesicular lesions is diagnostic. If the patient remains symptomatic and a careful search reveals no pathogen, or if the patient remains symptomatic despite appropriate therapy for any pathogen found or after empiric therapy, then the patient should be evaluated by a specialist for the possibility of inflammatory bowel disease or other diseases which are not sexually transmitted.

In those patients found to be immunocompromised and infected with HIV, a more extensive evaluation of the intestinal tract is required. A careful oral examination should evaluate for the presence of thrush and/or oral lesions of Kaposi's sarcoma. Dysphagia or odynophagia may suggest the presence of esophageal candidiasis and/or esophageal involvement with CMV or HIV infection. Systemic and/or abdominal lymphadenopathy and the presence or absence of gastrointestinal blood loss should suggest gastrointestinal neoplasms, including Kaposi's sarcoma and gastrointestinal lymphomas. Careful radiographic examinations of the esophagus, small bowel, and colon, as well as endoscopy and colonoscopy, may be warranted in these highly suspect patients. Stool examination should be carefully studied for the presence of cryptosporidia, *Isospora*, and mycobacteria, as well as the other enteric pathogens described above. Intestinal biopsies may be obtained of suspicious lesions and examined for CMV,

mycobacterium, intestinal protozoans, and other histologic features of infection or malabsorption.

Identification of any of the enteric pathogens should result in specific therapeutic regimens. Failure to respond to any specific antimicrobial regimens may represent drug resistance or, more commonly, the presence of additional pathogens, necessitating more comprehensive microbiologic and immunologic evaluation. If symptoms persist after eradication of infection or if no pathogens are identified, one must consider idiopathic inflammatory bowel disease, neoplastic lesions, or antibiotic-resistant opportunistic infections and institute diagnostic and therapeutic approaches to these diseases.

Because of the complexity of diagnosis and treatment of enteritis and proctitis in an STD population and the different levels of laboratory support at STD clinics and in office practice, we have outlined two algorithms. Algorithm A (Fig. 68-11) represents a systematic approach to diagnosis and treatment that is comprehensive and employs treatment only for identified pathogens. It basically represents a stepwise progression toward specific diagnosis and treatment of patient and exposed contacts. The major problem with this algorithm is that the microbiologic evaluation is expensive and time consuming, factors which may indirectly allow continued

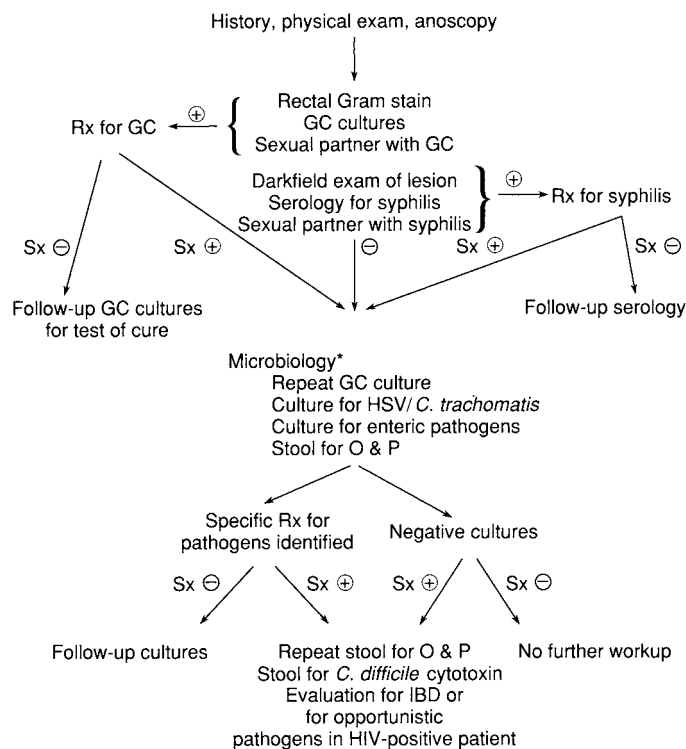


FIGURE 68-11. Algorithm A: Evaluation and treatment of anorectal and/or intestinal symptoms in homosexual men. This algorithm emphasizes a full diagnostic evaluation and treatment for the specific pathogens identified. Ideally, microbiologic evaluation should be based on presenting symptoms and sigmoidoscopy findings. Rx = treatment, Sx = symptoms, GC = *N. gonorrhoeae*, O & P = ova and parasites, a IBD = inflammatory bowel disease.

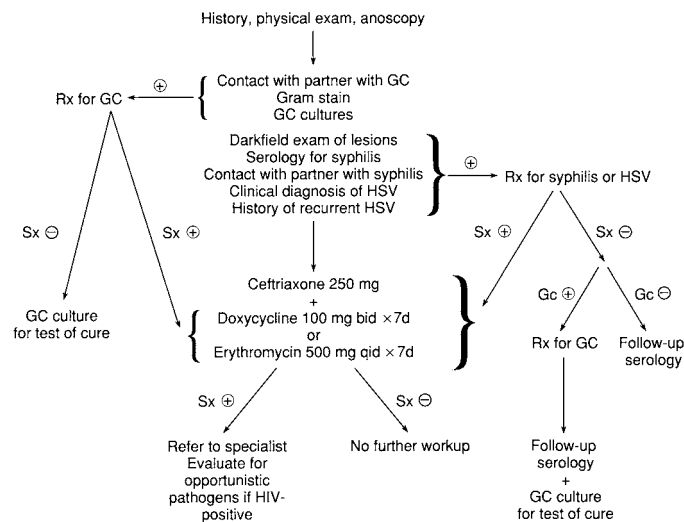


FIGURE 68-12. Algorithm B: Evaluation and treatment of anorectal and/or intestinal symptoms in homosexual men. This algorithm emphasizes empirical therapy after an initial evaluation for gonorrhea and syphilis. Empirical therapy consists of intramuscular ceftriaxone 250 mg, followed by either azithromycin 1 gm, doxycycline, or erythromycin. If the patient remains symptomatic, he is referred for more complete evaluation. GC = *N. gonorrhoeae*, Rx = treatment, Sx = symptoms.

discomfort of the patient and transmission of the pathogen before final diagnosis and treatment.

Algorithm B (Fig. 68-12) is based on empirical therapy, which has the advantage of decreasing the cost of laboratory tests and provides immediate therapy to patients who may not return for follow-up visits. Such empirical therapy has recently been shown to produce more rapid resolution of the symptoms and signs of acute proctitis in MSM than specific therapy.³⁶² Empirical therapy has the disadvantage, however, of treating a patient before the diagnosis is known. In the study just cited, unrecognized HSV proctitis was the major reason for the failure of an empirical therapy. The treatment may also convert the patient to an asymptomatic carrier, and most important, it interferes with public health efforts to trace contacts of the patient who may harbor a specific pathogen. Such public health efforts would be possible only if a specific diagnosis is made in the patient.

Selection between these two approaches must be based on clinic and public health priorities, budget, laboratory support, and patient population. Alternative approaches will undoubtedly become preferable as more is learned about the etiology and epidemiology of enteritis, proctitis, and proctocolitis in MSM.

REVENTION

Because of the relatively high prevalence of asymptomatic anorectal carriage of pathogenic organisms in MSM, a concerted effort involving the clinician and public health authorities is necessary to control these infections. Examination and

treatment of the sexual partners of MSM with STDs such as gonorrhea or syphilis is a conventional practice, yet similar management of the sexual contacts of MSM with enteric infection is not a routine procedure. Such an approach must be evaluated, not only for cases that come to medical attention through the STD clinic but also for those that are reported from other sources. We believe that when a specific pathogen is identified in a symptomatic homosexually active male patient, epidemiologic investigation of all sexual contacts within a time frame appropriate to the incubation period of the pathogen in question should be performed, and appropriate diagnostic tests for the pathogen(s) involved should be obtained from the contacts. This is especially important for those agents which can be eliminated by treatment, such as gonorrhea, *C. trachomatis*, syphilis, and the enteric pathogens. Because of the intermittent nature of virus shedding, HSV cultures in sex partners of men with rectal HSV infection is frequently unrewarding.

Most of the pathogens we have discussed should be reported to local public health workers, whose assistance in coordinating efforts to identify and examine culture contacts is helpful. Household as well as sexual contacts should be screened for infection when investigating the spread of enteric pathogens. After the acute infection subsides or following therapy, repeat laboratory tests should be performed to detect possible development of a carrier state. Infected individuals should abstain from sexual practices that might spread infection until repeat cultures are negative. Infected persons should also be educated regarding safe sex practices in the AIDS era.

Effective education of both physicians and patients about the different modes of transmission of these pathogens is necessary, along with more reliable and available laboratory techniques for diagnosis of some of them. Recognition of the importance of sexual transmission in the spread of these infections is a prerequisite to designing public health programs that will effectively prevent their spread in the community at large. In addition, recognition of the role that some of these pathogens (especially HSV and syphilis) may play in facilitating the spread of HIV infection provides added incentive for their prevention.^{363,364}

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PART 12

Clinical Management of HIV Infection

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Freya Spielberg and Ann E. Kurth

IMPORTANCE OF HIV TESTING

The importance of HIV counseling and testing for early clinical intervention has been clearly established, both to initiate highly active antiretroviral therapy (HAART) to delay progression to AIDS, as well as to prevent opportunistic infections once a diagnosis of AIDS has been established.¹

More recently the importance of early identification of HIV infection for HIV prevention has been established, through both biological and behavioral mechanisms. In acute HIV infection high viral titers lead to greater infectivity.² People who receive HAART have decreased viral titers and so are potentially less infectious.³ As importantly, people who learn that they have HIV are much less likely to engage in high-risk behaviors.⁴

To impact the HIV pandemic, testing is critical even in resource poor settings where HIV treatment is not yet available for all. Thus, in the 2006 guidelines from the Centers for Disease Control and Prevention (CDC) and the 2007 guidelines from the World Health Organization (WHO), a greater emphasis has been placed on expanding access and removing barriers to HIV testing in order to stem the continuing pandemic.^{5,6}

In the United States the CDC recommends opt-out screening for HIV among all people visiting health-care facilities, and no longer requires a separate written consent or risk-reduction counseling in these settings.⁵ For populations at highest risk the CDC continues to recommend expanded access to outreach HIV counseling, testing and referral services with integrated client-centered HIV risk-reduction counseling.

In global settings, the WHO has made similar recommendations for routine provider-initiated testing in populations with “generalized epidemics” (HIV prevalence among pregnant women >1%). Whereas in populations with “concentrated epidemics” (HIV prevalence in sub populations >5%, but <1% in pregnant women) or in “low-level epidemics” (HIV <5% in all populations, HIV <1% among pregnant women), the WHO advocates offering provider-initiated testing to

people with signs or symptoms of HIV, and to high risk populations.⁶

HIV EPIDEMIOLOGY

The estimated number of people with HIV has reached more than 1 million in the United States⁷ and over 40 million worldwide.⁸ Those who are aware of their risks and are willing to test have been identified, yet approximately one-fourth of the people infected with HIV in the United States (252,000–312,000)⁹ and over 80% globally are unaware that they are infected.⁸ Without the knowledge of their status, many people with HIV are likely to transmit the virus unknowingly⁴ and to miss early monitoring benefits.

Since 1998, in the United States, the estimated number of new infections has remained stable at 40,000 per year.¹⁰ Since 1980, however, the demographics of the HIV epidemic in the United States has changed, with increasing proportions of young people (<20 years), women, racial, or ethnic minorities, people who live outside metropolitan areas, and heterosexual women and men becoming infected.¹¹ Thus, the initial strategy of risk based or geographical testing for HIV is no longer effective.

An estimated 4.1 million new people globally were infected with HIV in 2005.⁸ The HIV incidence rate is believed to have peaked in the late 1990s, now decreasing in some countries, stable in many, and increasing in others.¹² In order to reduce HIV incidence globally, both the CDC and WHO/UNAIDS are promoting increased access to HIV testing in both health-care settings and in community settings.^{5,6}

■ TRANSMISSION OF HIV

Current evidence suggests that between 54% and 70% of the estimated 40,000 new HIV infections each year in the United States (and a higher percentage globally) occur through transmission from persons who are unaware of their HIV-positive status.¹³ Many persons receive their HIV diagnosis late in the course of the disease. In the United States, as many as 40–45% of persons testing positive for HIV received their

first positive test results less than a year before AIDS was diagnosed.¹⁴ In the United States and many low- and middle-income countries, people often first present for testing with symptoms of AIDS.

The efficiency of transmission of HIV varies greatly with the stage of disease.² Patients with the greatest viral burdens (acute HIV, AIDS, and rapid progressors) are most contagious. Subjects with acute HIV may be responsible for nearly half of new cases of HIV² and clusters of cases are easily detected.¹⁵ However, Fraser et al. and other mathematical modelers have argued that patients with established infection and moderate set-point viral burden may live so long (sexually active) that they will dominate the epidemic.¹⁶

■ TIME COURSE OF ASSAY DETECTION OF HIV INFECTION

To diagnose HIV infection, in most health-care settings in the United States a rapid enzyme linked immunoassay (EIA) or standard EIA is used, followed by Western blot for confirmation. In many global settings two to three rapid HIV tests are used for screening and confirmation.¹⁷ Initially the window period (the time during which someone is infected and antibody negative) was estimated to be 6 months. Third-generation antibody tests narrowed that window to 20–30 days after viremia (Fig. 69-1), with recombinant-DNA-based, antigen-sandwich assays sensitive to IgM becoming positive on day 20, as compared to viral-lysate EIAs insensitive to IgM that become positive on average 10 days later.¹⁸

With each generation of antibody assay, the timing of identification of HIV infections is reduced. Newer fourth-generation assays combine antibody and p24 antigen detection, and may simplify identification of chronic and acute HIV infection. One study¹⁹ that examined the timing of detection of HIV for a third- and fourth-generation assay on 92 seroconversion panels, showed that the fourth-generation assay detected HIV a mean of 4 days earlier than the third-generation assay

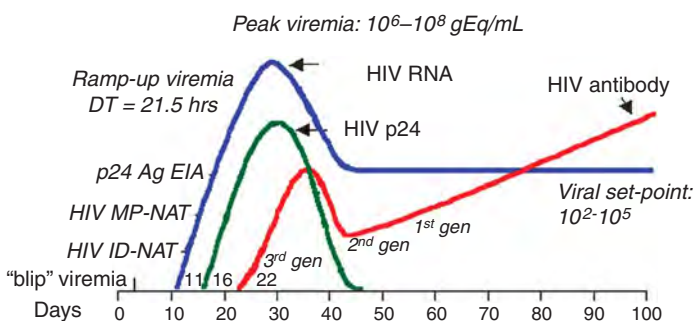


FIGURE 69-1. HIV viremia during early infection. DT, doubling time; gen, generation of enzyme immuno-assay (EIA); Ag, antigen; MP, mini pooled specimens; ID, individual specimens; NAT, nucleic acid testing. (M.P. Busch, Blood Systems Research Institute and University of California, San Francisco; and E.W. Fiebig, San Francisco General Hospital and University of California, San Francisco (Private Communication 3–2007)).

and a mean of 3 days later than a HIV-1 RNA RT–PCR assay. HIV can be detected earliest with RT–PCR for HIV-RNA on day 10 after infectious viremia. HIV DNA (PCR) in PBMC and P24 antigen assays lag behind and do not detect HIV infection until on average day number 15.¹⁸

In high-risk populations, pooling sera for nucleic acid amplification testing (NAAT) can be a cost-effective method for diagnosing acute HIV infection.^{20–22} In some public health clinics, pooled RNA testing is now routinely performed on specimens that are negative on EIA tests. In Atlanta,²¹ 2202 people receiving HIV testing at three sites were tested with third-generation antibody test, and if negative pooled specimens were tested with HIV NAAT. The prevalence of HIV in this population was 3.2%. Adding NAAT increased the sensitivity of the testing algorithm from 94.3% to 100% (by definition) and increased case identification by 6%. A smaller study among men who have sex with men (MSM) in Seattle demonstrated that adding NAAT testing of pooled specimens increased case identification by 13.5%.²²

■ BARRIERS TO TESTING

The reasons more people are not getting tested are varied.²³ Some have poor access to HIV testing. Others are unaware of their risks. Many remain afraid to find out their test results^{24,25} or they avoid testing due to stigma.²⁶ Others avoid testing because of a dislike of counseling, or because of the anxiety associated with waiting for their test result. Some are unaware that they would have access to effective treatment for HIV and so see no point in testing.²⁴

In health-care settings, reasons for late testing are complex and multifactorial, including a low index of suspicion on the part of the provider, client denial of risk, lack of awareness, or of access to HIV testing, and limited confidence in the benefits of early clinical intervention.²⁷ In a recent South Carolina study²⁸ the majority of patients with newly diagnosed HIV infections had been provided health care one or more times in the preceding months, especially in emergency rooms (ERs).

Other studies have attempted to compare the characteristics of persons who have been tested for HIV to those never tested. During May 2000 to February 2003, persons at 16 U.S. sites who were tested early in the course of HIV disease (early testers) were compared with persons who were tested late in the course of HIV disease (late testers). Late testers were more likely than early testers to be black or Hispanic, less educated, and exposed to HIV through heterosexual contact.²⁹

Even among those who test, there are additional barriers to getting HIV test results. Many HIV testing programs have reported that a high proportion of persons who are tested for HIV do not return for their test results. According to data from publicly funded HIV clinics, 30% of persons who tested HIV-positive during 2000 and 39% of persons who tested HIV-negative did not return.³⁰ But many of these individuals

were seeking STD services rather than HIV C/T, which was recommended by providers and not specifically sought. More recently this barrier has been overcome by the provision of rapid HIV testing that allows people to learn their status during the first visit.³¹ However, many clinical settings have been slow to implement rapid testing technology. Although rapid testing has been shown cost-effective from a payer perspective,³² some clinics are hesitant to implement because of the higher costs of the kits or the need for additional staff training. It is necessary for health-care providers to consider that the higher acceptability and effectiveness of rapid testing improves testing rates and staff efficiency³³ and costs less per test result provided than standard testing, even when the price of the rapid test is higher than that of the standard blood test.^{32,34}

Overcoming many of the barriers to HIV testing may require large-scale social marketing campaigns as well as modifications of counseling and testing programs. It will be important to develop interventions to address HIV-related stigma, especially in developing country settings. It will be necessary to make acceptable HIV counseling and testing strategies conveniently available. And it will be important to make people aware that the benefits of knowing one's status clearly outweigh the risks of testing. This is true even in countries where HAART is unavailable, because knowledge of HIV status is necessary to prevent further spread of the infection.³⁵

■ ROLE OF HEALTH-CARE PROVIDERS

Health-care providers can play a large part in increasing the number of people who are aware that they are infected with HIV. System changes will be necessary to ensure that patients are screened and offered HIV testing. One national survey showed that less than one third of the physicians routinely screen for STDs.³⁶ Judgmental providers have been cited as a barrier to eliciting honest information regarding past sexual behaviors.³⁷

In response to the recognition in the late 1990s that nearly two thirds of inpatients newly diagnosed with AIDS had received care in their health system during the year preceding admission, Grady Hospital in Atlanta, GA, began to routinely recommend HIV testing to patients presenting to the urgent-care clinic. Compared with 1999 when testing was based on symptoms or risk behaviors, the Grady study found that more patients were tested, more HIV infections were detected, and more infected persons learned their diagnosis and entered into care.³⁸

Studies examining the prevalence of unidentified HIV infection in urban and suburban emergency departments (ED) provide insight into the missed opportunities for risk assessment. A systematic review of seven ED-based testing studies found HIV seroprevalence rates of 2–17% with rates highest among MSM or injection drug users (IDUs). The authors concluded that the data supported the prior

recommendation that EDs offer HIV screening to high-risk patients (i.e., those with identifiable risk factors) or high-risk populations (i.e., those where HIV seroprevalence is at least 1%).³⁹ More recent studies have provided evidence that routine HIV testing in populations where prevalence is 0.1% would still be cost-effective,⁴⁰ and that's the threshold CDC recommended for routine testing.⁵ Universal testing can be justified based on this cost-effectiveness analysis, especially in clinical venues that lack accurate data on HIV prevalence.

■ HISTORY OF HIV COUNSELING AND TESTING RECOMMENDATIONS

The first diagnostic test for HIV, an EIA was approved by Food and Drug Administration (FDA) in 1985 to screen transfusion donors to keep the blood supply safe (see [Table 69-1](#)). Within the following 2 years, publicly funded HIV counseling and testing clinics were established so that people with suspected infection had an alternative to blood banks for diagnosis.

Early in the epidemic, prior to the availability of treatment, the benefits of testing were less clear. Some believed the stigma and public risks, such as loss of jobs or insurance, associated with having HIV outweighed the benefits of knowing one's status. Protections were developed for confidentiality, a separate consent form for testing was mandated in most states, and anonymous testing was made available.

A counseling model was developed with HIV testing to accommodate the 1–2 week delay for the required confirmatory testing with a Western blot test or Immuno-fluorescence assay (IFA). The standard model of HIV counseling and testing was designed to encompass four primary goals: (1) to identify HIV-infected persons for clinical interventions; (2) to provide counseling about risk reduction for HIV-negative persons at risk of HIV acquisition and for HIV-positive persons at risk of HIV transmission; (3) to provide referrals for medical and case management services for HIV-seropositives and for prevention interventions for those at high risk of HIV acquisition; and (4) to initiate partner notification with counseling and referral to prevention services for partners of HIV-positive clients.

Within 2 years of the first HIV antibody test in 1985, alternate testing sites were developed to provide high-risk persons places for HIV antibody testing other than blood banks. Over time, the alternate testing sites evolved to provide a greater emphasis on risk reduction counseling. After the first reports in 1989 of zidovudine's efficacy for HIV-positive persons with CD4 counts of less than 500,⁴¹ the focus of the counseling and testing sites (CTS) shifted to early detection of seropositive persons for clinical interventions.

By 1998 HIV counseling and testing was provided in 11,640 CDC-funded sites, up from 5149 sites in 1989. By 2002 nearly 40% of the U.S. adult population has been tested for HIV, according to telephone-based surveys of households.⁴² To

Table 69-1. Global HIV Counseling and Antibody Testing Innovations

Date	Innovation	Description	Reference
1985	First HIV antibody test FDA approved in the United States	Abbott Enzyme-linked immunoassay (ELISA) for screening transfusion donors	http://www.fda.gov/cber/products/testkits.htm
1987	Voluntary Counseling and Testing (VCT) Centers established in the United States	Voluntary counseling and testing center (VCT) establishment. HIV testing recommended for people at risk and those seeking STD treatment.	Public health service guidelines for counseling and antibody testing to prevent HIV Infection and AIDS. <i>MMWR</i> 1987; 38(No. S-7): 1–7
1987	Two test algorithm recommended – EIA followed by Western blot (WB) confirmation for diagnosis of HIV infection	Confirmatory testing recommended because of concern about false positive results from use of screening tests in low prevalence populations.	Public health service guidelines for counseling and antibody testing to prevent HIV Infection and AIDS. <i>MMWR</i> 1987; 38(No. S-7): 1–7
1989	Recommendation that test results not be provided before completion of confirmatory test results	CDC guidelines resulted in requirement of pretest counseling with 1–2 week delay for posttest counseling and result disclosure.	Interpretation and use of the Western blot assay for serodiagnosis of human immunodeficiency virus type 1 infections. <i>MMWR</i> 1989; 38(No. S-7): 1–7.
1989	Rapid testing for blood transfusion donor screening in developing country settings	A large study in Zaire evaluating five different rapid HIV tests demonstrated that some rapid HIV tests could be used to accurately screen transfusion donors for HIV in settings where blood is not stored and EIA/WB is not feasible.	Spielberg F, Mulanga Kabeya C, Quinn TC, et al. Comparative evaluation of rapid, visually read, HIV antibody screening assays at Mama Yemo Hospital, Kinshasa, Zaire. <i>Lancet</i> 1989; 1: 580–4.
1990	Research showed AZT can benefit persons with HIV	The first study was published showing the benefit of an antiretroviral medication	Volberding PA, Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, Balfour HH Jr, Reichman RC, Bartlett JA, Hirsch MS, et al. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. <i>N Engl J Med</i> 1990; 322(14): 941–9.
1990	Two rapid tests used for initial screening and confirmation of HIV diagnosis in developing country setting	A study demonstrated that two rapid tests could be used for both screening and confirmation with high accuracy.	Spielberg F, Mulanga Kabeya C, Auditore-Hargreaves K, et al. Performance and cost-effectiveness of a dual rapid assay system for screening and confirmation of Human Immunodeficiency Virus type 1 seropositivity. <i>J Clin Microbiol</i> 1990; 28(2): 303–6.
1991	Western blot FDA approved for confirmatory testing	The first confirmatory test for diagnosis of HIV infection	http://www.fda.gov/cber/products/testkits.htm

Table 69-1. (Continued)

Date	Innovation	Description	Reference
1992	Immuno Fluorescence assay FDA approved for confirmatory testing	Alternative confirmatory test based on immune-fluorescence	http://www.fluorognost.com/
1992	Rapid HIV test FDA approved in the United States	A serum- based rapid immunoassay FDA approved.	http://www.fda.gov/cber/products/testkits.htm
1992	WHO recommends use of rapid tests for screening and confirmation of HIV in developing country settings	Guidelines developed for HIV testing algorithms globally	Global programme on AIDS. Recommendations for the selection and use of HIV antibody tests. <i>Wkly Epidemiol Rec.</i> 1992; 67(20): 145–9.
1993	Extension of recommendations for testing to health-care settings in the United States	Routine HIV testing recommended in health-care settings with >1% HIV prevalence	CDC. Recommendations for HIV testing services for inpatients and outpatients in acute-care hospital settings. <i>MMWR</i> 1993; 42(No. RR-2): 1–10.
1994	Client-centered counseling recommended in the United States	Guidelines developed for counseling people with high-risk behaviors that specified the development of specific prevention goals and strategies for each client.	CDC. <i>Hiv Counseling, Testing and Referral: Standards and Guidelines.</i> Atlanta, GA: U.S. Department of Health and Human Services, CDC; 1994.
1995	HIV counseling and testing recommendations for pregnant women in the United States	After perinatal HIV was shown to be reduced with AZT treatment, it was recommended that all pregnant women be offered HIV counseling and testing.	CDC. Recommendations for human immunodeficiency virus counseling and voluntary testing for pregnant women. <i>MMWR</i> 1995; 44(No. RR-7): 1–15.
1996	Cost-effectiveness of rapid HIV testing	Research showed that rapid testing for HIV was both more effective than standard testing at providing people with knowledge of their test results, and was also more cost-effective.	Farnham PG, Gorsky RD, Holtgrave DR, Jones WK, Guinan ME. Counseling and testing for HIV prevention: costs, effects, and cost- effectiveness of more rapid screening tests. <i>Public Health Rep</i> 1996; 111: 44–53.
1996	Research showed that brief client-centered counseling can lower rates of STI	A large multisite U.S. based study (Project RESPECT) in STD clinics showed that two 20 minute sessions of pre-test counseling were more effective in lowering HIV risk behaviors than an educational message from a health-care provider, and was as effective as a longer multisession intervention.	Kamb ML, Fishbein M, Douglas JM Jr, Rhodes F, Rogers J, Bolan G, Zenilman J, Hoxworth T, Malotte CK, latesta M, Kent C, Lentz A, Graziano S, Byers RH, Peterman TA. Efficacy of risk- reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. <i>JAMA</i> 1998; 280(13): 1161–7.
1997	WHO update for HIV Counseling and Testing	Testing algorithms recommended	WHO/UNAIDS. Revised recommendations for the selection and use of HIV antibody tests. <i>Weekly Epidemiological Record</i> , 1997; 72(12): 81–87.

(Continued)

Table 69-1. (Continued)

Date	Innovation	Description	Reference
1998	Rapid HIV testing recommended for screening high risk populations	Data showing that most people who test in public sites do not return for their test results, and data showing the acceptability and cost-effectiveness of rapid HIV tests, resulted in changes in recommendations to allow provision of the results of a rapid screening test before confirmation.	CDC. Update: HIV counseling and testing using rapid tests. <i>MMWR</i> 1998; 47: 211–5.
2000	Research showed that HIV counseling and testing was cost-effective in developing country settings	Research made a case for expanding access to HIV testing in developing country settings to reduce sexual transmission of HIV.	Sweat M, Gregorich S, Sangiwa G, Furlonge C, Balmer D, Kamega C, Grinstead O, Coates, T. Cost-effectiveness of voluntary HIV-1 counseling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. <i>Lancet</i> . 2000; 356 (9224): 113–121.
2001	New recommendations for pregnant women to remove barriers to HIV testing in the United States	Simplification of consent and counseling requirements. Integration of HIV testing into routine prenatal testing panels.	CDC. Revised recommendations for HIV screening of pregnant women. <i>MMWR</i> 2001; 50(No. RR-19): 63–85.
2001	New recommendations for HIV testing among private and public sector health providers to expand HIV testing in health-care settings (>1% routine, <1% risk-based), in the United States	Recommendations for more accessible HIV counseling and testing in health-care settings, with routine screening when HIV prevalence was >1%, and targeted risk based testing for low prevalence settings.	CDC. Revised guidelines for HIV counseling, testing and referral. <i>MMWR</i> 2001; 50(No.RR-19): 1–62.
2002	FDA approval of a whole blood test that could be performed at the point-of-care	Previously, the only FDA-approved rapid HIV test required serum, so that point-of-care testing could not be done without venipuncture and a centrifuge. The availability of an FDA approved test that could be performed on fingerstick specimens increased the feasibility of use of rapid HIV testing among high risk populations in outreach settings.	CDC. Notice to readers: approval of a new rapid test for HIV antibody. <i>MMWR</i> 2002; 51: 1051.
2003	New recommendations to make HIV testing a routine part of medical care, and to use rapid testing during labor and delivery when women had not been previously tested, in the United States	Because counseling was perceived as a barrier to care by providers, CDC stressed that while prevention counseling is desirable, it may not always be feasible or appropriate, and should not be required for testing. Rapid HIV testing was advocated in outreach testing programs as a way to reach populations at risk with more effective testing programs	Advancing HIV prevention: new strategies for a changing epidemic—United States, 2003. <i>MMWR</i> 2003; 52: 329–332.

Table 69-1. (Continued)

Date	Innovation	Description	Reference
2004	FDA approved first rapid test to distinguish between HIV 1 and HIV 2.	Rapid test distinguishes between HIV 1 and HIV 2	Greenwood JL, Burnstein GR, Pincus J, Branson B. A Rapid Review of Rapid HIV Antibody Tests. <i>Curr Infect Dis Rep</i> 2006; 8(2)125–131.
2004	FDA approved first oral fluid rapid HIV test in the United States.	A rapid oral fluid test received FDA approval for use in point-of-care HIV testing. The test is as simple to perform as a pregnancy test. The test received a CLIA (Clinical Laboratory Improvements Amendments of 1988) waiver so that minimally trained health workers can provide rapid testing and counseling in outreach and/or clinical settings.	http://www.fda.gov/cdrh/oivd/CLIA-oraquick.html
2005	WHO/DHHS/CDC provided guidelines for assuring the reliability of HIV rapid testing: Applying a quality system approach.	The WHO, DHHS and CDC collaborate to publish guidelines for programs implementing rapid HIV testing, so that adequate training and ongoing quality assessment is ensured.	http://www.who.int/diagnostics_laboratory/publications/HIVRapidsGuide.pdf
2005	Research showed that HIV testing in U.S. health-care settings would be cost effective at prevalence >0.1%.	New research provided evidence that recommendations for routine HIV testing should be expanded in lower prevalence settings.	Paltiel AD, Weinstein MC, Kimmel AD, et al. Expanded screening for HIV in the United States – An analysis of cost-effectiveness. <i>NEJM</i> 2005; 352: 586–95.
2006	FDA approval of a qualitative RNA test.	Gen Probe Aptima qualitative RNA test FDA approved for diagnosis of acute infection (and for confirmation).	http://www.fda.gov/fdac/departs/2007/107_upd.html#hiv1
2006	Revised recommendations for HIV testing of adults, adolescents and pregnant women to expand routine testing in health-care settings to populations > 0.1%, in the United States.	In response to evidence documenting ongoing barriers to HIV testing in health-care settings, and in recognition of studies, which showed that routine HIV testing in health-care settings is cost effective even at prevalence's >0.1%, new recommendations were made to offer all sexually active individuals aged 14–65 years HIV testing in health-care settings, and to use an “opt out” strategy, so that testing would be performed unless patients declined. Annual screening was recommended for people at high risk. The guidelines stated that a separate consent for HIV testing should not be required, nor should prevention counseling, with HIV testing in health-care settings. These recommendations did not apply to outreach testing programs in high-risk populations.	Revised recommendations for HIV testing of adults, adolescents and pregnant women in health-care settings. <i>MMWR</i> 2006; 55(RR14); 1–17.

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Table 69-1. (Continued)

Date	Innovation	Description	Reference
2006	FDA holds hearings on over-the-counter HIV testing and urges companies to move forward through the FDA approval process.	The availability of simple oral fluid and fingerstick rapid HIV tests has brought the possibility of an over the counter (OTC) HIV test closer to reality. Hearings at the Blood Products Advisory Committee of the FDA in 2005 and 2006 reviewed the evidence supporting the potential effectiveness and safety of an OTC HIV test, and agreed that if an OTC test could be designed that was accurate and allowed access to adequate counseling services, the public health benefits would likely outweigh the risks. Clinical trials are now being planned and an OTC rapid HIV test kit is anticipated to be available in the United States in the near future.	http://aidsinfo.nih.gov/ContentFiles/FDA-3-3-06.pdf
2007	UNIADS published new Guidance for Provider-Initiated HIV Testing and Counseling in Health Facilities.	The draft recommendations focus on basic operational guidance for provider-initiated HIV testing and counseling in health facilities. HIV testing is recommended as a routine part of medical care with an “opt-out” approach in settings with generalized HIV epidemics. They recommend priority clinic venues for phasing in routine HIV testing.	http://www.unaids.org/en/MediaCentre/PressMaterials/FeatureStory/20070530_testing_counselling_guidance.asp . May 5 2007

determine the number of persons who were tested for HIV during the preceding 12 months, the CDC analyzed data from both the 2002 National Health Interview Survey (NHIS) and the 2002 Behavioral Risk Factor Surveillance System (BRFSS) survey. BRFSS is an ongoing, state-based, random-digit-dialed telephone survey of the U.S. civilian, noninstitutionalized population aged ≥ 18 years. In 2002, 37.8% of adults aged 18–64 years (95% confidence interval [CI] = 37.0–38.6%) reported that they had been tested for HIV at least once in their lifetime, compared with 5.7% in 1987 (CI = 5.3–6.1%).

Initially, HIV testing had been offered mainly at publicly funded HIV test sites and in clinical settings that serve populations at high risk of acquiring HIV infection.⁴³ However, by 1996, only 2 million of the approximately 24 million HIV tests performed were performed at HIV test sites; most were performed in medical-care settings such as the offices of physicians or health maintenance organizations (HMOs).⁴⁴ The majority of HIV counseling and testing still occurs in private settings.⁴²

Data from the 2002 National Health Interview Survey interviews regarding the most recent HIV tests indicated the

majority of tests were obtained from physicians and HMOs (43.5%) or hospitals (22.4%). Of 5.1% of tests reported as taking place “at home,” 93.4% were administered by a nurse or health-care worker. Testing sources that usually receive public funding (e.g., public health department clinics, family planning clinics, and prenatal clinics) accounted for 23.6% of tests during the preceding 12 months. Sources of HIV testing typically funded by CDC’s HIV-prevention programs accounted for 17.3% of the tests, yielding an estimated 3.4 million to 4.3 million tests.⁴²

The demographics of clients tested in public settings differ from those tested in private settings. Clients who are tested in publicly funded HIV testing sites are often uninsured; in fact, approximately half of the 885,046 clients who had HIV tests performed at publicly funded sites in 1992 were uninsured.⁴⁵ Although some states have enacted programs to provide early basic diagnostic and therapeutic services to HIV-infected persons without insurance or Medicaid, this coverage is far from universal or adequate and must be addressed to ensure adequacy of referrals from publicly funded counseling and testing sites.

Despite increases in HIV testing over the past decade, many people at risk were not accessing these services, and many were accessing testing only through blood transfusion centers. Data from the CDC 2002 BRFSS⁴² indicated that 43.5% of the 188,952 respondents from 50 states, the District of Columbia, Puerto Rico, Guam and the Virgin Islands had ever been tested for HIV outside of blood or plasma donation.⁴²

In 2001, the CDC revised the guidelines for HIV counseling, testing, and referral and highlighted the importance of early knowledge of HIV status and of making HIV testing more accessible. This guideline also addressed ways to improve the quality of HIV counseling testing and referral in diverse settings.⁴⁶

Based on data showing the benefit of HIV screening in ERs, hospitals, and urgent-care settings,^{40,47–49} in 2003 the CDC created additional recommendations that advocated HIV testing and counseling be incorporated into routine medical care and in high-prevalence areas outside medical settings, such as jails.

Despite these recommendations, many health-care settings found it difficult to implement routine testing. Regulations that proscribed client-centered pre- and posttest counseling with HIV testing made it impossible for many health-care settings to do anything other than refer patients to public testing sites for HIV counseling and testing, resulting in many missed opportunities as described above. Lack of staff skilled in counseling and lack of time for counseling implementation was a major barrier, as were requirements for a separate informed consent as that required additional staff time.⁵⁰ Another barrier, especially in ERs and Urgent-care settings, was the inability to follow up with patients to provide test results.

These barriers lead to the most recently revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings.⁵ The new guidelines for health-care settings recommend that routine opt-out HIV testing be offered to sexually active people aged 13–64 years in all health-care settings, offered without a separate written consent (but with verbal consent and the option to refuse), and offered in the absence of risk reduction counseling. A recent study in San Francisco showed that when policy was changed to allow provider documentation of verbal consent for HIV testing, rather than written consent, testing rates and identification of people with HIV significantly increased.⁵⁰ The goal of the new recommendations are to ensure that HIV testing is now treated in medical settings like testing for any other chronic disease. These recommendations did not apply to outreach testing programs in high-risk populations, where HIV risk-reduction counseling remains an important HIV prevention strategy.

Internationally, WHO/UNAIDS recently revised their guidelines to follow suit. The current⁶ recommendations focus on basic operational guidance for provider-initiated HIV testing and counseling in health facilities. HIV testing is recommended as a routine part of medical care with an “opt-out” approach in

settings with generalized HIV epidemics where peri-natal HIV prevalence is greater than 1%. They recommend priority clinic venues for phasing in routine HIV testing.

Although these recommendations will eliminate some of the barriers to routine provision of HIV counseling and testing in clinic settings, systems need to be developed to facilitate the process. For example the CARE interactive computer tool provides risk assessment, HIV consent, HIV risks reduction counseling, and recommended health referrals.⁵¹ In an urban urgent-care setting in Seattle that was not routinely offered HIV testing (because of inadequate counseling staff and concern about follow-up with standard antibody testing) a randomized trial ($n = 517$) offering computer assisted rapid testing versus no intervention showed that this program was both acceptable, effective, and relatively inexpensive.⁵² Nearly all (97%) of those randomized to computer-assisted rapid HIV testing received test results, as compared to those in the no intervention arm where no HIV tests were done and only two HIV test referrals were noted.

Other new strategies to overcome HIV related stigma may include inexpensive over-the-counter home HIV self-tests, which appeal to some populations, because of the increased privacy self-testing affords. Currently studies are underway to determine the necessary packaging and associated counseling support so that people who have positive screening tests for HIV will ultimately safely reach appropriate counseling and health care.

Studies evaluating the cost-effectiveness of conventional voluntary counseling testing and partner referral programs have shown that these programs are cost-saving in the United States⁵³ and in developing country settings.³⁵ In the United States a recent study suggested that it would also be a cost-effective HIV prevention strategy to test every person in the country for HIV once⁴⁰ as compared to other well accepted health-related screening strategies, such as breast and colon cancer screening programs. However, to achieve this goal, novel policies would be needed to (1) provide expanded access to HIV testing among people at risk in clinical and outreach settings, (2) provide alternative testing options that are more acceptable, more effective, and less costly, such as rapid oral fluid HIV testing, (3) eliminate requirements for extensive individual pretest counseling in settings where it is a barrier to testing and provide alternate counseling options such as videos or interactive computer counseling, and (4) provide alternative options for results disclosure such as same-day results or through telephone counseling when conventional testing is performed by health workers, and self-test results when an accurate and safe over the counter test becomes available.

CLINICAL GUIDELINES

Routine testing, at least once, is advocated for all sexually active individuals. Repeat testing is recommended annually for people in high-risk groups such as MSM, people with

multiple or untested sex partners, and injection drug users. Testing is recommended more frequently, every 3 to 6 months, for people with reported recent risks. People who require repeat testing for ongoing exposure should be provided or referred for additional HIV prevention services to assist them in reducing their risk behaviors. Various effective prevention-counseling methods exist, which are cost-effective to implement in the highest risk groups.⁵⁴

The following discussion will describe three important aspects of HIV counseling and testing for providers conducting counseling: (i) clinical indications for testing (ii) components of pre- and posttest counseling; and (iii) issues in providing and documenting HIV antibody test results.

■ CLINICAL INDICATIONS FOR TESTING

The CDC recommends offering testing to all sexually active adults aged 13–65 years and annual testing for those in high risk groups.⁵

After effective treatments became available to prevent perinatal HIV infection in 1994,⁵⁵ the IOM recommended opt-out testing for all pregnant women. As the epidemic spread into heterosexual populations, with higher prevalence among people of color, the populations being offered HIV testing needed to be expanded.

Relative contraindications to HIV antibody testing are few, and include acute psychiatric illnesses or active suicidal ideation. Unless needed for medical evaluation of management decisions, HIV testing of asymptomatic persons with acute psychiatric impairment or acute suicidal ideation should be postponed until those issues can be addressed by appropriate providers.

■ POSSIBLE OCCUPATIONAL OR NONOCCUPATIONAL EXPOSURE

Persons should seek HIV counseling and testing after a possible exposure to HIV. These persons are often highly distraught, and the clinician or interviewer must obtain detailed information about the event to assist in appropriate counseling and postexposure prophylaxis,^{56,57} and establish the absence of prior infection.

■ PREGNANT WOMEN

After the discovery that zidovudine (ZDV) during pregnancy dramatically reduced perinatal HIV infection, in August 1994, a U.S. Public Health Service (USPHS) task force first issued recommendations for the use of ZDV for reduction of perinatal HIV-1 transmission.⁵⁸

Several studies documented the difficulty in identifying HIV-positive pregnant women based on HIV risk history alone.^{59–62} Thus in July 1995, USPHS issued recommendations

for universal prenatal HIV counseling and HIV testing with consent for all pregnant women in the United States.⁵⁸ To further reduce barriers to prenatal identification of HIV infection, in 2006 revised guidelines were published, which stressed routine, opt-out testing, with no need for separate written consent. Repeat testing in the third trimester was also recommended for women at high-risk (IDUs, sex workers, high-risk or positive sex partner, and women with new sex partner during pregnancy). In addition, all women in jurisdictions with rates of HIV infection among pregnant women >0.1% should be repeat tested in the third trimester (preferably <36 weeks). Finally, for those who had not gotten prenatal testing, rapid testing during labor can enable pregnant women with undocumented HIV-1 status to learn their HIV-1 infection status so they can receive antiretroviral prophylaxis and be referred for comprehensive medical care and follow-up.⁶³

The rationale behind these recommendations is that the knowledge of HIV status will enable HIV-infected pregnant women to make informed choices about their own health care. In addition, HIV-infected pregnant women should be counseled about the benefits of intrapartum antiretroviral use⁶⁴ and breast-feeding choices to reduce the likelihood of transmitting HIV to the infant (see Chapter 85).

■ COMPONENTS OF PRE- AND POSTTEST COUNSELING

Pretest risk reduction counseling

As detailed in Chapter 47, brief clinic-based risk reduction interventions have been shown to reduce incident STIs,^{65–69} particularly among women. However, clinicians do not always have the resources to consistently deliver counseling³⁶ nor are such interventions translated widely into practice.^{70–72} Risk reduction counseling has been shown in a meta-analysis to reduce unprotected anal sex among MSM,⁷³ and to reduce injecting drug transmission behaviors.⁷⁴ If clinician resources are limited, abbreviated elements of some of these successful risk reduction counseling interventions may still be feasible to implement.⁷⁵ Simply asking the patient (without forcing the provider's agenda on the patient) what risk reduction behavior change step they might be willing and able to undertake (e.g., abstain from sex, reduce sex partners, use condoms correctly and consistently, get HIV/STI tests for oneself or one's partners, etc.) initiates the discussion and can help get the patient to a first step. When a risk reduction plan is defined, it can be charted and then reviewed at follow-up visits, to discuss behavioral successes, barriers, and new risk reduction plan(s) as appropriate.

While required counseling should not be a barrier to HIV testing, when possible, pretest counseling should be offered that is tailored to the individual, taking into account whether the client has been counseled and tested for HIV previously, his or her knowledge about HIV diagnosis and transmission, and

the client's level of reported risk. For the clients who are being tested for HIV for the first time, the discussion of HIV transmission and natural history may need to be more detailed than for persons who have been counseled previously. Several publications detail methods of ascertaining HIV risk and providing pretest counseling in primary-care settings.^{76–78} In-depth counseling about risk behavior may be less feasible in busy office settings than in publicly funded clinics, but at a minimum should include verbal informed consent and when possible should include a discussion of individual risk patterns and the creation of a personalized risk reduction plan.⁷⁹ If standard testing is performed, follow-up appointments for posttest counseling may provide an additional opportunity for reinforcement of risk reduction plans. However, in many settings the majority of patients will not return for their results. Thus, rapid testing for HIV with modified pre- and posttest counseling is encouraged,⁸⁰ or the provision of telephone results when rapid testing is not available.⁵

When providing HIV counseling it is helpful to enquire about the patient's knowledge regarding the difference between HIV (the virus) and AIDS (the clinical condition) and to determine if they are aware that a positive antibody test indicates HIV infection but not the clinical syndrome of AIDS. The clinician should clarify that the antibody test can be either positive, negative, or indeterminate, and that the risk of false-positive or false-negative antibody tests is extremely low.⁸¹ For clients with possible exposure to HIV in the past 3 months, the clinician should explain tests are generally positive within 1 month after exposure but may take up to 3 months to become positive (the "window period"). Therefore, repeat testing should be recommended 3 months after exposure, if the initial test is negative. If clinical suspicion of primary HIV infection is high an RNA test can be performed, which can detect presence of the virus as early as 11 days after exposure.⁸²

For clients with ongoing risk behavior despite adequate knowledge of safe behaviors, the clinician should assist the client in identifying factors related to his or her continued risk behavior (e.g., substance use, new relationship, difficulties with communication or safe sex negotiation, low self-esteem, and depression). The clinician may then either make appropriate referrals for more in-depth counseling or work with the client to develop a personal plan for risk reduction. Such a plan should pay attention to the triggers and context for high-risk behavior for that client. This client-centered approach⁸³ to counseling is more likely to be effective than simply admonishing the client to follow safe sexual or drug use practices or repeating a summary of HIV transmission.⁶⁵ Chapters 53, 95, and several reviews provide a more detailed discussion of behavioral intervention approaches.^{73,74,79,84}

To ensure receipt of test results rapid testing for HIV has now become the standard among high-risk populations. For those who test positive with rapid tests, it is critical that dur-

ing the pretest-counseling visit the clinician emphasizes the preliminary nature of the rapid test results and the importance of following up for confirmatory results. In sites with low HIV prevalence where standard testing may be less costly, offering the option of telephone results is now recommended to promote receipt of test results.⁵ Those with positive HIV results should be encouraged to follow up immediately for in-depth face-to-face counseling.

■ POSTTEST COUNSELING

Posttest counseling is usually provided 1–3 weeks later in the case of conventional antibody testing and 20–40 minutes later when rapid HIV tests are performed. During posttest counseling the clinician should inform the client of the test result and its interpretation, reinforce the individualized risk reduction plan for both seronegative and seropositive individuals, and provide clinical and psychological follow-up for the newly identified HIV-seropositive person. For the HIV-seronegative person, the clinician should reinforce the seronegative individual's plan for staying HIV-negative and determine the need for repeat HIV counseling and testing, depending on the time of the last possible exposure.

Occasionally clinicians will be faced with counseling individuals about indeterminate results, which occur in up to 10% of reactive EIA specimens.^{85–90} Indeterminate HIV test results can occur during acute HIV seroconversion and in the absence of HIV infection.^{82,85–90} In acute HIV, an initial p24 band develops on Western blot followed by additional envelope (gp41, gp120, and gp160) bands and then other anti-HIV bands over the next several weeks. This underscores the need for careful HIV risk assessment and serologic follow-up of high-risk persons with indeterminate Western blots.^{88,89} When possible, RNA testing should be used to diagnose acute HIV infection.

The majority of persons with indeterminate HIV Western blots are not infected with HIV and have cross-reacting alloantibodies or autoantibodies.^{89,90} Low-risk persons can be reassured of their very low likelihood of being infected and should be retested at 3 and 6 months to confirm the lack of seroconversion. Pregnant women with indeterminate Western blots are often understandably anxious about the significance of their tests; clinicians can explain the production of alloantibodies during pregnancy and obtain supplemental HIV tests (e.g., RNA testing) to resolve the indeterminate results more promptly.⁸⁷

While the importance of pre- and posttest counseling has been demonstrated, opt-out testing has the major advantage of speeding and routinizing diagnosis of HIV.⁵ The CDC has now moved for nationwide opt-out testing in all public sectors and for high-risk subjects.⁵ WHO has followed suit⁶ for communities with generalized epidemics, but continues to recommend symptom-based and risk-based screening for

communities where the HIV prevalence among pregnant women is less than 1%.

■ HANDLING OF POSITIVE HIV TEST RESULTS

The clinician who is counseling a client about a new diagnosis of HIV infection must allot adequate time to handle potential emotional distress and to ensure that the client has had the opportunity to ask all questions and express his or her reaction to the test result. If the confirmed positive antibody result is unexpected given the client's history, repeat serum should be drawn for confirmatory testing to rule out laboratory error. Some clinicians routinely confirm newly identified HIV-seropositive results, given the clinical and psychosocial importance of a positive test result. The clinician should again ensure that the client understands the difference between HIV infection and AIDS, discuss the natural history of HIV infection and immunosuppression, and emphasize the potential for slowing disease progression by early intervention with regular monitoring of the immune system and viral load, antiretroviral therapy, and prophylaxis against opportunistic infections. The provider should talk with the HIV-seropositive patient about their personal plan to follow safer sex practices, both to avoid HIV transmission to seronegative partners, to avoid acquisition of other STDs that theoretically may accelerate HIV disease, and to avoid acquiring a new strain of antiretroviral-resistant HIV (super-infection). Medical referrals should be made if follow-up for HIV care is not available at that site and the need for social and psychological services should be assessed. A follow-up appointment is advisable to reassess the client's ability to cope with the positive result, address the client's concerns, and discuss partner counseling and referral services. At this visit, the provider should ascertain the newly diagnosed HIV positive person's reaction to the diagnosis, and discuss in more depth the importance and means to have partners of HIV unknown or negative status referred for HIV counseling and testing, and for HIV positive partners, clinical care and counseling. The rationale and methods for partner counseling and referral services are outlined in the CDC Operational Guidelines for Partner Counseling and Referral Services,^{91,92} and discussed in more detail in Chapter 54.

Most states have passed legislation that allow clinicians to chart positive test results and share test results with other clinicians, provided the disclosure is related to clinical care and the patient has signed a release of information form. The clinician should be familiar with the laws governing confidentiality of positive test results and name-based reporting in the state or jurisdiction in which they are practicing.⁹³ By the end of 2007, All U.S. states and Washington, D.C., will begin recording HIV cases using name-based reporting systems rather than code-based reporting⁹⁴ in order to receive federal funding for treatment. The CDC rejected code-based systems

after finding they could lead to double counting and were cumbersome for health-care providers. The CDC announced its support for names-based HIV reporting in 1999, and strengthened that recommendation to a requirement for Ryan White funding eligibility in 2005. Although there has been much concern expressed about the impact of mandatory named reporting on test seeking behavior, to date there has been little evidence demonstrating a negative impact on HIV testing uptake or care seeking behaviors.

As a result of the clinical and social importance of a positive HIV antibody test, it is advisable to document a positive test before providing HIV-related clinical or social services, particularly before beginning antiretroviral therapy. Occasionally individuals who come in for HIV care believe they are HIV-positive based only on rapid test results or on a standard EIA-positive with either a negative or indeterminate Western blot.

National guidelines recommend that all HIV testing and counseling programs and laboratories perform confirmatory testing with an FDA-approved confirmatory assay such as a Western blot or immunofluorescence assay for all repeatedly reactive HIV EIA samples. Confirmatory testing differentiates those who have false-positive EIAs (those with negative confirmatory tests) from those with actual HIV infection (positive confirmatory tests). In Global settings, WHO recommends two to three accurate rapid EIAs for screening and confirmation,⁹⁵ rather than more costly Western blots or IFA confirmatory tests. The number of tests recommended for confirmation is dependent on local HIV prevalence.

The recent advent of expanded access to rapid HIV testing and the unlicensed use of home testing kits from overseas vendors may result in an increase in people presenting with unconfirmed positive EIA results. Providers should inquire about the type and timing of prior positive HIV tests.

■ NEW TESTING STRATEGIES FOR HIV SCREENING IN HARD-TO-REACH POPULATIONS

Testing technologies

Since FDA approval of the first EIA, this methodology has been standard for screening for HIV infection. Conventional EIA technology worked well for blood banks, which screened large numbers of specimens concurrently, using automated equipment. The specimens that have reactive EIA test results are confirmed using a Western blot assay, which shows reactivity with two of three HIV specific antigens, p24, gp41, or gp 120.

In developing country settings where blood is not stored, rapid HIV antibody tests were developed and shown to be accurate for screening transfusion donors.⁹⁶ Rapid tests are based on EIA and flow through technology where a membrane with antigen binds antibody in whole blood, plasma, or oral fluid. In most of the rapid assays either enzyme conjugate or a colloidal gold conjugate is then added, which results in

one or two colored bands within 10–20 minutes to indicate a working internal negative control and a reactive test. Agglutination tests have also been developed based on latex or red blood cells, which clump together when specimen is added that contains HIV specific antibody. If used in combination two different rapid EIAs can have close to 100% specificity and over 99% sensitivity.

While rapid tests have been used since the late 1980s in many countries both for screening blood products and for individual diagnosis, until recently in the United States there was only one agglutination test with relatively poor sensitivity, and one EIA that was cumbersome to perform. Thus, only in recent years has rapid testing positioned to become the standard of care for screening for HIV infection in clinical and outreach settings. Research has shown that rapid testing for HIV is both more effective in terms of test uptake and receipt of results^{33,80,97,98} and more cost-effective^{40,99–102} than standard testing in clinic and outreach settings.

As the epidemic progressed additional assays were designed to improve the acceptability of HIV testing. Oral fluid EIAs were FDA approved in December 1994, oral fluid Western blots in June 1996, urine EIAs were FDA approved in August 1996, and urine Western blots in May 1998. These specimens make mass testing in outreach settings easier to implement. If surveillance is the goal, conventional (non-rapid) oral fluid testing is an optimal strategy because of the increased acceptability and the ease of collection. However, if increasing the number of people who are aware that they are infected is the priority, rapid tests are more effective and more cost-effective. In November 2002, the OraQuick® test was FDA approved for use with fingerstick whole blood. In March 2004, the OraQuick® test became the first FDA-approved oral rapid HIV EIA. One early study showed the cost of the test itself (\$15–20) was more expensive than standard (\$1–10) or other rapid EIA tests (\$3–18). Yet, in outreach settings where staff costs are fixed, the increased acceptability of rapid tests made the overall cost per test result provided lower than for standard blood or oral fluid testing, and lower than for some other rapid tests that use finger-stick or venipuncture specimens.¹⁰²

As of February 2007,¹⁰³ six rapid HIV tests have been approved by the U.S. FDA: (1) OraQuick® (and its newer version OraQuick® Advance) Rapid HIV-1/2 Antibody Test (OraSure Technologies, Inc., Bethlehem, PA); (2) Reveal™ (and its newer version Reveal™ G2) Rapid HIV-1 Antibody Test (MedMira, Halifax, Nova Scotia); (3) Uni-Gold Recombigen® HIV Test (Trinity BioTech, Bray, Ireland); (4) Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories, Redmond, WA); (5) Clearview HIV 1/2 Stat Pak (Clinical Laboratory Improvement Amendments [CLIA]-waived version, Inverness Medical Professional Diagnostics, Princeton NJ); and (6) Clearview Complete HIV 1/2 (Inverness Medical Professional Diagnostics, Princeton NJ).¹⁰³

Of the currently available rapid HIV tests OraQuick is the only FDA-approved test for oral fluid. The Unigold and Clearview tests can be performed on whole blood from fingerstick specimens and are also CLIA-waived so that clinicians and outreach workers can use them in nonlaboratory settings. Studies are needed, which compare the relative acceptability, cost, and effectiveness of rapid oral fluid versus rapid whole blood tests to assist providers in test choice globally.

The price for the U.S. FDA-approved rapid HIV test kits, as of July 2005, range from \$14 to 25.¹⁰⁴ Costs for multidose external control vials range from \$20 to 26.25. According to the Centers for Medicare and Medicaid Services 2005 Clinical Laboratory Fee Schedule, average reimbursement for a CLIA-waived rapid HIV-1 antibody test (procedural terminology [CPT] code 86701QW) was \$12.41/test and for a CLIA-waived rapid HIV-1/2 antibody test (CPT code 86703QW) was \$19.17. Providers offering point-of-care, rapid HIV testing may be challenged by reimbursement not keeping pace with the list prices of the tests. However, competition between rapid testing providers may drive the cost of the test down. In addition, comparable with counseling for other health issues, HIV counseling by a nonphysician is not reimbursable. Physicians performing HIV counseling may attempt to collect reimbursement for it by billing for prolonged services. In global settings, many additional non-FDA-approved tests exist, which are accurate, can be used with whole blood and which costs less than U.S. \$1.00. Inexpensive rapid oral fluid tests, which are more acceptable and easier to use than fingerstick tests, are needed for HIV testing programs globally.

The rapid HIV tests may be particularly suitable for HIV testing sites and outreach testing programs with particularly poor follow-up rates, such as ERs, STD clinics, hospitals with high HIV prevalence, and HIV testing sites in developing countries. Rapid HIV tests may also be useful in labor and delivery suites to identify HIV-infected women who were not tested in pregnancy and who could benefit from interventions to reduce peripartum HIV transmission.

In clinical settings where acceptance rates of HIV testing is high and follow up for test results nears 100%, it may cost less to continue to offer conventional blood testing. However, in most test sites acceptance rates with rapid testing will be higher and the heightened rates of receipt of test results make rapid testing the most effective and most cost-effective strategy.^{101,102,105}

Other options for HIV testing include home specimen collection kits, first approved by the FDA in 1996.^{106,107} Home specimen collection using fingerstick specimens was developed to provide alternative anonymous testing options in areas where there was poor access to HIV testing or where stigma prevented people from requesting HIV tests in clinical venues. Currently there is one FDA-approved home specimen

collection kit (Home Access) that allows for people to collect a fingerstick specimen on a filter paper, mail it to a central laboratory, and receive results within a week via the telephone with verification through an anonymous code. Negative results may be given over the telephone by a prerecorded message, although clients may also have the option of speaking with a telephone counselor. Positive test results are generally provided by a counselor who conducts a standard posttest counseling session by telephone and provides referrals for both medical and psychosocial services. Persons receiving positive test results may have the option of receiving follow-up telephone counseling sessions.

Oral fluid kits have been licensed for provider use for EIA and Western blot antibody testing, and could be used for home specimen collection using a similar method of reporting test results.¹⁰⁸ One study,¹⁰⁹ that trained people to collect specimens using a video, showed that both home oral fluid and home fingerstick collection was feasible and highly accurate for frequent HIV testing among people at high risk; however, oral fluid collection was preferred by most, thus, may be utilized by more people if made available. However, no companies have announced plans to pursue FDA approval of an oral fluid home specimen collection test.

The role of home collection and testing in the United States and the potential for benefit and abuse through this system has been the subject of much debate.^{107,110–112} Although some of the issues are specific to HIV testing, Bayer¹⁰⁷ points out that much of the debate raises broader policy issues about “the role home-diagnostic techniques should have in the evolving practice of medicine in America and the extent to which federal regulatory bodies should protect people from technically accurate devices that may produce psychologically burdensome results.”

Home collection and self-testing could increase the proportion of at-risk persons who avail themselves of HIV antibody testing and potentially decrease the likelihood that persons would use blood donation as a mechanism for HIV antibody testing.

A concern that has been raised is whether telephone counseling is as effective as face-to-face counseling in assisting high-risk persons to decrease their risk behaviors. However, the efficacy of face-to-face counseling in promoting sustained risk reduction is under debate, as described previously, since few people who test actually receive the patient-centered counseling that has been proven effective. One national evaluation of the implementation of recommended client-centered counseling in public HIV testing sites revealed that only 61% of sites routinely completed personal risk reduction plans with clients.⁷¹

Another concern raised about home collection is that inadequate resources or follow-up will be available for persons learning of HIV-positive test results, particularly if large numbers of HIV-seropositive persons are newly identified.

However, Ryan White and other HIV care funding is linked to the number of HIV and AIDS cases, so increased detection could be accompanied by increased local resources for care services. Although there were early concerns that notification of positive test results may precipitate attempted suicides, to date there are no studies that validate those concerns. Vulnerable groups, such as adolescents, may need particular assistance when learning of positive test results. Mechanisms must be built into the counseling to provide local referrals for clients, including crisis counseling.

Concerns have also been raised about the likelihood and mechanisms for dealing with false-positive test results. In postmarketing studies of the OraQuick test on 135,724 whole blood and 26,066 oral fluid rapid tests, overall specificity was comparable with that of clinical trials (99.98% for blood and 99.89% for oral fluid). Although there were some sites that had lower than average specificity, a field investigation suggested that these were isolated clusters, and did not find a reason for the lower specificity.¹¹³ The sensitivity of the oral fluid HIV EIA for detection of antibodies during acute seroconversion is not known.

The future of HIV testing technology may be in over-the-counter rapid HIV tests which could, like home specimen collection kits, be provided by public health, sold in drug stores or purchased over the internet. Self-tests have been reported as significantly more acceptable than home specimen collection to populations at risk in two studies because of the rapid results and enhanced anonymity that self-testing offers.¹¹⁴ If low cost, this testing method could better serve populations who do not have access to standard VCT services or who because of privacy concerns, stigma, transportation costs, or other barriers do not use facility-based, standard HIV testing.

HIV counseling and testing is cost-effective in most populations in the United States^{40,115} and abroad³⁵ by any measure, because of the savings that result from preventing a case of HIV. Using conventional HIV counseling and testing strategies, the funds that would be required to test every person in a community may exceed national and international budgets for HIV prevention.⁹⁹ Over-the-counter rapid HIV tests have the potential to both dramatically improve access to HIV testing, as well as decreasing the public health cost of providing this service. One small study among people with HIV showed that oral fluid and fingerstick self-tests with only written instructions using the OraQuick device had fairly high sensitivity (94%) when participants interpreted blinded self-tests, somewhat lower specificity (88%) when participants interpreted blinded weak negative controls, and very high acceptability (61% would have preferred learning their status at home with a self-test rather than in a clinic).¹¹⁴ Even higher sensitivity will likely be possible with additional guidance in test performance and interpretation through the use of improved instructions, and video or web-based demonstrations.

While several of the currently available rapid HIV tests are simple enough to be used as self-tests, to date no company has designed a system to ensure adequate follow up and referral services for those who test positive. Models of counseling proposed include written educational materials, interactive computer counseling, and 24 hour access to telephone counselors.¹¹⁷ One company, OraSure Technologies, has announced their intention to consider the development of an over-the-counter rapid HIV test. Illegally available self-tests, which are currently advertised on the Internet, should be avoided because of questionable accuracy. Research is needed to determine the accuracy of self-testing for HIV and to understand what types of associated counseling may be required to ensure safe dissemination of self-testing for HIV both in developed and developing country settings.

Testing settings

Early in the epidemic it was necessary to go to a blood bank or a public testing site for a diagnostic HIV test. Now that widespread testing is recommended, it is acknowledged that testing should be made more widely available. Currently access to HIV testing can be improved through expanding the availability of testing in primary-care settings, ERs, and through mobile outreach to high-risk venues. While general HIV testing is clearly cost-effective, limited public health dollars should be targeted toward identifying populations at highest risk who otherwise would not access HIV testing, while others should be provided access to HIV testing through their primary health-care providers. For people who are concerned about confidentiality or for those with minimal access to clinical services, home specimen collection kits are available for those who can afford them.

For communities at high risk who do not access care in traditional clinical venues, outreach testing is recommended.¹¹⁸ For example mobile testing programs that utilize oral fluid and rapid testing, have successfully reached previously untested populations.¹¹⁹ Rapid testing for HIV has been found more acceptable and more cost-effective than standard blood or oral fluid testing among populations at risk for HIV and can overcome barriers to testing for those who dislike the anxiety that they experience while waiting for test results.¹²⁰

Components of successful outreach programs include the use of culturally similar recruiters, mobile testing, incentives, rapid or oral fluid testing, and convenient results disclosure through the telephone when nonrapid tests are used. Determining the best model for connecting clients who test in mobile outreach settings to clinical care is an ongoing challenge and merits further research.

Overcoming stigma^{26,121} for HIV testing will come as community norms change. In the meantime, some strategies to avoid this barrier include providing routine testing, or monetary incentives for HIV testing, so that people are able to accept HIV testing without publicly indicating their risk.

Other options for people who delay testing due to stigma include home specimen collection and, in the near future, over-the-counter rapid tests.

NEED FOR STATE ADMINISTRATIVE CODE REFORM

Early in the HIV epidemic in the United States, many states developed administrative codes to ensure that HIV counseling and testing was offered in a standardized manner with detailed written consent of people testing and prescriptive counseling. These regulations made testing more difficult to implement in many clinical settings. Some ERs and clinical venues elected to refer clients elsewhere for HIV testing rather than train or hire staff to provide the required counseling. Unfortunately, referral results in many missed opportunities for testing those at high risk, and follow-up rates for referrals are notoriously low. In recent years the awareness that the epidemic is being fueled by those who are unaware of their HIV status has resulted in changes in CDC recommendations and in State administrative codes.

New CDC guidelines⁵ recommend that providing knowledge of HIV status is the highest priority, and that while client-centered HIV risk-reduction counseling is recommended, when possible, it is not mandatory for HIV testing to be performed. Some people have expressed concerns that requiring explicit consent for HIV testing treats it differently than other medical tests, creates barriers to testing, and may contribute to the stigmatization of HIV. Requiring explicit detailed pre- and posttest counseling may make some health providers less likely to offer HIV testing. In response, states are revising their administrative codes to eliminate regulations that may create barriers to the provision of HIV testing. For example, Washington State recently made revisions to remove the requirement of a separate written consent. While explicit verbal consent is still required, eliminating the extra paperwork may make HIV testing easier for providers to offer. In addition, the requirement for prevention counseling with HIV testing has been deleted from the administrative codes, so that settings without the time or resources to provide prevention counseling will now be able to offer HIV testing.

New HIV counseling and testing strategies, and associated policy reform, is generating a new era of widespread HIV testing that will impact the spread of HIV globally within the next decade.

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Clinical Laboratory Diagnosis of HIV-1 and Use of Viral RNA to Monitor Infection

Robert W. Coombs

INTRODUCTION

Shortly after exposure to HIV-1, virus replication can be detected in the blood plasma or cells (Fig. 70-1). A cellular and humoral immune response develops thereafter. Most persons infected with HIV-1 are identified by the immune response, through a series of sensitive and specific tests that demonstrate antibodies reactive with this human retrovirus. However, HIV-1 infection can also be detected by nucleic acid target or nucleic acid target-signal amplification assays of viral RNA or proviral DNA in nearly all HIV-1-seropositive persons, and such tests may be particularly important in the person with very recent infection (before antibodies develop) or in the exceedingly rare person with antibody-negative infection.

Clinical suspicion of new (acute) HIV infection is raised by appropriate signs and symptoms, such as a self-limited mononucleosis-like illness, prolonged fever, fatigue or weight loss, onset of opportunistic infections, and/or high-risk behaviors: male-to-male sex; injection drug use; a recipient of multiple blood-product transfusions (in resource-constrained settings); heterosexual or homosexual contact with a high-risk or HIV-1-seropositive partner; residents of certain areas of Africa, Asia, or the Caribbean where HIV prevalence is exceptionally high; male or female prostitution; or a child born to parents who are members of these risk groups. However, physicians face a major challenge in diagnosing HIV infection in a person who may be acutely infected, who is asymptomatic, who has atypical signs and symptoms, or who denies being in a high-risk group.¹

Current U.S. government recommendations are to increase HIV screening of patients, including pregnant women in health-care settings,² and, once the decision is made to initiate antiretroviral therapy, to decrease vertical transmission,³ reduce HIV-related morbidity and mortality, improve quality of life, restore and preserve immunological function, and maximally and durably suppress viral load.⁴ These recommendations raise additional challenges to the clinician and

the clinical laboratory not only to diagnose infection as early as possible but also to assess quantitatively viral RNA, which provides prognosis for disease progression and the success or failure of therapy.

The current approach to the clinical management of HIV-1 infection is driven by clinical trial data that plasma viral RNA level and CD4 cell count are the most suitable biological markers of clinical progression and therapy efficacy.⁴ Although the adequacy of viral RNA alone as a surrogate for clinical outcome has been questioned,^{5,6} in patients with untreated HIV infection a single HIV-1 RNA measurement is still the strongest baseline predictor of time to AIDS and death and generally explains about half of the variability in these clinical outcomes.⁷ The antiretroviral management of HIV-1 infection is based on monitoring both viral RNA levels in plasma and CD4 cell counts in whole blood.^{4,8} To understand the usefulness and limitations of HIV-1 RNA measurement in clinical practice, the reader must be aware of caveats that pertain to the use of plasma HIV-1 RNA as a marker of viral replication and clinical prognosis. These caveats will be discussed later in this chapter.

For descriptive and technical purposes, laboratory detection of HIV-1 or HIV-2 infection can be stratified into assays that identify HIV-specific antibodies and those that identify infectious HIV virus, viral antigen, or viral nucleic acids. (The reader is referred to recent reviews for the technical details of the detection methods used for the laboratory diagnosis of HIV infection.^{9,10})

ACUTE HIV INFECTION

Recent improvements in the sensitivity and specificity of anti-HIV assays have resulted in a significant shortening of the preseroconversion window period from the 42–45 days (the mean infectious window period documented in the post-1987 look-back studies) to 20–25 days.¹¹ Introducing direct-virus detection assays into the testing algorithm would reduce the window period by 9 days for p24 antigen

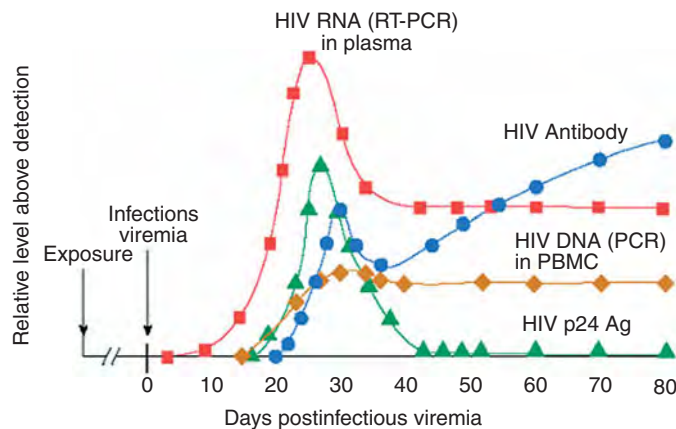


FIGURE 70-1. Sequence of the virological and serological time course associated with acute HIV infection—"seronegative window." Following exposure to and infection with HIV-1, there is a variable period of viral replication in mucosal and lymphoid tissue that drains the inoculation site. This phase is referred to as the "eclipse phase," usually lasts 1–2 weeks but is typically 10 days and occasionally up to 6 months. This is followed by the appearance of infectious viremia, as determined by infectious blood donation studies (time 0), which marks a consistent sequence of virological and serological events. Infectious viremia is followed by a viral RNA-only phase lasting 3–5 days, which is then followed by a 5-day period during which both viral RNA and p24 antigen are detected but the enzyme-immuno (EI)-assay antibody is negative—the "seronegative window" phase. Once p24 antigen is detected, viral RNA levels exceed 10,000 copies/mL. The detection of infected PBMCs coincides with the detection of PBMC-associated viral DNA. Anti-IgM appears between days 20 and 30 post viremia, peaks, and is followed by a slow rise in the anti-HIV IgG levels. During the first 4 months of infection, the level of anti-HIV may not be detected by less-sensitive EI assay formats—the so-called "detuned" assay; thus, the detuned assay may be used to estimate the point incident infection rates. Over the ensuing 3–6 months, seroconversion is associated with the suppression of the viral replication to a stable viral RNA level or "set point" that is prognostic of the risk for subsequent disease progression in the untreated person. (Adapted from Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. *Am J Med* 1997; 102: 117–124; Bush MP, Kleinman SH. Nucleic acid amplification testing and disease transmission. *Transfusion* 2000; 40: 143–159; and Coombs RW. Human immunodeficiency virus infection and the acquired immunodeficiency syndrome: Viral pathogenesis, laboratory diagnosis and monitoring. In: Morse SA, Ballard RC, Holmes KK, Moreland AA, eds. *Atlas of Sexually Transmitted Diseases and AIDS*, 3rd edn. New York: Mosby, 2003, pp. 177–194.)

or DNA PCR and 11 days for RNA PCR (Fig. 70-1). Although the majority of seroconversions occur within 2 months of exposure, delayed seroconversion is well established, with approximately 5% of occupational infections taking more than 6 months after the exposure to seroconvert.¹¹

Viremia, as detected by p24 antigen or HIV RNA, precedes anti-HIV seroconversion consistently by 1–3 weeks. The delay between exposure and infectious viremia (the viral "eclipse" phase) likely represents a period of localized viral replication at the mucosal site of inoculation and possibly in lymphoid tissues that drain inoculation sites, prior to systemic viremia and subsequent seroconversion.^{12,13}

HIV ANTIBODY ASSAYS

■ GENERAL CONSIDERATIONS

The HIV-1 testing algorithm recommended by the U.S. Public Health Service comprises initial screening by a Federal Drug Administration (FDA)-licensed enzyme immunoassay (EI assay) followed by confirmatory testing of repeatedly reactive specimens with an FDA-licensed supplemental test, e.g., immunoblot (Western blot) or immunofluorescence assay (IFA).^{14,15} Although the EI assays are highly sensitive and specific, the positive predictive value of the EI assay is highly dependent on the seroprevalence of HIV-1 antibody in the population to which the individual being tested belongs. Therefore, use of both the EI assay and a further supplementary test increases the accuracy of detecting HIV-1 infection. Clinical laboratory practice dictates that the results of a repeatedly reactive HIV EI assay should never be released to the clinician or patient by the clinical laboratory without the results of the more specific confirmatory testing.^{16,17} For the maximum diagnostic accuracy, the laboratory HIV test results should be interpreted by the clinician in conjunction with the clinical and epidemiological history of the person being tested.¹⁷

■ EI ASSAYS

EI assays were first developed to detect HIV-1 antibodies in infected potential blood donors. These tests have now been adopted for screening high-risk groups for HIV infection. Following the initial screening procedure, more specific tests confirm the diagnosis.

There are four basic formats for commercially available EI assays. First-generation assays use antigens derived from whole disrupted virus and an enzyme-conjugated anti-human IgG sandwich technique for capture and detection of anti-HIV antibodies. Second-generation assays use recombinant (rDNA) viral protein (antigen) and conjugated anti-human IgG, or they use rDNA antigen for both capture of anti-HIV antibodies and detection of these antibodies, using enzyme-conjugated rDNA proteins as probe.^{18,19} Third-generation assays use synthetic peptides.^{20,21} For example, the Genetic Systems™ HIV-1/HIV-2 Peptide EIA (Genetic Systems Corp., Redmond, WA) is comprised of four highly conserved, immunodominant peptide sequences of envelope (*env*) and polymerase (*pol*) gene products for HIV-1 and HIV-2 that are adsorbed onto the surface of a microwell plate. If IgG or IgM antibodies to either HIV-1 or HIV-2 are present, they bind to the adsorbed peptides and are recognized by an enzyme-conjugated anti-human IgG sandwich technique. Fourth-generation assays combine the attributes of the third-generation assay with detection of HIV-1 p24 antigen.²²

The median time interval between infection and confirmed seropositivity is approximately 3 months with the first- and second-generation EI assays, with 95% or more of subjects seroconverting by 6 months.²³ However, the more sensitive third- and fourth-generation assays have shortened the estimated antibody-negative “window period” of primary infection to 20 days or less.²⁴ The specificities of the current commercial EI assays are above 99.5%.^{25–28} False-positive reactions result from nonspecific cross-reacting antibodies in persons with underlying immunological disease, gravidity, multiple transfusions, or recent immunization for the first-generation assays^{29,30} and from cross-reacting antibodies to the yeast and bacteria that produce the commercial peptides used with the other generation assays. Several commercially available EI assays screen for both HIV-1 and HIV-2 antibodies. For epidemiological purposes, specialized EI assays are available to evaluate the level of anti-HIV antibody and estimate HIV-1 seroincidence.³¹

■ IMMUNOBLOT

As already mentioned, the positive predictive value of the EI assays are highly dependent on the seroprevalence of HIV antibody in the population from which the person being tested is from. Therefore, to prevent a false-positive diagnosis of HIV infection, confirmation of a reactive EI assay is required, using an independent testing method with high specificity. The immunoblot (or Western blot) is the most commonly used confirmatory test in the United States.¹⁵

The Western blot detects the serum antibodies directed against specific HIV proteins of varying molecular weights following their separation by gel electrophoresis and blotting onto nitrocellulose paper. The Western blot detects antibodies to the following specific HIV-1 proteins: core (p17, p24, and the gag precursors p40 and p55), polymerase (p31, p51, and p66), and envelope (gp41 and gp120/160). The reported analytic specificity of the immunoblot assay is 97.8%.^{15,25} The Western blot is interpreted as negative when no antibody–antigen band is present, positive when antibodies are present to core (p24) and envelope (gp41 or gp120/160) and, in some cases, integrase (p31). Although several organizations, including the World Health Organization³² and Consortium for Retrovirus Serology Standardization,³³ have proposed criteria for interpreting Western blot reactivity, the Centers for Disease Control and Prevention (CDC) endorses interpretative criteria that require the presence of antibodies to at least two of three HIV-1 antigens: p24, gp41, or gp120/160.^{15,17,34}

Regardless of the HIV-1 antibody seroprevalence, a reactive EI assay and confirmatory Western blot together have a positive predictive value of greater than 99.99%.^{35,36} In the blood donor population, approximately 10 of 10,000 persons (0.1%) without risk of HIV-1 infection will be repeatedly

reactive by the HIV-1 EIA. However, 8/10 low-risk persons with repeatedly reactive HIV-1 EI assays will be negative by the HIV-1 Western blot and 2/10 will be Western blot indeterminate.³⁶ False-positive results for HIV-1 antibody, when both the EI assay and the Western blot are reactive in a person who is not infected with HIV-1, are extremely rare (<1 in 100,000 persons screened).³⁵ Therefore, indeterminate Western blots (IWBs) are more common than false-positive Western blots in screening persons from populations with low HIV-1 antibody seroprevalence.³⁷ Fortunately, other HIV-1 detection tests (see below) allow for resolution of confusing serological results.

The combination of HIV-1 EI assay and confirmatory immunoblot has clearly established evidence against the “seroreversion” of HIV-1 antibody in seroreactive individuals.³⁸ In a retrospective cohort study that reviewed the results of 5,446,161 HIV-1 antibody tests performed on 2,580,974 individuals (the U.S. Army HIV Data System) from 1985 through 1992, only six of 4911 individuals were identified as potential seroreverters. Furthermore, in all six instances errors in specimen attribution or testing were identified.³⁹

■ OTHER CONFIRMATION METHODS

The indirect IFA is also approved for confirmatory testing,⁴⁰ but it is used less commonly than the immunoblot confirmation method.^{15,34} Other confirmation strategies have been reported.⁴¹ For example, the use of a first- or second-generation EI assay as a screen followed by a native HIV-1 gp160 EI assay,⁴² a recombinant DNA-derived antigen-based peptide EI assay,^{43,44} or an immunoblot assay (RIBA),⁴⁵ have all reported comparable results but are not FDA approved for this purpose. Nevertheless, the combination of rapid tests, for example, could be a cheaper and faster alternative to the conventional testing algorithm in developing countries.⁴⁶

■ INDETERMINATE IMMUNOBLOTS

With the increased use of HIV-1 antibody screening in low-risk populations, including health-care workers,⁴⁷ it is essential for the primary care provider to be able to interpret HIV-1 test results accurately.³⁷ Between 4% and 20% of serum samples that are repeatedly reactive by HIV-1 EI assay are interpreted as indeterminate by Western blot.^{17,36,48} IWBs in HIV-1-infected persons may result from early antibody formation against viral core antigens during primary infection,⁴⁹ from early detection of HIV-1 antibody by the more sensitive third- and fourth-generation EI assays before there is confirmation by immunoblot,^{50,51} and, rarely, from the loss of core-specific antibody late in infection due to severe immunosuppression.^{38,52,53} In HIV-1-negative persons, cross-reacting antibody to HIV-2 has been implicated.⁵⁴ False-positive

immunoblots are extremely uncommon and occur with a frequency of <1 per 135,000 tests.^{35,36}

In the only population-based case–control study (244 cases, 131 controls, and 83 sexual partners of cases) to assess risk factors for IWBs, Celum, and coworkers found that IWBs were associated with a low risk of HIV seroconversion (3.0%; 95% confidence interval, CI, 0.7–5.3%) for those with recent risk behaviors for HIV-1 acquisition and that for low-risk persons, the major risk factors identified for IWBs related to alloimmunization (i.e., parity or recent immunization) or autoantibodies (i.e., antinuclear antibodies and rheumatoid factor).⁵⁵ Of interest, conditional logistic regression analysis indicated that an additional independent risk factor for IWBs among male cases and controls was a recent sexual contact with a prostitute (odds ratio, 3.0; 95% CI, 1.0–9.5). Contrary to other reports, however, no cross reactivity was detected with HIV-2, human T-lymphotrophic virus type 1, feline immunodeficiency or feline leukemia, or bovine immunodeficiency viruses.

Celum and coworkers suggested four important principles for facilitating the management of IWBs for HIV-1 in the clinical setting.⁵⁵ First, approximately one-third of persons who present with IWBs will not be repeatedly reactive by EI assay and Western blot testing.⁴⁸ There is no need for further testing or follow-up of this group. Second, the most important factor for the association of seroconversion with an IWB was a p24 antibody band (approximately an 18% risk of seroconversion) and high-risk behavior, which could be determined from the risk history.⁴⁸ Repeat Western blot and selective supplemental testing with HIV-1 culture, p24 antigen, HIV-1 DNA polymerase chain reaction (PCR) amplification (and quite possibly RNA^{51,56}), or third- (and fourth-) generation recombinant EI assays were also useful in identifying persons with no history of high-risk behaviors who proved to have false-positive Western blots. Third, no cross reactivity with known human or animal retroviruses was shown. Fourth, in most cases the medical history is extremely important in identifying subjects with significant risk factors for IWBs (parity and autoantibodies among females, tetanus booster in the past 2 years, and sexual contact with a prostitute since 1978 among males).⁵⁵

In summary, the following recommendations are made for the clinical management of patients with an IWB. Low-risk individuals with a nonreactive EI assay upon repeat testing do not need further follow-up. High-risk individuals should be followed serologically for at least 6 months, especially those with a p24 band on Western blot. The early, selective use of supplemental tests such as HIV-1 p24 antigen, HIV-1 culture, HIV-1 proviral DNA, or plasma RNA may help determine the infectious status of high-risk individuals before full seroconversion occurs.^{48,57,58} Negative supplemental tests may also help alleviate the anxiety associated with an indeterminate HIV-1 serology.

■ SIMPLE/RAPID SEROLOGIC TESTING

Simple, rapid, reliable, and less expensive alternatives to the EI assay with confirmatory immunoblot have been sought for use in acute care settings, emergency rooms, sexually transmitted disease clinics, medical field settings, and developing countries.⁵⁹ Test designs are based on three formats: immunoconcentration (flow-through devices); immuno chromatography (lateral-flow devices), and particle agglutination.^{60–62} Currently, a total of six rapid HIV tests have been approved by the Food and Drug Administration (FDA) and are available in the United States; however, only three, the OraQuick Advance Rapid HIV-1/2 Antibody Test device (OraSure Technologies), the Uni-Gold Recombigen HIV Test (Trinity Biotechnologies), and the Clearview HIV-1/2 Stat-Pak (Chembio Diagnostics Systems), are CLIA waived and suitable for point-of-care (POC) testing; the others are of moderate complexity and thus more suitable for the laboratory setting.⁶² The procedure take less than 30 minutes, and negative results are available immediately. Positive tests must be confirmed with a Western blot or IFA. Generally, the positive predictive value of these assays is comparable to the standard EI assays (>80%), and the negative predictive values approach 100% in some circumstances^{61,63–66} but not in others.⁶⁷ The relative sensitivity (99.9%) and specificity (99.6%) of these tests and their ability to detect both IgM and IgG antibody may make them particularly useful for detecting early infection.⁶³ However, as some of these simple/rapid assays rely on detecting antibody to gp41 (e.g., OraQuick), any delay in producing anti-gp41 could reduce the sensitivity of these assays in early HIV infection (Joanne Steckler, MD, personal communication).

The CDC now recommends that diagnostic HIV testing and opt-out HIV screening be part of routine clinical care in all health-care settings, as this will greatly enhance testing programs by preventing the need for delayed counseling of seronegative patients and by providing preliminary results to seropositive patients, thus ensuring optimal clinical and preventive care.^{2,68} These preliminary results may encourage patients to return for confirmatory test results and to adopt risk-reducing behaviors sooner than occurs, using currently accepted testing algorithms.⁶⁹ In addition, the rapid HIV-1 screening of source contacts following occupational exposures to blood will minimize the duration of antiretroviral prophylaxis therapy for the exposed health-care worker, thus minimizing cost and alleviating anxiety following the exposure sooner if the test is negative.

■ OVER-THE-COUNTER TESTING

Only one over-the-counter HIV-1 test kit is available for home collection (Home Access™, Home Access Health Care). The test is based on previous evaluations of blood collected on filter paper for stability and for detection of

antibodies to HIV-1 by EI assay and confirmatory Western blot.^{70–72} The kit consists of instructions and equipment for obtaining blood from a finger-stick. The blood-spot specimen is sent to a commercial laboratory for testing with an EI assay and confirmatory IFA. The results and counseling are provided over the phone; for positive results, patients are referred by a counselor to a physician for additional counseling and care.

DETECTION OF HIV-1 ANTIBODY IN SALIVA AND URINE

HIV-1 antibodies can be detected reliably in the oral fluids of HIV-1-infected persons.⁷³ There are a number of obvious advantages to collecting specimens for HIV-1 testing using a noninvasive specimen collection procedure,⁷⁴ for example, greater safety, increased patient compliance, and an alternative to phlebotomy.⁷⁵ Earlier problems with low sensitivity have been corrected by using special collection devices that concentrate and stabilize the salivary-associated immunoglobulins.⁷⁵ Modification of the EI assay and Western blot have increased the sensitivity to 97–100% and the specificity to 98–100%, depending on the study.^{73,75,76} In June 2004, the FDA approved the OraQuick® Advance Rapid HIV-1/2 Antibody Test (OraSure Technologies) for the detection of HIV-1/2 antibodies in oral fluid as a POC test.

Early reports of discordant HIV-1 antibody results between antibody-negative blood serum and antibody-positive urine,⁷⁷ and the detection of the first case of HIV-1 group O in a patient who had urine antibody confirmed by Western blot but was serum Western blot seroindeterminate,⁷⁸ have suggested a compartmentalized antibody response to early HIV-1 infection. As such, there has been an interest in using urine for HIV-1 antibody screening.⁷⁹ This has led to the testing of an experimental urine HIV-1 envelope-based EI assay, Calypte™ Aware HIV-1/2 U rapid test (Calypte Biomedical, Berkeley CA; not available in the United States), which has demonstrated a positive predictive value of >99.2% and negative predictive value of >99.9% when combined with confirmatory immunoblot or immunofluorescence testing.^{80,81} At this time, the absence of an FDA-licensed Western blot for urine testing requires that urine reactive for HIV-1 antibody be confirmed by testing of a blood specimen.

HIV ANTIBODY TESTING IN RESOURCE-CONSTRAINED SETTINGS

Several challenges exist for HIV antibody testing in the resource-constrained setting. For example, approximately 80% of people living with HIV in low- and middle-income

countries do not know that they are HIV positive, and recent surveys in sub-Saharan Africa showed that just 12% of men and 10% of women have been tested for HIV and received their test results (<http://www.who.int/mediacentre/news/releases/2007/pr24/en/print.html>; last accessed 07/04/07).

In this setting, HIV testing should follow recommended CDC–UNAIDS–WHO HIV testing strategies and relevant national HIV testing algorithms for which a brief summary follows (http://www.who.int/diagnostics_laboratory/publications/HIVRapidsGuide.pdf; last accessed 07/04/07).

Testing algorithms involve either sequential (serial) testing or parallel testing (http://www.who.int/diagnostics_laboratory/en/; last accessed 07/04/07). EI assay-based algorithms are generally serial and require confirmation by a second positive test result that uses either different antigens or testing platform (or both) from the first test. A second reactive test result is considered confirmatory of the first reactive test result if the seroprevalence is 5% or more. In low seroprevalence settings, where false positives are more likely, a third confirmatory test may be required (e.g., HIV-1 RNA or DNA). Serial testing is less expensive, and a second test is only required when the initial test is reactive.

Parallel (simultaneous) testing is only recommended when using whole blood finger stick samples rather than venous blood and is suitable for simple/rapid testing, although serial testing may also be used. A parallel testing algorithm uses two tests based on either different antigens or platforms (or both), and the assays are conducted simultaneously. Concordant negative or positive results are considered as true negatives or positives, respectively.

When two test results are discordant, specialist laboratory advice may be required. The WHO and UNAIDS also recommend that specific tests have sensitivities of at least 99% and specificities of at least 98% and that combination testing algorithms need to be evaluated in the context of use before wide-scale implementation. To illustrate this point, a recent study from Uganda suggested that weak bands detected by simple/rapid antibody assays, and which otherwise should be reported as positive by the manufacturer, decreased the positive predictive value of the assay algorithm used in this study.²³⁶ As such, the presence of weak positive bands should be confirmed by EI assay and western blot before releasing the results, and quality control of the simple/rapid assays should use standard serological assays.²³⁶

DETECTION OF HIV-1 SUBTYPES

The envelope protein of HIV-1 isolates from different geographic locations worldwide can differ in more than 35% of amino-acid positions.⁸² As a consequence of this diversity, HIV-1 strains are divided into three groups: M (major, which is responsible for most of the infection in the Americas and Europe), O (outlier, a rare form found in Cameroon and

Gabon), and N (novel or non-M-non-O). Within the “major” group M, nine subtypes (or clades) designated A–D, F–H, J, K and 16 major circulating recombinant forms have been defined (<http://hiv.lanl.gov/content/hibdg/CRFs/CRFs.html>), e.g., AE, prevalent in Southeast Asia; AG, from west and central Africa; AGI, from Cyprus and Greece; AB, from Russia; FD, from Democratic Republic of Congo; BC, from China; BF, from South America; and several additional complex and unique recombinants that combine three or more subtypes.^{83,84,237} Group M and its subtypes are more clearly defined than others. Subtype B is the most common subtype in the United States and Europe, while subtypes A, C, and AE are prominent in Africa and Asia.⁸² Non-B subtypes are of increasing importance in the United States and may comprise approximately 5% of HIV infections nationally and even higher proportions in some local areas.²³⁸

Phylogenetic clades equivalent to group M subtypes have been described for viruses from the highly divergent “outlier” group O.²³⁹ The group O virus strain has been isolated from persons of west-central African origins^{85,86} with reports of group O virus from Europe^{78,87,88} and the United States.⁸⁹ Because the commercial EI assays and confirmatory immunoblot assays are based on the predominant HIV-1 clade B virus, not all early commercially available diagnostic assays could detect the divergent group O strains.^{90–92} Thereafter, diagnostic kit reagents were modified to ensure optimal sensitivity and specificity for group O virus antibody.^{93,94}

Since most of the primer pairs for HIV-1 DNA PCR amplification have been optimized for group B viruses (see below), it is not surprising that HIV-1 DNA PCR may also fail to detect HIV-1 group O and some group M subtypes.^{95–97} To accommodate this deficiency, primer pair modifications have been incorporated into the recent Roche Amplicor^(TM) HIV-1 DNA and Roche Monitor^(tm) HIV-1 RNA version 1.5 assays. Because of the large number of *pol*-specific synthetic oligonucleotide target probes used by the bDNA assay (Bayer Versant HIV-1 RNA 3.0 assay), detection of group O and different group B subtypes has not been a quantitative problem for the bDNA assay.⁹⁷

DETECTION OF HIV-2 ANTIBODIES

Although HIV-2 infection is less geographically dispersed than HIV-1, and the epidemic is primarily focused in western Africa, HIV-2 is present in the epidemic in India.^{98,99} In the United States, only a relatively few cases of HIV-2 have been reported.¹⁰⁰ HIV-2 among U.S. blood donors is extremely rare, with only three cases detected from screening 74 million donations up to June 1995.¹⁰¹ Of the 62 persons reported with HIV-2 infection in the United States, 44 (77%) were born in, had traveled to, or had a sex partner from western Africa.¹⁰¹ Nevertheless, diagnosis of HIV-2 infection will

continue to be an emerging problem in the United States;¹⁰² thus, antibody screening for both viruses is warranted.

HIV-1 and HIV-2 genomes share about 60% homology in conserved genes such as *gag* and *pol* and 35–45% homology in the *env* genes.¹⁰³ The core proteins of HIV-1 and HIV-2 display frequent cross reactivity, whereas the envelope proteins are more type specific.¹⁰⁴ Despite this cross reactivity, anti-HIV-1 EI assays used for screening blood donors in the United States are estimated to detect 55–91% of HIV-2 infections.¹⁰⁵ Western blots for HIV-1 antibodies may be positive, negative, or indeterminate with HIV-2-positive sera. (For the confirmation of HIV-2 EI assay reactivity, p26 and gp36 correspond to their HIV-1 counterparts p24 and gp41, respectively.¹⁰⁶) Busch and coworkers tested 913 anti-HIV-1-reactive blood donor sera using an anti-HIV-2 screening EIA, with confirmation by an anti-HIV-2 *env*-peptide EIA and an anti-HIV-2 Western blot. These 913 sera were derived from anti-HIV-1 screening of approximately 242,000 donations over a 3-year period. No HIV-2 infections were identified.¹⁰⁵

To examine HIV-2 seroprevalence in a higher-risk population, a sentinel surveillance for HIV-2 was conducted by testing 31, 533 anonymous blood specimens from patients at sexually transmitted disease clinics, injecting drug users at treatment centers and clients at HIV counseling and testing sites in 14 U.S. cities where West African immigrants often settle.¹⁰⁰ Specimens were tested by HIV-1 and HIV-2 whole virus and synthetic peptide EI assay and confirmed by HIV-1 and HIV-2 Western blots. Nearly 10% of 31, 533 sera were positive for HIV-1. In addition, two heterosexual male patients from West Africa were infected with HIV-2, and one of the HIV-2-positive specimens did not cross react on HIV-1 EI assay screening.¹⁰⁰

When HIV testing is indicated, tests for antibodies to both HIV-1 and HIV-2 should be obtained if epidemiological risk factors for HIV-2 infection are present, if clinical evidence exists for HIV disease in the absence of a positive test for antibodies to HIV-1, or if HIV-1 immunoblot results exhibit the unusual indeterminate pattern of *gag* plus *pol* bands in the absence of *env* bands.^{54,100,107} The following procedures are recommended if testing for both HIV-1 and HIV-2 is performed by means of a combination HIV-1/HIV-2 EI assay.⁵⁴ A repeatedly reactive specimen by HIV-1/HIV-2 EI assay should be tested by HIV-1 immunoblot (or another licensed HIV-1 supplemental test). A positive result by HIV-1 immunoblot confirms the presence of antibodies to HIV-1, and testing for HIV-2 is recommended only if HIV-2 risk factors are present. If the HIV-1 Western blot result is negative or indeterminate, an HIV-2 EI assay should be performed. If the HIV-2 EI assay is reactive, an HIV-2 supplemental test such as an HIV-1-specific Western blot should be performed.⁵⁴ In addition, HIV-2 DNA PCR has been used to determine infection with HIV-1, HIV-2, or both viruses^{108,109} (see below).

DETECTION OF HUMAN IMMUNODEFICIENCY VIRUS

■ CULTURE

The detection of HIV-1 by mixed-lymphocyte coculture is a specialized procedure that has extremely high specificity but lower sensitivity in patients with high CD4⁺ cell counts^{110–112} compared to viral nucleic acid detection methods (see below). HIV-1 coculture may be particularly useful as a supplemental test for assessing indeterminate immunoblots associated with primary infection, where culture has a comparable specificity to viral RNA detection.¹¹³ In the diagnosis of HIV-1 infection in perinatally exposed infants, a sequential-sample, combination assay algorithm comprising an HIV-1 DNA PCR on the first specimen followed by a culture of the second specimen was recommended over HIV-1 DNA PCR for diagnosis alone¹¹⁴ by Paul and coworkers.¹¹⁵ In a study of 208 HIV-1-exposed infants, they found that a positive HIV-1 DNA PCR result followed by a positive culture in the second sample confirmed infected status, while two consecutive negative PCR results reconfirmed as negative at 6 months of age established uninfected status.¹¹⁵

The lower sensitivity of HIV-1 coculture (other than for pediatric diagnosis) compared to currently available nucleic acid detection methods, as well as its greater cost, time requirements, and highly specialized technical nature, leaves HIV-1 culture restricted primarily to research laboratories. However, there may be a rekindled interest in using HIV-1 coculture for assessing viral containment following potent antiretroviral therapy^{116–118} and for obtaining primary clinical HIV-1 isolates for viral syncytium-inducing and drug susceptibility phenotypes.¹¹⁹

■ HIV-1 P24 ANTIGEN

With the advent of nucleic acid amplification methods for monitoring HIV-1, the measurement of HIV-1 p24 antigen has a much more limited role than it once had. Now the primary use for p24 antigen detection is for identifying subjects in the antibody-negative window period of acute HIV-1 infection, but this has more or less been supplanted by HIV nucleic acid testing (NAT). Although antigen detection is a less expensive alternative to viral RNA detection in this setting, both viral RNA and peripheral blood mononuclear cell (PBMC) culture are significantly more sensitive than detection of p24 antigenemia,^{50,51,113} even with the added sensitivity of p24 antigen acid dissociation.^{120,121} However, a tyramide signal amplification-boosted EI assay for quantification of heat-dissociated p24 antigen reportedly has equivalent sensitivity to viral RNA reverse transcriptase polymerase chain reaction amplification (RT-PCR) at 200–400 RNA copies/mL.¹²² The reactivity of the p24 antigen

EI assay requires confirmation by a neutralization assay; this is similar to the HIV-1-specific antibody by the EI assay.¹²³

With the advent of a licensed HIV NAT screening test, p24 antigen screening of the U.S. blood supply was discontinued.¹²⁴

■ VIRAL NUCLEIC ACID

The detection of viral nucleic acid (proviral DNA or viral RNA) by commercially available amplification technologies provides a specific and sensitive direct detection method to identify persons who are infected but who have not seroconverted,^{12,125} to identify infected infants,¹²⁶ and to resolve indeterminate HIV-1 antibody serologies.^{48,50,127} In addition, the quantification of plasma viral RNA has assumed a critically important role in assessing disease prognosis and response to antiretroviral therapy.^{128–130}

■ VIRAL DNA IN PBMCs

Qualitative HIV-1 DNA PCR amplification is a commonly used assay method for the diagnosis of HIV-1 infection in neonates and infants.^{131,132} The Roche Amplicor™ HIV-1 test kit (Roche Diagnostic Systems, Inc., Branchburg, NJ) is FDA licensed for this clinical use.

The major advantages of HIV-1 DNA PCR over culture are its increased sensitivity and more rapid reporting time, that is, 1 day compared to 2–4 weeks. However, the diagnostic performance of HIV RNA detection may match or exceed that of culture and HIV DNA detection.¹³³ There is always a possible risk of false-positive reactivity due to contamination of the specimen with amplicons (the so-called carryover product contamination),¹³⁴ although this is decreased somewhat by the use of the uracil *N*-glycosylase enzyme in the commercial assay.¹³⁵ False negatives can also occur because of inhibition of the PCR reaction by hemoglobin or heparin¹³⁶ or when there are fewer target cells in the assay than expected. To control for the latter, and to improve the precision of the assay, testing for HIV-1 DNA should also include concurrent amplification of a cell-associated host gene such as HLA-DQa or globin locus.¹³⁷ Participation in a quality assurance program will also ensure that problems with sensitivity and specificity are quickly identified.^{138–141}

The use of HIV-1 DNA PCR for diagnosis was assessed recently for 96 studies for which reported sensitivities for HIV-1 DNA PCR range from 10% to 100% and specificities range from 40% to 100%.¹⁴² The authors of this review concluded that the HIV-1 DNA PCR assay is not sufficiently accurate to be used for the diagnosis of HIV-1 infection without confirmation. Use of HIV-1 DNA PCR for the diagnosis of infection in adults should be limited to situations in which antibody tests are known to be insufficient^{48,143} or as a confirmation test when low levels of HIV RNA (<5000 RNA

copies/mL) are detected with suspected HIV primary infection.¹⁴⁴ HIV DNA level during early infection in adults helps to independently predict disease progression in some²⁴⁰ but not in other studies.²⁴¹

■ VIRAL RNA IN PLASMA

The detection of plasma HIV-1 RNA by RT-PCR amplification, nucleic acid sequence-based amplification (NASBA), bDNA signal amplification, or transcription-mediated amplification (TMA) is more sensitive than p24 antigen EI assay or culture for detecting virus.^{124,143–147} There is, therefore, much interest in using plasma HIV-1 RNA as a diagnostic test.^{57,148} As mentioned above, HIV-1 RNA has replaced HIV-1 p24-antigen screening of all donor blood in the United States.¹²⁴ However, only one commercial HIV-1 RNA assay is currently licensed for blood bank donor-screening purposes (APTIMA HIV-1 RNA Qualitative Assay, Gen-Probe). To avoid false-positive diagnosis, the HIV-1 RNA assay should be used diagnostically only as a supplemental test for detecting antibody-negative acute infection.^{57,142,144,149} Thus, in this particular diagnostic setting, a reactive HIV-1 RNA assay (particularly one with a low viral RNA copy number, <5000 copies/mL)^{57,144} should be confirmed by another nucleic acid technology, preferably HIV-1 DNA PCR—or HIV-1 p24 antigen or HIV-1 culture if available. Alternatively, one can retest for the development of HIV-1-specific antibody, which should generally occur within 2 or 3 weeks after viral RNA is detected.^{12,113} The presence of HIV-1 RNA alone requires a correlation with the medical and epidemiological history and, importantly, a repeat blood draw for confirmatory HIV-1 testing.

HIV-1 RNA quantitative assays

Three different FDA-approved commercial assays are available to detect and quantify viral RNA in plasma; each approaches the quantification of viral RNA differently. These assays quantify HIV-1 RNA by either amplifying the target RNA or the signal. The limits of quantification provide an acceptable sensitivity and range for most clinical purposes. The limit of quantification represents the level at which the intra-assay variation is less than $0.15 \log_{10}$ RNA copies/mL such that the 95% confidence limits for the difference between two estimates is equivalent to $\pm 0.5 \log_{10}$ RNA copies/mL or approximately a threefold difference in viral RNA that can be reliably measured.¹⁵⁰ This interpretation differs from the kit manufacturers who claim a lower level of quantification based on less strict criteria. A more detailed overview of the different methodologies may be found elsewhere.¹⁵¹

Briefly, the NASBA assay involves first obtaining nucleic acid isolation by lysis and binding of the viral RNA to silicon dioxide (silica) microparticles, followed by isothermal amplification

(the so-called target amplification) using a reverse transcriptase, RNase H, and T7 RNA polymerase.^{152–154} Three internal calibrators are added to the specimen and adsorbed along with the specimen prior to the lysis step. Amplification covers approximately 1200 bases in *gag* and *pol*. Detection is by means of chemiluminescence. The sensitivity of the assay is approximately 80 RNA copies/mL, the quantification limit is 500 copies/mL, and the dynamic range is up to 10,000,000 RNA copies/mL (bioMérieux NucliSens™ QT HIV-1 RNA assay). Acceptable whole blood anticoagulants include EDTA (lavender-top Vacutaner(tm) tubes [Becton Dickinson, Franklin Lakes, NJ]), ACD (acid citrate dextrose, yellow-top tubes), and heparin (green-top tubes).

The branched-chain DNA assay (Bayer VERSANT HIV-1RNA 3.0) is a nonisotopic sandwich nucleic acid hybridization assay that uses a series of target probes to span 1200 bases in *gag* and *pol* and hybridize the viral RNA target onto a series of capture probes attached to the surface of the microwell plate and also to the bDNA amplifier molecules.¹⁵⁵ Multiple alkaline phosphatase probes amplify the signal (the so-called signal amplification); detection is by chemiluminescence. An external standard curve is used to calculate the HIV-1 RNA copy number. The dynamic range is up to 1,000,000 RNA copies/mL, the sensitivity is 50 RNA copies/mL of plasma, and the limit of quantification is 75–100 copies/mL.¹⁵⁶ The whole blood anticoagulant of choice is EDTA.

The Roche Amplicor® HIV-1 Monitor™ Test uses the *Thermus thermophilus* rTth enzyme, which serves to catalyze both reverse transcription and DNA amplification of a 142-base *gag* sequence in a single reaction tube. An internal quantitative standard is used to adjust for recovery and calculate the final HIV-1 RNA copy number. The assay has an analytic sensitivity of 200 RNA copies/mL and a quantification limit of 400 RNA copies/mL, with a dynamic range of up to 750,000 RNA copies/mL. A centrifugation step (Amplicor HIV-1 Monitor™ Ultra Sensitive specimen preparation protocol, Roche Molecular Systems, Somerville, NJ) can be used to concentrate virus and thus increases the sensitivity of the assay to approximately 50 RNA copies/mL, with a lower quantification limit of 200 copies/mL.^{157,158} The whole blood anticoagulant of choice is EDTA or ACD. Two automated specimen preparation and real-time PCR amplification assay instruments, the Roche COBAS AmpliPrep/COBAS TaqMan HIV-1 Test (based on amplification of *gag* targets) and the Abbott RealTime HIV-1 assay (based on amplification of a *pol* [integrase] target), have been FDA approved for monitoring HIV-1 infection and should facilitate the processing of large numbers of clinical specimens for HIV-1 RNA quantification. Both automated assays detect and quantify HIV-1 subtypes across a broad dynamic HIV-1 RNA range (50–10 million RNA copies/mL of plasma).

Specimen considerations for HIV-1 RNA quantification

In order to minimize the variability of quantitative HIV-1 RNA test results, samples collected for a particular assay should be processed at the same time post blood draw, using the same anticoagulant blood-draw tube type.¹⁵⁹ In general, EDTA is the preferred anticoagulant. Based on the work of Holodniy and coworkers,¹⁵⁹ the general recommendation has been to separate and store plasma at ~70°C within 6 hours of collection. This rapid specimen processing may place a considerable burden on the laboratory. Moreover, a 6-hour processing requirement may be too stringent, and a recent study is reassuring in this regard.¹⁶⁰ For the Amplicor HIV-1 Monitor™ assay, viral RNA copy numbers were maintained within 0.5 log₁₀ (threefold) in both blood and plasma samples held at ambient temperature or 4°C for up to 3 days and remained stable despite limited freezing and thawing.¹⁶¹

As in the serologic diagnosis of HIV infection, the use of filter paper to collect and store whole blood for later analysis of viral nucleic acid is an attractive alternative to phlebotomy. Studies by Cassol, Fiscus, and others have shown that both HIV-1 DNA and RNA can be detected reliably from blood dried on filter paper; moreover, RNA quantification, corrected for the hematocrit, was comparable in terms of sensitivity and reproducibility to plasma.^{162–164} This collection method appears to be suitable for both quantification and sequencing of HIV specimens obtained under field conditions.^{164,165}

DETECTION OF HIV-1 SUBTYPE NUCLEIC ACID

As HIV-1 subtypes establish within different geographical areas, primer pairs and probes used for HIV nucleic acid detection and quantification have been modified to detect non-B subtypes. For example, the APTIMA HIV-1 RNA Qualitative Assay (Gen-Probe, San Diego, CA) is reported to show sensitive detection of all major HIV-1 group M subtypes, in addition to variants from groups N and O.¹⁶⁶ Primer pair modifications have been incorporated into the Roche Amplicor HIV-1 DNA and Monitor HIV-1 RNA assays (version 1.5)¹⁶⁷ and Abbott RealTime assays. Because of the large number of *pol*-specific synthetic oligonucleotide target probes used by the bDNA assay (VERSANT HIV-1 RNA 3.0 Assay, Bayer Corporation, Norwood, MA), detection of group O and different non-B subtypes has been less of a problem for the bDNA assay.¹⁶⁸

DETECTION OF HIV-2 NUCLEIC ACID

Specific primers and probes are necessary to detect HIV-2 nucleic acid.¹⁶⁹ Significant genetic diversity of HIV-2 divides this virus into five genetic subtypes, A–E, with subtype A being the most common. Similarly to HIV-1, recombination

of phylogenetically distinct HIV-2 viruses occurs but genetic recombination between HIV-1 and HIV-2 has not been reported.¹⁷⁰ In contrast to HIV-1, HIV-2 RNA levels in plasma and semen are generally lower, corresponding to a slower immunological deterioration and lower transmission rates.¹⁷¹

ANTIRETROVIRAL DRUG SUSCEPTIBILITY GENOTYPE AND PHENOTYPE

Incomplete inhibition of HIV-1 replication in vivo may arise because of poor drug absorption, patient noncompliance with therapy, variations in host antiretroviral drug pharmacokinetics, and compartmentalization or infection with drug-resistant virus variants (termed primary drug resistance). This incomplete inhibition may result in the emergence of drug-resistant HIV-1 variants (secondary drug resistance) and thus is an important cause of therapy failure.¹⁷² An assessment of drug resistance may be helpful in selecting antiretroviral therapy, but this has not been rigorously proven.¹⁷³ Nevertheless, commercial assays for antiretroviral drug resistance are available, and clinical studies suggest that viral drug resistance is often associated with poor virological response to therapy. Expert interpretation is recommended, given the complexity of results and assay limitations.^{174,175}

Antiretroviral drug susceptibility is determined either phenotypically, by assessing for the susceptibility of the virus isolate (or *pol*-recombinant) ex vivo, or genotypically, by assessing for mutations that confers resistance.

There are two phenotypic approaches.¹⁵¹ The first approach tests the sensitivity of the proviral population present in the PBMCs of the patient but is no longer used because it is too labor intensive and has been replaced by the second more rapid approach that uses recombinant technology. In the second approach, PCR-amplified *pol* gene-amplicons containing reverse transcriptase and protease are obtained from the plasma or serum-associated virus (vRNA) or from the cell-associated provirus (vDNA). These amplicons are inserted into a laboratory HIV DNA clone that has the RT and protease genes deleted.^{176,177} The infectious HIV DNA clone is then propagated in a permissive cell line to create a pool of infectious recombinant virus. This recombinant virus is used to determine the susceptibility to single antiretroviral drugs (unfortunately, the use of combinations of antiretroviral drugs is beyond the assay's capacity). A modification of this approach uses a recombinant test vector (RTV) HIV DNA that contains the patient's viral *pol* gene and an indicator gene (luciferase) that is inserted into the *env* gene, thus preventing the RTV from expressing HIV-1 envelope protein. Pseudo-typed virus particles are produced by cotransfecting permissive cells with RTV DNA and a plasmid that expresses the envelope proteins of amphotropic murine leukemia virus (MuLV). The ability of these pseudo-typed

virus particles to complete a single round of replication is assessed by measuring luciferase production in susceptible target cells. The antiviral activity of a protease inhibitor (PRI), for example, is measured by adding a PRI to the cotransfected cells, which results in the production of noninfectious pseudo-typed virions incapable of infecting new target cells. The antiviral activity of a reverse transcriptase inhibitor (RTI) is measured by adding an RTI to target cells and preventing the infection of these cells by the pseudo-typed virus that arises from the original cotransfected cells.¹⁷⁸

Genotypic methods to detect HIV resistance include DNA sequencing of the entire viral population or clones, selective PCR assay, determination of point mutations, and differential probe hybridization; enzyme-immunoassay modification of the oligonucleotide detection reaction assay; and the commercially available HIV-1 reverse transcription line probe assay.¹⁷⁹ Several kits are commercially available for genotypic resistance testing. HIV-1 Trugene (Visible Genetics/Bayer Healthcare, Suwanee, GA) and Viroseq (Celera/Abbott Laboratories, Rockville, GA, and San Francisco, CA) are FDA approved. However, genotypic changes may not always correlate with changes in drug susceptibility of the clinical isolate.¹⁸⁰ Therefore, before these techniques can be applied most effectively in the clinic, much still needs to be learned about the genotype–phenotype correlation in patients who receive antiretroviral therapy. While some advisory panels have recommended routine use of susceptibility testing in clinical practice,^{4,174} many clinicians continue to base decisions to start or change therapy on the viral RNA level, CD4⁺ cell count, and previous antiretroviral drug history, with careful attention to patient education about adherence to the prescribed therapy regimen.¹⁷³

It should be noted that primary HIV resistance can also be observed in viruses recovered from a substantial number of people with newly diagnosed infection; this is called “transmitted drug resistance.” Transmitted drug resistance is a clear demonstration of the failure of HIV prevention efforts. In addition, the risk of such resistance clearly requires consideration by the clinician for the patient about to start therapy.

USE OF HIV-1 RNA TO MONITOR INFECTION

■ PROGNOSTIC ABILITY OF HIV-1 RNA IN INFECTED ADULTS

Natural history

The assessment of immune dysfunction, as evaluated by the CD4 T-cell count, and the level of virological containment, as assessed by the plasma HIV-1 RNA level, assist the clinical assessment of patients with HIV-1 infection. The HIV-1 RNA level has become the premier laboratory marker of viral replication *in vivo*;¹⁸¹ however, to appreciate the benefits and

limitations of using viral RNA as a measure of disease progression requires an understanding of several critical elements of viral pathogenesis.

First, cell-free viral RNA in plasma represents a minority population of infectious virus and a majority population of noninfectious virus particles.¹⁴¹ The infectious to noninfectious particle ratio is higher for viruses with higher replicative efficiency and lower with an effective cytotoxic CD8 T-cell response and high levels of HIV-1 antibody.^{182,183} Second, the level of plasma viral RNA may not reflect the level of cell-associated infectious virus. Cell-associated infectious virus can be recovered from the majority of patients who have had plasma viral RNA levels suppressed to below the level of detection after prolonged, potent antiretroviral therapy.¹¹⁸ Third, the viral RNA level in plasma may not reflect the level of virus and kinetics of viral replication in other sites and compartments^{184–187} such as latently infected cells in the lymph nodes,¹⁸⁸ central nervous system,¹⁸⁹ and genital tract.¹⁹⁰ Fourth, independent of viral RNA level, syncytium-inducing viral phenotype (X4) is strongly and independently associated with disease progression.¹⁹¹ Fifth, coinfection with the flavivirus GB virus C (GBV-C, also designated as hepatitis G virus) is associated with reduced mortality rate and may lead to an inhibition of HIV replication in GBV-C viremic patients.^{192,193} Finally, patient attributes such as age,¹⁹⁴ gender, HLA phenotype,¹⁹⁵ and immune status¹⁹⁶ may cause substantial variability in the level of viral replication.¹⁹⁷ Together these factors may explain, in part, the differences in disease progression among patients with similar plasma viral RNA levels, and they represent a limitation to the use of plasma viral RNA as the sole marker of therapeutic efficacy and clinical outcome.

Nonetheless, one of the most important concepts to emerge from our understanding of HIV-1 disease pathogenesis is that the magnitude of HIV-1 replication in infected persons is associated with the rate of disease progression.^{181,198,199} The level of plasma HIV RNA reflects the infected person's ability to contain viral replication such that the replication and clearance of virus reaches a quasisteady state^{184–187} and thus defines, in part, the subsequent rate of disease progression.^{198–201} This quasisteady state has been referred to as the viral “set point” and appears to be established in the first 3–6 months following primary infection, during which time an HIV-specific humoral and cytotoxic lymphocyte response is established.^{202–204} Interestingly, the plasma viral RNA level prior to the establishment of the steady state is not predictive of subsequent disease progression.²⁰² The viral steady state represents the nadir of viral containment, after which time the plasma viral RNA level may increase slowly, conferring additional risk for the development of AIDS.²⁰² However, some patients may continue to have a decline in plasma viral RNA from the steady state, conferring additional clinical benefit.²⁰⁵

The viral steady state is not absolute, and each plasma viral

RNA level describes a range of times to the development of disease progression. To illustrate this point, Ioannidis and coworkers constructed a model to ascertain the predictive value of serum viral RNA in asymptomatic patients with >500 CD4 cells/ μL , an unknown time since seroconversion, and no prior antiretroviral therapy.¹⁹⁷ They found that the minimum and maximum estimated time to progression to AIDS varied considerably at assigned serum viral RNA levels. For example, patients with a viral load of 10,000 (10^4) RNA copies/mL of serum could take from 2.8 to 19 years to develop AIDS, and those with 30,000 ($10^{4.5}$) RNA copies/mL could take anywhere from 1.9 to 8 years.

In general, patients who are more likely to progress rapidly have a higher plasma viral RNA steady state than those who progress more slowly. However, the predictive value of high plasma viral RNA levels decreases over time, while the predictive value of low CD4⁺ cell count and CD4⁺ cell function increases over time. Thus, in the later stages of infection, immune deficiency is most predictive of disease progression.²⁰⁵ There is a monotonic relationship between the plasma viral RNA level and the rate of CD4⁺ cell decline, such that higher plasma viral RNA levels are associated with a greater rate of CD4⁺ cell decline.^{198,201} For example, the Multicenter AIDS Cohort Study of the natural history of HIV-1 infection showed that the mean (95% confidence interval) decrease in CD4⁺ cell count per year was -36.3 (-42.3 to -30.4) cells for subjects with less than 500 viral RNA copies/mL of plasma compared to -76.5 (-82.9 to -70.5) cells for subjects with greater than 30,000 viral RNA copies/mL of plasma.²⁰¹

In most untreated subjects, the plasma viral RNA steady-state level lies within a relatively narrow range between 1000 (10^3) and 100,000 (10^5) RNA copies/mL of plasma.^{181,191,198,205} For example, in the largest cohort study, 74.3% of 1531 untreated patients had plasma viral RNA levels of $<30,000$ RNA copies/mL by the bDNA assay.²⁰¹ Mellors and coworkers also defined five risk categories for disease progression based on the arbitrary distribution of 1531 subjects into HIV-1 RNA level quintiles. Highly significant differences in the proportion of patients who progressed to AIDS within 6 years of diagnosis were seen in these five risk categories: 500 copies/mL or less, 5.4% (95% CI, 0–17%); 501–3000 copies/mL, 16.6% (12–21%); 3001–10,000 copies/mL, 31.7% (7–43%); 10,001–30,000 copies/mL, 55.2% (25–84%); and more than 30,000 copies/mL, 80.0% (58–100%).²⁰¹

Clinical trials

Importantly, because there is a continuous gradient of risk of disease progression associated with the viral RNA steady-state level, one of the objectives of antiretroviral therapy is to “reset” this plasma viral RNA steady-state level to one with a lower risk of disease progression. Results from HIV-1 therapy trials show that inhibition of HIV-1 replication (as assessed

by plasma HIV-1 RNA level) is associated with a delay in clinical disease progression.^{129,130} Although the relative clinical benefit of any given decline in plasma viral RNA does not depend on the baseline level of plasma viral RNA, the absolute risk of clinical disease progression remains higher in the patient with the higher pretherapy plasma viral RNA level.¹⁸¹ In summarizing the data from seven large clinical trials involving 1330 subjects who received primarily nucleoside therapies, Marschner and coworkers¹⁸¹ showed that a 10-fold decrease in plasma viral RNA level from baseline to week 24 yielded a 72% reduction in the risk of progression (95% CI, 61–81%, $p < 0.001$) and that large reductions in plasma viral RNA level were the most desirable. Importantly, any reduction in excess of the natural variability of plasma HIV-1 RNA measurement (approximately threefold, or $0.5 \log_{10}$) was associated with a delay in disease progression. However, in this study and others, the prognostic interpretation of any given plasma viral RNA reduction also depended on the treatment response of the CD4⁺ cell count.^{181,206,207} Even though the change in plasma viral RNA is a better predictor of clinical progression than is the CD4⁺ cell response,⁷ together the viral RNA and CD4⁺ cell count responses more fully characterize the risk of disease progression than does either one alone.^{181,206,208} These clinical trial data indicate that a more complete assessment of a patient’s prognosis is achieved by monitoring the plasma viral RNA level and CD4⁺ cell count together.

MONITORING THERAPEUTIC RESPONSE

In general, nadir responses in plasma viral RNA occur in most patients 4–12 weeks following initiation of potent antiretroviral therapy. With some potent antiretroviral regimens, plasma viral RNA values will decrease to less than 500 RNA copies/mL by 16 weeks in 60–80% of subjects and to less than 50 viral RNA copies/mL by 24 weeks in approximately 70%. The number of patients in these categories will depend on the study population and their prior antiretroviral experience.^{130,209} With a stable response, continued monitoring at 3–4-month intervals seems warranted, with more frequent monitoring if a critical plasma viral RNA value is approached.²¹⁰ It is advisable to plot the plasma viral RNA values on a \log_{10} scale and only repeat the plasma viral RNA measurement for values that are greater than the upper 95% confidence interval found for the expected variation in plasma viral RNA level (that is, $0.5 \log_{10}$ above the mean nadir response value), thus ensuring that a change in plasma viral RNA level will lead to a change in therapy.^{211–214}

The target of therapy must be a durable reduction in the plasma viral RNA by at least threefold ($0.5 \log_{10}$) from pretherapy levels^{210,213} to below 1000 copies/mL¹⁸¹ and, by current consensus guidelines, preferably to an “undetectable” level.⁴ An analysis of 1083 patients from ACTG 320¹³⁰ showed

that only seven (5.6%) of 126 clinical events were associated with a preceding plasma HIV-1 level below 500 copies/mL, and for the remaining 119 clinical events, the plasma viral RNA level was above 500 copies/mL.²¹⁵ Nevertheless, the target for therapy should be at least one \log_{10} value lower than this, i.e., <50 RNA copies/mL of plasma.⁴

Importantly, therapy should also stabilize or increase the CD4⁺ cell count, at or above the expected level of biological variation, by more than 30% in the absolute cell number or by more than 3% in the proportion of cells.²¹⁶ Interpretation of any given plasma HIV-1 RNA reduction depends on the treatment response of the CD4⁺ cell count. Because of the interaction between viral RNA and CD4⁺ cell count, changes in both, along with a consideration of the clinical course, are necessary for defining therapeutic response. In an analysis of several clinical studies of primarily nucleoside therapy, for those subjects with no reduction in plasma HIV-1 RNA level, subjects with a reduction in CD4⁺ cell count had a 30% greater risk of clinical progression over 2 years, compared to those who had an increase in CD4⁺ cells above pretherapy levels.¹⁸¹

Additionally, therapy should provide an improved sense of patient well-being with minimal side effects. In targeting for the lowest plasma viral RNA level, consideration must be given to prior antiretroviral drug exposure, balancing therapy compliance, tolerability of the regimen, and long-term toxicity of the therapy regimen.^{4,217}

■ MONITORING HIV-1 RNA IN PREGNANT WOMEN

Monitoring of viral RNA levels in pregnant women is no different from that for nonpregnant women or men,^{3,4} and the natural history of plasma viral RNA during pregnancy is still being characterized. In two relatively small studies, the maternal viral load did not rise during pregnancy.^{218,219} However, in a larger cohort study of 198 HIV-1-infected women, plasma HIV-1 RNA levels were higher at 6 months postpartum than during antepartum in many of the women.²²⁰ Although both the plasma viral RNA level and the CD4 cell count are independently predictive of vertical transmission risk, the change in plasma viral RNA level only explains, at most, 50% of the benefit of zidovudine therapy.²²¹ These data strongly suggest that there is a prophylactic benefit from antiretroviral therapy on vertical transmission. The strong association between vertical transmission and maternal plasma viral RNA level^{221,222} indicates that plasma viral RNA levels should be suppressed to <1000 copies/mL and preferably to undetectable, to reduce the risk of vertical transmission during pregnancy to <1%.^{223–226} Furthermore, because transmission may occur when plasma HIV-1 RNA is not detectable,^{220,221} plasma HIV-1 RNA levels should not be the determining factor when deciding when to use antiretroviral prophylaxis.^{3,4} As such,

antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters for the purpose of preventing mother-to-child transmission.^{3,4}

■ USE OF PLASMA VIRAL RNA TO DEFINE VIROLOGICAL FAILURE

A precise definition of therapeutic failure based on viral RNA level has not been developed. Such a definition should embrace the clinical status of the patient, the CD4⁺ cell count, and the plasma viral RNA level. The failure of plasma viral RNA to decline by at least 30-fold (1.5 \log_{10}) or more from baseline following 4–8 weeks of therapy is generally considered to represent a suboptimal virological response.^{4,181} In addition, many clinicians would also consider the inability to achieve undetectable plasma viral RNA by 12–24 weeks of therapy as evidence for therapeutic failure. The consideration of undetectable viral RNA as a benchmark of success is based on the recognition that viral replication in the presence of selective antiretroviral drug pressure could potentially result in the development of drug resistance. However, many patients fail to achieve undetectable viral RNA levels or they experience a rebound in viral RNA after starting antiretroviral therapy.^{226,227}

It is important to consider that the relative benefit of a decline in plasma viral RNA is the same, no matter where the pretherapy viral RNA level started, although the pretherapy plasma viral RNA level itself confers an additional, independent risk of disease progression. For example, a decline from 10⁵ viral RNA copies/mL of plasma to 10⁴ viral RNA copies/mL of plasma represents the same relative 72% reduction (95% CI, 61–81%, $p < 0.001$) in risk of disease progression as a change from 10⁴ to 10³ viral RNA copies/mL.¹⁸¹ However, each of the two pretherapy plasma viral RNA levels of 10⁵ and 10⁴ copies/mL confers a different relative hazard of disease progression, after controlling for the baseline CD4⁺ cell count and therapy assignment. The target of reaching undetectable plasma viral RNA after 12–24 weeks of therapy is also affected by the pretherapy plasma viral RNA level. Achieving a detectable plasma viral RNA level of less than 10^{3.7} (5000) copies/mL when starting with 10⁶ copies/mL will confer clinical benefit and may be all that is obtainable, given a patient's prior antiretroviral therapy experience.

Viral resistance

It has been somewhat arbitrarily set that any sustainable 0.5 \log_{10} (threefold) rise in plasma viral RNA above the therapy-induced plasma viral RNA nadir, which is not attributable to intercurrent infection, vaccination, incomplete adherence to the antiretroviral therapy regimen, decreased absorption of antiretroviral drugs, altered drug metabolism, drug–drug interactions, or testing methodology, likely

represents viral failure due to the emergence of drug-resistant HIV variants^{4,210} or potential superinfection with a new drug-resistant strain of HIV. Although genotypic and phenotypic changes associated with drug resistance in vitro are not always synonymous with clinical drug failure, retrospective and prospective clinical trials on the predictive value of these tests have supported their adjunctive use for selecting the next antiretroviral regimen during virological failure.^{4,228} The correct interpretation of viral susceptibility is complicated by the complexity of the mutational patterns, undetected subpopulations of mutant virus, residual effects of prior antiretroviral therapy, and host factors including nonadherence. Moreover, the relationship between adherence and the development of antiretroviral drug resistance is complicated, and the level of adherence that creates the most efficient combination of drug pressure and viral replication to select for resistant virus is unknown.²²⁹ Thus, the clinician should approach the clinical management of patients using viral genotypic or phenotype assays cautiously until definitive, prospective data from clinical trial are available.¹⁷³ Until such data are available, the clinical management of when to initiate or change therapy in an HIV-infected patient should be individualized and based primarily on viral RNA level, CD4 cell count, and previous antiretroviral drug history, but not on antiretroviral resistance test results alone.¹⁷⁴

Discordant viral RNA and CD4 cell responses

The therapeutic response in plasma viral RNA and CD4 cell count may be discordant, with a sustained or continued rise in CD4 cell count despite a rise in viral RNA level on antiretroviral drug therapy.^{207,230} This discordance occurs in approximately 14% or more of patients who receive antiretroviral therapy.¹⁸¹ The discordant response has been associated with a decrease in disease progression, raising questions about the wisdom of changing antiretroviral therapy based solely on the plasma viral RNA response.²²⁶ Many clinical trials provide study patients with the endpoint measurement (i.e., plasma viral RNA level) on a real-time basis. This practice raises serious concerns about the introduction of selection bias and the ability to define a viral RNA-based therapeutic failure. Thus, in the absence of clinical trials data, if the sustained rise in plasma viral RNA while on therapy is to either less than 0.5 log₁₀ above the plasma viral RNA therapy nadir or less than 5000 (3.7 log₁₀) copies/mL, whichever is less, it might be prudent to observe carefully for a further deterioration in CD4⁺ cell count or clinical progression before considering a change of therapy. A sustained increase in plasma viral RNA that exceeds these criteria should warrant a reassessment of the antiretroviral regimen for adherence and possible therapy failure. A more contemporary approach would consider any sustained detection of plasma viral RNA worthy of a switch in therapy.⁴ However, neither approach has received validation by a controlled clinical trial.

CAVEATS FOR THE CLINICAL USE OF HIV-1 RNA TESTING

Uncertainty in measuring HIV-1 RNA level

There is uncertainty in assigning a value to a single plasma viral RNA measurement.¹⁴¹ This uncertainty arises from specimen handling, the performance characteristics of the assay, the technical variability of the assay, whether the different specimens are tested by batch or real time, and the infected person's natural variation in virus level.^{211–213} In total, these factors define, with 95% confidence, a variability in the estimated plasma viral RNA copy number of at least fivefold (0.7 log₁₀) for single RNA measurements. Consequently, a single measurement of plasma viral RNA is associated with a defined range of values above or below the measured value at least 95% of the time (2.5% of the time values may be greater than and 2.5% of the time less than this fivefold range). For example, a person with a plasma viral RNA value of 5,000 copies/mL obtained from a single plasma specimen taken today may have a measured viral RNA value anywhere from 1,000 to 25,000 copies/mL on repeat testing of another blood draw taken within the next few days to weeks, falling within this range 95% of the time.¹⁹⁰

A rigorous virology quality assurance program has shown that the intra-assay standard deviation for these assays ranges from less than 0.1 to 0.2 log₁₀ HIV-1 RNA copies/mL of plasma.^{141, 231} This precision enables the assays to distinguish reliably three- to eightfold changes in plasma viral RNA for batched testing and four- to 19-fold changes for real-time testing. Obviously, the uncertainty in defining the true plasma viral RNA level contributes important *uncertainty* for changing antiretroviral therapy based on a single plasma viral RNA value.

In addition to the above considerations, variability in interpreting absolute plasma viral RNA levels across different clinical studies arises because of the patient population studied, the use of serum or plasma to assess the viral RNA level, different viral RNA assay methods, and different anticoagulants and storage conditions. For example, viral RNA levels are generally one-half log value less for serum than for plasma, depending on the assay method used; bDNA values are generally twofold less than those for RT-PCR; and heparin interferes with the detection of viral RNA by both bDNA and RT-PCR assays but not for NASBA.^{141,160}

Thus, some patients could have successful therapy regimens inappropriately changed, based on estimates of plasma viral RNA levels that are associated with considerable uncertainty both in their measurement and in the clinical meaning of the plasma viral RNA value, particularly when the plasma viral RNA and CD4⁺ cell responses are discordant.¹⁸¹ This is of particular concern for aggressive therapy management, when decisions to change therapy are based on the quantification of viral RNA near the reliable limit of detection

for an assay. Plasma viral RNA assessments by both the bDNA and the RT-PCR assays are usually concordant for most patients below the level of quantification. However, these assessments will be discordant in approximately 20% of patients, and the decision to either maintain or switch antiviral therapy based on the assay quantification limit will be affected by the choice of the viral RNA assay used.²³²

Adequacy of plasma HIV-1 RNA level alone for explaining the clinical response to therapy

Much still remains to be learned about how the favorable and relatively short-term laboratory responses to potent antiretroviral therapy translate into the long-term survival of the individual infected with HIV-1. However, with current antiretroviral drug regimens, the majority of subjects in clinical trials remain suppressed for up to 6 years or more.²³³ Of particular concern, however, is the recovery of infectious virus from the presumably longer-lived resting T lymphocytes after prolonged, potent antiretroviral therapy.^{116,117} Nevertheless, with continued suppression of viral replication, and failure to demonstrate the development of genotypic resistance to therapy drugs, the long-term outlook for many patients is encouraging, providing the potent therapies are tolerated and drug regimens continue to become more simplified, which both promote adherence.

The use of plasma viral RNA to clinically monitor HIV-1 infection should be based on the following three critical validation points. First, plasma viral RNA is detected in most infected persons, and the level of plasma viral RNA is associated with disease progression. Second, a decline in plasma viral RNA with therapy is associated with improved clinical outcome, and a rise in plasma viral RNA is associated with clinical progression. Third, the change in plasma viral RNA level completely explains the clinical benefit of antiretroviral therapy.⁶ Clearly, fulfillment of these three validation criteria is necessary to completely understand the limitations of plasma viral RNA as a substitute marker for disease progression in clinical trials. The first two criteria for surrogacy have been fulfilled in several clinical studies, and the associations between plasma viral RNA level and disease progression are highly significant statistically.^{208,234} On the basis of both natural history and clinical trial studies (mostly from adult-based studies), it is now widely accepted that the lower the plasma viral RNA level, the better the clinical outcome.^{181,201}

Importantly, the third criterion has not been completely fulfilled. Change in plasma viral RNA level explains only a portion of the clinical response to therapy (probably less than one-half, but the estimates are very imprecise at this time)⁷; thus, plasma viral RNA is only a partial surrogate marker for clinical outcome.^{6,128,121} Although this may seem paradoxical, given fulfillment of the first two validation criteria and the strong association between the change in plasma viral RNA and disease progression, the partial surrogacy of plasma viral

RNA for clinical outcome means that other host and virus properties are necessary for a complete understanding of disease progression in the individual patient; presumably, such information may eventually help to better define the individual management of patients in clinical practice.²³⁵

CONCLUSION

The diagnosis of HIV-1 infection by detecting and confirming the presence of specific antibodies is now augmented by more simple/rapid antibody detection assays. These rapid assays are being used in sexually transmitted disease clinics, in urgent care settings, and at the time of labor and delivery for pregnant women without prior prenatal HIV testing. By providing a more rapid assessment of infection status, clinicians can offer more immediate and thus better HIV-1 counseling for patients.

The application of molecular techniques, such as PCR and other nucleic acid amplification technologies, provides earlier supplementary confirmation for the serologic determination of HIV-1 infection and in particular a more definitive and timely resolution of indeterminate immunoblot results. With repeat specimen collection and testing, the nucleic acid amplification technologies have a defined role for diagnosing HIV infection in the absence of antibody (i.e., acute infection) or in the presence of acquired antibody (e.g., neonatal infection).

The direct quantification of HIV-1 RNA in plasma has revolutionized the clinical management of HIV-1-infected patients over the past several years. However, there are other factors, such as the host's immune status, HLA haplotype, and the viral genotype and phenotype that contribute important prognostic information about disease progression, which are not necessarily captured by a single viral RNA value. Testing for HIV-1 drug resistance has become common for assessing virological failure, although the value of these tests in improving clinical outcomes (i.e., suppression of viral replication and the improvement of CD4 cell count) has not been consistently seen. As such, resistance testing may be helpful in selected clinical cases but must await further definitive clinical trial data before routine testing can be recommended.

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INTRODUCTION

Powerful forces shape the experiences of people living with HIV. Perhaps more so than for any medical condition in modern times, HIV disease evokes a strong negative response from society at large as the infection targets groups that are already marginalized. For many people living with HIV infection, the struggles that result from the psychological and social factors associated with the disease are as daunting as the biomedical consequences of ongoing viral replication and immune suppression.

The purpose of this chapter is to help clinicians caring for people living with HIV understand and, where appropriate, address the multiple psychological and social contextual challenges faced by their patients. As noted above, these challenges arise from a wide range of sources including: (1) intrapersonal factors, such as substance abuse, mental illness, or coping skills; (2) interpersonal factors, such as violence and victimization; and (3) factors that act at the community level such as social stigmatization. From the perspective of the HIV clinician, these realities are often important obstacles as the patient attempts to gain access to medical care and adhere to treatment recommendations. Further, as the disease advances from the time of diagnosis through the period of clinical latency to the appearance of opportunistic infections, the nature of these challenges may change. Several lines of evidence support the notion that, for many people living with HIV, achieving important biological outcomes such as maintenance of virologic suppression and prophylaxis of opportunistic infections is critically dependent on addressing these psychosocial factors.

One useful framework for understanding the influence of multiple psychosocial factors that act at several levels is Social Ecological Theory (SET). The SET provides a structure for conceptualizing various determinants of health across intrapersonal, interpersonal, and community levels. In the case of HIV/AIDS, it has been recognized since the earliest days of the epidemic that people belonging to traditionally marginalized groups {men who have sex with men (MSM), injection drug users, African American women, etc.} have been disproportionately

represented among those infected. The face of the epidemic is changing as well; increasingly new infections occur among the poor, minorities, and women,¹ particularly in the southeastern United States, where HIV incidence is increasing most rapidly in the United States.¹ Factors such as poverty, stigma, and individual health behavior conspire to produce a context in which group members are at high risk for poor physical and emotional health, as well as violence and victimization. It is important to note that membership in a group that is marginalized either as a consequence of a behavior or through discrimination based on race and/or ethnicity and resultant poverty may have significant effects on important health outcomes. For example, studies have shown that perceived discrimination is associated with higher levels of stress, general psychological distress, depression and substance abuse, and with lower levels of life satisfaction and perceptions of mastery and control.^{2,3} Individuals with incomes below the poverty level have a life expectancy that is estimated to be 5.6 years shorter than those not in poverty;⁴ across all income levels, the life expectancy of African Americans is approximately 4 years shorter than that of Caucasians.⁵ Individuals in poverty have difficulty accessing and paying for medical care,⁶ experience food insecurity and resultant medical problems,⁷ and often live in neighborhoods with high social disorganization and low social support.⁸ Many of these characteristics are also associated with a significantly increased risk of victimization and violence; an interview with low-income mothers found that 83% reported physical or sexual abuse during their lifetimes.⁹

Planning for a patient's HIV care must take these contextual factors into consideration for three primary reasons. First, even before HIV infection, many of these patients are likely to have been in poor health; ongoing risk factors for poor health must be considered when planning HIV treatment. Second, the trust of health-care providers may be lower in these patients because of the stressors and struggles they have experienced.¹⁰ Finally, psychosocial needs resulting from poverty, discrimination, etc. may take priority over HIV care for patients; if not addressed, these needs may

become barriers to patient participation in and adherence to treatment.

In addition to social contextual factors, psychological and behavioral aspects of HIV infection play a role in the course of disease. Patients' emotional response to diagnosis and other stressors, coping styles, and coping skills modify the effects that a person's environment has on his or her course of illness. Behavioral skills, health beliefs, and knowledge, in addition to social circumstances influence patients' abilities to take their medication as prescribed, to disclose their illness to others, and to reduce their risky behaviors.

STIGMA ASSOCIATED WITH LIVING WITH HIV

■ IMPACT OF STIGMA ON THE LIVES OF PEOPLE LIVING WITH HIV

Many of the challenges faced by people living with HIV, including adherence to medications and limiting risky HIV transmission practices, as well as finding employment and locating housing, may be traced to the stigmatized nature of the disease.¹¹ Since the beginning of the AIDS epidemic, the societal view of HIV infection has been defined largely by its association with stigmatized and vulnerable groups. The level of stigma directed toward people living with HIV appears to have declined as the etiologic agent and modes of transmission became more clearly defined. However, population-based telephone surveys indicate that about one-quarter of those surveyed reported that people with AIDS "have gotten what they deserve" and that 21.8% believe that people with AIDS do not care if they infect others.¹² Further, beliefs that people with HIV should be legally separated from others and that the names of people living with HIV should be made public so that others could avoid them were endorsed by 12% and 16.3% of the population, respectively.¹²

Several studies indicate that these stigmatizing attitudes have a significant impact on the lives of people with HIV. In one series of 142 patients diagnosed with HIV infection at a sexually transmitted diseases clinic, 4% reported that they had lost their job as a result of the diagnosis and 1% had been asked to move.¹³ Concerns about HIV-associated stigma may be associated with a reluctance to receive an HIV test and has emerged as a barrier for adherence to HIV medications.^{14,15} Of further concern are data suggesting that the stigma associated with HIV infection represents an obstacle for disclosing one's HIV serostatus to a partner.^{16,17} Not only do people living with HIV encounter stigma associated with the disease but family members and caregivers may face discrimination as well. In one study, perceived stigma was a predictor of volunteer burnout for AIDS organization workers, and concerns about stigmatization prevented potential volunteers from working for AIDS organizations.¹⁸

Interventions to minimize the stigma faced by people living with HIV and its impact have largely rested upon attempts to educate HIV uninfected individuals that the widely held stereotypes regarding people living with HIV are inaccurate.¹⁹ These studies have, in general, involved either information giving, counseling, or direct enforced contact with people living with HIV and have targeted either health-care workers or university students. The interventions have had mixed results in increasing empathy and decreasing negative attitudes toward people living with HIV.²⁰

Given the lack of success of these individual-based interventions, the persistence of HIV infection as a stigmatized condition, and the refractory nature of these attitudes, it seems likely that successful interventions require action at the community level. Overall, the goal of these interventions should be to promote the view that people with HIV are community members rather than a dangerous "other." Extensive efforts are required to include and take into account the perspectives of marginalized people living with HIV along with the views of opinion leaders in the larger community. The ability of an individual practitioner to effect change may be limited to modeling behavior by treating their HIV-infected patients with respect. However, by virtue of their standing within a community and their expertise in the management of the disease, clinicians may be in a position to play an important role in changing community attitudes.

HIV TESTING, PSYCHOLOGICAL RESPONSE, AND COPING WITH AN HIV DIAGNOSIS

■ DECISIONS TO GET TESTED FOR HIV

Early stage HIV disease, from the perspective of the patient, begins with the decision to get tested and unfolds following the receipt of a positive test.²¹⁻²⁷ Thus, HIV testing is one important phase in the continuum of HIV care and treatment. The patients' experience of testing is influenced by the social context in which it occurs. About 35% of Americans have been tested for HIV at some time.²⁸ Recent studies show that reasons for testing are shifting, and more people are having tests as a part of routine medical care rather than to find out whether they are positive.²⁸ Furthermore, although there has been a push for earlier testing, people seek testing at different stages of the disease. Several studies have shown that half of the people who test positive for HIV do not perceive themselves to be at risk for HIV or do not suspect they have it.^{21,27} Among those who do suspect they may be infected, most seek testing because of symptom development rather than because of a known exposure.^{22,27,29} Even in the era of highly active antiretroviral therapy (HAART), people's anxieties about the receipt of a positive test often cause them to put off getting the test including when they suspect they may have been exposed or infected.²¹⁻²⁵ Most women attending

STD clinics in New York, who were not tested for HIV, did not do so because of their anxiety about the possibility of a positive result.²⁵ In another study, 48% of subjects who suspected being infected with HIV had waited 1 year or more to get tested.²¹ Thirty percent of those who are tested never return for their test results.²⁸

HIV testing

Most people who get tested for HIV undergo voluntary counseling and testing (VCT) at a testing center, although about 13% of people become aware of their HIV status through mandatory testing.²⁸ The current VCT model, based on Centers for Disease Control and Prevention (CDC) guidelines, emphasizes an interactive rather than didactic approach focused on a risk reduction plan that is personalized.²⁸ Counselors not only provide information about HIV and HIV transmission but also counsel people about their individual risk behaviors, using a client-centered approach.³⁰ How a person is told about the diagnosis can have an impact on his or her psychological response to the illness.^{27,31} While currently it is recommended that all patients *should* receive pre- and posttest counseling at the time of testing, studies indicate that such counseling does not always occur.^{27,31} In one study, two-thirds of subjects were not satisfied with the way they were told about their diagnosis²⁶ although we could find no studies that have assessed this more recently. Patients were more satisfied when they received reassurance and sympathy from the provider and when they received more information about their illness.²⁶ It is incumbent upon the clinician caring for HIV-infected patients to review information about the disease, its causes, transmission, course, and treatment as well as to counsel patients about their own risks at the first visit, even if the patient has undergone testing elsewhere previously. Of note, while it is currently recommended that counseling be conducted before and after testing, some workers argue that the requirement to provide counseling impedes the use of testing and further promotes a sense of AIDS exceptionalism.³² Thus, there has been a shift among some groups toward eliminating the requisite to provide counseling at the time of HIV testing in order to increase access to testing.

Recently, researchers have developed methods to cost-effectively test people who are acutely infected with HIV (AHI), i.e., who are in the first 6 weeks following an exposure.³³ However, little is known about the emotional, psychological, or prevention needs of these patients because until recently, they have been difficult to identify. As methods to identify AHI begin to be used more widely and routinely, it will become important to understand the special needs of these patients. Patients with AHI, by definition, have recently engaged in high-risk behavior. Therefore, special opportunities are available in the setting of AHI to counsel patients about risky behavior and to identify others at risk through partner notification, but how best to do this is unstudied.

■ PSYCHOLOGICAL RESPONSES AND COPING WITH AN HIV DIAGNOSIS

The response to an HIV diagnosis varies from person to person, however, some general trends and a time course have been noted. As an immediate psychological response to a positive diagnosis, within the first 10 weeks, most patients experience increased anxiety, sorrow, and loss to which the clinician must be attentive.^{34–36} One study showed that for many patients, the level of distress experienced with a positive result was less than they had anticipated but that they still felt distressed.³⁷ Once diagnosed, individuals experience more negative life events compared with those testing negative, in particular, break-up of marriages and being neglected or disowned by family members.³⁸ For a substantial minority of patients, the psychological response to a diagnosis can be quite devastating. In one study in South Africa, 56% of newly diagnosed patients were also diagnosed with depression, dysthymia, PTSD, or alcohol dependency after diagnosis.³⁶ Men had more substance abuse and women more PTSD.³⁶ Other studies have shown that between 15% and 30% of patients experience PTSD during the first 6 months of diagnosis with at least 30% of PTSD occurring as a direct result of the diagnosis.^{39,40} Severe symptoms of distress are more likely to occur among those who had preexisting history of major depressive disorder, suicidality, social anxiety disorder,⁴⁰ or ineffective coping strategies, such as blaming or withdrawal.³⁴

While patients generally experience immediate distress from a positive diagnosis, most HIV-infected persons are able to cope effectively with the demands of the infection. Most patients with HIV show flexibility in their use of coping strategies and ultimately achieve high quality of life after an initial phase of sorrow and lack of orientation regarding future life.^{34,41,42} Among a national probability sample of nearly 3000 individuals in care for HIV, most made health-promoting changes following diagnosis, such as increased exercise, improved diet, quitting smoking, and reducing substance use. Those more likely to make a change had greater desire for involvement in their medical care and for information and had information-seeking positive coping.⁴² One study showed that health-related Internet use by HIV-infected men and women was related to a broader spectrum of health behaviors including HIV treatment adherence, active coping strategies, and indicators of better health.⁴³

■ RECOMMENDATIONS TO ASSIST PATIENTS TO COPE WITH A DIAGNOSIS OF HIV

HIV-infected persons with more effective coping skills are better adjusted to their HIV diagnosis and have a better quality of life.^{41,44,45} Spiritual well-being among HIV-infected people is associated with better quality of life, social support, and positive coping strategies and negatively related to perceived stress, uncertainty, psychological distress, and emotional

focused coping.⁴⁴ Stress management and coping skills programs can successfully teach more effective coping skills and stress management that improve quality of life among people living with HIV. One Cognitive Behavioral Stress Management Program consisted of 10 weeks of weekly 135-minute structured group-based GET SMART (Group Experienced Therapy for Stress Management and Relaxation Training) program aimed at increasing cognitive and behavioral skills and at increasing social support. Participants had significant improvement in cognitive coping strategies involving positive reframing and acceptance and in social supports involving attachment, alliances, and guidance compared with controls. Improved coping was associated with improvements in anxiety and mood.⁴⁶

DISCLOSURE OF SEROSTATUS

Fueled in part by the observation that as many as one-third of all people living with HIV continue to have unprotected sex, several organizations including the CDC have focused their HIV prevention efforts on limiting the risk behaviors of people who are already infected with HIV. Disclosure of one's HIV status to a sex partner has emerged as one of the cornerstones of these broader attempts to limit HIV transmission; proponents of disclosure suggest that providing information about one's HIV status increases the likelihood that partners will take preventive measures.

Unfortunately, there are often significant consequences that flow directly from revealing an HIV diagnosis. The decision to disclose has the potential to expose people living with HIV infection to HIV-associated stigma and its outcomes including loss of employment, housing, relationships as well as the potential for interpersonal violence. It is also important to note that, in some settings, revealing an HIV diagnosis may also raise questions about whether a partner has participated in other risk behaviors. For some people, a desire to avoid taking on an additional stigmatized identity (e.g., MSM or intravenous drug use [IVDU]) may therefore serve as an additional barrier to HIV serostatus disclosure. Many people living with HIV choose not to disclose their status (for a review, see Ref. 47); it has been estimated that as many as half of all people living with HIV fail to disclose their serostatus to sex partners.⁴⁸

Current published guidelines recommend incorporating HIV prevention efforts, including serostatus disclosure, into clinical care; unfortunately, few studies have rigorously examined approaches to promote discussions of HIV status. Although the available research literature provides clinicians with little guidance about how to encourage patients to disclose their HIV serostatus, several general strategies have been suggested.^{49,50} These include expressing empathy for the person disclosing this information, openly discussing the advantages and disadvantages of disclosure with the patient, avoid appeals

to moral arguments as part of attempts to influence behavior, and review personal experiences with successful disclosures.

ACCESSING SERVICES

■ ACCESS TO MEDICAL SERVICES

Although the widespread application of HAART and prophylaxis for opportunistic infections has decreased both the mortality and morbidity associated with HIV infection, the benefits of these treatments are limited to those patients with access to medical care.⁵¹ Studies conducted early in the epidemic, before the availability of combination antiretroviral therapy (ART), identified several variables that were associated with delayed receipt of antiretroviral monotherapy.^{52–54} African Americans, women, and injection drug users were all less likely to receive azidothymidine (AZT) therapy and the recommended prophylaxis for opportunistic infections. Of note, several studies have described a more precipitous disease course for HIV-infected members of these groups.⁵⁵ However, for patients enrolled in care at an academic center with well-developed care guidelines, no relationship was observed between race, gender, and recreational drug-use and disease progression.⁵⁶ These findings support the notion that the differences in outcome reported by other studies reflect differences in use of and access to medical care.

These results have been largely supported by extensive studies conducted during the HAART era, although reports suggest that the differences in access observed earlier in the epidemic are narrowing. A nationally representative sample of people living with HIV receiving medical care demonstrated that African American and Hispanic race/ethnicity as well as IVDU route of HIV exposure and insurance status (Medicare/Medicaid vs. private insurance) were associated with receiving suboptimal care.⁵⁷ Patients with lower incomes and less education were also less likely to have received optimal care. It appears that these same groups also experience limited access to clinical trials of new anti-HIV therapies; African Americans, Hispanics, and patients without fee-for-service health insurance are underrepresented among participants in research trials of experimental agents.⁵⁸

For many people living with HIV, limited access to care may reflect resources that are inadequate to meet both the expenses of medical care and subsistence needs. For example, one-third of a sample representative of the people living with HIV in the United States receiving medical care reported going without needed care because of competing subsistence needs.⁵⁹ Additional analyses indicate that, for these patients, contact with a case manager decreased the number of unmet needs for housing, home health, emotional counseling, and substance abuse treatment services.⁶⁰

Traditionally, the role of the individual clinician in promoting access to medical care has been limited. However,

the studies cited above suggest that clinicians can assist people living with HIV obtain care in a number of ways. At the level of the clinician-patient interaction, clinicians should keep in mind that a significant number of people delay care or go without it entirely. This may have a profound effect on clinical outcomes and the clinician should remain vigilant to this possibility and open to discussions about strategies to meet both medical and social service needs. To this end, at the level of the clinic, it seems prudent for social service providers to be closely integrated into the clinic setting. Further, given the reported relationship between case management services and better access to care, the routine provision of case managers for patients with limited resources and substantial subsistence needs may be advisable. Finally, clinicians should consider using their expertise and social position to advocate for policies that promote access to care for people living with HIV.

■ ACCESS TO NONMEDICAL SERVICES

Persons infected with HIV have a wide range of needs beyond medical care. For many individuals struggling with challenges and survival issues such as poverty, homelessness, lack of transportation, and food insecurity, accessing medical treatment becomes a less immediate priority in their lives. Because of their life circumstances, HIV+ individuals may be forced to make difficult choices between meeting immediate needs and medical care, the benefits of which may only be seen over time (see Chapter 20).

Research has shown that a significant number of HIV-infected individuals postpone or go without care in order to meet basic needs. In the HIV Cost and Services Utilization Study (HCSUS) data, analysis showed that nearly 12% of the sample reported going without care in order to pay for food, clothing, or housing, and over 15% reported going without care because they could not afford or access transportation. Experiencing any of these needs resulted in significantly higher chances of visiting an emergency room, never receiving antiretroviral medications, and having low overall self-reported access to care.⁶¹ Similarly, a survey of HIV-infected individuals in the southern United States found that over 27% reported needing help applying for benefits such as Medicaid, 17% reported difficulty with transportation, nearly 27% reported needing emergency housing, and over 27% reported needing emergency food in the past year.⁶²

Assistance finding and maintaining stable housing is a particularly important service for individuals with HIV infection. Housing instability is common in this population, with rates as high as 49% reported in some studies.⁶² Lack of stable housing and homelessness may have a large impact on health status in persons with HIV infection. In a study of rural HIV-infected patients receipt of housing was positively associated with access to medical care,⁶³ and a second study

demonstrated a positive association between housing stability and general physical health status.⁶⁴

■ USE OF CASE MANAGEMENT TO IMPROVE ACCESS TO NONMEDICAL SERVICES

Case management has been shown to be an effective intervention to address nonmedical needs in patients with HIV infection. Case managers can refer patients to a range of social services and provide assistance in accessing them. Evaluation of case management programs for persons who are HIV positive have demonstrated effectiveness in meeting psychosocial needs. Case managers have been shown to help integrate and increase access to both formal and informal helping services for patients⁶⁵ and for their caregivers⁶⁶ and to significantly decrease unmet basic needs.⁶⁷ Thus, if medical care for HIV infection is to be successful, a holistic assessment of patient needs and coordinated referrals to case management services and other social services in order to address subsistence issues are essential.

MENTAL HEALTH AND SUBSTANCE ABUSE

■ OVERVIEW OF MENTAL ILLNESS AND SUBSTANCE ABUSE AMONG PEOPLE LIVING WITH HIV

Substance use and mental health disorders are prevalent psychosocial challenges for individuals infected with HIV. These disorders can create substantial life distress, interfere with treatment adherence, are associated with a worse course of illness, and increase the likelihood of engaging in high-risk behavior for HIV transmission. Thus, identifying and addressing substance use and mental health disorders are essential elements of treatment for HIV-infected patients.

A number of studies have revealed high rates of mental disorders and substance abuse among HIV-positive individuals. The national HCSUS found higher prevalence of mental disorders (48%), substance abuse (19%), and comorbid mental illness and substance abuse (13%) in HIV-infected individuals than documented in the general population (22%, 9.5%, and 3%, respectively).⁶⁸ The most common mental disorders identified within the HIV-infected population include depression, severe and persistent mental illnesses such as bipolar disorder and schizophrenia, and posttraumatic stress disorder.^{69,70}

Mental illness and HIV

Rates of depression vary widely in studies of HIV+ individuals but are generally higher than in the HIV-negative population, with lifetime prevalences of 30–50%.⁷¹ Some studies suggest gender and sexual orientation differences in rates of depression, with particularly high rates of depression in HIV-infected women compared with their seronegative counterparts⁷² and higher rates in HIV-positive homosexual men

compared to HIV-positive heterosexual men.⁷³ HIV-positive individuals are found to have higher rates of serious mental illnesses such as schizophrenia, with one study showing nearly 6% of HIV-infected individuals diagnosed with schizophrenia.⁷⁴ Trauma exposure and resultant posttraumatic stress disorder and symptoms are also more common in individuals with HIV infection. High rates of sexual assault and childhood abuse have been reported in both HIV-positive women and men (up to 68% in some studies); frequently this is part of a pattern of repeated traumatization.^{75,76} Rates of posttraumatic stress disorder have been reported to be as high as 42% in HIV-positive populations.⁶⁹

Substance abuse among HIV-infected persons

Substance use disorders are common comorbid conditions with HIV. Lifetime prevalence of alcohol disorders in people who are HIV infected has been reported as high as 60% and lifetime prevalence of drug disorders as high as 56%.⁷⁰

Substance use disorders contribute most directly to HIV transmission through IVDU; up to 2001, 25% of the cumulative cases of AIDS in the United States were due directly to IVDU, and it has been estimated that over 35% of all U.S. cases of AIDS are directly or indirectly attributable to IVDU.⁷⁷ Substance use disorders also contribute to HIV transmission indirectly through a number of high-risk behaviors, including decrease of sexual inhibition and poor judgment, trading sex for money or drugs, and inconsistent condom use.⁷⁰

Clearly, unaddressed substance use disorders in a HIV-infected patient increase the risk for ongoing HIV transmission to others. In addition, unaddressed mental health disorders may increase the risk of transmission, particularly in disorders related to trauma. For example, research has shown that individuals with a history of childhood abuse are more likely to engage in unprotected sex, sex with multiple partners, sex work, and drug use than those without trauma histories.⁶⁹ Untreated substance use and mental health disorders are also associated with higher rates of nonadherence to antiretroviral therapy. In a sample of individuals in the HCSUS cohort, depression, anxiety, and substance abuse were associated with two times the odds of self-reported nonadherence to HAART,⁷⁸ and Ammassari and colleagues⁷⁹ found that both depression and IVDU were associated with nonadherence to HAART. Alcohol consumption has also been associated with reduced medication adherence, higher plasma HIV RNA levels, and lower CD4⁺ cell counts.⁸⁰ A study by Tucker and colleagues⁸¹ suggests that nonadherence in individuals with mental and substance use disorders may be mediated by difficulty getting medication and poor fit of medication regimen with lifestyle. It is encouraging that research also indicates that as mental health improves with treatment, adherence to antiretroviral medication also improves.⁸²

■ **PHYSIOLOGIC IMPACT OF SUBSTANCE USE AND MENTAL ILLNESS**

A final consideration is the physiological impact of substance use and mental health disorders on individuals with HIV infection. Studies in vitro have indicated enhanced HIV replication with alcohol exposure. Alcohol consumption is also associated with decreased levels of a range of immunomodulators.⁸³ Depression has also been shown to have potent immunologic effects on persons with HIV infection. Depression has been associated with a more rapid decline in CD4⁺ cell count and more rapid progression to AIDS and death, even controlling for sociodemographic and clinical characteristics. A prospective study of over 700 women with HIV infection found that those with chronic depression had mortality rates twice as high as nondepressed women, even when controlling for sociodemographic, clinical, and treatment factors.⁸⁴

■ **RECOMMENDATIONS TO ADDRESS SUBSTANCE ABUSE AND MENTAL ILLNESS OF PATIENTS WITH HIV**

Given these findings, several recommendations can be made for physicians caring for HIV-infected individuals. First, all patients should be regularly screened for substance use and mental health disorders. Identification of depression may be particularly challenging in this population, since a number of symptoms overlap with those of HIV infection, such as poor appetite, weight loss, loss of energy, and insomnia.⁸² A standardized screening tool may be useful in identifying these disorders. Whetten and colleagues⁸⁵ have developed a simple 13-item substance use and mental disorder screen specifically for HIV-infected patients that has demonstrated good sensitivity and psychometric properties. Risks and challenges faced by specific populations should also be considered during this screening, such as increased rates of depression and abuse in women and stresses related to poverty and discrimination, which may cause or exacerbate depression in minority patients.

Once identified, patients should be referred to mental health and/or substance abuse providers with whom the physician has a collaborative relationship. Treatment should consider both pharmacologic and psychological services, including cognitive behavioral and coping skill interventions. Care must be taken in the prescription of psychopharmacological agents; research indicates that certain antidepressants may interfere with some antiretroviral medications, as may methadone and possibly buprenorphine.^{73,83} In all cases, medical and psychosocial treatment should be integrated into a unified plan of care.

VIOLENCE VICTIMIZATION AMONG PEOPLE LIVING WITH HIV

Violence victimization and, in particular, abuse by an intimate partner, is a pervasive experience for many people living with HIV. In part, this reflects the prevalence of violence

in society at large; data collected by the U.S. Bureau of Justice Statistics indicate that as many as 6.5 million men and 5 million women are assaulted each year.⁸⁶ Physical assault from an intimate partner is particularly common for women. Women have a five- to eightfold higher risk for intimate partner violence than men, and physical abuse from a spouse or partner is the leading cause of injury for reproductive age women.⁸⁷ Several studies have examined the frequency with which people living with HIV experience physical abuse as well as their lifetime risk for abuse.^{88–91} Although results have varied with the methods used, these reports indicate that a significant number of people living with HIV describe physical abuse in an intimate relationship during adulthood.⁹² In addition to the immediate effects of violence victimization on health, physical abuse may have an indirect but significant impact on HIV care itself. For example, in a population-based study of people living with HIV and receiving medical care, MSM with a history of violence victimization were more likely to visit the emergency department and more likely to go without medical care because of the expense.⁹³ It has also been suggested that the trauma associated with physical and mental mistreatment may increase the risk for abuse of drugs and alcohol.⁹⁴ This, in turn, may complicate attempts to adhere to treatment regimens as well as HIV prevention efforts.

The reported risk factors for physical assault among people living with HIV vary somewhat based on gender and HIV-risk category. As is the case for the overall U.S. population, women with HIV appear to be at greater risk for physical assault from an intimate partner than men.⁹⁵ In one population-based survey of HIV-infected people receiving medical care, 20.5% of women, 11.5% of MSM, and 7.5% of men not reporting sex with men indicated that they had been “physically hurt by your partner or someone important to you” since their HIV diagnosis.⁹⁵ It is important to note that for this representative sample of people living with HIV, physical assault appeared to be a relatively common feature of their experience independent of their HIV infection. In fact, several studies suggest that while the prevalence of intimate partner violence is quite high among people living with HIV, HIV-infected individuals are at no greater risk for such violence after controlling for other factors, associated with physical assault, such as drug use.^{92,96,97}

What is perhaps most striking is the overlap between the variables associated with violence and those associated with acquiring HIV infection. These include homelessness, drug dependence, unemployment, and having multiple sexual partners.^{89–93} It has also been noted that increasing age and more advanced HIV disease as measured by lower CD4 counts appear to be protective for physical abuse.⁹⁸

These observations have important implications for clinical care. First, given the prevalence of violence victimization and particularly physical assault in intimate relationships, it

seems prudent for clinicians to screen all patients for physical abuse with a focus on those at greatest risk or who show signs of having sustained traumatic injuries consistent with abuse. Further, because violence victimization may be a barrier to adequate treatment response, clinicians should also explore physical abuse as a contributory factor in the setting of treatment failure. Unfortunately, few interventions to reduce physical abuse among people living with HIV have been rigorously tested.

ADHERENCE TO ANTIRETROVIRAL THERAPY (ART)

Adherence to antiretroviral therapy is one behavioral challenge that people living with HIV face in their efforts to obtain optimal treatment of their HIV infection. Available treatment for HIV can dramatically suppress viral load, enhance CD4 counts, and reduce morbidity and mortality related to HIV infection.^{99,100} However, if antiretroviral medications are not taken as prescribed, treatment failure as well as drug resistance may ensue.^{101–106} Although patients taking antiretrovirals generally achieve higher levels of adherence than do patients on other chronic medical regimens,^{101,103,104} ART regimens are complex and lifelong, and, as discussed above, many HIV-infected patients' living situations impose multiple obstacles to obtaining optimal medical care; not surprisingly, a large proportion of patients have difficulty achieving targeted levels of adherence that are quite high.^{101,103,104} Consequently, since 2002, the CDC and the United States Department of Health and Human Services (US-DHHS) National Treatment Guidelines¹⁰⁰ have recommended that assessment and promotion of ART adherence become a part of routine care for patients taking ART.

■ ESTIMATING ADHERENCE TO ART

Practice guidelines recommend that providers assess their patients' adherence routinely. Several studies, however, have demonstrated that, without guidance, providers inaccurately estimate adherence, most often overestimating patient adherence.¹⁰⁷ Often what is perceived as patients' overreporting of adherence reflects differences in patients' and providers' understandings of what was meant by “adherence.”¹⁰⁸ On average, patients on ART take 55–80% of prescribed doses although the level varies widely.^{101–103,109–111} Providers can improve their adherence assessment by asking open-ended nonjudgmental questions about how ART is taken rather than simply asking the number of doses missed. Brief self-administered patient questionnaires, such as a visual analog scale, also exist to supplement but not substitute information¹¹² obtained from open-ended inquiries.

■ FACTORS THAT HINDER AND HELP PATIENTS ADHERE TO ART

Medication adherence is a complex behavior that is influenced by many factors. Some salient issues stand out^{101,104,113–118}:

1. Patient factors

No demographic features have been consistently associated with poor adherence.^{104,115,116} However, studies have shown that HIV-infected patients who have more positive attitudes toward ART,¹¹⁴ better knowledge of their regimen,¹¹⁹ or greater confidence in their ability to take ART¹¹⁶ are more adherent. Providers can address patient factors by exploring patients' knowledge and beliefs about the medication, dispelling misconceptions, and clarifying for patients the link between nonadherence and poor outcomes.

Lower literacy levels,¹¹⁷ substance abuse^{104,114,115,120,121} and psychiatric illness have been linked with poor adherence.^{101,104} Active abuse of alcohol and other substances have consistently been shown to be barriers to adherence.^{104,114,115,120,121} Some studies have shown that a history of prior intravenous drug use is also associated with worse adherence^{115,121} whereas others found no link with prior drug use and others found that recovered intravenous drug users demonstrated better ART adherence.¹²⁰ These findings underscore the need for ongoing assessment of substance abuse as well as concurrent alcohol and drug counseling for patients on antiretroviral therapy.

2. Regimen factors

The more complex the antiretroviral regimens^{104,115,120} and the less well it fits with the other daily activities^{114,116} the less adherent patients are. Dose frequency (i.e., the number of times per day medications must be taken) appears to be a greater culprit than the total number of pills taken¹¹⁵ at least partly because patients have particular difficulty with the middle of the day dose.¹²² The impact of dosing complexity on adherence can guide clinicians to select medication regimens and delineates a role for adherence aids to help to remind patients of midday doses. Adherence aids (such as pill boxes, medication timers etc.)^{115,122,123} can improve adherence although many patients are unaware that such aids exist.¹²² Including standardized patient education about adherence aids during ART initiation is a practical way to introduce patients to these potentially valuable interventions.

3. Features of the clinical interaction

The quality of the provider-patient relationship, including the trust of the patient in the provider and the sensitivity of the physician to patients' needs has been shown to be also associated with ART adherence.¹²⁴ Taking the time to establish a good, trusting rapport with patients likely has a beneficial effect on patient outcomes.

4. Social/environmental factors

The social support^{121,125} that patients have available, often related to perceived stigma, as well as other factors in their environment, such as homelessness, competing demands, and chaotic routines have been shown to be associated with worse adherence to AR therapy.^{104,122,126} Exploring environmental barriers to adherence and identifying means to overcome such barriers, such as support from friends or family, is a fourth important aspect of addressing adherence.

■ INTERVENTION TO IMPROVE ADHERENCE

Recent studies had identified effective interventions that improve ART adherence.^{104,118,127–129} A Cochrane review of programs to promote ART adherence identified a pharmacist-led education and supportive counseling program that improved adherence to antiretroviral therapy. A recent review of 11 ART adherence interventions reported mixed results but identified successful educational ART adherence programs.¹²⁷ These included a psychoeducational adherence program for¹¹⁸ patients starting new treatment regimens, multidisciplinary team-delivered interventions,^{128,129} and an online paging reminder system.¹²³ Overall, interventions that improved adherence include pharmacist-based adherence clinics; adherence encounters at each visit, often multidisciplinary; reminders; alarms; pagers and timers; patient education aids, including regimen pictures, calendars, stickers; and clinician education aids (e.g., medication guides, pictures, calendars).

■ RECOMMENDATIONS TO IMPROVE PATIENTS' ADHERENCE TO ART

Based on the existing intervention studies as well as the 2002 guidelines put forth by the CDC and the US-DHHS, we outline below several recommendations to help patients on ART adhere to their regimens (Table 71-1). Guidelines recommend that providers use not only regimen-oriented and patient-related strategies but also specific "clinician and health team" strategies to improve adherence.¹⁰⁰ We also believe that it is important to address social-environmental factors.¹¹⁵ It is particularly important to spend adequate time when initiating therapy, assessing readiness, and educating patients about the specific requirements of their regimen and assessing their understanding. Because things change in people's lives, monitoring ongoing adherence and intensifying management in periods of low adherence can be particularly useful.¹⁰⁰

SEXUAL BEHAVIOR

While most new HIV infections are transmitted from people who are unaware of their HIV serostatus, it is estimated that about 45% of new infections occur from persons who know that they are infected.¹³⁰ On average, about one-third of people infected with HIV continue to engage in risky sexual

Table 71-1. Recommendations for Addressing Factors That Influence Patients' Adherence to ART

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| <p>1. Addressing provider factors</p> <ul style="list-style-type: none"> • Establish trust <ul style="list-style-type: none"> – talk openly, nonjudgmentally about adherence – use a client-centered approach; try to understand things from your patients' perspective • Teach patients <ul style="list-style-type: none"> – why ART adherence is so important – names of their medications – reasons for requirements • Write down <ul style="list-style-type: none"> – names of their medications – dosing schedule – dosing requirements – who to contact for questions <p>2. Addressing patient factors</p> <ul style="list-style-type: none"> • Assess your patient's readiness to adhere before initiation of therapy <ul style="list-style-type: none"> – prior experience taking medications – beliefs about ART – importance they place on adhering to ART – their self-efficacy or confidence that they can adhere to their particular regimen – barriers and facilitators they perceive to their taking ART – patient rehearsals (e.g., giving jelly beans) | <ul style="list-style-type: none"> • Screen for and treat conditions that impede adherence <ul style="list-style-type: none"> – depression and other psychiatric illness – screen for and treat substance abuse • Negotiate a concrete treatment plan in relation to daily schedule • Help the patient develop cues/reminders • Set and reinforce goals: enhance patients' self-efficacy or confidence by pointing out things they do well <p>3. Addressing regimen factors</p> <ul style="list-style-type: none"> • Involve your patient in the decision-making process regarding which ART regimen to choose • Assess your patient's preferences for the medication schedule and intake requirements (in relation to food) • Prepare your patients for potential side effects during initiation • Anticipate, treat, and manage side effects • Suggest regimens that are simpler to help patients juggle therapies • Help the patient develop cues/reminders <p>4. Addressing social factors</p> <ul style="list-style-type: none"> • Recruit family and friends • Assess need to take medicine in private • Ask about work, eating, and other patterns • Ask about weekend routines • Be familiar with community resources |
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practices and this proportion may be increasing^{131–140}; in some studies, 13–15% have other STDs.^{133,141} Pre- and posttest counseling has been shown to be inadequate alone to change risky behavior for HIV-infected persons.^{142–146} Recently, a few effective interventions have been identified to help people living with HIV practice safer sex.^{142–145,147,148} Because many factors can influence safer sex practices of people living with HIV,^{134,136,149–160} successful “prevention with positives” interventions generally use a client-centered, nonjudgmental approach and consider the social context in which sexual relationships take place. Other common elements of successful prevention with positive programs include addressing issues of disclosure, enhancing sexual negotiation /communication skills, taking a holistic view of sexuality,^{142–145,147,148,152} and providing transmission risk information (see Chapter 72). Specific guidelines have been developed and published in the *Morbidity and Mortality Weekly Report* (MMWR) to help health professionals incorporate prevention counseling into the routine care of persons living with HIV¹⁶¹ (see Chapter 72).

END OF LIFE

Increasingly effective pharmacological treatments for HIV disease have resulted in lower mortality rates and less focus on end of life issues than seen in the previous decade.¹⁶² However, HIV disease continues to be a prominent cause of death in adults in the United States; in 2002, HIV disease was one of the top 10 causes of death in adults, with mortality rates of 4.9 per 100,000.¹⁶³ Given this, end of life issues are clearly an important area in the psychosocial care of HIV-infected individuals. These issues include discussions between patient and physician about the reality of approaching death and exploration of the patient's preferences in aggressiveness of care, pain management, and location of death. In addition, patient and physician discussions on the creation of an advance directive or “living will” as a way to clearly and legally document preferences, as well as appointment of a health-care proxy through a health-care power of attorney are important issues to be explored.

Despite its importance, studies have demonstrated that a majority of persons with HIV do not discuss end of life care with their physician and do not prepare advance directives or appoint health-care proxies.¹⁶⁴ In addition, physicians and patients may have differing perceptions as to what constitutes an end of life discussion. For example, a study of patient–doctor communication about end of life care found that in 26% of cases patients and physicians disagreed about whether end of life communication had occurred at all.¹⁶⁵

There are multiple barriers to the discussion of end of life care experienced by both the physician and the patient. Patients may be reluctant to discuss death out of fear or a sense that talking “will bring it (death) closer.”¹⁶⁶ Facing death in an era where HIV-infected individuals are living longer may induce feelings of shame and failure or have a particularly tragic quality.¹⁶⁷ For physicians, end of life discussions may be difficult as a result of the characteristics of the patients who are dying. In the post-HAART era, patients who die are often different from those who are doing well. They are often non-adherent, more likely to abuse substances, and more likely to come from a chaotic and deprived environment where HIV is not their primary day-to-day focus. Physician frustration with these patients may make it difficult to establish the trusting relationship needed to discuss end of life issues.¹⁶⁸

The most extensive and informative study of end of life discussions and preferences in persons with HIV was completed using national survey data from the HCSUS. Wenger and colleagues¹⁶⁹ found that 35% of respondents reported having a conversation with their physicians about end of life care,¹⁶⁹ and that physicians communicated less frequently with black and Latino patients and more frequently with women and people with children. Only 38% of respondents had completed an advance directive; completing an advance directive was more likely if the respondent reported that their physician had discussed the topic with them, if they reported higher social support, and if they were white. When asked about desire for aggressive life-extending care, respondents had widely varied responses; from definitely desiring to extend life irrespective of pain levels (30%) to definitely relieving pain even if this shortened life (32%). These results echo findings from a smaller qualitative study, which found that HIV-infected individuals held widely divergent definitions of a “good death.”¹⁷⁰

Many HIV-infected patients with advanced disease experience pain with high frequency. In studies, physicians have been shown to underestimate and undertreat pain in HIV-infected patients. Reasons for this include doctor’s lack of knowledge of pain management, poor communication with patients, and patient concerns regarding addiction to analgesic medication. In addition, higher rates of uncontrolled pain have been noted in minorities and people in poverty.¹⁶⁶ Pain management is an important issue in end of life care and is closely related to decisions around the location of

death-wishing to die in the more comfortable setting of home or hospice rather than in hospital. However, access to hospice services is uneven among HIV-infected patients; it has been found that minority and impoverished HIV-infected patients are more likely to have a hospital death and less likely to utilize hospice care than white patients.^{166,171} For those patients wishing to die at home, informal home-based care is essential. However, informal supports have been found to be far less frequent for HIV-infected patients than others in hospice, and those family and friends that do provide care seldom receive targeted support and education.^{166,172}

Given the findings in the literature, physicians providing end of life care for patients with advanced HIV disease should attend to a number of issues. First and most importantly is the establishment of a trusting relationship with open communication regarding end of life care. Physicians may need to initiate, and in some cases repeatedly broach the subject with patients, discussing care preferences, advance directives, and health-care proxies. In addition, physicians should be aware of racial and cultural differences in openness to initiating these discussions and in care preferences themselves. Careful assessment of pain in advanced HIV disease is important, as is aggressive pain management. Physicians must also consider timely hospice referrals, ensuring that patients can access hospice with time to benefit from services, as well as ensuring that informal helpers involved with end of life care are provided the necessary support and education. Finally, physicians should be aware of their own assumptions and biases around a “good death.” Research has demonstrated that patients with HIV disease vary widely in their needs and preferences, and only through honest communication between physician and patient can end of life care needs be defined and implemented.

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Samuel W. Dooley and Mark Thrun

INTRODUCTION

HIV and AIDS rates in the United States decreased markedly from the beginning of the epidemic through the early 1990s, due at least in part to adoption of safer sex and drug use practices. However, since that time, new infections have remained stable at approximately 40,000 cases per year, and recent data suggest HIV incidence may be increasing in some subpopulations.¹ From the earliest days of the HIV epidemic, prevention efforts have mainly targeted persons who are at risk for HIV, but not yet infected. However, with the institution of more effective treatment, HIV-positive persons are living longer, and HIV/AIDS prevalence has risen dramatically.¹ Not only are HIV-positive persons living longer and healthier lives; they are also having longer, more active sex lives. Unfortunately, many are engaging in activities that facilitate HIV transmission and are increasingly being diagnosed with sexually transmitted diseases (STDs).^{2–10} In addition, rates of primary antiretroviral drug resistance are rising, further suggesting that HIV-infected persons on treatment are engaging in high-risk activities.^{11–13} Although prevention efforts should continue for high-risk persons not yet infected, it has become increasingly clear that targeting HIV-positive persons for prevention must be a key strategy for further reducing HIV transmission in this country. Because many HIV-positive persons receive ongoing medical care, health-care settings offer an excellent opportunity to reach them with HIV prevention interventions.

■ TRENDS IN HIV TRANSMISSION RISK IN THE UNITED STATES

The percentage of men who have sex with men (MSM) who consistently use condoms during sex has decreased over the last several years, and the number reporting multiple sex partners has increased.^{14–17} These increases in risk behaviors have been accompanied by increases in the number of MSM

recently diagnosed with STDs.^{14,18–20} Although STD incidence is considerably less than in the mid-1980s, it is no less concerning: in the 1980s and 1990s, HIV infection rates closely paralleled STD rates; therefore, recent increases in STD rates raise concerns that HIV incidence may also rise.

Numerous surveys have documented relatively high rates of unprotected sex among HIV-infected individuals.^{5,7} In fact, rates of unprotected anal sex among gay men in Seattle were higher among those with HIV infection than among those without HIV.¹⁰ In a survey of patients from a Midwest HIV clinic, 22% of 95 HIV-infected participants reported having unprotected anal or vaginal sex or injecting drugs in the past 3 months.⁶ Rural populations do not seem to fare any better. In a study of 216 HIV-positive persons from rural sites across the country, 59% of men who reported having anal sex with a man in the last 3 months had never or only rarely used a condom, and 31% of women who had vaginal sex in the last 3 months reported never using a condom.²¹ In another study of 277 people living with HIV in rural Wisconsin, only 41% of men and 17% of women reported always using a condom when having sex during the previous 6 months.²²

HIV-infected individuals in steady relationships with serodiscordant partners do not seem to use condoms more frequently. In a national surveillance project, 21% of 674 HIV-infected MSM who were aware of their infection reported having unprotected anal intercourse with their HIV-negative partner.²³ In a majority (56%) of unprotected intercourse episodes, the HIV-positive partner assumed the insertive role. This pattern is not limited to MSM: in a study of 104 serodiscordant heterosexual couples, 71% of HIV-negative partners reported having had unprotected sex with their infected partner in the last 6 months.²⁴ Collectively, these data demonstrate that HIV-infected persons are participating in behaviors known to transmit HIV and that this pattern spans gender, race, locale, and sexual preference.

Note: The views and opinions contained in this chapter are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the US Centers for Disease Control and Prevention.

Compounding this problem, many new STDs are being diagnosed in HIV-infected persons.^{2,10} As early as 1996, in STD clinics that collected information about HIV infection, up to 25% of new gonorrhea cases were coinfecting with HIV.¹⁸ More recently, in a report of 57 persons who had new syphilis infections and knew their HIV status, 34 (60%) were coinfecting with HIV.¹⁹

Also of concern are rates of primary antiretroviral drug resistance. Transmission of drug-resistant virus has been observed since the advent of antiretroviral drugs.^{25–27} Recent studies, however, suggest that rates of primary antiretroviral drug resistance are high and may be increasing, at least in some parts of the world.^{11–13,28–30} Thus, risky behavior among persons in HIV care not only results in transmission of HIV, but also transmission of drug-resistant strains of virus. Given the limited number of antiretroviral drugs currently available, and cross-resistance within classes of agents, the importance of primary resistance cannot be overstated.

Increasing rates of high-risk behavior may be at least partly attributable to the availability of highly active antiretroviral therapy (HAART). In addition to increasing HIV prevalence by increasing survival, HAART allows many persons to have longer, more active sex lives, resulting in more opportunities for high-risk behavior to occur. Furthermore, availability of HAART may decrease the extent to which HIV-positive persons perceive sex as being risky: In one study, persons on HAART were more likely than those not on antiretroviral medications to subsequently be diagnosed with an STD.³¹ Since the advent of HAART, there also appears to be a reduction in the perceived risk associated with HIV acquisition among persons not yet infected.^{17,32–35}

Ample opportunities for high-risk sex continue to abound. Cross-sectional studies have documented persistence of unprotected sex among frequent visitors to bathhouses, and a significant percentage of MSM practice “bare-backing,” the intentional act of having anal intercourse without a condom.^{36–38} Also, many persons are seeking sex partners on the Internet.^{39–42} In a cross-sectional study of 856 clients from an HIV counseling and testing site, those who found sex partners via the Internet were significantly more likely to report having had an STD, having more total partners, having more partners who were known to be HIV-infected, and having more anal sex.⁴¹

Knowledge alone does not seem to result in lower rates of risky sex. In a survey of HIV-infected patients, 85% of those reporting unprotected anal or vaginal sex in the last 3 months defined “safe sex” as using a condom.⁶ Thus, many HIV-positive persons apparently know how to protect themselves and others, but are not practicing protective behavior.

Several conclusions can be drawn from these and similar studies: (1) a wide spectrum of risk behaviors exists among persons in HIV care, ranging from no transmission risk to ongoing high levels of risk behaviors; (2) risk-taking behaviors

appear to span a variety of patient types and care settings; (3) many patients know how to prevent HIV transmission but have difficulty consistently translating this knowledge into safe behavior; and (4) to fully address the epidemic, prevention strategies must include persons already living with HIV.

HIV PREVENTION IN THE HEALTH-CARE SETTING

■ ROLE OF HEALTH-CARE PROVIDERS IN CHANGING PATIENT BEHAVIOR

Substantial evidence indicates that health-care providers can affect patient behavior in a variety of health areas, including smoking cessation, drug and alcohol dependence, seeking care for mental health issues, and encouraging diet and exercise.^{43–51} As many persons living with HIV in the United States have an identified provider, care settings provide an excellent opportunity to promote HIV prevention concepts. Visits to HIV-care providers generally occur several times yearly, affording excellent opportunities for providers to interact with patients, develop trusting relationships, and determine whether or not risk behaviors are occurring. They also provide opportunities to deliver brief prevention messages to all patients and more in-depth risk reduction counseling to patients at risk for transmitting HIV.

Despite the clear need for ongoing prevention efforts with HIV-positive persons, evidence supporting the efficacy of prevention in care, and the convenience of the care setting, many providers have not taken full advantage of the opportunity afforded by clinical visits consequently, incorporating HIV prevention into the care of persons living with HIV has not become standard practice.^{33,52} The Gonorrhea Community Action Project undertook a study in 1998 attempting to clarify providers’ practices regarding elicitation of sexual histories and barriers to this process.⁵³ In this study, 208 providers in 121 diverse clinics were interviewed about their opinions and practice patterns regarding elicitation of sexual histories and provision of education and counseling messages to patients. Only 57% of respondents stated that obtaining a sexual history was a routine part of medical care, with even fewer stating they inquire about the patient’s prior STD history (34%), sexual orientation (17%), or preferred types of sex (e.g., anal, oral) (15%). When discussing counseling practices, most providers stated that when education was offered, they offered facts about STD transmission (67%), but far fewer offered information on how to prevent an STD (30%), specific STD risk behaviors (17%), or long-term consequences of having an STD (21%).

Other studies of HIV-infected patients and their providers also reveal that providers discuss risk-taking behaviors with their patients infrequently. When 250 HIV-infected men in San Francisco and New York were interviewed about

health-care providers' safer sex messages, 1 in 4 stated their provider had never discussed safe sex with them.⁵⁴ Similarly, in a cross-sectional study of 839 diverse patients, including MSM, heterosexuals, women, Latinos, and blacks from six California public HIV clinics, 33% could not recall ever having a discussion about safer sex with their HIV-care provider.⁵⁵ From an institutional standpoint, two clinics reached over 90% of their patients with safer sex messages, whereas three clinics reached fewer than 60%. In a third study, among 317 providers asked to rate how frequently they discuss risk reduction related to HIV transmission and substance abuse with their HIV-infected patients, only 37% reported always asking about HIV transmission risk and only 24% asked about substance abuse.⁵⁶

■ BARRIERS TO PREVENTION IN CARE

There are many possible explanations for low rates of risk assessment and risk-reduction counseling among providers. In one study, the most common barriers to more intensive counseling cited by providers were concerns about the patients' emotional response (42%), lack of time (40%), patients' reluctance to discuss STDs (32%), patients' resistance to changing behavior (31%), and provider discomfort (13%).⁵³ Another study cited difficulty initiating conversations about STDs, provider discomfort, and a provider-centered rather than patient-centered counseling style.⁵⁷ Other studies have identified similar barriers, including perceived lack of time, provider discomfort, concern about inadequate counseling skill, concern about negative patient reaction, and concern that the provider-patient relationship may be harmed by asking questions that could be perceived by patients as judgmental or accusatory.^{33,53,58} To facilitate incorporation of prevention into care, these barriers must be addressed.

Given competing demands on clinicians, it is not surprising that the most frequently cited barrier is insufficient time. Yet, most persons in HIV care may have little or no risk for transmitting HIV and do not need in-depth assessment or extensive risk-reduction counseling.^{6,23} Indeed, brief risk screening, which need not be a time-consuming process, will reveal that the majority of HIV-infected persons seen in care are not currently having sex or are taking adequate steps to reduce risk and can be classified as having low risk for transmitting HIV to others.^{6,23} In fact, when informed of their HIV status, most persons significantly reduce their level of transmission risk when compared to those who have HIV but are unaware of their infection.⁵⁹ For these patients, simple acknowledgment of their success in keeping themselves and their partners free from risk may be all the risk discussion need entail.

A minority of persons seen in care will require longer discussion or more in-depth intervention, but even discussions with these patients need not be onerous and time consuming. Patients in HIV care are usually seen multiple times a year

and, frequently, significant relationships develop between the patient and the provider; thus, all factors related to risk need not be discussed in one visit. In fact, given the nature of progressive behavior change, it may be advantageous to distribute brief risk discussions over multiple visits. This model is not novel in medicine: patients rarely stop smoking because of a single discussion about the benefits of cessation. Rather, for many patients the conversation must occur repeatedly over many clinic visits. At each interaction, the provider helps the patient move closer to choosing when and how he or she will stop smoking. Brief risk discussions spread over many clinic visits need not take significant time away from other priorities at any single visit.

A second barrier frequently cited by providers is the need to address higher priority issues during clinic visits. Closely related to the barrier of time, this reflects the low priority often placed on prevention in care. Providers usually need to deal with issues of medication compliance, side effects, symptomatic complaints, and discussing laboratory results during the brief medical encounter, often squeezing prevention out of the visit. However, seemingly unrelated risk behaviors—be they HIV transmission risk or poor medication adherence—may be secondary to the same deeper issue. Frequently, different risk behaviors are linked by a common denominator, such as substance abuse or mental health issues, which may need to be addressed before a patient can change his or her behavior. Thus, time spent screening for transmission risk behaviors may uncover important information relevant to other aspects of a patient's care.

Another reason given by providers for not conducting risk discussions more frequently is concern about their own counseling skills and perception that their efforts to change patient behavior are not effective. Frequently, patients are counseled on smoking cessation or excessive alcohol use, only to return with cigarettes in their pocket or intoxicated at subsequent visits. Providers may also feel discomfort talking openly about intimate issues such as sexual behavior. Although counseling is an integral part of medical care, it is a skill in which many clinicians are not well trained. Yet, studies have shown that training can improve clinicians' skill and comfort in counseling about HIV transmission risks, which in turn can lead to patient behavior change.^{60,61} Furthermore, these skills can be extended to counseling for other behavioral issues, such as medication adherence. Thus, it is important for providers to become educated about behavior change, specifically behavior change related to reducing patients' risk for transmitting HIV.

Providers often report they do not discuss risk behaviors more often because they fear patients will respond negatively. Considering that risk discussions often focus on intimate behaviors, about which patients may already feel guilty or concerned, patients might feel uncomfortable broaching the topic themselves. Yet many patients would like their providers to initiate these conversations and rely on them doing so.

Finally, it is important to acknowledge that, though reimbursement is occasionally possible through documentation of time spent with the patient, providers are often not directly compensated for risk screening and risk-reduction counseling, be it about HIV transmission, medication compliance, diabetes self-care, or other behavioral issues. Despite lack of direct remuneration, the benefits of risk screening and counseling, from the tangible, such as reduction in STDs, to the intangible, such as improved patient-provider relationships, make these discussions worth the relatively brief amount of time they take.

In spite of these barriers, health-care providers can be effective in helping patients change HIV risk behaviors.^{61–63} By delivering general HIV prevention messages to all HIV-positive patients, screening patients for HIV risk behaviors and STDs, providing or facilitating more in-depth assessment, and counseling to patients with identified risk behaviors or STDs, and facilitating partner notification, health-care providers can help patients live healthier, more satisfying lives and reduce their risk for transmitting infection to others.

PREVENTION MESSAGES FOR ALL HIV-POSITIVE PATIENTS

All HIV-positive patients can benefit from brief prevention messages about adopting and maintaining safer behaviors to protect their own health and that of their sex or drug-injection partners. For patients actively engaging in risky behaviors, these messages may be a stimulus to think about changing behaviors; for those trying to reduce risky behaviors, brief prevention messages may provide encouragement; and for patients already practicing safer behaviors, such messages may provide support for maintaining those behaviors.^{64,65}

Although some patients are knowledgeable about HIV transmission and prevention, inadequate information and misconceptions about HIV transmission and methods for reducing or eliminating transmission risk remain common.^{66–74} Although information alone may be insufficient to produce behavioral change, change is also unlikely to occur in the absence of knowledge.⁷⁵ The most reliable strategy for ensuring patients have adequate information is systematically asking all new patients what they know about HIV transmission and prevention, affirming accurate information, correcting misconceptions, and periodically reinforcing this information.

The principal message for all patients is that the most effective way to prevent new HIV infections is to protect non-infected persons from exposure to HIV. For HIV-positive persons, the only certain methods for preventing sexual transmission to noninfected persons are sexual abstinence and limiting sex to partners already infected with HIV, although simply limiting sex to HIV-positive partners does not protect against transmission or acquisition of other STDs

or strains of HIV.⁷⁶ The only certain means by which HIV-positive persons can prevent injection-related transmission is abstaining from sharing drug-injection paraphernalia (e.g., needles, syringes, cottons, cookers, water). General messages for all patients should include their responsibility for appropriately disclosing HIV serostatus to current and prospective sex and drug-injection partners so that the partners can make informed decisions about their own behaviors.^{77–81}

Certain misconceptions about HIV transmission and prevention appear relatively common. For example, many patients believe HIV cannot be transmitted through fellatio; however, the risk for transmission through fellatio, while lower than for other acts, is not zero.^{82,83} They may also not appreciate that transmission risk is affected by numerous factors (e.g., coexisting STDs, high viral load) that may substantially increase the risk associated with a specific sexual act.^{84–90} Another common misconception is that persons with undetectable viral load cannot transmit infection.^{35,73,91–93} While lower viral load is associated with lower risk for transmission, patients with undetectable plasma viral loads may still be able to transmit HIV. In discussing risk with patients, clinicians may identify other locally prevalent misconceptions and knowledge gaps that should be addressed in the general information provided to all patients in that setting.

General messages about preventing HIV transmission should be delivered by patients' primary care providers and can be reinforced by other clinic staff, such as nurses, social workers, medication adherence counselors, case managers, or health educators.⁹⁴ These messages can be amplified by designing the clinic or office environment to convey non-judgmental support for prevention. Information can be provided in multiple formats throughout the clinic; for example, brochures and other educational materials containing prevention messages can be placed at strategic locations; posters encouraging safer sex and drug-use practices and disclosure of HIV serostatus to sex and drug-injection partners can be placed in waiting and examination rooms; and educational videos can be shown in waiting areas. This can set the tone for prevention discussions and prompt patients to begin thinking about their sex and drug-use practices. Providers can then ask patients if they have noticed the posters or read the brochures as a way of introducing risk screening or initiating discussion about risk. Computer-based prevention programs with interactive elements have been used to support prevention messages for other health issues and may be effective for HIV prevention with some patients.^{95,96} Condoms should be readily accessible. With other health issues, such as smoking cessation, repeating prevention messages in multiple formats throughout health-care encounters has been found to increase the likelihood that patients will successfully change their behavior.^{60,94}

RISK SCREENING

To determine whether a risk discussion is warranted, all patients should be screened for indicators and facilitators of HIV transmission risk. Screening in the clinical setting should include screening for behavioral risk, STDs, and pregnancy.

■ SCREENING FOR BEHAVIORAL RISK

Behavioral risk screening is a brief process by which providers can identify patients for whom more in-depth diagnostic assessment is needed.⁹⁷ Whereas diagnostic assessment is done to confirm and better understand problems in patients already suspected of practicing risky behavior, risk screening is performed in patients who offer no external indication of such behavior. Behavioral risk screening should be repeated periodically, preferably at each routine visit. Questions that do not uncover risk behaviors in one visit may do so in a future visit if a patient's life circumstances or relationships change. In addition, patients may need to develop a certain level of trust with their provider before feeling comfortable disclosing sensitive information.

Behavioral risk screening can be done through various means. Self-administered, written questionnaires, in which patients respond to questions regarding behaviors over recent months, can be completed by patients in waiting rooms, examination rooms, or other clinic areas before they see the provider. This can set the tone for the clinic visit by indicating that prevention is an important part of care. Alternatively, patients can answer questions using computer-assisted screeners that print out results for the provider. Although still in trial stages, some practices have developed software that not only reports HIV risk behavior screening results, but also classifies the patient in terms of readiness to change and gives the provider suggested prevention messages appropriate to the patient's stage of readiness. Screening can also be done face-to-face by medical assistants or nurses while checking patients in for clinic visits. Responses can be recorded, similar to documentation of presenting complaints or reason for the visit, and given to providers before they meet with patients.

For patients with negative screens, providers can deliver simple, brief, supportive messages, reinforcing the patient's safe behaviors. For patients with positive behavioral risk screens, the provider can conduct further assessment by asking more in-depth questions. In either case, these models provide repetition of prevention messages, through both the initial screening and the follow-up discussion with the primary provider, reinforcing the concept of prevention.

Often, the responsibility for behavioral risk screening rests with the primary provider. In this case, providers may incorporate screening into the visit as part of the review of systems or as a separate series of questions. This model exploits the

primary provider's role as a behavior change agent and helps emphasize how important the issues addressed by screening questions are to the patient's overall care. This model can also enhance the patient-provider relationship by demonstrating to the patient that the provider is truly concerned about his or her overall well-being.

The effectiveness of behavioral risk screening can be enhanced in several ways. First, providers should help patients understand how behavioral risk screening supports their care—that it is not done to identify “bad” behavior, but rather to better treat the patient. For example, patients engaging in unprotected sex risk not only transmitting HIV to partners, but also acquiring other STDs themselves, which may adversely affect their HIV disease. But this risk will not be identified unless the provider does behavioral risk screening. Screening is also an opportunity to identify and intervene in aspects of patients' lives that may affect care, such as recent change in a relationship, loss of a partner, or homelessness. Providers should convey to the patients that screening questions may help identify significant factors that can impact their health and medical care, and thus are merited in the context of the medical visit.

Second, patients should understand they are not being singled out, but rather that screening questions are routine and asked of all patients. This message can be delivered explicitly at the outset of the interaction, before screening questions are asked, and implicitly by including screening questions naturally in the review of systems.

Third, patients should be assured of confidentiality. Because providers are trained to keep all aspects of medical encounters confidential except under extenuating circumstances, many assume confidentiality need not be discussed explicitly with patients. Yet patients may perceive a difference between questions typically asked in a review of systems, which normally centers on external manifestations of illness, and more personal questions asked in behavioral screening. Patients may worry that their confidentiality will be breached and that disclosure of high-risk behaviors may have negative consequences; thus, providers should explain the conditions of confidentiality to them. Also, patients should be informed if laws or regulations require providers to report specific behaviors to any authority. Patients are more apt to be open in their responses if mutual trust has been established.

Questions used for behavioral risk screening should be sufficiently broad such that most patients with risk behaviors screen positive (Table 72-1). Screening may not identify all patients at risk for transmitting HIV—to do so would require an exhaustive list of questions. Nor is screening intended to reveal the intricacies surrounding, or reasons for, risky behavior. Screening is meant to identify most persons who merit further assessment; it should be brief and to the point. While screening tools for identifying persons at risk for transmitting HIV have been developed, none have been well-validated.

Table 72-1. Key Behavioral Risks to Include in Screening^a

Behavioral Risks	Strategies to Use for Behavioral Risk Screening	
	Open-Ended Questions	Directed (Close-Ended) Questions
<i>Sexual risk behaviors</i>		
Is the patient sexually active? If so:	"What's been going on with your sex life since your last visit?"	"Since your last appointment, have you had sex with anyone?"
Are any of the patient's sex partners HIV-negative or of unknown HIV status? If so:	"Tell me about the people you've been having sex with."	"Were any of the people you've had sex with HIV-negative, or are you unsure about whether they're infected?"
Does the patient disclose his or her serostatus to sex partners of negative or unknown serostatus?	"How do you feel about letting the people you're having sex with know you're HIV-positive?"	"If you've had sex with someone who's HIV-negative, or you're unsure whether they're infected, did you tell them you're HIV-positive first?"
Does the patient use condoms consistently and correctly for sex with partners of negative or unknown serostatus?	"What have you been doing about using condoms?"	"If you've had sex with someone who's HIV-negative, or you're unsure whether they're infected, did you always use a condom?"
What steps other than using condoms does the patient take to prevent sexual transmission?	"What are your thoughts about giving someone HIV and what else you can do to keep that from happening?"	"Have you been doing anything besides using condoms to keep from passing HIV to your sex partners?"
What is the patient doing to prevent pregnancy?	"What are your thoughts about getting pregnant (or someone you're having sex with getting pregnant)?"	"Are you using birth control pills or anything else to keep from getting pregnant?"
<i>Injection-drug-related risk behaviors</i>		
Is the patient injecting drugs? If so:	"Tell me what you've been doing with drugs since your last visit."	"Since your last appointment, have you shot up any drugs?"
Is the patient sharing injection paraphernalia? If so:	"What are you doing about sharing needles or works?"	"Have you been sharing needles or works with anyone?"
Is the patient sharing paraphernalia with any partners who are HIV negative or of unknown serostatus? If so:	"Tell me about the people you've been sharing needles or works with."	"Were any of the people you've shared needles or works with HIV-negative, or are you unsure about whether they're infected?"
Does the patient disclose his or her serostatus to needle-sharing partners of negative or unknown serostatus?	"How do you feel about letting the people you're sharing needles or works with know you're HIV-positive?"	"If you've shared needles or works with someone who's HIV-negative, or you're unsure whether they're infected, did you tell them you're HIV-positive first?"
Does the patient bleach needles and works before sharing them?	"What have you been doing about cleaning needles and works before sharing them?"	"Are you bleaching the needles and works before you share them?"
What steps other than bleaching needles and works does the patient take to prevent injection-related transmission?	"What are your thoughts about giving someone HIV and what else you can do to keep that from happening?"	"If you've shared with someone who's HIV-negative, or you're unsure whether they're infected, did you use the needles and works after they used them?"

^aThese are the key issues of concern in screening patients for behavioral risks. A positive response in any of these areas should prompt the provider to follow up with more in-depth discussion and assessment.

■ SCREENING FOR STDs AND PREGNANCY

STDs facilitate both transmission and acquisition of HIV.^{85,98–102} Epidemiological studies have found significantly increased risk for HIV transmission from HIV-infected persons with genital ulcer disease and inflammatory STDs that cause urethral or cervical discharge. Treatment of STDs has been found to reduce viral load in genital secretions, which presumably reduces risk for HIV transmission. Therefore, screening should assess for symptoms, signs, and laboratory evidence of STDs. Symptoms such as urethral, vaginal, or anal discharge; ulcerative lesions; testicular, epididymal, lower abdominal and pelvic, anal, or pharyngeal pain; and rash should be elicited. Presence of any symptoms or signs suggestive of STDs should prompt immediate diagnostic evaluation and appropriate treatment.

Because STDs are frequently asymptomatic, routine laboratory screening for STDs should be undertaken.^{103,104} Sexually active HIV-positive men and women should be screened for syphilis annually, and regular screening for gonorrhea and chlamydial infection should be strongly considered.^{76,103–105} Women should be screened for trichomoniasis annually. Screening should be done at anatomic sites corresponding to an individual's risk behaviors; thus, a man who is the receptive partner for oral sex with other men should be screened for pharyngeal disease.¹⁰⁴ Similarly, a female who has anal sex with her male partner should be screened for rectal disease. The interval between screenings should be reduced for persons at increased risk for STDs (e.g., those reporting multiple sex partners).

Because HIV-positive persons are living longer, healthier lives, unintended pregnancy may become more likely, and many have begun to contemplate intentional pregnancy.^{106–108} Therefore, patients should be asked about symptoms and signs of pregnancy, use of contraception to prevent unintentional pregnancy, and consideration of future planned pregnancy. Positive screens should prompt referral to providers with expertise in reproductive health for HIV-positive persons.

TAILORED APPROACHES FOR PATIENTS AT RISK FOR TRANSMITTING HIV INFECTION

Patients at risk for transmitting HIV infection to others, or acquiring new STDs, other HIV variants, or blood-borne infections themselves, require further assessment and intervention. This includes patients identified through risk screening as currently or recently engaging in risky sexual or drug-injection practices; patients who have a current or recent STD; patients interested in pregnancy or at risk for unintentional pregnancy; patients with other characteristics associated with increased likelihood of risky behaviors

(e.g., alcohol or other noninjection drug use, dissolution of a long-term relationship), even if their risk screen does not indicate current risky behavior; and patients who express concern to clinicians or other clinic staff. Whether the problem is relatively simple (e.g., inadequate knowledge) or complex (e.g., multiple risky behaviors with complicating comorbidities and significant barriers to change), a similar approach can be used: (1) do a risk assessment to guide the clinical approach to the patient; (2) provide brief, clinician-delivered, educational, and motivational counseling; (3) address comorbidities and contextual factors, directly or through referral; (4) provide referrals for more intensive or supplemental prevention services, if appropriate; and (5) follow up with the patient at subsequent visits.

■ TARGETED RISK ASSESSMENT AND CLINICAL APPROACH

Assessment of behaviors

Risk assessment is a natural extension of the briefer risk screen. A primary goal of risk assessment is to better understand behaviors patients are engaging in that may affect their risk for transmitting HIV, or for transmitting or acquiring other STDs or blood-borne infections, and may be amenable to change (Table 72-2).¹⁰⁵ This allows providers to focus behavioral change efforts on very specific behaviors relevant to individual patients. Risk assessment should include in-depth inquiry into patients' sexual and drug-injection behaviors. For women of child-bearing age, assessment should include whether they might be pregnant, are interested in becoming pregnant, or are not specifically considering pregnancy but are sexually active and not using reliable contraception, because risk for perinatal HIV transmission is high without appropriate intervention.^{106–108} For HIV-positive men with serodiscordant female partners, issues of current or future planned or unplanned pregnancy may be equally important. For both sexual and drug-injection behaviors, inquiry should specifically address both main and casual partners, because behaviors and barriers often differ significantly with the two.^{109–117}

Risk assessment is usually accomplished through face-to-face, personalized discussion with the patient. Open-ended questions that avoid simple "yes" or "no" responses may encourage patients to discuss personal risks and associated circumstances, often revealing unsuspected information that might be missed with a more directive style. On the other hand, using directed questions in a more structured style is a relatively rapid method of ensuring that important issues are not overlooked. Neither approach alone has been clearly demonstrated to be more effective, and many clinicians naturally combine the two styles. As with behavioral risk screening, face-to-face discussion can be preceded or supplemented

Table 72-2. Behaviors to Consider in Assessing Risk for HIV Transmission

Sexual Behaviors	Drug-Injection Behaviors
General	Use of new or sterilized paraphernalia
Number of partners	Sharing of paraphernalia
Number or frequency of sex episodes	Other risky injection practices (e.g., “backloading”)
HIV serostatus of partner(s)	
Serostatus disclosure to current or prospective partners	Number of paraphernalia-sharing partners
Types of sex acts	Number or frequency of paraphernalia-sharing episodes
Condom use	HIV serostatus of paraphernalia-sharing partners
Other methods used to reduce sexual transmission risk	Serostatus disclosure to current or pro-prospective partners
Barriers to abstinence or condom use	Sterilization of shared paraphernalia
<i>For women of child-bearing age</i>	
Current pregnancy	Distributive vs. receptive sharing
Interest in future pregnancy	Other methods used to reduce injection-related risk
Use of reliable contraception to prevent unintended pregnancy	Barriers to ceasing injection drug use or adopting safer injection practices

with self-administered written or computer-, audio-, or video-assisted questionnaires, which have been found more effective for eliciting self-reports of risky behaviors than face-to-face interview in some situations.^{112,118–121}

Assessment of comorbidities and contextual factors

A second goal of risk assessment is to identify comorbidities and contextual factors that may affect patients' HIV transmission risk behaviors. For example, risky behaviors have been found in some studies to be associated with mental illness (e.g., depression), substance abuse and addiction, sexual compulsivity, and history of childhood sexual abuse.^{113,117,122–130} Contextual factors, such as relationship issues (e.g., desire for intimacy, fear of rejection, power imbalance, partner conflict or violence; lack of emotional or social support; negative or positive social or cultural influences (e.g., stigma); living situation (e.g., homelessness); or financial insecurity (e.g., need to exchange sex for drugs, money, or other support)^{131–144} may also facilitate risky behavior or pose barriers to behavior change.

The circumstances under which risky behaviors occur (e.g., use of alcohol or other drugs before or during sex) may affect judgment and decision-making. Environmental factors may be important facilitators of risky behavior; for example, increased sexual risk has been associated with bathhouses

and sex clubs, public sex environments, circuit parties, and “cruising” on the Internet.^{36,145–153} Risk assessment should consider these factors.

Assessment of underlying factors

A third goal of risk assessment is to identify psychosocial factors that may underlie a given patient's risk behaviors. Several theories of behavior and behavior change have been applied to understanding HIV risk-taking behavior and collectively have identified a relatively discrete number of factors that appear to directly or indirectly determine a person's behavior: (1) information; (2) skills and abilities (behavioral or physical); (3) external constraints; (4) self-efficacy (belief in one's ability to do something, even under difficult circumstances); (5) attitude (derived from one's beliefs about the consequences of performing a behavior and one's evaluation of whether those consequences have a net positive or negative value); and (6) subjective norms (derived from one's beliefs about what certain important others, such as family, friends, spouse, or partner, think about the behavior and one's motivation to comply with those referent others). A given behavior may be driven by any one or combination of these factors in one individual, but may be driven by very different factors in another individual. Accordingly, the appropriate intervention for these two individuals will likely differ substantially.

Clinical approach

On the basis of risk assessment, clinicians can decide how best to help patients reduce or eliminate risky behaviors or adopt protective behaviors. For patients with multiple risk behaviors, this includes considering which behavior the patient is most ready to change, as stage of change may substantially affect outcome.^{64,65} Targeting behaviors the patient is not ready to consider changing will likely lead to failure, and to frustration for both the patient and clinician.¹⁵⁴ Other factors to consider include which of the patient's risk behaviors and underlying issues can be addressed by the clinician during regular medical visits and which might require referral (Table 72-3), as well as the level or intensity of intervention and support needed.⁹⁴

The clinician's role in behavioral risk reduction may vary substantially, depending on time available; clinician skill, interest, and personal bias; type and complexity of contributing factors; availability of other on-site resources (e.g., prevention counselor); and availability and accessibility of off-site resources (e.g., community-based organizations [CBOs] providing HIV risk reduction services). Clinicians can increase the likelihood that patients will receive appropriate prevention-related services by deciding in advance what role(s) they are able and willing to perform and identifying resources to meet other needs. Primary care providers, who have established ongoing relationships with patients, can be particularly influential in patients' efforts to change behavior; therefore, even when referral is chosen as the primary approach, they should remain

Table 72-3. Examples of Which Issues to Address and Which may Require Referral

Issues That Can Often be Addressed by Clinicians and Clinic Support Staff	Issues That Might Require Referral
Lack of knowledge about HIV transmission risks	Need for extensive HIV prevention intervention
Misconceptions about risk of specific types of sexual and drug-use practices	Excessive use of alcohol or recreational drug use
Misconceptions about viral load and HIV transmission	Drug addiction, including injection drug use
How to disclose HIV-seropositive status to a sex partner, family member, or friend	Depression, anger, guilt, fear, or other mental health needs
Importance of using condoms and not exchanging body fluids with partners	Need for social support
Ways to reduce number of sex or drug partners	Sexual compulsivity
Ways to keep condoms accessible	Sexual or physical abuse (victim or perpetrator)
Ways to remember to use condoms	Desire to have children
How to persuade partners to use condoms	Contraceptive counseling
Ways to obtain support (e.g., financial, emotional) from family, friends, and lovers	Housing or transportation needs
Ways to disinfect injection paraphernalia	Nutritional needs
Ways to obtain clean needles	Financial emergencies
Ways to avoid sharing paraphernalia	Child custody, parole, or other legal matters
Ways to deal with mild psychological distress stemming from situational circumstances	Insurance coverage

Adapted from Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV: Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2003; 52(No. RR-12): 1–25.

actively involved in the risk-reduction process and follow up with patients at subsequent visits.

■ CLINICIAN-DELIVERED RISK-REDUCTION COUNSELING

Counseling approaches

Clinicians can choose from a variety of counseling approaches, none of which has been clearly demonstrated to be consistently more effective than another. The manner in which a clinician interacts with patients may be at least as important as the specific approach used: counselors providing the same treatment in the same setting may have substantially different outcomes.¹⁵⁵ Several counseling approaches applicable in clinical settings have been described, of which client-centered HIV prevention counseling and various adaptations of motivational interviewing are examples.

Client-centered HIV prevention counseling. Client-centered HIV prevention counseling is an interactive approach that has usually, but not always, been delivered in the context of HIV testing.¹⁵⁶ In the testing context, this approach has traditionally included two steps, one prior to testing and one after testing. In the first session, the counselor and client (1) conduct a personalized risk assessment to help the client identify behaviors that put him or her at risk; (2) explore strategies for reducing the client's personal risk; and (3) identify a single, explicit step for doing so, to which the client commits. In the second session, test results are provided and the counselor and client follow up on the client's progress with the previously-identified risk-reduction step and identify additional, specific, client-appropriate risk reduction steps. Client-centered HIV prevention counseling in the testing context has been studied among HIV-negative, heterosexual, STD clinic patients in a large, randomized, controlled trial with two intervention arms in which clients received either two or four counseling sessions.⁶³ Compared with clients receiving only didactic information, both intervention arms were associated with significantly higher self-reported condom use and lower rates of subsequent STDs.

Although client-centered HIV prevention counseling was tested among HIV-negative clients, a similar approach may be adaptable for use with HIV-positive patients receiving ongoing care. Important elements recognized by many specialists include (1) in-depth risk assessment; (2) exploration of the details and context of risk behaviors; (3) exploration of successes and challenges associated with previous risk-reduction efforts; (4) support for positive steps already taken; (5) clarification of critical misconceptions; and (6) negotiation of a specific, achievable behavior-change step.¹⁵⁶ Client-centered HIV prevention counseling sessions typically take at least 20 minutes; therefore, they may be more appropriate for delivery by special counselors than for incorporation into a multipurpose medical visit.

Adaptations of motivational interviewing. Many interventions found effective for reducing HIV risk behaviors are probably most appropriate for patients already planning or beginning to take action. Less work has been done on interventions for persons who are not yet aware of, or thinking of changing, a risk behavior, and therefore not seeking help to do so. In encounters with patients seeking care for other problems, clinicians are often uniquely positioned to help patients recognize their problem behaviors and begin thinking about changing them. Motivational counseling approaches aim to increase patients' intrinsic motivation to change and may be particularly appropriate in such circumstances.^{157,158}

One such approach is motivational interviewing, which incorporates four general principles: (1) expressing empathy by using reflective listening and acknowledging that ambivalence is normal; (2) developing discrepancy between current behavior and important personal values; (3) "rolling with resistance" by avoiding confrontation and allowing the client to be the primary resource for finding solutions; and (4) supporting self-efficacy by allowing the client to take responsibility for choosing and carrying out change, and by recognizing that the counselor's belief in the client's ability (or inability) to change may have a powerful effect on outcome.^{159,160}

The principles and spirit of motivational interviewing seem very applicable to use in medical care settings, but motivational interviewing may involve numerous sessions of considerable duration. Clinicians providing primary medical care to HIV-positive persons frequently see patients repeatedly over time; however, time available for counseling in each visit is generally limited, especially for patients with complex medical problems. Consequently, use of motivational interviewing by clinicians in medical care settings requires adaptation into a briefer format.^{158,161,162} An example of such an adaptation is a 5- to 10-minute smoking cessation intervention in which clinicians do a quick assessment of a patient's readiness to change and self-efficacy for doing so, then build the patient's motivation and confidence by encouraging him or her to identify arguments for change or practical steps for accomplishing change.¹⁶³ The patient then establishes a specific target for change (if ready to do so), and follow-up plans are made. This model uses an open-ended, client-centered approach, but also has a directive, algorithmic format well-suited to a medical counseling style.¹⁵⁸

Special considerations. Patients may be at very different stages in terms of their readiness to change risky behaviors.⁶⁵ Some may not be aware of their risk or, if aware, not thinking of changing (*pre-contemplation* stage); others may be considering taking steps to reduce or eliminate the risky behavior in the future (*contemplation* stage); and others may have made a commitment to action and taken some small steps toward changing the behavior, but not yet reached the point of

effective action (*preparation* stage). Some may be actively changing their behavior or environment to reduce or eliminate the problem at hand (*action* stage) and others may have already changed their behavior and be working to prevent relapse (*maintenance* stage).

While these stages are often described as a linear sequence, progression through them is not necessarily linear.⁶⁵ People typically recycle through various stages multiple times, and relapse is the rule rather than the exception; however, many who relapse are able to recover and proceed in a positive direction. Also, people may be in different stages with different behaviors: a person may not be contemplating changing one risk behavior, but may be successfully maintaining another risk-reduction behavior. Clinicians should try to match prevention messages to the patient's stage of change with respect to the targeted behavior (Figs. 72-1 and 72-2).¹⁶⁴

Changes in behavior usually occur over time, often in small steps that may not be readily apparent.⁶⁵ If success is measured only by immediate, sustained change in the target behavior, it may be difficult to recognize incremental successes that are priming the patient for effective change. This may lead the clinician to question whether brief prevention messages during clinic visits are effective. However, the cumulative impact of brief discussions at each visit can, over time, help patients achieve and maintain safer behaviors.¹⁶⁵ The short-term objective for each interaction is to help the patient advance through the stages of change, ultimately leading to the desired behavior change.

Different patients may respond to different types of messages. For example, some patients may be more motivated by

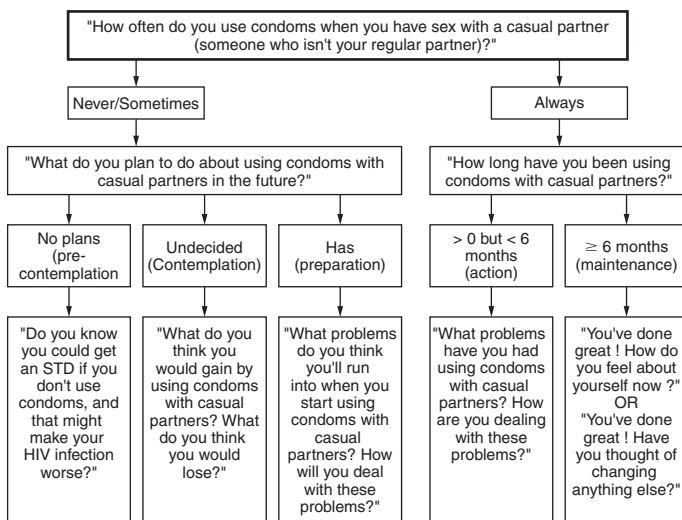


FIGURE 72-1. Example of tailoring messages regarding condom use for sexually-active, HIV-infected persons. (Adapted from Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV: Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2003; 52(No. RR-12): 1–25.)

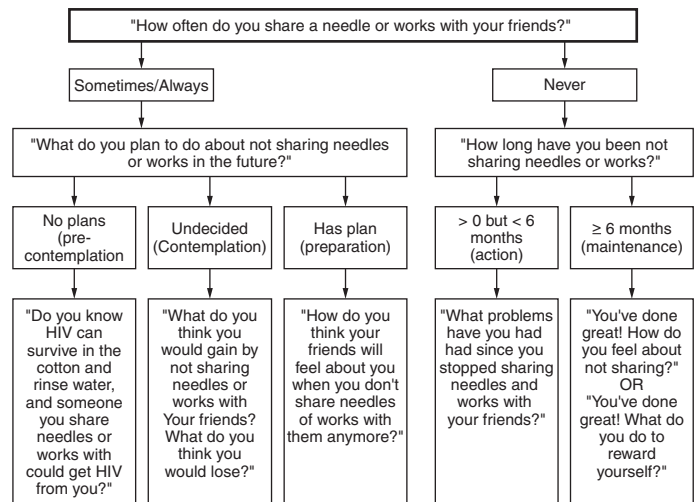


FIGURE 72-2. Example of tailoring messages regarding needle-sharing for HIV-infected persons who continue to inject drugs. (Adapted from Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV: Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2003; 52(No. RR-12): 1–25.)

altruistic feelings about protecting partners, while others may be more motivated by a sense of self-protection. Patients may also respond differently to whether a message is framed positively (“gain frame”) or negatively (“loss frame”).^{61,166–168} Similarly, counseling may need to be adjusted to a patient’s culture, language, sex, sexual orientation, age, or developmental level.¹⁵⁴ Attention to these differences may help the clinician tailor messages to specific patients more effectively.

Success may be more likely if psychosocial factors underlying a patient’s behavior are considered, comorbidities and contextual factors are identified, and the clinician’s approach is tailored accordingly. Success is also more likely if the target is a very specific behavior (e.g., always use a condom for vaginal sex with casual partners), rather than a broad behavioral goal (e.g., avoid transmitting HIV) or a behavioral category (e.g., practice safer sex; use condoms).¹⁵⁴ Finally, opportunities for developing skills (e.g., correctly putting on a condom, negotiating condom use with a partner) may increase the likelihood of success.¹⁶⁹

Specific patient strategies for eliminating or reducing transmission risk

A primary objective of clinician-delivered counseling is helping patients identify specific ways to eliminate or reduce HIV transmission risk. The ultimate goal being to eliminate transmission risk, but this may be difficult to achieve in one step. However, HIV-positive persons and their partners can choose among a range of strategies that can at least reduce their risk until elimination of risk is possible. Combining two or more risk reduction strategies may have a multiplicative effect; for example, in a serodiscordant relationship between two men, the risk for the HIV-negative partner becoming infected

during a single sexual act decreases 100-fold if he chooses insertive oral sex rather than receptive anal sex, and another 20-fold by using a condom, yielding an overall 2000-fold reduction in risk.¹⁷⁰

At a minimum, HIV-positive persons have a responsibility to disclose their serostatus to prospective sex and drug-injection partners, who can then make informed choices about the level of risk they are willing to take.^{77–81} HIV-positive individuals have used a variety of strategies to reduce transmission risk. In counseling patients, clinicians should be prepared to discuss these strategies and their potential roles in reducing or eliminating HIV transmission risk.

Sexual risk

Abstinence and partner choice. The only certain methods HIV-positive individuals can use for preventing sexual transmission of HIV to noninfected persons are sexual abstinence and limiting sex to partners known to be infected with HIV already. Limiting sex to already infected partners depends on knowing a partner's infection status with certainty, but people often make assumptions about one another's serostatus based on unreliable criteria, such as age, appearance, or willingness to engage in risky sexual behaviors (e.g., "If he is willing to have risky sex, he must be already infected").^{71,171,172} Also, restricting sex to HIV-positive partners does not protect against transmission or acquisition of other STDs unless condoms of latex, polyurethane, or other synthetic materials are used consistently and correctly.⁷⁶ Nevertheless, short of abstinence, limiting sex to already-infected partners is the most effective strategy for reducing new HIV infections.¹⁷⁰

Use of condoms. If serodiscordant partners who are aware of one another's HIV serostatus mutually decide to engage in sex, they should, at a minimum, use condoms made of latex, polyurethane, or other synthetic materials. Meta-analyses of published literature indicate that latex male condoms, used consistently and correctly, substantially reduce, but do not eliminate, risk for HIV transmission.^{173,174} A recent National Institutes of Health workshop panel concluded that "always" use of latex male condoms significantly reduces risk for HIV in men and women.¹⁷⁵ One analysis, synthesizing data from a variety of existing studies, concluded that using a condom can provide approximately a 20-fold reduction in the per-act risk of transmission of HIV.¹⁷⁰

Women unable to become pregnant because of elective sterilization or other medical causes may not use condoms because they are not concerned about unintended conception. These women should be counseled regarding the need to use condoms to reduce risk for transmission of HIV and other STDs.

Choice of sex act and strategic positioning. Numerous studies examining the risk for HIV transmission associated with different sex acts suggest that some sexual behaviors have substantially lower average per-act risk than others; however,

studies of transmission risk are subject to many limitations that make determination of absolute risk difficult.^{176–190} Also, risk for HIV transmission is affected by a wide variety of factors, such as stage of infection, viral load, antiretroviral therapy (ART), coexisting STDs, male circumcision, menstruation, and patterns of partnering.^{85–88,102,115,136,177,179,181–184,191–196} This leads to considerable heterogeneity in per-act risk, with some infections occurring after only a few contacts.^{188,189} Thus, risk estimates based on models assuming constant infectivity are unreliable, and estimates of the average per-act risk associated with specific acts could be misleading when applied to a specific person or situation.^{176,178,181,186,190} Nevertheless, these studies do allow reasonable estimates of the relative risks of various sex acts, and it is reasonable to conclude that substituting a higher-risk behavior with a relatively lower-risk behavior might further reduce HIV transmission risk when added to condom use (Table 72-4).¹⁷⁰ For example, all other factors being equal, transmission risk is likely reduced, though not eliminated, by choosing oral instead of anal sex, or by the HIV-positive partner assuming the receptive rather than the insertive role, a practice sometimes referred to as "strategic positioning."¹⁹⁷

Number of sex episodes and number of partners. Although the average absolute per-act risk for HIV transmission is relatively low compared with other STDs, risk for transmission obviously increases as the number of sex episodes increases. The effect of accumulating risk can be considerable; for example, if the per-contact infectivity of unprotected anal intercourse is 0.01, the cumulative risk after 10 episodes is about 10%.¹⁷⁴ Thus, in theory, cumulative transmission risk can be decreased by reducing the number of sex episodes. Interestingly, although some epidemiologic studies of transmission have found a positive association between number of contacts with a given partner and transmission, others have not found such an association.^{179–181,188,198} Finally, reducing the number of different partners decreases the number of persons who might become infected, thereby reducing overall transmission in the community, at least in the short term.¹⁹⁹

STD treatment. Because STDs facilitate HIV transmission and because treatment of STDs appears to reduce this risk.²⁰⁰ HIV-positive persons can reduce their risk for transmitting HIV by taking steps to prevent other STDs and immediately seeking diagnosis and treatment if they develop STD symptoms.

Withdrawal before ejaculation. Withdrawal before ejaculation has been cited as a strategy used by some MSM and heterosexuals attempting to reduce transmission risk.^{72,115,197,201,202} In one longitudinal study of transmission among heterosexual partners, no seroconversions were observed among women in couples that reported nearly always practicing withdrawal, while couples that reported practicing withdrawal in about half of sexual episodes had rate of 7.2% and those that reported rarely or never practicing withdrawal had a

Table 72-4. Estimated Per-Act Relative Risk for a Person Without Human Immunodeficiency Virus Infection Acquiring HIV Infection, Based on Sex Act^a and Condom Use^b

Risk Factor	Relative Risk for a Person Without HIV Infection of Acquiring HIV Infection
<i>Sex act</i>	
Insertive fellatio ^c	1
Receptive fellatio ^c	2
Insertive vaginal sex ^d	13
Receptive vaginal sex ^d	20
Insertive anal sex ^d	13
Receptive anal sex ^d	100
<i>Condom use</i>	
Yes ^e	1
No ^e	20

Note: This table quantifies the relative risk for HIV transmission in a way that can help compare the effects of a person's choices of sex act and condom use. It is presented from the point of view of a person without HIV infection and should be used to educate the HIV-infected patient regarding risks for transmission to partners who are not HIV infected or have unknown HIV serostatus. These risks are estimated from available data. Risks can vary depending on several factors, including presence of STDs in either partner and the HIV-infected partner's viral load. In addition, the relative frequency of performance of higher- and lower-risk sex acts will affect risk for transmission.

^aData regarding risk for transmission from sharing drug injection equipment are too limited to be included in this table.

^bSource: Varghese B, Maher JE, Peterman TA, Branson BM, Steketee RW. Reducing the risk of sexual HIV transmission: Quantifying the per-act risk for HIV infection based on choice of partner, sex act, and condom use. *Sex Transm Dis* 2002; 29: 38–43.

^cBest guess estimate, from Varghese et al.

^dSource: European Study Group. Comparison of female-to-male and male-to-female transmission of HIV in 563 stable couples. *Br Med J* 1992; 304: 809–813.

^eSource: Macaluso JM, Kelaghan J, Artz L, et al. Mechanical failure of the latex condom in a cohort of women at high STD risk. *Sex Transm Dis* 1999; 26: 450–458.

From Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV: Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2003; 52(No. RR-12): 1–25.

32.4% rate.¹⁷⁷ However, in a study of seroconverters in a cohort of gay men, believing withdrawal to be safe with regard to HIV transmission was an independent predictor of seroconversion.²⁰¹ Although there are hypothetical reasons that withdrawal may be partially protective (e.g., smaller viral

dose), there are substantial reasons for withdrawal to fail (e.g., presence of HIV in pre-ejaculatory fluid, failure to withdraw before ejaculation). Adequate data are not available to address this issue or to base estimates of any absolute or relative risk reduction this practice might afford.

Injection-related risk

Substance abuse treatment and abstinence from injection drug use.

For injection-related transmission, the only certain means by which HIV-positive persons can prevent transmission to noninfected persons, and avoid other injection-related health risks themselves, is abstaining from injection drug use. However, most injection drug users (IDUs) are not able to sustain long-term abstinence from injecting without substance abuse treatment.²⁰³ There is substantial evidence to support the effectiveness of substance abuse treatment, especially methadone and buprenorphine maintenance, for reducing injection drug use, and several studies have found associations between enrollment in substance abuse treatment and reductions in HIV transmission risk behaviors.^{204–211} Thus, for IDUs, referral and entry into substance abuse treatment programs is a key component of HIV prevention.

Refraining from sharing injection paraphernalia.

For IDUs unable or unwilling to stop injecting drugs, risk for transmitting HIV to others can be eliminated by not sharing injection equipment (i.e., needles, syringes, cottons, cookers, water).²¹² This is best achieved by once-only use of new, sterile syringes, although this approach does not eliminate other health risks to HIV-positive IDUs (e.g., soft tissue abscesses, endocarditis) unless strict aseptic technique is used.²¹³ Also, this is often not feasible due to difficulty obtaining new, unused syringes, and needles; thus, for IDUs who continue to inject, facilitating access to sterile syringes, needles, and other injection paraphernalia is a critical component of a comprehensive program for reducing transmission of HIV and other blood-borne infections.^{214–217} Cohort, case-control, and observational studies indicate that access to sterile syringes through syringe exchange programs (SEPs) reduces HIV transmission risk behavior and HIV seroconversion among IDUs and increases rates of entry into substance abuse treatment programs.^{111,218–225} Access to new, sterile syringes can also be increased through physician prescribing and pharmacy programs, although significant barriers to these approaches exist.^{226–232} If new, sterile equipment is not available, transmission risk can still be eliminated through use of sterilized equipment used by one person without sharing.

Partner choice. In spite of substantial evidence that substance abuse treatment and SEPs have reduced HIV transmission among IDUs, and that sharing of needles, syringes, and other injection paraphernalia has decreased in at least some areas, sharing remains common among both HIV-negative and

HIV-positive IDUs, especially among close friends, spouses, and sexual partners.^{115,116,138,233–240} One recent survey found very high rates of paraphernalia sharing among young suburban and urban IDUs in the Chicago area.²³⁹ Clinicians should continuously work to help patients eliminate this behavior; however, until this goal can be achieved, HIV-positive persons can prevent transmission to noninfected persons by limiting sharing of injection equipment to HIV-positive partners, analogous to sexual serosorting. This strategy clearly has major limitations, including mistaken assumptions about another person's serostatus, and the fact that restricting sharing to HIV-positive partners does not protect against transmission or acquisition of other serious blood-borne infections (e.g., hepatitis B, hepatitis C).^{71,171,172,241}

Cleaning injection equipment and other injection practices. If serodiscordant persons who are aware of one another's HIV serostatus mutually decide to share injection paraphernalia, they should, at a minimum, disinfect syringes and all other paraphernalia by boiling or flushing with bleach, and avoid other risky injection practices, such as “backloading” (a process in which drugs are drawn up in one syringe to measure and transfer a portion to a second syringe).²⁴² This may reduce risk for HIV transmission and has also been associated with lower rates of HCV seroconversion; however, reliable disinfection is difficult to achieve and patients need to understand that this practice is not as safe as using a new, sterile syringe.^{213,243–245}

Published studies of injection practices frequently focus on “receptive” needle sharing (i.e., using the syringe or needle after another person has used it), which, for HIV-negative persons, presents the greatest risk.^{111,236,239} However, for the HIV-positive person—analogous to the relative risks for receptive and insertive sexual practices—the greatest risk for transmitting HIV is with distributive sharing (i.e., using the needle or other paraphernalia before another person). Thus, if shared paraphernalia are being disinfected between use by two serodiscordant persons, risk for HIV transmission from the infected partner to the noninfected partner may be further reduced if the HIV-positive partner uses the shared equipment after the partner of negative or unknown HIV serostatus.

Number of injection episodes and number of partners. Cumulative transmission risk might be reduced by limiting the number of injection episodes. Also, decreasing the number of injection partners will reduce the number of persons who might become infected. However, as with sexual transmission, these strategies can only be viewed as additions to, not substitutes for, other precautions, such as disinfecting paraphernalia between injectors. Furthermore, from the perspective of the patient's overall health, the most desirable strategy is cessation of injecting or, failing that, once-only use of sterile paraphernalia.

Sexual behaviors. Risky sexual behaviors are also prevalent among IDUs, and a substantial proportion of IDU-related transmission results from unsafe sexual behaviors.^{111,138,236,246,247} While focusing on safer drug-use behaviors for IDUs, it is important to also screen for and address unsafe sexual behaviors.²⁴⁸

Perinatal transmission risk

Pregnancy prevention. The most reliable approach for preventing perinatal transmission is preventing pregnancy. Sexually active HIV-positive women who are not interested in becoming pregnant should use reliable contraception. It has been noted that some women mistakenly believe hormonal contraception is protective against HIV.^{66,67} Women need to understand that, in addition to using reliable contraception to avoid vertical transmission, they must also use condoms to reduce risk for horizontal sexual transmission of HIV or other STDs.²⁴⁹

Antiretroviral therapy. It is beyond the scope of this chapter to address perinatal transmission in detail; however for HIV-positive women who are pregnant or desire to become pregnant, risk for perinatal transmission can be substantially reduced by appropriate use of ART during pregnancy and at the time of delivery, delivery by elective cesarean section before onset of labor, administration of ART to infants during the first 6 weeks of life, and avoidance of breast feeding.²⁵⁰ HIV-positive women who are considering pregnancy, or are already pregnant, should be referred to a reproductive health specialist with expertise in management of HIV-positive patients, as should HIV-negative women who are considering pregnancy with HIV-positive partners.^{106–108}

Serostatus disclosure as a risk reduction strategy. HIV prevention efforts often emphasize encouraging HIV-positive persons to disclose their serostatus to current and prospective sex and drug-injection partners.^{80,251,252} This practice is based on the assumption that, if serostatus is disclosed, safer behavior will necessarily follow. However, the relationship between disclosure and safer behavior is complex: available studies have generally failed to demonstrate a consistent relationship between serostatus disclosure and safer sex.^{171,253–255} In fact, there are substantial disincentives to serostatus disclosure, including stigma, violence from partners and others, and fear of retribution.^{134,256–261} In a national probability sample of HIV-infected persons receiving care, 42% of gay or bisexual men, 19% of heterosexual men, and 17% of all women reported any sex without disclosure, and across all groups, 13% of serodiscordant partnerships involved unprotected anal or vaginal sex without disclosure.⁸⁰ Nevertheless, partners cannot make fully informed decisions without knowledge of one another's serostatus, and HIV-positive persons need to recognize their responsibility for disclosure of serostatus to current and prospective partners.^{77–81}

Adherence to antiretroviral therapy. ART should be initiated only for appropriate clinical indications—not to reduce risk for transmission. Also, since HIV can be detected in the semen, rectal secretions, female genital secretions, and pharynx of HIV-positive patients with undetectable plasma viral loads, clinicians and patients should assume that patients who are on therapy and have undetectable plasma HIV levels can still transmit HIV.^{262–266} However, high viral load is a major risk factor for HIV transmission: among untreated patients, risk for heterosexual HIV transmission has been shown to increase approximately 2.5-fold for each 10-fold increase in plasma viral load.¹⁹⁴ Therefore, ART that lowers viral load might reduce risk for sex- and injection-related transmission, as has been demonstrated with perinatal transmission and indirectly suggested for sexual transmission.^{267–273} However, consistent reduction of viral load depends on high levels of adherence to antiretroviral regimens, thus efforts at promoting adherence, such as adherence counseling, not only provide substantial clinical benefit to individual patients, but may also reduce the likelihood that the patient will transmit HIV to others.²⁷⁴ As important as the potential benefit may be, the degree to which ART actually reduces sexual transmission is not known, and this strategy should be considered a supplement to other methods (e.g., condom use), rather than a substitute.

Post-exposure prophylaxis. A discussion of potential HIV prevention strategies would not be complete without addressing nonoccupational postexposure prophylaxis (nPEP) for sexual, injection-drug-related, and other nonoccupational exposures to HIV. In the present context, this is most relevant because of the potential disinhibitory effect the availability of nPEP could have on HIV risk behaviors among both HIV-negative and HIV-positive individuals. Data from animal studies, postnatal prophylaxis in perinatal clinical trials, studies of postexposure prophylaxis for occupational exposures, and observational studies, taken together, suggest that nPEP might reduce risk for infection after nonoccupational exposure in some cases.^{270,275–285} On the basis of these data, the United States Public Health Service currently recommends prompt (i.e., within ≤ 72 hours after exposure) initiation of PEP in carefully defined circumstances of nonoccupational exposure]; however, nPEP is unlikely to prevent infection in all cases, and effectiveness may be hindered by medication side effects, toxicity, or poor adherence to the regimen.^{286–292} Therefore, potential availability of nPEP should not be viewed as an acceptable routine strategy for HIV prevention.

■ SUPPLEMENTARY PREVENTION SERVICES

On-site interventions

Some patients require more intensive intervention than most clinicians can provide in the limited time available during regular clinical visits. Also, it has been demonstrated with

HIV and other health behaviors (e.g., smoking) that successful behavior change is correlated with the intensity of intervention, and provision of other longer or more intensive interventions in the clinic setting can build upon the primary provider's efforts.^{94,169} These interventions are usually beyond what most clinicians have time or expertise to provide, but could be delivered by existing staff (e.g., nurses, social workers, adherence counselors) who receive additional training, or by counselors or other staff hired specifically for that purpose. It may be possible to develop collaborations with CBOs or other agencies, which may be able to provide staff to deliver these interventions on-site at the clinic.

Several multisession interventions in community service organization settings have been found effective at reducing sexual risk behaviors among HIV-positive persons (Table 72-5).^{144,293–295} These interventions resemble one another in that each addresses multiple life issues faced by HIV-positive persons, rather than focusing only on transmission risk reduction. Addressing contextual issues may increase the likelihood that patients will be able to make and sustain behavioral changes, in addition to making the intervention more appealing to patients who might otherwise not choose to attend.¹⁶⁹ Three of these interventions use a group format, which gives patients trying to change their behavior an opportunity to interact with, and derive support from, other persons who are struggling with similar issues.^{144,293,294} Although these interventions were not tested in health-care settings, they might be suitable for adaptation to the clinical setting if the intervention's core elements are preserved.^{296–299}

Prevention case management (PCM) is an intervention that provides ongoing, intensive, one-on-one, client-centered HIV prevention counseling, as well as assistance accessing other services to address issues that affect patients' health and ability to change HIV-related risk-taking behavior.³⁰⁰ PCM has been widely used with HIV-negative persons at risk for becoming infected and less often with HIV-positive persons; however, its efficacy has not been demonstrated in any rigorously controlled studies. Also, this intervention may be less relevant for many HIV-positive persons, who might benefit from intensive, one-on-one prevention counseling, but already have access to other services through case managers.

For HIV-negative or HIV-status-unknown persons, numerous interventions delivered in health-care settings have been found effective for reducing HIV risk behaviors (Table 72-5).^{62,63,301–321} Some of these interventions may be adaptable for use with HIV-positive persons in health-care settings; however, HIV-positive persons face numerous issues that may affect their ability to adopt and maintain safer behaviors, and interventions designed for HIV-negative or HIV-status-unknown persons may not adequately address these issues.

Table 72-5. Effective Individual- and Group-Level HIV Risk-Reduction Interventions

Reference	Intervention	Setting	Target Population	Format(s)	Sessions
1. HIV-positive					
Kalichman et al. ²⁹³	(HIV+) Healthy relationships	Community AIDS service organization	HIV-positive heterosexual males and females and MSM	Group	5
Rotheram-Borus et al. ²⁹⁴	Together Learning Choices (TLC)	Healthcare	HIV-positive heterosexual male and female and MSM substance abusing adolescent clinic patients	Group	31
Rotheram-Borus et al. ²⁹⁵	Choosing Life: Empowerment, Actions, Results (CLEAR)	Community	HIV-positive heterosexual male and female and MSM substance-abusing youth	Individual	18
Wingood et al. ¹⁴⁴	WILLOW	Healthcare	HIV-positive sexually- active female clinic patients	Group	4
2. HIV-negative, HIV status unknown or not specified, or mixed HIV status					
a. MSM					
Dilley et al. ⁶²	Self-justifications counseling	Healthcare (HIV testing clinic)	MSM	Individual	1
Koblin et al. ³²⁵	EXPLORE	Study site	MSM	Individual	10
Kelly et al. ³¹¹	Behavioral Self-management and assertion skills	Healthcare	Adult MSM with high-risk sexual behaviors	Group	12
Valdiserri et al. ³³⁴	Small group lecture plus skills training	Community-based establishment	MSM Male prostitutes	Group	1
b. Drug users					
Des Jarlais et al. ³²³	Sniffer	Community-based establishment	HIV-negative male and female heroin sniffers	Group	4
El-Bassel and Schilling ³⁰⁶	Skills building	Healthcare	Heterosexual female methadone patients	Group	5
Eldridge et al. ³⁰⁸		Healthcare	HIV-negative female drug users in treatment	Group	6
Latkin et al. ³²⁷	Self-help In Eliminating Life-Threatening Diseases (SHIELD)	Study site	Low-income male and female African American drug users	Group	10
Magura et al. 1994 ³²⁹	Rikers Health Advocacy Program (RHAP)	Correctional	Incarcerated inner-city male adolescent drug users	Group	4
McCusker et al. ³¹³	Project SMART	Healthcare	Male and female drug users in treatment	Individual group	8

Table 72-5. (Continued)

Reference	Intervention	Setting	Target Population	Format(s)	Sessions
Rhodes et al. ³⁵⁰	Safety counts	Community-based establishment	Out-of-treatment male and female IDUs and crack users	Individual group	≥9
Robles et al. ³¹⁷	PICUSS motivational interviewing	Healthcare (drug treatment centers)	Male and female Hispanic drug injectors	Individual	6 (or 8)
Sterk et al. ³³³	Female- and culturally-specific negotiation intervention	Study site	HIV-negative inner-city sexually-active out-of-treatment African American female crack users or drug injectors	Individual	4
Wechsberg et al. ³³⁵	Women-focused intervention	Community study sites	Inner-city sexually-active out-of-drug-treatment crack-using African American females	Individual group	4
c. Heterosexual adults					
Baker et al. ³²²	Choices: A Women's Health Project	Not reported	Low-income heterosexual females	Group	16
Carey et al. ³⁰¹	Health Improvement Project (HIP)	Healthcare	Mentally-ill male and female clinic patients	Group	10
Cohen et al. ³⁰²	Condom skills education	Healthcare	Male and female STD clinic patients	Group	1
Cohen et al. ³⁰³	Doing something different	Healthcare	Inner-city male and female STD clinic patients	Group	1
DiClemente and Wingwood ³²⁴	SISTA	Community-based establishment	Young low-income heterosexual African American females	Group	5
Ehrhardt et al. ³⁰⁵	Project FIO: The Future is Ours	Healthcare	Heterosexual females attending family planning clinics	Group	8 (plus 1 booster)
El-Bassel et al. ³⁰⁷	Project Connect	Healthcare	Heterosexual African American and Latino couples	Individual group	6
Hobfoll et al. ³⁰⁹	AIDS prevention and health promotion among women	Healthcare	Low-income inner-city single pregnant female clinic patients	Group	4
Hobfoll et al. ³¹⁰	Community-oriented AIDS prevention	Healthcare	Low-income inner-city female clinic patients	Group	6
Kamb et al. ⁶³	Project RESPECT	Healthcare	HIV-negative male and female STD clinic patients	Individual	2 or 4

(Continued)

Table 72-5. (Continued)

Reference	Intervention	Setting	Target Population	Format(s)	Sessions
Kelly et al. ³¹²	Cognitive behavioral skills training group	Healthcare	Low-income inner-city heterosexual racial/ethnic minority female clinic patients with STD, high-risk sex partners, or other high sexual risks	Group	5
Lauby et al. ³²⁸	Real AIDS Prevention Program (RAPP)	Community-based establishment	Low-income inner-city sexually-active females	Individual group community	2 years
NIMH ³¹⁴	Living in good health together (LIGHT)	Healthcare	Low-income urban male and female clinic patients with STD or other high sexual risks	Group	7
O'Donnell et al. ³¹⁵	Video Opportunities for Condom Education and Safer Sex (VOICES/VOCES)	Healthcare	Inner-city African American or Hispanic male clinic patients	Individual group	1
Shain et al. ³¹⁹	Sexual Awareness for Everyone (SAFE)	Healthcare	Mexican American and African American females with STD in public health clinics	Individual group	2
Wenger et al. ³²¹		Healthcare	Heterosexual male and female clinic patients	Individual	2
d. High-risk youth					
DiClemente et al. ³⁰⁴	Sistas Informing, Healing, Living, Empowering (SiHLE)	Healthcare	Sexually active African American female adolescents	Group	4
Jemmott et al. ³²⁶	Be proud! Be responsible!	Educational	Inner-city African American male adolescents	Group	1
Orr et al. ³¹⁶		Healthcare	Female adolescent clinic patients with STD	Individual	1
Rotheram-Borus et al. ³³¹		Community-based establishment	High-risk racial/ethnic minority adolescents	Group	3 or 7
Sellers et al. ³¹⁸	Poder Latino: A community AIDS prevention program for inner-city Latino youth	Multiple, including healthcare	Latino youth	Individual group community	18 months
St. Lawrence et al. ³²⁰	Becoming a Responsible Teen (BART)	Healthcare	Low-income African American male and female adolescents	Group	8

Table 72-5. (Continued)

Reference	Intervention	Setting	Target Population	Format(s)	Sessions
Stanton et al. ³³²	Focus on Kids (FOK)	Community-based establishment	Low-income urban African American male and female youth	Group	7 (plus 1 retreat)
Wu et al. ³³⁶	Focus on Kids + Informed Parents and Children Together (ImPACT)	Community sites	Low-income African American male and female youth	Group	9 (8 FOK plus 1 ImPACT)

MSM, men who have sex with men; IDU, injection drug user.

Adapted from Herbst JH, Collins CB, Jr, Kay LS, Crepez N, Lyles CM, and the HIV/AIDS Prevention Research Synthesis Team. Evidence-based HIV behavioral interventions in the United States identified through a systematic Review, 2000–2004. Poster presented at the 2005 HIV Prevention Leadership Summit, San Francisco, CA, July 31–August 3, 2005.

Off-site interventions

Patients who need additional support can often be referred to services in the community. Several community-based interventions for HIV-positive persons have already been listed and are available in some areas.^{144,293,295} For HIV-negative or HIV-status-unknown persons, a number of community-based interventions have been found effective (Table 72-5).^{322–336} These interventions may be available through health departments and CBOs in some areas; however, their adaptability for use with HIV-positive persons has not been demonstrated.

For patients who inject illicit drugs, referral to substance abuse treatment (or for those unable or unwilling to cease injection, access to sterile injection paraphernalia) is critical. In addition to the obvious risks of injection drug use, increased risk behavior and HIV transmission, especially among MSM, have been associated with use, before and during sex, of amyl nitrites (“poppers”), alcohol, stimulant drugs (e.g., powder and crack cocaine, methamphetamines), and “party” or “club” drugs, such as Ecstasy (3,4-methylenedioxymethamphetamine).^{112,149,150,337–340} Individuals using drugs of these types should also be referred for substance abuse treatment.

REFERRAL PROCESSES

Referrals for psychosocial and supplemental prevention services can be critical in addressing prevention needs of HIV-positive persons, but successful referral can be difficult to accomplish. Factors important for successful referral include patients’ willingness and ability to accept and complete referrals; patients’ self-identified priorities; appropriateness of providers to whom patients are referred, in terms of the patients’ culture, language, sex,

sexual orientation, age, and developmental level; availability of transportation or child care; compatibility with patients’ work schedules; and cost, accessibility, and convenience of services.¹⁵⁶ Successful referral may be more likely if these issues are addressed and if clinicians or other staff help patients schedule appointments and arrange for transportation, child care, and other needs. Knowing about available resources is important: referral guides that list local HIV prevention and supportive social services may be available from health department HIV/AIDS programs (Table 72-6). Clinicians often do not have time or capacity to make all referrals. Case managers or other staff, such as counselors or educators, can help make referrals and help patients complete referrals successfully.

TRAINING

Training can substantially increase the likelihood that behavioral risk reduction interventions will be successful. In a study of providers’ efficacy with smoking cessation counseling, 35 resident physicians were randomized to either a training program in which they learned to provide counseling that matched smokers’ motivation to quit or a didactic session on management of dyslipidemia.³⁴¹ At 12 months, patients cared for by the trained providers were significantly more likely to be abstinent from smoking (13% vs. 5% in the control group).

Providers can also improve their skill at assessing HIV transmission risk. In a study of HIV risk assessment and counseling, 961 providers were randomized to (1) a control group, (2) a group that was sent educational materials via the mail, or (3) a group that was sent the same educational materials and received an office visit from an instructor.³⁴² A significantly greater percentage of providers in the third

Table 72-6. Referral Resource Guide, Suggested Contents

Information to be included in referral resource guides
Name and address of service provider or agency
Range of services available
Target population(s)
Service area(s)
Contact names, telephone/fax numbers, e-mail address
Hours of operation
Competence in providing services appropriate to patient's culture, language, sex, sexual orientation, age, and developmental level
Charge for services
Eligibility
Application materials
Admission policies and procedures
Directions, transportation information, and accessibility to public transportation
Patient satisfaction with services

Adapted from Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV: Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2003;52(No. RR-12):1–25.

group (mailings plus instructor visit) reported increasing their assessment of patients' sexual histories (76%) than those in the control group (43%) or the group receiving the mailing alone (56%). A similar pattern was noted in the providers self-reported counseling practices. To assess possible reporting bias, equal numbers of providers in each group were evaluated using a standardized patient. Providers in the third group (mailings plus instructor visit) were significantly more likely to counsel the patient on using condoms (99%) than those in the control group (89%) or the mailing alone group (88%). In a study of an intervention to improve providers' HIV and STD assessment and counseling skills, patients seen by providers who received the intervention were significantly more likely than patients seen by providers who did not receive the intervention to have had the provider discuss HIV or STDs (OR 1.6), ask about sexual risk behaviors (OR 1.7), discuss HIV prevention in general (OR 2.4), and discuss personal

risk reduction (OR 2.6).⁶⁰ These results persisted in follow-up at 38 weeks. Thus, providers appear able to significantly improve their ability to assess and counsel for a variety of risk behaviors, including HIV transmission.

The Partnership for Health (PFH) intervention trial included a 4-hour training for all medical care providers and other staff in participating clinics, with a briefer, reinforcing session provided 1 month after the intervention was initiated.⁶¹ The Options Project intervention trial also involves clinician training, including a 4-hour training session on the protocol and motivational interviewing techniques, a 2-hour workshop on sexual and injection drug use risk behaviors and risk-reduction strategies, and a one-on-one booster session.³⁴³ Training on incorporating HIV prevention into care is also being developed by CDC for general use. Training on many of the other interventions listed in this chapter is available and would be appropriate for designated staff in clinics planning to implement any of these interventions on-site. Information about training can be obtained through CDC-funded STD/HIV prevention training centers (PTCs) (<http://depts.washington.edu/nnptc>), HRSA-funded AIDS education and training centers (AETCs) (<http://www.aids-ed.org>), and the Diffusing Effective Behavioral Interventions project (DEBI) (<http://www.effectiveinterventions.org>).

PARTNER SERVICES AND RELATED ACTIVITIES

■ PARTNER COUNSELING AND REFERRAL SERVICES

Several studies in geographically diverse areas have found that partner counseling and referral services (PCRS), including partner notification, can be effective for identifying HIV-positive individuals not aware of their infection.^{344–350} PCRS provides a valuable service to HIV-positive persons and their sex and drug-injection partners by (a) helping HIV-positive persons ensure that partners are aware of their risk and able to take steps to avoid becoming infected or, if already infected, to avoid infecting others and (b) helping infected partners gain earlier access to medical evaluation, treatment, prevention, and other services.^{351,352} Unfortunately, a recent survey of health departments in 22 jurisdictions with HIV reporting found that only 32% of persons with newly-diagnosed HIV infection were interviewed for PCRS.³⁵³ Several studies have found that the majority of HIV counselors and health-care providers support PCRS; however, studies also indicate that many counselors and health-care providers do not refer their HIV-positive patients for PCRS.^{354–359}

PCRS includes three main elements: (1) eliciting information from HIV-positive persons about sex and drug-injection partners, (2) notifying partners of their risk, and (3) helping them access HIV counseling and testing services.

PCRS is *voluntary*, in that infected persons decide which partners to identify to the interviewer, and *confidential*, in that partners are not told who reported their name or when the reported exposure occurred, nor is information about partners relayed back to the original patient.³⁵² In surveys of persons seeking HIV testing, HIV-positive persons, and notified partners, the majority of respondents have supported partner notification.^{360–362}

PCRS is most often conducted by health departments, but clinicians can play a key role by referring their HIV-positive patients to the health department for these services. In areas where laws and regulations permit, some clinicians choose to play a more active role by performing parts of PCRS, such as interviewing HIV-positive patients to elicit partner information. If so, this is best done in collaboration with the appropriate health department. Effective partner elicitation takes time and requires considerable motivational skill, which is best learned by specific training. Some studies have indicated patients are more likely to name close partners than more casual partners; clinicians eliciting partner information from patients should be sure to include casual partners, as well.^{363–365} Also, while reports regarding PCRS often focus on sex partners, it is important to include drug injection paraphernalia-sharing partners.³⁵¹ Because HIV is a chronic condition and new exposures may occur after the original interview, clinicians should periodically inquire whether patients have new sex or drug-injection partners who may benefit from PCRS.

Once partners are identified, they can be notified of their risk by a health department specialist (provider-referral), by the patient (patient- or client-referral), or by the patient and a health-care provider, together (dual-referral).³⁵² Most health departments offer another option, in which clients have a few days to notify partners; but, if partners have not reported for counseling and testing by an agreed-upon date, they are contacted by a health department specialist (contract-referral).³⁵² One randomized, controlled trial comparing notification strategies found that notification by health department specialists is substantially more effective than the notification by infected persons.³⁴⁹

Some clinicians may wish to take on the responsibility for informing partners. As with partner elicitation, notification requires considerable time, skill, and training. One observational study suggested health department specialists were more successful than physicians in interviewing patients and locating partners.³⁶⁶ Some reports of partner violence after notification suggest a need for caution^{367,368}; however, other studies have found that patients report few adverse reactions.^{362,364,367,369,370} When violence does occur, it is often in relationships where violence is already a problem.³⁷⁰ This emphasizes the importance of assessing potential for violence and, when identified, obtaining expert consultation before proceeding with notification.³⁵²

■ SOCIAL NETWORKS

Available evidence suggests the majority of new HIV infections in the United States originate from HIV-positive persons not yet aware of their infection and that most persons greatly reduce risky behaviors upon learning they are infected. Therefore, identifying HIV-positive persons and linking them to medical, prevention, and other services as soon as possible after they become infected is critical to HIV prevention. This is primarily an issue for public health practitioners; however, with relatively little effort, clinicians and medical facilities where HIV-positive persons receive care can help address this problem and reduce transmission in the communities they serve. By asking HIV-positive patients to identify persons in their social networks who may be at risk for HIV and accompany or refer them to HIV counseling and testing sites, clinicians can help reach high-risk persons who might not be reached through other strategies. This strategy has been used in a Los Angeles HIV clinic, a Chicago CBO, and, more recently, in demonstration projects located in seven cities across the country.^{369–371} Although more evaluation is needed before this strategy is widely implemented, initial results are promising.

INCORPORATING PREVENTION INTO CARE

■ SPECIFIC MODELS OF HIV PREVENTION IN CLINICAL SETTINGS

Comprehensive HIV prevention programs for persons living with HIV should be multifaceted. Relatively few models for incorporating theory-based HIV prevention interventions for HIV-positive persons into clinical settings have been described. Three examples are PFH, the Options Project, and the Healthy Living Project (HLP).

■ PARTNERSHIP FOR HEALTH

PFH is a theory-based, individual-level intervention that is intended to reduce sexual HIV transmission risk behaviors among HIV-positive men and women and is delivered to patients by their regular HIV care providers during routine care visits. This intervention, which requires approximately 3–5 minutes at each visit, emphasizes the importance of a patient–provider team approach to help patients stay healthy and involves discussing safer-sex goals and risk-reduction behaviors; providing general prevention messages to all patients; and delivering brief, tailored prevention messages to high-risk patients. The messages focus on self-protection, partner protection, and serostatus disclosure. A randomized, controlled trial of PFH targeting HIV-positive patients in six California HIV clinics demonstrated that “loss-framed” messages emphasizing positive outcomes that may be missed or

negative outcomes that may occur if the patient engages in unsafe sexual behavior (e.g., “If you don’t use condoms, you may get another STD or a strain of HIV that’s resistant to the medications you’re taking.”) were associated with significant reductions in unprotected anal or vaginal intercourse among patients with high baseline risk.⁶¹

Patients in PFH are given informational brochures and flyers at the reception desk, and posters emphasizing the importance of patient–provider teamwork and providing prevention messages are displayed in waiting and examination rooms. Clinicians use the brochures, informational flyers, and posters to facilitate counseling. Clinician and patient identify specific behavioral goals for the patient, and the provider gives the patient referrals to other appropriate services. At subsequent visits, providers follow up on patients’ progress toward their behavioral goals, provide additional counseling, and reinforce patients’ healthful behaviors.

■ THE OPTIONS PROJECT

The Options Project is an individual-level, clinician-delivered intervention aimed at reducing risky sexual and drug-use behaviors among HIV-positive patients. This intervention, based on the Information–Motivation–Behavioral Skills model, involves providing critical information, increasing patients’ motivation to change risky behaviors, and developing their behavioral skills for risk reduction (e.g., negotiating condom use).⁷⁵ In the Options Project, clinician and patient together assess the patient’s sexual and drug-use behaviors, then (1) select a specific behavior to target for change; (2) identify conditions under which the behavior occurs; (3) evaluate the patient’s readiness to change the behavior; (4) rate the patient’s confidence for changing the behavior; and (5) identify specific strategies for changing the behavior. They negotiate a specific behavior change plan and the clinician gives the patient a written “prescription” for the plan. This intervention requires about 5–10 minutes incorporated into each routine clinic visit and has been found acceptable to providers and patients and feasible in practice; behavioral outcome data are not yet available.

■ HEALTHY LIVING PROJECT

Healthy Living Project (HLP) is an ongoing randomized trial of a theory-based intervention involving women, heterosexual men, IDUs, and MSM in four urban US sites.^{112,372} This multidimensional intervention is intended for use in clinical care settings and addresses three key issues faced by persons living with HIV: stress and coping, transmission risk behavior, and medication adherence. In the intervention trial, HLP is delivered in fifteen 90-minute structured sessions by trained, ethnically diverse facilitators with a wide range of backgrounds, including community-based service providers, social workers, counselors, and doctoral-level therapists. Behavioral outcome

data are not yet available from HLP. Because each session is 90-minute long, this intervention is not appropriate for delivery by clinical care providers during routine medical visits; however, it could be delivered by other staff in clinical settings.

CONCLUSION

Stagnating rates of new HIV infection in the United States require a shift in thinking about HIV prevention to a model that includes both persons at risk for acquiring HIV and individuals already infected and at risk for transmitting the disease to others. Medical providers have a unique opportunity to screen HIV-infected patients for risk behaviors, initiate discussions about these risk behaviors, and offer prevention messages and counseling in an ongoing manner in HIV care settings.

Providers should deliver brief prevention messages to all patients. They should use brief screening to open the door to broader discussion about each patient’s risk for transmitting HIV and to identify persons for whom more in-depth assessment of risk is necessary. For those with identified behavioral risks, they should conduct further assessment of the risk, including the patient’s knowledge about the level of risk posed by the behavior, circumstances surrounding the behavior, and attitudes the patient has about the behavior.

Risk discussions and counseling should be tailored to individual patients. A plan of action should be discussed with the patient and documented in the medical record in order to facilitate follow-up at subsequent visits. Referrals should be made if needed to help facilitate behavior change. All HIV-positive persons should receive PCRS at the time of diagnosis, and subsequently if there are indications that transmission may have occurred to additional partners. This is usually best done by consulting health department staff trained in PCRS.

Structural approaches, such as development of risk screening tools for use by all providers in the clinic or identification of a prevention counselor may facilitate more rapid adoption of prevention in care by providers and greater acceptance from patients. Resources are available for providers and staff who do not feel they have the comfort or skill level to undertake risk discussions.

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Antiviral Therapy of Human Immunodeficiency Virus Infection

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Human immunodeficiency virus type 1 (HIV-1) causes a chronic viral illness that results in a gradual destruction in the host immune system manifested primarily as a loss in CD4⁺ lymphocytes and the occurrence of infections, malignancies, and other signs of immune impairment. The interaction between the infected host and HIV-1 is a complex interplay between viral replication and immune containment. Reduction, and perhaps eventually elimination, of HIV-1 replication is the goal of therapy. Antiretroviral therapy has been shown to improve the clinical course of HIV-1 disease and to result in prolongation of survival. In developed countries, the mortality from HIV-1 disease has dropped dramatically and opportunistic diseases and hospitalizations have decreased substantially. Over the last several years, antiretroviral therapy has become even more effective,¹ and the complex nature of highly active antiretroviral therapy (HAART) has been markedly simplified. The availability of a pill that allows three of the most commonly used antiretroviral agents to be coformulated in a single once daily dose emphasizes this point.

BRIEF OVERVIEW OF THE HIV-1 REPLICATION CYCLE

A retrovirus in the lentivirus subfamily, HIV-1 contains two single-stranded RNA molecules as its genome. The replication cycle of this virus requires attachment to the host-cell membrane (usually by an interaction between the viral envelope glycoprotein gp120 and the host cell CD4⁺ receptor), engagement of a second receptor on the cell surface, CCR-5 or CXR-4, fusion and entry into cell cytoplasm, followed by uncoating of the viral capsid, reverse transcription of HIV-1 RNA to proviral DNA, which is then transported to the cell nucleus. Once in the nucleus, the double-stranded DNA is integrated into the host chromosome by the HIV-1 integrase enzyme. The provirus can then remain latent and unexpressed, or RNA transcripts can be produced that allow replication to continue. The transcription of full-length HIV-1 RNA depends on interactions between host transcriptional

factors (NFkB and others) and the products of viral regulatory genes (e.g., *tat* and *rev*). Once full-length transcripts are formed, they are transported out of the nucleus and translated into proteins. These proteins are processed by proteolytic cleavage, and the envelope protein is glycosylated. The gag, pol, and protease proteins are produced as one polyprotein that requires cleavage by the HIV-1 protease enzyme for appropriate assembly of the HIV-1 nucleocapsid. During the final assembly of the nucleocapsid around the genomic RNA molecules, the viral particle buds from the cell to complete the life cycle.

Any process in the viral replication cycle that can be inhibited in a relatively specific manner is a potential target for antiretroviral therapy. Each of the three steps in HIV entry, attachment of gp120 to CD4⁺, binding to the chemokine coreceptor, and fusion with the cell membrane, has been successfully inhibited and an antiretroviral effect has been demonstrated.²⁻⁸ Enfuvirtide (ENF, T-20), which inhibits HIV fusion, is used frequently in highly treatment experienced patients.^{9,10}

Viral uncoating may be another step at which HIV can be inhibited. The human protein cyclophilin A appears to be used by some HIV-1 isolates in this step prior to reverse transcription, perhaps to prevent cellular degradation of the viral capsid and RNA.¹¹ Cyclosporine has been shown to inhibit HIV-1 in vitro perhaps by binding to cyclophilin A and interfering with capsid binding. Small molecule analogs of cyclosporine have now been developed that do not bind to calcineurin (avoiding the immunosuppressive effects of cyclosporine), but retain cyclophilin A binding and have anti-HIV effects in vitro.¹²

Reverse transcription has been one of the most successful targets for antiretroviral therapy. Reverse transcriptase inhibitors can be divided into two categories. One class of compounds are analogs to endogenous nucleosides and require phosphorylation to have activity against HIV-1. These are nucleoside and nucleotide analogs, and include zidovudine (ZDV), didanosine (ddI), stavudine (d4T), lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and

emtricitabine (FTC). These compounds when phosphorylated act as competitive inhibitors and chain terminators of the elongating DNA strand produced during reverse transcription. The second class of compounds, collectively known as nonnucleoside reverse transcriptase inhibitors (NNRTI), interacts with the reverse transcriptase in a noncompetitive manner, does not require phosphorylation for activity, and has extremely potent inhibitory activity *in vitro*. Nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV) are the currently available NNRTI, though additional agents are in development.

The movement of double-stranded HIV-1 DNA from the cellular cytoplasm to the nucleus may require specific nucleotide-binding sequences that interact with a transporter protein. The intracellular steroid receptor may be such a transporter protein, and interaction with the HIV regulatory protein *vpr* may be important in transport.¹³ Mifepristone, which is an inhibitor of the steroid receptor, has been shown to have anti-HIV effects *in vitro*;¹⁴ however, an *in vivo* proof of principle study showed no activity.¹⁵

HIV-1 encodes an integrase that allows incorporation of HIV-1 DNA into the host chromosomal DNA. This step is essential for the completion of the replication life cycle of HIV-1. In addition, integration and latent infection of resting CD4⁺ memory T cells is a substantial barrier for the eradication of HIV-1 infection.¹⁶ HIV-1 encodes three enzymes and while antagonists of RT and protease have been highly successful, inhibitors of HIV integrase that have favorable pharmacokinetics and acceptable preclinical safety profiles have been very difficult to develop. Inhibitors of HIV-1 integrase that rely on inhibition of the strand transfer step of HIV DNA integration into the cellular DNA have now reached clinical trials.^{17–20}

Control of transcription and translation of HIV-1 is a complex process that is influenced by cellular proteins and HIV-1 proteins such as *tat* and *rev*. Inhibitors of these HIV-1 proteins offer the promise of high specificity, although, as yet, no compounds with clinical activity have emerged.²¹

HIV-1 proteins require posttranslational modification prior to their incorporation into viable HIV-1 particles. The *gag* structural proteins and enzymes are translated as one polyprotein that must be cleaved into smaller protein components by the HIV-1 protease. Inhibitors of the HIV-1 protease have demonstrated potent *in vivo* activity²² that has translated into antiretroviral and clinical efficacy when given in the context of combination therapy.^{23–25} More recently, maturation of the *gag* proteins has also been inhibited *in vitro* and *in vivo* by blocking a specific *gag* cleavage site.²⁶ Later steps in the HIV-1 life cycle also may be amenable to inhibition, such as viral particle assembly or modification of viral glycoproteins by cellular glycosidases. As further information is gained about the replication cycle of HIV-1, newer or more precise targets for inhibition may be revealed.

HIV DISEASE PATHOGENESIS

Before discussing the clinical evaluation and application of antiviral therapies for HIV-1 infection, it is important to consider disease pathogenesis as it applies to therapeutic strategies. The duration of time from initial infection to onset of the defining symptoms and signs of AIDS can vary greatly, ranging from less than 3 years in some individuals to potentially as long as several decades.

PRIMARY INFECTION

Following exposure to HIV-1, most newly infected individuals experience a high initial level of HIV-1 replication, as measured by plasma HIV-1 RNA, and large numbers of T lymphocytes are infected, especially, it appears, in gut lymphatic tissue.^{27–32} HIV-1 rapidly disseminates to multiple body compartments including the gastrointestinal tract, central nervous system, and genital tract.³³ The level of viral replication and viremia is such that many persons experience an acute illness with lymphadenopathy and fever, sometimes accompanied by rash, pharyngitis, or aseptic meningitis.³⁴ Viral replication results in destruction of host CD4⁺ cells, with detectable decreases in CD4⁺ lymphocyte counts in the peripheral blood, occasionally declining to levels seen in later stages of the disease. These individuals may rarely become clinically immunocompromised, such that minor infections (thrush, herpes zoster, vaginal candidiasis) or AIDS-defining opportunistic infections (candida esophagitis, pneumocystis pneumonia) occur during this period. Whether therapeutic intervention during this early period of intense viral replication has either short- or long-term benefit remains an open question.³⁵ An early study of individuals with acute or early infection treated with only zidovudine was suggestive of a modest effect.³⁶ Whether other, more potent therapies would result in more profound improvements in CD4⁺ cell counts and in a delay in the appearance of HIV-1 disease-related symptoms or mortality remains unknown, although recent nonrandomized trials suggest a modest benefit.^{37,38} Several small, noncomparative studies suggested that the early therapy preserved HIV-specific immune function, though these benefits seem to wane over time.^{39–42}

LYMPH NODE DISSEMINATION AND DISEASE PROGRESSION

Following the primary infection period when HIV-1 is disseminated systemically, the host produces a cellular and humoral immune response that coincides with a marked decrease in HIV-1 replication, as measured by HIV-1 RNA levels in plasma.⁴³ During this period of clinical quiescence, infected individuals may be completely asymptomatic or have only minor signs or symptoms. This period can vary markedly in length,

though the median time from infection to first AIDS-defining symptom is 8–10 years.^{44,45} In most infected individuals, HIV-1 disease progression, involving progressive lymph node destruction and CD4⁺ cell count decline and ongoing replication of HIV-1, continues to occur during this period. The pace of disease progression is dictated by many factors, both viral and host. HIV RNA levels in plasma vary from individual to individual. Steady state or set point levels are established approximately 6 months following infection and are relatively stable over time. Plasma HIV RNA level correlates with CD4⁺ cell decline and disease progression in the absence of therapy.^{46–49} However, plasma HIV RNA level explains only a small fraction of CD4⁺ cell decline⁵⁰ and after more than two decades of study, the exact mechanisms of CD4⁺ cell loss are still debated. It is likely multifactorial and includes direct viral killing, apoptosis, and chronic immune activation.⁵¹ A more profound impact of the initial unchecked acute infection on CD4⁺ cell depletion has recently been postulated.^{31,32,52} Host factors also appear to affect disease progression.^{53–56}

In most individuals, HIV-1 infection is a very dynamic process, even during the clinically quiescent period, with marked virus replication and CD4⁺ cell turnover.^{57–59} These observations have important implications for the use of antiretroviral therapy. Given the underlying mutation rate of the HIV-1 reverse transcriptase enzyme of approximately one error per 10,000 base pairs,⁶⁰ and the replication rate of HIV-1 in the human host, the likelihood of resistance development during suboptimal treatment is high.⁶¹ This likelihood is especially high if single-drug therapies or even combination-drug therapies with only incomplete, modest suppression of HIV-1 replication are used. Hence an overriding goal of antiretroviral therapy is to suppress HIV-1 replication to the greatest extent possible. For most who are infected with HIV-1 disease, progression occurs in the absence of therapy. As peripheral blood CD4⁺ cell counts diminish, clinical signs and symptoms (e.g., fevers, malaise, weight loss) develop and opportunistic infections or neoplasms may occur.

HIV-1 DISEASE MARKERS: ASSESSING DISEASE PROGRESSION AND ANTIRETROVIRAL THERAPY RESPONSE

Disease staging is important for estimating the prognosis for an individual, as well as for epidemiologic and natural history studies. Disease staging is also an integral part of the clinical study of antiretroviral therapy and the use of antiretroviral and prophylactic therapies in clinical practice. The evaluation of antiretroviral agents relies on the effect of the agent or agents being studied on markers of HIV-1 disease, in particular, plasma HIV-1 RNA levels. Clinical endpoints such as disease progression and death have been used to validate the predictive capacity of surrogate markers both in the absence and presence of antiretroviral therapy and are now rarely

used as the primary endpoints in clinical trials of antiretroviral therapy. CD4⁺ cell counts and HIV RNA levels are used commonly in clinical practice to help clinicians estimate an individual's risk of disease progression prior to and after initiation of the antiretroviral therapy and to monitor the response to the antiretroviral treatment.

■ CD4⁺ CELL COUNT

CD4⁺ cell counts have been used as indicators of disease stage in HIV-1-infected patients for over 20 years. CD4⁺ cell counts are predictors of disease progression independent of disease duration or clinical symptoms, and can be used in conjunction with clinical symptoms to provide staging for an individual patient or a population of patients, and to compare groups of patients across different studies. The likelihood of specific opportunistic infections is related to the CD4⁺ cell count.^{62,63} In the context of HIV disease progression or response to therapy, the CD4⁺ count or a change in the CD4⁺ cell count explains only a fraction of the clinical progression rates or clinical responses to antiretroviral therapy.⁶⁴ Including clinical symptoms in the algorithms improves the prognostic value of these observations.⁴⁴

■ HIV-1 RNA LEVELS IN PLASMA

The ability to measure HIV-1 RNA levels in plasma led to fundamental changes in the understanding of HIV-1 pathogenesis, the prognostication of disease progression, the evaluation of antiretroviral agents, and the understanding of clinical progression in the context of antiretroviral treatment. Many groups have shown that measurement of HIV RNA levels, in conjunction with, and independent of, CD4⁺ cell counts, markedly improves the ability to predict the rate of disease progression.^{47–49,65,66} Individuals with low CD4⁺ cell counts and high HIV RNA levels progress to AIDS events or death most rapidly, whereas those with low HIV RNA levels and high CD4⁺ cell counts progress more slowly (Fig. 73-1). Measurement of plasma HIV-1 RNA levels in conjunction with potent antiretroviral therapy led to our understanding of the HIV-1 disease as a very dynamic state, with large numbers of virions produced daily and rapid turnover of infected, activated CD4⁺ cells with half-lives of the order of 1 to 2 days.^{57–59} Taken together, HIV-1 RNA level and CD4⁺ cell count provide important prognostic information of the likelihood of progression to AIDS in the absence of antiretroviral therapy (Fig. 73-1).

■ OTHER MARKERS

The combination of HIV RNA levels in plasma and CD4⁺ cell counts does not explain all the variability in disease progression that occurs from individual to individual. Additional viral factors are also likely have some role. The discovery of

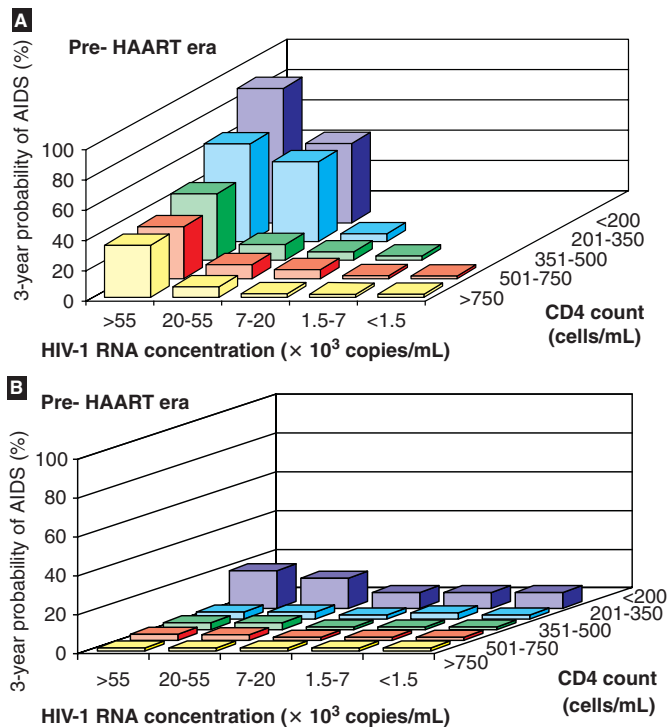


FIGURE 73-1 A. Three-year probability of AIDS by CD4⁺ cell count and HIV-1 RNA level prior to the highly active antiretroviral therapy (HAART) era and in the setting of HAART.⁶⁷ B. This figure represents a replication of the MACS analysis using data from the ART-Cohort Collaboration based on 5152 drug-naïve homosexual men who started HAART between 1996 and 2000 and is a Kaplan Meier estimate of the 3-year probability of AIDS by baseline CD4⁺ cell count and HIV-1 RNA level prior to antiretroviral therapy in the HAART era.⁶⁷

the second cellular receptors that must be engaged after the virus binds to the CD4⁺ molecule furthered our understanding of HIV pathogenesis.^{68,69} Two chemokine receptors, CCR5 and CXCR4, are the major chemokine receptors demonstrated to be used by the virus. HIV-1 variants may use CCR5 or CXCR4 exclusively or they may be dual tropic. An HIV-1-infected individual may have variants that use only CCR5 (R5 variants), primarily CXCR4 (X4 variants), or a mixture of variants, some using CCR5 some CXCR4, and some that can use both receptors.⁷⁰ Rarely, infected individuals have only X4 variants. Initially, most individuals are infected with R5-using variants. In some patients, X4 variants or variants that can use both CCR5 and CXCR4 emerge and this emergence is often associated with more rapid CD4⁺ cell decline and clinical progression,^{71,72} suggesting that X4 and dual tropic variants may be more pathogenic. In addition, virions lacking a key regulatory gene (*nef*) have been associated with slower disease progression.^{73,74} Host genetic factors may play a role in HIV disease progression independent of HIV RNA and CD4⁺ cell counts. Individuals lacking functional CCR5 receptors are much less likely to be infected with HIV-1,⁷⁵ and those who are heterozygous for the gene encoding the dysfunctional receptor, generally have HIV disease progress more slowly.^{76,77} Evaluation of multiple genetic factors may improve the prognostic value of these

assessments. An analysis that included multiple CCR5 genetic polymorphisms and the number of CCR5 ligand genes demonstrated that these host genetic factors are a very strong predictor of HIV disease progression.⁵⁵ An individual's HLA type also influences HIV disease progression.^{53,78} Simple factors such as an individual's age at the time of infection influence HIV disease progression, likely due in part to decreasing thymic function with increasing age.^{79–81} The sex of the individual or HIV-1 acquisition risk category does not appear to affect the rate of disease progression but gender may affect the relationship between CD4⁺ cell count and HIV RNA values and prognosis in the absence of antiretroviral therapy.⁸²

PROGNOSTIC MARKERS IN THE CONTEXT OF ANTIRETROVIRAL THERAPY

In the context of initial HAART, CD4⁺ cell counts and plasma HIV-1 RNA levels also are predictive of disease progression. In a landmark paper, Egger and colleagues demonstrated that in treatment-naïve individuals who were starting combination antiretroviral therapy, including at least three agents, baseline CD4⁺ cell count remained a strong predictor of overall mortality and progression to AIDS or death (Fig. 73-1).⁶⁷ Compared to individuals who began HAART with CD4⁺ cell counts less than 50/mm³ individuals in higher CD4⁺ group strata were progressively less likely to advance to AIDS or die during the observation period. For example, compared to those with CD4⁺ cell counts <50/mm³, individuals with CD4⁺ cell counts between 100–150/mm³ were half as likely to progress and those with CD4⁺ >350 cells/mm³ were approximately six times less likely to have an AIDS event or die. Plasma HIV RNA level prior to initiation of HAART was only predictive of disease progression if the viral load was >100,000 c/mL (Fig. 73-1). These results contrast with earlier studies in the pre-HAART era, when baseline plasma HIV RNA was a strong predictor of disease progression in the setting of non-HAART antiretroviral therapy.^{83,84} When the initial therapy is HAART, other independent predictors of disease progression were injection drug use, increasing age, and a previous AIDS-defining illness.⁶⁷ These data allow one to estimate an individual's risk of disease progression prior to initiating HAART. Once therapy is initiated, an individual's response to therapy is the overwhelming predictor of subsequent disease progression, trumping pretherapy plasma HIV RNA level and CD4⁺ cell count. In a follow-up study from the Antiretroviral Therapy Cohort Collaboration, Chene and colleagues analyzed the response to HAART by stratifying patients by their CD4⁺ cell counts and HIV RNA levels 6 months after HAART initiation.⁸⁵ In this analysis, both on-therapy CD4⁺ cell count and HIV RNA were predictive of subsequent disease progression or death. Over a 3-year follow-up period, the likelihood of AIDS progression or death in individuals in the lowest risk group (HIV RNA <500 q/mL and CD4⁺ cell count >350 cells/mm³) on therapy

was only 2.4%, whereas those who failed to respond ($CD4^+ < 25$ cells/ mm^3 and HIV RNA $> 100,000$ c/mL) had a greater than 80% probability of further AIDS events or death. Baseline $CD4^+$ cell count and plasma HIV RNA were no longer predictive of outcome when 6 month parameters were included in the model.

SPECIFIC ANTIRETROVIRAL THERAPIES

OVERVIEW

For individuals with HIV-1 infection requiring treatment, a combination of three or more agents (HAART) is the standard of care, both in the developed and the developing world. HAART has had a dramatic effect on survival and AIDS progression in the United States, other developed countries, and in the developing world.^{86–88} An important caveat in the treatment of HIV infection is that outcomes for patients improve when care is provided by clinicians with expertise in HIV treatment.^{89–91}

CURRENT RECOMMENDATIONS

The current recommendations for initial HIV-1 antiretroviral therapy in the United States are straightforward and relatively consistent between the two main guideline panels, the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents and the International AIDS Society USA (IASA-USA)^{92,93} (Table 73-1). The goal of the therapy is to suppress plasma HIV RNA levels to below the limit of detection, using the most sensitive assay available. For initial therapy, this goal should be possible for nearly all patients who can tolerate and adhere to the treatment.

A summary of recommendations for initial therapy is shown in (Table 73-1). For initial therapy, the DHHS guidelines allow for selection from a variety of preferred regimens. The basic recommendation is to select two nucleoside reverse transcriptase inhibitors (NRTI), one of which is lamivudine (3TC) or emtricitabine (FTC), plus either an NNRTI (efavirenz [EFV] is the preferred agent),^{94–96} or a protease inhibitor that is pharmacologically boosted by low-dose ritonavir (lopinavir/ritonavir [LPV/r], fosamprenavir/r, or atazanavir/r are the current preferred protease inhibitors).^{25,97} The second NRTI in the preferred regimen is either zidovudine (ZDV) or tenofovir (TDF). Recently, TDF, FTC, and EFV were shown to be superior to ZDV, 3TC, and EFV in a large randomized open-label study.⁹⁸ TDF, FTC, and EFV can now be administered together in a single coformulated pill once daily.

Multiple alternatives to these initial preferred regimens are listed in the DHHS guidelines. An important concept is that initial, as well as subsequent regimens should be tailored to the individual patient, taking into account her/his medical

conditions, concomitant medications, life style, and social supports. All alternative regimens include FTC or 3TC in first-line therapy. Nevirapine (NVP) is the alternative NNRTI, while there are multiple choices for alternative protease inhibitors (see Table 73-1). Abacavir (ABC) and didanosine (ddI) are considered alternatives to ZDV or TDF. Though the triple NRTI regimen of abacavir/lamivudine/zidovudine has been shown to be inferior to zidovudine/lamivudine and EFV,⁹⁵ this triple NRTI regimen, which is available as a fixed-dose combination, is still considered an acceptable therapy in certain clinical situations. Currently there is no evidence that more than three agents (not inclusive of low-dose RTV) are needed for initial treatment of HIV-1 infection, even in settings of high plasma viral load or low $CD4^+$ cell counts.^{99,100}

The IAS-USA guidelines for initial therapy are similar to the DHHS guidelines (Table 73-1).⁹² Protease Inhibitor choices include LPV/r, saquinavir with low-dose RTV (SQV/r), atazanavir with low-dose RTV (ATV/r), and fosamprenavir with low-dose RTV; the latter has been shown to be comparable to LPV/r in a large randomized comparative trial.⁹⁷ These guidelines list three dual nucleoside combinations, TDF/FTC, ZDV/3TC, and ABC/3TC, all of which are available in fixed-dose combinations. Efavirenz and nevirapine are recommended components of initial therapy, though nevirapine has significant limitations on its use because of rash and hepatotoxicity. Women with $CD4^+$ cell counts > 250 cells/ mm^3 and men with > 400 cell/ mm^3 should not be given NVP because of potential hepatotoxicity.

Certain combinations of antiretrovirals should be avoided. Stavudine and ZDV are antagonistic in vitro and in vivo.^{101,102} Stavudine and ddI lead to substantial serious toxicity such as peripheral neuropathy, lactic acidosis, and pancreatitis.^{96,103–106} The combination of TDF and ddI has been associated with declines in $CD4^+$ cell counts, especially if the ddI dose is not appropriately dose reduced^{107–111} and in combination with EFV, TDF plus ddI may result in more rapid virologic rebound.^{112,113} Therefore, this NRTI combination (even if ddI is appropriately dose adjusted) should not generally be used in initial therapy regimens. Two triple nucleoside combinations, ABC/TDF/3TC and ABC/ddI/3TC, also should not be used as initial therapy because of observed rapid plasma HIV RNA rebounds and emergence of resistance.^{114,115}

Combinations of NNRTI have not demonstrated any additional benefits to antiretroviral regimens with only one NNRTI. Combinations of protease inhibitors, especially with RTV-boosting, have been described in many noncomparative studies. While there may be added efficacy benefit in combining two or more PI in treatment-experienced patients with PI-resistant virus, the limited evidence for added activity, the risk of negative pharmacological interactions,¹¹⁶ and the added regimen complexity suggest that combinations of boosted protease inhibitors should not be used in antiretroviral regimens in treatment-naive patients.

Table 73-1. Preferred and Alternative Regimens for Initial Antiretroviral Therapy as Recommended by the DHHS and IAS-USA guidelines^{92,93} An NRTI Combination Plus Either a PI or NNRTI Are Recommended

Class	Medication	Recommendation
NRTI	Tenofovir/emtricitabine ^{a,b}	Preferred (IAS-USA and DHHS)
	Zidovudine/lamivudine ^{a,b}	Preferred (IAS-USA and DHHS)
	Abacavir/lamivudine ^{a,b}	Preferred (IAS-USA) Alternative (DHHS)
	Didanosine and lamivudine or emtricitabine	Alternative (DHHS)
NNRTI	Efavirenz ^c	Preferred (IAS-USA and DHHS)
	Nevirapine ^d	Preferred (IAS-USA) Alternative (DHHS)
PI	Atazanavir plus ritonavir	Preferred (IAS-USA and DHHS)
	Fos-amprenavir plus ritonavir (twice daily)	Preferred (IAS-USA and DHHS)
	Lopinavir/ritonavir ^a (twice daily)	Preferred (IAS-USA and DHHS)
	Saquinavir plus ritonavir	Preferred (IAS-USA)
	Atazanavir ^e	Alternative (DHHS)
	Fos-amprenavir	Alternative (DHHS)
	Fos-amprenavir plus ritonavir (once daily)	Alternative (DHHS)
	Lopinavir/ritonavir ^a (once daily)	Alternative (DHHS)

^aFixed-dose combinations (FDC).

^dEmtricitabine may be used in place of lamivudine and vice versa (not available as FDC).

^cEfavirenz is not recommended for use in the first trimester of pregnancy or in sexually active women who are not using effective contraception.

^dNevirapine should not be initiated in women with CD4⁺ cell counts >250/mm³ or men with CD4⁺ cell counts >400/mm³.

^eAtazanavir should be boosted with ritonavir when given with tenofovir.

The nucleoside sparing combination of a protease inhibitor (with or without RTV boosting) plus an NNRTI has been studied most recently in a large comparative trial that also examined EFV and two NRTI and LPV/r and two NRTI. In this study, EFV plus LPV/r had similar antiviral efficacy to EFV, 3TC, and either ZDV, d4T, or TDF.¹¹⁷ Nucleoside-sparing regimens are not yet recommended for initial therapy in the DHHS or IAS-USA guidelines (Table 73-1).

■ SPECIFIC CLASSES

Four classes of antiretroviral agents have been studied extensively. These classes are nucleoside analog reverse transcriptase inhibitors, NNRTIs, HIV-1 protease inhibitors, and an inhibitor of the fusion step of HIV-1 entry. Over 20 antiretroviral agents have been approved in

the United States for HIV-1 treatment, and several fixed-dose combinations are available.

REVERSE TRANSCRIPTASE INHIBITORS

■ NUCLEOSIDE AND NUCLEOTIDE ANALOGS

Nucleoside and nucleotide analog reverse transcriptase inhibitors are phosphorylated intracellularly to triphosphorylated active metabolites. They inhibit viral replication by competing with endogenous nucleotides for incorporation into the elongating HIV-1 DNA that is being synthesized from the HIV-1 RNA genome by the viral reverse transcriptase. Once incorporated, these agents terminate chain elongation because the 3' carbon lacks a hydroxyl group necessary for the addition of additional nucleotides.¹¹⁸ Some of the toxicity observed with these agents result from their affinity

for human DNA polymerases, though the affinity is less than that for the HIV-1 reverse transcriptase. The relative affinity of these agents for specific human DNA polymerases, in particular mitochondrial DNA polymerase gamma, varies for the different agents and may explain, in part, their differing toxicities. A toxicity associated with the class is lactic acidosis with hepatic steatosis, which may be due to effects on NRTI on mitochondrial function.

Zidovudine

Zidovudine (3'-azido-2', 3'-dideoxythymidine—ZDV, AZT, or Retrovir and a component of combivir and trizivir) is a thymidine analog with an azido group at the 3' location of the ribose ring. After triphosphorylation by cellular kinases, it competes with deoxythymidine triphosphate for reverse transcriptase binding and then terminates HIV-1 DNA chain elongation. Zidovudine is well absorbed orally (60–65% bioavailability). The ZDV serum half-life is short (1–1.5 hours), but the intracellular half-life of ZDV-triphosphate may be up to 4 hours¹¹⁹ and activity may correlate best with intracellular ZDV triphosphate levels.¹²⁰ Zidovudine penetrates into the cerebrospinal fluid (CSF) well.^{121,122} The current recommended dose is 300 mg twice daily. Zidovudine is metabolized predominantly by the liver via glucuronidation, and its one metabolite does not have antiretroviral activity. Agents that affect glucuronidation may affect ZDV metabolism.¹²³

The predominant long-term toxicity of ZDV is hematological, particularly anemia and neutropenia. When ZDV is administered at 600 mg/day to patients with less advanced disease or who are asymptomatic, hematological toxicity occurs less frequently.^{98,124} Headache and nausea have been associated with ZDV therapy, though in some controlled trials of combination therapy, these symptoms do not always occur at a substantially greater frequency than with non-ZDV HAART combinations.^{98,124} An additional toxicity seen in patients on prolonged ZDV therapy is myopathy, which is usually reversible with discontinuation of therapy.

Zidovudine as monotherapy was the first antiretroviral shown to improve survival in patients with AIDS.^{125,126} In combination with 3TC, ZDV was shown to be superior to either drug alone or other nucleoside combinations.^{127–129} Most importantly, in combination with 3TC and either NNRTI or protease inhibitors, ZDV has been one of the key components of many efficacious HAART regimens. ZDV along with either 3TC or FTC is a preferred nucleoside when combined with a PI or NNRTI for initial antiretroviral therapy in both the DHHS or IAS-USA guidelines (Table 73-1).^{92,93}

Variants of HIV-1 resistant to ZDV have been isolated from many patients receiving ZDV therapy, especially when it was given as monotherapy or in a dual nucleoside combination. Amino acid changes at five separate codons of the HIV-1 reverse transcriptase have been associated with HIV-1

resistance to ZDV, and these mutations are now referred to commonly as thymidine analog mutations or TAMs.^{130–133} These mutations lead to substantial cross-resistance to other nucleoside analogs. When ZDV is given in combination with 3TC and either an NNRTI or a boosted protease inhibitor as part of initial therapy, emergence of these TAM mutations is uncommon in virologic failure.^{25,98,99,134}

Didanosine

Didanosine (2' 3'-dideoxyinosine—ddI or Videx) is an adenosine analog that lacks a hydroxyl group at the 3' location. The active metabolite of ddI is dideoxyadenosine triphosphate (ddATP). Didanosine is absorbed poorly in an acid environment or in the presence of food and is available as an enteric coated formulation¹³⁵ or as buffered tablets or solutions. Didanosine should be administered either 30–60 minutes prior to eating or 2 hours after eating,¹³⁶ though with the enteric-coated formulation the effect of food on absorption is less.¹³⁷ The half-life of ddI in serum ranges from 0.6 to 2.8 hours, and the intracellular half-life of ddATP is 12–24 hours.¹³⁸ ddI is administered as 400 mg once daily, with dose adjustments for individuals weighing less than 60 Kg.

The long-term toxicity of ddI may include idiosyncratic pancreatitis, dose-dependent peripheral neuropathy, and less commonly, lactic acidosis.^{96,104,106,139–143} With correct dosing and dose adjustment, the incidence of peripheral neuropathy and pancreatitis in large-scale clinical trials of ddI is diminished, especially if the combination of ddI with d4T is avoided. Additional adverse effects of ddI included nausea, bloating, abdominal pain, and diarrhea, though these are much less common with the newer enteric-coated formulation.¹³⁵

As a component of HAART initial therapy, many early ddI studies combined this agent with stavudine (d4T), sometimes with the addition of hydroxyurea.^{96,139,144,145} Although in some studies these ddI-containing combinations had similar activity to other HAART regimens,¹⁴⁴ the combination of ddI, d4T, and either EFV or nelfinavir was shown to be inferior to ZDV/3TC/EFV in a large randomized trial.⁹⁶ These and similar results coupled with the recognition that ddI/d4T, with or without hydroxyurea, had substantial toxicity, predominantly peripheral neuropathy and pancreatitis,^{96,104,106,139–143} have diminished the use of this NRTI combination as a component of HAART, and it is now considered a combination that should be avoided.^{93,146} More recently, ddI combined with emtricitabine (FTC) and EFV was shown to be superior to ddI, d4T, and EFV in treatment-naïve subjects in a large randomized trial.¹⁴⁷ However, given the potential toxicity of ddI, this combination is considered an alternative 2 NRTI component of HAART, as opposed to a preferred 2 NRTI component (Table 73-1).^{93,146} Combinations of ddI with other NRTI such as TDF as a component initial therapy have led to disappointing antiviral responses, perhaps due to a specific interaction between drug-resistance mutations, and should be avoided.^{112,113}

Didanosine may have greater utility in treatment experienced patients with some degree of nucleoside analog resistance. Even in the setting of multiple nucleoside analog associated mutations (NAMs) and the M184V mutation associated with 3TC and FTC, didanosine still has clinically relevant activity¹⁴⁸ that may be harnessed in the context of combination second line or salvage therapy. These results have to be tempered somewhat by the demonstration of an interaction between tenofovir (TDF) and ddi that appears to result in diminished CD4⁺ cell responses even when plasma HIV RNA responses are robust. These effects appear to be most prominent when ddi is given at full dose (400 mg once daily).^{107–111} The use of the combination of ddi and TDF in the context of multidrug salvage regimens should always include appropriate ddi dose adjustment and be limited to situations where the potential antiviral activity of the combination outweighs the potential for a less robust CD4⁺ cell response. Isolates of HIV-1 resistant to ddi have been well described.^{149–152} The signature mutation for ddi resistance occurs at RT gene codon 74; however, combinations of other NAM and the M184V mutation also diminish the effectiveness of ddi to some degree.^{153,154}

Stavudine

Stavudine (3'-deoxy-2', 3'-didehydrothymidine-d4T or Zerit) is a thymidine analog with an oral bioavailability of 60–80%, a serum half-life of 1.5–2 hours, and an intracellular half-life as the triphosphate metabolite of 3–4 hours.^{155–157} Stavudine is excreted by both renal and nonrenal routes, with approximately 40% of an oral dose excreted unchanged in the urine.¹⁵⁸ The standard dose of d4T is 40 mg twice daily, reduced to 30 mg twice daily in persons who weigh less than 60 kg. No significant drug-drug interactions have been described.

The initial administration of d4T is usually well tolerated. Long-term toxicity includes sensory polyneuropathy, lipoatrophy, lactic acidosis, and increased triglycerides,^{94,104,140,159} which may be related to the effect of stavudine and other NRTI on mitochondrial DNA polymerase.^{105,160}

Stavudine with lamivudine and either an NNRTI or a ritonavir-enhanced protease inhibitor has been shown to be very effective antiretroviral combination for initial therapy.^{25,94,161} When d4T is combined with ddi and an NNRTI or nelfinavir, the regimen is less effective than 3TC or FTC-based therapy.^{96,147} Stavudine use is now limited by its metabolic toxicity. Use in the developing world remains considerable because of its inexpensive and convenient generic formulations. However, recent World Health Organization (WHO) Guidelines urge caution in using stavudine as a component of first-line therapy.¹⁶²

Mutations in the reverse transcriptase gene that are specific to d4T resistance have been described but appear uncommon,¹⁶³ TAMs, first described as selected for by zidovudine, are

also selected for by stavudine,¹⁶⁴ and cross-resistance between stavudine and zidovudine is believed to be extensive.

Lamivudine

Lamivudine (3TC or Epivir) is the (-)-enantiomer of the cytosine analog 2'-deoxy-3'-thiacytidine, which contains a sulfur atom in the ribose ring. This compound also lacks a 3' hydroxyl group. In addition to in vitro activity against HIV-1 and HIV-2, 3TC also inhibits hepatitis B virus (HBV) and has antiviral activity in patients with chronic active hepatitis B.^{165–167} Lamivudine has an oral bioavailability of greater than 80% in adults and greater than 60% in children.¹⁶⁸ The serum concentration is unaffected by food, and the intracellular half-life of 3TC triphosphate is 12–18 hours.¹⁶⁹ 3TC is administered either 150 mg twice daily or 300 mg once daily, and is frequently used in fixed dose combinations with zidovudine (Combivir), abacavir (Epzicom), or both (Trizivir). Lamivudine is excreted predominantly by the kidney, and dose reduction is required in patients with moderate-to-severe renal failure.

3TC appears to have relatively limited toxicity. In early studies of 3TC monotherapy, dose-limiting toxicity was not observed. At doses higher than currently recommended, neutropenia was observed in a minority of subjects.^{168,170,171} Mild headache may occur with the use of 3TC, but the addition of 3TC to ZDV appeared to show no additional adverse effects than those seen with ZDV alone.¹²⁷

Lamivudine and the similar compound emtricitabine (see below) are the key components of any initial regimen for treatment-naïve patients (Table 73-1).^{92,93} 3TC with zidovudine, stavudine, abacavir, or TDF in combination with an NNRTI or a ritonavir-enhanced PI has demonstrated consistent efficacy in large comparative trials in treatment-naïve patients.^{25,94,96–98,161,172}

Resistance of HIV-1 to 3TC develops rapidly in vitro and is common in HIV isolates from patients treated with 3TC who rebound on therapy.^{173–175} A single amino acid substitution at codon 184 (methionine to isoleucine or valine; M184V) of the reverse transcriptase results in a 100- to 1000-fold decrease in activity of the drug in vitro. A virus that contains this mutation may also have a decreased replicative capacity,¹⁷⁶ and despite high-level resistance, 3TC has been shown to have a persistent modest effect in vitro.¹⁷⁷ In infected individuals, 3TC clearly has a persistent effect on HIV-1 replication and viral load, even when the M184V mutation is present, and this persistent effect results in blunted CD4⁺ cell declines.^{127,178–180} The 3TC resistance mutation also impacts resistance to other agents. When the M184V mutation is introduced into virions with high-level resistance to ZDV, these virions frequently regain sensitivity to ZDV,¹⁸¹ and M184V also likely increases susceptibility to stavudine and TDF.^{182,183} This mutation results in a low level of cross-resistance to ddi, ddC, and abacavir.^{184,185}

Abacavir

Abacavir (ABC; Ziagen) is a carbocyclic 2'-deoxyguanosine nucleoside analogue that undergoes intracellular metabolism by a unique set of intracellular enzymes to a 2'-deoxyguanosine nucleoside analogue that is triphosphorylated (carbovir triphosphate) and inhibits HIV reverse transcriptase via chain termination. Carbovir triphosphate has limited affinity for human DNA polymerases. The bioavailability of abacavir is approximately 80% and its absorption is not affected by food. This drug undergoes hepatic metabolism by several enzymes including alcohol dehydrogenase,¹⁸⁶ though not via the p450 system. The plasma half-life of abacavir is short (<2 hours), though the intracellular half-life of carbovir triphosphate is substantially longer, perhaps >12 hours.¹⁸⁷ Dose modification in individuals with reduced renal function does not appear necessary.

Typical doses of abacavir are either 300 mg twice daily or 600 mg once daily, and abacavir is commonly used in fixed dose combinations with lamivudine (Epzicom) or lamivudine and zidovudine (Trizivir).

Abacavir is generally well tolerated with mild nausea, fatigue, and headache seen in early monotherapy trials. The predominant serious side effect is a hypersensitivity syndrome that usually includes fever and may include rash and gastrointestinal symptoms; respiratory symptoms may also be present. The symptoms tend to worsen with dose and improve rapidly after ABC discontinuation. Severe systemic reactions with hypotension, respiratory failure, and death have occurred when abacavir has been reintroduced in a patient with previous symptoms of hypersensitivity.¹⁸⁸ This syndrome occurs in approximately 5–10% of individuals treated, and appears less common in individuals of African descent. Abacavir hypersensitivity has been associated with the HLA allele B5701.^{189,190} Testing for this allele may reduce abacavir hypersensitivity reactions if patients with B5701 avoid use of this agent. However, whether all abacavir hypersensitivity reactions are mediated through this HLA allele is not known, and risk cannot be assumed to be zero in HLA B5701 negative individuals.

Abacavir is a potent nucleoside leading to 1.5 to 1.6 log₁₀ declines in plasma HIV RNA with monotherapy.¹⁹¹ Abacavir with zidovudine and lamivudine was used commonly as an initial therapy combination when the combination was shown to have similar activity to a combination of indinavir with zidovudine and lamivudine.¹⁹² Use as initial therapy increased when the combination was available as a single fixed dose combination tablet given twice daily. However, a large randomized trial comparing fixed dose combination abacavir/lamivudine/zidovudine to the triple nucleoside combination plus efavirenz or fixed dose combination zidovudine and lamivudine plus efavirenz showed inferiority of the three-nucleoside combination.⁹⁵ As initial therapy, abacavir is now most commonly used with lamivudine and a

third potent agent such as a ritonavir-enhanced protease inhibitor or efavirenz.⁹⁷ Abacavir, substituting for a protease inhibitor, has also been used to simplify therapy or reduced toxicity in patients already suppressed on three-drug therapy.^{193,194} Abacavir has also been used as a component of therapy in treatment-experienced patients,¹⁹⁵ with such therapy now typically guided by resistance testing.

As monotherapy, abacavir may select for the M184V mutation and also selects for L74V, Y115F, and less commonly, K65R.¹⁹⁶ In the context of combination therapy with lamivudine and zidovudine, M184V is selected and TAMs emerge over time.⁹⁵

Tenofovir

Tenofovir disoproxil fumarate (TDF; Viread) is an acyclic nucleotide analog of adenosine monophosphate, and is converted to tenofovir in vivo and then phosphorylated to tenofovir diphosphate, which is the active form. The intracellular half-life of TDF-DP is greater than 40 hours in resting peripheral blood mononuclear cells and 11 hours in activated PBMC.¹⁹⁷ Bioavailability is 25–40% and is highest in the fed state. There is no liver metabolism and tenofovir is mostly excreted unchanged in the urine. The adult dose is 300 mg daily and tenofovir is also available as a fixed dose combination with emtricitabine (Truvada) (see below) or with emtricitabine and efavirenz (Atripla). Dose reduction is required during decreased renal function, with a decrease to every other day dosing when creatinine clearance falls to less than 50 mL/min. This agent also has activity against HBV.

Tenofovir is generally well tolerated with mild gastrointestinal side effects as the main consequence of therapy. Tenofovir can be nephrotoxic, especially if given at higher than recommended doses and the effect is predominantly one of renal tubular dysfunction that can result in a Fanconi's like syndrome or acute renal failure.¹⁹⁸ However, at currently recommended doses, TDF appears to have limited renal toxicity with very few substantial rises in creatinine observed in randomized trials.^{94,98,199} Glomerular filtration rate decreases slightly on TDF-containing regimens, though the clinical significance of this is unclear.²⁰⁰

Tenofovir was first studied in treatment-experienced patients and showed modest but consistent activity in patients with NRTI-resistant virus, reducing plasma HIV RNA by 0.5 to 0.7 log₁₀ copies per mL.^{199,201} In patients with wild-type virus, tenofovir has substantially more activity.²⁰² More recently, in combination with emtricitabine or lamivudine and efavirenz, tenofovir has shown substantial and prolonged efficacy in treatment-naïve patients.^{94,98} The combination of tenofovir, emtricitabine, and efavirenz is now available in as a single once daily pill in the United States, and is one of the most commonly used first-line therapies, endorsed by both the DHHS and IAS-USA guidelines (Table 73-1).^{92,93} Tenofovir with 3TC or FTC and a protease inhibitor is also

likely to be very effective in treatment-naïve patients, though these combinations have been less well studied.

The signature-resistance mutation for tenofovir is K65R.²⁰³ This mutation arises relatively infrequently when tenofovir is given as part of a potent combination to treatment-naïve patients,^{94,98} but the overall prevalence of this mutation which leads to cross-resistance with ddI, abacavir, 3TC, FTC, and probably stavudine, is increasing in the population of treated patients. Viruses with K65R mutation are hypersusceptible to ZDV in vitro.²⁰⁴ TAMs and the multi-nucleoside resistance mutations at codon 69 (insertions) also affect tenofovir activity, though some activity remains against many viruses that have TAMs.^{183,205} The K65R mutation reverses some of the effects of TAMs, and the ability for these mutations to coexist on the same virus may be limited.²⁰⁶ The presence of the M184V mutation tends to modestly increase susceptibility to tenofovir.²⁰³

Emtricitabine

Emtricitabine (FTC; SP Emtriva) is a pyrimidine nucleoside analog with activity against HIV-1, HIV-2, and HBV that has a chemical structure, a *cis* enantiomer of 2', 3'-dideoxy-5-fluoro-3'-thiacytidine, very similar to that of lamivudine (3TC). These two agents have very similar activity. FTC may have greater short-term antiviral activity and has a longer plasma and intracellular half-life than 3TC.²⁰⁷ FTC has good oral bioavailability not affected by food. FTC is cleared by the kidney and must be dose adjusted in patients with decreased creatinine clearance. The standard adult dose is 200 mg daily, and this agent is coformulated with tenofovir (Truvada) and with tenofovir and efavirenz (Atripla).

Emtricitabine is well tolerated with mild nausea, headache, and abdominal pain reported in a minority of subjects in clinical studies. FTC is occasionally associated with skin discoloration, which appears to be more common in blacks and may predominantly affect the palms, soles, and nails.

Emtricitabine has potent activity in combination with two other antiretroviral agents in treatment-naïve patients. This drug has been shown to be superior to stavudine when given with ddI and efavirenz, and when combined with tenofovir and efavirenz had superior efficacy to zidovudine, lamivudine, and efavirenz.^{98,147} This agent is now a common component of initial therapy regimens (Table 73-1).

Like lamivudine, the signature-resistance mutation is at codon 184 with a switch from methionine to isoleucine or most commonly valine. This mutation occurs frequently in patients who have virologic rebound on either emtricitabine or lamivudine, though when emtricitabine is given with tenofovir and efavirenz emergence of this mutation with rebound in plasma HIV RNA may be somewhat less likely.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Nonnucleoside reverse transcriptase inhibitors are noncompetitive inhibitors of the HIV-1 reverse transcriptase that bind tightly and specifically to the HIV-1 reverse transcriptase (RT)^{208,209}; some have very potent in vitro activity.²¹⁰ Resistance to NNRTI emerges rapidly in vitro and in vivo if viral replication is not fully suppressed.^{211,212} However, these agents are very efficacious in combination with other agents, especially in patients who are naïve to antiretroviral therapy. There are three NNRTI approved for clinical use in the United States and Europe—nevirapine, delavirdine, and efavirenz, though delavirdine, is not commonly used.

NEVIRAPINE

The pharmacokinetics of nevirapine (NVP or Virammune) are favorable with rapid, nearly complete absorption, and a long half-life that supports twice-daily dosing.²¹³ Many clinicians also use nevirapine once daily. The predominant adverse effect of nevirapine is the incidence of rash, which occurs in approximately 30% of treated subjects. Some rashes may be severe, and Stevens-Johnson syndrome has been observed. Because there is autoinduction of nevirapine metabolism, a dose-escalation strategy from 200 mg daily to 400 mg daily reduces the incidence of rash. Nevirapine is also associated with a hypersensitivity syndrome, which includes fever, rash, and hepatotoxicity.²¹⁴ This syndrome has resulted in liver failure and death in some individuals, and women and men with a more intact immune system are at a greater risk. Nevirapine should not be given to women with CD4⁺ cell counts greater than 250/mm³ or men with CD4⁺ >400 cells/mm³ or HIV-uninfected individuals as postexposure prophylaxis (PEP).

Nevirapine in combination with 3TC and stavudine has similar activity in treatment-naïve patients to efavirenz given with the same two nucleosides in a large randomized study.¹⁶¹ There was greater hepatotoxicity when nevirapine was given once daily, though the nevirapine-containing regimens had a more favorable effect on lipids.²¹⁵ Nevirapine appears safe during pregnancy and therefore may be a reasonable choice for initial therapy in women of child-bearing potential provided CD4⁺ cell counts are less than 250/mm³. Nevirapine also has limited central nervous system side effects. Data are limited on the combination of nevirapine with the two commonly used fixed dose combination nucleosides, tenofovir/emtricitabine, and abacavir/lamivudine.

Resistance develops rapidly to NVP, and characteristic mutations in the RT gene have been described.^{211,216} The appearance of resistance is associated with a rapid loss of antiretroviral activity. Even single doses of nevirapine rapidly select for resistance mutations and these mutations may persist for months following a single dose.^{217,218} Nevirapine is an

inducer of the p450 enzyme system and may increase metabolism of other medications metabolized by this system, including HIV-1 protease inhibitors.

■ DELAVIRDINE

Delavirdine (DLV or Rescriptor) is an NNRTI with potent activity against a broad range of HIV-1 variants *in vitro*.²¹⁹ However, the pharmacokinetics of delavirdine require dosing three times daily limiting the utility of this medication. Unlike nevirapine and efavirenz, delavirdine inhibits cytochrome p450 enzyme isoform 3A4 and may result in increased levels of medications metabolized by this enzyme.

■ EFAVIRENZ

Efavirenz (EFV or Sustiva) has a similar mechanism of action to nevirapine and delavirdine despite a unique chemical structure.²²⁰ This agent is highly potent despite substantial protein binding. Efavirenz is well absorbed orally and has a prolonged half-life of 40–55 hours with long-term administration allowing once daily dosing. The standard dose is 600 mg daily. Efavirenz is metabolized by the p450 system in the liver (CYP3A4 and CYP2B6) and is also an inducer of the p450 system. Common central nervous system side effects include sleep disturbances and vivid dreams; rashes are also common though severe rash is rare. Liver function abnormalities may also occur. In most studies of efavirenz therapy in treatment-naïve patients, total cholesterol, LDL cholesterol, and HDL cholesterol all rose moderately.

Efavirenz is now a cornerstone of initial antiretroviral therapy. An array of randomized comparative studies that have combined efavirenz with lamivudine or emtricitabine and either zidovudine, stavudine, tenofovir, or abacavir have demonstrated that efavirenz-containing regimens achieve the highest virologic suppression rates in treatment-naïve subjects of any antiretroviral therapy combinations studied.^{94–96,98,99,117,124,221–223} In these trials, approximately 75% of individuals treated with efavirenz, lamivudine, or emtricitabine, and another nucleoside achieved plasma HIV RNA levels less than 50 c/mL at 48 weeks or longer. In one study, 69% of subjects treated with efavirenz, lamivudine, and stavudine and 73% treated with efavirenz, lamivudine, and tenofovir had HIV RNA levels <50 c/mL at 144 weeks in an analysis where all missing values were considered virologic failures.⁹⁴ Efavirenz is also a useful agent in later therapy regimens if a patient has not been exposed to NNRTI-based therapy. A history of previous treatment with an NNRTI-based regimen that resulted in virologic failure limits the usefulness of efavirenz in treatment-experienced patients, likely due to NNRTI resistance, whether that resistance can be detected by standard assays or not.¹⁹⁵

As with other NNRTI, resistance to efavirenz emerges rapidly in most individuals whose virus is not suppressed, or who have a rebound of HIV replication while on therapy.

While the number of virologic failures in the studies outlined above is typically small, the majority of those who fail and undergo resistance testing have had virus with NNRTI resistance (summarized in Ref. 222).^{94,95,98} While K103N is the most common resistance mutation selected by efavirenz-based regimens, other mutations may be selected (examples include V106M, Y188C/L, or G190A/S/E/Q).

PROTEASE INHIBITORS

Like other retroviruses, HIV-1 expresses the products of its *gag* and *pol* genes as a single precursor polyprotein that must be cleaved by the HIV-encoded protease in order to produce infectious viral particles. The amino acid cleavage sites for the HIV-1 aspartyl protease are specific and not similar to cleavage sites of human host proteases. Currently available protease inhibitors bind to the active site of the enzyme and are competitive inhibitors of the HIV-1 protease with K_i in the 1.0 nM range.

The HIV-1 protease is an enzyme that tolerates marked variability in amino acid sequence while still retaining function. Polymorphism has been shown to exist at almost half of the amino acid positions of this 99 amino acid homodimer. Some of these amino acid substitutions also emerge during protease-inhibitor administration *in vitro* and *in vivo* and are thought to contribute to resistance to protease inhibitors. Therefore, many individuals who are treated with protease inhibitors already have HIV-1 variants with amino acid substitutions that may contribute to protease inhibitor resistance once therapy is instituted.

■ SAQUINAVIR

Saquinavir (SQV, Invirase) is a peptidomimetic HIV-1 and HIV-2 protease inhibitor with *in vitro* activity in the nanomolar range. Saquinavir has a bioavailability of approximately 4% when given with a high-fat meal and substantially lower when given in the fasting state, due in part to first-pass metabolism by p450 3A4 enzymes in the intestinal wall and liver. Therefore, in order to be maximally effective, saquinavir must be given with the potent p450 inhibitor, ritonavir (see below) in order to achieve adequate levels. When given with ritonavir, saquinavir trough concentrations are increased substantially. Recommended dosing is either 1000-mg saquinavir plus 100-mg ritonavir twice daily,²²⁴ or 1500-mg (or 1600-mg) saquinavir and 100-mg ritonavir once daily.²²⁵ Because of multiple changes in the formulation of saquinavir over time, limited data are available at these doses. Adverse gastrointestinal effects can occur with saquinavir, but these symptoms are usually mild and infrequently result in treatment discontinuation, and are difficult to disentangle from the side effects of coadministered ritonavir.

Despite the fact that saquinavir was one of the first protease inhibitors introduced, there are very few studies that help guide use with the current formulation given with low-dose ritonavir. In a large randomized study comparing lopinavir/ritonavir to saquinavir boosted by ritonavir, each with nucleoside analogs, the proportion of patients with treatment failure was significantly higher on the saquinavir arm. Most treatment failures were due to discontinuation of saquinavir and ritonavir.²²⁶ The interpretation of this trial is muddled by the fact that the patient population enrolled in the trial did not belong to one treatment group but instead was composed of subjects naive to therapy, subjects suppressed on therapy, and subjects who had failed previous antiretroviral therapy.

Resistance of HIV-1 to saquinavir has been demonstrated both in vitro and in vivo. Resistant isolates selected by saquinavir contain protease gene mutations at either codon 48 or codon 90 or both. Mutations that are associated with saquinavir resistance have been demonstrated in 30–50% of subjects treated with saquinavir, with the mutation at codon 90 occurring most commonly. Other primary protease-inhibitor mutations may also be selected.²²⁷

■ INDINAVIR

Indinavir (IDV; Crixivan) is a hydroxyaminopentane amide compound that is a potent inhibitor of the HIV-1 protease enzyme with a K_i of 0.34 nM and nanomolar activity in tissue culture. This agent is not highly protein bound and has a short half-life, requiring three times daily dosing (800 mg) on an empty stomach. Like saquinavir, indinavir concentrations are substantially increased by low-dose ritonavir, and indinavir 800 mg with either 100 mg or 200 mg of ritonavir twice daily have been studied and used in clinical practice.^{229–232} There are several adverse events associated with indinavir therapy. The most common serious side effect is nephrolithiasis, which occurs in approximately 2–5% of patients²³³ and is due to precipitation of indinavir in the renal collecting system. Although less common, indinavir can lead to frank renal dysfunction. Indinavir is associated with increases in cholesterol and insulin resistance and may be associated with abdominal lipo-accumulation. Indinavir is also associated with skin changes and alopecia. Rises in indirect bilirubin are seen frequently, but are of little clinical consequence.

Indinavir with zidovudine and lamivudine was the combination of antiretrovirals that first showed the potential to suppress HIV replication to below detectable limits in the majority of treated patients.²³³ Suppression of replication to below detectable limits was also associated with a very durable response in this small original study.²³⁴ Indinavir in combination with zidovudine and lamivudine was also shown to be superior to zidovudine and lamivudine in reducing progression to AIDS/death.²³⁵ Introduction of newer agents coupled with thrice daily dosing, fluid requirement,

and adverse events limit indinavir use. Combination with low-dose ritonavir improves convenience substantially, but does not diminish and may actually increase adverse effects.

Viral variants resistant to indinavir have been isolated from patients in whom viral replication was not suppressed.²³⁶ The establishment of high-level resistance requires multiple mutations in the protease gene, and these mutations appear to be acquired serially over time. An array of mutations is associated with indinavir resistance, with mutations at codons 46, 82, and 84 being characteristic.²²⁷ Many viral variants with high-level resistance to indinavir are cross-resistant to several other protease inhibitors.

■ RITONAVIR

Ritonavir (RTV; Norvir) is a peptidomimetic protease inhibitor active in vitro that improved survival when added as a single agent to nucleoside antiretroviral therapy in patients with very advanced disease.²⁴ Full-dose ritonavir (600 mg twice daily) is so poorly tolerated, however, that this dose is almost never used. Instead, ritonavir's potent inhibition of p450 3A4 binding is what makes it one of the most commonly prescribed antiretrovirals today, at doses that have limited antiviral activity themselves, but that substantially enhance the concentrations of coadministered protease inhibitors. Higher doses of ritonavir are associated with substantial gastrointestinal side effects and perioral paresthesias. Some patients have similar side effects at the doses used for boosting of other PI (100 mg or 200 mg), once or twice daily, but this is typically a small minority of patients. Triglyceride levels increase with ritonavir, even at lower doses. Elevations in hepatic transaminases have also been more commonly associated with ritonavir-containing regimens at higher doses of ritonavir, especially in patients with hepatitis B or C coinfection.²³⁷ At lower doses used in boosting, ritonavir-containing regimens appear to have no additional risk of hepatic toxicity compared to other PI-containing combinations.²³⁸

Because ritonavir is both an inducer and inhibitor of the human liver p450 cytochrome system, multiple drug–drug interactions exist. These interactions must be carefully considered when using this agent even at lower doses.

Resistance of HIV-1 to ritonavir has been well documented, both in vitro and in vivo,^{239,240} with mutations at codons 82 and 54 occurring in a number of variants. Viruses with high-level resistance to ritonavir typically have cross-resistance to indinavir and lopinavir.

■ NELFINAVIR

Nelfinavir (NFV; Viracept) is a potent inhibitor of HIV-1 in vitro at low nanomolar concentrations.²⁴¹ This agent has an oral bioavailability of 17–47% in animals²⁴² and absorption is improved when given with food. The current recommended

dose is 1250 mg twice daily. The predominant side effect of nelfinavir is diarrhea, with approximately 15% of patients having substantial diarrhea in clinical studies.^{25,243} Frequencies of other nelfinavir-associated adverse events such as increased lipids, nausea, and elevated liver transaminases appear similar to other protease inhibitors. Nelfinavir, like other protease inhibitors, has the potential for drug-drug interactions with other medications that undergo hepatic p450 metabolism.

Because of its activity, relatively good tolerability, and twice daily dosing, nelfinavir became a common component of initial antiretroviral therapy. However, in comparative studies against EFV or lopinavir/ritonavir (each medication given with lamivudine and either zidovudine or stavudine), nelfinavir-containing regimens were inferior as measured by suppression of HIV replication.^{25,96} Consequently, nelfinavir is recommended as an acceptable but not preferred agent for first-line therapy in most guidelines.^{92,93} Some clinicians find nelfinavir useful in women of child-bearing potential and in pregnant women.

Resistance to nelfinavir usually occurs via selection of one of two initial mutations, either D30N or L90M, each of which can occur with secondary mutations.²⁴⁴ The D30N mutation occurs more commonly, at least in individuals infected with subtype B virus and virus with this mutation have limited cross-resistance to other protease inhibitors.^{245,246} The L90M mutation is associated with more broad cross-resistance.

■ LOPINAVIR/RITONAVIR

Lopinavir (LPV) is a C2 symmetrical peptidomimetic inhibitor of HIV-1 protease, and is available only in a form coformulated with ritonavir (LPV/r; Kaletra). Ritonavir inhibits the metabolism of lopinavir, resulting in high levels of the compound. Lopinavir is highly protein bound (98–99%), and when given with ritonavir has a half-life of 5–6 hours. Both lopinavir and ritonavir are metabolized by cytochrome P-450 enzymes, and the combination also inhibits several hepatic enzymes and induces the levels of others. Thus, drug–drug interactions are common between lopinavir/ritonavir and a variety of other agents, and these interactions must be considered when using this combination. A tablet formulation has replaced previously used capsule formulations, allowing a lower pill burden and potentially fewer adverse effects. Each tablet contains 200 mg lopinavir and 50 mg ritonavir, and the current recommended dose is two tablets (400/100 mg) twice daily. Once daily dosing (800/200 mg) is possible in treatment-naïve patients. Lopinavir/ritonavir may be taken with or without food, and the tablet does not require refrigeration. The predominant toxicities are gastrointestinal (diarrhea, nausea) and hyperlipidemia, particularly hypertriglyceridemia.

Several clinical trials have demonstrated potent antiretroviral activity when lopinavir/ritonavir is combined with two NRTIs. In one pivotal trial, lopinavir/ritonavir

was shown to be superior to nelfinavir (both combined with stavudine and lamivudine) in maintaining undetectable viral loads over 48 weeks.²⁵ In this study, no evidence of genotypic or phenotypic resistance to protease inhibitors was observed in lopinavir/ritonavir-treated subjects who did not attain or failed to maintain undetectable viral levels (<400 copies/mL), whereas 45% of such subjects in the nelfinavir arm developed PI resistance.²⁴⁴ Although very uncommon, HIV-1 protease mutation I47A confers high-level resistance to lopinavir (>100-fold), and may be the primary resistance mutation to this agent; this mutation confers cross-resistance to amprenavir [the active metabolite of fos-amprenavir (see below)], while enhancing susceptibility to saquinavir.²⁴⁷

Lopinavir/ritonavir-containing regimens are now recommended by many for initial therapy of treatment-naïve patients, as well as for individuals with previous treatment and little PI resistance (<5 protease-inhibitor resistance mutations).^{92,93}

■ FOSAMPRENAVIR

Fosamprenavir calcium (fosAPV; Lexiva) is a prodrug of the protease-inhibitor amprenavir²⁴⁸ and is available at a strength of 700 mg, equivalent to 600 mg of amprenavir. Ritonavir boosts fosamprenavir's half-life, making once daily dosing possible in treatment-naïve individuals at a dose of 1400 mg of fosamprenavir with 200 mg of ritonavir; in treatment-experienced patients, fosamprenavir/ritonavir should be taken twice daily (fosamprenavir 700 mg, ritonavir 100 mg twice daily). Fosamprenavir without ritonavir is also given twice daily (1400 mg twice daily), but is not as widely used.

Adverse effects include nausea, vomiting, perioral paresthesias, and rash. Rash occurs in approximately 19% of treated patients, but is generally mild or moderate, and often the drug can be continued during the rash or restarted later. Severe skin rashes, including Stevens-Johnson syndrome, however, have also been described.

Clinical trials have compared three drug regimens including fosamprenavir alone or fosamprenavir boosted with ritonavir to similar regimens containing nelfinavir;^{243,249} these studies showed similar or greater suppression in the fosamprenavir arms, particularly in subjects with pretreatment plasma viral loads >100,000 copies/mL. A more recent open-label trial compared lopinavir/ritonavir with fosamprenavir/ritonavir, each administered with the coformulation of abacavir/lamivudine⁹⁷; this noninferiority trial in 878 treatment-naïve subjects showed comparable suppression of plasma HIV RNA and increases in CD4⁺ cell counts, with similar adverse event profiles in the two arms over 48 weeks.

Although resistance profiles have been observed similar to those seen in patients taking amprenavir (e.g., I54L/M, V32I, I47V, M46I, and I50V),²⁵⁰ very little resistance was

observed in large trials employing three drug regimens including fosamprenavir/ritonavir.⁹⁷

■ ATAZANAVIR

Atazanavir (ATV; Reyataz) is an azapeptide inhibitor of HIV-1 protease. Administration with food enhances bioavailability and reduces pharmacokinetic variability. Atazanavir is highly protein bound and has a half-life of approximately 7 hours. It is metabolized by the cytochrome 450 enzyme CYP3A4, and administration with ritonavir boosts concentrations up to 10-fold.²⁵¹ The recommended dose when used without ritonavir in treatment-naïve patients is 400 mg once daily, and for treatment-experienced patients it is recommended that atazanavir 300 mg be taken with ritonavir 100 mg once daily. This dose is also used in treatment-naïve patients.

The principal observed adverse effect with atazanavir is indirect hyperbilirubinemia without accompanying liver function abnormalities; this may lead to jaundice and scleral icterus. Diarrhea and nausea may also occur. Atazanavir use has been associated with ECG PR prolongation, and the drug should be used cautiously in patients with cardiac conduction abnormalities. Importantly, atazanavir appears to have fewer adverse effects on lipid profiles than other available protease inhibitors,²⁵² and thus is becoming a popular choice in initial therapy regimens.

Early studies compared atazanavir-based regimens to either efavirenz or nelfinavir-based regimens, and showed comparability to both in antiretroviral-naïve patients after 48 weeks.^{253,254} In treatment-experienced subjects, atazanavir plus ritonavir showed comparable efficacy and safety when compared with lopinavir/ritonavir over 96 weeks; moreover, there were reductions in total cholesterol and fasting triglycerides and improved gastrointestinal tolerability in the atazanavir/ritonavir group.^{255,256}

The I50L protease mutation confers resistance to atazanavir but increases susceptibility to many other protease inhibitors.²⁵⁷ Resistance to atazanavir in treatment-experienced patients is also associated with protease mutations M46I/L, G73S/A/C, I84V, and L90M; fewer than 30% of individuals with these mutations will respond to atazanavir/ritonavir.^{258,259}

■ TIPRANAVIR

Tipranavir (TPV; Aptivus) is a nonpeptidic protease inhibitor of HIV-1 belonging to the class of 4-hydroxy-5, 6-dihydro-2-pyrone sulfonamides. Because absorption is limited, tipranavir is administered with ritonavir (500 mg tipranavir/200 mg ritonavir twice daily). It is highly protein bound and is metabolized primarily by hepatic CYP 3A4 mechanisms. Its half-life is 5.5–6.0 hours. Tipranavir and ritonavir together have multiple effects on cytochrome

p450 enzymes and transport proteins such as p-glycoprotein. Complex drug–drug interactions are possible and should be carefully considered when initiating this combination (reviewed in Ref. 260).

The most frequent toxicities of tipranavir are gastrointestinal (nausea, diarrhea). Liver enzyme abnormalities may occur, and severe liver inflammation has been observed, particularly in individuals with chronic HBV or HCV infection or with liver enzyme elevations at the onset of therapy. Marked elevations of cholesterol and/or triglycerides are also seen in some patients.²⁶¹ Fatal and nonfatal intracranial hemorrhages have been observed in patients receiving tipranavir/ritonavir; no pattern of abnormal coagulation function was observed in such patients, though in vitro data suggest that tipranavir may have antiplatelet activity. Rash occurs in 8–14% of patients, and since tipranavir contains a sulfa moiety, it should be used with caution in individuals with sulfonamide allergies.

Tipranavir/ritonavir has activity against many viruses resistant to other protease inhibitors. The combination has been evaluated primarily in patients in whom other regimens have failed.²⁶¹ The RESIST I and II trials compared tipranavir/ritonavir with other comparator ritonavir-boosted protease inhibitors, each combined with optimized background regimens. Subjects receiving tipranavir/ritonavir had greater reductions in plasma HIV-1 RNA, greater CD4⁺ cell rises, and longer median times to treatment failure than the comparator arm. In this heavily treated population, responses were best if more than two active drugs were in the regimen, particularly if one of them was enfuvirtide (see below). Thus, tipranavir/ritonavir-containing regimens are used primarily in individuals in whom other protease-inhibitor regimens are no longer effective.

In vitro resistance to tipranavir can be generated, with mutations appearing in the following order: 33F, 84V, 45I, 13V, 32I, 82L, 36I, 71V, 10F, and 54V/T. In clinical trials, the most commonly observed substitutions observed were L33V/I/E, V82T, and I84V. A tipranavir mutation score has been developed consisting of 16 protease positions and 21 mutations (10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, and 84V); HIV isolates displaying increasing numbers of these mutations have decreased susceptibility to tipranavir.²⁶² Cross-resistance with other approved protease inhibitors is modest, and viruses with single primary mutations generally are sensitive to tipranavir, with the exception of I84V and V82L or T.²⁶³

■ DARUNAVIR

Darunavir (DRV; Prezista; TMC-114) is an HIV-1 protease inhibitor that received accelerated approval from the US FDA in 2006 for use in combination with ritonavir (600 mg darunavir/100 mg ritonavir twice daily) by adults with

advanced HIV infection. This protease inhibitor has currently been best studied in treatment-experienced patients who have HIV strains resistant to other protease inhibitors. Darunavir should be taken with food, which increases C_{max} and AUC by 30%. The drug is 95% bound to plasma proteins, and its half-life when combined with ritonavir is 15 hours. It is metabolized in the liver, primarily by CYP3A4.

The most common side effects of darunavir have included diarrhea, nausea, and headache. Rash, ranging from mild to serious, occurs in approximately 7%. Elevations in liver enzymes, amylase, and lipids, particularly triglycerides, were similar to those of comparator protease inhibitors in clinical trials. Darunavir contains a sulfa moiety and, thus, should be used cautiously in patients who have sulfonamide allergies.

Two randomized controlled trials (POWER 1 and II) compared the safety and effectiveness of a darunavir/ritonavir-based combination with other ritonavir-boosted protease inhibitor combinations in subjects with extensive prior treatment with antiretroviral drugs; all subjects in these trials had resistance to other protease inhibitors and were given optimized background regimens with the assistance of resistance testing. At 24 weeks, the darunavir group showed substantially better virologic responses than the comparator group,^{264,265} and these differences were sustained to 48 weeks.²⁶⁶

The resistance profile of darunavir has not been characterized fully. Several protease mutations, including V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, and L89V, are associated with decreased responses to darunavir. When three or more mutations are present at baseline, the probability of treatment failure increases.²⁶⁷

■ ENTRY INHIBITORS

The interaction of HIV-1 with the CD4⁺ cell membrane involves several specific interactions between the virus and the host and is, therefore, an important target for antiretroviral therapy. First, there is a specific interaction between the HIV envelope protein, gp120, and the CD4⁺ molecule. This interaction is followed by a conformational change in gp120, allowing this protein to bind to the chemokine coreceptor (CCR5 or CXCR4). Finally, the HIV envelope fuses with the cell membrane via a structural change in the gp41 envelope protein.⁵

Antiretroviral agents are being developed to target each of the steps outlined above, though only one, enfuvirtide, is currently available for clinical use.

■ FUSION OF THE HIV ENVELOPE WITH THE CELL MEMBRANE

HIV-1 fusion with the CD4⁺ cell is a multistep process that we are beginning to understand more clearly.⁵ The HIV-1 envelope complex of gp120/gp41 is an oligomeric protein, most likely a

trimer of three noncovalently bound gp120/gp41 molecules. At some point after gp120 binds to the CD4⁺ molecule, the gp41 molecule extends its N-terminal end or fusion peptide into the cell membrane. At this point, gp41 undergoes a folding process pulling the HIV-1 membrane into close proximity to the cell membrane and allowing fusion of the membranes in a thermodynamically favorable protein-protein interaction. Enfuvirtide has an amino acid sequence identical to one region in the gp41 molecule allowing it to bind in a hydrophobic groove preventing folding of the gp41 molecule and fusion of the two lipid membranes.

■ ENFUVIRTIDE

Enfuvirtide (ENF, T-20, Fuzeon) is a 36-amino-acid peptide with a sequence that corresponds exactly to a region of HIV-1 envelope protein gp41. This agent is active *in vitro* against a wide variety of HIV-1 variants, including variants that use the CXCR4 chemokine receptor (X4), the CCR5 receptor (R5), and dual-tropic viruses. Because ENF is a peptide molecule, like insulin, it cannot be administered orally, and must be administered by a parenteral route. The standard dose is 90 mg twice daily delivered by subcutaneous injection.

The major adverse event with enfuvirtide is injection-site reactions.²⁶⁸ These reactions occur in almost all patients, are typically mild, but usually result in pruritic subcutaneous nodules, although larger painful inflammatory nodules are occasionally observed. In phase III trials, approximately 3% discontinued treatment because of local reactions. Rarely, allergic reactions can occur. Also in the phase III clinical trials, the use of enfuvirtide was also associated with pneumonias, including typical bacterial pneumonia.²⁶⁸ The pathophysiology of this association is not understood; however, respiratory symptoms in an individual on enfuvirtide should be investigated thoroughly.

Enfuvirtide will have activity against viruses resistant to agents from the RT and protease inhibitor classes. This fact, coupled with the fact that it is delivered by injection, results in enfuvirtide being used predominantly in moderately to highly treatment-experienced patients. Two parallel phase III studies of enfuvirtide, conducted in almost 1000 patients with extensive prior treatment experience, demonstrated that enfuvirtide added substantial antiretroviral activity to an optimized regimen of multiple agents selected on the basis of resistance testing.^{9,10} CD4⁺ cell responses were also substantially better. Enfuvirtide is probably most useful when combined with one or more agents with substantial activity against a patient's HIV-1. Most recently, this approach has been demonstrated with the newer protease inhibitors, tipranavir and darunavir.^{261,266}

Mutations in the region of gp41 at which enfuvirtide binds result in decreased binding of enfuvirtide.^{269,270} If combination therapy with enfuvirtide does not suppress

HIV-1 replication to below the limit of detection, resistance to enfuvirtide emerges relatively rapidly.

■ NEW ANTIRETROVIRAL AGENTS IN LATE-STAGE DEVELOPMENT

There are several agents in three classes in late-stage development, i.e., phase III studies that are nearing primary endpoints and early access programs that are opening in the United States and other developed nations.

Etravirine (TMC 125) is an NNRTI that has in vitro and in vivo activity against viruses resistant to the currently available NNRTI.²⁷¹ In short-term phase IIa studies, this agent was extremely active against wild-type virus and retained activity over a 7-day course against viruses resistant to EFV and/or NVP.^{272,273} More recently etravirine has been shown to add antiretroviral activity in the setting of late-stage salvage therapy in patients resistant to NNRTI and with three or more primary PI mutations. With rising rates of transmitted NNRTI resistance, this agent may also find utility in earlier stages of HIV treatment. To date, toxicity of this compound has been fairly limited though rash has certainly been observed. The dose of etravirine is 200 mg orally twice daily and will likely be used in later lines of therapy in NNRTI-experienced patients.

An integrase inhibitor, MK 0518 (raltegravir), is also in late-stage development and is widely available in the United States via early access programs. This stand-transfer inhibitor is very potent in vitro, active against viruses resistant to other classes and has demonstrated very potent short-term activity in treatment-naive patients.²⁷⁴ In a phase II comparative study in treatment-naive patients, MK 0518 combined with tenofovir and emtricitabine had similar response rates over 24 weeks as efavirenz plus the same two NRTI.¹⁹ Fewer adverse events were seen in the MK 0518 treated patients. In highly treatment experienced patients, MK 0518 was vastly superior to placebo when combined with an optimized background regimen in a randomized phase II study.²⁰ Approximately 65% of patients had HIV RNA levels <50 c/mL at 24 weeks. Adverse event rates were similar to placebo. MK 0518 is metabolized by glucuronidation and has limited interactions with other antiretrovirals and medications metabolized by p450 system. The dose of MK 0518 is 400 mg orally twice daily and also will likely be used, at least initially, in later lines of therapy. A second integrase inhibitor, GS 9137 (elvitegravir), is in early stages of development, has similar potency as MK 0518, requires only once daily dosing but must be given with ritonavir, and has pharmacokinetic interactions with protease inhibitors and NNRTI.²⁷⁵

A third class of new agents is the CCR5 antagonist. Two agents, maraviroc and vicriviroc, are in later stages of

development, though only maraviroc has begun initial phase III studies. These agents are active against viruses that use CCR5 (R5 viruses) and appear to have no clear antiviral activity in individuals who have HIV-1 that use CXCR4 or both receptors (so-called X4 or dual-mixed virus populations).⁷ In a phase II study in highly treatment experienced patients with R5 virus vicriviroc had substantial activity over 24 weeks (approximately 2.0 log₁₀ declines in plasma HIV-1 RNA from baseline).²⁷⁶ Maraviroc is expected to have similar activity. How these agents will be used and whether there will be long-term consequences or adverse events based on their mechanism of action are unknown.

PATIENT MANAGEMENT CONSIDERATIONS

■ WHEN TO START THERAPY

Current treatment guidelines allow for substantial clinical judgment in the timing of initiation of antiretroviral therapy in treatment-naive individuals in the developed world setting (Table 73-2). DHHS, IAS-USA, and WHO guidelines are consistent in recommending antiretroviral therapy for any individual with symptomatic HIV/AIDS or with a CD4⁺ cell count ≤200 cells/mm³. In fact, waiting to initiate therapy until CD4⁺ cell counts are <200 cell/mm³ results in substantially inferior clinical outcomes (AIDS events and death) in the analyses of multiple clinical cohort studies, even when controlling for lead-time and other biases.^{67,277} Unfortunately, many patients present for care with CD4⁺ cell counts <200 cells/mm³ or with clinical AIDS diagnoses.²⁷⁸

In the United States and other developed countries, guidelines are less directive for patients who have CD4⁺ cell counts >200 cells/mm³ (Table 73-2). For individuals with CD4⁺ cell counts between 201 and 350/mm³, current guidelines favor therapy initiation. Some cohort data suggest that initiation of therapy in this group results in a favorable clinical outcome, but the evidence is not consistent or overwhelming.⁶⁷ Most agree that therapy should be initiated prior to a CD4⁺ cell count of 200 cells/mm³; however, the precise CD4⁺ cell threshold for initiating therapy has not been established. Individuals who initiate HAART at higher CD4⁺ cell counts are more likely to survive AIDS-free longer. However, significant differences in AIDS-free survival between populations of patients started at CD4⁺ between 200 and 350 cell/mm³ and patients started with CD4⁺ >350 cells/mm³ have not been consistently seen, though differences have been observed in some studies, particularly in patients with higher viral loads.^{277,279} The movement to delay the start of therapy until CD4⁺ cell counts approached 200/mm³ was predominantly driven by antiretroviral side effects, especially metabolic and body shape

Table 73-2. Recommendations on Initiation of Antiretroviral Therapy in Treatment-Naive Adult and Adolescent Patients^a with Chronic HIV Infection

Clinical Staging	Recommendation
Symptomatic	
AIDS-defining illness or severe symptoms	Initiate antiretroviral therapy
Asymptomatic	
CD4 ⁺ <200 cells/mm ³	Initiate antiretroviral therapy
CD4 ⁺ >200 ≤350 cells/mm ³	Offer treatment (DHHS) Consider treatment (IAS-USA)
CD4 ⁺ >350 ≤500 cells/mm ³ HIV RNA >100,000 c/mL	Most clinicians defer; some recommend treatment (DHHS) Consider treatment ^b (IAS-USA)
HIV RNA <100,000 c/mL	Defer therapy (DHHS) Generally not recommended (IAS-USA)
CD4 ⁺ >500 cells/mm ^{3c}	Generally not recommended (IAS-USA)

^aMen and non-pregnant women.

^bIAS-USA guidelines also recommend considering therapy if there is rapid CD4⁺ cell decline.

^cThis CD4⁺ cell stratum not listed separately in DHHS Guidelines.

Adapted from Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society–USA panel. *JAMA* 2006; 296: 827–843; Panel on Clinical Practices for the Treatment of HIV Infection, DHHS guidelines, 2006.

changes, coupled with concern that patients would be at greater risk for accumulating resistant HIV-1. More recently, therapy has become much simpler, with initial regimens that are composed of only one or two pills daily. In addition, metabolic side effects are much better understood, and newer regimens are less likely to cause lipoatrophy, lipoaccumulation, peripheral neuropathy, insulin resistance, or marked hyperlipidemia. Also, potent initial therapies are very successful, and even individuals with virologic failure on initial treatment are very unlikely to have viruses exhibiting broad cross-class resistance.²⁸⁰ Logical arguments for earlier initiation of therapy have been made,²⁸¹ and many clinicians favor initiation of antiretroviral therapy when CD4⁺ cell counts are at or above 350/mm³.

■ WHEN TO SWITCH THERAPY

In clinical trials, the vast majority of patients receiving initial antiretroviral therapy have plasma HIV RNA levels that fall to and remain below detectable limits for 3 years or more.^{94,234,282} While results in clinical cohorts have not been as robust, proportions of treated patients who have HIV RNA levels suppressed below the limit of detection have been increasing. However, for those patients on initial or subsequent regimens

who have persistent detectable HIV-1 RNA or a rebound in plasma HIV RNA to above detectable limits, the precise time to switch to a new regimen has not been clearly defined. Typically, patients with relatively low levels of HIV RNA (<10,000 copies/mL) have stable CD4⁺ cell counts and do not show signs of clinical progression. A declining CD4⁺ cell count or a return of HIV/AIDS signs and symptoms would be a strong indication for changing antiretroviral therapy. If however the only indication that therapy is “failing” is a reproducibly detectable HIV RNA level, then altering therapy is based on clinical opinion and limited objective data. Factors that impact the decision include:

1. Assessment of adherence to the current regimen. Intermittent or partial adherence is a likely cause of persistent or recurrent viremia in a patient on a potent regimen with limited previous antiretroviral resistance. Altering therapy in a patient who is struggling with adherence is unlikely to lead to the desired therapeutic response.
2. Treatment options available. No matter how many previous regimens a patient has experienced, the goal of antiretroviral therapy should be to suppress HIV replication to below detectable limits. Therefore, if a regimen can be constructed that contains more than two active agents, a

Table 73-3. Recommendations for Resistance Testing

Clinical Scenario	Comments ^d
Antiretroviral-naïve individual^a	
Acute infection	Optimal time to detect transmitted drug resistance will influence drug choices if therapy is instituted
Recent infection	Earlier testing increases likelihood that transmitted resistant variants will be detected
Chronic infection (>2 yr)	Transmitted resistant variants may be seen in 5–15%; minority variants may not be detected
Antiretroviral-experienced individuals	
Suboptimal suppression following therapy initiation ^b	Minority resistant variants may emerge rapidly with the selective pressure of treatment
Virologic failure ^c	Will help maximize the number of active agents in a new regimen; Minimal resistance might suggest poor drug exposure or problems with adherence
Following ART discontinuation	Superior replication of wild-type virus occurs within 4–8 weeks; resistance testing after drug discontinuation may be misleading and is not recommended
Pregnancy	A pregnant woman with detectable plasma HIV RNA should have resistance testing regardless of treatment history

^aGenotype resistance testing may be optimal in this setting as some mutations that are clear markers of transmitted resistance may have little or no effect on phenotype.

^bThere is no precise definition but plasma HIV RNA level should fall by approximately 2 log₁₀ (100-fold) in 4 weeks.

^cIn patients with complex treatment history, a combination of genotype and phenotype resistance testing may be most helpful.

^dResistance testing is most likely to be successful if plasma HIV RNA level is >500–1000 c/mL.

Adopted from Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *JAMA* 2006; 296: 827–843; Hirsch MS, Brun-Vezinet F, Clotet B, Conway B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel. *Clin Infect Dis* 2003; 37: 113–128.

change in therapy is typically recommended. Determining “active” agents is done through a careful treatment history and resistance testing²⁸³ (Table 73-3). Medications from a class to which the patient is naïve are likely to have the most activity.

3. Clinical status. Patients with advanced disease, such as those with a low CD4⁺ cell count or ongoing AIDS diagnosis, may need to switch therapy even if a regimen with more than two active agents cannot be constructed.
4. Resistance risk. Ongoing viral replication in the presence of antiretroviral drugs will result in emergence of resistance over time.
5. The speed at which new mutations emerge depends on the strength of the selective pressure, the number of mutations required for the virus to “achieve” resistance,

and the relative fitness of the resistance variant. In general, single mutations that result in high levels of resistance emerge rapidly and can lead to accumulation of further resistance mutations. Patients on initial regimens are typically switched earlier following confirmed detectable HIV replication than those patients who already have HIV variants with substantial resistance mutation, as viruses in patients with fewer mutations tend to accumulate resistance mutations more rapidly.²⁸⁴

Varied opinions exist on whether to switch patients who have low-level viremia (plasma HIV RNA levels in the 50–1000 c/mL), especially in patients who are tolerating their treatment and have high, stable, or even rising CD4⁺ cell counts. Clinicians need to balance the risk of selection of

resistance mutations with the risks of any new therapy. Patients with treatment options that are very likely to be effective and are relatively uncomplicated may be served by changing therapy rapidly once HIV-1 replication is reproducibly detected and adherence and toxicity issues are addressed.

■ SALVAGE/RESCUE THERAPY

Highly treatment experienced patients with HIV-1 variants resistance to multiple agents present a common treatment challenge to clinicians. Many of these patients received non-HAART prior to receiving HAART, or they began therapy with less potent HAART regimens.²⁸⁰ In addition, transmission of multiple drug-resistant variants has been well documented.^{285,286} The ultimate goal of antiretroviral therapy is to preserve the long-term health of the infected individual. For most patients, this goal is likely to be achieved by suppression of HIV-1 replication to below detectable limits. Until recently, the goal of full virologic suppression was not possible for patients with highly resistant virus because the goal was unattainable or the number and combinations of ARV required was difficult to adhere to, poorly tolerated, and marginally successful. However, with the introduction of multiple new agents with activity against resistant variants, such as enfuvirtide, darunavir, and tipranavir, and the promise of new agents now in later stages of development, treatment guidelines now state that the goal of antiretroviral therapy in moderate to highly experienced patients is to suppress HIV-1 replication to below the limits of detection in blood plasma.^{92,93} If at least two new agents anticipated to have a high level of activity can be combined with additional agents with partial activity, then the likelihood that a highly treatment experienced patient will achieve a plasma HIV RNA below the limit of detection appears to be above 40%, and has been as high as 60–70% in studies of darunavir/ritonavir.^{109,261,264,266,268}

For an individual patient, knowing whether there are two or more active agents to which the patient's virus is susceptible, requires substantial clinical acumen. Advice of an expert HIV clinician may be particularly valuable. Treatment history is very important, and resistance testing is standard in this setting (Table 73-3).²⁸³ Antiretroviral drug prescribing information for the newer agents now routinely includes data on resistance and response, and this information may be particularly helpful for the newer protease inhibitors, darunavir and tipranavir. HIV-1 variants with high-level resistance to these agents are uncommon but can occur and, therefore, activity of either of these medications in highly treatment experienced patients should not be assumed. Fortunately, many variants that are resistant to one of these two agents may not be resistant to the other. In general, an antiretroviral agent from a class of

drugs to which the patient is naive is likely to have activity, though this activity can be quickly lost if the rest of the regimen has limited antiretroviral activity. Most experts would include nucleoside analogs in most salvage regimens. NRTI may have residual activity against viruses with resistance, perhaps by compromising fitness of the virus or via residual direct antiretroviral activity.^{179,180,287} Much of this activity may be attributed to lamivudine (3TC).¹⁷⁸ Information about when newer drugs will become available, either through expanded access programs or via regulatory agency approval, is essential for treatment decision making in the highly treatment experienced patient. If a new agent is likely to become available soon, postponing a change in therapy may be the best decision, assuming that the patient is not in serious clinical danger.

■ TREATMENT INTERRUPTIONS

Interruptions of antiretroviral treatment have been proposed as a strategy to address several clinical issues in different treatment situations. Current evidence, however, suggests that once an individual has HIV replication suppressed on therapy, that person needs life-long therapy. Treatment interruptions have been proposed as a way to address treatment fatigue and a way to avoid toxicity and conserve resources particularly in developing world settings. Two recent large randomized studies, one in resource rich countries and another in a resource poor setting, demonstrated that CD4⁺ cell count guided treatment interruptions, with therapy restarted when CD4⁺ counts fell to 250/mm³, significantly increased the risk of serious HIV/AIDS-related clinical events; in the developed world study, the cumulative risk of non-AIDS complications such as cardiovascular events, and liver and kidney failure was also significantly higher.^{288,289} Other strategies including fixed interval interruptions or CD4⁺ cell count guided interruptions with a higher CD4⁺ threshold are under study.²⁹⁰

A second proposed use for therapy interruption was in advanced patients with highly resistant virus who do not have HIV replication suppressed as measured by plasma HIV RNA levels. The hypothesis was that therapy interruption would allow outgrowth of wild-type virus that would then be more responsive to combination salvage antiretroviral therapy. This strategy also failed in several clinical trials.^{291–294} In two of the trials, not only were treatment responses no better following interruption compared to therapy switch without interruption, but there were increased clinical events in the group of patients who were randomized to interruption.^{292–294}

A third proposed use of treatment interruptions is in individuals with HIV replication suppressed on therapy. In this scenario, individuals undergo treatment interruptions to allow HIV to replicate and stimulate HIV-specific

immune responses, in a sense immunizing the patient. Therapy is then restarted and this cycle may be repeated several times. Ultimately antiretroviral treatment is stopped and viral set point is then examined. Multiple studies have investigated this approach, though few were randomized. In acutely infected patients treated with antiretrovirals very early after infection, this strategy was thought to have the greatest chance of success, as preservation of some HIV-1-specific immune responses could be demonstrated.²⁹⁵ In this population, initial results were encouraging but long-term sustained suppression of HIV replication off therapy was not observed.^{41,42} In a recent randomized trial in chronically infected patients, significant differences in viral replication parameters were observed following strategic treatment interruptions compared to patient maintained on continuous therapy when both groups stopped therapy.²⁹⁶ These results suggest that some measure of immune control can be induced; however, these responses appear modest, and more effective, safer strategies are needed. Notably in the same study, immunization with a canary pox HIV-1 vaccine had no effect on viral kinetics or set point.

Given the disappointing results in clinical trials evaluating each of the treatment interruption strategies, treatment interruptions in successfully treated patients should be discouraged. Even in patients who have incomplete suppression of their HIV replication and advanced immunosuppression, maintaining antiretroviral treatment is associated with better survival and fewer AIDS events. In clinical practice, however, patients will stop therapy either because of toxicity, treatment fatigue, mental illness, substance abuse, or other factors. If a clinician is aware that a patient is going to stop therapy, then careful follow-up with CD4⁺ cell count monitoring should be arranged. In addition, if a patient is on an NNRTI plus nucleoside (with or without other agents), the NNRTI should probably be stopped first, given the different half-lives between the two classes of drugs. The optimal timing of discontinuation is not known, but several studies have used 7 days between stopping efavirenz or nevirapine and stopping the nucleoside analogs.

SPECIAL CONSIDERATIONS

■ TRANSMISSION OF RESISTANT VIRUS

Drug-resistant HIV-1 variants can be transmitted from an infected individual to their sexual partners, while sharing needles, or during mother-to-child transmission (MTCT). Many groups around the world have attempted to quantify the prevalence of transmitted resistance in different locations.^{297–302} Primary resistance (transmission of virus with at least one resistance-associated mutation) has a prevalence

of 5–15%, depending on the population and how specific mutations are scored. Some resistance mutations such as those at RT codon 215 and NNRTI resistance mutations appear more commonly. Others, such as the 3TC resistance mutation M184V, which is highly prevalent in treatment-experienced patients, is uncommonly seen in patients with primary or transmitted resistance. Most treatment guidelines recommend resistance testing for treatment-naive patients when they enter care, especially if they are within a few years of acquiring the infection (Table 73-3). Any resistance mutation in this setting should raise concern, as other mutations may have been transmitted but reverted to the wild-type over time.

ANTIRETROVIRAL THERAPY IN THE DEVELOPING WORLD

A full discussion of antiretroviral therapy in the developing world is beyond the scope of this text, although some basic principles can be discussed. Recent WHO guidelines provide more detailed information.¹⁶² Because of the very large numbers of individuals that must be treated, as well as cost concerns, a public-health approach to antiretroviral therapy may be necessary.³⁰³ In such an approach, virtually all patients are treated with the same regimen and that regimen is usually selected based on a balance among antiviral activity, cost, convenience, toxicity, and availability.³⁰⁴ In early years, a fixed-dose combination of nevirapine, lamivudine, and stavudine was the mainstay of treatment for much of the developing world. This approach has been effective, though the limited monitoring available may result in substantial selection of resistant variants.³⁰⁵ In addition, the toxicities of stavudine in resource poor settings are considerable, just as they were in more resource-rich settings. Treatment guidelines from the WHO have been recently updated and encourage alternatives to stavudine, when possible.¹⁶² Recommendations also include beginning antiretroviral therapy at or above a CD4⁺ cell count of 200 cells/mm³ in asymptomatic patients, not waiting until the CD4⁺ cell count is less than 200/mm³ (Table 73-4). The progress in the roll out of antiretroviral therapy to many developing countries has been remarkable. However, without effective prevention strategies, infections will likely continue to outstrip our ability to provide sustained antiretroviral therapy to all those who need it.

■ MOTHER TO CHILD TRANSMISSION

In the developed world, interruption of MTCT focuses on suppression of HIV-1 replication in the pregnant woman using standard combination antiretroviral therapy (HAART)

Table 73-4. Recommendations on Initiation of Antiretroviral Therapy in Treatment-Naive Adult and Adolescent Patients with Chronic HIV Infection in Resource Limited Settings

CD4 ⁺ Criteria	Recommendation
<200 cells/mm ³	Treat irrespective of clinical stage
200–350 cells/mm ³ Stage 4 disease and some stage 3 (e.g., TB) All other individual	Initiate antiretroviral therapy Consider treatment and initiate before CD4 ⁺ cell count drops below 200/mm ³
>350 cells/mm ³	Do not initiate therapy

Adapted from World Health Organization. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents in Resources-Limited Settings: Towards Universal Access Recommendations for a Public Health Approach*, 2006.

guided, in many situations, with resistance testing (Table 73-3). Many clinicians would include zidovudine in the combination because of older efficacy data³⁰⁶ and considerable experience with this agent, and avoid efavirenz because of the risk of teratogenicity. Given that nevirapine should be avoided in women with CD4⁺ cell counts greater than 250/mm³, many MTCT regimens are protease inhibitor-containing regimens. Women who do not meet guidelines for treatment based on clinical status (CD4⁺ cell count, plasma HIV RNA level, and/or clinical symptoms) may discontinue therapy after delivery. HIV-1-infected women in developed countries should not breast feed their infants regardless of treatment status.

Full discussion of MTCT in the developing world setting is beyond the scope of this text.^{307,308} Single-dose nevirapine decreases vertical transmission substantially, is cost-effective, and can be implemented on a large scale.³⁰⁹ However, this strategy selects for nevirapine resistance in a substantial proportion of the women,^{217,218} and this may have an impact on subsequent NNRTI-based therapy.³¹⁰ Strategies to decrease selection of resistant virus in the mother are under investigation.³¹¹

■ ANTIRETROVIRAL DRUGS FOR PREVENTION

There are three ways antiretroviral therapy can be used to prevent transmission of HIV: by treatment of the infected individual, as preexposure prophylaxis (PrEP) or as PEP. This topic has been extensively reviewed.³¹²

The belief that ART treatment of the infected subject can interrupt transmission to discordant sexual partners comes from the well-recognized relationship between the viral load and horizontal transmission probability³¹³ and the experiences with HAART and MTCT. In addition,

recent observational studies have noted greatly reduced transmission of HIV in discordant couples where a partner has started ART.³¹⁴

The belief that ART can prevent HIV acquisition before or after exposure stems from extensive experiments with nonhuman primates. Tenofovir provided to macaques shortly before or within 72 hours after exposure reduces the probability of HIV transmission.³¹⁵ However, more recent work with tenofovir–emtricitidine suggests that the latter combination is more reliable in the macaque model.³¹⁶

Careful consideration of antiviral therapy for PEP has, de facto, become the standard of care in many settings and has been the subject of intense, worldwide policy formation. In all cases, therapy must be based on risk assessment, be started emergently, and use ART combinations that recognize the possibility of de novo resistance, toxicity, and adherence, and in some cases genital tract pharmacology.

Percutaneous exposure to blood from an infected individual carries an approximately 0.3% chance of seroconversion.³¹⁷ Mucous membrane exposure to HIV-1-infected blood or other body fluids conveys less risk.³¹⁸ The use of antiretroviral therapy as postexposure prophylactic therapy is now accepted standard of care for blood or specific body fluid exposures in the health-care setting. PEP following sexual exposure remains controversial. CDC recommendations for the PEP of occupational exposures to HIV are summarized in Table 73-5.³¹⁸ Some experts, including the authors, would strongly consider three-drug therapy in any setting in which PEP is being offered. The optimal duration for administration of PEP is unknown. Four weeks of therapy is recommended. PEP should begin as soon as possible after exposure, though the interval between exposure and initiation of PEP at which PEP is no longer effective is unknown.

Table 73-5. Recommendations for HIV Postexposure Prophylaxis

Percutaneous				
Exposure type	Infection Status of the Sources			
	HIV class 1 (low viral load)	HIV class 2 (AIDS, high viral load, resistant virus)	Unknown HIV Status ^c	Unknown Sources (e.g., needle box)
Less severe (solid needle or superficial injury)	Two-drug PEP ^a	≥Three-drug PEP ^b	No PEP; consider two-drug PEP if source had HIV risk factors	No PEP: consider two-drug PEP if exposure HIV-infected source is likely
More severe (hollow bore, deep puncture, visible blood, needle used in artery or vein)	≥Three-drug PEP	≥Three-drug PEP	No PEP; consider two-drug PEP if source had HIV risk factors	No PEP: consider two-drug PEP if exposure to HIV-infected source is likely
Mucous Membrane and nonintact skin				
Exposure type	HIV class 1 (low viral load)	HIV class 2 (AIDS, high viral load, resistant virus)	Unknown HIV Status ^c	Unknown Sources (e.g., needle box)
Small volume (few drops)	Consider two-drug PEP	Two-drug PEP	Generally no PEP warranted	Generally no PEP warranted
Large volume (e.g., major blood splash)	Two-drug PEP	≥Three-drug PEP	No PEP; consider two-drug PEP if source had HIV risk factors	No PEP: consider two-drug PEP if exposure to HIV-infected source is likely

^aTwo-drug PEP consists of two NRTI one of which is either lamivudine or emtricitabine; the preferred other is either zidovudine or tenofovir all at standard doses.

^bThree-drug PEP consists of the NRTI combinations listed above plus lopinavir/ritonavir at standard doses. Alternatives include atazanavir RTV, fosamprenavir RTV, Indinavir with or without RTV, Saquinavir RTV, nelfinavir, efavirenz.

^cIf the source patient is found to be HIV negative PEP should stop.

Note: If the source patient has resistant virus or a complex treatment history, PEP should NOT be delayed but expert opinion should be sought and the PEP regimen may be tailored to the viral variants likely to be present in the source. Resistance testing of the source virus may be useful, though not recommended by the CDC. PEP should NOT be delayed for results of resistance, viral load, or HIV testing from the source patient.

Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep* 2005; 54: 1–17.

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Preventing Opportunistic Infections Among HIV-Infected Persons

Jonathan E. Kaplan and Henry Masur

The natural history of untreated infection with the human immunodeficiency virus (HIV) is characterized by an inexorable decline in host immunity, culminating in the appearance of opportunistic infections (OIs) that define the acquired immunodeficiency syndrome (AIDS). In the early years of the AIDS epidemic, before treatment was available, the average time from acquisition of HIV infection to development of AIDS was estimated to be 8–11 years.¹

The circulating CD4⁺ T lymphocyte count is the best indicator of current susceptibility to OIs and to short-term prognosis. Because of the relationship between the CD4⁺ T lymphocyte count and the risk of OI, this parameter is the standard indicator for when specific chemoprophylactic regimens should be initiated. For example, *Pneumocystis jiroveci* pneumonia (PCP) generally occurs when the CD4⁺ T lymphocyte count is below 200 cells/mm³,³ and prophylaxis against PCP is recommended for persons with CD4⁺ T lymphocyte counts below this level. Disseminated *Mycobacterium avium* complex (MAC) disease generally occurs at CD4 counts less than 50 cells/mm³ (Fig. 74-1).

Chemoprophylaxis against PCP was recommended for adults and adolescents in 1989² and for HIV-exposed/infected children in 1991.³ Prophylaxis against MAC was recommended in 1994.⁴ The USPHS/IDSA Guidelines for the prevention of OIs in HIV-infected persons, which includes recommendations for chemoprophylactic, vaccine, and behavioral interventions, were first published in 1995,⁵ were revised in 1997, 1999, and 2002,^{6–8} and are undergoing further revision at the time of this writing.

The most significant intervention against OIs has been combination antiretroviral therapy (ART), introduced (as triple drug therapy) in 1995. Following the introduction of triple drug ART, incidence of all major OIs dropped markedly, including many for which specific prophylaxis and treatment were unavailable (Fig. 74-2). This effect was so pronounced that the incremental benefit of chemoprophylaxis and other prevention measures in persons on ART could be reasonably questioned. However, in one study, survival benefits of PCP and MAC prophylaxis and pneumococcal vaccination in AIDS patients were demonstrated even in the

presence of ART.⁹ Furthermore, low CD4⁺ T lymphocyte counts indicate immediate risk of OI, whereas the benefits of ART are only gradually accrued over a 3–6-month period.¹⁰ Therefore, chemoprophylaxis against OIs continues to be recommended based on CD4⁺ T lymphocyte count regardless of ART treatment, although many such regimens can be discontinued when CD4⁺ T lymphocyte counts increase in persons successfully treated with ART.⁸

Prevention of OIs in HIV-infected persons begins with the diagnosis of HIV. It is sobering that PCP, a preventable infection in HIV-infected persons, continues to occur and remains one of the most common AIDS-presenting illnesses, even in the era in which most AIDS cases are diagnosed immunologically, based on a CD4⁺ T lymphocyte count less than 200 cells/mm³.¹¹ In an analysis of cases of PCP reported in CDC's Adult and Adolescent Spectrum of Disease Project, 43% of cases of PCP occurred in persons previously undiagnosed with HIV or otherwise not in care (Fig. 74-3). Of the estimated 1,100,000 HIV-infected persons in the United States, about 1/4 are thought to be unaware of their HIV status.¹² Therefore, counseling and testing of persons at risk for HIV are critical for OI prevention, as well as for preventing transmission of HIV to others. HIV testing should be offered to persons with identifiable behavioral risk factors for HIV (men who have sex with men, injecting drug users, and persons with multiple sex partners) and persons with medical conditions suggestive of HIV infection.¹¹ In addition, all pregnant women should be tested for HIV.¹¹

This chapter summarizes important interventions for preventing OIs in HIV-infected persons; these recommendations apply to both persons taking and not taking ART. For the sake of brevity, not all materials presented in the USPHS/IDSA guidelines for preventing OIs in HIV-infected persons are included here. However, as in the USPHS/IDSA guidelines, recommendations are divided into those for preventing exposure to OI pathogens, those for preventing first episodes of OI, and those for preventing disease recurrence. Chemoprophylaxis and vaccination recommendations included in the USPHS/IDSA

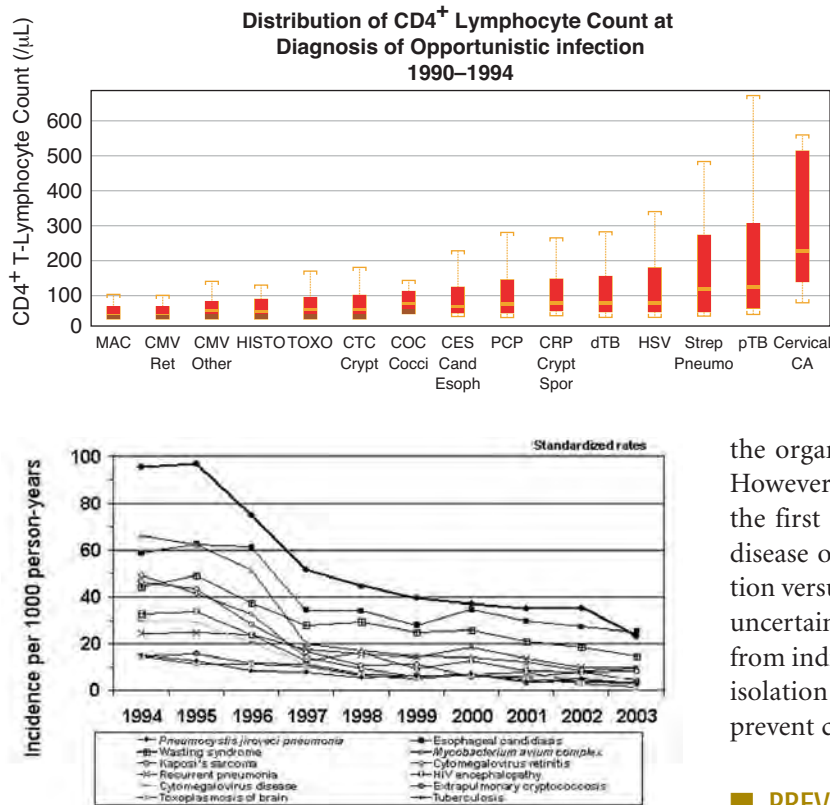


FIGURE 74-1. Distribution of CD4⁺ lymphocyte counts at diagnosis of opportunistic infection, 11 U.S. cities, 1990-1994. Source: Adult and Adolescent Spectrum of HIV Disease Project, Centers for Disease Control and Prevention. The bar represents the median CD4⁺ value; the box, the interquartile (25-75%) range; and the brackets, the range of values, excluding outliers. MAC = disseminated *Mycobacterium avium* complex; CMV = cytomegalovirus; HISTO = histoplasmosis; TOXO = toxoplasmosis; CTC = cryptococcosis; COC = coccidioidomycosis; CES = Candida esophagitis; PCP = *Pneumocystis jiroveci* pneumonia; CRP = cryptosporidiosis; dTB = disseminated tuberculosis; HSV = disseminated herpes simplex virus; CA = cancer.

FIGURE 74-2. Annual trends in the 12 most common incident opportunistic illnesses, Adult and Adolescent Spectrum of HIV Disease Project, 1994-2003. Incidence rates are standardized to the population of AIDS cases reported nationally by CD4 count, age, sex, race, HIV risk mode, and birth origin.

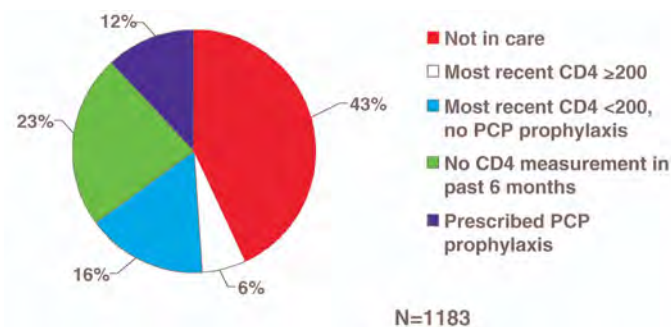


FIGURE 74-3. Classification of cases of *Pneumocystis jiroveci* pneumonia, Adult and Adolescent Spectrum of HIV Disease Project, 2000-2003.

guidelines, including those for discontinuing prophylaxis in patients whose CD4⁺ T lymphocyte counts have increased in response to ART, are included (Tables 74-1 to 74-3).

PNEUMOCYSTIS JIROVECI PNEUMONIA (PCP)

■ PREVENTING EXPOSURE

Although an environmental source may exist, *P. jiroveci* infection appears to be spread primarily from human to human. Thus, preventing exposure to humans, who are excreting

the organism, would be a logical method to avoid disease. However, almost all humans appear to be infected during the first few years of life,¹³⁻¹⁵ and it is not clear how often disease occurs due to reactivation of a latent focus of infection versus recent acquisition of a new strain.¹⁶⁻¹⁸ Given these uncertainties, it is reasonable to isolate susceptible patients from individuals known to have PCP. However, whether such isolation would prevent transmission of *P. jiroveci* and prevent cases of PCP is unknown.

■ PREVENTING DISEASE

Chemotherapy has been proven to prevent PCP and to prolong survival for HIV-infected patients. Patients with CD4⁺ T cell counts <200 cells/mm³ or <14% are known to be susceptible.¹⁹⁻²¹ Risk increases with decreasing CD4⁺ T lymphocyte count. In addition, patients with a history of PCP and patients who have had oropharyngeal candidiasis should be offered prophylaxis regardless of their CD4⁺ T lymphocyte count.^{19,20}

About 10-15% of cases of PCP occur in patients with CD4⁺ T lymphocyte counts >200 cells/mm³.¹⁹ Some but not all of these patients would have been eligible for PCP prophylaxis due to history of oral candidiasis. However, prophylaxis is not recommended for these patients in general because a very large number of patients would require prophylaxis in order to prevent a small number of cases of PCP.

Other risk factors for PCP include a previous episode of pneumonia of any type, unexplained weight loss, high HIV viral load, positive plasma CMV PCR, history of AIDS-defining illness, and rapid decline in CD4⁺ T lymphocyte count.²⁰

Trimethoprim-sulfamethoxazole (TMP-SMX) is the prophylactic agent of choice.^{2,22-25} TMP-SMX is more effective than other agents and is reasonably well tolerated. Patients may develop nausea and vomiting, rash, pruritis, hepatitis, anemia, leucopenia, or thrombocytopenia due to this agent. However, these complications are rarely life threatening. Chemoprophylaxis can often be continued despite these toxicities.

Table 74-1. Prophylaxis to Prevent First Episode of Opportunistic Disease Among Adults and Adolescents Infected with HIV

Pathogen	Indication	Preventive Regimen	
		First Choice	Alternative
I. Strongly recommended as standard of care			
<i>Pneumocystis jirovecii</i>	CD4 ⁺ count of <200/ μ L or oropharyngeal candidiasis	Trimethoprim-sulfamethoxazole (TMP-SMZ), 1 double-strength tablet (DS) by mouth, daily or TMP-SMZ, 1 single-strength tablet (SS) by mouth daily	Dapsone, 50 mg by mouth, twice daily or 100 mg by mouth daily; dapsone, 50 mg by mouth daily plus pyrimethamine, 50 mg by mouth weekly plus leucovorin, 25 mg by mouth weekly; dapsone, 200 mg by mouth plus pyrimethamine, 75 mg by mouth plus leucovorin, 25 mg by mouth weekly; aerosolized pentamidine, 300 mg monthly via Respigard II™ nebulizer (manufactured by Marquest, Englewood, Colorado); atovaquone, 1500 mg by mouth daily; TMP-SMZ, 1 DS by mouth three times weekly
<i>Mycobacterium tuberculosis</i> , Isoniazid-sensitive	Positive test for latent <i>M. tuberculosis</i> infection (tuberculin skin test or interferon-gamma release assay), or prior positive test without treatment, or contact with person with active tuberculosis, regardless of latent <i>M. tuberculosis</i> test result	Isoniazid, 300 mg by mouth plus pyridoxine, 50 mg by mouth daily for 9 mo or isoniazid, 900 mg by mouth plus pyridoxine, 100 mg by mouth, twice weekly for 9 mo	Rifampin, 600 mg by mouth daily for 4 mo or rifabutin 300 mg by mouth daily for 4 mo;
Isoniazid-resistant	Same as previous pathogen; increased probability of exposure to isoniazid-resistant tuberculosis	Rifampin, 600 mg by mouth daily for 4 mo or rifabutin, 300 mg by mouth daily for 4 mo	
Multidrug-resistant (isoniazid and rifampin)	Same as previous pathogen; increased probability of exposure to multidrug-resistant tuberculosis	Choice of drugs requires consultation with public health authorities; depends on susceptibility of isolate from source patient	
<i>Toxoplasma gondii</i>	Immunoglobulin G (μ gG) antibody to <i>Toxoplasma</i> and CD4 ⁺ count of <100/ μ L	TMP-SMZ, 1 DS by mouth daily	TMP-SMZ, 1 SS by mouth daily; dapsone, 50 mg by mouth daily plus pyrimethamine, 50 mg

(Continued)

Table 74-1. (Continued)

Pathogen	Indication	Preventive Regimen	
		First Choice	Alternative
			by mouth weekly plus leucovorin, 25 mg by mouth weekly; dapsone, 200 mg by mouth plus pyrimethamine, 75 mg by mouth plus leucovorin, 25 mg by mouth weekly; atovaquone, 1500 mg by mouth daily with or without pyrimethamine, 25 mg by mouth daily plus leucovorin, 10 mg by mouth daily
<i>Mycobacterium avium</i> complex	CD4 ⁺ count of <50/μL	Azithromycin, 1200 mg by mouth weekly or clarithromycin, 500 mg by mouth twice daily	Rifabutin, 300 mg by mouth daily; azithromycin, 1200 mg by mouth weekly plus rifabutin, 300 mg by mouth daily
Varicella-zoster virus (VZV)	Substantial exposure to chickenpox or shingles for patients who have no history of either condition or, if available, negative antibody to VZV	Varicella-zoster immune globulin (VZIG), 5 vials (1.25 mL each) intramuscularly, administered <96 h after exposure, ideally in <48 h	—
II. Usually recommended			
<i>Streptococcus pneumoniae</i>	CD4 ⁺ count of >200/μL	23-valent polysaccharide vaccine, 0.5 mL intramuscularly	—
Hepatitis B virus	All susceptible patients (i.e., antihepatitis B core antigen-negative)	Hepatitis B vaccine: 3 doses	—
Influenza virus	All patients (annually, before influenza season)	Inactivated trivalent influenza virus vaccine: one annual dose (0.5 mL) intramuscularly	Oseltamivir, 75 mg by mouth daily (influenza A or B); Rimantadine, 100 mg by mouth twice daily; or amantadine, 100 mg by mouth twice daily (influenza A only)
Hepatitis A virus	All susceptible patients at increased risk for hepatitis A infection (i.e., antihepatitis A virus-negative) (e.g., illegal drug users, men who have sex with men, hemophiliacs) or patients with chronic liver disease, including chronic hepatitis B or C	Hepatitis A vaccine: two doses	—

Table 74-1. (Continued)

Pathogen	Indication	Preventive Regimen	
		First Choice	Alternative
III. Evidence for efficacy but not routinely indicated			
Bacteria	Neutropenia	Granulocyte-colony-stimulating factor (G-CSF), 5–10 µg/kg body weight subcutaneously daily for 2–4 wks or granulocyte-macrophage colony-stimulating factor (GM-CSF), 250 µg/m ² subcutaneously for 2–4 wks	—
<i>Cryptococcus neoformans</i>	CD4 ⁺ count of <50/µL	Fluconazole, 100–200 mg by mouth daily	Itraconazole capsule, 200 mg by mouth daily
<i>Histoplasma capsulatum</i>	CD4 ⁺ count of <100/µL, endemic geographic area	Itraconazole capsule, 200 mg by mouth daily	—

Table 74-2. Prophylaxis to Prevent Recurrence of Opportunistic Disease After Chemotherapy for Acute Disease Among Adults and Adolescents Infected with HIV

Pathogen	Indication	Preventive Regimen	
		First Choice	Alternative
I. Recommended as standard of case			
<i>Pneumocystis jiroveci</i>	Prior <i>P. jiroveci</i> pneumonia (PCP)	Trimethoprim-sulfamethoxazole (TMP-SMZ), 1 double-strength tablet (DS) by mouth daily; TMP-SMZ 1 single-strength tablet (SS) by mouth daily	Dapsone, 50 mg by mouth twice daily or 100 mg by mouth daily; dapsone, 50 mg by mouth daily plus pyrimethamine, 50 mg by mouth weekly plus leucovorin, 25 mg by mouth weekly; dapsone, 200 mg by mouth plus pyrimethamine, 75 mg by mouth plus leucovorin, 25 mg by mouth weekly; aerosolized pentamidine, 300 mg every month via Respirgard II™ nebulizer (manufactured by Marquest, Englewood, Colorado); atovaquone, 1500 mg by mouth daily; TMP-SMZ, 1 DS by mouth 3 times weekly

(Continued)

Table 74-2. (Continued)

Pathogen	Indication	Preventive Regimen	
		First Choice	Alternative
<i>Toxoplasma gondii</i>	Prior toxoplasmic encephalitis	Sulfadiazine, 500–1000 mg by mouth 4 times daily plus pyrimethamine, 25–50 mg by mouth daily plus leucovorin, 10–25 mg by mouth daily	Clindamycin, 300–450 mg by mouth every 6–8 h plus pyrimethamine, 25–50 mg by mouth daily plus leucovorin 10–25 mg by mouth daily; atovaquone, 750 mg by mouth every 6–12 h with or without pyrimethamine, 25 mg by mouth daily plus leucovorin, 10 mg by mouth daily
<i>Mycobacterium avium</i> complex	Documented disseminated disease	Clarithromycin, 500 mg by mouth twice daily plus ethambutol, 15 mg/kg body weight by mouth daily with or without rifabutin, 300 mg by mouth daily	Azithromycin, 500 mg by mouth daily plus ethambutol, 15 mg/kg body weight by mouth daily with or without rifabutin, 300 mg by mouth daily
Cytomegalovirus	Prior retinitis	Valganciclovir 900 mg by mouth daily; or ganciclovir sustained-release implant every 6–9 months with or without oral valganciclovir	Ganciclovir, 5–6 mg/kg body weight/day intravenously 5–7 d weekly; foscarnet, 90–120 mg/kg body weight intravenously daily; cidofovir, 5 mg/kg body weight intravenously every other week with probenecid 2 gm by mouth 3 h before the dose followed by 1 gm by mouth 2 h after the dose, and 1 gm by mouth 8 h after the dose (total of 4 gm); or fomivirsen 1 vial (330 µg) injected into the vitreous, then repeated every 2–4 wk
<i>Cryptococcus neoformans</i>	Documented disease	Fluconazole, 200 mg by mouth daily	Amphotericin B, 0.6–1.0 mg/kg body weight intravenously weekly–3 times weekly; itraconazole, 200-mg capsule by mouth daily
<i>Histoplasma capsulatum</i>	Documented disease	Itraconazole capsule, 200 mg by mouth twice daily	Amphotericin B, 1.0 mg/kg body weight intravenously weekly
<i>Coccidioides immitis</i>	Documented disease	Fluconazole, 400 mg by mouth daily	Amphotericin B, 1.0 mg/kg body weight intravenously weekly; itraconazole, 200-mg capsule by mouth twice daily
Salmonella species, (nontyphi)	Bacteremia	Ciprofloxacin, 500 mg by mouth twice daily for >2 mo	Antibiotic chemoprophylaxis with another active agent

(Continued)

Table 74-2. (Continued)

Pathogen	Indication	Preventive Regimen	
		First Choice	Alternative
II. Recommended only if subsequent episodes are frequent or severe			
Herpes simplex virus	Frequent/severe recurrences	Valacyclovir, 500 mg by mouth twice daily; or famciclovir, 250 mg by mouth twice daily	Acyclovir, 200 mg by mouth 3 times daily or 400 mg by mouth twice daily;
Candida (oropharyngeal or vaginal)	Frequent or severe recurrences	Fluconazole, 100–200 mg by mouth daily	Itraconazole solution, 200 mg by mouth daily
Candida (esophageal)	Frequent or severe recurrences	Fluconazole, 100–200 mg by mouth daily	Itraconazole solution, 200 mg by mouth daily

Table 74-3. Criteria for Starting, Discontinuing, and Restarting Opportunistic Infection Prophylaxis for Adults with HIV

Opportunistic Illness	Criteria for Initiating Primary Prophylaxis	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Initiating Secondary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis	Criteria for Restarting Secondary Prophylaxis
<i>Pneumocystis jiroveci</i> pneumonia	CD4 ⁺ count of <200 cells/μL or oropharyngeal Candida	CD4 ⁺ count of >200 cells/μL for ≥ 3 mo	CD4 ⁺ count of < 200 cells/μL	Prior <i>Pneumocystis jiroveci</i> pneumonia	CD4 ⁺ count of >200 cells/μL for ≥ 3 mo	CD4 ⁺ count of <200 cells/μL
Toxoplasmosis	Immunoglobulin G (IgG) antibody to <i>Toxoplasma</i> and CD4 ⁺ count of <100 cells/μL	CD4 ⁺ count of >200 cells/μL for ≥ 3 mo	CD4 ⁺ count of <100–200 cells/μL	Prior toxoplasmic encephalitis	CD4 ⁺ count of >200 cells/μL sustained (e.g., ≥ 6 mo) and completed initial therapy and asymptomatic for <i>Toxoplasma</i>	CD4 ⁺ count of <200 cells/μL
Disseminated <i>Mycobacterium avium</i> complex (MAC)	CD4 ⁺ count of <50 cells/μL	CD4 ⁺ count of >100 cells/μL for ≥ 3 mo	CD4 ⁺ count of <50–100 cells/μL	Documented disseminated disease	CD4 ⁺ count of >100 cells/μL sustained (e.g., ≥ 6 mo) and completed 12 mo of MAC therapy and asymptomatic for MAC	CD4 ⁺ count of <100 cells/μL

(Continued)

Table 74-3. (Continued)

Opportunistic Illness	Criteria for Initiating Primary Prophylaxis	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Initiating Secondary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis	Criteria for Restarting Secondary Prophylaxis
Cryptococcosis		Not applicable	Not applicable	Documented disease	CD4 ⁺ count of >100–200 cells/μL sustained (e.g., ≥ 6 mo) and completed initial therapy and asymptomatic for cryptococcosis	CD4 ⁺ count of <100–200 cells/μL
Histoplasmosis		Not applicable	Not applicable	Documented disease	No criteria recommended for stopping	Not applicable
Coccidioidomycosis		Not applicable	Not applicable	Documented disease	No criteria recommended for stopping	Not applicable
Cytomegalovirus retinitis		Not applicable	Not applicable	Documented retinitis	CD4 ⁺ count of >100–150 cells/μL sustained (e.g., ≥ 6 mo) and no evidence of active disease; regular ophthalmic examination	CD4 ⁺ count of <100–150 cells/μL

One double strength tablet daily is the preferred regimen.⁸ However, one single strength tablet daily and one double strength tablet two or three times weekly are also effective.^{24,25} The double strength tablet regimen is effective against *Toxoplasma gondii*²⁶ and bacterial respiratory pathogens^{22,27} and is probably more effective than one single strength tablet daily. However, the higher dose regimen is probably not as well tolerated.

If patients do not tolerate TMP-SMX and the toxicity is not life threatening, the drug can often be successfully reintroduced by a gradual dose escalation. Oral regimens for desensitization have been published.^{28,29}

Dapsone and dapsone plus pyrimethamine are alternatives to TMP-SMX that have a high degree of efficacy.^{22,30,31} However, 70% of patients with hypersensitivity to TMP-SMX will have a hypersensitivity response to dapsone as well. Aerosolized pentamidine²³ and atovaquone^{32,33} are also reasonable alternatives. Atovaquone is expensive and absorption depends on food intake. Aerosolized pentamidine requires a

specialized facility for administration, and the coughing induced has the potential to spread concurrent respiratory pathogens.

Breakthroughs of PCP occur primarily in patients who are nonadherent with CD4⁺ T lymphocyte counts <50 cells/mm³ and patients receiving a regimen other than TMP-SMX.^{21,34}

Prophylaxis against PCP can be safely discontinued if patients demonstrate a CD4⁺ T lymphocyte response to ART with a count rising to >200 cells/mm³ for at least 3 months.^{8,35–43} If the CD4⁺ T lymphocyte count subsequently falls below this level, prophylaxis should be reinstated.

■ PREVENTING RELAPSE/RECURRENCE

Secondary prophylaxis, or chronic maintenance therapy, should be continued for life in patients with HIV infection who have survived an episode of PCP unless they initiate ART and their CD4⁺ T lymphocyte count increases to >200 cells/mm³ for ≥3 months.^{8,41} Numerous studies have demonstrated that

the risk of acquiring PCP in such patients is extremely low. However, if the CD4⁺ T lymphocyte count falls below 200 cells/mm³ again due to failure of ART or nonadherence, PCP prophylaxis should be reinitiated.

TOXOPLASMIC ENCEPHALITIS

■ PREVENTING EXPOSURE

T. gondii is transmitted to humans via ingestion of inadequately cooked meat or by inadvertent ingestion of cat feces.^{44,45} About 20% of individuals in the United States are infected with *Toxoplasma* compared to much higher prevalence in other countries; in Europe and certain developing countries, 60–80% of adult populations are infected.^{46–48} Most disease in humans appears to be due to reactivation of latent infection, although some cases appear to be due to acute, adult-acquired infection.

Patients with HIV infection can modify their behavior to reduce the risk of exposure to *Toxoplasma*. Eating meat that is fully cooked and avoiding contact with felines that are at risk for infection, i.e., those that eat uncooked meat, or are allowed to hunt small rodents outside, are potential strategies. Felines transmit *Toxoplasma* to humans via their feces. *Toxoplasma* oocysts in the feces become infectious after several days and can persist in dried feces for many months.⁴⁴ Transmission may occur when a cat litter box is emptied, during which time the oocysts may contaminate hands and be ingested or may be aerosolized and inhaled. Therefore, having another person dispose of the cat litter, emptying the litter box daily, and wearing gloves may reduce the risk of exposure.

■ PREVENTING DISEASE

HIV-infected individuals should be tested for IgG antibody to *Toxoplasma*.⁸ Individuals who are seropositive, i.e., those who have evidence of chronic infection, are candidates for chemoprophylaxis when their CD4⁺ T lymphocyte counts fall below 100 cells/mm³. There are virtually no well-documented cases of toxoplasmosis occurring in seronegative patients when the serology is performed in a reference laboratory. It must be pointed out, however, that some laboratories use relatively insensitive assays, and thus cases have been well documented where routine testing revealed a negative IgG test result.⁴⁹

The chemoprophylaxis of choice for IgG seropositive individuals with a CD4⁺ T lymphocyte count <100 cells/mm³ is TMP-SMX. One double strength tablet daily is recommended. There is less evidence supporting the use of a single strength tablet. Dapsone-pyrimethamine is an effective alternative.^{30,31} Atovaquone, with or without pyrimethamine, may also be effective.

From a practical perspective, the decision about *Toxoplasma* prophylaxis will be largely influenced by the

decision regarding PCP prophylaxis, which is triggered at a higher CD4⁺ T cell count. However, clinicians should recognize that one of the disadvantages of aerosolized pentamidine is its lack of activity against toxoplasmosis.^{22,26}

Prophylaxis against toxoplasmosis can be safely discontinued if patients demonstrate a CD4⁺ T lymphocyte response to ART with a count rising to >200 cells/mm³ for at least 3 months.^{8,50,51} If the CD4⁺ T lymphocyte count subsequently falls below 100 cells/mm³, prophylaxis should be reinstated.

■ PREVENTING RELAPSE/RECURRENCE

Secondary prophylaxis, or chronic maintenance therapy for toxoplasmosis should be continued for life unless the patient demonstrates immunologic response to ART.⁸ If a patient has received at least 6 weeks of antitoxoplasma therapy, the lesions are stable and the CD4⁺ T lymphocyte count has increased to >200/mm³ for at least 6 months, chronic maintenance therapy can be discontinued.⁸ Some clinicians would not stop therapy until the lesion disappears on MRI, but in some patients scarring and distorted anatomy persist indefinitely. If the CD4⁺ T lymphocyte count subsequently falls below 200 cells/μL prophylaxis should be reinstated.

CRYPTOSPORIDIOSIS

■ PREVENTING EXPOSURE

Cryptosporidiosis is a common worldwide intestinal parasite that is spread by fecal-oral spread from human to human or animal to human.^{52–56} This spread can occur by direct contact or via contaminated water.^{57,58} Children in day care centers are one reservoir. Cats and dogs, especially young ones, can also be infected and spread this parasite via their feces. There have been large outbreaks of cryptosporidiosis associated with public drinking water.⁵⁹ Outbreaks have also been associated with water parks, presumably because babies defecated into the water, and the parasites survived despite routine chlorination.^{60,61} Sexual contact, especially contact involving rectal intercourse, is also a mode of spread of this organism.

Patients with HIV can reduce their likelihood of acquiring cryptosporidia by avoiding contact with kittens and puppies, especially those from commercial breeders, or those that have been stray. Avoiding diapering infants who have been in childcare, or using gloves and handwashing after such exposure should also help reduce risk. Patients should also take precautions to avoid fecal exposure during anal intercourse.

HIV-infected patients should also be aware that surface water, and many municipal water supplies can be contaminated with *Cryptosporidium*. However, there is insufficient evidence to recommend that patients avoid swimming or avoid drinking municipal water except in outbreak situations.

■ PREVENTING DISEASE AND RELAPSE/RECURRENCE

No drug is known to be effective for preventing disease or for preventing recurrence. Some data have suggested that either rifabutin or clarithromycin, when used to prevent MAC disease, will also reduce the incidence of cryptosporidiosis.^{62,63} However, these data are not convincing enough to warrant recommending these drugs for this purpose.

MICROSPORIDIOSIS

■ PREVENTING EXPOSURE

Microsporidiosis, due to several different species of microsporidia, is thought to be acquired by exposure to infected animals or humans, especially via their stool.^{64–67} However, the routes of transmission have not been well defined.

■ PREVENTING DISEASE AND RELAPSE/RECURRENCE

Chemoprophylaxis is not recommended for microsporidiosis. No drug is known to be effective against *Enterocytozoon bieneusi*, the most frequent microsporidial cause of diarrhea. Albendazole and fumagillin appear to be effective against other species of microsporidia,^{68,69} but whether chemoprophylaxis provides any benefit is unknown.

When patients have been successfully treated for microsporidial disease, it would be logical to continue the effective drug as long as the CD4⁺ T lymphocyte count is below 100 cells/mm³, but there are no data confirming the efficacy or safety of such an approach.

TUBERCULOSIS

■ PREVENTING EXPOSURE

Since *Mycobacterium tuberculosis* causes disease exclusively in humans, and since patient populations at high risk for tuberculosis can be identified, there are strategies that logically could reduce exposure to *M. tuberculosis*.^{70–75} Employment on a pulmonary service in a hospital, or work in correctional facilities, with the homeless, or with certain immigrant populations could place patients at high risk for exposure to *M. tuberculosis*. Patients can be counseled regarding the risks of such activities and the feasibility of using masks to prevent transmission in such settings.

■ PREVENTING DISEASE

When HIV infection is first recognized, patients should be tested for *M. tuberculosis* infection using a tuberculin skin test (TST) or one of the new *in-vitro* assays that determine interferon (IFN) - gamma release in response to peptides

move specific for *M. tuberculosis*.^{8,76–78} Testing should be repeated annually if the patient has a significant risk of exposure to TB. Consideration should also be given to repeating the test if the initial test was performed when the patient was profoundly immunosuppressed, i.e., CD4⁺ T lymphocyte count <200 cells/mm³, and the patient has had a substantial increase in CD4⁺ T lymphocyte count due to ART.

All HIV-infected persons who have a positive test for *M. tuberculosis* infection should undergo chest radiography and clinical evaluation to rule out active TB.⁸ HIV-infected persons who have symptoms suggestive of TB should promptly undergo chest radiography and clinical evaluation regardless of their *M. tuberculosis* infection test result.

All HIV-infected persons, regardless of age, who have a positive test for *M. tuberculosis* infection but have no evidence of active TB and no history of treatment for active or latent TB should be treated for latent TB infection.^{8,79,80} Isoniazid daily or twice weekly for 9 months is the preferred regimen. A 4 month course of rifampin or rifabutin can also be used.^{8,80,81} The combination of rifampin plus pyrazinamide for 2 months has been shown to provide benefit, but severe hepatotoxicity and death have been observed in some HIV-uninfected patients who received this regimen.⁸² Therefore, it should not be used.

Rifampin and rifabutin both have substantial p450 cytochrome enzyme interactions.⁸⁰ They must be used with caution when concurrent drugs are administered to avoid increased toxicity or reduced efficacy of either the rifamycin or the other drugs.

■ PREVENTING RELAPSE/RECURRENCE

Tuberculosis is unusual among HIV-associated OIs in that it rarely recurs after completion of a full course of therapy, if the organism was sensitive to the chemotherapeutic agents used. Thus, after successful completion of therapy, chronic maintenance therapy is not necessary.

DISSEMINATED MYCOBACTERIUM AVIUM COMPLEX INFECTION

■ PREVENTING EXPOSURE

Mycobacterium avium-intracellulare is ubiquitous in dust, dirt, and in animals.^{83,84} Thus, it is not feasible to avoid exposure to this organism. Most humans have been exposed. It is not certain how often active disease is due to endogenous flora that were previously acquired, and how often disease is due to a recently acquired infection.

■ PREVENTING DISEASE

Adults and adolescents who have HIV infection should receive chemoprophylaxis against disseminated MAC

disease if they have a CD4⁺ T lymphocyte count of <50 cells/mm³.^{4,8} Clarithromycin^{85–87} or azithromycin⁸⁷ are the preferred prophylactic agents. The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a difference in survival when compared with azithromycin alone do not warrant a routine recommendation for this regimen.⁸⁷ In addition to their preventive activity for MAC disease, clarithromycin and azithromycin each confer protection against respiratory bacterial infections.

If clarithromycin or azithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for MAC disease, although rifabutin-associated drug interactions make this agent difficult to use.^{85,88} Before prophylaxis is initiated, disseminated MAC disease should be ruled out by clinical assessment, which might include obtaining a blood culture for MAC if warranted. Because treatment with rifabutin could result in rifampin resistance among persons who have active TB, active TB should also be excluded before rifabutin is used for prophylaxis.

Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to ART with an increase in CD4⁺ T lymphocyte counts to >100 cells/mm³ for ≥3 months.^{8,89} Two substantial randomized, placebo controlled trials and observational data have demonstrated that such patients can discontinue primary prophylaxis with minimal risk of developing MAC.^{90,91} If the CD4⁺ count subsequently falls below 50–100 cells/mm³, prophylaxis should be reinstated.

■ PREVENTING RELAPSE/RECURRENCE

Patients with disseminated MAC disease should receive life-long secondary prophylaxis (chronic maintenance therapy), unless immune reconstitution occurs as a result of ART.⁸ Patients are at low risk for recurrence of MAC when they have completed a course of >12 months of treatment for MAC, remain asymptomatic with respect to MAC signs and symptoms, and have a sustained increase (e.g., >6 months) in their CD4⁺ T lymphocyte counts to >100 cells/mm³ after ART.⁹² Secondary prophylaxis should be reintroduced if the CD4⁺ T lymphocyte count decreases to <100 cells/mm³.

BACTERIAL RESPIRATORY INFECTIONS

■ PREVENTING DISEASE

Adults and adolescents who have a CD4⁺ T lymphocyte count of ≥200 cells/mm³ should be administered a single dose of 23-valent polysaccharide pneumococcal vaccine (PPV) if they have not received this vaccine during the previous

5 years.^{93–96} One randomized placebo-controlled trial of PPV in Africa paradoxically demonstrated an increase in pneumonia among vaccinated subjects.⁹⁷ However, multiple observational studies in the United States have not identified increased risk associated with vaccination and have demonstrated benefit in persons with CD4⁺ T lymphocyte counts >200 cells/mm³.^{93–96} The majority of HIV specialists believe that the potential benefit of pneumococcal vaccination in the United States outweighs the risk. Immunization may also be considered for patients with CD4⁺ T lymphocyte counts of <200 cells/mm³, although clinical evidence has not confirmed efficacy. Revaccination can be considered for patients who were initially immunized when their CD4⁺ T lymphocyte counts were <200 cells/mm³ and whose CD4⁺ counts have increased to >200 cells/mm³ in response to ART. The recommendation to vaccinate is increasingly pertinent because of the increasing incidence of invasive infections with drug-resistant (including TMP-SMZ-, macrolide-, and β-lactam-resistant) strains of *Streptococcus pneumoniae*.

The duration of the protective effect of primary pneumococcal vaccination is unknown. Periodic revaccination should be considered, perhaps every 5 years.⁹⁵ However, no evidence confirms clinical benefit from revaccination.

TMP-SMX, when administered daily for PCP prophylaxis, reduces the frequency of bacterial respiratory infections. This should be considered in selecting an agent for PCP prophylaxis.²² However, indiscriminate use of this drug (when not indicated for PCP prophylaxis or other specific reasons) might promote development of TMP-SMX-resistant organisms. Thus, TMP-SMX should not be prescribed solely to prevent bacterial respiratory infection. Similarly, clarithromycin administered daily⁸⁶ and azithromycin administered weekly⁸⁷ for MAC prophylaxis might be effective in preventing bacterial respiratory infections; this should be considered in selecting an agent for prophylaxis against MAC disease. However, these drugs also should not be prescribed solely for preventing bacterial respiratory infection.

■ PREVENTING RELAPSE/RECURRENCE

Secondary prophylaxis (chronic maintenance therapy) after successful completion of antibiotic treatment for bacterial respiratory tract infections is not indicated, although administration of antibiotic chemoprophylaxis to HIV-infected patients who have frequent recurrences of serious bacterial respiratory infections might be considered.

The most effective method to prevent bacterial pneumonia in HIV-infected patients is probably optimization of ART. Annual influenza vaccine might be useful in preventing pneumococcal superinfection of influenza.⁸

BACTERIAL ENTERIC INFECTIONS

■ PREVENTING EXPOSURE

HIV-infected patients can reduce the risk of exposure to many enteric pathogens by avoiding certain high-risk food items. These include raw or undercooked poultry, raw eggs, raw seafood, and unpasteurized dairy products. Cross contamination is another route of infection that can be avoided through good food hygiene practices.

Animals can also be vectors for enteric bacterial pathogens. Kittens and puppies less than 6 months of age, stray animals, and animals from commercial breeders can all pose enhanced risk for transmitting enteric organisms. Pet reptiles, chicks, and ducks can also transmit such bacteria.

HIV-infected travelers to areas with poor sanitation need to be especially cautious about ingesting potentially contaminated food or water. HIV-infected patients need to consider carefully the likelihood of enteric infection when deciding whether to travel and should be aware of what medical resources will be available.

■ PREVENTING DISEASE

Preventive antibacterial agents are not recommended chronically to reduce the acquisition of enteric bacterial infections. While prophylactic antibacterial agents would be expected to be effective for short-term protection, they are associated with obvious toxicities. Chronic administration of antibiotics also promotes the development of antibiotic resistant flora.

■ PREVENTING RELAPSE/RECURRENCE

HIV-infected patients with Salmonella bacteremia have a high likelihood of relapse. Such patients should receive long-term prophylaxis with an active antibacterial agent. Whether such therapy needs to be continued lifelong is unknown.

BARTONELLOSIS

■ PREVENTING EXPOSURE

Among the multiple species of Bartonella, *B. henselae* and *B. quintana* are the most common causes of human disease among patients with HIV infection. *B. henselae* causes long-lasting infection in felines.^{98–101} Cat fleas, and probably cat scratches, bites, and licks can transmit this infection.^{102–104} Cats less than 1 year of age are more likely to be infected than older cats.

B. quintana is transmitted by lice.^{105,106} Homeless individuals are the patients most often recognized with disease caused by this organism.^{107,108} Improved hygiene should reduce the likelihood of infection.

■ PREVENTING DISEASE

Antibacterial prophylaxis for these infections is not recommended.

■ PREVENTING RELAPSE/RECURRENCE

Following therapy for acute Bartonella infection, patients should receive secondary prophylaxis (chronic maintenance therapy). Therapy with erythromycin, azithromycin, or doxycycline should be considered.^{109–111} There are no large studies that clearly define the optimal length of secondary prophylaxis, or the relationship of CD4⁺ T lymphocyte count to relapse.

CANDIDIASIS

■ PREVENTING EXPOSURE

Candida are ubiquitous in the environment.^{112–114} All humans are colonized with these organisms. Thus, prevention of acquisition of Candida is not likely to be a successful strategy for reducing the incidence of Candida disease. However, in health-care settings, fluconazole resistant Candida are likely to be common, and using barrier precautions to reduce superinfection of patients would seem to be a reasonable strategy.

■ PREVENTING DISEASE

Primary chemoprophylaxis with fluconazole is effective for reducing the frequency of candidiasis and cryptococcosis.^{115,116} However, chronic administration of fluconazole is expensive and is associated with toxicities and drug interactions and it promotes the development of azole resistant yeast. In addition, Candida almost never cause invasive disease. Mucosal candidiasis can be readily treated in most cases. Thus, the majority of clinicians would not recommend primary drug prophylaxis for candidiasis.

■ PREVENTING RELAPSE/RECURRENCE

Chronic maintenance therapy following resolution of acute candidiasis is not recommended by most experts for the same reasons that primary prophylaxis is not usually advocated.⁸ However, some recommend secondary prophylaxis for several months following an episode of candida esophagitis. There may be other patients in whom relapses are so frequent or so severe that chronic therapy could be considered. In such a case, fluconazole or itraconazole would be reasonable options to consider. However, since azoles are cytochrome p450 inhibitors, drug interactions must be considered. In addition, the emergence of azole resistant Candida is a particular concern.

CRYPTOCOCCOSIS

■ PREVENTING EXPOSURE

Cryptococcus neoformans is present in bird feces.^{117–119} However, there is no strategy known to be effective for avoiding exposure to this organism.

■ PREVENTING DISEASE

Primary prophylaxis with fluconazole or itraconazole is effective for reducing the incidence of cryptococcosis.¹¹⁵ However, as discussed above for candidiasis, most experts would not recommend primary prophylaxis solely to prevent cryptococcosis. First, the incidence of cryptococcosis is not high in most settings. Second, cryptococcal disease can be readily treated if it occurs. Third, no survival benefit has been demonstrated for prophylaxis against this disease.

Clinical disease could theoretically be prevented by screening patients periodically with serum cryptococcal antigen testing and treating CRAG+ persons before symptoms develop.¹²⁰ However, the likelihood of this test being positive in asymptomatic patients is low and the efficacy of such a strategy has not been demonstrated.

■ PREVENTING RELAPSE/RECURRENCE

Patients who have completed an initial course of therapy for cryptococcosis have a high likelihood of recurrence unless ART results in immune reconstitution. Thus, maintenance therapy with fluconazole is recommended for life unless the patient has successfully completed initial therapy, is asymptomatic, and the CD4⁺ T lymphocyte count has increased to >100–200 cells/mm³ for at least 6 months on ART.^{8,121–123} If the CD4⁺ count subsequently falls to below these levels, secondary prophylaxis should be reinstated.

HISTOPLASMOSIS

■ PREVENTING EXPOSURE

Acquisition of histoplasmosis can be associated with certain high-risk activities that involve exposure to bird feces, including chicken feces.¹²⁴ Thus, working in chicken coops, or disturbing soil below bird-roosting sites, or cleaning areas where birds have roosted are all high-risk activities.

■ PREVENTING DISEASE

Routine skin testing with histoplasmin and serologic testing for *Histoplasma* antibody or antigen in histoplasmosis-endemic areas are not predictive of disease and also are not generally available. Data from a prospective randomized controlled trial indicate that itraconazole can reduce the frequency

of histoplasmosis among patients who have advanced HIV infection and who live in histoplasmosis-endemic areas.¹²⁵ However, no survival benefit was observed among persons receiving itraconazole. Nevertheless, prophylaxis with itraconazole can be considered for patients with CD4⁺ T lymphocyte counts <100 cells/mm³ who are at high risk because of occupational exposure or who reside in a community with a hyperendemic rate of histoplasmosis (≥ 10 cases/100 patient-years).

■ PREVENTING RELAPSE/RECURRENCE

Patients who have completed an initial course of therapy for histoplasmosis are at high risk of recurrence unless they receive chronic maintenance therapy. Itraconazole is the drug of choice.^{8,126,127} Some experts would use tablets because that is the preparation used in most trials that have demonstrated efficacy. Others would use the oral formulation since it is better absorbed. However, better absorption is associated with increased toxicity, especially nausea and vomiting. Some specialists advocate measuring serum levels of itraconazole: free itraconazole levels of 1 mg/mL or free plus hydroxylated metabolite of 2 g/mL are considered sufficient. Patients whose CD4⁺ T lymphocyte count has increased to >100 cells/mm³ on ART may be able to discontinue maintenance therapy, but the number of persons in whom prophylaxis has been discontinued is too small to allow recommending this approach with confidence.¹²⁷

COCCIDIOIDOMYCOSIS

■ PREVENTING EXPOSURE

Coccidioides is transmitted by aerosolization of spores of *Coccidioides immitis*. In endemic areas, activities that increase risk include those related to exposure to dust and soil, e.g., working in building excavation sites, farming, and gardening.^{128–130} Dust storms are also likely to be associated with acquiring infection.

Prior infection can be assessed by the coccidioidin skin test. However, this skin test is not predictive of disease and therefore is not generally recommended. Serologic tests can also identify infection but they are not sufficiently useful to warrant routine use.

■ PREVENTING DISEASE

Primary chemoprophylaxis is not recommended for coccidioidomycosis.

■ PREVENTING RELAPSE/RECURRENCE

After completing therapy for coccidioidomycosis, patients should receive life long therapy with either fluconazole or

itraconazole.^{8,131} Patients who have a CD4⁺ T lymphocyte count >100 cells/mm³ may be able to discontinue their azole therapy, but the number of patients in whom treatment has been discontinued is too small to recommend this approach.

CYTOMEGALOVIRUS DISEASE

■ PREVENTING EXPOSURE

CMV can be acquired by sexual contact, by exposure to oral secretions, or via blood transfusion. In the United States, 60–70% of the population has been infected.¹³² Almost all patients who are HIV-infected also have latent infection with CMV.¹³³ The use of barrier contraception can prevent infection or reinfection with CMV.

■ PREVENTING DISEASE

Oral ganciclovir has been shown to be effective for preventing the development of CMV disease in patients with CD4⁺ T lymphocyte counts <50 cells/mm³.^{134,135} However, oral ganciclovir is associated with toxicity, especially marrow suppression, is expensive and may induce development of ganciclovir-resistant CMV. In addition, the drug is no longer commercially available.

Oral ganciclovir has been replaced by oral valganciclovir, which attains higher serum levels than oral ganciclovir. These higher serum levels are associated with higher rates of adverse events. Thus, oral valganciclovir, while likely to be effective for prophylaxis, is not recommended.⁸

Acyclovir is not effective for prophylaxis against CMV. The optimal approach to prevent severe sequelae of CMV disease is to recognize manifestations early and to institute appropriate treatment.

■ PREVENTING RELAPSE/RECURRENCE

After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) is recommended for life,⁸ unless patients generate a CD4⁺ T lymphocyte count >100–150 cells/mm³ for 6 months on ART and have stable disease.^{136–141} Regimens effective for chronic suppression include oral valganciclovir, parenteral or oral ganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration through intraocular implant or repetitive intravitreal injections of fomivirsen.^{142–146}

Repetitive intravitreal injections of ganciclovir, foscarnet, and cidofovir have been effective for secondary prophylaxis of CMV retinitis in uncontrolled case series. However, clinicians should recognize that local therapy

does not provide systemic protection or protection for the contralateral eye.

If chronic maintenance therapy is stopped, patients should be followed carefully by an experienced ophthalmologist. If the lesion is near the optic disk, some clinicians would be reluctant to discontinue it.

Chronic maintenance therapy is not routinely recommended for gastrointestinal disease but should be considered if a relapse occurs. There are few data about the need for chronic maintenance therapy following the infrequent cases of CMV pneumonia.

HERPES SIMPLEX VIRUS DISEASE

■ PREVENTING EXPOSURE

HIV-infected patients can acquire herpes simplex via sexual intercourse. Thus, latex condoms should be used to prevent exposure to HSV and other STIs and to prevent transmission of HIV to others. Patients should also avoid contact with obvious orolabial or genital HSV lesions.

■ PREVENTING DISEASE

Primary prophylaxis with acyclovir after exposure to HSV or to prevent an initial episode of HSV¹⁴⁷ is not recommended. Prompt therapy of acute episodes with acyclovir is preferred.

■ PREVENTING RELAPSE/RECURRENCE

Since HSV rarely disseminates, the preferred strategy for treating recurrent HSV is to treat episodes when they occur. However, chronic therapy with acyclovir will reduce recurrences of disease. If episodes are frequent or severe, chronic suppressive therapy is a logical strategy provided the virus is acyclovir-sensitive. Famciclovir and valacyclovir can also be used and have the advantage of more convenient dosing schedules.^{148–151}

VARICELLA-ZOSTER VIRUS DISEASE

■ PREVENTING EXPOSURE

HIV-infected persons who are seronegative for varicella-zoster virus (VZV) can acquire VZV by aerosol spread from an individual with primary varicella or disseminated zoster. Patients with dermatomal zoster can also transmit varicella via infected scabs.

If an HIV-infected patient is seronegative for varicella, immunization of household contacts is a useful strategy to reduce the likelihood that varicella infection will be introduced into the household.

■ PREVENTING DISEASE

Patients who are exposed to varicella zoster and who are VZV-seronegative should receive zoster immune globulin within 96 hours of exposure. Alternatively, patients might receive acyclovir, which can be given during the window of likely disease occurrence, i.e., from day 10 to day 20 in most patients. However, there is little evidence that either zoster immune globulin or acyclovir is effective in preventing VZV in HIV-infected persons.

Varicella vaccine contains live, attenuated virus. The safety of this vaccine in HIV-infected patients is not well studied at any CD4⁺ T cell count. Thus, the use of this vaccine in HIV-infected patients is not recommended.⁸

■ PREVENTING RELAPSE/RECURRENCE

Secondary prophylaxis to prevent the recurrence of zoster is not routinely indicated. However, if recurrences are frequent or severe, chronic therapy with acyclovir, famciclovir, or valacyclovir would be reasonable, but efficacy of these regimens has not been demonstrated in HIV-infected persons.

HCV INFECTION

■ PREVENTING EXPOSURE

In the United States, Hepatitis C virus (HCV) is transmitted primarily via injection drug use.¹⁵² A small percent of infections may be transmitted sexually and for another small segment the route is unknown.^{153–155} Thus, any intervention that can prevent injection drug use could be expected to reduce the incidence of HCV infection in HIV-infected persons. Since HCV is a blood-borne pathogen, any other practice that results in exposure to blood could potentially transmit HCV. Thus, tattooing or body piercing, if performed with unsterile equipment, could result in exposure to HCV.

■ PREVENTING DISEASE

Current guidelines recommend that all HIV-infected patients be screened for hepatitis C.⁸ Knowledge of HCV status is important for interpreting liver function test abnormalities, i.e., deciding whether such abnormal test results are due to antiretroviral drugs, other chemotherapeutic agents, or HCV. Such testing is also important for clinicians to determine whether further diagnostic studies are warranted to determine the severity of HCV disease and the need for therapeutic intervention.

Persons coinfecting with HCV and HIV should be advised not to drink excessive amounts of alcohol; avoiding alcohol altogether might be prudent because whether even occasional alcohol use increases the incidence of cirrhosis among HCV-infected persons is unclear.

Patients coinfecting with HCV and HIV who are susceptible to Hepatitis A virus (HAV) (i.e., lack antibody to HAV) should be vaccinated against hepatitis A, since hepatitis A can cause particularly severe disease in HCV-infected persons.⁸

HIV-infected persons should also be screened for hepatitis B coinfection.⁸ Seronegative persons should receive hepatitis B vaccine.

■ PREVENTING RELAPSE/RECURRENCE

For patients who have had a virologic and histologic response to therapy for hepatitis C, the optimal duration of therapy is unknown. Therefore, no recommendations are available for chronic maintenance therapy in this setting.^{156,157}

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Clinical Management of HIV Infection: Management of Opportunistic Infections

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INTRODUCTION

The widespread use of potent antiretroviral therapy (ART) and chemoprophylaxis for opportunistic infections (OIs) has resulted in a marked reduction of most OIs in human immunodeficiency virus (HIV) infected persons.¹⁻⁴ However, OIs continue to occur in both patients who are not receiving medical care and in patients who receive aggressive medical management.⁵

The persistence of OIs in the United States is due to several factors. Many persons remain unaware of their HIV diagnosis and do not receive ART or appropriate prophylaxis against OIs. Until access to care becomes more available in the United States, and until HIV testing and awareness improves, this population will continue to present with OIs as their initial indication of HIV infection. In addition, only a minority of those receiving ART will achieve and remain virologically suppressed.⁶ With ART being or becoming ineffective in some patients, long-term virological failure will cause progression of disease, and hence will increase the risk for OIs. These patients benefit from OI prophylactic strategies. Clinicians need to be cognizant of the value of such prophylaxis while they focus on optimizing ART.

DIAGNOSIS OF OPPORTUNISTIC INFECTIONS

When patients present with new symptoms or signs, clinicians are faced with the decision: should the physician attempt to establish a specific diagnosis, or treat the patient empirically. Such a decision depends on the resources available, the potential severity of the syndrome, and the certainty the clinician has that the correct causative process can be identified by either presumptively or specifically. For instance, for a patient presenting with dysphagia, white oral plaques, and a CD4⁺ T-cell count below 100 cells/ μ L, the pathogen is almost always azole *Candida*, and the disease is rarely life-threatening. Thus, empiric therapy with fluconazole would be a reasonable approach. Alternately, a patient with a similar CD4⁺ T-cell count and respiratory failure with

diffuse pulmonary infiltrates could have a wide variety of infectious and noninfectious processes causing respiratory failure. A specific diagnosis would be more urgent to be certain that the correct causative process was being treated.

Clinicians must be cognizant that HIV-infected patients can develop non-OIs. OIs are defined as those that occur with increased frequency or increased severity. HIV-infected patients are at risk of such infections regardless of their CD4⁺ T lymphocyte cell counts. For instance, pneumococcal respiratory infections and tuberculosis occur with increased incidence at all CD4⁺ T lymphocyte cell counts. However, as the CD4⁺ T lymphocyte cell count declines, the incidence and severity of OIs increase. In addition to the opportunistic processes, HIV-infected patients are also susceptible to community and hospital acquired pathogens that are not opportunistic. For instance, they can develop pneumonia due to *Legionella*, *Influenza*, or *Acinetobacter*. The issue to recognize is that non-OIs and other disease processes both occur and must be appropriately diagnosed and treated. This is especially relevant when HIV-infected patients have other risk factors such as advanced age, substance abuse, tobacco use, or environmental exposures.

When an HIV-infected patient presents, clinicians are often tempted to treat the patient empirically. This may well be appropriate, especially if the syndrome is not severe and the clinician is reasonably confident of the pathologic diagnosis. However, opportunistic processes can present in typical and atypical manners. Inadequately treated processes can progress rapidly and unnecessary drugs can produce preventable toxicity. Thus, establishing specific diagnoses to assure that treatment is appropriate remains an important strategy in dealing with this patient population.

ART: SHOULD IT BE INITIATED OR CONTINUED IN PATIENTS WITH OPPORTUNISTIC INFECTIONS?

When an OI is diagnosed, clinicians are often faced with the question as to whether or not ART should be started or continued. For patients not currently on ART and who have an

acute OI, there is a rational reason to consider starting ART. ART may increase immune function if the virus is susceptible to available drugs. Such therapy might hasten resolution of the syndrome and prevent other HIV-related complications from occurring. Thus, such therapy is an attractive option. There are a number of disadvantages to starting therapy. ART drugs are almost all oral; thus, patients with acute OIs may not be able to predictably absorb oral drugs if they are critically ill, or if they have gastrointestinal dysfunction. If serum levels of ART are suboptimal, HIV viral resistance may be promoted. Therefore, initiating ART when patients are acutely ill and unable to reliably take and absorb drugs may have serious long-term consequences relevant related to the success of ART.

If ART is absorbed, drug interactions with concurrent agents may substantially alter ART pharmacokinetics. Patients with acute OIs are often receiving multiple drugs to treat the OI and to treat concurrent and related problems. Thus, serum levels of either the antiretroviral agent, or the anti-infective, may be excessively high, promoting toxicity, or excessively low, reducing efficacy.

It is also important to note that when toxicities such as rashes or liver function abnormalities occur in patients with acute OIs, it will be difficult to determine if these are due to the OI, the recently introduced ART agents, or the drugs used to manage the OI. Thus, most clinicians would opt not to initiate ART unless there is a compelling reason such as a lack of alternative treatment of the OI, as might be the case with progressive multifocal leukoencephalopathy, cryptosporidiosis, or disease due to *Enterocytozoan bienewisi*.

The potential for immune reconstitution syndrome (IRIS) is another factor to consider when determining whether or not to initiate ART. IRIS occurs within days, weeks, or months of starting ART. As the viral load falls, even before the CD4⁺ T lymphocyte cell count rises, generalized and nonspecific immune activation decreases, and specific immune responses augment. In some patients, especially those with low CD4⁺ T lymphocyte cell counts and high viral loads who have a prompt response to ART, immunologic reactions can occur at sites of latent or active infection. Thus, for a patient who has never been symptomatic, and who is starting ART solely because of laboratory markers, clinical manifestations may occur at the site of a sequestered, clinically silent infection such as a fungal or mycobacterial focus. Focal lymphadenopathy, an inflammatory lung nodule or infiltrate, or dysfunction at some other organ can thus occur. These syndromes have been most often described in association with active or latent mycobacterial or fungal disease, but can occur with a wide variety of infectious and apparently noninfectious entities.

For patients with active infection, such as pulmonary tuberculosis, pneumocystosis, or cryptococcal meningitis, initiation of ART can be associated with exacerbation of the

clinically apparent disease. This may be undesirable for patients who already have significant organ dysfunction; it can even be life-threatening. Patients may manifest new clinical findings related to the causative organism. Patients with apparent pulmonary tuberculosis may develop worsening pulmonary disease or pericarditis or meningitis due to augmented inflammatory response at sites that had been clinically silent.

Patients who start ART after recovering from an OI may experience a flare in their apparently cured disease. Patients who have been successfully treated for CMV retinitis, for example, usually experience a flare in inflammation in their vitreous. This flare can be asymptomatic, or can obscure their vision. Patients who have been treated for tuberculosis or cryptococcal meningitis also have frequently been reported with such syndromes: adenopathy, fever, or focal organ dysfunction can develop and be mild or life-threatening.

How often these IRIS syndromes occur is not certain. Their frequency depends on host factors, such as the viral load and CD4⁺ T cell count at the time ART was initiated. The frequency of IRIS syndromes also depends on environmental factors: such syndromes are more common in areas endemic for tuberculosis or cryptococcosis than in areas where these diseases are unusual. There are many anecdotal reports and small series of these occurrences. How often they occur and what factors are predictive need further study. How to manage such syndromes has also not been clearly defined; nonsteroidal agents, corticosteroids, and ARV withdrawal have been used, but no guidelines currently exist to define when such interventions are appropriate.

An ongoing randomized controlled trial has been initiated within the Adult AIDS Clinical Trials Group comparing outcomes between ART-naive patients who start ART immediately after presentation with an acute OI, and patients who start ART at least 4 weeks after the OI has resolved. This trial should help identify the factors supporting early or delayed initiation of antiretrovirals. Current recommendations for treatment of common HIV-associated OIs are summarized in [Table 75-1](#), which is modified from current CDC guidelines.

■ PNEUMOCYSTIS JIROVECI

Pneumocystis pneumonia (PCP), which is caused by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*), remains a frequent initial manifestation of HIV infection.^{4,7} *P. jiroveci* is a fungus that appears to be ubiquitous in the environment.⁸ The taxonomy has been modified; *P. carinii* refers to the species that infects rodents, and *P. jiroveci* is the species that infects humans. Serologic data in the United States indicates that most humans become subclinically infected with *P. jiroveci* in childhood.⁹ There is emerging literature suggesting that primary infection and reinfections may be associated with clinical symptoms, including sudden

Table 75-1. Treatment of AIDS-Associated Opportunistic Infections in Adults

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
<i>Pneumocystis jiroveci</i> Pneumonia (PCP)	<p><i>Acute therapy:</i></p> <ul style="list-style-type: none"> Trimethoprim-Sulfamethoxazole (TMP/SMX): [15–20 mg TMP and 75–100 mg SMX]/kg/day IV given q6h or q8h (AI); or Same daily dose of TMP/SMX PO in 3 divided doses (AI); or TMP-SMX DS 2 tablets 3 times a day (AI) <p>Total duration = 21 days (AII)</p> <p><i>Chronic maintenance therapy</i> (secondary prophylaxis): First choice</p> <ul style="list-style-type: none"> Trimethoprim-sulfamethoxazole (TMP-SMX) 1 double-strength tablet (DS) PO QD (AI); or TMP-SMX 1 single-strength tablet (SS) PO QD (AI) <p>Alternatives</p> <ul style="list-style-type: none"> Dapsone 50 mg PO twice daily or 100 mg PO daily (BI); or Dapsone 50 mg PO daily plus pyrimethamine 50 mg PO weekly plus leucovorin 25 mg PO weekly (BI); or Dapsone 200 mg PO plus pyrimethamine 75 mg PO plus leucovorin 25 mg PO weekly (BI); aerosolized pentamidine 300 mg every month via Respigard II™ nebulizer (manufactured by Marquest, Englewood, Colorado) (BI); or Atovaquone 1500 mg PO daily (BI); or TMP-SMZ 1 DS PO 3 times weekly (CI) 	<p><i>For severe PCP:</i></p> <p>Pentamidine 4 mg/kg IV QD infused over at least 60 minutes (AI), some experts reduce dose to 3 mg/kg IV QD because of toxicities (BI)</p> <p><i>For mild-to-moderate PCP:</i></p> <ul style="list-style-type: none"> Dapsone 100 mg PO QD and TMP 15 mg/kg/day PO (3 divided dose) (BI); or Primaquine 15–30 mg (base) PO QD and Clindamycin 600–900 mg IV q6h to q8h or Clindamycin 300–450 mg PO q6h to q8h (BI); or Atovaquone 750 mg PO BID with food (BI); or Trimetrexate 45 mg/m² or 1.2 mg/kg IV QD with leucovorin 20 mg/m² or 0.5 mg/kg IV or PO q6h (leucovorin must be continued for 3 days after the last trimetrexate dose) (B1); addition of dapsone or sulfamethoxazole or sulfadiazine might improve efficacy (CIII) 	<p>Indications for corticosteroids (AI): PaO₂ <70 mm Hg at room air; or alveolar-arterial O₂ gradient >35 mm Hg</p> <p>Prednisone doses (beginning as early as possible and within 72 hours of PCP therapy) (AI): 40 mg BID days 1–5, 40 mg QD days 6–10, then 20 mg QD days 11–21</p> <p>IV methylprednisolone can be given as 75% of prednisone dose</p> <p>Chronic maintenance therapy (secondary prophylaxis) should be discontinued if CD4⁺ T lymphocyte count increases in response to ART from <200 to >200 cells/μL for ≥3 months (AI)</p>
<i>Toxoplasma gondii</i> encephalitis	<p><i>Acute therapy:</i></p> <p>Pyrimethamine 200 mg POx1, then 50 mg (<60 kg) to 75 mg (≥60 kg) PO QD and Sulfadiazine 1000 (<60 kg) to 1500 mg (≥60 kg) PO q6h + Leucovorin 10–20 mg PO QD (can increase up to 50 mg or higher) (AI)</p>	<ul style="list-style-type: none"> Pyrimethamine (leucovorin)* and Clindamycin 600 mg IV or PO q6h (AI); or TMP-SMX (5 mg/kg TMP and 25 mg/kg SMX) IV or PO BID (BI); or Atovaquone 1500 mg PO BID with meals (or nutritional supplement) 	<p>Adjunctive corticosteroids (e.g., dexamethasone) should be given when clinically indicated for treatment of mass effect attributed to focal lesions or associated edema (BIII) and discontinued as soon as clinically feasible</p>

(Continued)

Table 75-1. (Continued)

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
	<p>Total duration for acute therapy is at least 6 weeks (BII)</p> <p><i>Chronic maintenance therapy:</i> (Secondary Prophylaxis) <i>First choice:</i></p> <ul style="list-style-type: none"> Sulfadiazine 500–1000 mg PO 4 times daily plus pyrimethamine 25–50 mg PO daily plus leucovorin 10–25 mg PO daily (AI)- <p><i>Second choice:</i></p> <ul style="list-style-type: none"> Clindamycin 300–450 mg PO every 6–8 hours plus pyrimethamine 25–50 mg PO daily plus leucovorin 10–25 PO daily (BI); or Atovaquone 750 mg PO every 6–12 hours with or without pyrimethamine 25 mg PO daily plus leucovorin 10 mg PO daily (CIII) 	<p>and Pyrimethamine (leucovorin)* (BII); or</p> <ul style="list-style-type: none"> Atovaquone 1500 mg PO BID with meals (or nutritional supplement) and Sulfadiazine 1000–1500 mg PO q6h (BII); or Atovaquone 1500 mg PO BID with meals (BII); or Pyrimethamine (leucovorin)* and Azithromycin 900–1200 mg PO QD (BII) <p><i>For severely ill patients who cannot take oral meds:</i> TMP-SMX IV and Pyrimethamine PO (CIII)</p> <p>For other regimens with limited experience (CIII), see text.</p>	<p>Anticonvulsants should be administered to patients with a history of seizures (AIII)</p> <p><i>Secondary prophylaxis may be discontinued if:</i> free of TE signs and symptoms; and sustained CD4⁺ T lymphocyte count of >200 cells/μL for \geq6 months of ART (CIII)</p>
Cryptosporidiosis	<p>Symptomatic treatment of diarrhea (AIII)</p> <p>Effective ART therapy (to increase CD4⁺ count to >100 cells/μL) can result in complete, sustained clinical, microbiological and histologic resolution of HIV-associated cryptosporidiosis (AII)</p>	<p>Nitazoxanide 500 mg PO BID Paromomycin 25–35 mg/kg PO in 2 to 4 divided doses</p>	<p>Supportive care including hydration, nutritional support</p>
Microsporidiosis	<p>Initiate or optimize ART with immune reconstitution to CD4 >100 cells/μL (AII)</p> <p><i>For disseminated (not ocular) and intestinal infection attributed to microsporidia other than Enterocytozoon bienuesi:</i></p> <ul style="list-style-type: none"> Albendazole 400 mg PO BID (AII), continue until CD4 >200 cells/μL (AIII) <p><i>For ocular infection:</i></p> <ul style="list-style-type: none"> Fumidil B 3 mg/mL in saline (final conc. is fumagillin 70 μg/ml) eye drops continued indefinitely (not available in U.S.) (BII) and Albendazole 400 mg PO BID for management of systemic infection (BIII) 	<p><i>Disseminated disease:</i> Itraconazole 400 mg PO QD and Albendazole for disseminated disease attributed to <i>Trachipleistophora</i> or <i>Brachiola</i> (CIII)</p>	<p>Fluid support in patients with diarrhea resulting in severe dehydration (AIII)</p> <p>Nutritional supplement for patients with severe malnutrition and wasting (AIII)</p> <p>Treatment for ocular infection should be continued indefinitely (BIII). With immune reconstitution, it is possible that this treatment can be discontinued (CIII).</p> <p>Chronic maintenance therapy may be discontinued if patients (CIII):</p> <ul style="list-style-type: none"> Remain asymptomatic with regards to signs and symptoms of microsporidiosis;

Table 75-1. (Continued)

	<p>For gastrointestinal infections caused by <i>Enterocytozoon bienuesi</i>:</p> <ul style="list-style-type: none"> Fumagillin 60 mg PO QD (not available in U.S.) (BII) 		<ul style="list-style-type: none"> Sustained CD4⁺ T-lymphocyte counts >200 cells/μL for \geq6 months on ART
<i>Mycobacterium tuberculosis</i> (MTB)	<p>For drug-sensitive MTB</p> <p><i>Initial phase (8 weeks) (AI):</i></p> <p>Isoniazid (INH) 5 mg/kg (max: 300 mg) PO QD and [Rifampin 10 mg/kg (max: 600 mg) PO QD or Rifabutin 300 mg PO QD (or dose adjusted based on concomitant meds³)] and Pyrazinamide (PZA) (dose based on wt%) PO QD and Ethambutol (EMB) (dose based on wt%) PO QD</p> <p><i>Continuation phase (18 weeks) (AI):</i></p> <ul style="list-style-type: none"> INH 5 mg/kg (max: 300 mg) PO QD and [Rifampin 10 mg/kg (max: 600 mg) or Rifabutin 300 mg PO QD]; or INH 15 mg/kg (max 900 mg) PO BIW or TIW + [Rifampin 10 mg/kg (max: 600 mg) or Rifabutin 300 mg PO or TIW] <p>In patients with delayed clinical or microbiological response to initial therapy (e.g., sputum culture (+) after 2 months or if cavitory pulmonary lesions are present), total duration up to 9 months (BII)</p>	<p>Treatment for drug-resistant MTB:</p> <p><i>Resistant to INH:</i></p> <ul style="list-style-type: none"> discontinue INH (and streptomycin, if used) Rifamycin, PZA, and EMB for 6 months (BII); or Rifamycin and EMB for 12 months (preferably with PZA during at least first 2 months) (BII) <p><i>Resistant to rifamycin:</i></p> <ul style="list-style-type: none"> INH and PZA and EMB and a fluoroquinolone (e.g., levofloxacin 500 mg/day) for 2 months, followed by 10–16 additional months with INH and EMB and fluoroquinolone (BIII) <p><i>Multidrug resistant (MDR) TB, i.e., both INH and rifamycin resistant:</i></p> <ul style="list-style-type: none"> Therapy should be individualized based on resistance pattern and with close consultation with experienced specialist (AIII) <p>TB treatment in patients with liver disease</p> <p><i>If AST \geq3 times normal before treatment initiation:</i></p> <ul style="list-style-type: none"> Standard therapy with frequent monitoring; or Rifamycin and EMB and PZA for 6 months INH and rifamycin and EMB for 2 months, then INH and rifamycin for 7 months (BII) <p><i>For patients with severe liver disease:</i></p> <ul style="list-style-type: none"> Rifamycin and EMB for 12 months (preferably with another agent such as fluoroquinolone for first 2 months) (CII) 	<p>Treatment by Directly Observed Therapy (DOT) is strongly recommended for all HIV patients (AII).</p> <p>Rifabutin has less drug interaction potential and can be used in place of rifampin</p> <p>Rifapentine given once weekly can result in development of resistance, it is not recommended in HIV patients (EI)</p> <p>Twice weekly intermittent regimen containing rifamycin might lead to rifamycin resistance, particularly in advanced HIV patients with CD4 cell count <100 cells/μL; in this situation, therapy must be given as daily or 3 times weekly</p> <p>For paradoxical reaction that is not severe—may be treated with nonsteroidal anti-inflammatory drugs (NSAIDs) without change in TB or HIV medications (BIII)</p>

(Continued)

Table 75-1. (Continued)

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
Mycobacterium avium complex disease	<p><i>At least 2 drugs as initial therapy:</i> Clarithromycin 500 mg PO BID (AI) and Ethambutol 15 mg/kg PO QD (AI)</p> <p>Consider adding third drug for patients with advanced immunosuppression (CD4 <50), high mycobacterial loads, or in the absence of effective ART: Rifabutin 300 mg PO QD (AI) (dosage may be adjusted based on drug-drug interactions) (CIII)</p> <p>Duration (Chronic Maintenance Therapy): Lifelong therapy unless in patients with sustained immune recovery on ART (AII).</p> <p><i>Chronic maintenance therapy:</i> (Secondary Prophylaxis)</p> <p><i>First choice:</i></p> <ul style="list-style-type: none"> • Clarithromycin 500 mg PO twice daily (AI) plus ethambutol 15 mg/kg PO daily (AII); with or without rifabutin 300 mg PO daily (CI) <p><i>Second choice:</i></p> <ul style="list-style-type: none"> • Azithromycin 500 mg PO daily (AII) plus ethambutol 15 mg mg/kg body weight PO daily (AII); with or without rifabutin 300 mg PO daily (CI) 	<p><i>Alternative to clarithromycin:</i> Azithromycin 500–600 mg PO QD (AII)</p> <p><i>Alternative third or fourth drug for patients with more severe symptoms or disseminated disease (CIII):</i></p> <ul style="list-style-type: none"> • Ciprofloxacin 500–750 mg PO BID; or • Levofloxacin 500 mg PO QD; or • Amikacin 10–15 mg/kg IV QD 	<p>NSAIDs may be used for patients who experience moderate to severe symptoms attributed to ART-associated immune reconstitution syndrome (CIII)</p> <p>If symptoms persist, short term (4–8 weeks of systemic corticosteroid (20–40 mg of prednisone) can be used (CIII).</p> <p>Maintenance therapy can be discontinued in patients who (BII):</p> <ul style="list-style-type: none"> • completed ≥ 12 months therapy, and • remain asymptomatic, and • have sustained (≥ 6 months) CD4 count >100 cells/μL
Bacterial pneumonia	<p><i>Empiric therapy (targeting towards Streptococcus pneumoniae and Hemophilus influenzae):</i></p> <ul style="list-style-type: none"> • Extended spectrum cephalosporin (e.g., cefotaxime, or ceftriaxone) (AIII); or • Fluoroquinolone with enhanced activity against pneumococcus (e.g, gatifloxacin, levofloxacin, or moxifloxacin) (AIII) <p><i>Empiric therapy in patients with severe illness:</i></p> <ul style="list-style-type: none"> • Extended-spectrum cephalosporin and a macrolide (AIII) 	<p><i>For high-level penicillin-resistant isolates (MIC ≥ 4.0 $\mu\text{g/mL}$):</i></p> <ul style="list-style-type: none"> • Consider adding vancomycin or a fluoroquinolone (CIII) • <i>Empiric therapy in patients with severe immunodeficiency (CD4 ≤ 100), a known history of previous pseudomonas infection, bronchiectasis, or relative or absolute neutropenia) (BIII):</i> Broaden empiric coverage to include antimicrobials with activities against <i>P. aeruginosa</i> and other gram-negative bacilli, e.g. ceftazidime, cefepime, piperacillin- 	<p>Patients with CD4⁺ T-lymphocyte count of ≥ 200 cells/μL should receive a single dose of 23-valent polysaccharide pneumococcal vaccine (if not received during the preceding 5 years) (BII)</p> <p>Yearly influenza vaccine—might be useful in preventing pneumococcal superinfection after influenza respiratory infection (BII)</p> <p>Antibiotic prophylaxis may be considered in patients with</p>

Table 75-1. (Continued)

		tazobactam, a carbapenem, or high dose ciprofloxacin or levofloxacin	frequent recurrences (CIII)—caution should be taken for the risks for developing drug resistance and drug toxicities
		<ul style="list-style-type: none"> If ceftazidime or ciprofloxacin is used, addition of another antibacterial with optimal coverage for gram-positive infection is recommended 	
Salmonellosis	<p><i>Salmonella gastroenteritis:</i></p> <ul style="list-style-type: none"> Ciprofloxacin 500–750 mg PO BID (or 400 mg IV BID) (AIII) <p><i>Duration:</i></p> <ul style="list-style-type: none"> Mild gastroenteritis without bacteremia: 7–14 days (BIII) Advanced HIV (CD4 < 200) and/or bacteremia: at least 4–6 weeks (BIII) <p><i>Chronic Suppressive Therapy:</i></p> <ul style="list-style-type: none"> For patients with <i>Salmonella</i> bacteremia—ciprofloxacin 500 mg PO BID (BII). Should be given for ≥2 months or until ART-induced immune reconstitution (BIII) 	<ul style="list-style-type: none"> TMP-SMX PO or IV (BIII) Third generation cephalosporin such as ceftriaxone (IV) or cefotaxime (IV) (BIII) 	<p>Treatment is recommended in HIV patients because of high risk for bacteremia in this population (BIII)</p> <p>Newer fluoroquinolones (e.g., levofloxacin, gatifloxacin, or moxifloxacin) might also be effective (BIII)</p>
<i>Campylobacter jejuni</i> infections	<p><i>For mild disease:</i> might withhold therapy unless symptoms persist for several days</p> <p>Optimal therapy: not well defined; options include:</p> <ul style="list-style-type: none"> ciprofloxacin 500 mg PO BID (BIII); or azithromycin 500 mg PO QD (BIII) <p>*Consider addition of an aminoglycoside in bacteremic patients (CIII)</p> <p><i>Duration:</i></p> <ul style="list-style-type: none"> Mild to moderate disease: 7 days Bacteremia: at least 2 weeks 		<p>There is an increasing rate of quinolone resistance</p> <p>Antimicrobial therapy should be modified based on susceptibility reports</p> <p>Role of aminoglycoside is unclear</p>
Shigellosis	<p>Fluoroquinolone IV or PO for 3–7 days (AIII)</p> <p>Duration for bacteremia: 14 days (AIII)</p>	<ul style="list-style-type: none"> TMP-SMX DS 1 tab PO BID for 3–7 days; or (BIII) Azithromycin 500 mg PO on day 1, then 250 mg PO QD for 4 days (BIII) <p>Duration for bacteremia: 14 days (AIII)</p>	<p>Therapy is indicated both to shorten the duration of illness and to prevent spread of infection (AIII)</p> <p>Shigella infections acquired outside of U.S. have high rates of TMP-SMX resistance</p>

(Continued)

Table 75-1. (Continued)

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
Bartonella infections	<p><i>Non-CNS infections</i></p> <ul style="list-style-type: none"> Erythromycin 500 mg PO QID (or IV at same dose if unable to take PO) (AII); or Doxycycline 100 mg PO or IV q12h (AII) <p><i>CNS infections:</i></p> <ul style="list-style-type: none"> Doxycycline 100 mg PO or IV q12h (AIII) <p><i>Duration:</i> At least 3 months (AII) Life-long therapy for patients with relapse (AIII)</p>	<ul style="list-style-type: none"> Azithromycin 600 mg PO QD (BII) Clarithromycin 500 mg PO BID (BII) Fluoroquinolones have variable activity in case reports and in vitro—may be considered as alternative (CIII) 	
<i>Treponema pallidum</i> infection (syphilis)	<p><i>Early stage (primary, secondary, and early latent Syphilis):</i></p> <ul style="list-style-type: none"> Benzathine penicillin G 2.4 MIU IM for 1 (AII) <p><i>Late-latent disease (≥1yr or of unknown duration, without CNS involvement)</i></p> <ul style="list-style-type: none"> Benzathine penicillin G 2.4 MIU IM weekly for 3 doses (AIII) <p><i>Late-stage (Aortitis and gummata)</i></p> <ul style="list-style-type: none"> Infectious diseases consultation (AIII) <p><i>Neurosyphilis (CNS involvement including otic and ocular disease)</i></p> <ul style="list-style-type: none"> Aqueous crystalline penicillin G 3–4 MIU IV q4h or total dose by continuous IV infusion for 10–14 days (AII) +/- Benzathine penicillin G 2.4 MIU IM weekly for 3 after completion of IV therapy (CIII) 	<p><i>Early stage (primary, secondary, and early latent syphilis) treatment with close clinical monitoring (BIII):</i></p> <ul style="list-style-type: none"> Doxycycline 100 mg PO BID for 14 days; or Ceftriaxone 1 g IM or IV QD for 8–10 days; or Azithromycin 2 g PO for 1 dose <p><i>Late-latent disease (without CNS involvement):</i></p> <ul style="list-style-type: none"> Doxycycline 100 mg PO BID for 28 days (BIII) <p><i>Neurosyphilis:</i></p> <ul style="list-style-type: none"> Procaine penicillin 2.4 MIU IM QD and Probenecid 500 mg PO QID for 10–14 days (BII) +/- Benzathine penicillin G 2.4 MIU IM weekly for 3 after completion of above (CIII); or For penicillin allergic pts: Ceftriaxone 2 grams IM or IV QD for 10–14 days (CIII) 	<p>Desensitization to penicillin might be a better option than ceftriaxone in penicillin allergic patients with neurosyphilis (BIII)</p> <p>Combination of procaine penicillin and probenecid is not recommended for patients with history of sulfa allergy because these patients might be at risk for hypersensitivity reactions to probenecid</p>
Candidiasis (mucosal)	<p><i>Oropharyngeal candidiasis:</i></p> <p><i>Initial episodes (7–14 day treatment):</i></p> <ul style="list-style-type: none"> Fluconazole 100 mg PO QD (AI); or Itraconazole oral solution 200 mg PO QD (AI); or Clotrimazole troches 10 mg PO 5 times daily (BII); or 	<p><i>Fluconazole-refractory oropharyngeal candidiasis:</i></p> <ul style="list-style-type: none"> Itraconazole oral solution ≥200 mg PO QD (BII); or Amphotericin B suspension 100 mg/mL (not available in U.S.)—1 mL PO QID (CIII); or Amphotericin B deoxycholate 0.3 mg/kg IV QD (BII); or 	<p><i>Suppressive therapy—generally not recommended (DIII) unless patients have frequent or severe recurrences</i></p> <ul style="list-style-type: none"> Oropharyngeal candidiasis - fluconazole or itraconazole oral solution may be considered (CI).

Table 75-1. (Continued)

	<ul style="list-style-type: none"> Nystatin suspension 4–6 mL QID or 1–2 flavored pastilles 4–5 times daily (BII) <p><i>Esophageal candidiasis (14–21 days):</i></p> <ul style="list-style-type: none"> Fluconazole 100 mg (up to 400 mg) PO or IV QD (AI); or Itraconazole oral solution 200 mg PO QD(AI) Voriconazole 200 mg Po BID (AII) Caspofungin 50 mg IV qd (AII) <p><i>Vulvovaginitis:</i></p> <ul style="list-style-type: none"> Topical azoles (clotrimazole, butoconazole, miconazole, tioconazole, or terconazole) for 3–7 days (AII) Topical nystatin for 14 days (AII) Oral Itraconazole 200 mg BID for 1 day or 200 mg QD for 3 days (AII) Oral Fluconazole 150 mg for 1 dose (AII) 	<ul style="list-style-type: none"> Caspofungin 50 mg IV qD (BIII) Voriconazole 200 mg PO or IV BID (CIII) <p><i>Fluconazole-refractory esophageal candidiasis:</i></p> <ul style="list-style-type: none"> Caspofungin 50 mg QD (BIII); or Voriconazole 200 mg PO or IV BID (CIII) Amphotericin B 0.3–0.7 mg/kg IV QD (BII); or Amphotericin liposomal or lipid complex 3–5 mg/kg IV QD (BII) 	<ul style="list-style-type: none"> Vulvovaginal candidiasis: daily topical azole for recurrent cases (CII) Esophageal Candidiasis-fluconazole 100–200 mg daily (BI). <p>Chronic or prolong use of azoles might promote development of resistance.</p>
<i>Cryptococcus neoformans</i> meningitis	<p><i>Acute infection:</i></p> <ul style="list-style-type: none"> Amphotericin B deoxycholate 0.7 mg/kg IV QD ± flucytosine 25 mg/kg PO QID for 2 weeks (AI); or Liposomal Amphotericin B 4 mg/kg IV QD ± flucytosine 25 mg/kg PO QID for 2 weeks (AI) <p><i>Consolidation therapy:</i></p> <ul style="list-style-type: none"> Fluconazole 400 mg PO QD for 8 weeks or until CSF cultures are sterile (AI) <p><i>Maintenance Therapy:</i></p> <ul style="list-style-type: none"> Fluconazole 200 mg PO QD; life-long unless immune reconstitution as a result of ART (AI) 	<p><i>Acute infection (alternative):</i></p> <ul style="list-style-type: none"> Amphotericin B 0.7 mg/kg/day IV for 2 weeks (BI); or Fluconazole 400–800 mg/day (PO or IV) for less severe disease Fluconazole 400–800 mg/day (PO or IV) and flucytosine 25 mg/kg PO QID for 4–6 weeks (BII) <p><i>Consolidation therapy (alternative):</i></p> <ul style="list-style-type: none"> Itraconazole 200 mg PO BID (BI) <p><i>Maintenance therapy (alternative):</i></p> <ul style="list-style-type: none"> Amphotericin B 1 mg/kg IV per week—for patients with multiple relapse on azole(s) or intolerant of azole(s) (CI); or Itraconazole 200 mg PO QD—for patients intolerance of or failed fluconazole (BI) 	<p>Repeated lumbar puncture might be indicated as adjunctive therapy for patients with increased intracranial pressure (AII).</p> <p>Discontinuation of antifungal therapy can be considered in patients who remain asymptomatic, with CD4⁺ T-lymphocyte count >100–200 cells/μL for ≥6 months (CIII)</p> <p>Some might consider performing a lumbar puncture before discontinuation of maintenance therapy</p>
<i>Histoplasma capsulatum</i> infections	<p>Severe disseminated:</p> <p><i>Acute phase (3–10 days or until clinically improved):</i></p> <ul style="list-style-type: none"> Amphotericin B deoxycholate 0.7 mg/kg IV QD (AI); or Liposomal amphotericin B 4 mg/kg IV QD (AI) 	<p>Severe disseminated:</p> <p><i>Acute phase (alternative):</i></p> <ul style="list-style-type: none"> Itraconazole 400 mg IV QD (BIII) <p><i>Continuation phase alternatives:</i></p> <ul style="list-style-type: none"> Itraconazole oral solution (BIII) Fluconazole 800 mg QD (CII) 	<p>Acute pulmonary histoplasmosis in HIV-1 infected patients with CD4⁺ T-lymphocyte count >500 cells/μL might require no therapy (AIII).</p>

(Continued)

Table 75-1. (Continued)

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues (AIII).
	<p><i>Continuation phase (12 weeks):</i></p> <ul style="list-style-type: none"> Itraconazole 200 mg cap PO BID (AII) <p>Less severe disseminated:</p> <ul style="list-style-type: none"> Itraconazole 200 mg cap PO TID for 3 days, then 200 mg PO BID for 12 weeks (AII) <p>Meningitis:</p> <ul style="list-style-type: none"> Amphotericin B deoxycholate or liposomal for 12–16 weeks (AII) <p><i>Maintenance therapy (Chronic suppression):</i></p> <ul style="list-style-type: none"> Itraconazole 200 mg cap PO QD (AI) 	<p>Mild disseminated:</p> <ul style="list-style-type: none"> Fluconazole 800 mg PO QD (CII) 	<p>Some experts would consider discontinuation of antifungal therapy (CIII) in patients who are:</p> <ul style="list-style-type: none"> in remission serum and urine histoplasma antigen, 4 units completed 1 year itraconazole CD4 cells count > 150 cells/μL
Coccidioidomycosis	<p>Nonmeningeal infection:</p> <p><i>Acute phase (diffuse pulmonary or disseminated disease):</i></p> <ul style="list-style-type: none"> Amphotericin B deoxycholate 0.5–1.0 mg/kg IV QD continue until clinical improvement, usually 500–1000 mg total dose (AII) <p><i>Acute phase (milder disease):</i></p> <ul style="list-style-type: none"> Fluconazole 400–800 mg PO QD (BIII); or Itraconazole 200 mg PO BID (BIII) <p>Meningeal Infections:</p> <ul style="list-style-type: none"> Fluconazole 400–800 mg IV or PO QD (AII) <p><i>Chronic Suppressive Therapy</i></p> <ul style="list-style-type: none"> Fluconazole 400 mg PO QD (AII); or Itraconazole 200 mg capsule PO BID (AII) 	<p>Nonmeningeal infection:</p> <p><i>Acute phase (diffuse pulmonary or disseminated disease):</i></p> <ul style="list-style-type: none"> Some experts add azole to amphotericin B therapy (BIII) <p>Meningeal infections:</p> <ul style="list-style-type: none"> Intrathecal Amphoterin B (CIII) 	<p>Not enough data to recommend discontinuation of chronic suppressive therapy at this point.</p>
Invasive aspergillosis	<p>Voriconazole 400 mg IV or PO q12h for 2 days, then 200 mg q12h (AIII)</p> <p>Duration of therapy: based on clinical response</p>	<ul style="list-style-type: none"> Amphotericin B deoxycholate 1 mg/kg/day IV (AIII); or Lipid formulations of amphotericin B 5 mg/kg/day IV (AIII) Voriconazole and caspofungin (CIII) 	<p>Not enough data to recommend chronic suppression or maintenance therapy (CIII)</p>

Table 75-1. (Continued)

Cytomegalovirus (CMV) disease	<p>CMV retinitis: <i>For immediate sight-threatening lesions:</i> Ganciclovir (GCV) intraocular implant and valganciclovir 900 mg PO QD (AI)</p> <p><i>For peripheral lesions:</i> Valganciclovir 900 mg PO BID for 14–21 days, then 900 mg PO QD (AII)</p> <p><i>Chronic maintenance therapy (secondary prophylaxis):</i></p> <p>First choice:</p> <ul style="list-style-type: none"> Valganciclovir 900 mg by mouth daily (BI) Foscarnet 90–120 mg/kg body weight intravenously daily (AI); or <p>Second choice:</p> <ul style="list-style-type: none"> Cidofovir 5 mg/kg body weight intravenously every other week with probenecid 2 g by mouth 3 hours before the dose followed by 1 g by mouth 2 hours after the dose, and 1 g by mouth 8 hours after the dose (total of 4 g) (AI); or Fomivirsen 1 vial (330 µg) injected into the vitreous, then repeated every 2–4 weeks (AI); or <p>CMV esophagitis or colitis:</p> <ul style="list-style-type: none"> Ganciclovir IV or Foscarnet IV for 21–28 days or until signs and symptoms have resolved (BII); oral valganciclovir may be used if symptoms are not severe enough to interfere with oral absorption (BII) Maintenance therapy is generally not necessary, but should be considered after relapses (BII) <p>CMV pneumonitis:</p> <ul style="list-style-type: none"> Treatment should be considered in patients with histologic evidence of CMV pneumonitis and who do not respond to treatment of other pathogens (AIII) 	<p>CMV retinitis:</p> <ul style="list-style-type: none"> Ganciclovir 5 mg/kg IV q12h for 14–21 days, then 5 mg/kg IV QD (AI); or Ganciclovir 5 mg/kg IV q12h for 14–21 days, then Valganciclovir 900 mg PO QD (AI); or Foscarnet 60 mg/kg IV q8h or 90 mg/kg IV q12h for 14–21 days, then 90–120 mg/kg IV q24h (AI); or Cidofovir 5 mg/kg IV for 2 weeks, then 5 mg/kg every other weeks; each dose should be given with IV saline hydration and oral probenecid (AI); or Repeated intravitreal injections with fomivirsen (for relapses only, not as initial therapy) (AI) 	<p>Choice of initial therapy for CMV retinitis should be individualized, based on location and severity of the lesion(s), level of immunosuppression, and other factors such as concomitant medications and ability to adhere to treatment (AIII)</p> <p>Initial therapy in patients with CMV retinitis, esophagitis, colitis, and pneumonitis should include optimization of ART (BIII)</p> <p>Some experts suggest delaying ART in patients with CMV neurological disease due to concerns of worsening of condition as a result of immune recovery inflammatory reaction (CIII)</p> <p>Preemptive treatment of patients with CMV viremia without evidence of organ involvement is generally not recommended (DIII).</p> <p>Maintenance therapy for CMV retinitis can be safely discontinued in patients with inactive disease and sustained CD4⁺ T-lymphocyte (>100–150 cells/mm³ for ≥6 months); consultation with ophthalmologist is advised (BII)</p> <p>Patients with CMV retinitis who discontinued maintenance therapy should undergo regular eye examination for early detection of relapse (AIII).</p> <p>Immune recovery uveitis (IRU) might develop in the setting of immune reconstitution. Treatment of IRU: periocular corticosteroid or short courses of systemic steroid.</p>
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(Continued)

Table 75-1. (Continued)

Opportunistic Infections	Preferred Therapy and Duration	Alternative Therapy	Other Options/Issues
	<ul style="list-style-type: none"> The role of maintenance therapy is not yet established (CIII). <p>CMV neurological disease:</p> <ul style="list-style-type: none"> GCV IV and Foscarnet IV continue until symptomatic improvement (BII) Maintenance therapy should be continued for life (AI) 		Because of its poor oral bioavailability and with the availability of valganciclovir, oral ganciclovir should not be used (DIII).
Herpes simplex virus (HSV) disease	<p><i>Orolabial lesions and Initial or recurrent genital HSV:</i></p> <p>Famciclovir 500 mg PO BID or Valacyclovir 1 g PO BID or Acyclovir 400 mg PO TID for 7 days (AII)</p> <p><i>Moderate-to-severe mucocutaneous HSV infections:</i></p> <ul style="list-style-type: none"> Initial therapy Acyclovir 5 mg/kg IV q8h (AII) After lesions began to regress, change to Famciclovir 500 mg PO BID or Valacyclovir 1 g PO BID or Acyclovir 400 mg PO TID. (AII) Continue therapy until lesions have completely healed <p><i>HSV keratitis:</i></p> <ul style="list-style-type: none"> Trifluridine 1% ophthalmic solution, one drop onto the cornea every 2 hours, not to exceed 9 drops per day, for no longer than 21 days (AII) <p><i>HSV Encephalitis:</i></p> <ul style="list-style-type: none"> Acyclovir 10 mg/kg IV q8h for 14–21 days (AII) 	<p><i>Acyclovir-resistant HSV:</i></p> <ul style="list-style-type: none"> Foscarnet 120–200 mg/kg/day IV in 2–3 divided doses until clinical response (AI) Cidofovir 5 mg/kg IV weekly until clinical response (AI) <p><i>Alternative for acyclovir-resistant HSV infections:</i></p> <ul style="list-style-type: none"> Topical trifluridine Topical cidofovir <p><i>Note:</i> Both of the above preparations are not commercially available. Extemporaneous compounding of these topical products can be prepared using trifluridine ophthalmic solution and cidofovir for intravenous administration</p>	Chronic suppressive therapy with oral acyclovir, famciclovir, or valacyclovir may be indicated in patients with frequent or severe recurrences.
Varicella zoster virus (VZV) disease	<p><i>Primary VZV infection (chicken pox):</i></p> <ul style="list-style-type: none"> Acyclovir 10 mg/kg IV q8h for 7–10 days (AII) Switch to oral therapy (Acyclovir 800 mg PO QID or Valacyclovir 1g TID or Famciclovir 500 mg TID) after defervescent if there is no evidence of visceral involvement (AII) <p><i>Local dermatomal herpes zoster:</i></p> <ul style="list-style-type: none"> Famciclovir 500 mg or Valacyclovir 1 g PO TID for 7–10 days (AII) 		Corticosteroids for dermatomal zoster are not recommended (DIII)

Table 75-1. (Continued)*Extensive cutaneous lesion or visceral involvement:*

- Acyclovir 10 mg/kg IV q8h, continue until cutaneous and visceral disease clearly resolved (AIII)

Progressive Outer Retinal Necrosis (PORN):

- Acyclovir IV 10 mg/kg q8h and Foscarnet 60 mg/kg IV q8h (AIII)

infant death syndrome and exacerbation of chronic obstructive lung disease.^{10–12}

Pneumocystis is probably transmitted by respiratory spread from human to human. There is speculation that asymptomatic individuals can transmit infection and that disease can occur either due to reactivation of latent infection, or acquisition of a new strain. Thus, all episodes of PCP may not be due to reactivation of latent disease, but may represent reinfection with the same or a different strain of the organism.^{13,14}

Before the widespread use of ART and primary PCP prophylaxis, PCP occurred in 70–90% of patients with HIV infection.¹⁵ Approximately 90% of cases occurred among patients with CD4⁺ T lymphocyte cell counts <200 cells/ μ L.^{4,16} The current CD4⁺ T lymphocyte cell count continues to be the major determinant of susceptibility. The nadir CD4⁺ T lymphocyte cell count is not a major factor for determining susceptibility.^{3,17} Thus decisions regarding differential diagnosis and the need for chemoprophylaxis should be made on the basis of the current count. HIV viral load is also a risk factor for PCP. However, most decisions are made based on the CD4⁺ T lymphocyte cell count. A substantial number of cases of PCP in the United States continue to occur among patients who are not aware of their HIV infection. A significant number also occur among patients who are aware of their infection but are not receiving care.^{7,18}

Pneumocystis has an unusual tropism for the lung. The biologic basis of this tropism is not understood. However, from a clinical perspective, *P. jiroveci* rarely causes clinical disease outside the lungs. If patients are systematically imaged, lesions in the liver, spleen, and kidneys, that can resolve with therapy, can be identified, and thus appear to be due to pneumocystis. There are reports of occasional cases of pneumocystis involving the eye, ear, liver, spleen, kidney, and lymph nodes.^{19–21} Cases of disseminated disease with

abundant organisms in multiple capillary beds have been described.²² Many but not all of these cases occurred in patients receiving aerosolized pentamidine prophylaxis.^{19–22} Thus, these cases were purported to be related to high drug concentrations in the lung, with limited drug in other organs. Whether disseminated disease is truly more common among patients receiving aerosol pentamidine prophylaxis, or whether reporting bias has overrepresented such cases, is not clear.

Patients with pneumocystis present with fever, shortness of breath, and dyspnea. There is nothing specific for PCP as opposed to other pulmonary processes in the presentation. The cough is usually nonproductive, or productive of scant amounts of watery sputum. The shortness of breath typically presents slowly, progressing over many days or weeks. There is usually no chest pain or hemoptysis. A substernal “catching” on deep inspiration can often be elicited.^{23,24} The onset is typically more indolent than the presentation of PCP in patients immunosuppressed by virtue of corticosteroids or antineoplastic chemotherapy.

Physical examination is often unrevealing, except for fever and tachypnea. Routine laboratory testing is also unremarkable except for nonspecific elevations of serum lactate dehydrogenase.²⁵ Hypoxemia may range from mild-moderate (room air arterial oxygen [pO₂] of >70 mm Hg or alveolar-arterial O₂ difference [A-a] DO₂ <35 mm Hg) to moderate-to-severe levels (pO₂ <70 mm Hg or [A-a] DO₂ >35 mm Hg). Patient and health-care provider education can enable cases to be identified earlier in their natural history, before patients have severe symptoms, and at a time when their likelihood of responding to therapy is greatest.

The typical chest radiograph is one of diffuse and symmetrical bilateral increased interstitial markings.^{26–30} When patients are identified early, before symptoms are severe, the chest radiograph may be normal, although a high-resolution

CT scan will show diffuse interstitial infiltrates. As disease progresses, interstitial infiltrates become apparent, followed by diffuse alveolar involvement. Pleural effusions, lymphadenopathy, and cavities are unusual unless another pathogenic process is present. Pneumatoceles, however, are quite characteristic. When they are subpleural and rupture, pneumothorax can develop.

P. jiroveci pneumonia can present with “atypical” radiographs; asymmetric involvement, upper lobe disease, lobar infiltrates, and nodules are among the presentations that have been described. Thus, imaging cannot confirm the diagnosis of PCP, and therefore, a microbiologic diagnosis should be established.

Because *P. jiroveci* cannot be routinely cultivated, definitive diagnosis requires the demonstration of cysts or trophozoites within tissue or body fluids. Organisms are recognized via colorimetric or immunofluorescent stains. The development of monoclonal antibodies provides a rapid, sensitive, and easy-to-perform immunofluorescence assay, which is more sensitive than conventional staining.^{31,32} Organisms can almost always be identified in bronchoalveolar lavage. At many institutions, induced sputum also has a very high sensitivity; over 90% of diagnoses can be established in patients with HIV or other immunodeficiencies.^{31,32}

PCR has been developed for diagnosis by research laboratories. For bronchoalveolar lavage, sputum, or oral rinses, PCR can be very sensitive and quite specific.³³ A negative PCR test is an extremely sensitive method for excluding PCP. A positive PCR can represent true disease, or subclinical infection. A quantitative test can provide better specificity than a qualitative assay. Serologic assays to diagnose PCP have been studied, but are not yet clinically useful.

Trimethoprim-sulfamethoxazole (TMP-SMX) is the agent of choice for the initial treatment of acute PCP.^{34,35} Parenteral pentamidine is the alternative choice for patients with severe disease. TMP-SMX is as effective as parenteral pentamidine but is less toxic. Atovaquone, clindamycin-primaquine, and dapsone-pyrimethamine are reasonable options for patients with mild disease. For patients with moderate or severe disease, parenteral trimetrexate can also be used.

Patient outcome depends on host, microbiologic, and therapeutic factors.^{35,36} Patients have a better prognosis if therapy is started before disease is severe, and if their immunologic status is relatively preserved. Patients without severe underlying lung disease, and patients without serious concurrent disease processes, also have better prognoses.

Oral outpatient therapy with TMP-SMX is highly effective among patients with mild-to-moderate disease.³⁷⁻³⁹ In many series, survival for patients with mild-to-moderate disease is >90-95%. As noted above, patients with mild disease can be treated successfully with other oral regimens, including dapsone plus pyrimethamine, atovaquone, and clindamycin

plus primaquine. Parenteral pentamidine and parenteral trimetrexate are options for patients with more severe disease.

TMP-SMX is associated with a high frequency of adverse effects. Pruritis, nausea, rash, leukopenia, hepatitis, and nephritis have commonly been reported.^{35,37-41} Mild adverse events do not necessarily require discontinuation of TMP-SMX. Often these toxicities can be watched carefully, or managed symptomatically while therapy is completed. In the past, all pneumocystis organisms were presumed to be sensitive to TMP-SMX. However, no assay was available to determine if this were true. More recently, both the target enzymes for sulfa and for trimethoprim have been sequenced from human isolates. Mutations associated with resistance to sulfa drugs have been documented.⁴² There are conflicting reports in case series as to whether or not these mutations are associated with poorer outcome when TMP-SMX is used for therapy.^{43,44} Patients who develop PCP despite TMP-SMX prophylaxis are usually effectively treated with standard doses of TMP-SMX. This suggests that at least some cases of resistance involve low level reduction in drug activity, and that such resistance can be overcome with high doses. Whether such resistance will become more difficult to overcome as TMP-SMX exposure continues, remains to be determined.

Intravenous pentamidine is the most effective alternative to TMP-SMX.³⁴ This drug can only be given parenterally for therapy, as aerosol pentamidine is not sufficiently effective for acute therapy to be a recommended regimen. Intravenous pentamidine can be associated with substantial toxicities, including renal dysfunction, pancreatitis, and hyper and hypoglycemia.^{35,40} Patients also become hypoglycemic at unpredictable times, either early during the course or weeks after the final dose. Patients may then become hyperglycemic due to destruction of pancreatic beta cells.

Trimethoprim-dapsone is as effective as TMP-SMX, but the dapsone probably has a 50% cross reactivity with sulfonamides.³⁹ Primaquine-clindamycin is effective for mild-to-moderate disease; however, primaquine is only available as oral preparation and is associated with rash and G-6-PD associated hemolysis.^{45,46} Atovaquone is less effective than TMP-SMX for mild disease, but is very well tolerated.³⁸ Absorption can be an issue in patients unable to ingest high fat foods.³⁸ Trimetrexate with leucovorin is less effective than TMP-SMX, but can be used if TMP-SMX is not tolerated and an intravenous therapy is needed.⁴⁷

Moderate-to-severe disease (pretherapy pO₂ <70 mm Hg on room air) should be treated with adjunctive corticosteroids in addition to the specific anti-*Pneumocystis* regimen. The use of adjunctive corticosteroids substantially decreases morbidity and improves survival for patients with moderate-to-severe disease.^{34,48} Use of corticosteroids is not recommended if the diagnosis of PCP is not promptly confirmed. However, it should be intuitively obvious that patients with moderate-to-severe disease should have a specific diagnosis

established to ascertain that the correct causative process is being treated.

Therapy for PCP is usually continued for 21 days. However, no trial has demonstrated superiority of 21 days over 14 days. Moreover, patients with severe disease are often treated for more than 21 days if their response is slow, or is incomplete, after 21 days of therapy.

As noted above, many authorities recommend delaying the initiation of ART until the completion of anti-PCP therapy, given the possibility of IRIS that may complicate the treatment of PCP.⁴⁹ For patients with severe hypoxemia, such an IRIS can precipitate respiratory failure. The initiation of ART can also complicate the management of toxicities. For instance, when skin rash or abnormal liver function tests develop, it may be difficult to determine which drug was most likely to cause the toxicity.

All patients who have survived an episode of PCP should receive lifelong secondary prophylaxis unless ART is initiated and their CD4⁺ T lymphocyte cell count persists above 200 cells/ μ L.⁵⁰ TMP-SMX is the drug of choice for both primary and secondary prophylaxis. If patients do not tolerate TMP-SMX and the toxicity is not life-threatening, an oral desensitization regimen can be useful for permitting patients to tolerate the drug. For patients who are intolerant of TMP-SMX,⁵¹⁻⁵³ dapsone, atovaquone or aerosolized pentamidine may be used with a high degree of efficacy.⁵⁰

PROTOZOAL INFECTIONS

Toxoplasma gondii

Toxoplasma gondii, an intracellular coccidian protozoan, causes zoonosis. Primary infection occurs after eating undercooked or raw meat containing tissue cysts, or via ingestion of oocysts that have been shed in cat feces. Transmission of the organism does not occur via person-to-person contact. Primary infection is usually asymptomatic in immunocompetent hosts. Clinical disease occurs when hosts are immunosuppressed years after their primary infection.

Seroprevalence indicating chronic, latent disease varies geographically, with seroprevalence being 75–90% in Africa and European countries, but 15% in the United States.^{34,50,54} In the pre-ART era, of those HIV-infected patients who were seropositive for toxoplasma, 50% would develop clinical toxoplasmosis.⁵⁵ The incidence of clinical disease has decreased substantially since the introduction of ART and the use of prophylaxis in those who were seropositive for *T. gondii*. Clinical toxoplasmosis rarely occurs until the CD4⁺ T lymphocyte cell count falls below 100 cells/ μ L.⁵⁵⁻⁵⁸

The predominant clinical presentation of toxoplasmosis among AIDS patients is a focal mass lesion of the central nervous system. Patients may present with headache, confusion, seizure, or motor weakness. Patients are often not

febrile. Disease outside the central nervous system is unusual, but cases involving the gastrointestinal tract, lung, heart, kidney, and eye have been reported.⁵⁸

Cerebral toxoplasmosis is usually established presumptively by the presence of an enhancing central nervous tract lesion on CAT scan or MRI scan, and response to therapy.^{34,58,59} Positron emission tomography (PET) or single-photon emission computed tomography (SPECT) scanning might be helpful in distinguishing between toxoplasmosis and primary central nervous system lymphoma.^{60,61} However, literature correlating PET or SPECT imaging with pathology or definitive response to anti-toxoplasma therapy is sparse.

Serology can be very helpful in establishing the diagnosis. HIV-infected patients with toxoplasmosis are almost always seropositive for anti-toxoplasma IgG antibodies when testing is done at a reference laboratory. The absence of IgG antibody makes a diagnosis of toxoplasmosis highly unlikely. Anti-toxoplasma IgM antibodies are usually absent; thus, this test is not helpful diagnostically.⁵⁸ The use of polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) for the detection of *T. gondii* has a low sensitivity and is available from a few reference laboratories.^{62,63}

The definitive diagnosis of toxoplasmic encephalitis (TE) requires the demonstration of organism on brain tissue via brain biopsy. Brain biopsy is generally reserved for patients failing to respond to therapy or for patients in whom an alternative diagnosis is likely from the clinical presentation. In a patient with a compatible CD4⁺ T lymphocyte cell count and a presumptive radiologic diagnosis, it is appropriate to begin empirical treatment for toxoplasmosis, especially if the patient is known to be seropositive for toxoplasma infection and not receiving anti-toxoplasma prophylaxis. CSF testing for antibody or for PCR positivity can be helpful.⁶²⁻⁶⁴ However, these tests and their interpretation are not standardized. A biopsy is indicated if there is no clinical and radiographical improvement in 10–14 days.^{34,55,58}

The preferred treatment for toxoplasmosis is the synergistic combination of pyrimethamine and sulfadiazine plus leucovorin. The latter is used to offset hematologic effects of pyrimethamine.^{34,55,65} In those who are unable to tolerate this regimen, the preferred alternative regimen is pyrimethamine plus clindamycin and leucovorin, which appears to have comparable efficacy.^{34,55,65} Other agents that have shown efficacy include dapsone, atovaquone, and azithromycin, all of which should probably be administered with pyrimethamine, based on limited experience.^{58,66,67}

Acute therapy should be continued until the clinical abnormalities and radiologic lesions show no additional signs of improvement. Most clinicians would continue therapy for at least 6 weeks.

Adjunctive corticosteroids can be used if patients are symptomatic and there are radiologic signs of brain edema or mass effect. Anticonvulsants should only be administered to patients with seizure activity and should not be given prophylactically.³⁴

Patients who have successfully completed a 6-week course of induction therapy should receive lifelong secondary prophylaxis, unless, through the use of ART immune reconstitution, their CD4⁺ T lymphocyte cell counts increase to >200 cells/ μ L for greater than 6 months, and the patients have maintained virologic suppression.^{34,68–70}

Cryptosporidiosis

Cryptosporidia are coccidian protozoa that infect the small bowel mucosa. In immunocompromised patients, the large bowel, the biliary-pancreatic tree, and occasionally the respiratory tract can also be involved. There are several zoonotic species found in feces of cattle and domestic pets, and that contaminate rural and urban water supplies, all of which can infect humans despite standard chlorination.⁷¹ Person-to-person transmission can occur, especially among men who engage in oral–anal sex, and among individuals who work in day-care centers, or whose children spend time in day-care centers. Exposure to cryptosporidia can occur in day-care centers during diapering, or due to fecal contamination of environmental sources.

In immunocompetent hosts, infection generally leads to a mild, self-limited disease, in contrast to patients with AIDS who develop a persistent chronic enteritis of variable severity. The most common presentation of cryptosporidiosis is acute or subacute onset of profuse nonbloody diarrhea, which can be associated with nausea, vomiting, crampy lower abdominal pain, and fever. Severe disease occurs primarily in those with CD4⁺ T lymphocyte cell counts less than 100 cells/ μ L.^{72,73} Since the wide availability of ART, the incidence of cryptosporidiosis has decreased.

Diagnosis of cryptosporidiosis is based on identification of oocysts on direct microscopic evaluation of stool, intestinal biopsy, or other fluids or tissues. Oocysts also can be detected by direct immunofluorescent or enzyme-linked immunosorbent assays.^{72–74}

No drugs specifically used against cryptosporidiosis are clearly effective. However, ART with immune reconstitution (an increase in CD4⁺ T lymphocyte cell counts to >100cells/ μ L) has been associated with complete resolution of cryptosporidiosis.^{34,75,76} Therefore, optimizing ART to achieve full virologic suppression is essential.

Paromomycin, a nonabsorbable aminoglycoside has been used, but a controlled trial of this drug failed to show benefit compared to placebo.^{34,77,78} Combination therapy with paromomycin and azithromycin appeared to show some clinical benefit in a single study, but patients rarely have had microbiologic cure.⁷⁹ Nitazoxanide has some efficacy in HIV-uninfected children, but evidence of efficacy in patients with HIV infection has been unimpressive.⁸⁰ Aggressive fluid support, antimotility agents, and total parenteral nutrition can be helpful management tools.³⁴

Microsporidia

Microsporidia organisms are obligate spore-forming intracellular protists, related to fungi in taxonomy. They are ubiquitous in nature, likely zoonotic and waterborne in origin.^{81,82} There are five major genera that have been identified as human pathogens including *Enterocytozoon*, *Septata*, *Nosema*, *Encephalitozoon*, and *Pleistophora*. The incidence of microsporidiosis has declined dramatically with the widespread use of ART. Those at risk have CD4⁺ T lymphocyte cell counts <100 cells/ μ L.⁸²

Like cryptosporidiosis, the most common manifestation of microsporidiosis is diarrheal illness. However, encephalitis, ocular infections, sinusitis, myositis, and disseminated infection have been reported.^{82–86} Manifestations differ for each microsporidial species.

Enterocytozoon bienersi is the most commonly recognized enteric pathogen responsible for approximately 90% of human infection and is associated with malabsorption, diarrhea, and cholangitis. It is important to recognize which species of microsporidium is causing disease, since response to therapy differs dramatically among species.

Diagnosis of microsporidiosis is made by modified trichrome staining of the stool or by light and electron microscopy of small bowel biopsies.^{74,85} ART is the only specific intervention, which is effective. ART with immune restoration (increase of CD4⁺ T lymphocyte count >100 cells/ μ L) can be associated with a resolution of symptoms in microsporidiosis.^{87,88} Patients with severe diarrhea may not absorb ART efficiently, and thus may not have an optimal immunologic or virologic response. Short of ART, no specific treatment is consistently effective against *E. bienersi*, the most common cause of microsporidial diarrhea.^{86–89}

For other types of microsporidiosis, albendazole can be effective for initial therapy of intestinal and disseminated (not ocular) microsporidiosis caused by microsporidia other than *E. bienersi*.^{90,91} Fumagillin has been reported to also be effective when used as an oral or a topical agent; however, fumagillin is not available in the United States.⁹²

Isospora belli and *Cyclospora*

Isosporiasis is a disease caused by the coccidian protozoa *Isospora belli*, which is commonly found in the tropical and subtropical climates. It is endemic in AIDS patients in Haiti and Africa. *Isospora* causes disease in the proximal small intestine leading to a severe diarrheal illness.⁹³ Diagnosis is made by identifying acid-fast oval oocysts in stool specimens. The disease is effectively treated with TMP–SMX. Pyrimethamine or ciprofloxacin may also be effective.⁹⁴ Lifelong maintenance therapy is necessary to prevent relapses in AIDS patients, unless immune restoration occurs due to ART. Immune restoration with ART is associated with more rapid resolution of symptoms and less frequent relapses.³⁴

Cyclospora infection in HIV-infected patients is similar to isosporiasis in that it is common in the tropics, responds to treatment with TMP–SMX,^{95–98} and has a high-resolution rate with immune reconstitution due to ART.⁵⁰ *Cyclospora* are waterborne, and disease occurs predominately in the summer months. Outbreaks have been reported due to fruits or vegetables imported into the United States. Clinically, watery diarrhea is present with cramping, fatigue, and weight loss.^{95,97,98} Diagnosis is made by identifying acid-fast organisms in stool samples. Therapy with TMP–SMX or possibly ciprofloxacin appears to be effective.

FUNGAL INFECTIONS

Candida species

For patients with HIV disease, *Candida* predominantly causes mucosal disease. Invasive disease is unusual: when it occurs it is associated with other risk factors such as intravascular catheters or intravenous substance abuse.⁹⁹ Candidiasis most often manifests as oral thrush, esophagitis, or vulvovaginitis in patients with HIV infection. The majority of infections are caused by *Candida albicans*. However, the widespread use of fluconazole has been accompanied by a gradual emergence of nonalbicans *Candida* species, such as *C. glabrata* and *C. krusei*.^{100,101} These organisms are often azole resistant and can cause fluconazole refractory mucosal candidiasis in patients with advanced AIDS.^{99,102–109}

The occurrence of oropharyngeal or esophageal candidiasis in patients with no prior AIDS manifestations is recognized as an indicator of clinical progression and immune suppression: this alone is an indication for primary PCP prophylaxis regardless of CD4⁺ T lymphocyte count. Vulvovaginitis, in contrast, occurs in patients at all CD4⁺ T lymphocyte cell counts and may be unusually frequent in patients with HIV, especially those with low CD4⁺ T lymphocyte cell counts.³⁴ Some of these cases occur at CD4⁺ T lymphocyte cell counts >200 cells/ μ L. However, most cases occur in patients with CD4⁺ T lymphocyte cell counts <200 cells/ μ L.^{98,105}

Oropharyngeal candidiasis presents with white plaques, having a very characteristic appearance, on the buccal mucosa and tongue. Scrapings of lesions can be diagnostic if much yeast is seen. Esophagitis usually presents with dysphagia, odynophagia, or retrosternal discomfort. Because *Candida* is a much more likely cause of these symptoms than any other pathogen, an empiric course of antifungal therapy is usually reasonable. Odynophagia is said to be more characteristic of CMV esophagitis than candida esophagitis, but in practice, this distinction often does not hold up. Endoscopy for diagnosis is indicated only if there is no response to a 7–10 day course of empiric therapy.¹⁰⁷

Topical clotrimazole or nystatin can be effective for mild oral candidiasis. Both are well tolerated and inexpensive.

Many clinicians and patients prefer oral fluconazole or itraconazole. Oral azole therapy is also effective for esophagitis or vaginitis. Voriconazole is also effective, but there is no strong reason to prefer voriconazole over fluconazole or itraconazole in most cases. Caspofungin or micafungin are also effective, but these agents are only available as intravenous preparation, and are thus used only for refractory cases. An amphotericin B preparation could also be used for refractory cases.

Effective ART reduces the frequency of occurrence of mucosal candidiasis.³⁴ Secondary prophylaxis is generally not given to prevent recurrences, unless the recurrences are particularly frequent or severe. Prophylaxis is not recommended because of the cost, inconvenience, and potential drug interactions of fluconazole, as well as the potential for chronic prophylaxis to promote the occurrence of azole-resistant strains.³⁴

Cryptococcus neoformans

Before the advent of ART, cryptococcosis occurred in 5–10% of patients with HIV infection in North America.^{110–113} Pigeon and other bird droppings are most often considered the environmental source. The incidence has declined dramatically with the use of ART, and the majority of cases are seen in patients with CD4⁺ T lymphocyte cell counts <50 cells/ μ L.¹¹¹

Meningitis is the most common clinical manifestation, although pulmonary and disseminated disease is well described.¹¹² Meningitis typically presents subtly with fatigue and headache. Meningismus is present in only 22% and fever is present in 65% of the patients. Thus, subtle presentations should be watched for. Extrameningeal disease can present as pneumonia with fever and cough, as disseminated disease with skin lesions, and as fever with severe malaise. Diagnosis of cryptococcosis is established by the presence of the organism on stain or culture, or by detection of cryptococcal antigen in the serum, CSF, or less often, some other tissue or fluid such as bone marrow, bronchoalveolar lavage fluid, or lymph node.^{112,114} Clinicians suspicious of cryptococcal disease will typically obtain a serum cryptococcal antigen, blood cultures for fungus, and spinal fluid for culture and antigen determination.

The recommended initial treatment for acute disease is intravenous amphotericin B in preference to fluconazole.^{34,111,114–119} The addition of flucytosine does not appear to offer a significant benefit or improve immediate outcome in the setting of AIDS, but does appear to be associated with decreased risk for relapse.^{34,116,119} Lipid formulations of amphotericin B also appear to be effective.^{116,117}

The availability of oral azole antifungal agents has led to several studies evaluating these as alternatives to amphotericin in the initial treatment of cryptococcal meningitis. The greatest experience has been with fluconazole, which has a high bioavailability, and adequate CSF levels are readily

attained. Fluconazole has been found to be effective; however, it has been associated with a higher mortality in the first 2 weeks of treatment and a longer time to attain a negative CSF culture as compared with amphotericin.^{34,115,116} Itraconazole is not an appropriate choice for initial management due to low penetration of the blood–brain barrier. Azole therapy should almost never be used as the sole therapy before at least 2 weeks of amphotericin B has been given.

Increased intracranial pressure can cause clinical deterioration. In such cases, the CSF opening pressure is usually >200 mm H₂O.¹²⁰ In one large clinical trial, 93% of deaths occurring in the first 2 weeks were associated with increased intracranial pressure.¹¹⁸ The intervention for reducing symptomatic elevated intracranial pressure is repeated daily lumbar punctures. CSF shunting may also be considered.³⁴ Corticosteroid therapy is not known to be beneficial.

After a 2-week period of successful induction therapy, consolidation therapy should be initiated with fluconazole administered for 8 weeks.^{111,114,121} Some clinicians would advocate repeating the lumbar puncture after 8 weeks to assess the sterility of the CSF. Fluconazole maintenance therapy is recommended following the 8-week course. Maintenance treatment for cryptococcal disease is lifelong, unless immune reconstitution occurs as a consequence of ART.³⁴

Histoplasma capsulatum

Histoplasma capsulatum is a dimorphic fungus that grows as a mold in soil contaminated by bat or bird excreta. Primary infection occurs when microconidia are inhaled into the lungs, where they grow as the pathogenic yeast phase. Histoplasmosis occurs in 2–5% of patients with AIDS. Most cases occur in the Midwest and Puerto Rico.^{34,122,123} In areas where the disease is not endemic, it most often occurs among those who have previously lived in an endemic area. Disease may occur due to either primary infection or reactivation.^{122–124} Clinical disease does not usually occur until the CD4⁺ T lymphocyte cell count is below 150 cells/ μ L.

Patients typically present with pulmonary disease or with fever. Patients with higher CD4⁺ T lymphocyte cell counts may have localized pulmonary infiltrates. Patients with CD4⁺ T lymphocyte cell counts below 100 cells/ μ L have diffuse pulmonary disease, or a sepsis-like syndrome. A severe sepsis syndrome with hypotension and multiorgan system dysfunction is seen in 10% of cases; this is referred to as progressive disseminated histoplasmosis. Febrile patients may have a prolonged syndrome with fever and weight loss. Hepatosplenomegaly may also be present. Other less common presentations include central nervous system, gastrointestinal, chorioretinitis, and cutaneous manifestations.

Diagnosis of histoplasmosis is established either by recovery of the organism in culture or by visualization in histopathologic specimens.^{124,125} Fungal stain of blood smears or tissues might yield a rapid diagnosis, but the

sensitivity is $<50\%$. Detection of *Histoplasma* polysaccharide antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated histoplasmosis, but insensitive for localized pulmonary infection. Levels of *Histoplasma* antigen decline with therapy and increase with relapse, providing a useful tool for monitoring the response to therapy.¹²⁴

The initial treatment for histoplasmosis should be intravenous amphotericin B.^{34,126,127} Either the deoxycholate or liposomal formulation can be used. This should induce remission in 85–90% of patients. Liposomal amphotericin B (AmBisome) is better tolerated than the deoxycholate preparation.¹²⁶ Liposomal amphotericin is preferred in patients with severe or moderately severe disseminated histoplasmosis. Itraconazole can be used for mild disease.¹²⁷ Chronic maintenance therapy should be continued for life, unless ART results in immune reconstitution.³⁴

Coccidioides immitis

Coccidiomycosis is endemic to the deserts of the southwestern United States, Mexico, and Central America. The incidence of disease in endemic areas ranged from 2% to 5% in the pre-ART era. Increased risk is associated with extensive exposure to disturbed soil, as might be seen with gardening, farming, or excavations.^{34,128,129} Active disease may represent either reactivation of latent disease or recently acquired primary infection. Coccidiomycosis in HIV-infected patients usually occurs in those with a CD4⁺ T lymphocyte cell count <250 cells/ μ L and a previous diagnosis of AIDS.^{128,129}

The most common clinical presentation in HIV-infected patients is diffuse pulmonary disease, which presents as cough, fever, night sweats, fatigue, and weight loss. The chest radiograph typically shows a diffuse reticulonodular infiltrate. Disseminated extrapulmonary disease manifests as generalized lymphadenopathy, skin nodules, cutaneous ulcers, peritonitis, liver lesions, and osteomyelitis.¹²⁸ Definitive diagnosis is based on culture of the organism from sputum, bronchoalveolar lavage fluid or tissue, or demonstration of spherules on histopathology. Blood cultures are rarely positive. IgG antibody is positive in the majority of cases, but antibody does not identify acute versus chronic disease.

For nonmeningeal pulmonary or disseminated disease, amphotericin B is the preferred initial therapy.^{34,130–132} It should be continued until clinical improvement is observed, which usually requires a total of 1–2.5 g. Fluconazole or itraconazole might be appropriate alternatives for patients with mild disease. Coccidioidal meningitis should be treated with fluconazole, which has been reported to be successful in approximately 80% of patients.¹³¹ Lifelong suppressive therapy should be administered with daily fluconazole. Some clinicians recommend stopping therapy for patients with CD4⁺ T cell responses to levels ≥ 200 cells/ μ L after prolonged therapy, but the safety of such an approach is not well established for all forms of coccidiomycosis in this patient population.

Itraconazole could also be used for suppression of non-meningeal disease.^{130–132}

CYTOMEGALOVIRUS INFECTIONS

In the pre-ART era, disease due to reactivation of latent cytomegalovirus (CMV) infection affected 40% of AIDS patients.^{34,133} Incidence of new cases of CMV end-organ disease has decreased substantially.³⁴ End-organ disease caused by CMV occurs among persons with CD4⁺ T lymphocyte cell counts <50 cell/ μ L, who are either not receiving ART or have failed to respond to ART.^{34,133–136}

The majority of patients with HIV infection are seropositive for CMV, with highest rates among men that have sex with men (rates up to 95%) and intravenous drug users. In patients whose only risk factor is heterosexual contact, the rate may be substantially less. Most CMV disease is caused by reactivation of latent disease, but primary infection or reinfection may be responsible for some cases. The most common manifestation of end-organ disease is retinitis, although colitis, esophagitis, and neurological disease are also well recognized. CMV pneumonitis is a rare occurrence.^{133–136}

The diagnosis of CMV retinitis is based on characteristic ophthalmologic findings. Diagnosis of CMV esophagitis or colitis is based on histopathologic demonstration of characteristic intranuclear and intracytoplasmic inclusions. Neurologic disease is diagnosed based on either brain biopsy or PCR testing of CSF.

CMV can be detected in blood by culture or PCR.¹³⁵ CMV can also be found by culture or PCR in urine, other body fluids, and various tissues. However, the presence of CMV by culture or PCR does not necessarily imply that CMV is the cause of disease. The demonstration of CMV inclusion bodies in cytologic preparations or in tissue may not necessarily indicate that CMV is causing disease and should be treated. CMV involvement can be focal; thus, disease may be missed even when large pieces of tissue are sampled. Alternatively, a few CMV inclusion bodies can be seen even when this virus is not the true cause of the predominant pathologic process.

CMV retinitis requires immediate treatment, especially when the fovea or optic disk is threatened. Without appropriate care, CMV retinitis will progress rapidly and produce substantial visual loss. There are five FDA-approved treatments for CMV retinitis: intravenous ganciclovir, oral valganciclovir, intravenous foscarnet, intravenous cidofovir, and an ocular device containing ganciclovir.^{34,133–136}

The choice of initial therapy for CMV retinitis should be based on the location and severity of lesions, the patient's ability to adhere to a regimen, and the level of underlying immune suppression.^{34,134} Oral valganciclovir has become the preferred therapy for treatment of patients with peripheral lesions that are not immediately sight-threatening. This regimen is preferred due to the ease of administration and

lack of surgical or catheter-associated complications.³⁴ Drug resistance can occur among patients receiving long-term therapy and can contribute to relapses.

Adverse effects of ganciclovir and valganciclovir include neutropenia, thrombocytopenia, and nausea. Some patients require G-CSF in order to maintain their white blood count while receiving ganciclovir or valganciclovir. Foscarnet and cidofovir are associated with nephrotoxicity and chelation of cations.

For patients who have had CMV retinitis, the initiation of ART can be associated with flares in ocular disease.^{137–139} Within days or weeks of initiating ART, patients may experience inflammation in their posterior or anterior chamber, along with a decrease in visual acuity. Even in patients who do not note a change in acuity, fluorescein angiography can demonstrate capillary inflammation and leak. It is not clear if this is associated with the presence of live virus, or whether this can occur due to the presence of CMV antigen alone. Patients are often treated with periocular corticosteroids or short courses of systemic steroids.^{137–139} However, the optimal therapeutic approach to this syndrome is not clear.

Discontinuing secondary prophylaxis (chronic maintenance therapy) should be considered for patients with a sustained (>6 months) increase in CD4⁺ T lymphocyte cell counts >100–150 cells/ μ L in response to ART. Regular ophthalmologic monitoring for early evidence of relapse and for immune recovery uveitis should continue.^{34,137–141}

Herpes simplex virus

Herpes simplex virus (HSV), types 1 and 2, cause mucocutaneous involvement of the orolabial, genital, anorectal, and esophageal areas. Disseminated disease is extremely unusual, even in patients with very advanced disease.^{34,142}

Approximately 95% of HIV-infected persons are seropositive for either HSV-1 or HSV-2.¹⁴² Infection and reactivation disease can occur at any time during the course of HIV disease, but the most severe and chronic manifestations occur at CD4⁺ T lymphocyte cell counts below 100 cells/ μ L.

The diagnosis of HSV infection is often made empirically on the basis of characteristic vesicular lesions. Definitive diagnosis may be readily attained by HSV antigen testing, Tzanck smear, or viral culture. When lesions are atypical, or do not respond to empiric courses of acyclovir or valaciclovir or famcyclovir, such definitive diagnosis, and susceptibility testing, is appropriate.

Severe mucocutaneous HSV lesions are best treated initially with intravenous acyclovir.^{143,144} Patients may be switched to oral therapy after the lesions have begun to regress. Oral therapy may be used for less severe disease; several agents are effective, including oral acyclovir, famcyclovir, or valaciclovir. Intravenous acyclovir is usually well tolerated, but may occasionally cause renal impairment or

CNS toxicity.³⁴ Treatment failure related to viral resistance should be suspected if lesions do not indicate signs of resolution within 7–10 days.^{34,143} If the thymidine kinase enzyme has mutated, the treatment of choice is intravenous foscarnet. If the mutation is in the polymerase, the virus may be resistant to ganciclovir, foscarnet, and cidofovir. For such resistant virus, topical cidofovir and topical trifluridine have been successfully used.

Varicella-zoster virus

Varicella-zoster virus (VZV) can cause primary disease in patients with HIV. Clinical chicken pox can be a severe and even fatal disseminated viral process in this patient population. However, most patients develop reactivation disease, which manifests as dermatomal zoster. Unlike some other immunosuppressed populations, patients with HIV infection rarely develop disseminated zoster.

The incidence of VZV is 15–25 times greater in HIV-infected persons than in the general population, and 3–7 times greater than among the elderly. VZV can occur at any CD4⁺ T lymphocyte cell count and may be the initial presentation of HIV.

There are some rare manifestations of VZV to be aware of. For patients with higher CD4⁺ T lymphocyte cell counts, acute retinal necrosis can occur. For patients with lower CD4⁺ T lymphocyte cell counts, peripheral outer retinal necrosis can occur. Therapy for the former is sometimes successful with acyclovir; therapy for the latter is rarely successful. Combination therapy with ganciclovir plus foscarnet is often used. Zoster ophthalmicus can also occur, as can a variety of neurologic lesions, including carotid artery intima involvement and stroke.

Diagnosis is based on characteristic appearance of the lesions. Cutaneous vesicles can be scraped, and a definitive diagnosis can be made on the basis of characteristic multinucleated giant cells, or the detection of antigen or the isolation of the virus.

The treatment for dermatomal zoster depends on the extent and severity of the episode. In severe cases, when more than one dermatome or the ophthalmic division of the trigeminal nerve is involved, or disseminated disease is present, the treatment should be intravenous acyclovir for 7–14 days or longer if the clinical response is slow. Localized VZV can be treated with oral famciclovir or valaciclovir until lesions are crusted.³⁴ Adjunctive corticosteroid therapy to prevent post-herpetic neuralgia is not recommended for HIV-infected patients. Acyclovir-resistant VZV can occur in patients already receiving acyclovir. Foscarnet should be used in these patients.^{34,144} Maintenance regimens following acute therapy are not indicated. Dermatomal VZV may recur, but recurrences are rarely frequent enough to warrant chronic therapy.

BACTERIAL INFECTIONS

Mycobacterium tuberculosis

Mycobacterium tuberculosis (MTB) infection in HIV-infected patients is not common in the United States, but HIV-infected patients do have a disproportionate incidence of the disease.^{145–151} Progression to disease among those with latent TB infection is more likely to occur in HIV-infected patients than in HIV-uninfected persons.¹⁵⁰ HIV-uninfected persons with a positive tuberculin skin test (TST) have a 5–10% lifetime risk for developing TB, compared with a 7–10% annual risk in the HIV-infected patient with a positive TST.^{34,151,152} TST of >5 mm to a standard purified protein derivative (PPD) is considered positive in HIV-infected patients. A negative test is not useful for ruling out tuberculosis infection due to the frequency of anergy, especially in patients with low CD4⁺ T lymphocyte cell counts.^{34,153} Patients with TB have higher HIV viral loads and a more rapid progression of their HIV illness than comparable HIV-infected patients without TB.¹⁵¹

In the developing world, the concurrence rates of TB and HIV can be impressively high. In the United States, the majority of HIV-infected patients with tuberculosis are immigrants.^{146–148} Tuberculosis in the United States is also characteristically seen in native-born individuals who have been incarcerated or who have abused intravenous drugs.

MTB occurs among those with HIV infection at all CD4⁺ T lymphocyte cell counts. Clinical manifestations depend on the degree of immunosuppression. Patients with CD4⁺ T lymphocyte cell counts >200 cells/ μ L have manifestations that are not substantially different from HIV-uninfected patients. Those with CD4⁺ T lymphocyte cell counts <200 cells/ μ L are more likely to have atypical infiltrates (lower lobes, unilateral, or military) and often have extrapulmonary and/or disseminated disease.^{150,151,154,155}

Active tuberculosis may be the presenting manifestation of HIV infection. The clinical and radiographic presentation depends on the degree of immunosuppression.^{150,151,154,155} Patients with higher CD4⁺ T lymphocyte cell counts tend to have upper lobe disease with cavities, in contrast to those with lower CD4⁺ T lymphocyte cell counts, who develop lower lobe disease and adenopathy. Extrapulmonary disease may occur in up to 60% of the cases and virtually all organ systems can be affected, from adenitis to meningeal involvement. Histopathological findings are also affected by the degree of immunosuppression. Patients with relatively intact immune function have typical granulomatous inflammation associated with TB disease. With advanced immunosuppression, granulomas become poorly formed or can be completely absent.^{154,155}

Diagnosis of tuberculosis is based on identifying the acid-fast organisms in any clinical specimen. Such specimens can include sputum, bronchoalveolar lavage, lung

biopsy, blood, bone marrow, CSF, or urine. HIV-infected patients are more likely than uninfected persons to have negative smears, probably because cavities, which produce huge organism loads, do not usually occur at low CD4⁺ T lymphocyte cell counts.^{155–157} Nucleic-acid amplification tests are useful for providing rapid identification of *M. tuberculosis* from sputum smear-positive specimens.^{158–160} The specificity of this test is close to 100%. The sensitivity is not 100% however, especially when smear-negative specimens are probed.

Mycobacterial blood cultures can be useful, even in patients who appear to have localized pulmonary disease.^{161–163} Blood should be inoculated into special mycobacterial media, or into isolator tubes and then plated on an appropriate solid medium. If acid-fast organisms are present on smear of any clinical specimen, *M. tuberculosis* should be routinely considered as part of the differential diagnosis. Clinicians often assume that a mycobacterium is *M. avium*, only to discover that it is really MTB after multiple health-care workers have been exposed, and after ineffective therapy has been given for months.

Culture of *M. tuberculosis* requires 10–21 days to detect growth using radiometric techniques. The time to positivity depends on the size of the inoculum and the specific MTB strain involved. Identification is rapid once adequate growth occurs, when gene probe techniques are used. Drug susceptibility tests can also be available in 10–21 days.

Treatment of HIV-related TB should follow the general guidelines developed for TB treatment among uninfected persons.^{34,152} Directly observed therapy (DOT) is strongly recommended. Treatment of drug-susceptible TB in HIV-infected patients should include the use of a 6-month regimen consisting of an initial phase of isoniazid (INH), rifampin (RIF) or rifabutin, pyrazinamide (PZA), and ethambutol (EMB) given for 2 months, followed by INH plus RIF (or rifabutin) for 4 months for susceptible organisms.³⁴ The optimal duration of therapy for HIV-related TB is 6 months if patients defervesce promptly and are smear negative by the end of 2 months of therapy.³⁴ DOT should be administered at least 3 times weekly. Fewer observed administrations have been associated with an unacceptable therapy failure rate, especially among patients with CD4⁺ T lymphocyte cell counts <100 cells/ μ L.^{34,152, 164–168}

Antituberculous therapy is a major challenge to administer to patients with HIV infection.^{169,170} The first issue to address is whether ART should be instituted when patients with tuberculosis are found to have HIV infection. Most authorities would wait for at least 2 months, although data proving that to be the most effective strategy is limited. If patients are started on ART before a minimum of 2 months of anti-tuberculous therapy, there is a major risk they will develop an IRIS. Such syndromes may include mild exacerbation of the initial lesions, flares at new sites, or fever and hypotension. Such

syndromes appear to occur with less frequency if TB has been treated for at least 2 months.

Anti-tuberculous drugs have many toxicities that overlap with HIV disease and with toxicities emanating from the ART. These overlapping toxicities can be exceedingly difficult to manage. Drug interactions are also a significant problem, especially with the rifamycins, which are potent inducers of cytochrome p450 metabolic enzymes.³⁴ Rifabutin is a less potent inducer than rifampin.³⁴ Several sources document drug doses to be used when anti-tuberculous and anti-HIV therapies must be administered simultaneously.³⁴

Mycobacterium avium complex

Mycobacterium avium complex (MAC) is a ubiquitous organism found in the environment, including water, food, and soil. The mode of transmission of MAC is thought to be through ingestion, inhalation, or inoculation through the respiratory or gastrointestinal tract portals of entry.^{152,171–175} Colonization appears to occur before dissemination. Household or close contacts of those with MAC disease do not appear to be at increased risk for experiencing disease, and person-to-person transmission is unlikely.^{171–175}

Disseminated MAC is rarely seen until the CD4⁺ T lymphocyte cell count falls below 50 cells/ μ L. In the absence of effective ART and chemoprophylaxis in those with CD4⁺ T lymphocyte cell counts <50 cells/ μ L, the incidence of disseminated MAC ranges from 20% to 40% in the United States and Western Europe.^{152,171–175} Colonization appears to occur before dissemination. Household or close contacts of those with MAC disease do not appear to be at increased risk for experiencing disease, and person-to-person transmission is unlikely.^{171–175} For reasons that are not clear, MAC has not been commonly recognized in developing countries where MTB is common.

Fever, fatigue, night sweats, weight loss, abdominal pain, and diarrhea are the most common clinical manifestations of disseminated MAC. Elevations of alkaline phosphatase levels and severe anemia are characteristically present. Hepatosplenomegaly or lymphadenopathy may be seen by physical examination or by imaging techniques.

IRIS, characterized by focal lymphadenitis and fever, can be seen in response to ART. Immune reconstitution can be difficult to distinguish clinically from active infection. Patients with immune reconstitution are not expected to be bacteremic.

Definitive diagnosis of localized or disseminated MAC is based on the isolation of MAC from blood, bone marrow, or other normally sterile body tissue or fluid.^{172–177} Cultures of sputum or stool are diagnostically unhelpful because a positive result may indicate colonization rather than invasive disease.

Disseminated MAC disease requires lifelong therapy with combination chemotherapy, unless immune restoration

occurs. Clarithromycin plus ethambutol is the preferred regimen. This combination is associated with a rapid clearance of MAC from the blood.^{176,177} Azithromycin plus ethambutol is also effective; azithromycin appears to cause fewer drug interactions than clarithromycin.

Some clinicians add rifabutin as a third agent to treat disseminated MAC. However, there is not consistent evidence that triple therapy enhances survival, and thus most clinicians do not use triple therapy, especially since the addition of a rifampin alters the pharmacokinetics of many drugs.^{34,178–180}

Duration of therapy should be lifelong in the absence of effective ART. For patients who are started on ART, become asymptomatic, and have a robust CD4⁺ T cell response (CD4⁺ T lymphocyte count >100 cells/ μ L for at least 6 months), 12 months of treatment appears to be sufficient.^{34,178–180}

When MAC becomes resistant to clarithromycin, treatment is usually unsuccessful. Rifabutin, quinolones, linezolid, and amikacin have activity against most strains of MAC. However, unless ART can substantially augment CD4⁺ T cell counts, the prognosis has been poor so far using various combinations of these drugs with in vitro activity.

Secondary prophylaxis may be discontinued if the CD4⁺ T lymphocyte cell count increases to >100 cells for >3 months. It should be reinstated if the CD4⁺ T lymphocyte cell count falls below 100 cells.^{34,181,182}

Bacterial pneumonia

Bacterial pneumonia is one of the most common causes of HIV-related morbidity.^{34,183,184} Compared to HIV-uninfected controls, HIV-infected patients have a five times greater risk of developing bacterial pneumonia and a higher rate of sinusitis and bronchitis, and the risk increases as the CD4⁺ T lymphocyte cell count decreases.¹⁸³ In addition, intravenous drug abusers have a higher incidence of pneumonia. Among patients with lower CD4⁺ T lymphocyte cell counts, cigarette smoking has been associated with an increased incidence of infections.

Streptococcus pneumoniae and *Haemophilus influenzae* are the most common causes of bacterial respiratory infections.^{183–185} Oxacillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa* are also probably overrepresented.

Infection with *S. pneumoniae* is 150–300 times more common among HIV-infected patients than age-matched HIV-uninfected controls.¹⁸⁶ Its incidence has declined since the introduction of HAART.¹⁸⁷ Recurrent pneumococcal pneumonia with the same or unrelated serotype has been frequently observed.¹⁸⁶

There is nothing unusual about the diagnosis or treatment of bacterial processes compared to HIV-uninfected patients. Prevention of infections due to *S. pneumoniae* with the 23-valent polysaccharide vaccine is currently recommended for

all HIV-infected patients.¹⁸⁸ Antibody responses decrease as HIV disease progresses. The durability of antibody response is also likely to be diminished. There is no evidence that the 7-valent polysaccharide vaccine provides additional benefit. Influenza vaccine is also useful for reducing the incidence of post-influenza bacterial pneumonias. PCP prophylaxis with TMP–SMX has been shown to provide some protection against bacterial infections. Further, the use of MAC prophylaxis with azithromycin decreases the incidence of bacterial infections. Effective ART reduces the incidence of bacterial infections.³⁴

Bartonella

In AIDS patients, *Bartonella* spp. are the etiologic agents of bacillary angiomatosis. This syndrome can be caused by *Bartonella henselae*, which is transmitted by fleas and by cats, and by *Bartonella quintana*, which is transmitted by lice. Thus, *B. quintana* is generally a disease of the homeless, while *B. henselae* is usually, but not invariably, linked to cats.

Bacillary angiomatosis often occurs late in HIV infection in patients with CD4⁺ T lymphocyte cell counts of <50 cell/ μ L.^{189,190} Bacillary angiomatosis presents with subcutaneous and cutaneous vascular lesions that often appear similar to the lesions of Kaposi's sarcoma. Patients are almost invariably febrile with fatigue and anemia. Lesions often occur in the head and neck region, although they can be found in lymph nodes, bone, brain, and mucosal surfaces. Histopathologically, vascular proliferation can be seen. Organisms can be visualized by Warthin-Starry staining. Organisms can also be found in lesions of peliosis hepatis, although these are histopathologically different from cutaneous lesions; peliosis is by definition large, blood-filled spaces. Splenic lesions may occur with areas of fibrosis in the presence of organisms.

Bartonella sp. can be isolated from blood using lysis centrifugation, but organisms are difficult to isolate from tissue unless an enriched medium is used.^{188–190} Erythromycin and doxycycline have been used successfully to treat bacillary angiomatosis, peliosis hepatis, bacteremia, and osteomyelitis. Erythromycin is generally considered the drug of choice, although azithromycin has also been used successfully.

OPPORTUNISTIC INFECTIONS OF SPECIAL GEOGRAPHIC INTEREST

The OIs that manifest are a reflection of their immune defect, as well as the pathogens they have been exposed to. As physicians see more and more immigrants, they must remember that certain diseases uncommon in the United States may require diagnosis and therapy. Thus, leishmaniasis, trypanosomiasis, isosporiasis, and penicilliosis may require special diagnostic techniques and must be considered in differential diagnoses.

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OVERVIEW

Individuals with HIV infection have an increased risk of certain cancers. These HIV associated malignancies include Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL), and cervical cancer; these three cancers have been designated by the Centers for Disease Control as AIDs defining diagnoses.¹ Other HIV-associated malignancies such as anal cell cancer,^{2,3} Hodgkin's disease,⁴ squamous cell carcinomas, lung cancer, testicular seminoma, and soft-tissue sarcomas have been shown to occur at a higher rate in HIV infected individuals.⁵⁻⁷ At least some of these HIV-associated malignancies, particularly those linked to immunosuppression,⁸ have the common link to, if not causative role of, an oncogenic virus. It is noteworthy, though, that the most common cancers seen in non-HIV-infected individuals such as prostate, breast, lung, and colon, occur at approximately the same rate as in HIV-infected individuals and individuals must be appropriately screened for these cancers. With the introduction of highly active antiretroviral therapy (HAART) in the mid to later 90s, incidence of many of the HIV-related malignancies has declined. Still, two malignancies, Kaposi's sarcoma and NHL, continue to occur at greater frequencies in HIV-infected patients and when they occur in this population, both malignancies have unique characteristics and special management considerations.

KAPOSI'S SARCOMA

■ EPIDEMIOLOGY

Kaposi's sarcoma was first recognized and described by Moritz Kaposi in the late 1800s. It was rare in the United States before 1981, particularly in healthy young adults. When it did occur, it generally afflicted elderly men of Ashkenazi Jewish descent, most often affecting the feet and lower extremities. This variant, now referred to as classic KS, had an indolent course and was not associated with a known immune deficiency. Classic KS can be seen occasionally in

gay men who remain HIV-negative.⁹ Well before the AIDS epidemic, KS was known to be a common malignancy in Central Africa, where some of its variants were seen to be aggressive and infiltrating even in children and young adults without immune deficiencies.¹⁰⁻¹² This form of Kaposi's sarcoma has been termed endemic KS.

In the early 1970s, KS was reported to be associated with iatrogenic immune suppression, generally in the setting of organ transplantation. It had been reported most commonly in renal allograft recipients as well as in patients treated for various autoimmune diseases with corticosteroids.^{13,14}

In 1982, a cluster of cases of KS was reported in homosexual men.^{15,16} It was subsequently demonstrated that KS was much more common in homosexual men with AIDS than in heterosexual AIDS patients.^{17,18} At its peak incidence, KS was the initial AIDS diagnosis in 30% of HIV-infected gay men.¹⁹ The incidence has declined in the HAART era; recent data shows an incidence of 0.7 cases per 100 patient years compared to 4.1 cases per 100 patient years in the pre-HAART era.²⁰ This decline in incidence is likely not only related to HAART but also to the adoption of safer sexual practices in gay men.

Risk factors for developing KS in HIV-positive patients include the detection of the virus, human herpes virus-8 (HHV-8) in the blood of patients, and the HHV-8 viral load²¹ as well as declining CD4 counts and increasing duration of HIV infection.

PATHOGENESIS

Based on the epidemiology of AIDS-related KS, a sexually transmitted coinfection had long been suspected²²⁻²⁴; in 1994, a newly recognized herpes virus, HHV-8, was discovered within KS lesions.²⁵ HHV-8 is found in endothelial spindle cells^{26,27} of all types of KS including classic KS, African or endemic KS, transplant-associated KS, and AIDS-related KS.²⁸ The virus can also be found in peripheral blood mononuclear cells in many KS patients. In one population based study, the coinfection of HIV and HHV-8 resulted in a

10-year probability of the development of KS of 49%.²⁹ The HHV-8 virus is also associated with rare lymphoproliferative diseases most often seen in HIV-infected individuals, including Castleman's disease and a subtype of NHL known as primary effusion lymphoma (PEL).³⁰

The virus can be transmitted in a number of different ways. Transmission occurs by blood and by semen but these routes are relatively inefficient. The most efficient mechanism for transmission is through saliva.³¹

The mechanism by which HHV-8 causes KS lesions is complex. The tumor, microscopically composed of spindle shaped cells, typically arises synchronously in multiple sites. These tumor cells are derived from lymphatic endothelial cells³² that are infected with the HSV-8 virus. Viral genes, showing some homology with corresponding human genes and likely interacting with the HIV tat protein, produce cytokines with angiogenic properties.³³ Cell cycle controls and apoptosis mechanisms are altered resulting in cellular proliferation. Some evidence supports KS being a monoclonal process,³⁴ although it may be a polyclonal proliferative process in other cases, especially in the initial phases of the disease process.

■ NATURAL HISTORY

The natural history of AIDS-related KS is variable. The disease can manifest at a wide range of CD4 counts but becomes more common as the CD4 count drops. Although an occasional patient will have a spontaneous remission or long interval without disease progression, others have a rapid progression. Patients with limited KS and no symptoms suggesting other underlying infectious disease (e.g., fevers, night sweats, weight loss) do reasonably well. More often, however, in the setting of uncontrolled HIV infection, KS progresses rapidly.

The clinical course of the newly diagnosed KS patient is difficult to predict, but several factors are associated with disease progression and shorter survival: previous opportunistic infections, night sweats, fever, weight loss, anemia, elevated erythrocyte sedimentation rate, a low helper to suppressor T-cell ratio, an absolute helper-cell count of less than 100 cells/mm³, and gastrointestinal (GI) or pulmonary lesions.^{35,36} Patients with the best prognosis have only a few small nodular lesions, no previous serious infections, and no recent weight loss, fevers, or night sweats. Neither the site of cutaneous involvement nor the presence or absence of lymph node involvement appears to be particularly important prognostically. Visceral KS, however, does imply a poor prognosis. The AIDS Clinical Trials Group Oncology Committee has devised a staging system for patients with Kaposi's sarcoma with the intent of risk stratification; however, in the HAART era, the staging system is less successful as a prognostic tool and recommendations for revision have been proposed.³⁷ Specifically, with HAART, the importance

of CD4 as a prognostic factor is eliminated whereas tumor extent, HIV associated symptoms and complications are better predictors of survival. The use of HAART has also impacted the natural history of the disease; an analysis of the Multicenter AIDS Cohort study demonstrated a reduction in the risk of death of 81% in patients with KS receiving HAART.³⁸

■ CLINICAL MANIFESTATIONS

Most patients with AIDS-related KS have subcutaneous tumor nodules or lymphatic involvement.³⁹⁻⁴¹ Cutaneous lesions are typically pigmented red or purple, even early in the disease process. They are usually palpable, painless, and nonpruritic. Occasionally, surrounding ecchymosis is apparent, especially in the cases of rapidly progressing disease. Lesions typically appear on the face and in the oral cavity or on the feet and lower legs, although they may affect almost any site. KS frequently involves the plantar surfaces of the foot but rarely the palm. Other notable sites of disease include the tip of the nose, the region behind the ear, the conjunctiva, and the penis. Vascular sites devoid of lymphatic vasculature, such as the retina, rarely if ever develop KS. Lesions tend to be circular, but those on the back or around the neck can be linear, apparently following cutaneous lymphatic drainage patterns.

Exophytic tumor masses rarely occur in AIDS-related KS, but when they do they can ulcerate, bleed, and when present on the feet, be painful. With advanced disease, plaques of coalesced lesions are common, especially over the medial aspect of the inner thigh. Inactive, previously treated KS lesions may fade entirely but more commonly leave a permanent pigmentation due to hemosiderin-laden macrophages that have engulfed extravasated erythrocytes.

Lymphedema is a common sequela of AIDS-related KS, is often striking, and is most typically seen in the face, where it causes disfigurement and potentially physical obstruction of vision and hearing. Involvement of the lower extremities is also common, with associated upper thigh, scrotal, and penile edema, which can be rapidly progressive and debilitating. In any location, lymphedema may be out of proportion to the extent of cutaneous tumors, reflecting obliteration of small cutaneous lymphatics. Once lymphedema is extensive it can be difficult to reverse even with effective chemotherapy, and many would advocate for early treatment of KS to prevent this complication.

Up to one-third of patients with AIDS-related KS have oral involvement at the time of diagnosis. KS lesions in the oral cavity commonly affect the mucosa of the hard and soft palate and less commonly the posterior pharyngeal wall or the tonsillar pillars.⁴²

Visceral involvement is common in AIDS-related KS. Almost any organ can be involved, although central nervous

system (CNS) involvement is exceedingly rare.⁴³ The GI tract is affected in as many as 50% of patients, even early in the course of the disease.⁴⁴ GI involvement is often an incidental finding because it is most often asymptomatic. It can, however, produce obstructive symptoms, bleeding, and malabsorption. Pulmonary involvement tends to be progressive and can be rapidly fatal without treatment. A dry cough, intermittent hemoptysis, dyspnea, fevers, and an abnormal chest radiograph are typical.⁴⁵ Lymphadenopathic or visceral KS may occur in the absence of cutaneous manifestations.

■ DIAGNOSIS

KS lesions are generally readily recognizable but, irrespective of risk group or clinical appearance, a biopsy should be performed to establish the histologic diagnosis. The differential diagnosis of KS includes other pigmented processes such as bacillary angiomatosis, dermatofibromas, granuloma annulare, insect bite reactions, pyogenic granuloma, stasis dermatitis, and cutaneous lymphoma. The biopsy can be performed at any site, but skin is most convenient. A small punch biopsy (2–4 mm) is usually adequate, but it is helpful to include unaffected adjacent skin in the punch specimen. Enlarged peripheral lymph nodes can also be biopsied. Aspiration cytology has also been used to diagnose KS.

If a biopsy shows KS in a patient without previously established HIV infection, a serologic test is necessary. Patients with a positive test are diagnosed with AIDS, no matter what their CD4 count is. If the serologic test is negative, the KS is not considered to be AIDS-related, even if the patient is a member of an AIDS risk group.

In the initial evaluation of a KS patient, tumor extent should be determined by a complete skin examination. The oral cavity should also be carefully examined. However, clinically important visceral KS can occur in the absence of cutaneous or oral manifestations in approximately 15% of cases. If unexplained GI or pulmonary symptoms are present, endoscopy should be performed. The classic appearance of small submucosal vascular nodules establishes the diagnosis of visceral KS. Biopsies are diagnostic in only a minority of cases of GI KS because the tumors are generally submucosal, but biopsy specimens may exclude other diagnoses. Endobronchial biopsy is discouraged because of the risk of hemorrhage.

In all KS patients, associated symptoms such as fevers, night sweats, and weight loss should be recorded and immunologic status, including CD4 cell count and HIV viral load, assessed.

■ THERAPY

When to initiate therapy and the choice of therapy for AIDS-related KS are problematic for several reasons. (1) The natural

history of KS is highly variable and thus unpredictable.⁴⁶ (2) Because of advances in HIV treatment, affected patients are living longer and may therefore have a more protracted course of KS. (3) Use of cytotoxic chemotherapy may impair cellular immunity and thus increase the risk of opportunistic infections. Other acute or cumulative toxicities include myelosuppression, allergic reaction, neuropathy, pulmonary fibrosis, and other risks depending on the agent used. (4) With initiation of HAART, lesions may regress without the use of cytotoxic chemotherapy.⁴⁷ Concurrent initiation of HAART and chemotherapy may make the response rate of drugs used in clinical trials somewhat difficult to interpret. (5) Even though the AIDS Clinical Trials Group staging system and tumor response criteria have led to better standardization among trials,⁴⁸ the clinical benefits obtained by patients are sometimes not well documented by these criteria, and the criteria may now not be as reliable as in the pre-HAART era when the criteria system was devised.⁴⁷ (6) Finally, therapeutic drug studies that have used different response criteria are difficult to compare.

When to initiate treatment must be decided on a patient-by-patient basis. Even disease that does not appear to be medically complicated may raise difficult issues for the patient because KS may be so recognizable and socially stigmatizing. When treatment is initiated and disease activity increases, the treatment alternatives are to maximize the dose and frequency of the agent being used or to change to a new agent. When the disease is quiescent, the alternatives are to use a tolerable agent intermittently or to discontinue therapy until a clear progression is seen.

Therapeutic approaches may be classified as local or systemic. The disease is often systemic even if the manifestations seen are only localized, but patients with indolent disease activity and a limited number of lesions may be managed with local therapy for long periods. In general, treatment is considered palliative and patients' desires for improved quality of life should be balanced against the toxicities and risks of therapy.

■ LOCAL THERAPY

Surgery, cryotherapy, intralesional chemotherapy, and laser therapy

Several effective local control methods can be used for small, superficial, discrete cutaneous lesions. Although surgery is often used to biopsy lesions, in general, it should not be a routine choice for treatment due to problems with local recurrences around the wound site despite attempts at wide excisions. Cryotherapy with liquid nitrogen, easily performed in the office setting, can be effective for small, superficial lesions. Its use in dark skinned individuals can result in noticeable hypopigmented skin due to destruction of

melanocytes. Topical application of topical 9-cis-retinoic acid (0.1% gel) has been shown to have responses in up to 41% of patients; side effects include local irritation and erythema.⁴⁹ Intralesional administration of vinblastine causes necrosis of the KS, often accompanied by several days of pain, but the result may be cosmetically satisfactory and possibly long-lasting.

Other local treatments include laser therapy and photofrin photodynamic therapy. Laser therapy can be very effective in controlling often painful mouth lesions and results in less morbidity and improved outcomes than other forms of local treatment.⁵⁰

Radiation therapy

Radiation therapy is very useful in managing AIDS-related KS, particularly if the tumor has associated symptoms such as pain, bleeding, or edema.^{51–53} Superficial lesions are best treated with a low-energy electron beam, which only penetrates a short distance into tissues, sparing deeper structures. Facial lesions, especially those on the nose or eyelid, can be successfully treated this way, with good cosmetic results. Larger, plaque-like areas of disease or areas with considerable edema may require coverage with megavoltage photons. Even with low doses, brawny induration in the radiation field can develop, and radiation recall resulting in skin erythema over the radiation field and even skin necrosis can occur when the patient moves on to systemic chemotherapy with anthracyclines. Optimal dosing and fractionation regimens will vary depending upon tumor size and location of the tumor as well as goals of therapy. A single treatment at low dose (8–12 Gy) produces a complete response in approximately 50% of lesions so treated with almost 100% of patients experiencing symptomatic improvement, but the duration of response is often shorter than if higher doses are given over a protracted course.⁵⁴

■ SYSTEMIC THERAPY

Chemotherapy

Many older chemotherapy agents including vinblastine, vincristine, bleomycin, doxorubicin, and etoposide have been studied, either alone or in combination, as therapy for KS. However, conventional chemotherapy has rarely produced durable remissions and has been associated with significant acute and chronic toxicity. For AIDS patients battling a number of chronic symptoms or intermittent infections, chemotherapy toxicity was often an excessive burden. Therefore, the goal of therapy was palliation of symptoms, and systemic chemotherapy was reserved for intermittent use during exacerbations of KS. Combination regimens, although intended to produce quick and sustained responses in the most symptomatic patients, have largely been supplanted by better-tolerated single agents such as liposomal anthracyclines and paclitaxel. Liposomal doxorubicin (Doxil

and liposomal daunorubicin (DaunoXome) are encapsulated anthracyclines that are approved as single agents for the treatment of advanced KS. In a large randomized trial, Doxil produced a response rate nearly twice that of a combination of doxorubicin (Adriamycin), bleomycin, and vinblastine (ABV).⁵⁵ In a similar study, a fourth of patients responded to either DaunoXome or ABV, but DaunoXome use was associated with a trend toward more opportunistic infections.⁵⁶ Even with long-term use of these liposomal anthracyclines, cardiotoxicity and other cumulative toxicity have not been seen. Mild myelosuppression is the most common side effect and generally develops after several cycles. The usual dose of Doxil is 20 $\mu\text{g}/\text{m}^2$ every 3 weeks or DaunoXome 40–60 $\mu\text{g}/\text{m}^2$ every 2–3 weeks, each given intravenously over 30 minutes.

Paclitaxel (Taxol) appears to have significant amount of activity.⁵⁷ It is approved as second-line treatment of KS and is frequently used for patients whose disease has progressed during therapy with liposomal anthracyclines. Two dosing schedules have activity, 100 $\mu\text{g}/\text{m}^2$ every 2 weeks and 135 $\mu\text{g}/\text{m}^2$ every 3 weeks. Side effects such as hair loss, myelosuppression, and neuropathy make it less appealing for some HIV-infected patients.

Biologic agents and investigational therapies

Since the association between HHV-8 and KS was identified, there has been attempts to treat the underlying herpes viral infection or molecular pathways. One study has shown that the incidence of KS can be reduced by the antiviral agent ganciclovir but to date, antiviral drugs have not been shown to significantly affect established KS lesions.⁵⁸

Alpha-interferon is active against KS, especially in those patients with relatively well-preserved immune systems as measured by their CD4 counts.⁵⁹ It is also one of the few agents that have been able to induce durable remissions, albeit in a minority of patients. Although neutropenia may develop, alpha-interferon has immune-enhancing and antiviral properties, in addition to its antineoplastic and antiangiogenic effects. The major drawbacks are that it requires daily subcutaneous injections and is associated with toxicity such as a flu-like syndrome. In addition, responses occur up to 6–8 weeks or more following initiation of therapy. Antiretroviral therapy should be given with alpha-interferon as older studies demonstrated that response rates appeared to be higher when an antiretroviral drug was given with alpha-interferon. Doses generally used are 4–18 million units by subcutaneous injection daily as a single agent; doses of 1–10 million units when combined with newer antiretrovirals are currently being studied.

As the histologic manifestation of Kaposi's sarcoma is characterized by vascular proliferation; drugs targeted at inhibiting angiogenesis are being explored in studies. Thalidomide has shown some promise⁶⁰; other antiangiogenesis drugs

such as bevacizumab and sorafenib are being evaluated in clinical trials.

Summary of treatment guidelines

HAART, with either local therapy, alpha-interferon, watchful waiting or experimental agents are all reasonable approaches to the patient with limited disease or an indolent disease course. Effective control of HIV should be the first step.

Patients with associated B-symptoms (fevers, sweats, weight loss), edema, symptomatic visceral disease, or the rapid appearance of a number of new lesions should receive effective systemic therapy. Reasonable options include alpha-interferon or chemotherapy with Doxil, DaunoXome, or Taxol. Doxil has become the most frequently used agent, followed by taxol if control is inadequate with Doxil.

As durable remissions are possible, periodic trials off chemotherapy should be allowed to determine which patients may discontinue chemotherapy. More often, patients will require ongoing or intermittent chemotherapy to maintain the benefits that they achieved. However, any residual pigmentation, which may be permanent, needs to be distinguished from ongoing KS disease. Close observation during any period off chemotherapy, looking for progressive disease, may be the only way to determine if ongoing chemotherapy is still required.

NON-HODGKIN'S LYMPHOMA

Since the first cases of high-grade NHL were reported in the early 1980s,⁶¹⁻⁶³ many reports of aggressive lymphoma in patients at risk for AIDS have been published. In June 1985, the CDC amended its case definition of AIDS to include patients with high-grade, B-cell NHL in the setting of documented HIV infection.¹

NHL IN IMMUNODEFICIENT NON-HIV-INFECTED POPULATIONS

It has been recognized for more than 30 years that in patients with congenital immune deficiency in which there is impaired cell-mediated immunity, such as the Wiskott-Aldrich syndrome, the incidence of cancer is up to 100 times greater than expected and malignant lymphomas comprise the majority of these malignancies.⁶⁴ Patients typically have marked generalized lymphadenopathy for several years before the diagnosis of lymphoma,⁶⁵ and lymph node biopsies can often initially show a pattern of reactive hyperplasia, as they do in renal transplant patients receiving immunosuppressive medications.^{66,67} Overall, renal transplant patients have a 35-fold increased risk of developing NHL, often in unusual sites.⁶⁸

In one-third of patients with NHL associated with renal transplantation, the disease is confined to the CNS.⁶⁹

Lymphoproliferative disease may appear as a relatively benign polyclonal proliferation in renal transplant patients or as an invasive and aggressive monoclonal large-cell NHL.⁶⁵ An etiologic role for Epstein-Barr virus (EBV) is supported by serologic studies as well as the finding of multiple copies of the EBV virus within the tumor cells. Lymphoproliferation occurs when the host immune response is unable to control the proliferation of the EBV infected B cells.

NHL IN AIDS

■ EPIDEMIOLOGY

NHL in HIV-infected patients has many similarities to NHL seen in transplant patients. The rate of NHL among HIV-infected persons is about 200-fold greater than that in the general population and is fairly uniform throughout all HIV exposure risk groups.⁷⁰ The incidence of primary central nervous system lymphoma (PCNSL) is 1000-fold higher than that seen in the general population. The risk of lymphoma increases with the severity as well as the duration of immunosuppression. Although HAART has decreased the incidence of lymphoma by about 50%,⁷¹ it is anticipated that the number of cases will rise as other AIDS-related complications are controlled and patient survival is prolonged.

■ PATHOGENESIS

The pathogenesis of AIDS-related NHL is complex.^{72,73} The same regulatory dysfunction seen in the lymphoproliferative disorders of transplant patients likely plays a similar role in AIDS related NHL. A state of chronic B-cell stimulation evidenced by polyclonal hypergammaglobulinemia and follicular (B-cell) hyperplasia typifies HIV infection. One-third of patients diagnosed with NHL have histories of persistent generalized lymphadenopathy. HIV appears to induce the production of a host of cytokines or growth factors that serve to induce a state of ongoing B-cell activation, differentiation, and proliferation. In the context of impaired T-cell immunity, ongoing EBV infection can drive polyclonal B-cell activation. EBV nuclear antigen (EBNA) has been identified in 40-50% of AIDS related lymphomas, and most patients have shown evidence of previous EBV infection. Virtually all PCNSLs contain EBV. The inherent genetic instability of EBV-infected and immortalized B-cell clones eventually leads to *c-myc* gene rearrangement, resulting in the emergence of a fully transformed, EBV-containing monoclonal B-cell lymphoma. AIDS-related NHL does not infrequently carry *c-myc* rearrangements in the absence of EBV. A variety of other chromosomal translocations involving oncogenes have been described in AIDS-related NHLs, and multiple alternative molecular pathways likely contribute to lymphomagenesis in the setting of HIV.⁷⁴ In summary, major contributing

factors for the development of lymphomas in HIV-infected individuals are the HIV induced immunosuppression, chronic antigenic stimulation, cytokine overproduction, and eventually genetic alterations in *c-myc*, *bcl-6*, *ras*, and/or *p53*.

■ CLINICAL MANIFESTATIONS

Systemic NHL comprises approximately 80% of all AIDS-related NHLs; the other 20% are confined to the CNS. The vast majority of systemic lymphomas are diffuse large B-cell (DLBCL), intermediate- or high-grade DLBCL, typically presenting with advanced disease and involving extranodal sites.

In 1984, Ziegler et al. reported a retrospective, multiinstitutional study of 90 homosexual men with HIV-associated NHL.⁶¹ Of 77 patients diagnosed antemortem, 33 had a prodrome of generalized lymphadenopathy, 15 had previous opportunistic infections, and 9 had KS before NHL developed. All but two patients had evidence of extranodal disease; 42% of patients had CNS disease, and 33% had bone marrow involvement. Meningeal infiltration developed in two-thirds of patients by the time of death. The GI tract has become the most common extranodal site of involvement since CNS prophylaxis with intrathecal chemotherapy became standard practice. However, virtually any organ site may be infiltrated with NHL. The lungs and liver are also common sites.

Patients presenting with ascites or with pleural or pericardial effusions will be diagnosed with PELs, which is a subtype of DLBCL. This subtype of AIDS related lymphoma accounts for approximately 1–5% of lymphomas in HIV-infected persons.⁷⁵ PEL is especially aggressive and is associated with resistance or only partial responses to chemotherapy resulting in relatively poor overall survival in the range of 6–9 months. Malignant cells universally contain HHV-8, often in conjunction with EBV.

DLBCL confined to the CNS or PCNSL should be considered in any patient belonging to a risk group for AIDS who shows focal neurologic findings or has more nonspecific symptoms such as confusion or memory loss. Brain involvement tends to be multifocal. Most patients have late stage HIV disease with CD4 counts less than 50/mm³. Survival is poor with a median survival of about 4 months.⁷⁶ With the use of HAART, the incidence of PCNSL has fallen considerably from the pre-HAART era.⁷⁷

■ DIAGNOSIS

The diagnosis is often elusive because patient presentation can be so variable. Fevers and declining functional status, signs of organ compromise due to NHL infiltration, or the onset of asymmetric lymphadenopathy are common presentations. The differential diagnosis includes opportunistic infections, other malignancies such as KS, or benign

lymphadenopathy. Fine needle aspiration with flow cytometry is appropriate for peripheral or accessible intra-abdominal masses and can often make the diagnosis, but additional tissue may be required to confirm the diagnosis. The major histologic subtypes by the WHO classification are diffuse large B-cell lymphoma (DLBCL) and Burkitt's lymphoma. PELs are best diagnosed by fluid sampling with flow cytometry of the cells. Suspected PCNSL should be biopsied if possible.

■ THERAPY

AIDS-related lymphomas in the pre-HAART era were difficult to treat. Standard treatment commonly used in HIV-patients frequently caused more immunosuppression and increased the risk of death due to opportunistic infections. More than a decade ago, Ziegler and colleagues⁶¹ reported that morbidity and mortality appeared to be directly related to the degree of previous HIV-related illness. Patients who were asymptomatic at the time of diagnosis showed the best treatment results. Only two of 21 patients with a previous AIDS diagnosis remained alive and well. Thirty-eight of 66 evaluable patients had died, half from progressive lymphoma and half from opportunistic infections.

Much has changed over the last 2 decades largely due to HAART and also in part due to work in identifying tolerable regimens for HIV-positive patients on HAART. In the pre-HAART era, important prognostic features such as CD4 count and existing prior AIDS diagnosis were important prognostic components, differing from factors important in non-HIV infected lymphoma patients.

The poor outcomes in these patients prompted the use of attenuated doses of combination chemotherapy. Levine and colleagues initiated this approach with a study of low dose m-BACOD (methotrexate, calcium leucovorin, bleomycin, doxorubicin, cyclophosphamide, vincristine, and dexamethasone).⁷⁶ This led to a large multi-institutional trial, conducted in the pre-HAART era, of standard-dose m-BACOD versus low-dose m-BACOD.⁷⁷ This trial demonstrated a median survival in both arms of approximately 8 months, with less than 20% of patients surviving longterm. No subgroup could be identified in whom standard-dose therapy was more beneficial. In a similar attempt to identify a tolerable but more effective regimen, the Eastern Cooperative Oncology Group (ECOG) performed a phase II trial in patients with HIV-associated lymphoma evaluating infusional therapy with cyclophosphamide, doxorubicin, and etoposide.⁷⁸ Of note, this trial had approximately equal numbers of patients receiving HAART and no HAART; this allowed investigators to assess the effect of HAART on outcomes. Although complete remission rates were similar between the HAART and no-HAART groups (44% vs. 47%, respectfully), survival favored the HAART group with 47% of patients alive compared to only 30% of patients receiving no HAART.

Rituximab (humanized anti-CD20 antibody) has emerged as a standard component of all CD20⁺ lymphomas in HIV⁻ patients following demonstration in the randomized Groupe d'Etude de Lymphome de l'Adulte (GELA) study in patients over 60 years of age showing a survival benefit in patients treated with CHOP chemotherapy plus rituximab versus patients treated with CHOP alone.⁷⁹ However, the same clear benefit has not yet been demonstrated for HIV-infected patients. In an AMC sponsored randomized trial in HIV-infected patients with NHL looking at CHOP with or without rituximab, there was no difference in survival between the two groups but a significant increase in deaths associated with bacterial infections in the rituximab group of 14% versus 2% in the CHOP alone arm.⁸⁰ Sixty percent of the deaths were seen in patients with CD4 counts less than 50/m³. Some have advocated that rituximab should be used in HIV-infected lymphoma patients with careful attention to supportive medical care and early intervention for infectious complications.⁸¹

The prognosis for patients with PCNSL is extremely poor.^{82,83} Most will die with recurrent disease within 1 year. Radiation therapy is the standard treatment approach, although combination chemotherapy followed by radiation can be used in patients with adequate immune function. There is evidence that the use of HAART along with antineoplastic treatment can improve survival.⁸⁴

In summary, treatment of AIDS-related lymphoma will almost always offer at least palliation of cancer-related symptoms and clearly improves survival compared with no therapy at all. Patients treated with HAART and relatively preserved immune function will fare better with standard cytotoxic chemotherapy. Although the prognosis for patients with AIDS-related lymphoma has improved substantially, the outcome is still less favorable for these patients when compared to non-HIV infected patients. Further narrowing of this gap awaits identification of better tolerated and more effective regimens along with advances in HIV treatment.

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Management of Neurological Disease in HIV-1 Infection

Kevin Robertson and Colin Hall

Early in the human immunodeficiency virus type 1 (HIV) epidemic, it was recognized that neurologic disease occurred in up to 70% of infected patients, often with disastrous consequences.^{1,2} Neurologic opportunistic infections such as cytomegalovirus (CMV), progressive multifocal leukoencephalopathy, cryptococcal meningitis, toxoplasmosis, and central nervous system (CNS) neoplasms, primarily lymphoma, were very frequent before the era of highly active antiretroviral therapy (HAART), and are still highly prevalent in resource-limited settings.^{3–6} Treatment of these diseases is covered elsewhere in this book. In this chapter, we will concentrate on nervous system diseases that appear to be the result of HIV alone. They include a clinically unique dementing process that has been called HIV-associated dementia (HAD) or AIDS dementia complex (ADC) and a milder clinical impairment labeled minor cognitive motor dysfunction (MCMD), myelopathy, peripheral neuropathy, and myopathy.^{7–18} With the advent of HAART, there has been a dramatic decline in the incidence of dementia in the developed world, although, since effective treatment has resulted in increased survival, the relative prevalence has not yet shown a clear decline.^{19–21} The incidence and prevalence of HIV-related neurological disorders in resource-limited settings where the majority of the disease burden remains have yet to be characterized.^{22,23} HIV is known to cross the blood–brain barrier by way of trafficking lymphocytes within the first days of infection and to remain sequestered in the CNS, particularly in microglial cells throughout the course of the infection.^{24–26} An acute but generally mild and self-limiting meningoencephalitis may occur at that time, but neurological signs and symptoms generally do not occur until many years later, usually in conjunction with severe immune compromise.^{26–28} We will describe the different presentations and their treatment individually, but it should be remembered that these conditions frequently occur concomitantly.

DEMENTIA

From the earliest stages of the HIV epidemic, it has been recognized that some patients developed severe and progressive

intellectual dysfunction that had a rather unique clinical presentation.²⁹ Recognizing that this condition usually involved more than cognitive loss, Price and colleagues labeled this as ADC.^{5,30} The American Academy of Neurology later suggested the term HAD.³¹ The terms are used interchangeably. HIV encephalopathy and AIDS dementia are also terms in common usage.^{5,30} Patients without dementia but with mild and often subclinical cognitive dysfunction have been labeled as having MCMD.³¹

■ HIV-ASSOCIATED DEMENTIA

Incidence and prevalence

Before effective antiretroviral (ARV) therapy was available, HAD was reported in up to one-third of infected patients,^{1,13} with an annual incidence rate of between 3.5% and 14%.^{32,33} The vast majority was severely immune compromised with peripheral CD4 lymphocyte counts below 200 cells/ μ L, and many had other manifestations of AIDS including lymphadenopathy, wasting, and a history of AIDS-related opportunistic infections and/or cancers. Other risk factors include increasing age, intravenous (IV) drug use, and lower hemoglobin levels.^{33–36} The CDC reported 2.8% of patients presented with HAD, and a large European study found HAD in 4.5% of patients at the time of AIDS diagnosis.^{35,37} With the availability of effective ARVs, there has been a marked reduction in the incidence of HAD in the developed world.³⁸ ADC was seen in 39% of patients in the Netherlands before zidovudine treatment, and 6% after with a later study by the same group showing a 7.5% prevalence.³⁹ The incidence in the United States is reported as now being less than 1%.⁴⁰ In the developed world, almost all those presenting with classical HAD are either HAART-naïve or have severely inadequate viral control. As could be expected with the greatly increased longevity associated with treatment, the prevalence of HAD has not yet shown a comparable decline, and has been reported as high as 15%. The incidence and prevalence likely remain high in resource-poor settings, but accurate figures are not currently available.^{19–21}

Clinical findings

HAD is somewhat unique in its constellation of symptoms and signs, which generally include cognitive, behavioral, and motor dysfunction (see Table 77-1). Untreated, the condition generally starts insidiously but progresses over weeks or months to a profound and devastating dementia affecting all spheres of function. Early cognitive findings include forgetfulness, lack of concentration, and loss of interest in activities that may be mistaken for depression. This progresses to flattening of affect and inability to understand written materials, maintain conversation, and cope with activities of daily living. A common late feature is progressive slowing of cognitive and motor responses to where the patient may take many seconds to offer an answer to the simplest questions. Behavioral changes may include delusions, hallucinations, irrational actions, and at times mania. There is almost always an associated decline in motor function. Early signs may include mild clumsiness and unsteadiness on rapid turns. Gait difficulty may progress to require a cane and eventually wheelchair. There may be increasing limb incoordination, loss of facial expression, paucity of movement, and motor weakness.^{1,13} Movement disorders including myoclonus,

tremor, and other parkinsonian features may accompany HAD, and may also occur in nondemented patients, even as the first manifestation of AIDS.⁴¹ The deep tendon reflexes are increased although the ankle jerks in particular may be suppressed if there is concomitant neuropathy. The plantar responses may be extensor, along with prevalent prominent jaw jerk and frontal release signs including snout and grasp responses. Sphincter disturbances are common. Untreated patients who do not first expire from intercurrent infection or other causes progress to become mute, unresponsive, and bed bound with urinary and fecal incontinence.

Clinical research criteria (see Table 77-2) for the diagnosis of HAD include a combination of motor symptoms, cognitive symptoms, and changes in activities of daily living and function in the absence of other confounding neurological or psychiatric disease.^{11,13,42} The Memorial Sloan Kettering (MSK) ADC staging system (see Table 77-3), developed by Price, Brew, and Sidtis, has proven useful in characterizing the severity of the dementia in research studies, and is also helpful in the general clinical setting.¹⁴ At Stage 0, patients have no functional disability and normal cognitive-motor functioning. In Stage 0.5 (*equivocal/minimal*), patients have some signs or symptoms consistent with ADC, but do not have functional deficits. In Stage 1, mild impairments of cognition and motor function exist that lead to functional deficits such that the patients cannot engage in their usual activities, but can still perform the less demanding aspects of work. In Stage 2, moderate impairments of cognitive motor functioning exist, and normal work becomes impossible. Stage 3 shows marked slowing, difficulty with conversation and personal events, and inability to walk unaided. In Stage 4, the patient is nearly vegetative, with little or no spontaneous language or responsiveness, paraplegia, and double incontinence.^{14,15}

Table 77-1. Early Symptoms of the AIDS Dementia Complex Seen in 44 Patients

Symptoms	Number of Patients (%)
Cognitive	29 (66%)
Forgetfulness	17 (39%)
Loss of concentration	11 (25%)
Confusion	10 (23%)
Slowness of thought	8 (18%)
Motor	20 (45%)
Loss of balance	15 (34%)
Leg weakness	9 (20%)
Deterioration of handwriting	4 (14%)
Behavioral	17 (39%)
Apathy, social withdrawal	16 (36%)
Dysphoric mood	5 (11%)
Organic psychosis	2 (4%)
Regressed behavior	1 (2%)

Source: Modified from Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Ann Neurol* 1986; 19(6): 517-524.

■ HIV-ASSOCIATED MINOR COGNITIVE MOTOR DISORDER

Early cohort studies of HIV-infected patients showed that subjects who did not meet the criteria for dementia often had less severe cognitive dysfunction, and this was more prevalent than in matched control subjects. In 1991, an American Academy of Neurology working group developed the term MCMD to describe this entity.⁴³ While patients with HAD have clear abnormalities that disrupt work ability and activities of daily living, those with MCMD have either no clear impairment or difficulty with only the most demanding tasks. The bedside mental status examination is generally within normal limits, and more specific and demanding neuropsychological tests are required to establish the diagnosis. Nonetheless, the presence of MCMD does predict difficulties, including in work performance and driving. Before HAART, it also had predictive value in the development of HAD.

Table 77-2. HIV-Associated Dementia Diagnosis**Confirmed**

1. Acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living (verifiable by report of other), not attributable solely to severe systemic illness or medication adverse effects
2. Abnormalities from at least two of the following categories:
 - a. Motor abnormality—for example, slowed rapid movements, release signs, abnormal gait, limb incoordination, diffuse hyperreflexia, hypertonia, or weakness
 - b. Behavioral abnormality—for example, change in personality with apathy, inertia, irritability, and/or emotional lability or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition
 - c. Cognitive abnormality in two or more domains of memory, judgment, flexibility, visual, constructional difficulties, reaction time, speed of mental processing, attention, and/or concentration as determined by appropriate neuropsychological testing
3. No other etiology confirmed by MRI/CT scan, negative CSF cryptococcal antigen or CSF CMV PCR: exclude active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance use, or substance withdrawal

Probable

1. Acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living, not attributable solely to severe systemic illness or medication adverse effects

2. Abnormalities from at least two of the following categories:
 - a. Motor abnormality—for example, slowed rapid movements, release signs, abnormal gait, limb incoordination, diffuse hyperreflexia, hypertonia, or weakness
 - b. Behavioral abnormality—for example, change in personality with apathy, inertia, irritability, and/or emotional lability or new onset of impaired judgment characterized by socially inappropriate behavior or disinhibition
 - c. Cognitive abnormality in two or more domains of memory, judgment, flexibility, visual, constructional difficulties, reaction time, speed of mental processing, attention, and/or concentration as determined by appropriate neuropsychological testing

3. Tests for other possible etiology (active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance abuse, or substance withdrawal) are not completed, results are not available, or results do not exclude other CNS processes

Possible

1. Acquired cognitive/motor dysfunction for at least 1 month causing impairment of work or activities of daily living, not attributable solely to severe systemic illness or medication adverse effects
2. Other possible CNS processes cannot be excluded (active CNS opportunistic infections or malignancy, active psychiatric disorders, active alcohol or substance abuse, or substance withdrawal)

Source: Modified from Appendix 60: Diagnoses Appendix. 2004, AIDS Clinical Trials Group.

However, it is not clear that HAD represents the progression of MCMD, or whether different mechanisms may be responsible for the two conditions. It is not established that MCMD responds to any treatment other than optimal treatment for the underlying HIV infection.

Pathology

The changes resulting from HIV-1 infection in the brain first and most profoundly involve the white matter and subcortical gray matter.¹ Early autopsy series reported neuropathological abnormalities in over 90% of brains, 33% of spinal cords, and up to 100% of peripheral nerves of AIDS patients, many of whom had not shown overt neurological disease. Changes in the brain include myelin pallor, formation of microglial nodules, rarification and vacuolation of white matter, and inflammatory changes that include multinucleated giant cells. While the presence of multinucleated giant cells

does correlate with dementia, they are only present in a quarter of demented patients.^{1,42,44,45}

Pathogenesis

HIV-1 DNA, RNA, and viral antigen are found in macrophages, microglial cells, and multinucleated giant cells in the CNS, particularly in white matter and deep gray matter structures, indicating productive viral infection in these cells.^{46–49} Vascular endothelial cells also show evidence of HIV infection.^{49,50} However, astrocytes do not show productive infection,^{51–53} and there has not been convincing evidence of direct infection of neurons.^{47,54} Despite this, neuronal loss is common, starting in the clinically asymptomatic stages and progressing with advancing disease. Studies have found loss of up to 50% of cortical neurons in AIDS patients, both demented and nondemented.^{55–60} It has been therefore proposed that neuronal death is the result of secondary indirect

Table 77-3. Staging Scheme for the AIDS Dementia Complex

ADC Stage	Characteristics
Stage 0 (normal)	Normal cognitive and motor function
Stage 0.5 (equivocal)	Either minimal or equivocal symptoms of cognitive or motor dysfunction characteristic of ADC or mild signs (snout response, slowed extremity movements) but without impairment of work or capacity to perform activities of daily living; gait and strength normal
Stage 1 (mild)	Unequivocal evidence (symptoms, signs, neuropsychological test performance) of functional, intellectual, or motor impairment characteristic of ADC, but able to perform all but the more demanding aspects of work or ADL; can walk without assistance
Stage 2 (moderate)	Cannot work or maintain the more demanding aspects of daily life, but able to perform basic activities of self-care; ambulatory but may require single prop
Stage 3 (severe)	Major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output) or motor disability (cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well)
Stage 4 (end stage)	Nearly vegetative; intellectual and social comprehension and responses are at a rudimentary level; nearly or absolutely mute; paraparetic or paraplegic with double incontinence

Source: Modified from Sidtis JJ, Price RW. Early HIV-1 infection and the AIDS dementia complex. *Neurology* 1990; 40(2): 323–326.

mechanisms. In vitro models suggest that macrophages and microglia are upregulated by HIV-1 infection to release substances that may act both directly and indirectly through upregulation of astrocytes to give neuronal apoptosis.^{61–65} While the exact mechanism is not established, a wide array of proposed toxins have been postulated, including the viral gene products *gp120*,^{66–68} *tat*,^{69–71} *nef*,⁵¹ and *rev*,⁵¹ cell-derived toxins such as quinolinic acid,^{72,73} and cytokines including tumor necrosis factor alpha (TNF- α),^{74–76} eicosanoids,^{74,77} platelet-activating factor,⁷⁸ and nitric oxide.^{79,80} Glutamate receptors, voltage-dependent calcium channels, or both have been implicated as the final common pathway, leading to increases in intracellular calcium concentrations and neuronal injury or death, and agents blocking these effects have been shown to protect neurons exposed to HIV in culture.^{79,81–83} Other studies have suggested that while cellular death is related to calcium influx, the final pathway may not be glutamate mediated.⁸⁴

Diagnosis

While the clinical presentation in the late stages is quite typical, HAD remains a diagnosis of exclusion, to be considered when patients present with cognitive changes, particularly in association with motor and/or behavioral abnormalities. Individuals with HAD show impaired performance on neuropsychological tests that target motor function, attention and concentration, speed of information processing, and visuospatial performance.^{15,31,85} However these tests, while

sensitive, are not specific to HIV.¹⁵ It is necessary to rule out opportunistic infection or neoplasm of the brain, encephalopathy due to other end organ failure, medication effects, and psychogenic states. Complaints of cognitive disturbance, particularly in the earlier stages of infection, may result from anxiety or depression.⁸⁶ Toxoplasmosis CMV encephalopathy,^{87–89} seen commonly in the early epidemic and once considered as the cause of HAD, is now rare but cognitive changes still occur with other viral infections, including progressive multifocal leukoencephalopathy⁹⁰ and herpes infections⁹¹ toxoplasmosis,^{92–94} cryptococcosis,⁹⁵ syphilis,⁹⁶ tuberculosis and lymphoma should be considered, as well as a number of less common infectious agents. Medications that affect CNS function should be considered. While ARVs do not usually cause significant intellectual changes, efavirenz may elicit mood change, irritability, and sleep disturbance, particularly in the first few months of treatment.⁹⁷

Cerebrospinal fluid (CSF) examination and neuroimaging are particularly helpful in the differential diagnosis of HAD. If there is any suspicion of a mass lesion in the brain, it is prudent to perform computerized tomography (CT) or magnetic resonance imaging (MRI) before lumbar puncture. While neuroimaging is of most value in excluding alternative infectious and neoplastic causes of dementia, MRI is more sensitive than CT in this respect, although it should be noted that some viral infections, cryptococcosis, and even lymphoma may present without obvious neuroimaging changes. A typical pattern in advanced HAD is of diffuse brain atrophy with

patchy changes in white matter that may fluctuate over time. However, both CT and MRI may show considerable brain atrophy, even in the asymptomatic stages of infection with no intellectual dysfunction, and white matter changes may not be obvious, even with HAD.^{13,98–103}

Attempts to identify a reliable surrogate marker for HAD in the CSF have been largely unsatisfactory. Absolute levels of CSF HIV RNA and comparisons with blood levels have not proven reliable indicators. Studies on patients before the availability of HAART indicated a relationship between CSF HIV-1 RNA viral load and dementia severity.^{104,105} CSF viral load correlated with cognitive scores, and CSF viral load greater than 10,000 copies per milliliter (cps/mL) correlated both with severity of dementia¹⁰⁶ and with the likelihood of abnormalities on neuroimaging.¹⁰⁷ However, patients undergoing HAART treatment do not show a clear correlation between CSF viral load and nervous system dysfunction.^{45,108} While data from the MACS suggest that a CSF beta-2-microglobulin concentration of >3.8 mg/dL in a CSF specimen with a normal WBC count is specific for the diagnosis of HAD, and p24 antigen and neopterin are also elevated in dementia, none of these has proven sensitive enough to have value in the clinical setting.^{109–116} There is also evidence that the utility of these markers has been further reduced in the HAART era.

While conventional CSF analysis is useful in excluding opportunistic infections of the CNS, it must be realized that CSF abnormalities are frequent in HIV-infected patients without any signs of neurological disease.^{117–119} These include increased WBC, particularly mononuclear, count, increased protein, the presence of oligoclonal bands, and blood–brain barrier compromise. A high granulocyte cell count and hypoglycorrhacia, on the other hand, are likely to indicate intercurrent infection. Identification of viral antigen by using polymerase chain reaction (PCR) has greatly increased the value of CSF evaluation. Positivity for JC virus, herpes viruses, and CMV, while not highly sensitive, has very high specificity for active nervous system disease caused by these agents, and PCR for Epstein Barr virus is almost 100% positive in the presence of CNS lymphoma.^{87–91,120}

Recent efforts have been made to address the diagnostic criteria and definitions of HIV-related neurological disease, especially with changes some have noted in the presentation of neurological disease in the HAART era. An NIMH/NINDS panel found that some modification of the prior AAN criteria was needed. Among other changes, the panel recommended that an *asymptomatic neurocognitive impairment* category be added to the existing diagnostic schema to describe impaired performance on testing without substantial functional impact.¹²¹

Treatment

Zidovudine is the only single agent that has undergone double-blind placebo-controlled randomized trial for efficacy in the treatment of HAD.¹²² There was evidence of efficacy,

but experience soon showed that the beneficial effects were quite limited in both degree and duration.^{123–127} However, while little is described on the effectiveness of individual agents, there is a great deal of evidence that effective systemic HAART therapy has led to a reduction in the incidence of ADC.^{128–130} There is also strong anecdotal evidence of improvement, often dramatic, in demented individuals following the institution of effective HAART. The standard of care for dementia is therefore to optimize viral suppression using HAART. This approach is particularly likely to be beneficial in patients who are HAART naive or who have had a protracted period off medication. In fact, such patients comprise the vast majority of those who now present with dementia. There is also evidence that cognitive function is improved by effective viral suppression, even in patients who do not show evidence of dementia.¹³⁰

The exact mechanism behind this therapeutic effect is not known. ARVs have poor penetration into the CNS, particularly protease inhibitors which are highly protein bound in plasma and are a substrate of the P-glycoprotein efflux mechanism which limits entry.^{131,132} This has led to speculation that virus may become sequestered in the CNS, increasing the likelihood of the development of resistant virus behind the blood–brain barrier, and maintaining the propensity for neurological disease even in the face of adequate systemic treatment.^{133,134} Another complication could be reseeding of the systemic compartment with resistant virus from the CNS.¹³⁴ It should be stressed that, although there is evidence that virus in the CNS compartment can show different mutations from those in the systemic compartment in individual patients, there is no reliable evidence that this affects the likelihood or intensity of neurological disease.^{133–135} However, it has raised the possibility that ARV regimens with higher CNS penetration may provide increased protection from neurological disease (see [Table 77-4](#) for comparative CNS penetration of ARVs). Although earlier retrospective reports found no difference,^{130,136} recent studies have suggested improved neurological outcome in high over low CNS penetrant regimens.^{130,137–139} So, there is mounting evidence to support the use of ARVs known to have higher CNS penetrance, especially in patients showing evidence of CNS dysfunction.^{136,140–142} Higher CNS penetrating regimens have been associated with reduced CSF viral load, and improved cognitive functioning.^{143,144}

Based on the premise that neuronal loss is a secondary effect rather than a direct result of viral infection, a number of agents have been tested for their neuroprotective effects in HAD. Early phase two trials with medications available by prescription include the anti-oxidant selegiline,^{145,146} and the calcium channel antagonist nimodipine.¹⁴⁷ Although each demonstrated a trend for improvement in individual aspects of the extensive neuropsychological battery used in testing, neither showed significant benefit. Other agents continue to be studied, but none can yet be recommended.

Table 77-4. CNS Penetration/Efficacy

High	NRTI	ZDV	ABV			
	NNRTI	NVP	DLV			
	PI	ATV-r	APV-r	f-APV-r	IDV-r	LPV-r
Medium	NRTI	3TC	FTC	D4T		
	NNRTI	EFV				
	PI	APV	f-APV	ATV	IDV	
Low	NRTI	TFV	DDI	DDC		
	PI	NFV	SQV	SQV-r	RTV	TPV-r
	FI	T20				

Note: High, medium, low denote level of penetration/efficacy within the CNS.

NRTI, nucleoside reverse transcription inhibitors; NNRTI, non-nucleoside reverse transcription inhibitors; PI, protease inhibitors; FI, fusion inhibitors. The suffix r refers to ritonavir boosting.

Source: Letendre SL, Ellis RJ, Grant II, McCutchan JA and the HNRC Group. The CSF Concentration / IC50 Ratio: a Potential Predictor of Antiretroviral Efficacy in the CNS. Eighth Conference on Retroviruses and Opportunistic Infections, 2001. Robertson K, Parsons T, Robertson W, Hall CD. Antiretroviral CNS Penetration and Neurocognitive Outcomes. HIV Infection and the Central Nervous System, Developed and Resource Limited Settings, Frascati, Italy, 2005.

Other adjunctive therapies that can be considered in treatment include antidepressants, psychostimulants to counter some of the psychomotor, attention and speed of processing symptoms,¹⁴⁸ and antipsychotics to treat delusional or hallucinatory symptoms. Behavioral techniques that focus on compensation for lost abilities in early dementia and on providing a structured environment in late dementia may be helpful.^{149,150} Clinical trials of other adjunctive therapies such as nimodipine, memantine, and lexipafant have not been very successful. Trials of selegiline have just completed, and upcoming trials of minocycline are planned after promise in SIV model has been demonstrated.

Course

Before the availability of ARV medication, dementia was generally rapidly progressive with survival ranging from 6 to 8 months.^{33,35,39} Zidovudine, the first available ARV, was shown in a controlled study to have benefit in reversing some symptoms of HAD, and the incidence of dementia in studied populations declined with the availability of the nucleoside reverse transcript inhibitors as a group. With the availability of HAART, there has been a marked improvement in both the incidence of dementia and the prognosis for recovery, as described above.

■ DEMYELINATING DISEASE

Although it is not unusual to have MRI evidence of white matter disease in late stage AIDS, particularly with dementia, there have

been a number of reported cases of multiple-sclerosis-like illness with more prominent demyelination and with no evidence of opportunistic viral or other infections of the brain. The initial reports were of patients early in the course of infection,^{151,152} but later descriptions were in more advanced disease.^{153,154} It has been suggested that a severe form associated with dementia and death may be the result of immune restoration inflammatory syndrome.¹⁵⁵ There have been no formal studies of treatment for this condition, but a tapering course of corticosteroids has provided temporary improvement in one of our patients.

■ HIV-1 MYELOPATHY

Clinical presentation

Early descriptions of HIV-infected cohorts included patients who had clear evidence of spinal cord involvement.^{29,156,157} Patients with HIV myelopathy develop symptoms that are predominantly in the lower limbs. These include weakness, spasticity of tone in the legs with increased reflexes, extensor plantar responses, sensory loss that particularly involves joint position and vibration sense, sexual dysfunction, and sphincter disturbance. In untreated patients, the course is generally of subacute or chronic decline, with progressive loss of gait and eventual wheelchair confinement. On occasion, this presents as a pure myelopathy with no evidence of other nervous system involvement. However, the clinical picture is often much more complicated by concomitant evidence of brain and/or

peripheral nerve involvement. These patients may have cognitive dysfunction and frontal release signs such as snout, grasp and palmomental responses and an increased jaw jerk due to brain involvement, or hyperreflexia at the knees with suppressed ankle reflexes due to peripheral neuropathy. It may not be clinically possible to distinguish the different areas involved. An abnormal spinal component of lower limb sensory evoked potentials may suggest spinal cord involvement, but there is not a close correlation between this and symptomatic spinal disease.¹⁵⁷

Pathology

The autopsy findings associated with HIV myelopathy show prominent vacuolation in the white matter, particularly in the dorsal and lateral columns, and most prominently in the thoracic spinal cord.^{2,158} As with the brain, there is no clear evidence that spinal cord neurons are directly infected by HIV.^{159–161} The degree of pathological change not only correlates with the degree of clinical dysfunction but also with the presence of dementia, suggesting that a similar process could be involved in both the processes.^{160,162}

Differential diagnosis

In the HAART era, clinical HIV myelopathy has become rare, and it is particularly important to rule out other potential causes of spinal cord dysfunction. Opportunistic infections to consider include herpes simplex,^{162,163} varicella-zoster virus,^{164,165} CMV,^{166–169} *Toxoplasma gondii*,^{170–173} mycobacteria,¹⁷⁴ and syphilis.¹⁷⁵ Compression of the cord due to degenerative disease and tumor must also be ruled out. Evaluation should include MRI of the cord and CSF studies, including appropriate PCR evaluations.

Treatment

There is no defined treatment for HIV myelopathy, but the marked decline associated with HAART suggests that effective ARV therapy should be the goal. The pathological changes are similar to those seen with Vitamin B12 deficiency, and while there is no clear evidence of efficacy, it is prudent to ensure adequate B12 levels.^{157,160,161,176}

PERIPHERAL NEUROPATHY

In the developed world, and probably globally, neuropathy is the commonest neurological manifestation of HIV infection, and may be due to a number of different pathological processes.¹⁷⁷

Opportunistic infections that may result in neuropathy include varicella-zoster, hepatitis C and its treatment, human T-lymphotropic virus type 1, CMV and rarely toxoplasma, syphilis, or cryptococcus. Some neuropathies are immune mediated. The commonest form, however, is a primarily

painful distal sensory polyneuropathy (DSPN), generally occurring in late disease. A clinically similar neuropathy is associated with ARV medications.

■ IMMUNE-MEDIATED NEUROPATHIES

These generally occur in the clinically asymptomatic and early symptomatic stages of HIV infection, when the immune system is still able to mount a vigorous response.¹⁷⁸

Clinical presentation

Cranial nerve and more rarely individual peripheral nerve palsies may occur very early in the course of infection. The commonest is of the facial nerve.^{3,8,9,11} This is generally self-limiting. While no formal studies have been performed, it may be treated over 1–2 weeks with a tapering course of high-dose steroids, as this has reduced morbidity in traditional Bell's palsy. As Bell's palsy has been associated with herpes simplex infection, acyclovir or valacyclovir may also be given.^{179–182}

An acute inflammatory demyelinating polyneuropathy (AIDP) indistinguishable from Guillian-Barre syndrome (GBS) may also occur. This generally presents as a rapidly progressive primarily motor neuropathy, most commonly but not always starting in the lower limbs and like GBS can lead to quadriparesis with respiratory failure over days or even hours.^{183–189} Some patients will progress to or develop de novo a more slowly progressive chronic inflammatory demyelinating polyneuropathy form (CIDP).^{29,184,190–193} Generally there is weakness, sensory symptoms that may be more prominent than actual sensory loss, and loss of reflexes. The CSF will show elevated protein after the first few days.^{29,184} Unlike non-HIV-related inflammatory neuropathies, there may be CSF pleocytosis.^{29,184} Nerve conduction studies will generally be compatible with a demyelinating neuropathy, but axonal forms have also been described.²⁹ Treatment with either plasma exchange, starting with three infusions per week for 2 weeks, or IV immunoglobulin, 2 g/kg infused as 400 mg/kg/day for 5 days, is generally effective in both the forms, but may need prolonged repetitions in CIDP. CIDP is also often responsive to corticosteroids, although these carry the risk of further immune compromise.^{29,191}

There have also been isolated reports of biopsy-confirmed vasculitic mononeuritis and mononeuritis multiplex, some with response to immunoglobulins or corticosteroids.^{29,191–193}

A rapidly ascending paralysis similar to GBS but associated with lactic acidosis and exposure to nucleoside reverse transcriptase inhibitors has also been reported. This entity remains poorly defined but has been suggested to be the result of mitochondrial toxicity.^{194–196}

Facial palsy and peripheral neuropathy may also be seen as part of the diffuse infiltrative lymphocytosis syndrome resulting from persistent CD8 hyperlymphocytosis.¹⁹⁷ Corticosteroids may have efficacy in severe cases.

■ DISTAL SYMMETRIC SENSORY POLYNEUROPATHY

Distal symmetric sensory polyneuropathy (DSP) is the commonest nervous system manifestation of HIV infection in the developed world, affecting about a third of patients with advanced disease.^{9,17,190,192,193} The incidence and prevalence of DSP in resource-poor settings is not well characterized, but initial studies have similar prevalence as in the developed world.^{198,199}

Pathologically it is a “dying back” axonal neuropathy, first affecting the distal branches of the longest nerves, then progressing proximally.¹⁹¹ As with the CNS, there is no evidence that HIV infects or replicates in peripheral neurons, and the condition is likely due to an indirect process, with activated macrophages causing neuronal death by liberating cytokines and/or other toxic products.^{9,18,65,200–203} Nutritional factors have also been postulated as having a role.^{17,18,76}

Clinical presentation

DSP has a characteristic clinical presentation with paresthesia numbness aching and/or burning in the toes progressing to the feet over weeks to months.^{7,17} There is variable objective sensory loss and generally loss of ankle reflexes or at least depression when compared to knee reflexes. Pain may be very severe, greatly impairing quality of life. Motor loss is usually absent or mild. Autonomic neuropathic features may occur late in the course.

Diagnosis

While electrodiagnostic studies and sural nerve biopsy may indicate an axonal neuropathy,^{17,18} this remains primarily a diagnosis based on history and clinical examination.^{204,205}

Treatment

The effect of HAART on the incidence and prevalence of DSP is not clear,^{7,126,127} but it appears prudent to attempt effective viral suppression. If patients are on an ARV regimen that contains a “d-drug” including ddi, ddC, or D4T, then it is possible that these ARVs could be responsible for the neuropathy symptoms. The symptoms and signs of DSP are indistinguishable from those reported with exposure to the nucleoside reverse transcriptase inhibitors ddi, d4T, and ddC, particularly in combination, and reduction or withdrawal of these medications may need to be considered.^{206–211} Although, it does appear that if a patient can tolerate d-drug therapy initially without development of neuropathy, the majority can safely tolerate this regimen for longer term treatment.²¹²

Treatment is otherwise aimed at control of pain and usually involves the sequential trial of systemic agents including gabapentin,^{213,214} lamotrigine,²¹⁵ valproic acid,²¹⁶ carbamazepine, and tricyclic antidepressants.²¹⁷ Topical lidocaine

or capsaicin may also be helpful.^{218–220} Some patients require chronic narcotic use, but this is of limited effectiveness.

Differential diagnosis

As noted above, toxic side effects of the NRTI's ddi, ddC, and D4T, and some ARVs, are indistinguishable from DSP. Reduction or withdrawal of these medications may need to be considered to determine if the symptoms are due to the toxic side effects of the d-drugs or from HIV.^{206–211} Alcohol can lead to neuropathy symptoms similar to HIV DSP, and an assessment of alcohol should be considered. Correction of deficiencies of nutritional factors such as vitamin B12¹⁷⁶ and withdrawal of other potentially neurotoxic medications should also be considered.

MYOPATHY

Nonspecific myalgias are common in HIV infection.²²¹ A usually noninflammatory myopathy, generally but not always associated with diffuse wasting, or “slim disease” is frequently associated with late-stage untreated or inadequately treated HIV infection, and probably results from a combination of poor nutritional intake and cachexia related to upregulation of proinflammatory cytokines.^{222,223} Small uncontrolled studies have suggested that corticosteroids or anabolic steroids may result in clinical improvement,^{16,223,224} but the most important therapy is adequate viral suppression.

Otherwise, disease of muscle is less commonly encountered than other neurological complications of HIV infection. However, myopathy may still present at any stage.^{223,225} HIV-associated polymyositis is generally indistinguishable from that disease in non-HIV-infected patients in presentation and response to treatment.²²⁶ Subacute progressive proximal muscle weakness, often with myalgias, is accompanied by elevation in serum creatine kinase level, electromyographic changes compatible with inflammatory myopathy, and muscle biopsy showing perivascular and endomysial inflammatory infiltration with necrosis and regeneration of individual fibers.^{221–225} The pathology is believed to be immune mediated, and the disease generally responds to the same forms of immune modulation that are of benefit in non-HIV-infected patients, although there are no controlled clinical studies of treatment.²²⁷ Prednisone at a starting dose of 1 g/kg and tapered over weeks according to response may provide rapid symptomatic relief, although it does raise concerns of further immune compromise.^{226,228} Methotrexate starting at a weekly dose of 7.5 mg, azathioprine, or mycophenolate mofetil may be used as single therapy or added in cases of steroid failure. IV immunoglobulin 2 mg/kg given over a 5-day course may give excellent clinical improvement without the danger of further immune compromise, but this will generally require repeated infusions titrated to response, and/or combination

with immunosuppressant drugs. Steroid-responsive polymyositis may also present in the course of HAART-related immune restoration syndrome²²⁹ and diffuse infiltrative lymphocytosis syndrome.^{202,226}

Rare reports of other apparently immune-mediated muscle disorders have been described. One was a case of inclusion body myositis with typical clinical and pathological findings.²³⁰ A painless myopathy responsive to prednisone and associated with nemaline rods on biopsy has also been described.^{231,232} There are rare reports of myasthenia gravis with or without antibodies to acetylcholine receptors in association with HIV infection, and it can be assumed that this too is in some way related to immune upregulation.^{233,234}

Zidovudine therapy has been associated with a toxic myopathy with a clinical presentation very similar to polymyositis, with myalgias, proximal muscle weakness, and elevated creatine kinase levels.^{235,236} There is a relationship between myopathy and cumulative dose of zidovudine, and the mechanism is thought to be due to mitochondrial toxicity of the drug. Muscle biopsy may or may not show “ragged red” fibers characteristic of mitochondrial myopathy. The clinical abnormalities are reversible on withdrawal or even reduction of the zidovudine dose, and while biopsy may help distinguish this entity from polymyositis, if the clinical picture is not severe, withdrawal of medication may establish the diagnosis without reverting to biopsy.

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PART 13

STI/HIV in Reproductive Health and Pediatrics

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Charles S. Morrison and Willard Cates, Jr.

INTRODUCTION

Using contraception has two main benefits¹⁻⁶: prevention of unplanned pregnancies and protection against sexually transmitted diseases (STDs). Abstinence from sexual intercourse provides nearly absolute protection against both outcomes. For those choosing to be sexually active, contraception reduces, but does not eliminate, the risk of either pregnancy and/or STDs. Unfortunately the contraceptives with the best record for pregnancy prevention provide minimal STD protection. Some contraceptives may even raise the risk of certain infections.

Moreover, the interaction of contraception and STDs cuts both ways: Not only does the choice of contraception affect the risk of STDs, but also the perception of STD risk affects contraceptive choice. Thus, decisions about contraception by individuals, communities, and policymakers should involve balancing the relative need to prevent both unplanned pregnancies and STDs.

At the personal level, contraceptive use by couples is affected by the perceived risks and costs of STDs and/or pregnancy.⁷ These involve such complex *individual* factors as rate of sex partner change, partner selection, relationship context (new vs. established and primary vs. secondary relationship), coital frequency, timing of coitus within the menstrual cycle, safety of the contraceptive method, availability and cost of the method, and acceptance of the method by the sex partner.⁸

At the community level, contraceptive *acceptance* is affected by the social norms of particular cultures.^{9,10} This involves such complex *community* factors as the relative value of fertility within specific societies, local customs about sexual activity at early ages, community pressures on teenagers to bear children, societal norms about touching the genitals, and religious proscriptions against use of particular contraceptives.

At the policy level, contraceptive *emphasis* by policymakers is affected by the aggregate risks and costs of STDs and unplanned pregnancies in that particular society.³ These involve such complex *public health* factors as the local prevalence of sexually transmitted infections (STIs) and

unplanned pregnancies, the level of unprotected sexual activity, the political acceptance of individual choice over sexual and reproductive decisions, and the economic capacity of the society to support the existing population growth rate.

The choice of contraception is further complicated when considering its long-range reproductive implications. Contraceptive use has an influence not only on the acute risks of STDs and unplanned pregnancy but also on the eventual reproductive capacity of those making contraceptive decisions. Therefore, personal choices, community programs, and/or policy decisions made in the short run to prevent STDs and unplanned pregnancies can simultaneously improve (or harm) chances of planned procreation in the long run.^{11,12}

THE EFFECT OF STD/HIV ON CONTRACEPTIVE USE

Concerns about STDs can affect contraceptive choice and family planning services from a variety of perspectives.¹³ At the clinical level, the impact of managing a client with a potential acute STD depends on whether the infection is symptomatic or asymptomatic, whether the infection is curable, and what STD services are available from the family planning provider. If the infection is symptomatic, it should be diagnosed and treated during the same patient visit in which contraceptive services are requested; in the absence of laboratory facilities, clinical algorithms (albeit imperfect) have been recommended.^{13,14} If no symptoms are present, the visit by sexually active women to family planning providers offers an opportunity to screen for asymptomatic infections that can be treated in the lower genital tract before they result in complications.

In developed countries, contraceptive providers already play a key role in detecting STDs. More STD screening occurs during routine family planning visits in the United States than through any other type of healthcare.¹⁵ The benefit-to-cost ratio of STD screening in family planning clinics, especially in areas where STDs have a low prevalence, can be

improved by using a variety of factors to increase yield.¹⁶⁻¹⁸ For example, if the patient has a new sex partner, this should trigger both screening for current lower genital tract infection and also counseling regarding safer sexual practices to reduce future infection risk. If the woman is found to have a cervical infection such as chlamydia or gonorrhea, not only should she be immediately treated, but also barrier contraceptive methods should be encouraged, and insertion of an intrauterine device (IUD) at that time should be discouraged.

In resource-poor settings, the same criteria can be used to both initiate presumptive STD treatment and guide contraceptive choice (Fig. 78-1). The mix of demographic, behavioral, clinical, and epidemiologic factors that predict STD risk form a continuum to aid family planning providers in managing their clients more appropriately.¹³ For example, clients with a high likelihood of being currently infected (symptoms, recent exposure to an infected partner) can be treated on epidemiologic indications. Likewise, clients without very high individual STI risk can generally be considered candidates for an IUD.¹⁹

At the operational level, the increasing provision of an array of health services by family planning providers has squeezed limited budgets.²⁰⁻²² During the past 20 years, federal funds for family planning services have declined making it a challenge to meet evolving needs. Inflation adjusted Title X funds have declined by 60% since the early 1980s forcing agencies to seek funding from multiple sources.^{21,22} Today, many publicly funded family planning agencies offer a wider range of contraception methods, perinatal care, primary healthcare, education, and counseling along with integrating services for men, thus causing an increase in cost.²² By 2000,

almost all agencies test clients who meet screening criteria for bacterial STIs as well as treat infected patients for these infections. In addition, 85% test for HIV infection, 35% provide treatment for HIV positive clients, and at least two-thirds screen for UTI and HPV infection.²² Because of these pressures to offer more clinical services to an increasing number of clients with decreasing funds, time, and money focused on contraceptive care has declined.^{20,22}

At the community level, some hypothesize that STDs may have a negative impact on family planning programs.¹⁷ High prevalence of STIs can serve to decrease acceptance and/or continuation of family planning methods directly and indirectly. (1) Directly—STDs, if perceived as a complication of contraceptive methods, may result in nonuse or discontinuation of the methods. For example, trends in IUD use have been directly related to adverse publicity and litigation about its risks of upper genital tract infection. In some countries the view that male condoms are primarily a device for STD protection has probably limited its acceptability as a contraceptive method. (2) Indirectly—STDs, by compromising healthy childbearing in a community, may hinder any willingness to delay initial childbearing or space out live births.⁹ In addition, in regions with high HIV prevalence, perceptions of shortened duration of life expectancy may accelerate desires to achieve the desired family size at an early age although this may now be mitigated by the increasing availability of antiretroviral therapy (ART) in some countries.

These direct and indirect perceptions of STIs can be addressed by effective community health/education programs and by improvements in the quality of reproductive health services including family planning services. During

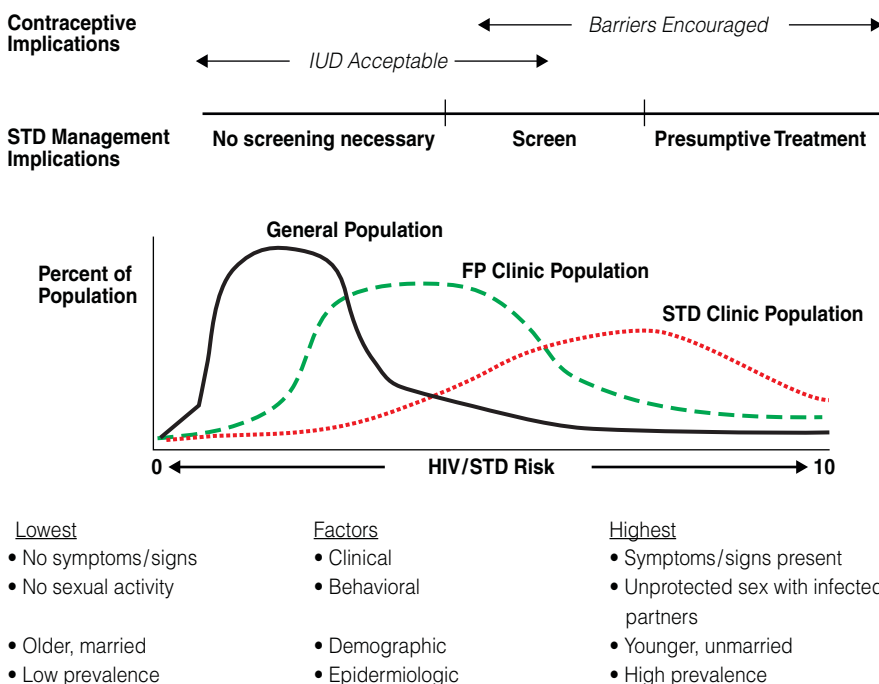


FIGURE 78-1. Estimated levels of HIV/STD risk among different populations—implications on contraceptive and STD management. (Adapted from Cates W, Jr. A risk-assessment tool for integrated reproductive health services. *Fam Plann Perspect* 1997; 29: 41-43.)

the 1994 International Conference on Population and Development in Cairo it was emphasized that provision of clinical services to reduce STDs in family planning settings will be regarded as essential for ensuring a healthy reproductive future. In a recent UN report reviewing the progress made since the 1994 International Conference, the need for access to quality reproductive health services, including family planning, emergency obstetric services, and prevention and management of STI, remains a priority.^{23,24}

THE EFFECT OF CONTRACEPTIVE USE ON STD/HIV

Recent scientific literature has been replete with reviews of the effects of different contraceptives on the risk of STDs/HIV.^{1–6,25–28} In general, they all come to the same conclusion. Male condoms used correctly and consistently provide good protection against most STDs, both bacterial and viral. N9 spermicides alone provide no protection against bacterial or viral STDs. Mechanical barriers, such as diaphragms, may provide some protection against bacterial STD; their impact on HIV prevention is currently under study.²⁹ Hormonal contraception may enhance acquisition of some cervical infections, but its impact on *upper* genital tract infection and HIV is still unsettled. The IUD does not appear to be associated with STD acquisition (although evidence is weak) and appears to be associated with acute pelvic inflammatory disease (PID) only during the first 20 days postinsertion.³⁰

The remainder of the chapter focuses on the relationship between highly effective contraceptive methods (hormonal methods, the IUD, and sterilization) and the acquisition of genital tract infections. We also discuss issues associated with contraceptive use by HIV-infected women and the clinical and policy implications of the dual needs for pregnancy and infection prevention. Chapters 93 and 94 will address the use of condoms and microbicides, respectively, for prevention of STI and HIV acquisition and transmission.

■ HORMONAL CONTRACEPTIVES

Hormonal contraceptives have an array of noncontraceptive health benefits, but their influence on STDs, HIV, PID, and eventual reproductive sequelae remains unsettled.

■ HORMONAL CONTRACEPTION AND STI ACQUISITION

Existing prospective studies suggest an increased risk of cervical chlamydial infection among oral contraceptive (OC) and depot medroxyprogesterone acetate (DMPA) users compared to nonusers. Six prospective studies have evaluated the association between use of combined OCs and risk of *Chlamydia*

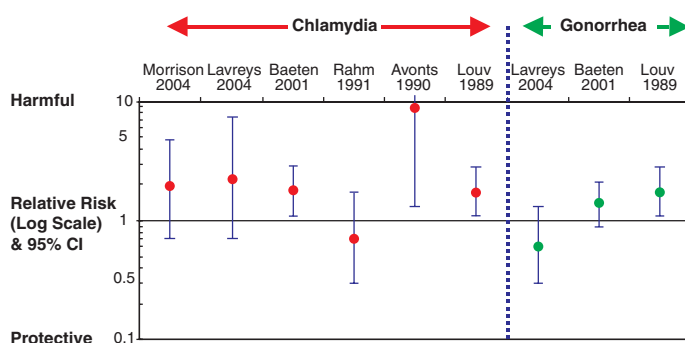


FIGURE 78-2. Prospective studies of OCs and Chlamydia and Gonorrhea acquisition.

trachomatis, and three of these present statistically significant evidence of a harmful association (Fig. 78-2).^{31–33} Three other studies found nonsignificant associations between OC pills and chlamydial infection: two reported risks suggestive of a harmful relationship,^{34,35} while the third study suggested a modest protective association.³⁶ A meta-analysis that pooled results from 29 cross-sectional studies reported a crude pooled odds ratio (OR) of 1.9 (95% confidence interval [CI] 1.8–2.1) for the effect of OCs on the risk of chlamydial infection, compared to non-OC users.³⁷ When the meta-analysis compared pill users to barrier method users, the pooled OR rose to 2.9 (95% CI 1.9–4.6). This increase in risk may be due to the protective effect of condoms and demonstrates the importance of careful selection of a referent group for these studies. Three prospective studies have evaluated the risk of chlamydial infection associated with DMPA use (Fig. 78-3).^{33–35} Each found a statistically significant association between DMPA use and the risk of chlamydial infection with hazard ratios (HR) ranging from 1.6 to 4.3.

Recent prospective research provides little evidence of an association between OC use and the acquisition of gonococcal infections (Fig. 78-2). Of the three studies that assessed this relationship cite mixed results, one produced a statistically significant harmful association for the effect of OC pills,³¹ whereas the other two found no significant association between OC use and gonococcal infection.^{33,35} Two of these prospective studies also investigated the effect of DMPA on risk of gonococcal infection; both found virtually no risk,^{33,35} suggesting no association between DMPA use and acquisition of *Neisseria gonorrhoeae* (Fig. 78-3).

Previous research has suggested that the association between OC use and cervical infections may be mediated through cervical ectopy, which is commonly associated with OC use.^{31,38,39} However, more recent studies suggest that while cervical ectopy may confer an independent risk for STI acquisition, it does not appear to be the primary mediator of increased acquisition of cervical infection among hormonal contraceptive users.^{33,34} Other potential mechanisms for such an association are that both estrogen and progesterone

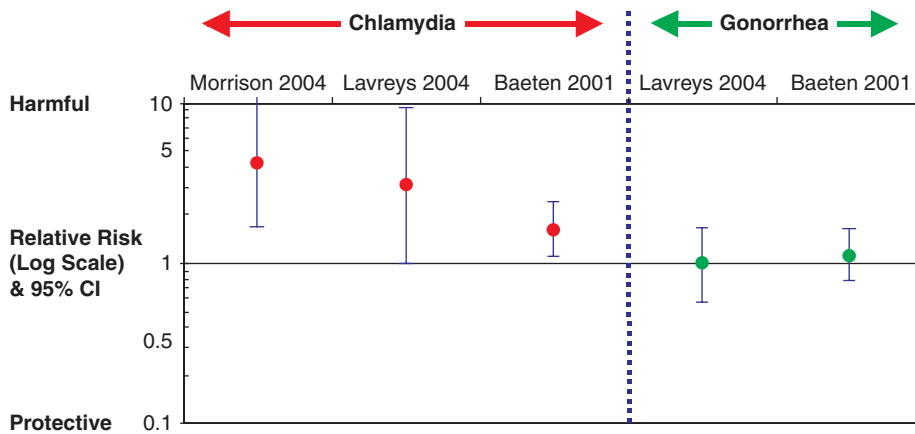


FIGURE 78-3. Prospective studies of DMPA and Chlamydia and Gonorrhea acquisition.

enhance the growth and persistence of *C. trachomatis* infections in animal models,⁴⁰ suppression of the local immune response by sex hormones,^{41,42} and changes in vaginal flora associated with the hypoestrogenic effect as an outcome of DMPA administration.^{43,44}

Studies of highly effective contraception and risk of trichomoniasis are inconclusive. Of the three prospective studies of OC use and risk of trichomoniasis, one study found a nearly null risk,³³ one found a statistically significant protective association,⁴⁵ and one found a nonstatistically significant protective relationship.³² This third study compared IUD to OC users, and although only 10 cases of *Trichomonas vaginalis* were identified, IUD users appeared to be at substantially higher risk of infection than OC users. The single study of DMPA and trichomoniasis yielded a borderline statistically significant protective effect.³³ The relationship between trichomoniasis infection and other highly effective contraceptive methods cannot be established from the existing literature.

The prospective and cross-sectional studies report inconsistent findings about the effect of OC use on the risk of HPV acquisition. Three prospective studies have evaluated OC use as a risk factor for HPV acquisition: one study found a significant harmful effect,⁴⁶ a second study reported a significant protective effect,⁴⁷ and a third study found a nonsignificant protective effect.⁴⁸ A case-control study nested within a prospective cohort found that the risk of acquisition of oncogenic HPV subtypes was significantly increased both for women using OCs for less than and equal to or more than 6 years.⁴⁹ A review of 19 largely cross-sectional studies on OCs and HPV infection found no evidence for a strong negative or positive association.⁵⁰ One prospective study has evaluated DMPA as a risk factor for incident HPV, finding a statistically nonsignificant protective effect.⁴⁷ In addition, one cross-sectional study found a statistically significant elevated risk of prevalent HPV for current users of DMPA.⁵¹ The same study reported a significantly increased risk of HPV for “ever use” of Norplant.

No prospective studies have evaluated the association between OC use and HSV incidence, though several cross-sectional studies have been conducted with mixed findings.^{52–56} In addition, no prospective studies have evaluated the relationship between DMPA use and HSV incidence. One cross-sectional study⁵² reported a nearly null association for DMPA users compared with pill users.

The data on hormonal contraceptive use and infection with *Treponema pallidum* is also scarce. One prospective study described earlier found statistically nonsignificant protective effects for both OCs and DMPA on syphilis risk.³³

No prospective studies have evaluated the newer formulations of hormonal methods—the combined estrogen—progestin-releasing patch, ring, or injectables or progestin-only methods including pills, injectables other than DMPA, or implants—on the risk of acquisition of STIs.

■ HORMONAL CONTRACEPTIVE USE AND UPPER GENITAL TRACT INFECTIONS

The influence of OC use on the upper genital tract may be different from that on the lower genital tract; however, studies from Europe and the United States^{57,58} have revealed that women using OCs are half as likely to be hospitalized for PID, compared with women who are sexually active but who do not use contraception. In a multicenter case-control study from the United States,⁵⁹ the protection was observed only among women who had been using OCs for more than 12 months. Past use of OCs conferred no protection. In Lund, Sweden,⁶⁰ OC use was associated with a significant reduction in the risk of gonococcal PID; the protective effect was not as strong for chlamydial PID. In Seattle, however, women using OCs apparently were differentially protected against chlamydial compared to gonococcal PID.⁶¹ Whether these findings are real, or whether they represent an artifact of clinical detection of PID, is unclear. OC users tend to have milder upper genital tract infection with *C. trachomatis*, as manifested by antibody response⁶² and laparoscopy.⁶³

OC users also have increased risks of unrecognized endometritis.⁶⁴

Possible mechanisms for the consistent protective effect of OCs on symptomatic PID remain speculative. The progestin component of combination OCs thickens the cervical mucus. Changes in either mucus composition or its immunologic properties might account for this protection. Likewise, the thinner endometrium and/or the decreased menstrual flow associated with OC use may play a role. Alternatively, if OC use tends to mask the symptoms of PID, they will appear protective even though unrecognized inflammation may be occurring.⁶⁴

Consistent with this latter explanation, use of hormonal contraception seems to modify the acute clinical course of PID favorably. As judged by laparoscopic examination, women with PID who were using OCs had milder inflammation compared to women not using OCs.⁶³ Sex steroids can modify immunologic function⁶⁵ and so their impact on infectious inflammation is plausible, though still unproven.

■ HORMONAL CONTRACEPTIVE USE AND HIV ACQUISITION

Whether hormonal contraception, and in particular OC and DMPA use, alters the risk of HIV acquisition is a critical unresolved public health issue.^{66,67} Animal models, using simian immunodeficiency virus (SIV) as the HIV surrogate, have raised concerns. Acquisition of SIV was increased nearly eightfold in monkeys with progesterone implants compared to monkeys challenged with SIV in the follicular phase of a normal menstrual cycle⁶⁸ and more than twofold compared to monkeys challenged randomly through a normal cycle.⁶⁹ This effect appears to be related to a state of estrogen deficiency that is associated with the use of progesterone including DMPA.⁷⁰ In a second study, 18 ovariectomized macaques received either progesterone or estrogen implants or no treatment followed by intravaginal SIV inoculation. All of the untreated macaques and five of six progesterone-treated macaques became infected, while none of the estrogen-treated animals became infected. In a follow-up study, 12 ovariectomized macaques were treated with vaginal estriol cream and 8 macaques with a placebo cream. Following vaginal challenge with SIV, 1 of 12 macaques treated with estriol and 6 of the 8 macaques receiving the placebo became SIV infected ($p = 0.004$). Use of the estriol cream was associated with significant cornification and thickening of the vaginal epithelium but appeared to have no systemic effect.⁷¹ Finally, among macaques previously immunized with nonpathogenic simian-human immunodeficiency virus (SHIV89.6), treatment with DMPA led to a lower rate of protection after intravaginal challenge with SIV and higher acute postchallenge plasma SIV RNA levels compared with animals not treated with DMPA.⁷² These studies raise the

possibility that the progesterone component of various hormonal contraceptives may increase risk of HIV acquisition.

Epidemiologic studies in humans have produced equivocal results, however.⁶⁶ First, studies examining the effect of DMPA use on the thickness of human vaginal epithelium suggest no clinically important differences among women using and not using DMPA.^{43,44,73} In addition, no RCTs have been performed of hormonal contraceptive use and HIV acquisition due to the ethical and practical issues related to randomizing some women to contraceptive methods, which may be less effective and are not their preferred method of contraception. This is an important issue because allowing women to use their preferred contraceptive method is associated with higher contraceptive continuation rates—an important methodologic consideration in such studies.⁷⁴

Eleven prospective studies have examined OC use and HIV acquisition;^{19,39,41,72,75–87} two found a statistically significant increased risk,^{75,85} three a nonstatistically significant increased risk (risk ratios ≥ 1.8),^{80,81,86} and six found no association.^{76–79,82,84} (Fig. 78-4) Six prospective studies have addressed DMPA use and HIV acquisition;^{79,81–85,88} two found a statistically significant increased risk,^{79,83} one a nonstatistically significant increased risk,⁸⁸ and three found no association.^{81,82,84} (Fig. 78-5)

Two reviews have been published with conflicting conclusions concerning the risk of HIV acquisition among OC users.^{89,90} Most studies reporting an increased HIV risk involved high-risk populations, such as sex workers^{75,79,81,83,85} or women attending STI clinics.⁸⁶

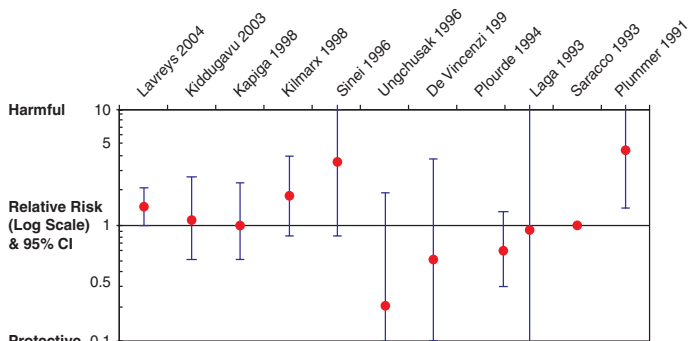


FIGURE 78-4. Prospective studies of OC use and HIV acquisition.

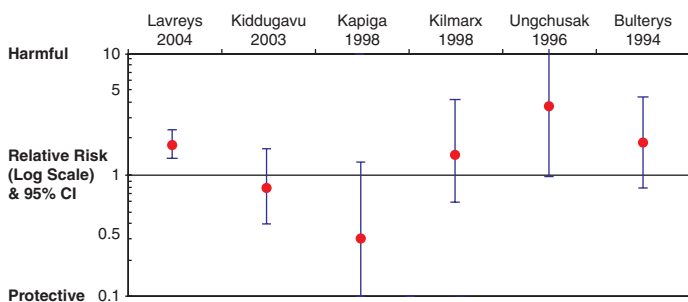


FIGURE 78-5. Prospective studies of DMPA use and HIV acquisition.

However, these studies were not specifically designed to assess the hormonal contraception–HIV relationship and most had important methodologic shortcomings, including poor measurement of contraceptive exposure (i.e., ever vs. never use), few hormonal contraceptive users, and therefore low power to detect differences between contraceptive groups, inaccurate measurement of the timing of contraceptive use versus HIV acquisition and poor follow-up. Also studies conducted among selected high-risk groups (e.g., sex workers) from a particular city or region have limited generalizability to women seeking family planning services worldwide.

A large, multi-country study was recently sponsored by the National Institute of Child Health and Human Development (NICHD) to specifically evaluate the relationship between hormonal contraception and HIV acquisition. Approximately 6100 HIV-negative women were recruited from 14 sites in Uganda, Zimbabwe, and Thailand. In this prospective cohort study, most women were recruited from the general population seeking reproductive health services. They were equally divided among three exposure groups: users of OCs, users of DMPA, and women not using hormonal contraception. Overall, the study found no statistically significant association between the use of either OCs or DMPA and HIV acquisition.⁹¹

The study also explored whether STIs modified the relationship between hormonal contraceptive use and HIV acquisition. Neither the presence of vaginal infections (trichomoniasis, bacterial vaginosis, and candidiasis) nor cervical infections (chlamydia and gonorrhea) modified this relationship. However, among the approximately half of African study participants testing negative for HSV-2 at enrollment, those who used either OCs or DMPA had a statistically significant increased rate of HIV acquisition compared to nonusers.⁹¹ Because a biological mechanism for this finding is unclear and other studies have not examined it, further research is needed to validate this finding. Based on the preliminary results of this study, neither the World Health Organization nor the International Planned Parenthood Federation plan to change their guidelines for hormonal contraceptive use.

While the exact mechanism by which hormonal contraception might facilitate HIV infection is unknown, possibilities include increased cervical ectopy associated with OC use^{31,39}; increased cervical chlamydial infection (and associated purulence)^{31,33,34,86}; a hypoestrogenic effect associated with DMPA use resulting in a reduction in hydrogen peroxide producing lactobacilli and irregular uterine bleeding^{43,44,50}; suppression of the local (cell-mediated) immune response^{41,72,83,92}; and increased recruitment of inflammatory and other target cells to the genital tract^{72,83,92,93} or through a direct effect on the infecting virus inoculum by upregulating HIV gene expression and associated viral replication.^{72,83,92} In addition, the particular type and dosage of estrogens and progestins contained in OCs or injectable hormonal contraceptives may

play an important role in any relationship between hormonal contraceptive use and HIV acquisition or transmission.⁶⁷

■ INTRAUTERINE DEVICES

Current data suggest no association between IUD use and risk of STI acquisition (i.e., the risk of lower genital tract infections). One of the previously cited studies examined chlamydial infection in OC users compared to women with IUDs,³² finding that IUD users were at significantly lower risk of chlamydial infection compared to OC users. More than 20 cross-sectional studies have also assessed the association between IUD use and chlamydia; none found significantly increased risks of chlamydia among IUD users compared to either OC users or to women using no contraception, and a review article concluded that the IUD was unrelated to cervical chlamydial infection.⁹⁴ Thirteen cross-sectional studies have assessed the association between IUD use and gonorrhea; none found significantly increased risks among IUD users compared either to pill users or to women using no contraception.^{95–105}

The existing evidence suggests that IUD use does not increase the risk of HIV acquisition. Only three prospective and eight cross-sectional studies have examined this relationship. None of the prospective studies^{80,82,83} found evidence of an increased risk of HIV acquisition associated with IUD use, and only two of the eight cross-sectional studies found an association between IUD use and prevalent HIV infection.^{106–113}

However, again many of these studies had important methodologic limitations, including the lack of an appropriate comparison group (IUD users were often compared to users of OCs and DMPA). Moreover, IUD users in these studies were screened for lower risk of STI infection before IUD insertion, thus increasing the likelihood of selection bias.

The possible association between IUD use and the development of upper genital tract infection remains a controversial topic in contemporary contraception. Epidemiologic evidence from the 1980s showed the initial association between IUD use and PID found in the 1970s to be overestimated.¹¹⁴ Three particular methodologic problems in the early studies contributed to their overly pessimistic assessment. First, women using barrier or OCs served as the comparison group in most studies.¹¹⁵ Since these methods *reduce* the risk of symptomatic PID, such comparisons artifactually elevated the apparent risk associated with IUD use. Second, the PID diagnosis often rests on highly subjective symptoms and signs that are difficult to assess.¹¹⁶ Since the putative association between IUD use and PID has been recognized since the 1960s, PID “diagnostic bias” might occur among IUD users. Third, early analyses did not adjust for type of IUD and the timing of its insertion. If either of these factors creates a disproportionate degree of PID risk, the overall crude risk for IUDs as a group is also spuriously elevated.

More sophisticated studies^{30,117–119} have revised our understanding of the IUD–PID association. Current evidence suggests that the smaller, but still measurable, increased risk of PID associated with IUD use occurs around the time of insertion, and specifically in the 20 days following IUD insertion.³⁰ Thus, contamination of the endometrial cavity at insertion may be more responsible for IUD-related PID than the device itself.

Because of the association of PID to the timing of IUD insertion, short-term antibiotics might help reduce the risks. In Kenya,¹²⁰ Nigeria,¹²¹ and the United States,¹²² randomized clinical trials of antibiotics given at the time of IUD insertion were limited by rates of IUD-associated PID that were much lower than expected, even among the placebo group. Because of the infrequency of IUD-related PID and because of the limited size of the studies, they had insufficient power to distinguish any statistically significant differences among treatment and placebo groups. Nevertheless, the low prevalence of PID among IUD users both with or without the provision of antibiotics and in areas of high and low STI prevalence is reassuring.

Many perceive the IUD's safety today as vastly different from that a decade ago. With proper screening of clients, the IUD poses little, if any, added PID risk. Likewise, current evidence suggests no substantive impact of IUD use on subsequent fertility.¹²³ For example, a large case-control study compared women with primary infertility with documented tubal occlusion with women with primary infertility without tubal occlusion (infertile controls) and with primigravid women (pregnant controls). The study found no increase in the odds of previous IUD use among the women with tubal occlusion compared with either the infertile or the pregnant controls. However, the presence of antibodies to *C. tracomatis* was associated with infertility.¹²⁴ In another study, among women who had used copper IUDs and who had only one sex partner, no increase occurred in the risk of either PID or tubal infertility.¹¹⁸

Thus, the future challenge will be to establish criteria, based on a combination of demographic, behavioral, and clinical factors, to expand the proportion of women for whom the IUD is recommended.¹³ Finally, some evidence suggests that the newer IUDs containing levonorgestrel are associated with even lower rates of PID.¹²³ If subsequent research confirms a preventive effect of the levonorgestrel IUD on PID risk, its use may be especially appropriate in populations with a high prevalence of cervical infections.

Based on recent research, the WHO has made important revisions in its *Medical Eligibility Criteria for Contraceptive Use* for IUD use by women with STIs or HIV.¹⁹ In relation to STIs, only the presence of current purulent cervicitis or documented chlamydial or gonococcal infection definitively rules out an IUD insertion (but does not rule out ongoing IUD use). In addition, a high general STI risk (e.g., as when living in an area with high STI prevalence) does not rule out

either an IUD insertion or ongoing IUD use. Finally, women with other STIs including vaginitis and HIV infection (unless the woman has AIDS and is not clinically well on ARV therapy) can generally either have an IUD inserted or continue the use of the ongoing IUD.

■ OTHER METHODS

Fertility awareness methods

Fertility awareness methods (FAM), also referred to as natural family planning, describe methods of planning or preventing pregnancy based on using naturally occurring signs and symptoms of the fertile and infertile phases of the menstrual cycle. Use of FAM for pregnancy prevention requires abstinence from intercourse on potentially fertile days. The pregnancy rates for this method vary widely, depending on the FAM approach used and the dedication of the users. No studies of the association between FAM and STD/HIV transmission have been conducted. Since these methods offer no obvious protection against infection, sexually active persons who wish to use FAM to prevent pregnancy and who are not having intercourse with partners known to be uninfected should be advised to use condoms for HIV/STD prophylaxis.

Lactational amenorrhea method

Breastfeeding, currently known as the lactational amenorrhea method (LAM), provides for another means of natural family planning. For some women, lactation-associated anovulation is a primary means of spacing births and avoiding pregnancies. Within the first 6 months following delivery, women who fully (or nearly fully) breastfeed have a low risk of pregnancy, 2% or less, prior to the return of menses.¹²⁵

Breast milk is also an avenue for transmission of infectious agents, however. Both cell-free HIV and HIV-infected cells have been detected in breast milk, and more than one-third of cases of mother-to-child transmission among HIV-infected breastfeeding women are thought to occur through breastfeeding.^{126–128} Several methods for reducing the risk of transmitting HIV through breastfeeding now appear promising including engaging only in exclusive breastfeeding,¹²⁹ limiting breastfeeding to the first six months of life,¹³⁰ and provision of antiretroviral treatment to breastfeeding women throughout the breastfeeding period.^{131–132} Nevertheless, a complex trade-off exists between the contraceptive effect of LAM preventing an HIV-infected woman from becoming pregnant (and thus not at risk of transmitting HIV to her next child) versus the risk of transmitting HIV through breast milk to the child she is currently nursing.

For the mother who is uninfected, breastfeeding provides no protection against HIV or other STDs. Women who are using LAM as their contraceptive method, and who are at risk

of STDs/HIV, should use condoms to protect themselves against STI/HIV acquisition.

Tubal sterilization

Tubal sterilization protects against PID, but this protection is not absolute. Most typical cases of PID are thought to arise from ascent of cervical pathogens via the endometrial cavity; hence, disrupting the continuity of this passage should prevent inoculation of the distal fallopian tubes. Even though endometritis and proximal salpingitis are potentially possible, PID is rarely observed among women after tubal sterilization.¹³³ Anecdotal cases of PID and tubo-ovarian abscess continue to be reported. A more likely mechanism for poststerilization PID is the iatrogenic contamination of the tubes during the operative procedure; in the less developed world, where sterile conditions are more difficult to maintain, this risk may be further elevated.

Abortion

Women who have cervical infection with either *N. gonorrhoeae* or *C. trachomatis* have an increased risk of endometritis following induced abortion performed under proper hygienic conditions. The risk appears to be at least tripled with either organism.¹³⁴ A number of studies suggest that use of prophylactic antibiotics at the time of the abortion procedure reduces the risk of infection by one-half to two-thirds.¹³⁵ While preoperative screening for infection with these organisms is desirable, a brief perioperative course of an antibiotic such as azithromycin seems both safe and cost-effective and is recommended both by the WHO¹³⁶ and the American College of Obstetricians and Gynecologists.¹³⁷ Women later found to be infected by *N. gonorrhoeae* and/or *C. trachomatis* can be followed up with a full course of recommended antibiotics, with notification and treatment of their sex partner(s).

The greatest risk of upper genital tract infection associated with induced abortion occurs in circumstances where sterile conditions are not maintained. In countries where abortion services are restricted by law or practice, and especially in resource-poor regions where, even if legal, access to sanitary procedures is limited, postabortion infection poses risks not only to future fertility but also to the woman's life.¹³⁸ An estimated 67,900 annual abortion-related deaths occur worldwide with the highest rates in Africa, followed by South-central Asia and Latin America and the Caribbean. The global case-fatality rate associated with unsafe abortion is approximately 700 times higher than the case-fatality rate associated with legal abortions in the U.S. and over 99% of abortion-related deaths are due to unsafe abortions occurring in developing countries.¹³⁹

In both the developed and less-developed worlds, carrying a pregnancy to term leads to greater risks of infection and death than terminating it through induced abortion.^{140,141} Under sterile conditions, abortion is five to ten times safer

than childbearing. Under less hygienic conditions, the risks of adverse outcomes for *both* abortion and term delivery increase, and the gap between the infection risks from abortion and childbirth probably narrows. In these circumstances, use of any method of contraception to reduce pregnancy has simultaneous effects on reducing pregnancy-associated infection (see later).

CONTRACEPTIVE USE AMONG HIV-INFECTED WOMEN

A number of international initiatives support the right of all persons, including HIV-infected women and men, to freely decide about their sexual and reproductive lives, including decisions about pregnancy and childbearing.^{142,143} In addition to the direct health benefits conferred by prevention of unwanted pregnancies (reduction of maternal morbidity and mortality, reduction in abortions), offering high-quality and accessible family planning services to HIV-infected women and men provides additional important health and social benefits.

■ CONTRACEPTION AS AN HIV PREVENTION STRATEGY

From a public health perspective, the rationale for making highly effective contraception accessible to HIV-infected women who do not wish to become pregnant is strong. The use of effective contraception by HIV-infected women to prevent HIV sequelae remains one of the best-kept secrets in the field of HIV prevention. Most reviews of perinatal prevention strategies begin with the infected pregnant woman and emphasize antiretroviral prophylaxis to prevent transmission from the woman to her infant. However, earlier stages of prevention can be both more profound and more cost effective. The WHO has proposed a four-staged perinatal prevention strategy that includes the use of contraception as its second phase. The four-stage approach involves (1) preventing HIV in women overall, (2) preventing unintended pregnancies in HIV-infected women, (3) preventing transmission from an HIV-infected pregnant woman to her infant, and (4) providing support—and eventually treatment—for the mother and her family.^{142,144}

A number of models have demonstrated that the impact of provision of family planning services to HIV-infected women who do not wish to become pregnant can have a dramatic effect on the number HIV-infected infants and orphans and is at least as cost-effective as providing ART to mothers and infants.^{145–147} The differential impact of these strategies can be demonstrated by comparing stages 2 and 3, namely, providing effective contraception and delivering low-cost nevirapine to a population of 1000 HIV-infected women. Using assumptions based on the best available data, the number of infants infected with HIV either during delivery or the breastfeeding interval and the number of uninfected infants becoming

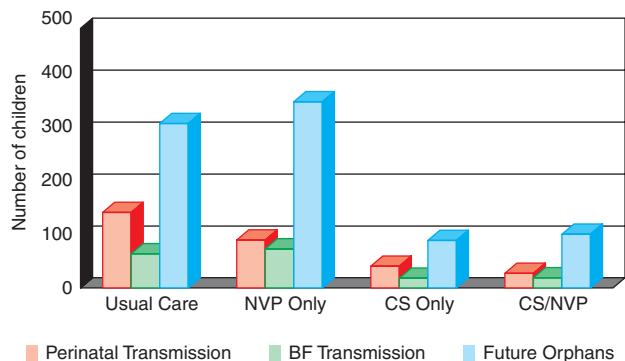


FIGURE 78-6. Comparative outcomes of providing single dose nevirapine (NVP) and effective contraceptive services (CS) to 1000 HIV-infected women during 1 year of service delivery.

orphans are shown in Fig. 78-6.¹⁴⁸ We compared four categories of care: (1) the “usual” standard of care (namely, no care in most resource-poor settings), (2) providing single-dose nevirapine as in stage 3 only, (3) providing contraception as in stage 2 only, or (4) providing both stages 2 and 3 sequentially.¹⁴⁸

Focusing on the delivery interval, without any intervention, 150 infants would be infected with HIV. If nevirapine were available and chosen by pregnant, HIV-infected women, this number could be reduced to 82, which is the expected 47% decline. If effective contraceptive services were available to all HIV-infected women who did not wish to become pregnant, this number would be reduced to 49, and finally, if both these strategies were employed, we could further decrease the number of infected infants to 25.

During the breastfeeding interval, a paradoxical effect occurs with nevirapine compared to no intervention. Because the number of infants uninfected at birth rises with nevirapine, so does the denominator of HIV-uninfected babies exposed during the breastfeeding interval. Thus the number of infants infected during breastfeeding increases with the use of nevirapine. This does not occur with contraceptive services, since the pregnancies themselves are prevented.

Finally, the most dramatic effect of these two strategies is on the number of future infants orphaned because their mothers die of HIV infection. Without any intervention, 300 orphans will eventually be left behind by the death of their mother. Using nevirapine to prevent transmission again has the paradoxical effect of creating more orphans since a greater number of infants will be uninfected and live longer, whereas their mothers will die in the absence of antiretroviral treatment. However, with effective contraceptive services, the number of unintended orphans declines dramatically, to less than 100 since the unintended pregnancies themselves are prevented. When both strategies are used together, not surprisingly, the overall impact is the best.

Further estimates suggest that the current contraceptive use prevents over 173,000 HIV-infected infants each year in sub-Saharan Africa or 474 HIV-infants per day.¹⁴⁹ Moreover,

Table 78-1. Issues Related to Contraceptive Use by HIV-Uninfected and Infected Women

Population	Issue
Uninfected	<ul style="list-style-type: none"> • HIV susceptibility • Contraceptive efficacy
Infected	<ul style="list-style-type: none"> • Changes in fertility desires • Breastfeeding issues • Changes in HIV infectivity • Impact on HIV disease progression • Contraceptive safety, side effects and efficacy (esp. with concomitant ART use)

given that the proportion of unintended births is about 25% in sub-Saharan Africa, provision of effective contraception to HIV-infected women who do not wish to become pregnant has the potential to prevent more than 160,000 additional HIV-infected infants annually.¹⁴⁹ These data are compelling. Providing effective and safe contraceptive choices to HIV-infected women who do not wish to currently become pregnant optimizes the prevention of HIV-infected births and the number of future orphans. Thus, the provision of family planning is a critical adjunct to prophylactic ART for reducing worldwide mother-to-infant HIV transmission.

For the HIV-uninfected woman the primary issues related to contraception and STDs are the complex trade-offs between pregnancy and infection prevention. For the HIV-infected woman the issues are even more complex (Table 78-1). These include (1) possible changes in fertility desires related to HIV infection status and the need for contraceptive choice to reflect these desires, (2) breastfeeding issues (as discussed above), (3) possible changes in her HIV infectivity related to contraceptive use (as measured by HIV genital shedding), (4) potential alteration in HIV disease progression related to the use of some contraceptive methods, and (5) possible differences in the safety profile, side effects, or efficacy of a contraceptive method when used by an HIV-infected woman, especially with concomitant use of ART.

■ DIFFERENCE IN FERTILITY AND FERTILITY DESIRES OF HIV-INFECTED WOMEN

Evidence suggests differences in fertility between HIV-infected and uninfected women. Such changes stem from possible reductions in fertility in HIV-infected women from a desire to avoid pregnancy,^{150,151} decreased sexual activity,¹⁵²⁻¹⁵⁴

reduced fecundity from the infection,^{155,156} and increased risk of pregnancy loss.^{87,157,158} Nevertheless, fertility rates remain high among HIV-infected women—on the order of 11 to 20 births per 100 person-years.¹⁵³ Several studies in Africa suggest that about half of pregnancies occurring postpartum among HIV-infected women are unwanted with large numbers ending up with induced abortions.^{159,160}

Nevertheless, many HIV-infected women want to continue childbearing. This desire is likely to become stronger as more highly effective antiretroviral regimens become available for both prevention of mother-to-child transmission and for treatment of the woman's chronic HIV infection.¹⁶¹ Thus, access to highly effective reversible contraceptive methods is essential so that HIV-infected women may either avoid or delay pregnancy.

■ CONTRACEPTION AND HIV TRANSMISSION

A theoretical concern exists that hormonal contraceptive use by HIV-infected women might increase genital tract shedding of HIV and thus potentially increase HIV transmission to uninfected sex partners. The majority of reported studies have been cross-sectional and have provided conflicting data. For example in a study of 318 women attending an STD clinic in Kenya, use of both low-dose and high-dose OCs and DMPA was associated with an increased detection of HIV-1 DNA in endocervical secretions.¹⁶² However, in a cross-sectional analysis of women participating in the Women's Interagency HIV Study (WIHS) Study from the United States, hormonal contraception was not associated with increased genital tract shedding of HIV-1 RNA.¹⁶³ The sole prospective study of the effect of hormonal contraceptive use on genital tract shedding of HIV, conducted among a population of family planning clients in Mombasa, Kenya, detected a significant but modest increase in the proportion of women with detectable HIV-1 DNA after initiation of various hormonal contraceptives (including low and high-dose combined OCs, DMPA and progestin-only OCs) compared with before initiation. Yet, no significant difference was detected in the concentration of cervical HIV-1 RNA (or in plasma HIV-1 RNA). This suggests the possibility that hormonal contraception does not affect HIV replication in the genital tract but instead increases the recruitment of HIV-infected cells from systemic compartments to the genital tract.¹⁶⁴

The issue of factors associated with HSV-2 shedding among HIV-infected women has also been recently examined. In a cross-sectional study of 273 women seropositive for HSV-1, HSV-2, and HIV-1, hormonal contraception including both OCs and DMPA were significantly associated with cervical shedding of HSV infection.¹⁵⁴ However, in a subsequent prospective study of 200 women seropositive for HSV-2 and HIV-1, who were tested for HSV-2 shedding before and after initiation of combined OCs and progesterone-only contraception

(pills and DMPA), no statistically significant differences were found in either the proportion of women exhibiting HSV-2 shedding or in the quantity of HSV in cervical secretions for either contraceptive group after as compared to before contraceptive initiation.¹⁶⁵

Few data examine IUD use and HIV genital shedding. One prospective study from Kenyan family planning clinics found no increase in the prevalence of cervical shedding of HIV-1 DNA 4 months after insertion of an IUD compared to that before the IUD was inserted.¹⁶⁶ No studies have compared the levels of HIV-1 RNA from the genital secretions of HIV-infected women using and not using IUDs.

■ HORMONAL CONTRACEPTION AND HIV DISEASE PROGRESSION

Whether hormonal contraceptive use at or near the time of HIV infection affects disease progression is also of concern. In a prospective study of HIV acquisition among 1350 sex workers in Mombasa, Kenya—161 of whom were followed up for a median of 34 months after being infected with HIV—it was found that the use of DMPA at the time of infection was associated with a higher HIV viral set point.¹⁶⁷ This finding suggests that the use of DMPA at the time of infection may hasten HIV-related deterioration of the immune system and the natural course of HIV infection.¹⁶⁷ In a subset of these HIV-infected sex workers (82 of whom used any hormonal contraception and 68 of whom did not), hormonal contraceptive use near the time of HIV acquisition was associated with infection with multiple strains of the virus.¹⁶⁸ This relationship appeared to mediate the relationship between DMPA use and a higher viral set point. Moreover, infection with multiple strains appears to be related to a higher viral set point and faster CD4 decline, two key indicators of HIV disease progression.¹⁶⁹

In a study conducted among the WIHS cohort in the United States, no differences were seen in plasma viral load either cross-sectionally (at baseline) or in changes in levels over time between women using hormonal contraception and those not using them. In contrast, the authors reported a statistically significant increase in CD4 lymphocyte counts among users of hormonal contraception both cross-sectionally and longitudinally when compared with women not using hormonal contraception. However, these increases were small, and the authors believe the difference not to be clinically relevant.¹⁷⁰

Since much of the data on the possible impact of hormonal contraception on HIV disease progression has come from studies conducted among Kenyan sex workers, and some of the findings have not been corroborated by other studies, further research among other populations of women in diverse geographic locations is needed. Several ongoing studies of hormonal contraceptive use among various populations of HIV-infected women in Africa are expected to clarify this issue.

■ SAFETY, SIDE EFFECTS, AND EFFICACY OF CONTRACEPTIVE USE AMONG HIV-INFECTED WOMEN

Few data exist on the side effects and efficacy of the use of highly effective reversible contraception by HIV-infected women. A study from Thailand conducted among 43 asymptomatic HIV-infected women reported that Norplant progestin implants appeared to be well tolerated with side effects and menstrual patterns similar to HIV-uninfected Norplant users. Likewise, no pregnancies occurred during 1 year of use among these women.¹⁷¹ No evidence suggests reduced safety or efficacy of other hormonal contraceptives, including OCs and DMPA among HIV-infected women who are not using ART. Consequently, the WHO MEC guidelines include no restrictions or concerns for the use of hormonal contraception by HIV-infected women not using ART.

A study of IUD use among 649 women in Kenya (including 156 HIV-infected women) found no increased risk in either overall or infection-related complications among HIV-infected compared with uninfected women.^{172,173} In contrast, women with chlamydial or gonococcal infections near the time of IUD insertion were at increased risk of both overall and infection-related complications. Given these findings and the finding that IUD use does not appear to increase genital shedding of HIV, the WHO MEC has changed its guidelines so that HIV-infected women can generally either have an IUD inserted or continue ongoing IUD use (unless the woman has AIDS and is not clinically well on ARV therapy).¹⁹

■ HORMONAL CONTRACEPTIVES AND USE OF ART

Hormonal contraception and many types of ART are metabolized in the liver and the same liver enzymes (cytochrome P450) are involved in the metabolism of both types of drugs. A number of NNRTI and protease inhibitors have been found to speed the metabolism of hormonal contraceptives and thus alter the steroid hormone levels in the blood. For example, studies have found that the use of nevirapine resulted in a 29% decrease in the levels of ethinyl estradiol and an 18% decrease of the levels of norethindrone among women using OCs.¹⁷⁴ Among women taking the protease inhibitor ritonavir, a 43% reduction in ethinyl estradiol was observed.¹⁷⁵ Because of these changes in hormonal levels, theoretical concerns exist about the possibility of decreased contraceptive efficacy of hormonal contraception, decreased efficacy of ART and/or an increase in side effects related to either the use of hormonal contraceptives or ART.

To date, no studies have examined the effects of simultaneous use of hormonal contraception and ART on contraceptive effectiveness, ovulation or breakthrough bleeding. However, given the reduction in blood hormone levels with coadministration of OCs and ART, some providers have recommended prescribing OCs containing 50 µg of estrogen

instead of the low-dose OCs (20–35 µg of ethinyl estradiol) most commonly used. However, use of higher dose OCs carry an increased risk of severe side effects including deep vein thrombosis, heart attacks, and strokes. Currently, the WHO recommends that OC users may continue to use low-dose pills while on ART, but should also use condoms as a back-up contraceptive method.¹⁹

Only one published study has considered the effect of simultaneous use of hormonal contraception and ART on ART effectiveness. Among 77 hormonal contraceptive users and 77 nonusers matched for age, ethnicity, CD4 lymphocyte count, and HIV viral load who began using ART, no statistically significant differences were found in increases in CD4 lymphocyte count or in the proportion of women who had reduction in viral loads to undetectable levels.¹⁷⁶

Based on the relatively sparse data on concomitant use of hormonal contraception and ART, WHO suggests that although women using ART can generally use OCs and other types of hormonal contraception, dual use of condoms is recommended.¹⁹

CLINICAL AND POLICY IMPLICATIONS

■ CONTRACEPTIVE/STD PREVENTION TRADE-OFFS

In ideal circumstances, consistent and correct use of male or female condoms can prevent *both* pregnancy and STDs. In typical situations of inconsistent use, however, they provide lower rates of protection against these conditions. Moreover, if couples choose to use contraceptive methods other than condoms, those with the best record for pregnancy prevention provide little STD protection. Thus, trade-off choices are necessary.

For those whose families are not completed, yet who do not currently wish to become pregnant, hormonal contraceptives and the IUD remain the most effective reversible methods available to prevent unintended pregnancy. However, they provide no protection against vaginal or cervical infection, and inserting the IUD carries temporary risks to the upper genital tract. Hence, for persons who are not mutually monogamous, addition of a barrier method, such as a condom, will help reduce the risk of STDs as well as unplanned pregnancies. Under typical conditions, however, barrier methods are substantially less effective in preventing conception than hormonal methods, yet they offer important protection against STDs. To maximize protection against both unintended pregnancy and STD, a barrier method should be used in conjunction with a hormonal method or IUD.

Worldwide, for couples whose families are complete, male or female sterilization is an increasingly popular method of contraception.¹⁷⁷ While these operations protect against upper genital tract infections in sterilized persons, they confer no protection against lower genital tract infections.

Alternatives to sterilization are hormonal implants or the IUD; both are effective methods of reversible contraception, but they offer no protection against cervical infection. Sterilized persons would still need to use barrier methods to protect against infections in the lower genital tract.

Because both mechanical and chemical barrier prophylaxes are coitally dependent, their efficacy in preventing either infection or unplanned pregnancy depends entirely on adherence by the couple. Some targeted high-risk populations have demonstrated high levels of barrier-method use. For example, in Thailand, a “100% condom policy” in commercial sex facilities has led to widespread use among the workers and their clients; this, in turn, has been associated with marked reductions in HIV and other STDs.^{178,179} In the United States, women working in Nevada brothels have had similar success.¹⁸⁰ Unfortunately, to date, most heterosexual populations worldwide have not reported the same magnitude of condom use and have not experienced decreases in the traditional STDs.¹⁸¹

The reasons for relatively low global condom use rates vary. In many settings, a woman cannot insist on a male-dependent method such as a male condom. For example, in South Africa, female sex workers serving male truck drivers were unable to persuade most of their customers to use condoms; fear of economic loss and personal violence limited any ability to negotiate.¹⁸² However, in Cameroon, sex workers provided with condoms and regular counseling reported using condoms with their clients in nearly 90% of sexual acts.¹⁸³ Moreover, cultural taboos against discussing sex limit the practical negotiations that can take place. In some societies, use of condoms is associated with commercial sex, which makes them unacceptable for use in any primary relationship. Finally, in all surveys, men consider condom use to be a major inhibition to their sexual enjoyment.

Another important aspect for assessing trade-off concerns is whether conditions exist for safe, sterile childbirth and/or abortion. If pregnancy itself, regardless of whether it is terminated or continued, carries markedly high “iatrogenic” risks of genital infection, then the pregnancy prevention efficacy of the contraceptive choice takes on greater weight. In addition, some studies suggest that pregnancy itself may increase the risk of HIV acquisition.¹⁸⁴ By preventing undesired pregnancies, the contraceptive method(s) simultaneously protect against pregnancy-associated infections of the reproductive tract. In the developing world, postabortal and puerperal infections are important causes of tubal infertility. In Africa, where the infectious etiology of infertility was most evident,¹⁸⁵ genital infections occurring both before and after the first pregnancy were associated with tubal occlusion. In Asia, abortion appeared to play a larger role than childbirth in contributing to infectious infertility, whereas in Latin America the reverse was found.¹⁸⁶

■ DUAL METHOD VERSUS DUAL PURPOSE

Another complex issue for reproductive health providers serving clients at risk of STD/HIV is whether to encourage the use of dual methods—one to prevent pregnancy and the other to prevent STD/HIV.⁵ Clinicians promoting dual use must weigh interacting factors such as extra cost and effect on user adherence, as well as the level of STDs in particular client populations. Moreover, clients may attach differing priorities to preventing either pregnancies or infections, and these priorities may change over time and among various relationships. Studies on dual-method use are limited and have focused on the use of the male condom added to other methods of contraception.^{187–197} In general, based on investigations where participants were using primary methods other than the condom, the more effective the primary contraceptive method was in preventing pregnancy, the lower the level of consistent use of the male condom.

Several reasons can explain why concurrent condom use may decrease as perceived contraceptive effectiveness increases. First, many persons—even those with sexual behaviors putting them at risk of STDs—see pregnancy as a greater immediate threat. Thus, having taken proactive precautions against unintended pregnancies, they would be less motivated to undergo the extra effort and expense to use condoms. Second, situational differences in one’s routine may exist between the adherence-independent contraceptive methods and the adherence-dependent methods, including both barriers and OCs. Those who are sterilized or who are using implantable or injectable hormones or IUDs do not have the coitally based requirements of barriers or the daily schedules of OCs to help keep them continually aware of, and prepared for, prophylactic needs. Without regular reminders of the need to protect against both pregnancy and STDs, individuals may be less likely to have condoms available when sexual opportunities arise.

A recent creative approach to the use of dual methods is based on the availability of emergency contraception (EC), which describes contraceptive methods that people can use after intercourse to prevent pregnancy.¹⁹⁸ Common methods of EC include using levonorgestrel (progestin-only) pills or a heightened dose of combined OCs. While EC in itself provides no protection against HIV or other STDs, making EC more widely available as a backup to barrier contraception may cause more couples to choose (and use) barriers as a *dual-purpose* method.¹⁹⁹ This dual-purpose approach, namely using condoms to protect against both unplanned pregnancies and STDs/HIV, needs to be investigated through operational research designs. To the extent that the availability of EC increases overall barrier-method use, it would have a positive impact on the overall level of STDs/HIV within the community.

More research is clearly needed on the best mix of contraceptives. Studies that examine the use of the female condom or the diaphragm, in conjunction with long-term methods will help clarify this issue. In addition, the patterns of dual-method use with different sex partners need to be evaluated. For example, if an individual uses one method with one partner and adds condoms with other partners, this might reduce the risk, even if the dual-method use is not consistent with the primary partner.

■ SERVICE INTEGRATION

The 1994 International Conference on Population and Development's Programme of Action highlighted the need for integrated reproductive-health services.²⁴ However, most publicly supported family planning, maternal/child health, and STD clinics were begun as independent entities rather than one integrated reproductive-health unit. In contrast, the women being served by these clinics frequently had overlapping health needs.¹⁴ For example, in family planning clinics in developed countries, risk assessment surveys have found that approximately one-quarter of women report behaviors that put them at increased risk for HIV and the other STDs.²⁰⁰ In STD clinics, up to half of the sexually active women of reproductive age report using no method of contraception,²⁰¹ despite most having histories of both STDs and unintended pregnancies.

In developing countries, the need for integrated care is even more acute. Since so few facilities are available for healthcare, they should not be fragmented.^{14,202} Moreover, because access to health services is usually more cumbersome and time consuming in resource-poor settings, when patients make the effort to obtain one particular "categorical" service, the full range of clinical preventive care should be offered.

These overlapping needs have provided those interested in STD/HIV and family planning with a unique opportunity to deliver more broad-based reproductive healthcare. In the United States, this collaboration was initiated in the early 1970s, when family planning clinics became crucial allies for the federal gonorrhea control program.²⁰³ In the 1980s, half of all women receiving family planning services were simultaneously screened for STD, primarily gonorrhea; this screening appropriately targeted those women who had the highest infection risks.¹⁵ Moreover, efforts to screen for chlamydia in family planning settings have also been productive, especially when selective criteria are applied, such as age less than 24 years, more than one sex partner in the past 2 months, or signs of cervical infection.^{204,205} The most successful of these has been the Region X chlamydia screening program, which led to a regional reduction in the prevalence of chlamydia.²⁰⁶ The extension of STD services in family planning clinics has had its costs, however,¹⁷ because the proportion of time and resources available for contraceptive care decreased.

In a reciprocal manner, some STD clinics increasingly have been providing rudimentary contraceptive services, especially barrier methods. Recent concerns with incurable viral STDs, especially HIV, have provided the necessary social environment and financial resources both to emphasize condom use during client-counseling sessions and to increase advertising of condoms in the media. The development of women-controlled mechanical or chemical barrier contraceptives may be of further value in reducing STD risks.^{207,208} For this reason, diaphragms (which protect only the cervical os), female condoms, and eventually microbicides may play a wider role in upcoming efforts to prevent STDs/HIV.

The urgency of the HIV pandemic has hastened the need to integrate STDs and family planning services.²⁴ In the developing world, where heterosexual transmission predominates, family planning and maternal/child health facilities have increased their HIV/STD roles.²⁰⁹ Agencies have begun both to counsel women on how to reduce their risks and also to provide services to diagnose and treat those STDs that themselves may further facilitate acquisition/transmission of HIV.²¹⁰ A strong case may also be made for the integration of family planning services into MTCT prevention programs.²¹¹ The experience of integrating family planning services into VCT programs in Haiti and Rwanda has resulted in an increase in family planning users,^{150,212} and a reduction in contraceptive discontinuation and the annual pregnancy rate among HIV-infected women.^{150,211}

Client and service providers' knowledge of an individual's HIV status is becoming increasingly important in the provision of high-quality contraceptive services. Thus if the client's HIV status is known, more specific counseling is warranted. For uninfected women, culturally sensitive messages regarding ways to protect themselves from STD/HIV exposure are essential. For HIV-infected women, family planning choices involve complex personal, ethical, and policy issues. Providers need to ensure the woman's right to determine her reproductive future, improve her quality and duration of life, decrease the risk of perinatal HIV transmission, and decrease the risk of further HIV transmission within the community.²¹¹

CONCLUSION

Because contraception affects not only the risk of unplanned pregnancies but also that of STIs, the choice of particular methods is important to future fertility. Important trade-offs exist, however. Contraceptives with the best record of preventing pregnancy provide little protection against STDs and can, in some instances, even increase the risk of some genital tract infections. The provision of highly effective contraception to HIV-infected women wishing to avoid or delay pregnancy is an important and underused strategy in the prevention of

mother-to-child HIV transmission. While most forms of highly effective contraception appear appropriate for HIV-infected women receiving medical follow-up, more research related to contraception method use, HIV disease progression and possible interactions with the use of ART is warranted. Finally, epidemiologic studies are equivocal regarding the value of either recommending dual methods of contraception or relying on the condom alone to prevent both unplanned pregnancies and STDs. Continued biologic and behavioral research will be necessary to untangle these complex relationships.

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Harold C. Wiesenfeld and Willard Cates, Jr.

Sexually transmitted diseases (STDs) affect human fertility primarily through infections of the female upper genital tract and their sequelae. Except for the rare bilateral epididymitis and obstruction of the male epididymis or vas deferens, STDs produce infertility in men less frequently. Therefore, this chapter will focus on infertility resulting from sexually acquired infections that ascend to produce endometritis and salpingitis. Acute pelvic inflammatory disease (PID) has long been recognized as an important cause of tubal factor infertility, ectopic pregnancy, and chronic pelvic pain.¹ Despite this well-known relationship, there is a growing body of the literature suggesting that the greatest burden of postinfectious tubal infertility results from PID that is unrecognized by the patient and her physician. In this chapter, we will outline the historical evidence linking subclinical PID with adverse reproductive outcomes. Associations between lower genital tract infections and subclinical PID will be explored and the reproductive outcomes of women with acute and subclinical PID will be discussed.

DEFINITIONS

Infertility is typically defined as the inability to conceive after 1 year of regular intercourse without the use of contraception.² In the general population, the conception rate is 10–15% per cycle (Fig. 79-1), whereas in couples who have been infertile for 1 year, it is 5–6% per cycle. Approximately 10–15% of couples meet the clinical definition of infertility. Tubal infertility refers to infertility caused by damaged fallopian tubes. These fallopian tubes may be either blocked due to adhesions involving the external surfaces of the tubes, as in women with previous pelvic surgery or salpingitis, by distortion of the fallopian tube affecting tubal motility, as seen in women with pelvic adhesions or endometriosis, or due to blockage of the tubal canal due to salpingitis or congenital causes. We will address infertility only as it relates to salpingitis.

Salpingitis is an inflammation of the epithelial surfaces of the fallopian tubes caused by active infection with one or

more of a number of organisms, of which most are either sexually transmitted or are components of vaginal microflora. These organisms ascend along mucosal surfaces from the cervix to the endometrium to the fallopian tubes and, in some women, to the peritoneum.³ Acute PID is used to describe the symptoms and signs clinically associated with acute salpingitis, including patient report of pelvic pain and the finding of tenderness of pelvic organs on bimanual examination. Clinical criteria for the diagnosis of acute PID are inaccurate. Only about two-thirds of patients with a clinical diagnosis of PID actually have visual evidence of acute salpingitis by laparoscopy.⁴ Further, as will be described in detail below, many women with upper genital tract inflammation experience an asymptomatic or minimally symptomatic infection. In this chapter, we will use the term subclinical PID to describe the condition of upper genital tract inflammation in women who fail to meet the classic criteria for acute PID.

HISTORY

An association between gonorrhea, PID, and tubal infertility was first reported in the preantibiotic era.^{5,6} Upper genital tract infection, especially severe tubo-ovarian abscess, was a feared consequence of gonococcal infection and rates of postgonococcal tubal obstruction of up to 70% were reported.⁷ With the advent and use of sulfonamides and penicillin in the 1940s, both lower- and upper-genital tract infection caused by gonococci could be treated more effectively and their sequelae were reduced.

The classic cohort studies of Westrom and colleagues in Lund, Sweden in the 1960s demonstrated the impact of STD and salpingitis on subsequent tubal infertility.^{1,8,9} These studies contributed data on such crucial topics as

1. the clinical difference between PID and salpingitis;
2. the importance of chlamydia (in addition to gonorrhea) as a cause of tubal infertility;
3. the effects of different risk factors on fertility;

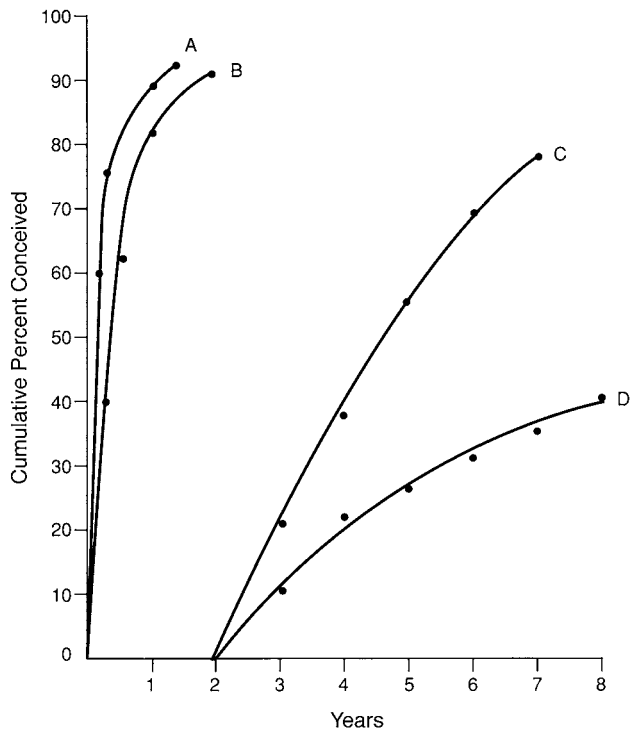


FIGURE 79-1. The conception rates of a normal population of parous, **A**, and nulliparous, **B**, women are compared with the cumulative conception rates of apparently normal women with secondary infertility, **C**, and primary infertility **D**. No conceptions occurred before the 2- to 3-year interval in the infertile groups, as this was part of the selection criteria for these patients. From Lenton EA, et al.: Long-term follow-up of the apparently normal couple with a complaint of infertility. *Fertil Steril* 1977; 28: 913. Used with permission in STD 3rd Edition.

- the effects of different antibiotic regimens used for treatment of acute PID on fertility;
- the impact of PID severity on fertility outcome; and
- the importance of timely therapy to preserve fertility.

During the 1970s, the polymicrobial etiology of PID, and especially the role of *Chlamydia trachomatis*, became increasingly appreciated.^{10,11} The influence of contraceptives on both PID and tubal factor infertility has become clearer (Chapter 78). Intrauterine devices, especially the Dalkon Shield®, appeared to increase the risk of PID and infertility, whereas more modern IUDs do not substantially increase the risk of PID aside from the brief period around insertion.¹² Further, barrier methods, both mechanical and chemical, appear to be protective.^{13–15} Finally, an increased understanding of the role of subclinical PID as a prelude to tubal obstruction has emerged from recent studies.¹⁶

DEMOGRAPHIC EFFECTS OF STD-RELATED INFERTILITY

In areas of the world where *Neisseria gonorrhoeae* and *C. trachomatis* infection are common, tubal infertility is also more frequent.^{17,18} Particularly, strong data link the epidemiology of gonococcal infection with infertility. For instance, in

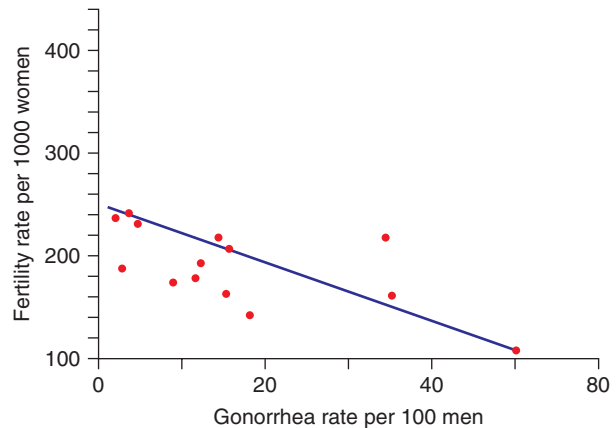


FIGURE 79-2. Correlation between the annual reported incidence of gonococcal urethritis in men and the general fertility rate, Uganda health districts, 1960s. (Data from Griffith HB: Gonorrhea and fertility in Uganda. *Eugen Rev* 1963; 55: 103.)

Uganda, 15 districts recorded a significant inverse correlation between the annual reported incidence of gonococcal urethritis in men and the general fertility rate (Fig. 79-2).¹⁹ A subsequent population-based study conducted in two rural districts of Uganda demonstrated that the rate of gonococcal infections in females and males was inversely related to the general fertility rates in the population, even after controlling for the effects of maternal nutrition and malaria.^{20,21}

To explore the potential relation between gonococcal and chlamydial infections and human population growth, mathematical models have been developed that combine epidemiologic and demographic data.^{22,23} These models predict that in areas where untreated gonococcal and chlamydial infections are prevalent, STD-related infertility has a major impact on fertility and, concomitantly, on net population growth. Gonococcal infection was predicted to exert a greater demographic impact than chlamydial infection because of its greater incidence and higher prevalence of postinfection infertility.²⁴ Specifically, the models concluded that a 10% prevalence of gonorrhea in sexually active adults would result in a 25% reduction in net population growth; a 10% prevalence of chlamydia in sexually active adults would result in a 10% reduction in net population growth.^{22,23} Because demographers have raised valid questions regarding the assumptions underlying the mathematical models, additional demographic research into the recent expansion of world population is needed.²⁴

Further information on the association between STDs and infertility derived from the WHO-sponsored investigation on infertility that evaluated infertile couples from 33 countries from the developed and developing world.²⁵ This monumental effort enrolled participants from 1979 to 1984 and utilized a standardized approach to the evaluation of infertility and completed the infertility investigation for over 5800 couples. Self-reported frequency of a history of STDs was more common in couples from Africa than in couples

from developed and other developing regions (Asia, Latin America, and Eastern Mediterranean). The great majority of African women suffered from infertility that was most attributable to prior infection, whereas prior infection was deemed responsible for infertility in only a minority of women from the other regions (both developed and developing). These results are likely explained by the high prevalence of *N. gonorrhoeae* and *C. trachomatis* infections in African populations. Thus, STD-related infertility may be a major and underrecognized demographic factor affecting the rate at which populations expand.

PREVALENCE OF TUBAL INFERTILITY

The prevalence of infertility can be assessed by measuring the absence of recent pregnancies in noncontracepting sexually active couples.²⁶ Using these definitions, rates of infertility have ranged from 1% to 16% of couples, with considerable regional variation.²⁷ When the denominator is confined to women who have actually attempted to become pregnant, about one in four had experienced infertility for at least 1 year and about 4% had never achieved a pregnancy.^{28–30}

The presence of tubal damage can be identified only in women who undergo gynecologic evaluation by a specialist. In the United States, couples in the middle to upper classes are more likely to seek such evaluation.³¹ Because STD and salpingitis occur less frequently in these populations, the prevalence of tubal infertility is probably underestimated. In Bristol, England, where medical care is less subject to this bias, an average of 1.2 couples per 1000 population annually requested infertility advice from a specialist.³² At this rate, approximately one in six couples (with an average length of infertility of 2.5 years) would seek help from a specialist at some time in their lives. Tubal damage was demonstrated in 14% of these infertile couples. In a representative Denmark population, nearly half of infertile couples had sought infertility services. One in five were diagnosed with tubal infertility, with older women (age >35 years) having higher rates.²⁸

Internationally, the WHO multicenter study compared STD-related infertility in five different regions of the world.^{25,33} More than 8000 infertile couples were enrolled in the study and more than 6000 (71%) completed evaluation of the fallopian tubes. Almost two-thirds of infertility in African women was attributed to infection, including 49% with bilateral tubal occlusion and 24% with pelvic adhesions (Table 79-1). The prevalence of tubal occlusion in Africa was more than three times that of any other region. Developed countries had an 11% prevalence of tubal occlusion in infertile women. Non-African developing areas had higher rates of tubal occlusion than developed countries, although well below those of Africa. Across various regions worldwide, the burden of female infertility due to infection is considerable. In studies

Table 79-1. Cause of Female Infertility, by Region

Categories	Percent of Cases Associated with Each Cause			
	Developed Country	Africa	Asia	Latin America
No demonstrable cause	40	16	31	35
Bilateral tubal occlusion	11	49	14	15
Pelvic adhesions	13	24	13	17
Acquired tubal abnormalities	12	12	12	12
Anovulatory regular cycles	10	14	9	9
Anovulatory oligomenorrhea ^a	9	3	7	9
Ovulatory oligomenorrhea	7	4	11	5
Hyperprolactinemia	7	5	7	8
Endometriosis	6	1	10	3
Total ^b	115	128	114	113

^aIncludes amenorrhea.

^bTotal greater than 100 percent due to the presence of more than one factor in some women.

Adapted from Arya OP, Nsanzumuhire H, Taber SR. Clinical, cultural, and demographic aspects of gonorrhoea in a rural community in Uganda. *Bull World Health Organ* 1973; 49(6): 587–595.

in Israel, Australia, and India, tubal damage, often attributed to prior salpingitis, has been documented to be present in one in five women with infertility.^{34–36} In cohorts of infertile couples in Western Siberia and Mongolia, tubal damage was present in one-third of women and was the most frequent cause of female infertility.^{37,38}

Another approach to estimating the prevalence of tubal infertility utilizes extrapolation from the annual reported incidence of STDs. For example, approximately 2.8 million cases of chlamydia and over 700,000 cases of gonorrhea are estimated to occur each year in the United States.³⁹ More than half of these infections occur in young people under the age of 25 years, those with many years of future reproductive potential. Assuming 30% of these cause salpingitis, and that 17% of salpingitis lead to tubal occlusion, an estimated annual incidence of 125,000 cases of STD-related infertility occurs each year in the United States.^{40–42} Converting these to cumulative numbers, we estimate that approximately 2 million reproductive-age women (range 200,000–2.7 million) currently have tubal occlusion in the United States. However, only about one-half may desire more children and a smaller percentage will seek infertility services.⁴³

Although the preceding estimates are crude, they are internally consistent with the annually reported number of STDs, the number of ambulatory and hospitalized cases of

PID, the number of infertility visits to private clinicians' offices, and the cross-sectional number of self-reported cases of PID and infertility in the American population of reproductive-age women.

ACUTE PELVIC INFLAMMATORY DISEASE AND INFERTILITY

Acute PID has long been associated with fallopian tube damage and subsequent infertility. The greatest body of knowledge concerning PID-related infertility stems from the longitudinal cohort study of women with acute PID in Lund, Sweden.¹ This study documents the long-term reproductive outcomes of 1844 women with laparoscopically diagnosed acute PID. Overall, approximately 11% of women with laparoscopically confirmed acute PID subsequently became infertile due to occluded fallopian tubes, compared to none of the women without PID. Among a cohort of 28 Finnish women with laparoscopic-proven acute PID who were subsequently attempting to conceive, Heinonen and Leinonen documented an infertility rate of 10.7%.⁴⁴ Less robust data from American cohorts support the association between PID and infertility. Using the National Survey of Family Growth, Cycle III, infertility was observed in twice as many women with a self-report of PID than in women without PID (44% compared to 21%).⁴⁵ Another US-based study described an infertility rate of 35% following the diagnosis of acute PID.⁴⁶

What has also become evident from the Swedish and other studies is that there are a number of factors that predict outcomes (Table 79-2). First, the greater the number of episodes of acute PID that a woman experiences, the greater

Table 79-2. Rate of Tubal Infertility Among Women Trying to Conceive, by Age, Number of PID Episodes, and Severity of PID—Lund, Sweden, 1960–1984

Number of PID Episodes	Age		Total
	<25	≥25	
One	7.7	9.1	8.0
Mild	0.8	0.0	0.6
Moderate	6.4	5.6	6.2
Severe	20.1	25.0	21.2
Two	18.4	25.9	19.5
Three or more	37.7	75.0	40.0
Total	11.2	12.0	11.4

Adapted from Farley TM, Rosenberg MJ, Rowe PJ, Chen JH, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. *Lancet* 1992; 339(8796): 785–788.

the risk of subsequent infertility. The infertility rate following one episode of acute PID was 8%, while a second and third episode of acute PID exponentially increased the subsequent rates of infertility to 19.5% and 40% respectively.¹ Second, the severity of inflammation directly correlated with subsequent infertility. Those women with severe cases of acute PID had a 21% rate of infertility, while 6.2% of those with moderate infertility suffered from infertility. However, the rate of infertility in women with mild cases of acute PID was only 0.6%. A later analysis of the Lund data demonstrated that earlier treatment is associated with improved reproductive outcomes. Women treated for PID within 2 days of onset of symptoms were 2.6 times less likely to develop infertility compared to women treated later in the course of PID (8.3% vs. 19.2%)⁴⁷ Taken together these data, which demonstrate improved reproductive outcomes in women with less frequent, milder PID and in those treated earlier in the course of infection, indicate that fertility is optimized with earlier recognition and treatment of PID.

PATHOGENESIS OF PID-ASSOCIATED TUBAL INFERTILITY

■ NEISSERIA GONORRHOEAE

Unraveling the complex etiologic relationships between STDs, PID, and infertility is complex and largely remains unknown. The paradigm of STDs leading to infertility is demonstrated in Fig. 79-3. The antecedent condition is the presence of microbial pathogens in the lower genital tract that commences the pathogenic chain of events culminating in microbe-influenced inflammation and damage of the fallopian tubes. As noted earlier, clinical features of acute PID relate to the risk of developing infertility, including previous episodes of salpingitis, severity of illness, and timeliness of treatment.^{1,47} Not all women diagnosed with PID will suffer impaired fertility, and the protective elements and factors causing damage on the cellular or tissue level remain to be fully characterized.

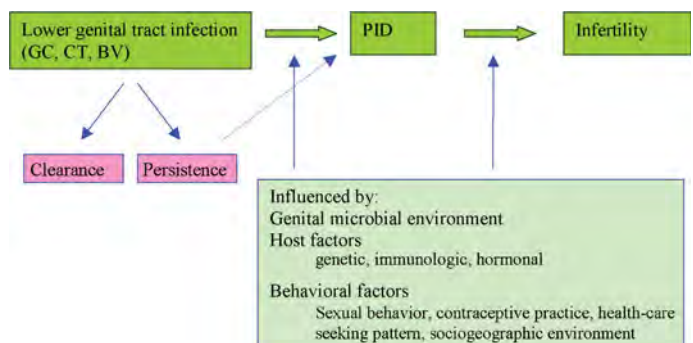


FIGURE 79-3. Relationships among STDs, PID, and tubal infertility.

The ciliated epithelial cells of the fallopian tube function to transport the ovum to the ampullary portion of the fallopian tube for fertilization and then transport the fertilized ovum to the uterus for implantation. Damage to the delicate cilia of these tubal epithelial cells impairs tubal transport, resulting in infertility or ectopic pregnancy formation. In the fallopian tube, *N. gonorrhoeae* initiates its attack by attaching to the nonciliated mucosal cells but its dominant impact on tubal damage is by sloughing of ciliated mucosal cells.⁴⁸ This epithelial damage may be toxin-mediated, as sterilized supernatant from gonococcal infection results in fallopian tube damage similar to direct infection with the gonococcus.⁴⁹ In a fallopian tube organ model, experimental challenge with *N. gonorrhoeae* induced expression of the proinflammatory cytokines IL-1 α , IL-1 β , and TNF- α .⁵⁰ TNF- α appears to play an important role in mediating mucosal damage from *N. gonorrhoeae* infection.⁵¹ TNF- α induces apoptosis of fallopian tube epithelial cells, which may represent a host defense protecting against tubal damage. The gonococcus appears to be able to modulate and inhibit TNF- α mediated damage and possibly permit ongoing infection.⁵² Lipopolysaccharide (LPS) expressed on the surface of gonococci can be toxic to epithelial cells but its role in salpingitis is largely unknown.⁵³ Other characteristics of *N. gonorrhoeae*, including transparent colony phenotype and serotype have been associated with salpingitis.^{54,55}

■ CHLAMYDIA TRACHOMATIS

Seroepidemiologic study of women with tubal infertility has shown that women with *C. trachomatis*-associated infertility have antibody to a distinctive chlamydial antigen of 57,000 Daltons molecular mass.⁵⁶ Molecular study showed that this antigen was a highly conserved heat shock protein 60 (Hsp-60) whose homologs are widely found in both bacterial and eucaryotic cells.⁵⁷ Hsp-60 has been shown to be a potent T-cell antigen capable of eliciting an intense inflammatory response when applied to the mucosal surfaces of the fallopian tube of immunologically primed animals.^{58,59} These characteristics are highly suggestive of the hypothesized chlamydial hypersensitivity antigen implicated in chlamydial immunopathology and tissue fibrosis.⁶⁰

Chlamydial Hsp-60 antibodies are associated with acute PID and correlate with severity of infection and tissue damage. In a cohort of women with laparoscopically confirmed PID by Eckert et al., chlamydial Hsp-60 antibodies were found in the sera of 80% of women with occluded fallopian tubes and in only 19% of women with patent tubes ($p < 0.001$).⁶¹ Further, higher titres have been observed in women diagnosed with PID who have severe pelvic adhesive disease and perihepatitis.⁶² As there is considerable homology between human and chlamydial Hsp-60, an autoimmune response may occur during chlamydial PID, whereby chlamydial Hsp-60

antibodies cross-react and target fallopian tube mucosa, causing damage and scarring.⁶³

The host's inflammatory response to *C. trachomatis* salpingitis plays an essential role in resultant tubal damage.^{64,65} A T-helper (Th-1) cytokine response is seen following experimental chlamydial salpingitis.⁶⁵ And while IFN- γ demonstrates chlamydial killing and clearance in experimental models, IFN- γ can promote fibrosis.⁶⁶⁻⁶⁸ A Th-2 response is also observed during chlamydial infection, with higher levels of IL-10 secretion observed from chlamydia Hsp-60-stimulated peripheral blood mononuclear cells obtained from women with tubal factor infertility than from women infertile from other reasons.⁶⁹ Whether the antiinflammatory cytokine response suppresses host clearance and allows for persistent infection is unclear.

The exponential increase in tubal damage and infertility following repeated episodes of PID as demonstrated in the Swedish cohort (see above) lend support to the importance of an immunologic basis for tubal damage.¹ In the animal model employing the pig-tailed macaque, Patton et al. demonstrated that a single inoculation with *C. trachomatis* causes a self-limited infection of the lower genital tract.⁷⁰ Repeated inoculation in this animal model results in fallopian tube obstruction. In another monkey model study, development of peritubal adhesions was related to increased number of cervical inoculations with *C. trachomatis*.⁷¹ Similar fibrosis is observed in the macaque subcutaneous salpingeal pocket model after repeated chlamydial infections.⁶⁵ Experience in humans corroborates animal data suggesting that repeated *C. trachomatis* infections cause considerably greater damage to the fallopian tubes than single infections.

RECENT TRENDS ON SEVERITY OF PELVIC INFLAMMATORY DISEASE

Between 1979 and 1988, hospitalizations for acute PID in the United States decreased by 36%, and in the subsequent decade from 1990 to 2000, the number of such hospitalizations further dropped by approximately one-half.^{72,73} The same findings were seen in an analysis of hospitalizations for acute PID in Norway, where a 35% reduction in hospitalized cases of acute PID was observed comparing two time periods separated by 10 years (1990–1992 and 2000–2002).⁷⁴ Provider behavior was likely not a factor in this decline in rates of inpatient treatment of acute PID, as there were no changes in policy regarding admission criteria for acute PID. Despite this observed decline in hospitalization for acute PID, the number of ambulatory visits to physicians' offices for PID remained stable over the same period. While practice patterns have changed in recent years, focusing on ambulatory treatment to reduce medical costs, it is likely that the decline in hospitalization rates for acute PID reflects the evolving trends in the microbiologic etiology of PID in

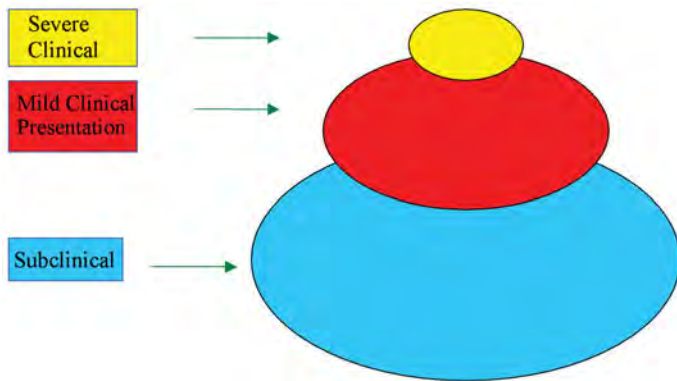


FIGURE 79-4. Spectrum of clinical presentation of pelvic inflammatory disease (PID).

many populations. Specifically, the recent decline in the rate of *N. gonorrhoeae* in the United States, which has not been observed with the prevalence of *C. trachomatis* infection, may have resulted in fewer cases of PID associated with gonorrhea and a relative increased proportion of cases associated with chlamydia. As PID involving *N. gonorrhoeae* is typically a more clinically severe condition than PID caused by *C. trachomatis*, decreased hospitalizations for acute disease would be expected if most cases of PID are nongonococcal in etiology. As the trends in clinical presentations of PID are evolving toward less severe clinical presentations, much attention is focused on milder forms of pelvic infection, recognizing that atypical, silent, or clinically unrecognized cases of PID are commonplace. Despite the absence of clinical evidence of an acute inflammatory response, these cases of subclinical or silent PID are believed to be associated with reproductive health risks. The new paradigm of PID reflects the shifting spectrum of clinical presentations from acute, symptomatic illness to subclinical disease (Fig. 79-4).

EVIDENCE LINKING INFERTILITY WITH PRIOR EPISODES OF SUBCLINICAL PELVIC INFLAMMATORY DISEASE

The body of the literature linking subclinical PID with infertility has largely involved retrospective analyses, given the challenges in arriving at the diagnosis at the time of occurrence. Tubal factor infertility ranks among the most common causes of infertility in women worldwide. Many of these women do not have an obvious current explanation for fallopian tube damage such as endometriosis or post surgical adhesive disease. While PID can cause tubal damage and subsequent infertility, many women with otherwise unexplained tubal factor infertility do not report a history of acute PID (Figs. 79-5 and 79-6). Investigations of these women have examined serologic evidence of remote infection in women with fallopian tube damage and have implicated subclinical PID as a possible cause of tubal obstruction.

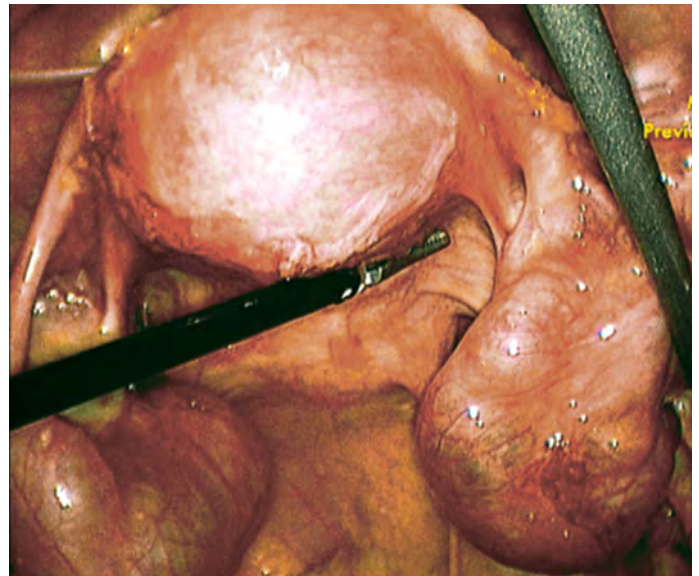


FIGURE 79-5. Laparoscopic view of the pelvis of a 28-year-old infertile woman with a prior history of gonorrhea but denied a history of acute PID. Both fallopian tubes are obstructed and dilated.

SEROLOGIC EVIDENCE OF PRIOR CHLAMYDIAL INFECTION IN WOMEN WITH INFERTILITY

A number of studies among women from various communities worldwide have examined sera from women with tubal damage to determine the prevalence of antibodies to *C. trachomatis*. Moore et al. tested sera from infertile women for *C. trachomatis* antibody by micro-immunofluorescence.⁷⁵ Distal occlusion of the fallopian tubes was evident by laparoscopy in 33 infertile women. Twenty-four (73%) of these women were seropositive for *C. trachomatis* antibodies, compared to 0/35 infertile women without tubal disease. In the Netherlands, Tjiam performed a similar study of 53 women who were infertile for at least 18 months. All subjects had undergone an evaluation that included documentation of fallopian tube patency by hysterosalpingography (HSG) and laparoscopy.⁷⁶ Among women with tubal factor infertility, antibodies to *C. trachomatis* were detected in 7 (21.2%) of 33, whereas none of the 20 infertile women without tubal disease tested positive for chlamydial antibodies. In a U.S. cohort of 218 infertile women who underwent HSG and laparoscopy, Meikle et al. reported that *C. trachomatis* antibodies were present in the sera of 68 (78%) of 87 women with tubal disease, whereas only 36% of infertile women without tubal disease had antichlamydial antibodies.⁷⁷ Another U.S.-based study of 210 infertile patients examined the association between antichlamydial antibodies and fallopian tube damage.⁷⁸ Only 9% of this cohort reported a prior history of chlamydial infection or PID, yet 40% were seropositive for *C. trachomatis*. Among those women undergoing laparoscopy, all 43 (100%) with high titres of *C. trachomatis* IgG antibodies had tubal disease, compared to 19 (30%) of 63 seronegative women ($p < 0.001$).

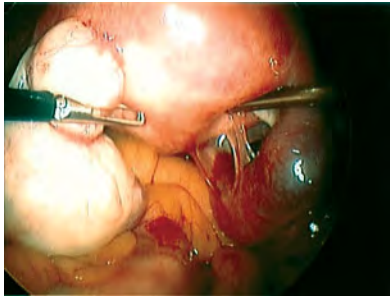


FIGURE 79-6. Laparoscopic view of the pelvis of a 23-year-old woman with an ectopic pregnancy in the right fallopian tube. The right fallopian tube is distended by the ectopic gestation. Adhesions are readily evident. This patient had a prior history of chlamydia but no history of PID.

Bilateral tubal blockage was 3 times more common in women with high titres compared to seronegative women. Similar results were found by the WHO's Task Force on the Prevention and Management of Infertility multicenter case-control study of women reporting at least 12 months of infertility performed in Thailand, Slovenia, and Hungary. Antichlamydial antibodies (using an enzyme-linked immunosorbent assay) were present in 32 (71%) of 45 women with bilateral tubal occlusion detected either by HSG or laparoscopy, compared to this finding in 31 (32%) of 96 women with other etiologies for infertility.¹⁸ Rather than comparisons to women with other etiologies of infertility, some studies have used cohorts of fertile women as the comparison group to evaluate seroprevalence. Sellors et al. compared the seroprevalence of antibodies to *C. trachomatis* (measured by enzyme immunoassay) of women with tubal factor infertility to the rates in two control cohorts, women undergoing tubal sterilization, and women undergoing hysterectomy.⁷⁹ The seroprevalence of *C. trachomatis* in the two fertile control groups was 34%. In contrast, three of four women (32/43, 74.7%) with tubal factor infertility had serologic evidence of prior infection with *C. trachomatis*. The authors concluded that women with evidence of prior chlamydial infection are approximately 6 times more likely to develop tubal factor infertility than women without prior infection. Results from numerous other investigations add considerably to the findings of an association of tubal factor infertility with *C. trachomatis* antibodies (Table 79-3).

■ SEROLOGIC EVIDENCE OF PRIOR GONOCOCCAL INFECTION IN WOMEN WITH INFERTILITY

Gonococcal PID is also an important cause of fallopian tube damage. While fewer data are available linking serologic evidence of past *N. gonorrhoeae* infection and tubal factor infertility than with *C. trachomatis* in cohorts of women without a history of PID, the data are noteworthy for their consistency (Table 79-4). Tjiam et al. measured antibodies to *N. gonorrhoeae* pili antigens by ELISA in a Dutch cohort of infertile women who underwent HSG and laparoscopy to

determine fallopian tube status.⁷⁶ Antigonococcal antibodies, indicating remote infection with *N. gonorrhoeae*, were identified in 20 (60.6%) of 38 women with fallopian tube damage and in only 5 (25%) of 20 infertile women with normal fallopian tubes. In the WHO study mentioned earlier, antibodies to the pili of *N. gonorrhoeae* were present in 28 (62.2%) of 45 infertile women with bilateral tubal occlusion compared to 36 (37.5%) of 96 women with other etiologies of infertility and without tubal occlusion ($p < 0.01$).¹⁸ Miettinen et al. did not identify prior gonococcal infection in any infertile women without fallopian tube damage, yet serologic evidence of past gonococcal infection was found in 14% of women with infertility and fallopian tube abnormalities.⁸⁰ Finally, among a cohort of 172 women in Thailand, serum antibodies to the alpha pili of *N. gonorrhoeae* were more commonly seen among infertile women with tubal damage, as assessed by laparoscopy, than among infertile women with normal fallopian tubes and fertile controls.⁸¹ Robertson et al., however, found no such relationship between serologic evidence of prior *N. gonorrhoeae* infection and infertility.⁸²

■ SEROLOGIC EVIDENCE OF PRIOR STDs IN WOMEN WITH ECTOPIC PREGNANCY

While tubal factor infertility is the most common complication of PID, another important late sequela is ectopic pregnancy. A number of studies have outlined the relationship between previous infection with *C. trachomatis* and ectopic pregnancy (Table 79-5). In 1983, Gump and colleagues examined 204 infertile women for an association between *C. trachomatis* and infertility.⁸³ Eleven (14%) of the 76 women who subsequently became pregnant were diagnosed with an ectopic pregnancy. Prior history of chlamydial infection was far more common in the ectopic pregnancy group. Among women diagnosed with an ectopic pregnancy, the prevalence of antichlamydial antibodies was 82% (9/11), while only 29% (19/65) of women with an intrauterine pregnancy were seropositive for *C. trachomatis*. Svensson and associates reported a case control study of 112 women with ectopic pregnancies. One-half were determined to have prior episode(s) of PID based on operative findings of the presence of tubal adhesions. Sixty-five percent (73/112) of women with ectopic pregnancies were seropositive for antichlamydial antibodies, statistically greater than the rate of 21% seen in the control group of pregnant women ($p < 0.001$).⁸⁴ Brunham et al. divided a cohort of 50 women with ectopic pregnancy into two groups according to the presence or absence of ectopic pregnancy risk factors (tubal ligation or intrauterine contraceptive device) and compared these two groups to a group of 49 women with an intrauterine pregnancy.⁸⁵ Serologic evidence of prior *C. trachomatis* infection was present in 18% of women with known risk factors for

Table 79-3. Antibodies to *Chlamydia Trachomatis* and Infertility

Study	Infertile women		Fertile Women
	Tubal Factor	Nontubal Factor	
Moore ⁷⁵ (1982)	73% (24/33)	0% (0/35)	–
Gump ⁸³ (1983)	64% (34/53)	28% (38/134)	–
Kane ¹³⁴ (1984)	36% (25/70)	12% (6/52)	11% (22/200)
Conway ¹³⁵ (1984)	75% (36/48)	31% (23/75)	47% (48/103)
Brunham ⁵⁶ (1985)	72% (13/18)	9% (6/70)	22% (11/49)
Tjiam ⁷⁶ (1985)	21% (7/33)	0% (0/20)	–
Sarov ¹³⁶ (1986)	87% (26/30)	20% (10/50)	10% (10/100)
Robertson ⁸² (1987)	73% (35/48)	34% (26/77)	38% (25/63)
Sellors ⁷⁹ (1988)	75% (32/43)	–	34% (26/77)
Garland ¹³⁷ (1990)	65% (22/34)	22% (5/23)	–
Miettinen ⁸⁰ (1990)	46% (32/69)	7% (2/28)	–
Meikle ⁷⁷ (1994)	78% (68/87)	36% (47/131)	–
WHO ¹⁸ (1995)	71% (32/45)	32% (31/96)	–
Akande ¹³⁸ (2003)	82% (358/434)	34% (192/572)	–
Den Hartog ¹³⁹ (2004)	54% (32/59)	8% (20/254)	–

Table 79-4. Antibodies to *Neisseria Gonorrhoeae* and Infertility

Study	Infertile women		Fertile Women
	Tubal Factor	Nontubal Factor	
Tjiam ⁷⁶ (1985)	21% (7/33)	0% (0/20)	–
Robertson ⁸² (1987)	2% (1/48)	3% (2/77)	16% (10/63)
Miettinen ⁸⁰ (1990)	16% (11/69)	0% (0/28)	–
WHO ¹⁸ (1995)	71% (32/45)	32% (31/96)	–
Swasdio ⁸¹ (1996)	29% (16/55)	5% (3/58)	3% (2/59)

ectopic pregnancy and 22% of women with intrauterine pregnancy. Thirty-two women with ectopic pregnancy in this cohort had no identifiable risk factor for ectopic pregnancy (they did not use an intrauterine contraceptive device and did not previously undergo a tubal ligation) and 56% of these women were positive for *C. trachomatis*

antibodies. Many in this group of women who lacked known risk factors for ectopic pregnancy were believed to have previously experienced subclinical infection of the fallopian tubes. While most investigations examining the relationship between chlamydia and ectopic pregnancy used pregnant women as their control groups, other researchers

Table 79-5. Antibodies to *Chlamydia Trachomatis* and Ectopic Pregnancy

Study	Ectopic Pregnancy	Intrauterine Pregnancy
Gump ⁸³ (1983)	82% (9/11)	29% (19/65)
Svensson ⁸⁴ (1985)	65% (73/112)	21% (18/86)
Brunham ⁸⁵ (1986)	56% (18/32)	22% (11/49)
Robertson ⁹¹ (1988)	76% (38/50)	38% (19/50)
Walters ¹⁴⁰ (1988)	82% (49/60)	58% (35/60)
Chow ¹⁴¹ (1990)	71%	39%
Kihlstrom ¹⁴² (1990)	78% (7/9)	13% (7/55)
Ville ⁹² (1991)	84% (38/45)	46% (34/74)
Chrysostomou ¹⁴³ (1992)	76% (37/49)	46% (26/56)
Odland ¹⁴⁴ (1993)	80% (24/30)	44% (22/50)
Mehanna ¹⁴⁵ (1995)	21% (14/66)	12% (6/51)
Sziller ¹⁴⁶ 1998	52% (35/67)	27% (12/45)

have classified women with ectopic pregnancies into groups with and without prior PID based on the gross appearance of the fallopian tubes at the time of surgery. For example, adhesions of the contralateral fallopian tube in women with ectopic pregnancy would be suggestive of remote pelvic infection. In a study of women undergoing laparotomy as treatment for ectopic pregnancies, Hartford et al. demonstrated that antichlamydial antibodies were present in 50% (5/10) of women with damage of the contralateral fallopian tube compared to 0% (0/14) of women with normal-appearing contralateral tubes.⁸⁶ Sheffield et al. similarly reported nearly a doubling of prevalence rate of antichlamydial antibodies among women with ectopic pregnancies who had damage of the contralateral fallopian tube compared to women with ectopic pregnancies and normal tubes.⁸⁷

A recent population-based study from Norway linked women with a hospital discharge or outpatient diagnosis of ectopic pregnancy with a county database containing information on prior *C. trachomatis* testing.⁸⁸ Among women aged 20–34, prior *C. trachomatis* infection was associated with a twofold increase in risk for ectopic pregnancy. Such a relationship was not observed in a Danish population-based study.⁸⁹ The Norwegian study further suggested a dose-response relationship with the number of prior chlamydial infections.⁸⁸ Similarly, Hillis and colleagues, examining data

from a chlamydia prevention program and hospital discharges in Wisconsin USA, found that recurrent chlamydial infections increase the risk of hospitalization for ectopic pregnancy.⁹⁰ Compared to women with a history of one reported chlamydial infection, those with two and three or more reported infections were 4 times and 11 times as likely to be diagnosed with an ectopic pregnancy. Overall, retrospective and population-based studies support an association between *C. trachomatis* infection and ectopic pregnancy formation.

The association between prior genital infection with *N. gonorrhoeae* and ectopic pregnancy has also been recognized, albeit the data is less extensive. Robertson detected antibodies to gonococcal pili in 16 (32%) of 50 women with ectopic pregnancy, while only 2 (4%) of 50 fertile women with intrauterine pregnancies had serologic evidence of prior gonococcal infection ($p < 0.001$).⁹¹ Similarly Ville et al. demonstrated that in a cohort from Gabon, gonococcal pili antibodies were evident twice as often (49% vs. 23%) in women with ectopic pregnancy than in pregnant women.⁹²

PERSISTENT UPPER GENITAL TRACT INFECTION

Evidence that pathogens can infect the upper genital tract in the absence of classic signs or symptoms of acute PID would add substantially to the argument that many cases of PID are clinically subtle or silent. A number of studies have revealed that PID-type pathogens can be recovered from the upper genital tract in women in the absence of symptoms of acute PID. Among the earliest observations was a report by Henry-Suchet in 1980 describing the isolation of *C. trachomatis* from the abdomen in 6 of 23 infertile women without pain or other evidence of acute pelvic infection.⁹³ A larger study further expanded on this preliminary series, documenting that in women undergoing laparoscopy for infertility, a large proportion had evidence of upper genital tract infection.⁹⁴ Among these women without clinical evidence of acute PID, *C. trachomatis* was recovered from the abdominal cavity from 23.3% of women with tubal damage and laparoscopic evidence of chronic inflammation. The chlamydial isolation rate among women with tubal damage but without inflammation was 15.4%, while only 2% of women without tubal damage had evidence of chlamydial infection. Sweet and colleagues' study of women with acute PID added to the evidence that *C. trachomatis* can persist in the upper genital tract in the absence of symptoms.⁹⁵ Despite clinical resolution of symptoms, endometrial cultures following treatment were positive for *C. trachomatis* in 12 of 13 women treated with a cephalosporin agent, which does not have activity against this pathogen. These early findings suggest two important features about PID: first, the need for antichlamydial therapy for acute PID, and second that *C. trachomatis* infection of the upper genital tract can occur in

the absence of symptoms of acute PID. In an elegant study of fallopian tube specimens from women with laparoscopic-confirmed postinfectious tubal infertility, Patton et al. searched for evidence of *C. trachomatis* by culture, in situ hybridization, immunoperoxidase staining, and transmission electron microscopy.⁹⁶ Persistent infection with *C. trachomatis* was evident in nearly 80% of women by these techniques. Taken together, these studies provide strong evidence to suggest that *C. trachomatis* can cause a persistent and clinically silent infection of the upper genital tract.

PREGNANCY LOSS—DOES ENDOMETRITIS PLAY A ROLE?

An inflammatory process of the endometrium would pose a challenge to the implantation of the embryo and may cause pregnancy loss. To that end, the influence of inapparent chlamydial infections on the success of embryo implantation has been studied. Licciardi et al. examined *C. trachomatis* IgG antibodies in the sera of 145 women undergoing in vitro fertilization (IVF).⁹⁷ Spontaneous abortion was strongly associated with the presence of chlamydial IgG antibodies. While there were no active *C. trachomatis* infections detected in this cohort, remote chlamydial infection was nearly 3 times more common among those experiencing pregnancy loss. Antichlamydial antibodies were found in 20 (69%) of 29 women who experienced a spontaneous abortion compared to 9 (24%) of 38 women with successful pregnancies ($p < 0.001$). A nonsignificant relationship was observed by Keltz et al., who found a pregnancy loss rate of 35% (6/17) among women positive for serum *C. trachomatis* IgG antibodies compared to a rate of 17% (8/47) observed in seronegative women.⁷⁸ Witkin and colleagues identified an association between undetected and untreated chlamydial infection and both failure to conceive and spontaneous abortion in women undergoing IVF.⁹⁸ Other data conflicts with this theory. Spandorfer did not find an association between IVF outcome and antibodies to either chlamydial 10 kDa heat shock protein 10 (Chsp 10) or chlamydial surface antigen.⁹⁹ Claman found a similar lack of association among women attending a university-based IVF program.¹⁰⁰ Similar conflicting data concerning prior chlamydial infections have been observed when examining women with recurrent pregnancy loss. High titre antichlamydial antibodies were found in 13.5%, 12.8%, 12.1%, 41%, and 60% of U.S. women with zero, one, two, three, or four spontaneous abortions, respectively ($p < 0.01$), linking recurrent pregnancy loss with prior chlamydial infection.¹⁰¹ However, immunoglobulin G antichlamydial antibodies were not associated with recurrent pregnancy loss in cohorts of women from the UK and Finland.^{102,103} Similarly, a prospective study of women undergoing miscarriage found no relationship between antichlamydial antibodies and miscarriage.¹⁰⁴

As endometrial sampling for inflammation is impractical at the time of, or in the days leading to implantation, the mechanisms of pregnancy loss in these women remain to be determined. One plausible theory is that low-level persistent chlamydial infection, and its associated inflammation of the endometrium, adversely affects implantation. Alternatively, immune activation could interfere with implantation, perhaps via production of antibody to the chlamydia heat shock protein, which has similar features as mammalian heat shock proteins. Such immune activation may cause an autoimmune-type of hostile response to the embryo. Clinical data examining active *C. trachomatis* infection and pregnancy loss are limited. Studies of women diagnosed with chlamydial infections in pregnancy have provided conflicting results regarding a link between *C. trachomatis* and preterm birth (Chapter 80).^{105,106} No data are available on the influence of active chlamydial infections on early pregnancy outcomes. Another theory is that remote chlamydial infection may have caused irreparable damage to the endometrium, prohibiting successful implantation. While the mechanistic explanation for upper genital tract inflammation and pregnancy loss is lacking, the association between remote chlamydial infection and pregnancy loss suggests that upper genital tract inflammation creates a hostile environment for embryo implantation.

HISTOPATHOLOGY OF SUBCLINICAL PID

Further light has been shed on the devastating impact of subclinical PID on fertility by studies examining the pathologic findings of the fallopian tubes in women with acute and subclinical PID. Patton et al. examined the morphologic changes of the fallopian tube mucosa from women undergoing salpingostomy to repair distal tubal occlusion.¹⁶ These women were divided into two groups based on the presence or absence of a clinical history of salpingitis (overt PID and subclinical PID, respectively) and compared to a control group that consisted of women with normal tubes undergoing hysterectomy. One-half of the women in each of the two PID groups had serologic evidence of prior chlamydial infection, while antichlamydial antibodies were not identified in any of the control women. Fallopian tube damage was assessed by light, scanning, and transmission electron microscopy, assessing for evidence of flattened mucosal folds, deciliation, and damage to the secretory epithelial cells (Figs. 79-7 and 79-8). The findings of this study clearly demonstrate that the morphologic damage to the fallopian tube was very similar among women with acute PID and subclinical PID. Further, the characterization of the damage was strikingly similar, suggesting very similar pathophysiologic mechanisms. The investigators further assessed tubal damage by measuring ciliary beat frequency. The beat frequency was similar in the tubes from women with acute and subclinical PID; the beat

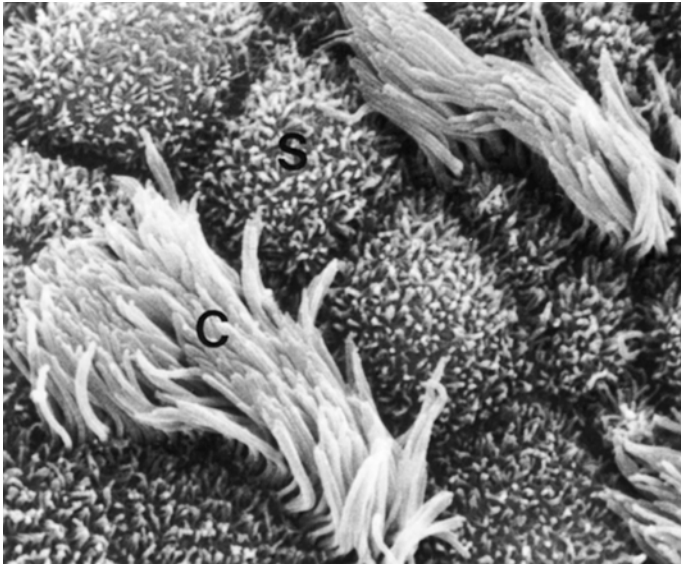


FIGURE 79-7. Normal fallopian tube. Secretory cells (S) with abundant microvilli are surrounded by clumps of long, slender cilia (C) atop the ciliated cells. 4800 \times . (SEM provided by Dr. Dorothy L. Patton, Departments of Obstetrics and Gynecology and Biological Structure, University of Washington.)

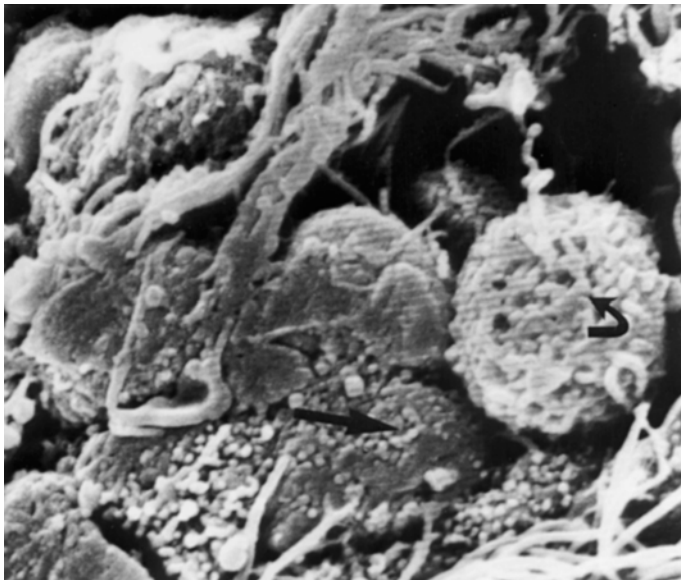


FIGURE 79-8. Infertile fallopian tube following infection. Pronounced deciliation (straight arrow) of the ciliated cells and clubbing of the microvilli on the secretory (curved arrow) cells are evident in this biopsy taken from a distally occluded fallopian tube. 5200 \times . (SEM provided by Dr. Dorothy L. Patton, Departments of Obstetrics and Gynecology and Biological Structure, University of Washington.)

frequency was 3 times faster in the fallopian tubes of the control women than the tubes from either the women with acute or silent PID. Thus, both the histologic appearance of the fallopian tube is altered and the function of the tube is impaired. The results from this important work highlight that fallopian tube damage from acute and subclinical PID is nearly identical. Subclinical PID is responsible for considerable damage to the structure and function of the fallopian tube with the possible adverse impact on fertility potential.

LIMITED UTILITY OF HISTORY TAKING IN TUBAL FACTOR INFERTILITY

As *N. gonorrhoeae* and *C. trachomatis* are important causes of acute PID, one can surmise that the serologic data linking these two sexually transmitted organisms with infertility and ectopic pregnancy reflect prior episodes of acute PID. However, many of these women do not recall being diagnosed with acute PID. Studies of women with tubal factor infertility have shown the inaccuracy of patient recall.¹⁰⁷ Studies of women with infertility have consistently shown that only approximately one-third report a history of a prior diagnosis of acute PID.^{17,56,83} Further, recall of past PID was unrelated to chlamydial serology.⁷⁹ Similar findings were noted among infertile women with damaged fallopian tubes and antibodies to *N. gonorrhoeae*, with only 45% of women reporting a history of prior PID.⁸⁰ In the WHO study investigating the relationship between chlamydia and gonorrhea serology and infertility, only one-third of women with bilateral tubal occlusion and serologic evidence of past gonococcal or chlamydial infection reported prior symptoms suggestive of acute PID.¹⁸ It is probable that recall bias may explain some of these discrepant findings. However, the great discrepancy between suspected prior PID and recall of such a history lends credence to the argument that a large proportion of infection-mediated tubal damage is subclinical; the high frequency of antibodies to *C. trachomatis* and *N. gonorrhoeae* in women with infertility or ectopic pregnancy reflects prior acute PID in only a minority of women. Fallopian tube damage that occurs as a result of chlamydial or gonococcal infections indicates that many cases of postinfectious tubal damage arise from subclinical PID rather than acute PID.

SUBCLINICAL PID IN WOMEN WITH CERVICITIS AND VAGINITIS

The sexual pathogens *N. gonorrhoeae* and *C. trachomatis* are considered to be the etiologic agents of a substantial proportion of acute PID cases (see Chapter 56). A growing body of the literature suggests that these pathogens are implicated in the pathogenesis of subclinical PID. In one of the earliest studies examining a small cohort of 35 women with suspected cervicitis, Paavonen identified histologic endometritis in 40%, and that endometritis was correlated with the presence of chlamydial or gonococcal cervicitis.¹⁰⁸ Korn et al. studied 111 women with lower genital tract infection.¹⁰⁹ Using criteria of the presence of any plasma cells in the endometrial specimen, 56% of women (15/27) with gonorrhea and 57% of women with chlamydia (17/30) had plasma cell endometritis.

Wiesenfeld et al. performed a cross-sectional study evaluating the relationship between lower genital tract infection and subclinical PID among 556 women between 15 and 30 years of age who were attending STD and ambulatory

clinics.¹¹⁰ Lower genital tract infections were common in this cohort, with 57 diagnosed with cervical *N. gonorrhoeae* infection, 103 women were infected with *C. trachomatis*, and 377 were diagnosed with bacterial vaginosis. None of the participants had clinical evidence of acute PID. Using endometrial histology criteria for subclinical PID as validated by Kiviat et al., the diagnosis of subclinical PID required the presence of neutrophils and plasma cells in the endometrial sample.¹¹¹ Subclinical PID was detected in 27% of women with *C. trachomatis* infection and in 26% of women diagnosed with gonorrhea. The odds ratio for subclinical PID among women with chlamydial cervicitis was 3.4 (95% confidence interval 1.8, 6.3), while that for gonococcal cervicitis was 2.4 (95% confidence interval 1.1, 5.1). Thus, it is apparent that clinically inapparent upper genital tract inflammation, also termed subclinical PID, is found in a substantial minority of women with seemingly uncomplicated gonococcal or chlamydial cervicitis.

Bacterial vaginosis has been implicated as an important cause of ascending pelvic infection, with studies demonstrating associations between bacterial vaginosis and preterm labor and premature rupture of the fetal membranes (much of which is related to ascending infection), postcesarean section endometritis, and PID.^{112–114} Bacterial vaginosis is found in a high proportion of women diagnosed with acute PID and bacterial vaginosis-associated microorganisms have been isolated from the upper genital tract of women with PID.^{115,116} Given the relationship between bacterial vaginosis and PID, several investigations have explored whether women with bacterial vaginosis are at risk for subclinical PID. Korn et al. studied the relationship between bacterial vaginosis and plasma cell endometritis in women without signs or symptoms of acute PID.¹¹⁷ Twenty-two women with bacterial vaginosis but without *N. gonorrhoeae* or *C. trachomatis* infection were compared to an uninfected control group of 19 women. Plasma cell endometritis was present in 10 (45%) of 22 women with bacterial vaginosis and in only 1 (5%) of 19 controls ($p < 0.05$). As evidence of clinically inapparent ascent of vaginal microflora to the upper genital tract, these investigators recovered bacterial vaginosis-associated organisms from the endometria more frequently from those women with bacterial vaginosis than those without bacterial vaginosis. Moreover, these organisms were isolated nearly twice as often from women with plasma cell endometritis than from those without endometritis, suggesting that the microbiologic findings from the endometrium did not reflect contamination from the lower genital tract. In a later study published by the same group of investigators comprising women attending an inner-city hospital or an STD clinic, plasma cell endometritis was found in 42% of 57 women with bacterial vaginosis and in only 13% of the 24 women without BV.¹⁰⁹ In women without clinical evidence of acute PID, Wiesenfeld et al. identified plasma cell

endometritis in 39% of women with bacterial vaginosis, which was significantly greater than the 29% rate of endometritis in women without bacterial vaginosis; this difference was not found to be significant after adjustment for confounding variables.¹¹⁰ However, using stricter histopathologic criteria (the presence of both neutrophils and plasma cells), endometritis was statistically associated with bacterial vaginosis. As with the sexually transmitted pathogens *C. trachomatis* and *N. gonorrhoeae*, bacterial vaginosis is not only implicated in the pathogenesis of acute PID but is suspected in the development of subclinical PID.

As detailed above, substantial retrospective data associated prior PID with infertility. Despite the virtual unanimity of these observations, there are no prospective data published to date on the risk of infertility in women with gonococcal or chlamydial cervicitis or bacterial vaginosis. Current prospective studies are underway examining whether women with subclinical PID are at risk for tubal factor infertility, and preliminary data indicate that women with subclinical PID are at increased risk for subsequent involuntary infertility.¹¹⁸

ENDOMETRIAL PATHOLOGY OF SUBCLINICAL PID

The current gold-standard diagnostic test for confirming the presence of PID is direct visualization of the pelvic organs (via laparoscopy) but the cost and surgical risks limit the widespread utility of this approach. Rather, endometrial amplifying is a much safer office procedure that is becoming more widely employed to identify upper genital tract inflammation. Histopathologic interpretation typically takes 2 days or more, precluding its use to timely influence therapeutic management. However, its utility in confirming or refuting the presence of upper genital tract inflammation is a considerable advantage and offers important prognostic information to the patient and clinician.

Lack of consistent criteria for endometritis has posed challenges both in clinical care and in research investigations. Investigators have used several different histologic criteria to define endometritis. The presence of plasma cells in the endometrium, referred to as plasma cell endometritis, has been associated with lower genital tract infection in cohorts of women at risk for STDs.^{109,117} Some investigators rely solely on the presence of a single plasma cell in the entire endometrial specimen.^{117,119,120} Paukku et al. studied the association between *C. trachomatis* infection and plasma cell endometritis by reexamining paraffin-embedded endometrial biopsy specimens for the presence of *C. trachomatis* by PCR and immunohistochemistry.¹²¹ Detection of *C. trachomatis* within the biopsy specimen was performed using DNA extraction and PCR of paraffinized endometrial tissue to amplify *C. trachomatis* DNA and by immunohistochemistry. Overall, 5 (24%) of 21 samples with plasma cell endometritis (at least one

plasma cell per 120x field) were positive for *C. trachomatis*, compared to 1 (4%) of 28 specimens that did not have plasma cell endometritis. This study is limited by its small size and by potential selection bias. Further, more than one-half of women whose biopsies revealed plasma cell endometritis were febrile and had lower abdominal pain, suggesting that many of these women had acute rather than subclinical PID. Contradicting these results, Stern et al. did not find an association between the presence of plasma cells in the endometrium and chlamydial infection in a study using nested PCR to detect the presence of *C. trachomatis*.¹²⁰ Paavonen compared endometrial pathology with laparoscopy-confirmed PID among 27 women with suspected acute PID.¹⁰⁸ While the sensitivity of the finding of plasma cells for the diagnosis of acute PID was 89%, the specificity was only 67%; one-third of women with plasma cell endometritis did not have laparoscopically-confirmed acute PID.

What is the significance of endometrial plasma cells? Traditionally, plasma cells have not been considered as normal constituents of the endometrium.¹²² The presence of plasma cells in the endometrial sample may be unappreciated, perhaps because their appearance is similar to lymphocytes and stromal cells. As such, special stains, particularly methyl-green pyronine, are useful to highlight the presence of plasma cells. Plasma cells appear to be commonly found in the endometrium, and their presence in low numbers and in the absence of other inflammatory cells (e.g., neutrophils), may not signify an ongoing inflammatory process. Among women 3 months postpartum, Andrews et al. identified plasma cell endometritis in 39% of 506 specimens.¹²³ This high rate of plasma cell endometritis in post partum women raises the suspicion that this endometrial histopathologic diagnosis may not represent a pathogenic process. In Wiesenfeld's study of 556 women without clinical evidence of acute PID, infections with *N. gonorrhoeae*, *C. trachomatis* or bacterial vaginosis were not associated with plasma cell endometritis.¹¹⁰ A cross-sectional study of women with proven fertility undergoing tubal ligation (i.e., low risk for PID) found that endometrial plasma cells were identified in one-third of the asymptomatic fertile women and were not associated with lower genital tract infection.¹²⁴ A further analysis of the postpartum cohort by Andrews et al. did not demonstrate an association between bacterial vaginosis and plasma cell endometritis; in fact, nearly identical proportions of women with and without bacterial vaginosis had plasma cell endometritis (39.8% and 39.2%, respectively).¹²⁵ Thus, plasma cells can be commonly found in endometrial samples from healthy women and their presence (at least in small numbers) may not represent ongoing upper genital tract inflammation.

The most comprehensive evaluation of endometrial histopathology in women with PID has been performed by Kiviat et al.¹¹¹ Sixty-nine women with clinically suspected acute PID underwent endometrial biopsy, laparoscopy, and

endosalpingeal cytology along with cultures from the cervix, endometrium, fallopian tube, and cul-de-sac. Several histologic features of the endometrium were analyzed according to the presence of upper genital tract infection and salpingitis. The best histologic criteria that predicted upper genital tract infection and salpingitis was the combined presence of at least five neutrophils per 400x field in the endometrial surface epithelium and one or more plasma cells per 120x field of endometrial stroma. These stringent criteria had a sensitivity of 92% and a specificity of 87% for predicting PID. A number of studies utilizing endometrial histology in PID studies have used these criteria to diagnose endometritis.^{110,126–128} In Wiesenfeld's study of women without acute PID, lower genital tract infection with gonorrhea, chlamydia, or bacterial vaginosis was associated with endometritis using the criteria described by Kiviat et al. but was not associated with plasma cell endometritis.¹¹⁰ As these criteria are the best validated, future studies should examine the endometrium for the presence of both neutrophils and plasma cells as previously outlined.¹¹¹ Histopathologic changes in the endometrium of women with subclinical PID need to be correlated with long-term outcomes (i.e., infertility) to determine the optimum histologic criteria of subclinical PID.

CLINICAL FINDINGS IN WOMEN WITH SUBCLINICAL PID

The clinical diagnosis of acute PID is imprecise, with the sensitivity of clinical criteria of approximately 70%.^{129,130} Given the difficulty in confirming acute PID, the task to identify women with subclinical pelvic infections is challenging. Cates et al. attempted to identify clinical predictors of subclinical PID by comparing characteristics of women with tubal infertility who had a history of overt PID to characteristics of those with infertility without a prior known history of acute PID (subclinical PID).¹³¹ Sociodemographic characteristics of women with subclinical PID were more similar to those of fertile women than of women with post-PID infertility. Reports of number of sexual partners, illicit drug use, and douching were identified in women with subclinical PID at rates intermediate between the rates in fertile women and women with infertility due to overt PID. Wiesenfeld et al. also conducted a study comparing the characteristics, clinical findings, and microbiology of women with subclinical and acute PID. Several demographic characteristics of women with subclinical PID were found at intermediate rates between those in women with acute PID and without PID, including age, race, and education. However, no strong predictors were found that could aid in the identification of women with subclinical PID.

Given the broad range and severity of symptoms of acute PID, clinical findings have limited predictive value for acute PID.³ Some have suggested that subtle symptoms and signs of PID may be present and can alert the clinician to con-

sider the diagnosis of subclinical PID. To elucidate these clinical findings, Wiesenfeld et al. compared cohorts of women with acute PID, subclinical PID, and controls.¹³² Subclinical PID was identified in women lacking the diagnostic symptoms of acute PID but who had lower genital tract infection (gonorrhea, chlamydia, or bacterial vaginosis) and had histologic evidence of upper genital tract inflammation. Abdominal pain was reported at slightly higher levels in women with subclinical PID compared to women without PID. Adnexal tenderness was uncommon (11%) in women with subclinical PID but more often found than in controls (3%). While 4–5 times more common in women with subclinical PID than in women without subclinical PID, pelvic organ tenderness was nonetheless uncommon in women with subclinical PID. Microbiologic findings in women with subclinical PID fall between those seen in acute PID and in women without PID. Specifically, endometrial recovery of *C. trachomatis* among women with acute PID, subclinical PID, and controls was 20%, 10% and 2%, respectively (p for trend <0.001). A similar relationship was seen with endometrial *N. gonorrhoeae* (9%, 3%, and 0.3%, p for trend <0.001). The hidden nature of subclinical PID makes the identification of this disease very difficult, even by experienced clinicians.

ENDOMETRITIS IN HIV-INFECTED WOMEN

It may be expected that women with immune dysfunction may be at risk for upper genital tract inflammation. Eckert et al. characterized histologic endometritis in a cohort of human-immunodeficiency virus infected women who did not have clinical evidence of acute PID.¹²⁷ None of the 42 women enrolled in the study were infected with *C. trachomatis* or *N. gonorrhoeae* and 29% had bacterial vaginosis. Histologic endometritis was identified in 16 (38%) of 42 women in the cohort, indicating a high rate of subclinical PID in this cohort of HIV-infected women. These results suggest that subclinical PID in HIV-infected women may be related to pathogens other than (or in addition to) *N. gonorrhoeae* and *C. trachomatis*, or that these women may have altered immune function predisposing to upper genital tract inflammation. Further work is needed to determine the impact of HIV on subclinical PID and the sequelae of subclinical PID in HIV-infected women.

DO ANTIBIOTICS CLEAR ENDOMETRIAL INFLAMMATION?

Further evidence of the abnormal nature of histologic endometritis in women without PID stems from a treatment study of women with subclinical PID by Eckert et al.¹²⁸ This prospective trial enrolled women without clinical evidence of PID who presented for evaluation at an STD clinic or who had abnormal uterine bleeding. Endometrial biop-

sies were performed prior to oral antibiotic treatment, which consisted of single doses of cefixime and azithromycin and a 1 week course of metronidazole. Of the 48 women who had endometrial biopsies before and after treatment, 18 had histologic endometritis before treatment, while only two had endometritis following therapy ($p <0.001$). A study from Alabama demonstrated that antimicrobial therapy impacts microbial flora of the endometrium.¹³³ In a secondary analysis of a trial evaluating the effect of antibiotic therapy on recurrent preterm birth, treatment with metronidazole and azithromycin resulted in enhanced endometrial eradication and reduction of acquisition of *Gardnerella vaginalis* and other gram-negative rods. These results demonstrate that antibiotic therapy can alter the microbial environment and possibly eliminate inflammatory changes of the upper genital tract in women without clinical evidence of acute PID. Moreover, these data indicate that such histologic changes are not normal findings in otherwise healthy women and imply that these histopathologic findings represent ongoing upper genital tract inflammation.

REPRODUCTIVE SEQUELAE OF SUBCLINICAL PID

The data available to date on subclinical PID reveals that this disorder is commonly found in women with seemingly uncomplicated lower genital tract infection. Moreover, the presenting symptoms are nearly uniformly vague and mostly absent. Likewise, physical findings of pelvic infection are absent, making the identification of this condition difficult. There are substantial retrospective data that strongly imply that subclinical PID is associated with subsequent fallopian tube damage, as many women with tubal factor infertility or ectopic pregnancy have evidence of remote infection. Current prospective studies are underway examining whether women with subclinical PID are at risk for tubal factor infertility. Preliminary data indicate that women with subclinical PID are at increased risk for subsequent involuntary infertility.¹¹⁸ Should this hypothesis be proven in a prospective manner, subsequent research would be focused on determining the most favorable therapeutic regimen to optimize fertility in women with subclinical PID. Subclinical PID is present in a substantial proportion of women with otherwise uncomplicated gonococcal or chlamydial cervicitis and bacterial vaginosis. Given the STD epidemic worldwide, far more women may be at risk for infertility from subclinical PID than from acute PID.

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Bacterial Sexually Transmitted Infections in Pregnancy

Jane Hitti and D. Heather Watts

As the spectrum of bacterial sexually transmitted infections (STI) has broadened, the medical and social consequences of STI in pregnancy have become more apparent. Ectopic pregnancy, spontaneous abortion and stillbirth, prematurity, congenital and perinatal infections, and puerperal maternal infections represent outcomes of pregnancy in which bacterial sexually transmitted infectious agents play important etiologic roles. The incidence of many bacterial STI has increased during the last three decades, and the number of pregnancies per year is also increasing; the superimposition of the one factor on the other can be expected to further amplify the effects of bacterial STI on pregnancy and neonatal morbidity.

In general, bacterial STI appear to pose a much greater problem in pregnant adolescents and young adults (less than 25 years) compared to older pregnant women who are more likely to be involved in a stable monogamous sexual relationship at the time of conception. Adolescents have miscarriages more often than do older women—a difference that may be attributable in part to bacterial STI. Although the average age at which women first bear children is increasing, the average age at which women first initiate sexual activity has decreased, and teenage pregnancy remains common in many parts of the world despite the relative availability of contraception. Among sexually active women, whether pregnant or nonpregnant, the prevalence of many bacterial STI agents, such as *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, is highest among women younger than 25 years. The younger the patient, the greater is the likelihood that any given infection is a primary infection. Although immunity to most bacterial STI agents is not well defined, it is likely that, in general, primary infections cause the greatest morbidity.

The two classic venereal agents, *N. gonorrhoeae* and *Treponema pallidum*, have pronounced effects on pregnancy. Fortunately, measures for the diagnosis and management of these infections in pregnancy are readily available and routinely employed where resources permit. Introduction of such measures still remains a major achievable goal in resource-limited settings and in subpopulations that may not access

prenatal care consistently in developed countries. Certain bacterial STI pathogens such as *C. trachomatis* are even more common during pregnancy, are more difficult to diagnose without advanced technology such as polymerase chain reaction (PCR), and currently represent a greater dilemma to the obstetrical care provider in resource-limited settings.

Molecular methods to detect bacteria by PCR have identified microorganisms that are not cultivable using conventional microbiological techniques. These methods promise to greatly increase our understanding of the scope of bacterial STI and possibly also infectious causes of pregnancy complications. On the horizon, novel bacterial STI agents such as *Mycoplasma genitalium*, *Leptotrichia*, and other uncultivable organisms may prove to be important infections in pregnancy. However, the prevalence of these agents in pregnancy and their effect of pregnancy outcome is as yet largely undefined.

Infections of the placenta, chorioamnion membranes, fetus, uterus, and fallopian tubes make the effects of bacterial STI on pregnancy particularly important (Chapter 79). Infection prior to pregnancy can influence the process of implantation, causing infertility and ectopic pregnancy. Infection during pregnancy can produce spontaneous abortion, chorioamnionitis, amniotic fluid infection, preterm birth, and congenital (fetal) infection. Genital infection present at delivery can cause maternal and neonatal infections.

Pregnancy modifies the manifestations of many bacterial STI and presents unique problems for diagnosis and management. Some agents, such as *Candida albicans*, produce disease more commonly during pregnancy. The susceptibility of the pregnant host to infection may be enhanced, owing either to alterations in host defense mechanisms or to changes in anatomic structure.

ALTERATIONS OF HOST-PARASITE RELATIONSHIPS DURING PREGNANCY

■ IMMUNOLOGIC CHANGES

Immunologic rejection of the fetus does not normally occur during pregnancy, possibly in part because of suppression of

maternal immunocompetence. Suppressed maternal immune function may in turn affect the natural history of many infectious diseases. For instance, higher attack rates or more severe morbidity has been recorded for pneumococcal pneumonia,¹ candidiasis,² and malaria³ in the pregnant host than in the nonpregnant host. Immunologically mediated diseases caused by infectious agents may lessen in severity during pregnancy; for example, in the pre-antibiotic era it was observed that symptomatic syphilis was ameliorated during pregnancy.⁴ Animal studies also support the notion that pregnancy interferes with maternal defense mechanisms through immune suppression.^{5,6}

Factors other than immunosuppression also may contribute to the increased maternal susceptibility to certain infections during pregnancy. For example, excessive mortality from bacterial pneumonia during pregnancy has been attributed to altered pulmonary mechanics, and the increased susceptibility to renal infection during pregnancy may be related to changes in ureterovesicular muscular tone induced by high levels of progesterone or to partial ureteral compression by the gravid uterus.

ANATOMIC ALTERATIONS IN PREGNANCY

The anatomy of the genital tract changes dramatically during pregnancy. Figure 80-1 illustrates the relationship of the cervix and mucus plug, chorioamnion, and placental bed as seen in late pregnancy. Vaginal walls become hypertrophic and engorged with blood. The glycogen content of the vaginal epithelium increases, and the intravaginal pH significantly decreases during pregnancy.⁷ These changes probably influence vaginal microbial flora. The cervix hypertrophies and a larger area of columnar epithelium on the exocervix is exposed to microorganisms.⁸ Similar cervical anatomic changes are evoked among nonpregnant women by oral contraceptives and have been associated with an increased prevalence of infection with *C. trachomatis* and *N. gonorrhoeae*.⁹ It is not certain whether the higher prevalence of chlamydial and gonococcal infections in nonpregnant women with cervical ectopy is due to increased susceptibility to infection or enhanced cervical shedding among previously infected women or both. The increased area of cervical ectopy during pregnancy also may predispose the cervix to infection, but this has not been well studied. The cervix secretes highly viscid mucus during pregnancy, forming the so-called mucous plug. This mucus is generally believed to limit the access of microorganisms into the uterus, but little research has been done to study the actual effectiveness of cervical mucus as a physical or antimicrobial barrier.¹⁰ Fetal growth is accommodated by uterine growth and by tremendous enlargement of uterine vessels. The risk of salpingitis decreases during pregnancy, especially after the twelfth week,¹¹ and the risk of chorioamnionitis and amniotic fluid

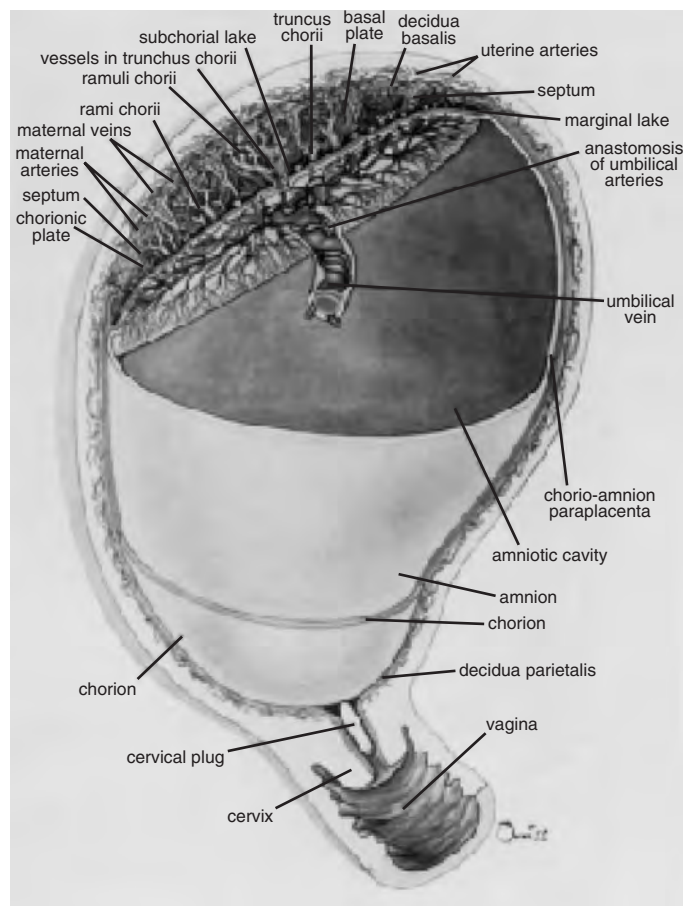


FIGURE 80-1. The relationship within the gravid uterus of the mucus plug, fetal membranes (chorion and amnion), decidua, and placenta. (With permission from JD Boyd and WJ Hamilton, *The Human Placenta*.)

infection increases after the sixteenth week of gestation.¹² After the twelfth gestational week, the uterine cavity becomes obliterated as the chorioamnion becomes juxtaposed with the decidua vera. The risk of infection of the uterine cavity and fallopian tubes is diminished by the elimination of this space. By the sixteenth week, the chorioamnion overlies the cervical os, which may be a factor in the increasing risk of chorioamnionitis during middle and late pregnancy.

The human placenta is of fetal origin and is directly perfused by maternal blood. The trophoblastic placental epithelium projects into the maternal vascular system. This trophoblastic layer regulates fetal uptake of many substances. Anatomically, two layers of trophoblastic epithelium are present, an inner multicellular stratified layer (cytotrophoblast) and an outer unicellular syncytial layer (syncytiotrophoblast). These layers can be seen in (Fig. 80-2). With advancing gestation, Langhan's layer becomes less noticeable but does not regress completely. Lying within the stroma of the mature placenta are placental macrophages that act as a first line of fetal defense to transplacental infection.

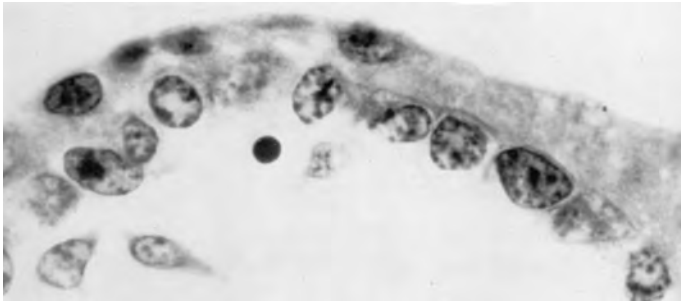


FIGURE 80-2. Photomicrograph of the human triphoblast illustrating the outer (maternal) syncytiotrophoblast on the convex surface; and inner (fetal) cytotrophoblast of Langhan's layer. (With permission from JD Boyd and WJ Hamilton, *The Human Placenta*.)

ALTERATIONS IN CERVICOVAGINAL MICROBIAL FLORA DURING PREGNANCY

The vaginal flora is a heterogeneous ecosystem of anaerobic and facultative bacteria.¹³ Several studies have found that during pregnancy, the number of bacterial species present in the vagina decreases, particularly the number of anaerobic species, while the prevalence and the quantity of lactobacilli increase and the rate of carriage of Enterobacteriaceae, group B streptococci (GBS), and other facultative bacteria remains unchanged. The mechanisms that may promote the reported changes in vaginal flora might include changes in the vaginal pH, glycogen content, and vascularity of the lower genital tract, as described above. Following delivery, an increase in rates of isolation of *Escherichia coli* and *Bacteroides* species (which may promote puerperal endomyometrial infections) has been reported, but this observation also requires confirmation.¹⁴

ECTOPIC PREGNANCY

Infertility and ectopic pregnancy are recognized consequences of salpingitis. Two sexually transmitted organisms, *N. gonorrhoeae* and *C. trachomatis*, produce the majority of cases of primary salpingitis (see Chapter 56). The risk of ectopic pregnancy increases about 10-fold after an initial episode of salpingitis. The incidence of ectopic pregnancy has increased fivefold since 1970 in the United States, and this trend has also been observed in Sweden, Canada, and England.¹⁵ It is likely that this rising incidence of ectopic pregnancy is due in part to an increasing incidence of gonococcal and chlamydial infections and of resulting tubal infections. Ectopic pregnancy and infertility are discussed further in Chapter 79.

POSTABORTAL INFECTIONS

Bacterial STI and other vaginal infections are frequently detected among women presenting for elective termination of pregnancy.¹⁶ *C. trachomatis*, *N. gonorrhoeae*, and bacterial

vaginosis (BV) have each been associated with an increased risk of febrile morbidity after surgical abortion. In addition, infection rates after abortion were reduced with routine screening and treatment, if indicated, for both *C. trachomatis* and BV.^{17,18} Routine screening for *N. gonorrhoeae*, *C. trachomatis*, and BV is indicated in most populations undergoing surgical abortion. Whether bacterial STIs are a risk factor for pelvic infections after medically induced abortions has not been studied,¹⁹ but screening similar to that done before surgical abortion would seem reasonable, since suction procedures are still required in a small number of women after medical treatment.

INTRAUTERINE INFECTION

Intrauterine infection can result from either hematogenous or ascending microbial spread. Other routes of spread such as extension from infection in areas adjacent to the uterus occur rarely. A hematogenous origin appears to be the major route of spread for organisms present in maternal blood, such as *T. pallidum* or *Listeria monocytogenes*. Hematogenous infection initially involves the placenta, producing the characteristic pathologic lesion of villitis. Placental macrophages likely serve as the initial antimicrobial defense in this situation.

Ascending infection by microorganisms present in the cervix or vagina can occur through intact or compromised fetal membranes, producing the characteristic pathologic lesion of chorioamnionitis and the syndrome of amniotic fluid infection. The integrity of the chorioamnion and the antimicrobial activity of amniotic fluid likely serve as the first line of fetal defense in this situation.

HEMATOGENOUS INFECTION

Only rarely does maternal bacteremia give rise to placental or fetal infection. The nature of the defense mechanisms responsible for protection of the developing placenta and fetus from bacteremic spread is not presently known. It appears that microbial agents inhibited primarily by a cell-mediated immune response are more likely to establish placental infection than are agents inhibited primarily by a humoral immune response, suggesting either that pregnant women are most susceptible to systemic spread of those agents that are inhibited by cellular immunity or that placental defense mechanisms are less effective against such microorganisms.

Microorganisms arrive at the placental bed within lymphocytes, monocytes, or neutrophils, or they may not be cell associated. Fetal defense mechanisms during placental infection include placental macrophages and local production of immune factors such as antibody and cytokines. The immune role of the trophoblast is not well understood, but since this epithelium possesses Fc receptors for

immunoglobulin and unique antigenic determinants and secretory products that regulate lymphocyte reactivity in vitro, an important effect on the maternal immune response seems likely.²⁰ Placental histopathology following infection with *T. pallidum* serves to illustrate the range of responses detectable in this tissue. *T. pallidum* infected placentas are inappropriately large with focal proliferative villitis and vasculitis with areas of plasma cell infiltration and Langerhans' giant cell formation²¹ (Fig. 80-3).

With hematogenous infection, placental infection generally precedes fetal infection, although theoretically it is possible for organisms to traverse the chorionic villi directly by pinocytosis or placental leaks or within maternal leukocytes. The fetal immune response to placental infection may be effective enough to limit infection to this site. Such circumscribed infection has been seen in syphilis.²² Often, however, spread from infected placental sites to the fetus occurs either by involvement of fetal blood vessels or by extension from placenta to fetal membranes with consequent infection of the amniotic fluid.

The manifestations of fetal infection depend to a great extent on the gestational age at which infection occurs. The infectious agents capable of transplacental infection can produce similar effects. Abortion, stillbirth, preterm birth, growth restriction, congenital disease, and persistent post-natal infection have all been described following infection with *T. pallidum*, the protozoan *Toxoplasmosis gondii*, and with congenital viral infections such as cytomegalovirus and rubella. The similarities in outcome with these disparate infectious agents suggest a common pathway in fetal response to transplacental infection, with severity largely mediated by gestational age at exposure.

ASCENDING INFECTION: CHORIOAMNIONITIS AND AMNIOTIC FLUID INFECTION

Acute inflammation of the fetal membranes (chorioamnionitis) and umbilical cord (funisitis) is seen even more frequently than hematogenous placentitis and often is associated with preterm birth, prolonged rupture of the

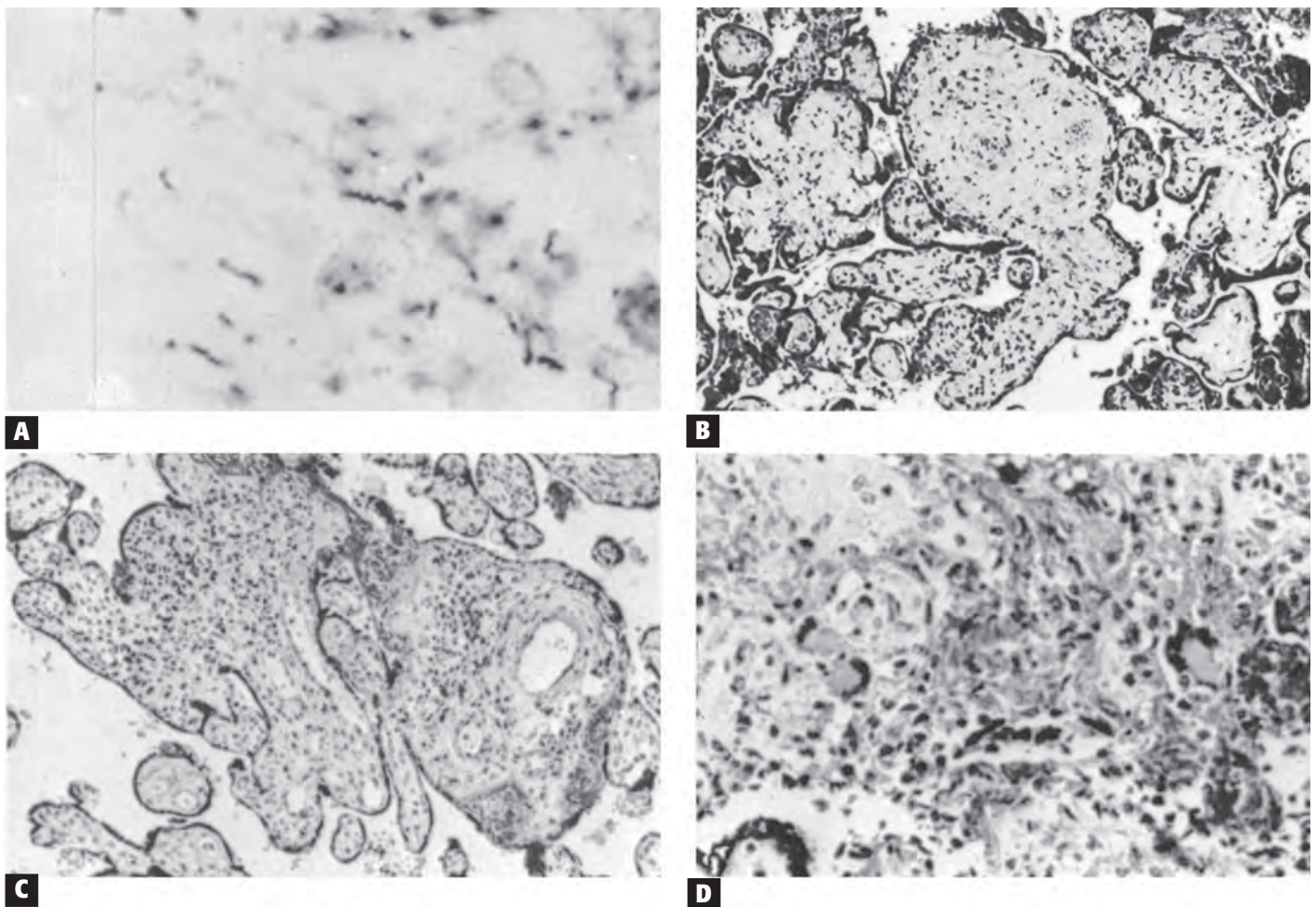


FIGURE 80-3. Placental abnormalities of congenital syphilis. **A.** Typical corkscrew morphology of *T. pallidum* (Warthin-Starry, $\times 2000$ magnification); **B.** Endovascular proliferation and villitis (H&D stain, $\times 150$ magnification); **C.** Villitis with plasma cell infiltration (H&E stain, $\times 300$ magnification); **D.** Proliferative villitis with granulomatous and giant cell formation (H&E stain, $\times 400$ magnification). (Courtesy of G. Altshuler.)

membranes (PROMs), intrapartum fever, and perinatal sepsis. Chorioamnionitis is defined histologically by the presence of polymorphonuclear leukocytes (PMNs) in the membranes—usually within the chorion²³; in some cases this acute inflammation is seen only on the fetal side of the discoid placenta. The migration of maternal PMNs from the intervillous spaces or of fetal PMNs through the amnion suggests transcervical infection of amniotic fluid rather than primary hematogenous infection. **Figure 80-4** diagrammatically illustrates the patterns and stages of the maternal and fetal inflammatory response to amniotic fluid infection.

The etiology of acute chorioamnionitis is in many cases unknown. Delayed delivery following PROM is an important correlate of acute chorioamnionitis, but most cases of

chorioamnionitis are not associated with PROM as an antecedent event.¹² The correlation of chorioamnion or amniotic fluid culture results with histologic chorioamnionitis in several studies is shown in **Table 80-1**.^{23–29} The varied rate of isolation of microorganisms among women with histologic chorioamnionitis can be accounted for by differences in patient populations and specimen handling and sampling, variable use of culture techniques to isolate genital mycoplasmas and fastidious anaerobes, and increasing rates of antibiotic use before delivery in the last decade. Limited microbiologic studies have strongly linked *Ureaplasma urealyticum* to chorioamnion inflammation. The organisms isolated from the chorioamnion are similar to those found in the vagina of women with BV, and in fact, when evaluated, positive chorioamnion and amniotic fluid cultures were associated with BV.²³

Perinatal bacterial infections, especially those occurring within the first 48 hours of life, are commonly acquired by ascending infection *in utero*. Russell¹² found evidence of neonatal sepsis in the first 48 hours of life in almost one-quarter of neonates whose placentas showed chorioamnionitis; neonatal sepsis was rare in the absence of placental inflammation. This and subsequent studies provide compelling data linking chorioamnionitis, amniotic fluid infection, preterm birth, and perinatal sepsis.

Bacteria recovered from amniotic fluid of patients with chorioamnionitis include facultative organisms such as GBS, enteric gram-negative rods, *Haemophilus influenzae*, and strict anaerobic organisms such as peptostreptococci, *Fusobacterium* spp., *Bacteroides* spp., and *Prevotella bivia*.^{30–32} These infections are often polymicrobial, resembling the spectrum of organisms found in the upper genital tract of women with salpingitis or postpartum endometritis, and also

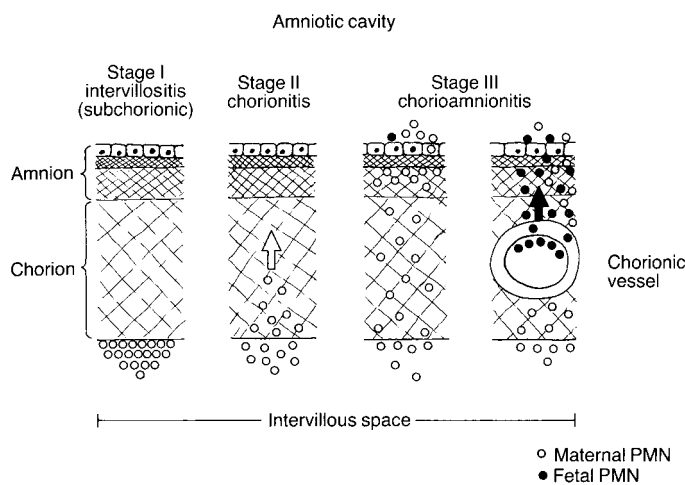


FIGURE 80-4. The stages and patterns of maternal and fetal response to amniotic fluid infection.

Table 80-1. Frequency and Relative Risk of Positive Placental Cultures With and Without Histologic Chorioamnionitis

Author	Chorioamnionitis	No Chorioamnionitis	Relative Risk	95% CI
Pankuch et al. ²⁴	18/25 (72%)	6/39 (15%)	14.1	3.6–60
Hillier et al. ²³	21/29 (72%)	14/65 (22%)	7.2	2.7–19
Quinn et al. ²⁵	10/14 (71%)	8/29 (28%)	6.5	1.3–3.5
Kundsin et al. ²⁶	32/84 (38%)	21/146 (14%)	3.7	1.8–7.3
Svensson et al. ²⁷	7/10 (70%)	31/69 (45%)	1.6	0.5–5.0
Zlatnik et al. ²⁸	26/51 (51%)	12/44 (27%)	3.4	1.2–10.0
Hillier et al. ²⁹	32/101 (32%)	33/167 (20%)	1.9	1.1–3.5

CI, confidence interval.

include many of the organisms found in the vagina of women with BV. The relationship of amniotic fluid infection, membrane infection, and histologic chorioamnionitis to preterm birth is discussed in more detail below.

The risk of chorioamnionitis is generally highest among patients of low socioeconomic status who have not received prenatal care.^{33,34} These demographic characteristics of patients with chorioamnionitis are similar to those of patients with bacterial STI.

FETAL WASTAGE, PRETERM BIRTH, AND PRETERM RUPTURE OF MEMBRANES

Pregnancy loss and preterm birth comprise a spectrum of adverse pregnancy outcomes. The preterm parturition syndrome is a pathologic process and does not mimic the events of normal term spontaneous labor.³⁵ Rather there are multiple contributing pathways to preterm parturition, including infectious and inflammatory causes. Spontaneous abortion, stillbirth, and preterm birth may all be caused by infection. However, the proportion of these events attributable to infection is not yet well defined and no doubt varies in different populations. Spontaneous abortion, defined as the delivery of a previable fetus before the twentieth week of gestation and weighing less than 500 g, is a frequent outcome in pregnancy. It is estimated that 50% of fertilized ova fail to implant, and of those which do implant, at least 15–30% subsequently abort.³⁶ The majority of losses occur in the first trimester; less than 3% of women with normal fetal cardiac activity by ultrasound at 7–12 weeks experience a loss by 20 weeks.³⁷ This distinction is clinically useful, since first-trimester abortions are frequently associated with phenotypic or chromosomal fetal abnormalities. Second-trimester abortions and stillbirths (weight \geq 500 g, gestation \geq 20 weeks) are more often associated with an otherwise normal fetus. Genital infections may thus be a relatively more important cause of fetal wastage in the second and third trimesters than in the first trimester, although there are some data suggesting BV is associated with implantation failure after in vitro fertilization³⁸ and first trimester abortion.³⁹

Low birth weight, defined as \leq 2500 g, usually results from a preterm birth but can also be caused by intrauterine growth restriction. Both conditions have been associated with infectious agents. The proportion of cases of preterm birth caused by infection versus that caused by noninfectious factors (e.g., diet, smoking, hypertension) remains to be defined. Among preterm births, approximately one-third are obstetrically indicated deliveries for maternal or fetal conditions such as hypertension or fetal distress, one-third are related to progressive preterm labor, and one-third are related to preterm PROM. As discussed in this section, a high proportion of early preterm labor leading to delivery and a majority of cases of preterm PROM appear to be related to infection.

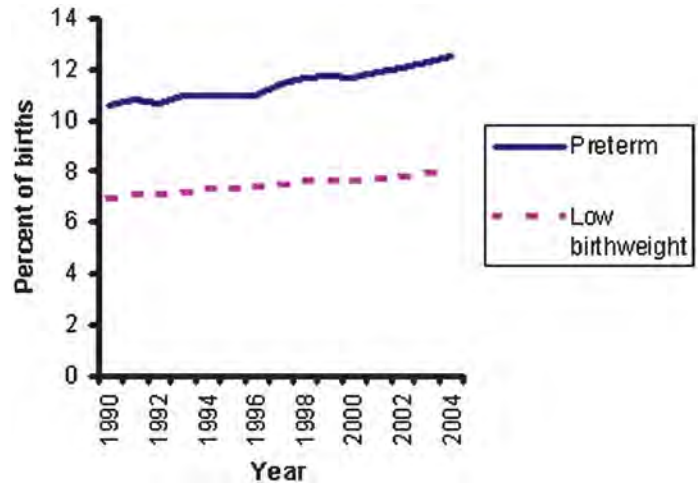


FIGURE 80-5. Steadily rising rates of preterm birth (< 37 weeks' gestation) and low birth weight (< 2500 g), United States, 1990–2004. Data from National Center for Health Statistics.²⁷¹

Despite a remarkable decline in the perinatal mortality rate in the United States in the last 40 years, the preterm birth rate has remained essentially unchanged, and has actually increased over the past decade⁴⁰ (Fig. 80-5). Between 70% and 80% of all perinatal deaths that are not attributable to congenital malformation occur following preterm birth. Since prematurity and perinatal mortality are so strongly linked, it appears that the decline in perinatal mortality achieved during the last 30 years must be attributable to improvements in perinatal and neonatal care and not to improvements in preterm birth rates. The decline in perinatal mortality has thus been achieved as a result of enormously burgeoning costs of perinatal and neonatal intensive care.⁴⁰ The elucidation of preventable causes of preterm birth should ideally lead to interventions that would further reduce both the perinatal mortality and the long-term morbidity rate seen in some infants who survive preterm delivery and substantially decrease health-care costs. Unfortunately, prevention efforts focused on treating infectious causes of prematurity thus far have had little or no impact on preterm birth rates.

In recent years, increasing attention has been brought to racial disparities in health outcomes. In the United States, there is a persistent and troubling disparity in pregnancy outcomes between African American and white women, with the rates of low birth weight, very low birth weight (< 1500 g), and infant mortality among African Americans over twice that seen in whites^{41,42} (Fig. 80-6). The increased rates of these adverse outcomes are not readily explained by socioeconomic or other risk factors alone. Environmental factors and other stressors may contribute to the increased rate of preterm birth and infant mortality among African Americans in the United States. One cross-sectional study has shown that microenvironmental factors such as neighborhood stability are associated with BV in pregnancy, among an urban,

predominantly African American population.⁴³ A secondary analysis of associations between several lower genital tract infections and preterm birth in the vaginal infections and prematurity cohort demonstrated that the proportion of preterm birth associated with infection was considerably higher among African Americans compared to white or Hispanic women⁴⁴ (Table 80-2). Clearly, the underlying basis for the racial disparity in preterm birth requires further investigation in order to address this health inequity and improve pregnancy outcomes.

Intriguing data implicating infectious agents in prematurity were serendipitously derived from studies over 40 years ago by Elder et al.⁴⁵ In the course of investigating the role of urinary tract infection in prematurity, 279 nonbacteriuric women seen prior to 32 weeks of gestation were alternately allocated to treatment with 6 weeks of oral tetracycline at 1 g per day or with placebo. The patients in both groups were of comparable age, gravidity, race, and marital status. As seen

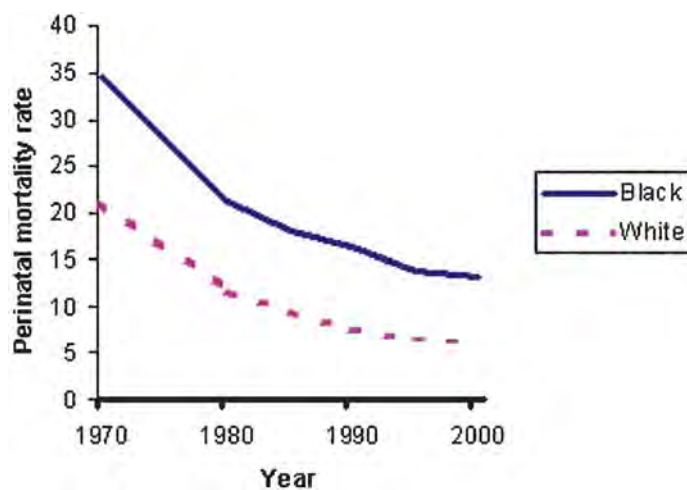


FIGURE 80-6. Trends in perinatal mortality by race. Perinatal mortality is defined as late fetal (≥ 28 weeks) plus neonatal (≤ 28 days age) deaths per 1000 live births plus late fetal deaths. Data from National Center for Health Statistics.²⁷¹

in Table 80-3, even in those without urinary tract infection, the tetracycline-treated group had significantly longer gestations, fewer preterm infants, fewer episodes of postpartum fever, and fewer neonatal complications than the placebo-treated group. Although tetracyclines are now considered contraindicated in pregnancy, these data are intriguing because the salutary effect of long-term broad-spectrum antibiotics suggested the presence of unidentified susceptible microorganism(s) that could have contributed to prematurity in the placebo group. *C. trachomatis* and BV-associated organisms are examples of potential lower genital tract pathogens susceptible to tetracycline. In a subsequent treatment trial, Kass et al.⁴⁶ randomized 148 women to erythromycin therapy given for 6 weeks in the third trimester or to placebo. Infants in the placebo group weighed less than infants in the treatment group (3187 versus 3331 g, $p = 0.04$). A more recent study in an African population with a high prevalence of bacterial STI showed a modest reduction in low birth weight (4.0% versus 9.2%, $p = 0.08$) and postpartum endometritis (3.8% versus 10.4%, $p = 0.05$) and a higher mean birth weight (3209 versus 3056 g, $p = 0.01$) among 200 women treated at 28 to 32 weeks' gestation with a single 250-mg intramuscular dose of ceftriaxone compared with 200 women randomly assigned to placebo.⁴⁷ A large randomized trial of presumptive STI treatment versus iron, folate, and syphilis treatment among pregnant Ugandan women demonstrated significant reductions in preterm birth and neonatal mortality.⁴⁸ However, a second multicenter randomized trial of universal treatment of pregnant African women with metronidazole/erythromycin at 24 weeks' gestation and in labor did not prevent histologic chorioamnionitis and preterm birth; the lack of observed treatment effect in this study may be related to the relatively late gestational age at treatment and/or the choice of antibiotic regimen.⁴⁹ The effects of universal antibiotic treatment on birth weight, at least in some studies, suggest that prematurity may sometimes result from unrecognized maternal infection, perhaps

Table 80-2. Proportion of Preterm Birth Associated with Lower Genital Infection,^a Stratified by Racial

Group	N	Preterm Birth Rate		Prevalence of Infection ^a (%)	Total Preterm Birth Rate (%)	Population Attributable Risk Percent (%)
		Infection Present ^a (%)	Infection Absent (%)			
African American	4479	7.9	5.1	47.2	6.4	20.7
Hispanic	3567	5.1	3.3	24.5	3.8	11.6
White	3864	5.5	4.2	17.0	4.4	5.0

^aLower genital infection includes *C. trachomatis*, *T. vaginalis*, and bacterial vaginosis (Hitti et al.⁴⁴).

Table 80-3. Effect of 6 Weeks of Oral Tetracycline Given Prior to 32 Weeks on Outcome of Pregnancy in 279 Nonbacteriuric Women

Measurement	Tetracycline (N = 148)		Placebo (N = 131)		p
Mean gestation (weeks)	39.1		38.1		<0.025
Mean birth weight (g)	3277		3141		NS ^a
	Number	%	Number	%	
Premature liveborn	8	(5.4)	20	(15.2)	<0.025
Stillborn	2	(1.4)	1	(0.8)	
	Number/Total	%	Number/Total	%	
PROM	14/142	(10)	16/128	(13)	NS
Postpart fever	8/142	(6)	15/129	(12)	<0.001
Neonatal resuscitation	11/140	(8)	24/125	(19)	<0.005
Respiratory distress	1/140		9/125	(7)	<0.05

From Elder HA et al. The natural history of asymptomatic bacteriuria during pregnancy: The effect of tetracycline on the clinical course and the outcome of pregnancy. *Am J Obstet Gynecol* 1971; 111: 441.

^aNonsignificant.

bacterial STI involving the lower genital tract. However, both the prevalence of bacterial STI and the rate of infection-associated preterm birth would have to be remarkably high to justify further exploration of a strategy of universal antibiotic treatment for STI to decrease preterm birth. There are other potential disadvantages to universal treatment strategies, not the least of which is the potential to increase antibiotic resistance among bacterial STI and other pathogens.

Many studies have been done comparing the rate of preterm birth and preterm PROM between women with or without specific bacterial lower genital tract infections either early in pregnancy or on admission for delivery. These studies will be discussed in detail below in sections dealing with specific infections. Conclusions from the studies are often limited because only one or a few genital microorganisms could be evaluated in each study. Concomitant risk factors for preterm birth that may be more prevalent among women with genital infections, such as smoking or drug use, often were not considered as potential confounders. Further, if gestational age at enrollment may have been later than the gestation when complications sometimes occur, this could lead to ascertainment bias and underestimation of any association between infection and adverse pregnancy outcome. Despite these limitations, several lower genital tract infections, including *N. gonorrhoeae*, *C. trachomatis*, BV, and *T. vaginalis* have been

associated with increased risk of preterm birth. In studies of women with gonorrhea, chlamydial infection, and BV, rates of preterm birth have been reduced among treated compared with untreated women, at least in some populations. Thus, routine screening and treatment of certain genital infections in high-risk populations has the potential to lead to a reduction in the rate of preterm birth.

Increased rates of chorioamnion inflammation and infection and amniotic fluid infection among preterm compared with term deliveries also imply an infectious etiology. The increased rate of neonatal sepsis among preterm infants may be related not only to a less mature immune system but also to frequent exposure to microorganisms in placental and amniotic fluid infection that caused the preterm delivery.

Russell¹² clearly documented the correlation of acute histologic chorioamnionitis with preterm birth. [Figure 80-7](#) illustrates the prevalence of chorioamnionitis by gestational age at delivery. Chorioamnionitis was found in 95% of pregnancies at less than 25 weeks' gestation, 35–40% of pregnancies from 25 to 32 weeks, 11% of pregnancies from 33 to 35 weeks, and only 3–5% of term pregnancies. The mean birth weight of neonates in the chorioamnionitis group was much lower than in a control group without chorioamnionitis (2811 versus 3320 g, $p < 0.001$). The lower birth weight of those with chorioamnionitis was appropriate for gestational age and not attributable to intrauterine growth

restriction. Although chorioamnionitis frequently can be asymptomatic, especially when present near term, two-thirds of the group with chorioamnionitis had intrapartum fever, PROMs, and/or preterm labor.

Many subsequent studies have confirmed the association between histologic chorioamnionitis, chorioamnion infection, and preterm birth.^{12,23,24,26,27,29,50–52} These studies are

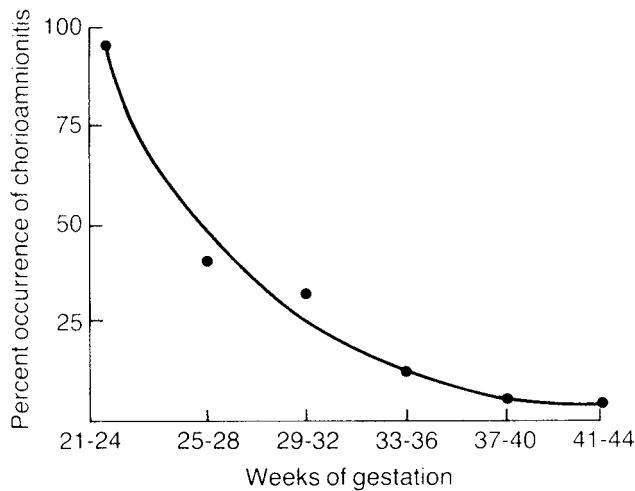


FIGURE 80-7. Rate of chorioamnionitis among deliveries at the stated gestational lengths. The risk of chorioamnionitis is extremely high in preterm deliveries.

summarized in Table 80-4. As discussed earlier, microorganisms are isolated more frequently from between the chorioamniotic membranes or from biopsy of placentas with histologic inflammation (see Table 80-1). The frequency of histologic chorioamnionitis decreases from over 90% of placentas delivered before 24 weeks' gestation to about 10% at term. Microorganisms isolated most frequently from the placental membranes are *U. urealyticum*, *Gardnerella vaginalis*, GBS, *Escherichia coli*, anaerobic gram-positive cocci, *Bacteriodes spp.*, *Prevotella bivia*, and *Fusobacterium nucleatum*.

Among afebrile women presenting in preterm labor without other obvious cause, bacteria have been isolated from the amniotic fluid obtained by amniocentesis in 131 (10%) of a total of 1275 women in several studies (range, 0–19%).^{31,53–68} The range of results can be explained by differences in enrollment criteria, interval from presentation to amniocentesis, gestational age distribution, laboratory methods, and the increasingly common use of antibiotics prior to study enrollment for prevention of neonatal group B streptococcal sepsis. The majority of women with positive amniotic fluid cultures delivered within 2 days (range, 0–4 days) of admission despite tocolytic therapy, while women with negative cultures delivered on average 29 days (range, 25–51 days) after amniocentesis. Women with positive cultures had a lower gestational age at amniocentesis than those with negative cultures. The curve

Table 80-4. Relationship of Positive Chorioamnion Cultures and Histologic Chorioamnionitis to Preterm Birth

Author	No. with Positive Chorioamnion Culture/Total (%)			95% CI
	Preterm	Term	Odds Ratio	
Hillier et al. ²³	23/38 (61%)	12/56 (21%)	3.8	1.5–9.9
Kundsin et al. ²⁶	61/196 (31%)	40/312T (13%)	3.1	1.9–4.9
Pankuch et al. ²⁴	27/53 (51%)	6/22 (27%)	2.8	0.8–9.4
Svensson et al. ²⁷	8/16 (50%)	33/70 (47%)	1.2	0.3–3.8
Hillier et al. ²⁹	36/112 (32%)	29/156 (19%)	2.1	1.1–3.8
		No. with Histologic chorioamnionitis/Total (%)		
Russell ¹²	123/659 (19%)	269/6846 (4%)	5.6	(4.4–7.1)
Cooperstock et al. ⁵⁰	287/1445 (20%)	817/17342 (5%)	5.0	(4.3–5.8)
Guzick and Winn ⁵¹	80/244 (33%)	253/2530 (10%)	4.4	(3.2–5.9)
Fox and Langley ⁵²	16/34 (47%)	186/836 (22%)	3.1	(1.5–6.5)
Hillier et al. ²⁹	66/112 (60%) ^a	35/156 (22%)	2.1	(1.1–3.8)

CI, confidence interval.

^a≤34 weeks.

of the frequency of amniotic fluid culture positivity by gestational age is similar to that of the frequency of histologic chorioamnionitis or positive membrane culture by gestational age, albeit at a lower level. The higher but parallel frequency of membrane infection or inflammation as compared with amniotic fluid infection suggests that infection ascends via the decidua and membranes with secondary infection of the amniotic fluid. Microorganisms most commonly isolated from the amniotic fluid include *F. nucleatum*, *Bacteroides spp.*, *E. coli*, *GBS*, *U. urealyticum*, *G. vaginalis*, and viridans Streptococcus. Bacteria isolated from the amniotic fluid are similar in distribution to those isolated from the chorioamnion, and in many cases, the same species are found in the vagina with BV.

As the frequency of positive amniotic fluid cultures among women in preterm labor became apparent, investigators began to evaluate the amniotic fluid and vagina for markers of inflammation. Macrophage products including the pro-inflammatory cytokines tumor necrosis factor alpha (TNF- α), interleukin 1 (IL-1), and interleukin 6 (IL-6) in the amniotic fluid have been associated with preterm delivery, positive amniotic fluid culture, and histologic chorioamnionitis.^{64,65,67-76} IL-6 is most consistent in predicting rapid delivery among women in preterm labor, even among those with negative amniotic fluid cultures, suggesting either insensitivity of the culture or infection that is limited to the membranes or decidua. Many investigators believe that pregnancy outcomes for women with a negative amniotic fluid culture but high IL-6 concentration are identical to those for women with a positive amniotic fluid culture.⁷⁷ Recent studies using PCR to detect bacterial ribosomal DNA have demonstrated the presence of bacteria in amniotic fluid of women with elevated IL-6 concentrations and negative amniotic fluid cultures, suggesting that low bacterial concentrations and/or fastidious organisms may contribute to preterm labor in these cases.⁷⁸ *Leptotrichia* species, an uncultivable organism that can be identified only by PCR, has been identified from amniotic fluid in the setting of preterm delivery.⁷⁹ This raises the possibility that other as-yet unidentified organisms may be associated with amniotic fluid infection and preterm birth.

Increased concentrations of pro-inflammatory cytokines in amniotic fluid have also been associated with an increased frequency of neonatal complications. Respiratory distress syndrome, intraventricular hemorrhage, and periventricular leukomalacia have all been detected significantly more frequently, even after adjusting for gestational age at delivery, among neonates born to women with, compared with those without, high concentrations of pro-inflammatory cytokines in the amniotic fluid.⁸⁰⁻⁸² Thus infection-related preterm birth may be doubly damaging, both because of the earlier gestational age of delivery and because of cytokine-mediated complications in the infant.

A monkey model for the study of infection-induced preterm labor has been employed to demonstrate a causal relationship

between experimental intraamniotic infection and preterm delivery.⁸³ Findings from this model are consistent with observations in humans with preterm labor and amniotic fluid infection. Chronically catheterized pregnant rhesus monkeys were inoculated intraamniotically with GBS, and amniotic fluid was sampled serially for levels of GBS, TNF- α , IL-1, IL-6, and prostaglandins E₂ and F_{2 α} . Intraamniotic cytokine levels rose between 9 and 18 hours after infection, with parallel increases in PGE₂ and PGF_{2 α} levels. Increased uterine contractility occurred 10-20 hours after increased cytokine and prostaglandin levels were detected. This delay implies that when women present with preterm labor and amniotic fluid infection, they may have had elevated cytokine levels in the amniotic fluid for several hours or even days. Amniotic fluid and prostaglandin levels in the infected animals were severalfold higher than in control animals in spontaneous labor at term. None of the monkeys with intraamniotic infection developed fever or leukocytosis during labor, consistent with observations in humans presenting in preterm labor with amniotic fluid infection. In a similar design, intraamniotic infusion of IL-1 without bacteria induced preterm labor in all treated animals.⁸⁴ This animal model appears to mimic infection-induced preterm labor in humans, allows serial sampling to determine the sequence and timing of cytokine and prostaglandin production, and should provide a valuable tool for evaluation of interventions such as cytokine inhibitors to arrest infection-induced preterm labor.

In addition to the infection-induced production of cytokines and prostaglandins leading to preterm labor and delivery, infection and the resulting inflammatory response may directly damage the fetal membranes leading to rupture. Preterm PROM with resulting delivery accounts for up to one-third of preterm deliveries and frequently is associated with histologic chorioamnionitis. Pathogens commonly found in the genital tract, such as *Bacteroides spp.*, *GBS*, and *T. vaginalis*, produce proteases that have been shown in vitro to reduce the strength and elasticity of the membranes.^{85,86} In vitro addition of *E. coli* or *GBS* to cultured chorioamnion reduces the bursting pressure of the membranes.⁸⁷ Many bacteria produce phospholipases that may directly damage the membranes or lead to prostaglandin production. Thus, exposure of the membranes near the cervical os to lower genital tract bacteria may lead to direct damage and rupture of the membranes or to ascending infection, causing similar resulting damage as well as an inflammatory response leading to cytokine and prostaglandin production and preterm labor.

Since data implicating infection as a cause of preterm labor and preterm PROM are mounting, addition of antibiotics to standard treatments for these conditions might be expected to prolong pregnancy. However, placebo-controlled studies of antibiotics in addition to tocolytics for preterm labor

Table 80-5. Randomized, Placebo-Controlled Trials of Antibiotics for Preterm Labor with Intact Membranes ≤ 34 Weeks

Author	Antibiotic Regimen	Total <i>N</i>	Prolonged Gest Age	Reduced Neonatal Morbidity	Reduced Maternal Morbidity
McGregor et al. ⁸⁸	Erythromycin	58	No ^a	No	No
Winkler et al. ⁸⁹	Erythromycin	19	9 d ABX	ND	ND
Newton et al. ⁹⁰	Ampicillin Erythromycin	103	No	ND	ND
McGregor et al. ⁹¹	Clindamycin	103	10 d ABX	No	No
Romero et al. ⁹²	Ampicillin Erythromycin	277	No	No	No
Watts et al. ⁹³	Mezlocillin Erythromycin	56	No	No	Yes
Newton et al. ⁹⁴	Ampicillin/sulbactam Indomethacin	86	No	No	ND
Gordon et al. ⁹⁵	Ceftizoxime	117	No	No	No
Cox et al. ⁹⁶	Ampicillin/sulbactam	78	No	No	No
Svare et al. ⁹⁷	Ampicillin Metronidazole	112	20 d ABX	No	No
Kenyon et al. ⁹⁸	Erythromycin Amoxicillin/ clavulanic acid	6295	No	No	Yes
Keuchkerian et al. ⁹⁹	Amoxicillin/sulbactam	96	No	No	No

ABX, antibiotic group.

^aGestation prolonged by 10 d in antibiotic compared to placebo group among subset of women with cervical dilatation ≥ 1 cm at enrollment.

with intact membranes have not shown prolongation of pregnancy^{88–99} (Table 80-5). Since antibiotic levels in the amniotic fluid and the fetus approach or exceed maternal levels and the majority of microorganisms isolated are sensitive to the antibiotics, the infection should be eradicated. However, as shown in the monkey model, contractions are a late finding in the cascade of events leading to preterm birth, and antibiotics at this late stage would not be expected to reverse the cytokine and prostaglandin response. Indeed, lysis of microorganisms during antibiotic treatment actually may increase the inflammatory response. Treatments aimed at blocking the cytokine and prostaglandin response while treating infection must be developed and tested in animal models.

Trials of antibiotic therapy after preterm PROM have yielded more variable results in prolonging pregnancy, probably because the treatments used after preterm PROM have varied considerably^{100–108} (Table 80-6). In particular, the Mercer protocol using ampicillin and erythromycin has been demonstrated to prolong gestation after preterm PROM, particularly among the subset of women colonized with GBS.¹⁰⁷ The proportion of infants delivered more than

1 week after membrane rupture has been higher in the antibiotic treatment group than in the placebo group in several studies, although infant hospital stay was not necessarily shortened. The incidences of fever during labor and of postpartum endometritis also were reduced in the antibiotic treatment group in most studies, and infant sepsis and pneumonia were decreased. These findings have led to consensus among experts to provide antibiotic prophylaxis with a macrolide-containing regimen in the context of preterm PROM.¹⁰⁹

Multiple lines of evidence including epidemiologic studies, data on upper genital tract infection, and animal models implicate lower genital tract infections in the early pathogenesis of a significant proportion of cases of preterm labor and preterm PROM. Since antibiotic treatment of infection-related preterm labor to prolong pregnancy has been largely unsuccessful, and antibiotic adjunctive treatment for preterm PROM is not curative, the best strategy is prevention of these conditions by early detection and treatment of lower genital tract infections before complications occur. Pregnant women should be screened for *C. trachomatis*, *N. gonorrhoeae*,

Table 80-6. Randomized, Placebo-Controlled Trials of Antibiotics in Patients with Preterm Rupture of Membranes

Author	Antibiotic Regimen	Total N	Prolonged Gestation	Reduced Neonatal Morbidity	Reduced Maternal Morbidity
Blanco et al. ¹⁰⁰	Ceftizoxime	306	No	ND	ND
Johnston et al. ¹⁰¹	Mezlocillin Ampicillin	85	Yes	Yes	Yes
McGregor et al. ¹⁰²	Erythromycin	55	No	No	No
Mercer et al. ¹⁰³	Erythromycin	220	No	No	No
Kurki et al. ¹⁰⁴	Penicillin	101		No	No
Lockwood et al. ¹⁰⁵	Piperacillin	75	Yes	No	No
Ernest and Givner ¹⁰⁶	Penicillin	148	No	No	Yes
Mercer et al. ¹⁰⁷	Ampicillin Erythromycin	614	Yes	Yes	ND
Kenyon et al. ¹⁰⁸	Erythromycin Amoxicillin/ clavulanic acid	4826	Yes	Yes	ND

ND, analysis not reported.

syphilis, and *T. vaginalis* on the first prenatal visit and treated if positive. Repeat screening later in pregnancy should be done for women in high-risk groups for bacterial STI or with symptoms.

Women of reproductive age should be educated regarding the importance of early prenatal care, safer sexual practices, and STI screening. Pregnant women and their partners should be counseled on symptoms of preterm labor, safer practices, and measures to avoid acquiring new STI during the pregnancy.

MATERNAL PUERPERAL INFECTION

Puerperal endometritis, the most common maternal postpartum infection, can be divided into early infections occurring within the first 48 hours and late infections occurring from 2 days to 6 weeks after delivery.¹¹⁰ Cesarean delivery greatly increases the risk of early postpartum infection. Without antimicrobial prophylaxis, 36–65% of women who undergo nonelective Cesarean delivery develop infectious morbidity; women delivered by Cesarean are up to 20 times more likely to develop infectious morbidity than are women delivered vaginally. The high infection rate following Cesarean delivery probably results from direct myometrial and peritoneal contamination by organisms present within the amniotic cavity at the time of surgery. Factors that increase microbial contamination of the uterus before delivery such as long duration of labor or rupture of membranes, chorioamnionitis, and number of vaginal examinations

also increase the risk of early postpartum endometritis and puerperal sepsis.

Early postpartum endometritis and bacteremia among women following Cesarean delivery usually are due to the anaerobic and facultative bacteria of the cervicovaginal flora, predominantly but not exclusively those associated with BV¹¹¹ (Table 80-7). Indeed, the presence of BV diagnosed by Gram stain on admission for delivery was an independent risk factor for postpartum endometritis among women undergoing Cesarean delivery (adjusted odds ratio 5.8, 95% confidence interval [3.0–10.9]).¹¹² In a separate study assessing reasons for failure of antibiotic prophylaxis with cefoxiten or cefotetan to prevent postpartum endometritis, only the presence of GBS or enterococci in the upper genital tract (amniotic fluid, decidua, chorioamnionic membranes) at delivery was associated with the development of endometritis.¹¹³ Among women without GBS or enterococci in the upper genital tract at delivery who developed endometritis, microorganisms associated with BV were isolated.

In contrast, late postpartum endometritis, occurring 3 days to 6 weeks after delivery, has been correlated with *C. trachomatis* infection.¹¹⁰ Wager et al.¹¹⁴ found that approximately 30% of pregnant women with untreated antepartum *C. trachomatis* subsequently developed puerperal infection. One-third of these cases had intrapartum fever attributed to chorioamnionitis and two-thirds had late postpartum endometritis. Clinical manifestations of puerperal chlamydial endometritis, like those of nonpuerperal chlamydial endometritis and salpingitis, are generally mild.

Table 80-7. Microorganisms Isolated from the Endometrium via Triple Lumen Catheter and from Blood from 150 Febrile Women with Early Postpartum Endomyometritis

Microorganism	Endometrium(N = 150) (Number, %)	Blood(N = 150) (Number, %)
<i>Facultative</i>		
<i>Streptococcus agalactiae</i> (GBS)	12 (8%)	5 (3%)
Enterococcus	18 (12%)	1 (1%)
Viridans streptococci	11 (7%)	5 (3%)
<i>Staphylococcus aureus</i>	3 (2%)	0
<i>Gardnerella vaginalis</i>	57 (38%)	10 (7%)
<i>Escherichia coli</i>	12 (8%)	2 (1%)
Other <i>Enterobacteriaceae</i>	9 (6%)	0
<i>Haemophilus influenzae</i>	3 (2%)	1 (1%)
<i>Anaerobes</i>		
<i>Prevotella bivia</i>	14 (9%)	4 (3%)
<i>Bacteroides fragilis</i>	3 (2%)	0
<i>Bacteroides</i> species	27 (18%)	2 (1%)
<i>Peptostreptococcus assacharolyticus</i>	22 (15%)	4 (3%)
Other <i>Peptostreptococcus</i> species	43 (29%)	5 (3%)
<i>Clostridium perfringens</i>	4 (3%)	0
<i>Fusobacterium nucleatum</i>	1 (1%)	0
<i>Mycoplasmas</i>		
<i>Ureaplasma urealyticum</i>	107 (71%)	6 (4%)
<i>Mycoplasma hominis</i>	36 (24%)	4 (3%)
<i>Chlamydia trachomatis</i>	10 (7%)	0

Source: From Watts DH et al. Early postpartum endometritis: The role of bacteria, genital mycoplasmas, and Chlamydia trachomatis. *Obstet Gynecol* 1989; 73: 52-60.

Patients are often afebrile, with mild uterine tenderness and usually with no adnexal tenderness. Such minimally symptomatic postpartum chlamydial infections may contribute to the high rate of Chlamydia antibody among women with secondary infertility because of distal tubal obstruction (see Chapter 79).

The frequency of involvement of the fallopian tubes during postpartum pelvic infection is unknown, since no laparoscopic studies have been reported. The observation that peritoneal infection (as assessed by culdocentesis) commonly accompanies postpartum pelvic infection suggests that fallopian tube

infection may not be rare.¹¹⁵ Similarly, the relationship of postpartum pelvic infection to secondary infertility due to tubal scarring is also unknown. Nevertheless, secondary infertility, usually due to tubal obstruction, is a major problem in Africa,¹¹⁶ where the prevalence rates of untreated maternal gonococcal and chlamydial infection and the incidence rates of postpartum pelvic infection are very high. However, in the United States, where the majority of postpartum infections occur after Cesarean delivery, no evidence of an increased rate of impaired fertility has been seen after postpartum endometritis.¹¹⁷

NEONATAL CONSEQUENCES OF SEXUALLY TRANSMITTED DISEASES

Systemic perinatal bacterial infection is acquired *in utero* or during delivery in 1 to 5 per 1000 live births.¹¹⁸ Perinatal bacterial infections are two to three times more common than are perinatal viral and protozoal infections. The past 20 years have shown great reductions in major neonatal pathogens, such as early-onset GBS sepsis¹¹⁹ and ophthalmia neonatorum, as a result of improved screening and treatment protocols. However, as intrapartum prophylaxis for GBS sepsis has become standard of care in the past decade, the dramatic decrease in early-onset GBS sepsis among term infants has unfortunately been accompanied by a concomitant increase in gram-negative sepsis among preterm infants, often with ampicillin-resistant organisms.¹²⁰ This undesirable consequence of a well-intentioned and effective strategy to decrease neonatal GBS sepsis illustrates the challenges in devising appropriate interventions for improving perinatal outcomes, and the importance of monitoring results.

CONSEQUENCES, RECOGNITION, AND MANAGEMENT OF SPECIFIC SEXUALLY TRANSMITTED DISEASES DURING PREGNANCY

■ SYPHILIS

Epidemiology and manifestations

Syphilis remains a common complication of pregnancy in some parts of the world, despite availability of cheap, accurate diagnostic tests, and continued sensitivity of *T. pallidum* to penicillin. Congenital syphilis, discussed in detail in Chapter 82, is entirely preventable with appropriate case detection and treatment programs.^{121,122} The provision of adequate prenatal care to all pregnant women remains the foundation for prevention of congenital syphilis. The clinical manifestations of syphilis in adults are well described in Chapter 37 and are not altered by pregnancy. The majority of pregnant women diagnosed with syphilis are asymptomatic, underscoring the need for routine serologic screening of all pregnant women as early as possible in pregnancy. Pregnant women in high-risk groups should have repeat serologic screening for syphilis in the third trimester in addition to their first visit. All patients diagnosed with syphilis should be counseled and tested for HIV infection as well. Women who have fetuses noted to have nonimmune hydrops on ultrasound or who experience stillbirth should always undergo serologic testing for syphilis. Darkfield examination of the amniotic fluid for spirochetes also may be helpful in the evaluation of stillbirth when syphilis is suspected but probably adds little to the evaluation of the patient with syphilis with a live infant.¹²³

Pathogenesis

Placental infection with *T. pallidum* occurs during maternal spirochetemia, which is intense until resolution of the secondary stage. Whether pregnancy promotes recrudescence of spirochetemia, accounting for the congenital infections that occur occasionally in late syphilis, is uncertain.

A detailed clinical description of congenital syphilis is provided in Chapter 82. Untreated primary or secondary syphilis during pregnancy affects virtually 100% of fetuses, with 50% of such pregnancies resulting in preterm delivery or perinatal death.¹²¹ Untreated early latent syphilis during pregnancy results in a 40% rate of prematurity or perinatal death. Ten percent of infants born to mothers with untreated late syphilis show signs of congenital infection, and the perinatal death rate is increased approximately 10-fold. Whereas syphilis is rarely sexually transmissible longer than 2 years after acquisition, women with untreated syphilis apparently may remain infectious for their fetuses for many years, although the proportion of affected fetuses and the severity of fetal disease decrease with longer duration of untreated maternal infection. More recent reports have confirmed the abysmal prognosis with untreated syphilis in pregnancy. In a recent report of 56 cases, only 7 of whom received treatment during pregnancy, 34% were stillborn, and the mean gestational age at delivery was 32.3 weeks.¹²⁴ Other studies have shown a 28% incidence of preterm birth even among women with some treatment during pregnancy.¹²⁵ Presumptive evidence of congenital syphilis was seen in 15 (26%) of 57 women treated (not always adequately) by 24 weeks' gestation and in 41 (60%) of 70 women treated in the third trimester.¹²⁵

Case detection

Congenital syphilis can be prevented by early prenatal diagnosis and treatment. Nontreponemal serology (rapid plasma reagin, RPR) remains the most useful screening test for syphilis in pregnant women, although there is also a screening treponemal enzyme immunoassay now available.¹²⁶ Signs or symptoms are confirmatory but often are not demonstrable; of over 14,000 cases of early syphilis in women, only 11% had a primary lesion, 41% had secondary lesions, and 48% had no manifestations and were detected only by serology.¹²⁷

Infected individuals will develop antibodies to *T. pallidum* by the time of chancre formation or within 2–3 weeks afterward. Virtually all patients with secondary syphilis have a positive serologic test for syphilis, provided steps are taken to avert the prozone phenomenon. This phenomenon occurs when there is an overwhelming excess of antibody in the patient's serum that interferes with the binding to antigen in the flocculation test. If syphilis is strongly suspected

and initial results are negative, the specimen should be diluted before retesting.¹²⁸ After lesions of secondary syphilis resolve, latent syphilis is detected serologically.

Despite the low prevalence of maternal syphilis in many developed countries, cost–benefit analysis still favors prenatal first-trimester serologic screening.¹²⁹ For instance, in Norway, with a 0.02% maternal prevalence rate, the cost–benefit ratio of the program was still 3.8. Only with an estimated prevalence of maternal syphilis of less than 1 per 20,000 would the costs of the screening program exceed the benefits. This analysis excluded intangible benefits of screening that cannot be measured in economic terms. The US Centers for Disease Control and Prevention recommend serologic testing at the beginning of prenatal care, with repeat testing at the beginning of the third trimester (28 weeks) and at delivery for high-risk women.¹³⁰

The many barriers to detection of syphilis early in pregnancy include those that lead to delayed prenatal care, particularly in developing countries and among poor and minority women in industrialized countries. Approximately one-fourth of pregnant women in the United States receive no first-trimester prenatal care, with a disproportionately higher percentage among Medicaid recipients and uninsured women. Specific practical measures to improve early detection in pregnant women include on-site pregnancy testing in STD clinics and drug-addiction programs of women whose menstrual periods are late, routine RPR testing whenever a positive pregnancy test is obtained in all pregnancy testing programs, and early testing by prenatal programs, before the regularly scheduled prenatal visit when the waiting time for the first scheduled visit is long. In settings with limited resources for testing and early return visit for test results and treatment, rapid clinic-based testing and treatment at the first prenatal visit is essential, even while confirmatory tests are pending.

Treatment

A positive screening RPR test should be further evaluated with a quantitative nontreponemal test (VDRL) and a confirmatory treponemal test such as the fluorescent treponemal antibody-absorption test (FTA-ABS) or microhemagglutination–*T. pallidum* (MHA-TP) test.

Women with a positive treponemal test who do not have clear documentation of previous adequate treatment for syphilis require treatment. Women with an epidemiologic history of recent exposure to an individual with proven syphilis should be treated, regardless of serologic results.

It is not necessary to re-treat women who have had documented adequate treatment for previous syphilis so long as no evidence of serologic or clinical relapse exists. If clinical or serologic relapse or reinfection occurs, therapy should, of course, be reinstated. If doubt exists about the adequacy of previous therapy, re-treatment should be given promptly.

Treatment of syphilis in the pregnant woman is generally the same as that in the nonpregnant patient and depends on the duration of infection and the presence or absence of central nervous system involvement. Recommended choices and schedules of antimicrobials for the various clinical forms of syphilis are found in Chapters 37 and 82. Pregnant women who develop a Jarisch-Herxheimer reaction after initiation of treatment for early syphilis may have precipitous onset of preterm labor. In one report, 15 (65%) of 23 pregnant women with primary or secondary syphilis compared to none of 10 with latent syphilis experienced the Jarisch-Herxheimer reaction. Symptoms and signs developed within 2–8 hours of therapy, peaked at 6–12 hours, and abated by 16–24 hours after treatment.¹³¹ Uterine contractions and decreased fetal movement or signs of fetal distress on fetal monitoring occurred in 67% of women with the Jarisch-Herxheimer reaction. We recommend hospitalization of women beyond 20 weeks' gestation who have early syphilis for close observation during initiation of therapy to permit fetal monitoring and early tocolytic therapy, if needed. Pregnant women treated for early syphilis should have monthly quantitative serologies throughout pregnancy. Those who do not show a fourfold drop in titer at 3 months or who show a fourfold rise in titer should be re-treated.

Pregnant women who report serious penicillin allergy should be hospitalized for desensitization and penicillin therapy, since there are no other alternatives available that provide adequate treatment to the fetus as well as the mother. Unfortunately, skin antigen testing for penicillin allergy is no longer available. Desensitization can be achieved rapidly by oral administration of increasing doses of penicillin V. One desensitization schedule used in 15 pregnant women who had positive penicillin skin tests involved a starting oral dose of 100 units of penicillin V; the oral dose was doubled every 15 minutes, for a total of 14 doses, each diluted in 30 mL of water, given over a total elapsed time of 3 hours and 45 minutes, with the final dose equal to 640,000 units.¹³² Women were desensitized in the hospital, with an intravenous line in place and a physician available at all times. After a further 30-minute observation period, parenteral penicillin was begun. Five patients had evidence of allergic reaction, one requiring epinephrine. After completion of the procedure, full doses of parenteral penicillin therapy can be instituted.

■ GONORRHEA

The recognition that maternal gonococcal infection posed a threat to the newborn's sight motivated Crede's prophylaxis—a major achievement of modern preventive medicine. In the 1880s, ophthalmia neonatorum was a frequent neonatal infection. In Crede's original series, 10% of newborns acquired ophthalmia neonatorum. Rothenberg¹³³ estimated that the maternal gonococcal infection rate among patients studied by Crede must have approached the astounding figure of 30%.

Epidemiology

The reported prevalence of gonococcal infection among pregnant women shows wide variations, determined by differences in populations studied. Generally, studies of indigent populations in the United States have shown higher prevalence rates than studies from other industrialized countries, and rates in most of the developing world are higher. Risk factors for infection remain the same in pregnancy as in the nonpregnant state. In North America, gonococcal recovery rates are highest in young, nonwhite, unmarried mothers of low socioeconomic status, particularly in large cities. Isolates resistant to penicillin, fluoroquinolones, and other antibiotics have increased in frequency.¹³⁴

Manifestations and pathogenesis

The manifestations and pathogenesis of gonococcal infection in the pregnant host have some unique features.¹³⁵ The rate of pharyngeal infection as the sole site of infection may be increased during pregnancy. In some studies, 15–35% of infected pregnant women have had *N. gonorrhoeae* isolated only from the throat and not from the endocervix or anal canal.^{136,137} These findings suggest that the frequency of oral sexual activity relative to vaginal intercourse may be increased during pregnancy. Pharyngeal colonization with gonococci may increase the risk of dissemination (see Chapter 35), and some studies have suggested an increased risk of disseminated gonococcal infection among pregnant women.¹³⁸

The frequency of upper genital tract involvement following endocervical gonococcal infection during pregnancy is unknown. Among nonpregnant women, 10–20% with cervical gonorrhea have clinical evidence of pelvic inflammatory disease (PID), and up to 50% of women with recently acquired gonorrhea developed signs suggesting PID in one study.¹³⁹ In contrast, acute gonococcal PID appears to be a rare event during pregnancy. Gonococcal infection in pregnancy is occasionally associated with fever and pain, and surgically verified cases of gonococcal salpingitis in pregnancy have been reported between 7 and 12 weeks' gestation (prior to obliteration of the endometrial cavity).¹⁴⁰ However, lower abdominal pain in pregnant women should not be ascribed to PID unless other causes of pain potentially requiring surgical treatment, such as ectopic pregnancy or appendicitis, have been ruled out.

Local cervical factors may decrease the risk for ascending gonococcal infection in pregnancy. Serum progesterone concentrations are greatly increased in pregnancy, and concentrations of progesterone 50–200 times that occurring during pregnancy are known to inhibit the growth of *N. gonorrhoeae* in vitro.¹⁴¹ The menstrual cycle effects phenotypic changes in gonococci that may alter gonococcal virulence; the effects of pregnancy on phenotypic properties of *N. gonorrhoeae* have not been studied. Cervical mucus becomes impermeable to

motile sperm (and perhaps impedes ascent of microorganisms) under the influence of progesterone. Perhaps most important, after the twelfth week of gestation, the chorion attaches to the endometrial decidua with obliteration of the intrauterine cavity, obstructing the route for ascending intraluminal spread of gonococci. All these factors may limit the spread of gonococci from the cervix to the endometrium and fallopian tubes during pregnancy, particularly after the first trimester.

We hypothesize that the chorioamnion itself may become the site of infection by ascending gonococci after the twelfth week of gestation. Among women hospitalized with gonococcal infection during pregnancy, in one study, 35% had septic abortion.¹¹ This observation has not been addressed subsequently.

In retrospective studies, data have been conflicting regarding the impact of gonococcal infection on preterm birth^{142–148} (Table 80-8). Edwards et al.¹⁴⁴ found an increased rate of prematurity among women with positive intrapartum, but not antepartum, gonorrhea cultures. Amstey and Steadman¹⁴³ found high preterm birth rates even in women treated for gonorrhea early in pregnancy who remained culture-negative after treatment, while Charles et al.¹⁴⁹ found no difference in outcome between women treated early in pregnancy and those who did not have gonorrhea in pregnancy. Likewise, the association between gonorrhea and increased perinatal mortality, premature PROM, and maternal morbidity has been inconsistent among retrospective studies. Overall, data from these studies suggest that cervical gonorrhea infection in the third trimester may be a risk factor for preterm birth, PROM, and maternal febrile morbidity.

Data from recent prospective studies have been more consistent. In a case-control study of patients with preterm PROM, *N. gonorrhoeae* was isolated from 13% of patients with preterm PROM and no term controls.¹⁵⁰ All patients in the study had been screened and, if positive, treated for gonorrhea early in pregnancy. Two studies from Africa showed a three- to sixfold increased risk of preterm birth and low birth weight among women with untreated gonorrhea, independent of other risk factors.^{146,147}

In uncontrolled studies of maternal gonococcal infection, Berstine and Bland¹⁵¹ reported that 32% of women with antenatal gonococcal infection had puerperal infectious morbidity. A related observation can be found in a matched-pair analysis of 228 cases of endometritis among 4823 women following elective abortion.¹⁵² These investigators found a threefold increased relative risk for endometritis in patients who had untreated gonococcal infection when compared with uninfected control subjects ($p < 0.05$).

In Nairobi, Kenya, Plummer et al.¹⁵³ found that postpartum endometritis was significantly correlated with intrapartum gonococcal and/or chlamydial infection. Forty-seven percent

Table 80-8. Pregnancy Outcome with Positive *N. Gonorrhoeae* Cultures

Reference	N	Preterm Delivery	Perinatal Mortality	PROM	Maternal Morbidity
Positive any time					
Israel et al. ¹⁴²	69	no increase over controls			
Amstey and Steadman ¹⁴³	222	25% ^a	7.6% ^a	26% ^a	20%
Edwards et al. ¹⁴⁴	178	12.3%	28%	28%	9.5% ^a
Stoll et al. ¹⁴⁵	435	15.7%	2.2%		
Donders et al. ¹⁴⁶	167	56% ^a			
Positive intrapartum					
Elliott et al. ¹⁴⁷	166	OR = 2.9 (1.2–7.2) ^a			
Israel et al. ¹⁴²	39	12.8%	2.6%		28.2% ^a
Edwards et al. ¹⁴⁴	19	42.1% ^a	10.5% ^a	63% ^a	31.6% ^a
Maxwell and Watson ¹⁴⁸	11		9%		18% ^a

PROM, premature rupture of membranes; OR, odds ratio.

^aSignificant increase from controls ($p < 0.05$).

of women with intrapartum gonococcal infection developed postpartum endometritis; approximately 22% of endometritis was attributable to gonococcal infection in this setting, where the prevalence of maternal gonococcal infection was 6%.

These studies collectively provide convincing evidence that maternal gonococcal infection is detrimental to pregnancy. Gonococcal endocervicitis may cause preterm birth, preterm PROM, and chorioamnionitis by infecting the lower pole of the chorioamnion. The effects of gonococcal infection on early pregnancy are less well studied than its effect on late pregnancy, but early infection may cause septic abortion. Acute salpingitis also occurs during the first trimester, but very infrequently. Disseminated gonococcal infection may occur more frequently during pregnancy. The risk of postpartum febrile morbidity is increased among women with cervical gonococcal infection, and neonatal gonococcal ophthalmia represents a frequent and severe complication.

Case detection and treatment

Because of these adverse effects on pregnancy, and because of the risk for neonatal infection, detection of *N. gonorrhoeae* by nucleic acid amplification tests or culture during the initial antenatal visit is justified in most populations.¹⁵⁴ Repeat testing at 36 to 38 weeks' gestation is also indicated among high-risk individuals. Nearly 40% of pregnant women with gonorrhea give a past history of gonorrhea; therefore,

past history of gonorrhea is a strong indicator for repeated screening. In patients with preterm PROM, intrapartum fever, or septic abortion, an endocervical swab for *N. gonorrhoeae* testing also should be obtained.

In screening pregnant women for *N. gonorrhoeae*, culture on antibiotic-containing selective medium has long been the preferred method of detection, but is increasingly being replaced by the more sensitive nucleic acid amplification assays for detection of *N. gonorrhoeae* and *C. trachomatis*. Cervical, urine, and vaginal specimens appear to be equally sensitive.¹⁵⁵ Gram stains are not a sensitive test, and enzyme immunoassay methods and fluorescent antibody staining of direct cervical smears lack consistent sensitivity and specificity.^{156–158}

Uncomplicated gonorrhea in the pregnant patient can be treated with ceftriaxone, 125 mg in a single intramuscular dose, or cefixime, 400 mg orally in a single dose.¹³⁰ In patients who cannot tolerate cephalosporins, spectinomycin, 2 g in a single intramuscular dose, should be used. Tetracycline should not be used because of potential maternal and fetal toxic effects. Azithromycin or amoxicillin, in dosages discussed below, should be added to treat possible coexisting *C. trachomatis* infections. Reinfection after treatment is common. Gonococcal reinfection rates of 11–30% have been reported despite efforts to treat partners. Notification and treatment of sexual partners should be pursued vigorously. If sexual partner therapy is not accomplished, repeat monthly testing is appropriate.

For complicated gonococcal infection in pregnancy (e.g., septic abortion, chorioamnionitis), we recommend treatment for several days with ceftriaxone or cefoxitin plus an antibiotic effective against possible coexisting chlamydial infections, as recommended for PID (see Chapter 56).

Neonatal gonococcal infection: implications for management of gonorrhea in pregnancy

In a recent study in Kenya, 42% of 67 newborns not receiving ocular prophylaxis who were exposed to maternal gonococcal infection acquired gonococcal ophthalmia neonatorum.¹⁵⁹ In addition to this well-recognized neonatal manifestation of exposure to maternal gonorrhea, infection at other body sites also can occur. *N. gonorrhoeae* has been recovered from orogastric aspirate samples from approximately 30% of neonates born of infected mothers.¹⁶⁰ Extraocular sites of neonatal gonococcal infection may be associated with a higher risk of disseminated infection.

The risk of gonococcal amniotic fluid infection syndrome and gonococcal ophthalmia appears to be increased after PROM.^{161,162} The failure of silver nitrate ocular prophylaxis to prevent gonococcal ophthalmia may result from *in utero* acquisition of *N. gonorrhoeae* in the setting of PROM.¹⁶³

Gonococcal sepsis occurs in the newborn, although infrequently today. “Natural” bactericidal antibody to gonococci resides in the IgM fraction of serum and is absent from neonatal serum.¹⁶⁴ Whether neonates are at higher risk for gonococcal sepsis than are adults because of this lack of protective antibody is not established. Of importance is the fact that because neonates delivered of mothers with intrapartum gonococcal infection are more likely to be preterm or to suffer prolonged labor, bacterial sepsis due to any etiology occurs more often.

For these various reasons, ophthalmic prophylaxis alone will not prevent all the manifestations and complications of gonorrhea in the neonate. Diagnostic screening and early treatment of infected women during pregnancy represent a more effective means of preventing neonatal gonococcal infection, as well as preventing complications in pregnancy itself.

In addition, in areas where the prevalence of maternal gonococcal infection is greater than 1% or where maternal screening is not undertaken, ophthalmic prophylaxis is useful and should be required.¹³³ The recommendations made by the Centers for Disease Control and Prevention for the prevention of gonococcal ophthalmia neonatorum (also endorsed by the American Academy of Pediatrics) state that ophthalmic ointment or drops containing 1% tetracycline, 0.5% erythromycin, or 1% silver nitrate are effective and acceptable. One randomized clinical trial of prophylaxis for gonococcal ophthalmia compared the effectiveness of 1% silver nitrate with 1% tetracycline ointment, and one study compared each of those agents to 0.5% erythromycin ointment.^{165,166} Both studies found the agents studied to have

similar efficacy in reducing the incidence of gonococcal ophthalmia. The prophylactic agents also were highly effective against multidrug resistant *N. gonorrhoeae*. However, the efficacy of topical 1% tetracycline in preventing gonococcal ophthalmia in neonates exposed to gonococci with resistance to tetracycline (25% of US gonococcal isolates in 1995 and a much higher percentage of isolates from other regions) remains uncertain.

Neonates born to mothers with documented untreated antepartum or intrapartum gonococcal infection are at high risk for infection and should receive parenteral antibiotics in standard curative dosage (see Chapter 83) in addition to topical ocular prophylaxis.

■ C. TRACHOMATIS INFECTIONS

Epidemiology

C. trachomatis infection rates for pregnant women have varied from 2% to 30%. Single marital status and young age, especially adolescence, are the major demographic correlates of chlamydial infections in pregnancy. Adolescents studied routinely have a prevalence of chlamydial infection of over 10%.¹⁶⁷ Although chlamydial infection rates have been highest among nonpregnant women in inner cities, higher rates of chlamydial infection have been reported among pregnant women in rural compared with urban areas in some parts of the country.¹⁶⁸

Whether pregnancy per se influences shedding of *C. trachomatis* from the cervix is unknown. The rate of isolation of *C. trachomatis* has been reported to be higher during the third trimester than during the first or second trimester.^{169,170} However, women who sought prenatal care in the first trimester in these cross-sectional studies may have had a lower risk of bacterial STI than those who did not seek care until the third trimester. Shedding of *Chlamydia* might be influenced by the frequent development of ectopy in pregnancy, which is positively correlated with *C. trachomatis* isolation in nonpregnant women, or by alteration of the immune response to the organism.

Maternal IgG antibody undergoes active transplacental transfer beginning as early as day 38 after conception.¹⁷¹ The level of transfer remains fairly constant until the seventeenth week of gestation, at which time proportionate increases occur with advancing gestational age. Infants born to seropositive mothers with current or past *C. trachomatis* infection acquire antibody to this organism. Since about two-thirds of exposed neonates become infected (see Chapter 83), it is clear that passively acquired antibody is not completely protective. The influence of maternal antibody on the risk of acquisition of infection or on the severity of disease is unknown. The presence of antibody to *C. trachomatis* in breast milk or colostrum and the role of such

colostral antibody in preventing or modifying neonatal chlamydial infection have not yet been evaluated.

Influence of *C. trachomatis* on reproduction and pregnancy

In some areas, up to two-thirds of cases of tubal infertility have been attributed to *C. trachomatis* infection.¹⁷² If incomplete blockage of fallopian tubes occurs with infection, there is an increased risk of ectopic pregnancy (see Chapters 56 and 79). In one study, 10 (59%) of 17 of patients with a history of ectopic pregnancy had antibodies to *C. trachomatis*.¹⁷³ In another case-control study, more women with ectopic pregnancy not related to intrauterine devices or previous tubal ligation had antibodies to *C. trachomatis* than did women with intrauterine pregnancies [18 of 32 (56%) versus 11 of 49 (22%), $p = 0.0021$].¹⁷⁴ Kosseim et al.¹⁷² estimated that approximately one-third of cases of ectopic pregnancy may be attributable to chlamydial infection. Whether *C. trachomatis* infection can cause abortion is unknown. *C. psittaci* infection is an important cause of spontaneous abortion in other mammals,¹⁷⁵ and Schachter¹⁷⁶ reported that *Chlamydia* were isolated from 4 of 22 first-trimester spontaneous abortuses in humans. Further work is needed to define the relationship of chlamydial infection to abortion.

The role of genital *C. trachomatis* infection in prematurity and in perinatal mortality has been under active investigation. Examination of birth weights and gestational ages of infants with *C. trachomatis* infection has given conflicting

results. Of infants with *C. trachomatis* ophthalmia neonatorum, 15–42% have had birth weights less than 2500 g.^{162,177,178} Prospective studies of *C. trachomatis* and pregnancy outcome are summarized in Table 80-9.^{179–185} Three separate studies at the University of Washington, each involving a different study design, have all shown a correlation of antenatal chlamydial infections with prematurity, defined by preterm delivery and/or low birth weight.^{180,183,186} However, Frommell et al.¹⁸⁷ and Heggie et al.¹⁸⁸ found no association of antenatal *C. trachomatis* infection with prematurity. In a prospective study of 1365 pregnant women, Harrison et al.¹⁷⁹ observed no significant correlation of *C. trachomatis* infection with prematurity but did find a significantly increased risk of low birth weight and of preterm PROM and a shorter gestation among women with serologically defined primary infection with *C. trachomatis* than among other culture-positive women or among culture-negative women. Similarly, Berman et al.¹⁸⁴ and Sweet et al.¹⁸² confirmed the association of preterm birth with IgM seropositivity among *C. trachomatis* culture-positive women. The biologic basis for these serologic correlations among *C. trachomatis* infected women is not defined. Possibilities could include higher bacterial load and/or more extensive chlamydial infection or inflammation in a relatively nonimmune host. In an early study, Martin et al.¹⁸⁰ observed a correlation of antenatal *C. trachomatis* infection not only with preterm birth but also with perinatal mortality. The latter observation has not been confirmed in other studies.

Table 80-9. Cohort Studies of the Effects of *Chlamydia Trachomatis* on Pregnancy Outcome

Author	Gest. Age at Culture	N	Adverse Outcome ^a		p
			Ct+	Ct–	
Martin et al. ¹⁸⁰	<19 weeks	268	33%	8%	<0.01
Thompson et al. ¹⁸¹	1–2 trimester	433	14%	12%	N.S.
Harrison et al. ¹⁷⁹	1–3 trimester	1185	14%	8%	<0.025 ^b
Sweet et al. ¹⁸²	1–3 trimester	540	19%	8%	0.03 ^b
Gravett et al. ¹⁸³	2–3 trimester	534	36%	12%	<0.01
Berman et al. ¹⁸⁴	<24 weeks	781	9%	6%	N.S.
			19%	5%	0.06 ^b
Polk et al. ¹⁸⁵	23–30 weeks	803		RR 1.7	0.01

Gest. gestational; Ct, *Chlamydia trachomatis*.

^aIncludes abortion, low birth weight, stillbirth, neonatal death.

^bComparison of women with *C. trachomatis* and chlamydial IgM antibody to women without *C. trachomatis*.

The role of *C. trachomatis* in maternal puerperal morbidity

Studies of pregnant women in Seattle and in Nairobi, Kenya, have confirmed that antepartum chlamydial infection, if not treated, is correlated with puerperal infection. Wager et al.¹¹⁴ found that intrapartum fever (clinically ascribed to amnionitis) and late postpartum endometritis were both significantly correlated with untreated antepartum chlamydial infection (Table 80-10). Overall, among women who delivered vaginally, puerperal infectious morbidity occurred in 10 (34%) of 29 women with and in 23 (8%) of 300 women without antenatal *C. trachomatis* infection ($p < 0.001$). Plummer et al.¹⁵³ subsequently reported from Nairobi that 24% of 183 women with intrapartum chlamydial infection developed postpartum endometritis, a rate significantly greater than that observed in uninfected women (15%, $p = 0.02$). Chlamydial infection accounted for approximately 22% of endometritis in this setting; this rate may be representative of other African populations in the absence of routine prenatal screening for *C. trachomatis*. These studies collectively suggest that antepartum *C. trachomatis* infection causes amnionitis and late postpartum endometritis, although attempts generally have not been made to isolate *C. trachomatis* at the time these complications have occurred.

Postabortal pelvic inflammatory disease

A syndrome related to postpartum pelvic infection is seen following therapeutic abortion. An excess rate of postabortal PID has been seen among women with chlamydial infection at the time of the procedure.^{17,189,190} In settings where gonococcal infection is much less prevalent than chlamydial infection, up to 60% of cases of postabortal PID may be

attributable to chlamydial infection. In one study, the risk of postabortal PID among *Chlamydia*-infected women was inversely related to serum antibody titers to *Chlamydia*.¹⁹¹ We recommend that women undergoing therapeutic abortion should be screened for chlamydial infection to prevent postabortal ascending infection. As noted below, BV also has been associated with postabortal pelvic infection, and it is quite likely that in some populations gonococcal infection also contributes to this condition.

Current recommendations for diagnostic testing for chlamydial infection during pregnancy

The importance of detecting and treating chlamydial infection of the genital tract in pregnant women is certainly no less than in nonpregnant women. In fact, the unquestioned risk of intrapartum transmission to the neonate and the growing evidence that chlamydial infections cause complications of pregnancy and postpartum pelvic infection dictate that a very high priority be given to detecting and treating chlamydial infection in pregnant women. Nucleic acid amplification tests provide a rapid and highly sensitive means to screen for *C. trachomatis* and *N. gonorrhoeae* simultaneously.¹⁵⁵ The ability to test cervical, vaginal, and urine specimens makes these assays relatively easy to perform even in settings where a speculum examination may be less feasible.

As a minimum preventive intervention at present, we advocate selective diagnostic testing of pregnant women who are at high risk for chlamydial infection. A strong argument could be made for screening all pregnant women for *C. trachomatis*, particularly those less than 25 years of age.

Treatment

Tetracyclines, the drugs of choice for *C. trachomatis* infection in nonpregnant adults, cannot be recommended for

Table 80-10. Puerperal Infectious Morbidity in Patients With and Without Antepartum *Chlamydia Trachomatis* Infection, Matched for Demographic Characteristics and Parity

Complication	<i>C. trachomatis</i> Isolated (N = 32)		<i>C. trachomatis</i> Not Isolated (N = 350)		
	Number	Percent	Number	Percent	
Intrapartum fever >38°C	3	9	5	1	<0.025
Early postpartum fever <48 h	1	3	26	7	0.06
Late postpartum endometritis, 48 h to 6 weeks postpartum	7	22	18	5	<0.005
Total infectious morbidity	11	34	49	14	<0.01

From Wager GP et al. Puerperal infectious morbidity: Relationship to route of delivery and to antepartum *Chlamydia trachomatis* infection. *Am J Obstet Gynecol* 1980; 138: 1028.

pregnant or breastfeeding women. Azithromycin and amoxicillin are considered the drugs of choice for treating chlamydial infections in pregnant women.¹³⁰ A single dose of azithromycin, 1 g, is optimal as this regimen is simple, safe, effective, and well tolerated in pregnancy.¹⁹² Alternatives include erythromycin base or erythromycin ethylsuccinate for 7 days; however, adherence to these regimens may be less than perfect because of gastrointestinal side effects. In pregnancy, a test of cure should be obtained 3 weeks after treatment to assure clearance of infection.

Prevention of neonatal *C. trachomatis* infections

Hammerschlag et al.¹⁹³ reported that erythromycin ocular ointment was significantly more effective than 1% silver nitrate in preventing neonatal chlamydial conjunctivitis. A later study found 0.5% erythromycin ointment to be of similar efficacy to 1% tetracycline ointment or 1% silver nitrate.¹⁶⁶ Others have been unimpressed with the use—effectiveness of topical erythromycin for this purpose in actual practice.¹⁹⁴ Laga et al.¹⁶⁵ compared 1% tetracycline ointment and 1% silver nitrate drops for the prevention of chlamydial ophthalmia. Both agents reduced the incidence of chlamydial conjunctivitis 68–77% in comparison with a historical control group of newborns who had not received ocular prophylaxis. Nonetheless, long-term follow-up of infants exposed to maternal chlamydial infection who received ocular prophylaxis revealed that 23–31% ultimately developed ocular *C. trachomatis* infection.¹⁹⁵ Most of these infections were subclinical. As with gonococcal infection, the detection and treatment of chlamydial infection during pregnancy, together with ocular prophylaxis, would be preferable to neonatal ophthalmic prophylaxis alone.

■ GENITAL MYCOPLASMAS

Many reproductive disorders have been ascribed to infection with the genital mycoplasmas, *U. urealyticum* and *M. hominis*. However, the ubiquity of these organisms and the high frequency of other coexistent risk factors for adverse pregnancy outcome and coinfection with other bacterial STI agents make it difficult to assess their etiologic roles in such disorders. Isolation of *M. hominis* is strongly associated with the presence of BV, making it difficult to differentiate adverse effects related to *M. hominis* from the other bacteria found at increased levels in BV. *M. hominis* has been linked to preterm birth, endometritis, and postpartum fever, while *U. urealyticum* has been associated with amniotic fluid infection, chorioamnionitis, low birth weight, and preterm birth.

Several studies have compared the rate of detection of genital mycoplasmas among women with spontaneous abortion compared with those with continuing pregnancies. The

majority have shown no difference in recovery of either *U. urealyticum* or *M. hominis*,^{181,196,197} with one study finding a lower rate of *U. urealyticum* recovery from women with spontaneous abortion.¹⁷⁹ All have been limited by the high frequency of *Mycoplasma* carriage, lack of testing for many other microorganisms, and poor characterization of other risk factors in the population. Harwick et al.¹⁹⁸ detected *M. hominis* bacteremia in 8% of women with febrile abortion versus none of those with afebrile abortion. Serologic evidence of infection with *M. hominis* was found in 50% of septic abortions versus 17% of afebrile abortions. These provocative data require confirmation, with studies of other relevant microbial species together with *M. hominis*. Several studies have found an increased frequency of isolation of genital mycoplasmas from spontaneous abortions than from induced first- and second-trimester abortions,^{199,200} but it is unclear whether the infection was present before embryonic or fetal death or occurred as a consequence of nonviability of the pregnancy. In a more recent study, isolation of *U. ureaplasma* from products of conception did not correlate with the presence of histologic inflammation among specimens from spontaneous abortions.²⁰¹ Among women with recurrent miscarriage, the rate of isolation of genital *Mycoplasma* from the cervix was similar to the rate among control patients, but *Mycoplasma* were isolated from the endometrium more frequently among women with spontaneous abortion (28%) or infertility (50%) than among controls (7%).²⁰² Uncontrolled studies have suggested a benefit from treating women with recurrent abortion and genital *Mycoplasma* colonization with doxycycline or erythromycin, but controlled studies are lacking.^{202,203} In summary, current data do not support a significant role for *M. hominis* or *U. urealyticum* in spontaneous first- or second-trimester abortion.

U. urealyticum and *M. hominis* must be considered individually when evaluating the potential role of genital mycoplasmas in prematurity. The isolation of *M. hominis* from the lower genital tract is strongly associated with the clinical or Gram stain diagnosis of BV, making it difficult to assess the independent contribution of *M. hominis* to prematurity, if any.^{204,205} Isolation of *U. urealyticum* from the lower genital tract during pregnancy is more common with young maternal age, black race, first pregnancies, low income, being unmarried or less educated, having more sexual partners, smoking, and use of marijuana or cocaine, all factors previously associated with an increased risk of preterm delivery.²⁰⁶ Thus, colonization with *U. urealyticum* may be a marker for other factors contributing to preterm birth, and not necessarily a primary pathogen. Studies of lower genital tract colonization and pregnancy outcome are summarized in [Table 80-11](#).^{179,184,196,206–215} Overall, the data do not suggest an increased risk of preterm delivery or low birth weight among women colonized in the lower genital tract with *U. urealyticum*, with prevalences ranging from

Table 80-11. Cohort Studies of *Ureaplasma Urealyticum* in the Lower Genital Tract and Pregnancy Outcome

Author	UU+/total (%)	Pregnancy Outcome
Foy et al. ¹⁹⁶	115/119 (58%)	No difference
Braun et al. ²⁰⁷	388/485 (80%)	Decreased BW in UU+
Harrison et al. ²⁰⁸	46/196 (48%)	No difference
Ross et al. ²⁰⁹	71/162 (44%)	Decreased preterm del in UU+
Harrison et al. ²⁰⁸	983/1365 (72%)	No difference
Upadhyaya et al. ²¹⁰	59/135 (44%)	No difference
Minkoff et al. ²¹¹	151/233 (65%)	More preterm labor, not del in UU+
Berman et al. ¹⁸⁴	942/1163 (81%)	No difference
Carey et al. ²⁰⁶	3256/4934 (66%)	No difference
McGregor et al. ²¹²		No difference
McGregor and French ²¹³	112/176 (64%)	No difference
Luton et al. ²¹⁴	172/218 (79%)	No difference
Choudhury et al. ²¹⁵	(40%)	No difference

UU, *Ureaplasma urealyticum*; BW = birth weight; del, delivery.

44% to 81%. Likewise, treatment studies using erythromycin in colonized women have not shown clear benefit in reducing prematurity. McCormack et al. demonstrated higher birth weights among colonized women treated in the third trimester for at least 6 weeks with erythromycin compared with placebo but did not show benefit with second-trimester therapy.²¹⁶ In the large, multicenter NICHD Collaborative Study of vaginal infections in pregnancy among 1181 women with *U. urealyticum*, administration of erythromycin for up to 14 weeks during the third trimester had no effect on birth weight, gestational age at delivery, or neonatal outcome in comparison with women randomized to placebo.²¹⁷ The recovery rates of *U. urealyticum* at delivery were similar between the erythromycin- and placebo-treated groups, probably because erythromycin has minimal antimicrobial activity at the lower pH of the vagina. Reports of eradication of *U. ureaplasma* from the amniotic fluid with erythromycin suggest potential activity of erythromycin at that site,²¹⁸ although efficacy for treating chorioamnion infection has not been evaluated.

Upper genital tract (amniotic fluid, chorioamnion) infection with several facultative or anaerobic bacteria has been strongly associated with preterm delivery and low birth weight, but isolation of *U. urealyticum* from the amniotic

fluid is less clearly associated with preterm birth. In several studies of women in preterm labor with intact membranes, those with other bacteria in the amniotic fluid presented in preterm labor at 27–29 weeks' gestation and delivered within 1 day of admission. Women with negative amniotic fluid cultures presented with preterm labor at 31–32 weeks and delivered an average of 5 weeks after onset of preterm labor. Like those with negative cultures, women with *U. urealyticum* alone in the amniotic fluid also presented at 31–32 weeks' gestation, with an average interval to delivery of 4–5 weeks.^{59,66} Chorioamnion infection with *U. urealyticum* has been found more commonly among women delivering preterm than among those delivering at term in case-control studies, but this has not been confirmed in cohort studies of prematurity. In fact, the presence of other bacteria in the chorioamnion was more consistently related to prematurity, as in the studies employing amniotic fluid cultures. However, isolation of *U. urealyticum* from the chorioamnion has been consistently associated with histologic chorioamnionitis in all studies.^{25,26,29} These data suggest that *U. urealyticum* may induce a form of chorioamnionitis that is perhaps indolent and does not frequently lead to preterm delivery.

Whether or not *U. urealyticum* in the upper genital tract is a factor causing preterm delivery or a secondary finding,

U. urealyticum has been implicated as a cause of congenital and neonatal pneumonia, especially in preterm infants.²¹⁹ In addition, *U. ureaplasma* infection among infants weighing less than 1250 g at birth appears to increase the risk of chronic lung disease by two- to threefold, possibly through an indolent, undiagnosed pneumonia.²¹⁹ Thus far, *M. hominis* has not been implicated as a cause of neonatal pneumonia or chronic lung disease.

Data link *M. hominis* to postpartum fever. Platt et al.,²²⁰ in their follow-up study of 535 patients, found that 14 (50%) of 28 postpartum fevers were associated with rises in titers of antibody to *M. hominis*. Positive genital colonization and low predelivery antibody titer to *M. hominis* were predictive of postpartum fever. Harrison et al.¹⁷⁹ also reported a significantly increased risk of postpartum fever among women with antepartum *M. hominis* colonization who were delivered vaginally. However, given the strong association between vaginal *M. hominis* isolation and BV, increased relative risk of PPE with BV,¹¹² and the almost uniform isolation of other microorganisms with *M. hominis* from the endometrium,¹¹¹ it is unclear which microorganisms are most important in the infection. Only a small proportion of colonized women developed this complication.

M. genitalium is a fastidious organism associated with nongonococcal urethritis, cervicitis, and PID.^{221–223} This organism cannot be cultured and requires molecular methods such as PCR for detection.²²⁴ Since *M. genitalium* is associated with PID, it is plausible that this organism could invade the upper genital tract in pregnancy and possibly cause adverse pregnancy outcome. To date, the evidence linking *M. genitalium* and preterm birth are conflicting. One case-control study in Lima, Peru, showed a twofold increased risk of preterm birth associated with *M. genitalium*,²²⁵ whereas other studies have not shown an association with preterm birth or other adverse pregnancy outcome.²²⁶ Further study is required to understand whether this is a significant pathogen in pregnancy.

Current recommendations for management of genital *Mycoplasma* infection during pregnancy

Colonization of the lower genital tract with *M. hominis* or *U. urealyticum* does not appear to increase the risk of spontaneous abortion, preterm delivery, or preterm PROM, and routine screening of pregnant women for these microorganisms is therefore not recommended. The presence of *U. urealyticum* in the upper genital tract is clearly related to histologic chorioamnionitis but not necessarily to preterm birth. Isolation of *U. urealyticum* alone from the amniotic fluid is not an indication for delivery, but treatment with erythromycin could be considered. Further study of the impact of *Ureaplasma*-induced inflammation on preterm birth (chorioamnionitis) and neonatal chronic lung disease (pneumonitis) in preterm infants is required before routine treatment is recommended. Inclusion of antimicrobials with activity against genital mycoplasmas does not appear to be

required in the antimicrobial treatment of women with postpartum endometritis, but might be considered for women with recalcitrant infections or for those in whom other bacteria cannot be isolated.

BACTERIAL VAGINOSIS

BV is characterized by a nonpurulent, homogeneous, malodorous vaginal discharge, by an increase in vaginal pH, by the presence of characteristic amines and organic acids in vaginal fluid, and by changes in vaginal flora with a decrease in H₂O₂-producing facultative *Lactobacillus* and an increase in frequency and concentration of *Gardnerella vaginalis*, *M. hominis*, and several anaerobic species²²⁷ (see Chapters 18 and 42).

The prevalence and natural history of BV are similar in pregnant and nonpregnant women.^{204,227,228} BV is detected in 12–50% of pregnant women depending on the population studied and the method of diagnosis. Factors associated with an increased risk of BV among pregnant women have included African American race, being unmarried, and not having used antibiotics recently.^{228,229}

BV and pregnancy complications

A growing body of evidence links BV with an increased risk for pregnancy complications, including postabortal infections, preterm labor and delivery, preterm PROM, fever during labor, and postpartum endometritis (see Chapter 42). In studies from Sweden, the risk of postabortal infection was found to be elevated among women with clue cells in the vagina,²³⁰ and the elevated risk of infection was reduced among women with BV by treatment with metronidazole before and after the procedure.¹⁸

Among women with clinically diagnosed amniotic fluid infection during labor, *G. vaginalis*, *M. hominis*, *P. bivia*, and peptostreptococci were frequent isolates.²³¹ Women with BV were significantly more likely to develop clinical manifestations of amniotic fluid infection than those with normal vaginal flora on Gram stain.^{68,112,231} In addition, detection of BV by Gram stain at delivery has been associated with an odds ratio of 5.8 for the development of post-Cesarean endometritis.¹¹² Microorganisms associated with BV are isolated in over 60% of women with post-Cesarean endometritis,¹¹¹ and these same bacteria have been associated with increased rates of wound infection after Cesarean delivery.²³² BV clearly increases the risk of maternal morbidity during pregnancy.

Of even greater significance is the association of BV with preterm PROM, and preterm birth. Table 80-12 summarizes several studies that established BV as a risk factor for pregnancy complications.^{183,186,204,233–239} BV consistently has been identified as a risk factor for preterm delivery, with odds ratios of 1.4–6.9. When preterm PROM was assessed, this also was increased by a factor of 2.1–7.3. The potential role of BV in initiating or continuing preterm labor leading to

Table 80-12. Association of Bacterial Vaginosis with Preterm Labor, Preterm Delivery, and Preterm Rupture of Membranes

Author	Study Design	GA at Test	Reason for Test	Method of Diagnosis	Outcome Odds ratio (95% CI)	Location
Kurki et al. ²³³	cohort <i>n</i> = 790	8–17	Screen	Culture	PTL 2.6 (1.3–4.9) PTD 6.9 (2.5–18.8) PROM 7.3 (1.8–29.4)	Sweden
Riduan et al. ²³⁴	cohort <i>n</i> = 490	16–20	Screen	GS	PTD 2.0 (1.0–3.9)	Indonesia
Hay et al. ²⁰⁴	cohort <i>n</i> = 783	9–24	Screen	GS	PTD 2.8 (1.1–7.4) del 16–37 wks 5.5 (2.3–13.3)	UK
McGregor et al. ²³⁵	cohort <i>n</i> = 271	16–27	Screen	GS	PTB 3.3 (1.2–9.1) PROM 5.7 (0.9–36.1)	Denver, CO
McGregor et al. ²³⁶	cohort <i>n</i> = 559	1st visit	Screen	GS	PTD 1.9 (1.2–3.0) PROM 3.5 (1.4–8.9)	Denver, CO
Hillier et al. ²³⁷	cohort <i>n</i> = 10397	23–26	Screen	pH + GS	PTD of LBW 1.4 (1.1–1.8)	Multicenter USA
McGregor et al. ²³⁸	cohort <i>n</i> = 202	24	Screen	GS	PTL 2.6 (1.1–6.5) PTD 1.5 (0.2–14.2)	Denver, CO
Gravett et al. ¹⁸³	cohort <i>n</i> = 534	13–42	L & D	GLC	PML 2.1 (1.4–3.8) PROM 2.1 (1.4–4.2)	Seattle, WA
Martius et al. ¹⁸⁶	case control <i>n</i> = 231	20–42	L & D	GS	PTD 2.3 (<i>p</i> = 0.03)	Seattle, WA
Holst et al. ²³⁹	case control <i>n</i> = 87	23–42	L & D	clue cells + GS	PTD 2.1 (1.2–3.7)	Sweden

GA, gestational age; CI, confidence interval; GS, Gram stain; L + D = admission to labor and delivery; GLC, gas liquid chromatography; PTL, preterm labor; PTD, preterm delivery; PROM, preterm rupture of membranes.

delivery is further indicated by the frequent detection of BV-associated bacteria in the amniotic fluid of women with preterm labor and intact membranes,^{59,66} by isolation of BV-associated bacteria from the chorioamniotic membranes more commonly from women delivering preterm than from those delivering at term,²³ and by the association of such bacteria with histologic inflammation. Most important, systemic (oral) therapy for BV has decreased the rate of preterm birth in studies of pregnant women at high risk of preterm birth^{240–242} (Table 80-13). However, the data are conflicting regarding efficacy of BV treatment to prevent preterm birth in subsequent large treatment trials of lower-risk populations. The late timing of therapy and specific antibiotic strategy may have contributed to the lack of protection seen in one large multicenter trial.²⁴³ A more recent randomized trial utilizing oral clindamycin in the early second trimester for treatment of asymptomatic BV among low-risk pregnant women demonstrated a significant reduction in late miscarriage and preterm birth.²⁴⁴ The inconsistent efficacy of topical clindamycin therapy in preventing BV-associated prematurity^{235,245–249} may be related to a lack of effect on established, indolent upper tract infection or to effects related to vaginal overgrowth by *E. coli* and enterococcus.²⁰⁵

In summary, these data suggest that pregnant women with BV who are at increased risk of preterm birth may benefit from treatment, while treatment for asymptomatic, low-risk pregnant women is probably not justified.

G. vaginalis infrequently has caused neonatal bacteremia, cutaneous abscess, and congenital pneumonia.²⁵⁰ Anaerobes, however, may be relatively important in neonatal sepsis. Neonatal anaerobic sepsis is often associated with prematurity, amniotic fluid infection, and prolonged ineffective labor. Chow et al.²⁵¹ found that 26% of all cases of neonatal bacteremia observed at their institution were associated with anaerobes, with 1.8 episodes of anaerobic bacteremia per 1000 live births. Anaerobic isolates were identified predominantly as species belonging to *Bacteroides*, *Peptococcus*, and *Peptostreptococcus*. The anaerobic flora associated with BV may provide a large inoculum and thus increased risk of anaerobic sepsis in the neonate.

Case detection and treatment

The sensitivity and specificity of methods available for the diagnosis of BV (see Chapter 42) do not seem to be altered by pregnancy. The two most practical methods for clinical use in pregnancy are the clinical criteria and vaginal Gram stain. BV

Table 80-13. Treatment of Bacterial Vaginosis in Pregnancy and Outcome

Author	N	GA at Rx	Rx	Treatment Efficacy	Drug	Preterm Birth Rate	
						Placebo	p
<i>Systemic (oral) therapy</i>							
Morales et al. ²⁴⁰	80	13–20	Metronidazole	89%	18%	39%	<0.05
Hauth et al. ²⁴¹	258	22–24	Metronidazole, erythromycin	86%	31%	49%	0.006
McDonald et al. ²⁴²	480	24	Metronidazole	ND	4%	6%	NS ^a
	46 ^a				9%	42%	
Carey et al. ²⁴³	1953	16–24	Metronidazole	78%	12%	12%	NS
Ugwumadu et al. ²⁴⁴	494	12–22	Clindamycin	ND	5%	16%	<.001
<i>Intravaginal therapy</i>							
McGregor et al. ²³⁵	129	16–27	Clindamycin	90%	15%	7%	0.26
Joesoef et al. ²⁴⁵	681	14–26	Clindamycin	86%	15%	14%	0.65
Rosenstein et al. ²⁴⁶	227	16–20	Clindamycin	70%	7%	8%	NS
Kekki et al. ²⁴⁷	375	10–17	Clindamycin	66%	5%	4%	NS
Lamont et al. ²⁴⁹	409	13–20	Clindamycin	ND	4%	10%	<.03
Guaschino et al. ²⁴⁸	112	14–25	Clindamycin	ND	12%	16%	.78

GA, gestational age; Rx = treatment.

^aIn McDonald's study, a subset analysis of women with a prior preterm birth who were randomized to oral metronidazole showed a significant reduction in recurrent preterm birth.²⁴²

is diagnosed clinically when at least three of the following criteria are present: (1) vaginal pH above 4.5, (2) thin, homogeneous white or gray vaginal discharge, (3) clue cells present on saline preparation of vaginal discharge, and (4) presence of fishy amine odor with addition of 10% potassium hydroxide to vaginal fluid.²⁵² Diagnosis of BV by vaginal Gram stain is based on an absence or decrease of *Lactobacillus* morphotypes and an increase in small gram-variable or gram-negative rods (*G. vaginalis* and *Bacteroides morphotypes*) with or without the presence of curved gram-variable rods (*Mobiluncus* morphotypes).²⁵³ Gram stain diagnosis may be especially helpful in the presence of bleeding or ruptured amniotic membranes when the pH and other clinical signs may be altered. Pregnant women with symptomatic vaginal discharge should undergo pelvic examination, pH testing, vaginal wet mount or Gram stain examination, and if indicated, testing for other bacterial STI. Current data suggest that pregnant women with a previous preterm delivery after preterm labor or PROM should be screened routinely and offered treatment for BV if it is present. Currently, the potential

benefit in reducing preterm birth of screening low-risk pregnant women and treating those with BV remains unproven. In the absence of definitive data, we recommend screening and treatment of BV in pregnancy for all women at high risk for preterm birth, ideally as early in pregnancy as possible. Women should be offered treatment with oral metronidazole, 500 mg twice daily for 7 days, or oral clindamycin, 300 mg twice daily for 7 days. Oral metronidazole appears to be safe and well tolerated in the first trimester.^{254,255} Although topical therapy with intravaginal clindamycin or metronidazole has been found effective in eliminating BV,^{205,256} systemic therapy is desirable to eradicate any potential colonization of the decidua and amniotic fluid. Pregnant women with symptomatic BV who are not at high risk for preterm birth may also be offered treatment to ameliorate their symptoms, and in this case, either oral or intravaginal metronidazole would be acceptable. Intravaginal clindamycin should be avoided in the second half of pregnancy, as this treatment has been associated with an increased risk of preterm birth.^{235,245,257} Routine treatment of male sexual partners has not been shown to

reduce rates of recurrent BV, although there is some evidence that BV may be sexually transmitted between women.²⁵⁸ Treatment of female sexual partners may be reasonable, although there are no data as yet to show efficacy.

■ TRICHOMONAS VAGINALIS VAGINITIS

The prevalence of *T. vaginalis* infection in pregnancy has ranged from 3% to 48% depending on the population studied. Among 13,816 pregnant US women studied between 23 and 26 weeks' gestation at six urban centers in the Vaginal Infections and Prematurity Study (VIP Study) during the late 1980s, the culture-positive rate was 12.6%.²⁵⁹ Factors associated with having *T. vaginalis* in this study were black race, cigarette smoking, single marital status, less education, a history of gonorrhea, greater number of lifetime sexual partners, and lack of barrier or hormonal contraception in the 6 months before pregnancy. Many of these factors have been noted in other studies and are also associated with an increased risk of preterm delivery. Thus, sociodemographic factors and coexisting infections also must be taken into account when assessing a possible role of *T. vaginalis* in preterm birth.

T. vaginalis has been associated with an increased risk of preterm delivery,^{236,260–262} preterm PROM,^{211,263} and maternal puerperal morbidity.²⁶⁴ The largest cohort study to evaluate lower genital tract infections and preterm birth, the VIP Study discussed above, has noted a 1.3-fold increased risk of preterm birth with *T. vaginalis* detected by culture at 23–26 weeks of pregnancy, even after adjustment for demographic, behavioral, and other infectious factors associated with preterm birth.²⁶² The potential role of *T. vaginalis* in preterm birth is further supported by in vitro studies showing that clinical *T. vaginalis* isolates and cell-free filtrates decrease the elasticity, the work to rupture, and the bursting tension of chorioamniotic membranes in an inoculum-dependent fashion.²⁶⁵ This effect may be due to the organism itself, the proteases produced, the host inflammatory response, or a combination effect.

In 1931, Bland et al.²⁶⁴ reported postpartum fever in 48% of 92 women with untreated antenatal trichomoniasis, compared with 25% of 110 women without trichomoniasis ($p = 0.001$). The difference was independent of race. Possible confounding by other STI and BV and by several other risk factors was not addressed, and the results were not subsequently confirmed by Trussell et al.,²⁶⁶ who noted postpartum fever in 8.5% of 223 women with trichomoniasis compared with 8.3% of 657 women without trichomoniasis. It remains uncertain whether *T. vaginalis* might produce intra- or postpartum pelvic infections either on their own or through associated increases in anaerobic vaginal flora.

Neonatal infection with *T. vaginalis* is detected infrequently and causes little morbidity. Because of estrogenic influence during pregnancy, the vaginal mucosa of female neonates is susceptible to infection or colonization with *T. vaginalis*. This is reversed spontaneously within 3–4 weeks after delivery. The risk of neonatal infection with *T. vaginalis* overall is less than 1% and among exposed neonates is approximately 5%. Purulent vaginitis and urinary tract infection have been described as neonatal manifestations of infection.²⁶⁷ Recently, *T. vaginalis* has been suspected as a cause of some cases of neonatal pneumonia.

Case detection

Whether totally asymptomatic pregnant women should undergo screening for *T. vaginalis* is unsettled. Vaginal culture is more sensitive than direct microscopy of vaginal secretions, but *T. vaginalis* can be detected by microscopy in most women with symptomatic disease.^{268,269} Inoculation of vaginal secretions into commercial culture systems will detect the 25–50% of vaginal trichomonal infections that are asymptomatic (see Chapter 43). Vaginal fluid should be examined microscopically at any antenatal visit on all women with symptoms or signs of vaginitis; and in view of the association of *T. vaginalis* infections with preterm birth, screening of all pregnant women who are considered at increased risk for preterm birth or for *T. vaginalis* infection should be considered, using either wet-mount examination, culture, or DNA probe examination. Trichomonal infections suspected on Papanicolaou smears of the cervix should be confirmed by wet-mount examination or culture before treatment during pregnancy.

Treatment

Most clinicians would recommend treatment with oral metronidazole for pregnant women with symptomatic infections. Treatment of asymptomatic *T. vaginalis* in pregnancy is more controversial. Although this organism is clearly associated with preterm birth and puerperal morbidity, one multicenter randomized trial that treated asymptomatic pregnant women in the early third trimester actually demonstrated an increase in preterm birth after metronidazole treatment.²⁷⁰ It is possible that treatment early in pregnancy would be more effective in preventing preterm birth; this requires further investigation. Metronidazole is safe, effective, and well tolerated in the first trimester.^{254,255} Clotrimazole, used intravaginally, has reportedly relieved symptoms in some women with *T. vaginalis* vaginitis and thus represents an alternative treatment, although a topical therapy could not be expected to decrease preterm birth risk. Other alternative treatments are discussed in more detail in Chapter 43.

SUMMARY: APPROACH TO MANAGEMENT OF SEXUALLY TRANSMITTED DISEASES IN PREGNANCY AND THE PERINATAL PERIOD

The most important approach to preventing pregnancy morbidity related to bacterial STI is to prevent infection in women of reproductive age through effective STI prevention programs. Another central prerequisite is ensuring adequate, early prenatal care for all women; the potential for early detection and preventing STI-related morbidity in pregnancy represents one of the strongest arguments for extending prenatal care to all women. As an initial approach to the management of STI in pregnancy, a standard history concerning sexual behavior and past STI should be obtained from all pregnant patients. Information on age, ethnicity, socioeconomic status, marital status, and health care behavior also may help identify those at highest risk of having a bacterial STI. Specific questions, for example, should include (1) prior modes of contraception including intrauterine device use, (2) previous history of gonorrhea, chlamydia, syphilis, HIV infection, vaginitis, genital warts, genital herpes, or PID, (3) current sexual habits, number of current sexual partners

(e.g., last 2 months), partner characteristics, and likelihood of having a high-risk partner (4) past sexual experience (e.g., age at first coitus, lifetime number of sexual partners), and (5) intravenous or other drug abuse history that could predispose to transactional sex (cocaine, methamphetamines). Patients should be advised about the risks of acquiring STI during pregnancy and provided with concrete information about how to reduce sexual risk, including safer sexual practices and assessment of the potential risk from their partners.

Pregnant women in most populations should routinely undergo cervical, urine, or vaginal screening tests for gonorrhea and chlamydia and serologic testing for syphilis. Those with a history of past gonococcal infection, who have more than one current sex partner or whose partner has multiple partners should be screened again in late pregnancy. BV or trichomoniasis should be screened for in women at high risk of preterm birth or with vaginal symptoms, as discussed earlier.

During pregnancy, a number of clinical situations occur in which the patient should be evaluated for selected STI. Dysuria, a common complaint in pregnancy, should not be automatically attributed to urinary tract infection without excluding vaginitis, cervicitis, or urethritis as possible causes

Table 80-14. Disorders of Pregnancy and the Puerperium That Have Been Associated with Bacterial STI Agents in One or More Studies

Clinical Event	Associated STD Agents
Ectopic pregnancy	Prior <i>C. trachomatis</i> infection; also, 50% of cases have histologic evidence of prior salpingitis
Spontaneous abortion	<i>N. gonorrhoeae</i> , bacterial vaginosis
Post therapeutic abortion-pelvic inflammatory disease	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , bacterial vaginosis
Premature delivery, premature and prolonged rupture of membranes	<i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , bacterial vaginosis, <i>M. hominis</i> , <i>U. urealyticum</i> , <i>T. pallidum</i> , <i>Trichomonas vaginalis</i>
Amniotic fluid infection	Bacterial vaginosis, <i>N. gonorrhoeae</i> , <i>Ureaplasma urealyticum</i>
Congenital abnormalities	<i>T. pallidum</i>
Intrauterine growth restriction	<i>T. pallidum</i>
Puerperal endomyometritis	
Early (<48 h postdelivery)	Bacterial vaginosis, <i>Strep. agalactiae</i> , <i>U. urealyticum</i> , <i>M. hominis</i> , <i>T. vaginalis</i>
Late (>48 h postdelivery)	<i>C. trachomatis</i>
Perinatal	
Stillbirth	<i>T. pallidum</i> , <i>C. trachomatis</i>
Neonatal death, neonatal infection	<i>N. gonorrhoeae</i> , <i>C. trachomatis</i> , <i>T. pallidum</i>

(see Chapter 55). Both gonorrhea and chlamydial infection can cause dysuria. Endocervical, vaginal, or urine assays for *N. gonorrhoeae* and *C. trachomatis* should be obtained from women at any stage of gestation who have signs of mucopurulent cervicitis or a history of exposure to a sex partner with urethritis. Neonatal chlamydial conjunctivitis or pneumonia dictates examination and treatment of mother and father for chlamydial infection. It is to be emphasized that in the setting of neonatal STI, both parents must be interviewed, examined, and treated where appropriate. Women with otherwise unexplained complications such as septic abortion, preterm labor, preterm PROM, and intrapartum fever should be evaluated for STI. Treatable infections (e.g., *N. gonorrhoeae* and *C. trachomatis*) should always be excluded in women with these complications. Women with late-onset endometritis also should be evaluated for *C. trachomatis* infection.

Special surveillance of the neonate may be necessary when the mother is at high risk for STI or develops puerperal infection or intrapartum fever. Such neonates may have to be closely monitored in the hospital for clinical evidence of sepsis and out of the hospital for evidence of ocular or respiratory infection. Considerable controversy surrounds the use of neonatal ocular prophylaxis. To permit initial maternal–neonatal bonding, the American Academy of Pediatrics recommendations allow for prophylaxis to be delayed for up to 1 hour following birth. Presently, silver nitrate, erythromycin, and tetracycline ointment have all been recommended for the prevention of gonococcal ophthalmia neonatorum. An additional benefit of ocular prophylaxis may be the prevention of chlamydial conjunctivitis; the 1-hour delay in applying prophylaxis may reduce the efficacy of prophylaxis for this purpose.

In summary, as shown in Table 80-14, a spectrum of clinical events occurring during pregnancy is associated with infection by bacterial STI agents. The obstetrical consequences of antepartum bacterial STI largely have been neglected until recently and, in fact, represent one of the most important areas for future research on STI. Many studies have shown a relationship of individual STI agents to specific obstetrical complications, as reflected by the large number of citations in this relatively selective review of bacterial STI in pregnancy. Many studies are sometimes difficult to interpret because coinfection with more than one STI agent is common and infection itself may be associated with other noninfectious risk factors for obstetrical morbidity. Primary or new infection with particular STD agents may carry a higher risk than chronic or recurrent infection with the same agents. It may be that coinfection with multiple bacterial STI agents is synergistic in causing obstetrical morbidity. For example, primary infection with an agent such as *C. trachomatis* or *N. gonorrhoeae* might produce chorioamnionitis and lead to preterm PROM, which in turn might lead to a particularly high risk of amniotic fluid infection syndrome in the presence of BV or *T. vaginalis* because of the increased

concentration of anaerobic pathogens and/or pro-inflammatory cytokines in the vagina with these vaginal infections. Thus study of the impact, diagnosis, treatment, and prevention of bacterial STI in pregnancy must remain a high priority.

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D. Heather Watts

Several viral STIs may have a significant effect on pregnant women and their fetuses and infants. While primary viral infections such as rubella during gestation are most often associated with adverse effects in pregnancy, several of the sexually transmitted viral infections may cause significant maternal and infant morbidity even with recurrent infection. The changes during pregnancy that may increase the susceptibility to STIs are discussed in Chapter 80. The impact and management of viral agents with sexual transmission as a major feature including cytomegalovirus (CMV), herpes simplex virus (HSV), human papillomavirus (HPV), and hepatitis B virus (HBV) are summarized here. Management of HIV-1 infection during pregnancy is discussed in Chapter 85.

CYTOMEGALOVIRUS INFECTION

CMV is the most common cause of congenital viral infection of the fetus and is the most common infectious cause of mental retardation. The role of sexual transmission in the epidemiology of CMV is discussed in Chapter 25, and the management of pediatric CMV infections is discussed in Chapter 84.

■ EPIDEMIOLOGY OF CMV INFECTION DURING PREGNANCY

Several studies have shown increasing rates of isolation of CMV from pregnant women with advancing gestation. Women with the highest prevalence of CMV infection may tend to seek care later in pregnancy. Stagno et al.¹ isolated CMV from nonpregnant women at the same rate as from demographically similar pregnant women studied in the third trimester and suggested that lower rates of recovery in early pregnancy are actually due to suppression of CMV shedding in early pregnancy rather than to increased shedding in late pregnancy. Epidermal growth factor, which interferes with the tissue culture isolation of CMV, is present in urine during early pregnancy and may artificially suppress recovery of CMV early in pregnancy.²

Reynolds et al.³ found that young primiparous women are most likely to be cervical shedders of CMV. In one study, 17% of women 14 years of age or younger were culture-positive for CMV compared with 0% of women 30 years of age or older.¹ Most women from whom CMV is isolated during pregnancy have reactivation or recurrent infection rather than primary infection. Depending on the serologic technique employed and the population studied, up to 90% of pregnant women have had serum antibody to CMV. Stagno et al.^{4,5} found that 36% of pregnant women in a middle- to high-income group and 77% of women in a low-income group were seropositive.

Among women who are seronegative at the beginning of pregnancy, primary infection occurs relatively frequently. In three studies, from 0.6% to 4.3% of seronegative women developed primary infection during pregnancy.⁶⁻⁸ Currently, primary CMV infection is undoubtedly many times more common than primary rubella infection during pregnancy. Women most commonly acquire CMV during pregnancy either from sexual transmission or exposure to young children.

Fetal, neonatal, and infant infections with CMV all occur frequently. Congenital infection, as detected by isolation of CMV within the first week of life, occurred in 0.4–2.0% of live-born infants studied in Western countries.^{9,10} Prevalence rates of CMV shedding increase during the first few months of life and peak between 3 and 9 months of age at rates ranging from 5.8% to 56% of all infants. Some areas of the world have high rates despite relatively advanced economic development. Starr¹¹ studied epidemiologic characteristics of mothers whose neonates developed congenital infection. The mean maternal age of 19.0 ± 4.1 years was significantly younger than that of the general population of pregnant women (22.9 ± 5.9 years, $p < 0.01$), and the frequency of primiparity (62%) was significantly greater than that of the general population (31%, $p < 0.01$). These data are also consistent with the concept that primary CMV infection during pregnancy is more likely to be transmitted to the fetus than recurrent infection. With primary infection, congenital infection will occur in approximately 40% of pregnancies, while

transmission to the fetus occurs in 1.0–3.4% of women with reactivation or reinfection during pregnancy. Stagno et al.⁴ found in a prospective study that congenital CMV infections were attributable to primary maternal CMV infection in about half the cases among high-income patients, who were less likely to enter pregnancy with preexisting antibody to CMV, but were usually attributable to recurrent maternal infection among low-income patients. Importantly, primary maternal infections were significantly more likely than recurrent maternal infection to result in clinically apparent congenital CMV infection during the neonatal period when infection occurred within the first half of gestation.

■ MANIFESTATIONS IN PREGNANT WOMEN AND IN THE NEONATE

In the majority of pregnant women who develop primary CMV infection, no recognized clinical illness is discerned. Starr¹⁰ could find no difference in the frequency or type of antenatal illness between 32 women who gave birth to congenitally infected infants and matched controls. All but 1 of 14 primary CMV infections observed by Griffiths et al.⁸ in pregnant women were asymptomatic. Heterophile-negative mononucleosis is occasionally recognized in a mother with a primary infection, and Bell's palsy accompanying primary CMV infection has been described during pregnancy.¹² A fetal ultrasound abnormality such as hydrocephalus,¹³ intracerebral or hepatic calcifications,^{14,15} or hyperechoic bowel¹⁶ may be the first manifestation of primary CMV infection in the mother and fetus.

Women with recurrent (nonprimary) CMV infections almost always have no recognizable clinical abnormality. Women shedding CMV from the genital tract often have simultaneous shedding in the urine and milk.¹ CMV has been isolated from placental tissue, and infected placentas may show chronic villitis with mononuclear or plasma cell infiltrates. Typical cytoplasmic inclusion bodies are not always seen.¹⁷ Amniotic fluid infection syndrome, histologic chorioamnionitis, and spontaneous abortion have not been recognized as manifestations of primary or recurrent maternal CMV infection, although CMV may be isolated frequently from the amniotic fluid of women with primary infections during pregnancy.¹⁸

Congenital infection is most often associated with early clinical manifestations among neonates born to nonimmune mothers who developed primary CMV infection during pregnancy. Approximately 40% of women with primary CMV will transmit CMV to the fetus transplacentally and 10–20% of these infants will have signs of infection at birth including microcephaly, hepatosplenomegaly, and petechiae. In the largest study of congenitally infected infants born to mothers of known infection status in pregnancy, 24 (18%) of 125 infected infants born to mothers with primary infection

were symptomatic at birth.¹⁹ Ninety percent of infants with symptomatic CMV infection at birth will die or have serious sequelae, including microcephaly, mental retardation, developmental delay, seizures, sensorineural hearing loss, and ocular abnormalities.^{19,20}

Congenital infection is less frequent and much less often clinically apparent among neonates born to mothers with preexisting CMV infection. Stagno et al.²¹ noted that 7 (3.4%) of 208 seropositive women delivered congenitally infected neonates. None of these neonates had apparent clinical involvement. In a more recent study from the same institution, among a cohort of 47 infants born with symptomatic infection, eight cases among 20 with definitively classifiable infection status were documented to have been born to women with anti-CMV antibody before conception.²² The severity of clinical abnormalities in the infants did not differ from those seen in symptomatic infants born to women with primary infection. Similar findings have been reported by others.²³ On further study of women with preexisting antibody delivering infants with congenital CMV infection, acquisition of new antibody specificities to CMV glycoprotein H were demonstrated among 10 of 16, suggesting reinfection with a different strain, significantly higher than among CMV antibody positive women whose children were uninfected.²⁴ Given the high prevalence of seropositivity throughout the world, Stagno et al. suggested that recurrent rather than primary infection during pregnancy may be the leading cause of intrauterine CMV infection.⁴ Stern et al.^{7,25} concluded that cellular immunity may play a role in preventing intrauterine transmission of CMV. In their small study of women with primary CMV infection, they found that the eight women with positive lymphocyte transformation (LT) responses had unaffected infants in contrast with four congenitally infected infants born to the six women who had negative LT responses.

Intrapartum CMV infection and infection during infancy and childhood occur much more frequently than does congenital infection. By the end of the first year of life, 5–50% of infants have been infected. Intrapartum infection can result from exposure to maternal cervical CMV infection, while postpartum maternal-infant transmission can result from ingestion of infected maternal breast milk.⁹ No short- or long-term ill-effects are known to result from intrapartum or early postpartum CMV infection among full-term infants. Several studies have documented a high frequency of reactivation of CMV during breast-feeding with transmission to preterm infants. Approximately 10–20% of preterm infants infected through breast-feeding will be symptomatic with sepsis-like findings or viral hepatitis.^{26–28}

■ CASE DETECTION AND MANAGEMENT

Although the incidence and clinical severity of congenital CMV infection are high following primary CMV infection

during pregnancy in the United States, no recommendations currently exist for early identification of seronegative pregnant women who are at risk for primary infections. Women who develop a mononucleosis like illness during pregnancy should have serologic studies performed to exclude primary CMV, although most primary CMV infections in pregnancy are asymptomatic. Women at highest risk for seroconversion, e.g., women working in day-care centers with children under age 3,²⁹ may benefit from preconceptual testing, with follow-up testing in pregnancy if seronegative. In addition, women with abnormal findings on fetal ultrasound that may be related to congenital CMV infection (intracerebral or intrahepatic calcifications, hyperechoic bowel, hydrops, hydrocephaly, severe symmetric growth retardation) should have serologic testing. Often serum from serologic testing earlier in pregnancy for rubella, syphilis, or HIV may be available for testing to document seroconversion or preexisting immunity early in pregnancy. If earlier specimens are not available, then maternal primary infection can be documented by the presence of IgM by radioimmunoassay or enzyme-linked immunoassay. IgM antibody may be present for up to 4 months after primary infection and rarely with reactivation.³⁰ IgG avidity testing is a research test that may be useful in differentiating primary from recurrent CMV infection. The avidity of binding increases with duration of infection with avidity below 25–30% consistent with recent infection.^{31,32}

If maternal primary infection is confirmed, amniocentesis or fetal umbilical blood sampling may be helpful in determining the fetal infection status.^{18,33–38} Amniotic fluid culture and polymerase chain reaction (PCR) testing appear to have a high specificity and a sensitivity of over 80% for the diagnosis of fetal infection status when performed after 20 weeks' gestation or at least 6 weeks after maternal infection. However, the detection of CMV in amniotic fluid does not predict the severity of infection in the fetus. In the presence of an abnormal ultrasound, detection of CMV in the amniotic fluid suggests severe infection. Among women tested because of seroconversion, fetal umbilical blood sampling to evaluate for abnormal transaminase levels or thrombocytopenia may be helpful to detect severely affected infants but these abnormalities may be transient. The patient needs to understand that normal ultrasound and fetal blood studies in the presence of a positive amniotic fluid culture or PCR do not rule out significant fetal damage. Although the risk of damage to the fetus with recurrent CMV infection in pregnancy appears lower than with primary infection, severe fetal infections may occur and may be more likely among immunosuppressed women, such as those with AIDS or after solid organ transplant.^{39–41}

Four antiviral drugs, ganciclovir, valganciclovir, foscarnet, and cidofovir, are currently licensed in the United States for treatment of end organ disease among immunosuppressed individuals.⁴² All are associated with significant toxicities,

and all but valganciclovir require parenteral administration. In addition, CMV immune globulin is licensed for prophylaxis against CMV in transplant recipients and as adjunctive therapy for CMV pneumonitis in immunosuppressed patients. Several case reports of use of ganciclovir in pregnancy for treatment of maternal disease among liver transplant recipients or HIV-infected women suggest that it is reasonably well tolerated.⁴² Ganciclovir crosses the placenta and reaches the amniotic fluid. Case reports of use of ganciclovir either parenterally to the mother or by intra-amniotic injection to attempt to treat fetal infection have been limited and do not allow assessment of potential benefit. Given the potential toxicity and lack of data to suggest benefit for fetal infection, use of ganciclovir in pregnant women should be reserved for treatment of end organ disease in the mother or only in carefully designed clinical trials. Experience with other antiviral drugs for CMV in pregnancy is even more limited. Treatment of the neonate and infant diagnosed with congenital CMV infection is discussed in Chapter 84.

Recently, use of intravenous CMV hyperimmune globulin among women with documented primary CMV infection in pregnancy to try to ameliorate the effects of CMV on the fetus among women with CMV detection in the amniotic fluid or to prevent fetal infection among those with recent infection or those declining amniocentesis was reported.⁴³ In some cases, intra-amniotic or intraumbilical doses were given. In this nonrandomized study, symptomatic CMV disease at birth with persistent handicap occurred among 1(3%) of infants born to 31 treated women compared to 7(50%) of 14 infants born to untreated women ($p < 0.001$). In the prevention group, congenital infection occurred among 6(16%) of infants born to 37 treated women compared to 19(40%) of 47 women not receiving hyperimmune globulin ($p = 0.02$). While these results are encouraging, efficacy must be confirmed in a randomized trial with standardized dosing and more complete assessment of CMV infection status of the fetus at enrollment before this expensive and logistically difficult therapy can be recommended.⁴⁴ In addition, practical and reliable algorithms for identification of women with primary CMV infection must be developed before implementation of treatment programs.

Currently, the best preventive measure against congenital CMV infection appears to be prevention of maternal infection through education.⁴⁵ Congenitally or perinatally infected infants often shed large amounts of the virus in saliva, respiratory secretions, and urine. Pregnant women should not be exposed to infants recognized to be shedding CMV. Pregnant women should avoid contact with toddler urine and saliva, because toddlers, especially those in day care, have a high rate of infection and shed high levels of virus. Ultimate prevention of severe congenital CMV infection awaits a safe and effective vaccine. Although several vaccines are in development, their potential for protection against congenital infection has

not been evaluated.^{46–48} If pregnant women or fetuses require blood transfusion, CMV-negative blood should be used.

HERPES SIMPLEX VIRUS INFECTION

The primary concern with genital herpes virus (HSV) infection during pregnancy is the risk of transmission to the neonate during labor and delivery, although primary infection during pregnancy may also increase the risk of pregnancy loss and preterm birth. Neonatal HSV is estimated to occur in about 1 in 3200 live births.⁴⁹ Approximately 85% of neonatal HSV infections are acquired from exposure to HSV in the birth canal, about 10% are due to exposure to other sources of HSV such as orolabial HSV in caregivers, and about 5% occur after transplacental infection.⁵⁰

■ EPIDEMIOLOGY

Antibody to HSV-2, which causes about 80% of cases of genital herpes in women, has been measured in the U.S. National Health and Nutrition Examination Survey (NHANES) of a random sample of U.S. adults. The prevalence of antibody to HSV-2 increased by 30% from the period 1976–1980 to the period 1988–1994^{51,52} (see Chapter 24). Women were more likely than men to be HSV-2-seropositive, and African American women were more likely than Caucasian women to be HSV-seropositive. Among U.S. pregnant women, HSV-2-seroprevalence has ranged from 16.5% to 32%, with the majority being unaware of their genital herpes infection.^{53–55} A significant proportion of genital HSV infections are caused by HSV-1 rather than HSV-2. A recent study found that among women, 21.4% of initial genital HSV infections were culture-positive for HSV-1 rather than HSV-2.⁵⁶ Factors associated with new genital HSV-1 infections on multivariate analysis included white race, receiving oral sex, and lack of vaginal intercourse. As discussed below, genital HSV-1 infections may be transmitted to the neonate and acquisition during pregnancy is associated with a high risk of transmission.

■ NATURAL HISTORY AND MANIFESTATIONS OF GENITAL HSV INFECTION DURING PREGNANCY

Primary genital infection with HSV in women may be characterized by clinical illness averaging about 3 weeks in duration, with high concentrations of virus shed from vulvar and cervical lesions, inguinal adenopathy, and frequent systemic manifestations such as fever suggesting viremia. However, only about 25% of women with HSV-2 antibody are aware that they have had genital herpes, suggesting that most primary episodes must be asymptomatic or only produce mild or unrecognized symptoms. Further difficulty in recognizing primary infection in pregnancy was illustrated by a study of acyclovir for primary HSV in pregnancy. This study

was terminated when it was found that of the 23 women enrolled with first clinical episodes of HSV, with symptoms suggestive of primary HSV (bilateral lesions, malaise, myalgia, or headache), only 1(4%) was truly primary (seronegative for antibody to HSV-1 and HSV-2), while 3(12%) had nonprimary first episodes (seropositive for antibody to HSV-1 at presentation) and 19(84%) were recurrent (already seropositive at presentation).⁵⁷ Type-specific antibody testing is needed for women with their first clinical episode of genital HSV in pregnancy to identify those with true primary or initial infections. Several assays that detect antibodies to HSV-1 glycoprotein G (gG1) and HSV-2 glycoprotein G (gG2) are now available and should be used in this setting to distinguish primary, first episode nonprimary, and recurrent infection.⁵⁸ Among the 70–85% of women who are seronegative to HSV-2 or HSV-1 early in pregnancy, 0.25–1.3% will seroconvert by delivery.^{53,55} In the largest study, 94(1.3%) of 8508 women seroconverted to HSV during pregnancy. Among women who were HSV-seronegative, HSV-1-seropositive, or HSV-2-seropositive at the first prenatal visit, adjusted rates of seroconversion to either HSV type were 3.7%, 1.7%, and 0%, respectively.⁵⁵ The risk of development of a primary genital HSV infection (HSV-1 or HSV-2) adjusted for the entire length of pregnancy was approximately 2%.

Primary genital HSV infection in pregnancy has more potential for an adverse impact than nonprimary first-episode infection or recurrent infection, underscoring the benefit of serologic confirmation of the status of women with a first symptomatic episode of genital HSV in pregnancy. Transplacental infection with HSV during initial viremia appears to be rare, since congenital infection is diagnosed infrequently. Only 8(4%) of 210 neonates with HSV infection enrolled in an antiviral trial were diagnosed as having congenital rather than neonatal infection.⁵⁰ Symptomatic primary genital HSV infection in pregnancy has been associated with a significant increase in spontaneous abortion, preterm labor, and low birth weight. Nahmias et al.⁵⁹ reported a spontaneous abortion rate of 54% among women with primary infection before 20 weeks' gestation. In that study, among women with symptomatic primary infection after 20 weeks' gestation, 35% of the infants had a birth weight below 2500 gm and 50% developed neonatal herpes. In another study, among 15 episodes of primary HSV during pregnancy, 6(40%) were associated with severe perinatal morbidity (preterm birth, growth retardation, or neonatal HSV infection).⁶⁰ Poor outcomes were observed among 4(80%) of the 5 women with primary infection in the third trimester. Among the 14 women with nonprimary, first-episode disease in pregnancy, no cases of preterm delivery, growth retardation, or neonatal HSV occurred. The lack of increase in preterm birth or fetal growth retardation among women with recurrent genital HSV has been confirmed in a larger study.⁶¹

Among women with asymptomatic seroconversion in pregnancy, whether with or without preexisting antibody to the heterologous HSV type, the principal risk appears to be for preterm labor and increased risk of neonatal infection among those women without homologous antibody to the genital strain at delivery, e.g., with recent acquisition. Women with recent acquisition of HSV are also more likely to be shedding HSV, are more likely to shed both from the cervix and the vulva, and more likely to shed asymptotically.⁶² Asymptomatic cervical shedding of HSV-2 was detected by culture at 10.6% of visits among women with symptomatic primary genital HSV infection earlier in pregnancy and in 0.5% with nonprimary, first-episode disease earlier during the pregnancy.⁶⁰

Data regarding the effects of pregnancy on recurrences of genital herpes are conflicting. Vontver et al.⁶³ followed 80 pregnant women with a history of recurrent genital HSV with serial cultures. Fifty-six (70%) had at least one positive culture during pregnancy. The proportion with positive cultures did not change with advancing gestation. A subsequent study of 147 women with a history of recurrent genital herpes detected an increase in the number of recurrences from a mean of 0.97 in the first trimester to a mean of 1.63 in the third trimester.⁶² A study using daily home collection of vulvovaginal specimens for cultures and PCR testing among a small group of women in the third trimester of pregnancy with a history of recurrent genital herpes antedating pregnancy did not show a change in the rate of symptomatic recurrences, asymptomatic shedding, or PCR-positivity with advancing gestation.⁶⁴ Cultures were positive on 3.4% of days and HSV was detected by PCR on 16.8% of days.

Taken together, the data suggest that women with symptomatic primary genital HSV infection in pregnancy may be at increased risk for spontaneous abortion and preterm labor. The risk of preterm labor also appears to be increased among women with asymptomatic seroconversion late in pregnancy. Both groups have increased risk of transmitting infection to the neonate.

■ RISK OF NEONATAL TRANSMISSION

The incidence of neonatal HSV infection in the United States is estimated to be 1:1400–1:30,000 deliveries.⁶⁵ Most neonatal HSV infection is presumed attributable to intrapartum exposure to HSV in the birth canal. While the majority of cases of neonatal HSV are due to HSV-2, in the largest study reported to date incorporating serology and HSV cultures at delivery, 8(44%) of 18 cases of neonatal HSV were caused by HSV-1.⁴⁹ Few neonates are affected at birth and most develop signs of infection in the second week of life. Up to one-half of neonates acquiring HSV infection have been exposed to mothers with primary infection occurring late in pregnancy. Whitley et al.⁶⁶ observed that 41% of neonates with HSV infection

weighed less than 2500 gm at birth and that 51% lacked antibody to HSV in the initial serum sample. Primary genital infection with HSV is a greater risk factor for neonatal acquisition of HSV for several reasons. The association with prematurity makes delivery during the primary infection likely, at a time when the inoculum of virus present in the birth canal is large, cervical involvement is extensive, maternal viremia may occur, maternal antibody is absent, and the infant may be immunologically immature. Neonates born to mothers with recurrent HSV-2 infection appear to acquire protective immunity from the mother and are at low risk of acquiring HSV infection, particularly invasive disease.⁶⁷

The risk of neonatal HSV infection based on maternal HSV antibody status in early pregnancy is summarized in Fig. 81-1.^{49,53–55,59,60,63,68–70} Of note, the risk of neonatal HSV is highest among infants born to women who enter pregnancy without HSV antibody because of the higher risk of HSV shedding with recent infection and lack of antibody transfer to the infant. In five studies of infants born to women with first-episode genital infections at delivery, 19(44%) of the 43 infants developed neonatal infection.^{55,59,60,69,70} In the one study in which it was evaluated, transplacentally acquired HSV-1 antibody did not decrease the risk of neonatal HSV-2 infection.⁷⁰ Two large studies have found much lower rates of neonatal HSV among infants born to women with positive cultures at delivery related to reactivation. Neonatal HSV occurred among 1(3%) of 34 infants and 0 of 34 infants born to women with recurrent HSV and positive cultures at delivery.^{67,70} Positive genital HSV cultures at delivery were detected in 0–2.4% of asymptomatic women with a history of recurrent genital herpes.^{54,63,68} The risk of HSV shedding at delivery among women with acquisition of genital HSV during pregnancy varies depending on the timing of acquisition.⁵⁵ In some cases, preterm labor may occur coincident with primary infection, leading to high levels of HSV in the genital tract, whereas the risk of shedding among women with acquisition in the first trimester may be more similar to women with infections antedating pregnancy. Given the higher risk of transmission after primary infection during pregnancy, at least half of neonatal HSV infections are related to maternal primary infections, although only 1–2% of women have primary infection during pregnancy compared with up to 30% who have preexisting antibody to HSV-2. Therefore, any strategy directed at preventing neonatal HSV must address both prevention of primary infection in pregnant women and detection or prevention of reactivation of recurrent disease at delivery.

Early studies suggested that the route of delivery and duration of rupture of the membranes correlated with risk of neonatal infection when mothers have primary genital herpes at term. Approximately 50% of neonates exposed to such mothers during vaginal delivery acquired the disease. In contrast, only 1(6%) of 16 neonates delivered by cesarean section

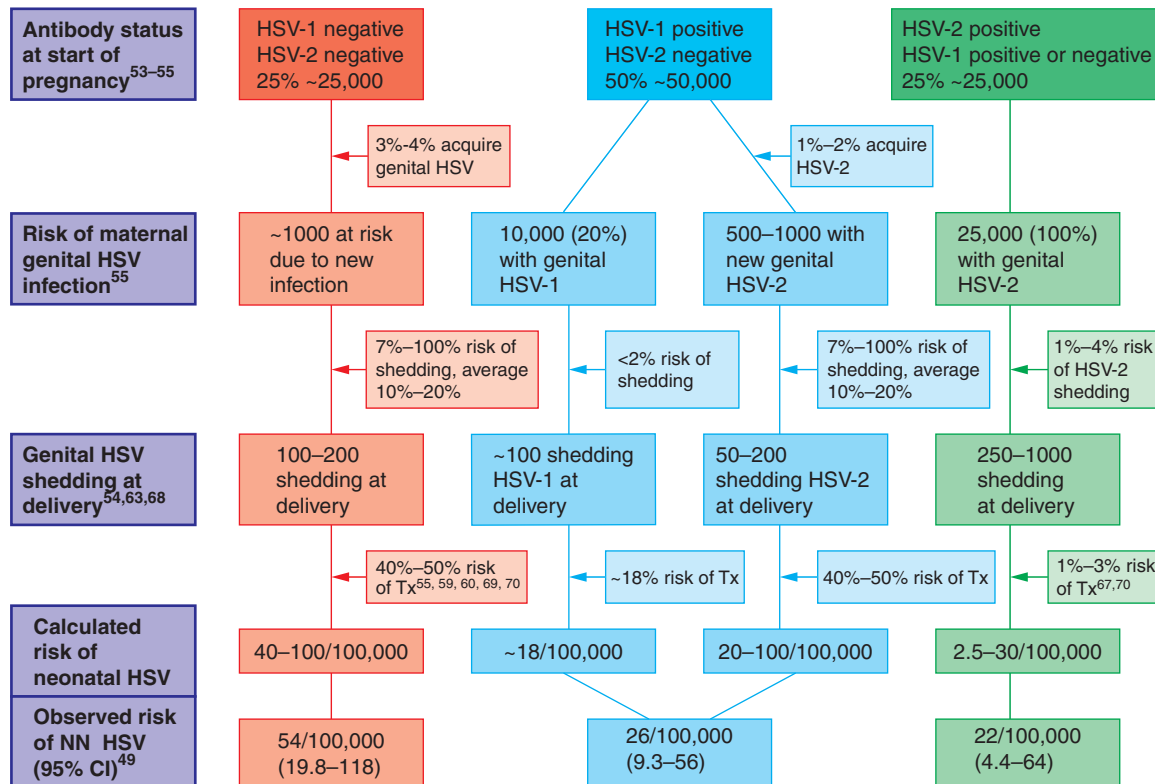


FIGURE 81-1. Calculated and observed risk of neonatal herpes simplex virus (HSV) infection according to maternal HSV antibody status at first prenatal visit among theoretical cohort of 100,000 women.^{53-55,59,60,63,68-70}

within 4 hours of rupture of the membranes acquired the disease.⁶⁰ In cases where the membranes had been ruptured for more than 4 hours, six of seven exposed neonates acquired the disease irrespective of the route of delivery. A more recent study suggests the value of cesarean delivery even among women with recurrent HSV at delivery.⁴⁹ Among over 40,000 women undergoing genital culturing at delivery, positive cultures were detected in 202. The risk of transmission was reduced among all women with HSV detected by culture with cesarean delivery (odds ratio 0.14, 95% CI 0.02-1.08). One case (1.2%) of neonatal HSV occurred among the culture-positive women delivered by cesarean delivery compared to nine cases (7.7%) among 117 women delivering vaginally. However, when adjusted for type of HSV isolated, first episode versus recurrent disease, and isolation from the cervix, mode of delivery was no longer significant. Risk of transmission was increased on multivariate analysis with isolation of HSV-1 (AOR 34.8, 95 CI 3.6-335), first episode disease (AOR 59.3, 95% CI 6.7-525), and viral isolation from the cervix (AOR 15.4, 95% CI 1.8-133) as opposed to the vulva only. Thus, cesarean delivery continues to be recommended for women with active herpes lesions at the onset of labor or among women with acquisition of genital HSV near delivery with a high risk of genital, including cervical, shedding and no homologous maternal antibody.⁷¹ For women with a history of genital HSV but no lesions undergoing

labor and vaginal delivery, use of invasive monitoring and instrumental delivery (forceps or vacuum extraction) should be avoided whenever possible, because these procedures may cause breaks in the skin which increase the risk of neonatal infection in the presence of asymptomatic shedding.⁴⁹

Whereas other neonatal viral infections are often subclinical, the majority of neonates with HSV infection have clinical manifestations of disease (see Chapter 84). Infection may be manifest as skin, eye, and mouth disease with involvement limited to the skin and mucous membranes; encephalitis; or disseminated infection with multiorgan involvement. Mortality and long-term morbidity rates remain high with encephalitis or disseminated infection, despite use of antiviral therapy.⁷² The unique neonatal propensity to severe HSV infection, which persists for several months following delivery, is presumably related to a poor cellular immune response against HSV during this period.

■ CASE DETECTION AND MANAGEMENT

Since it is not practical to perform routine screening cultures for HSV on all women at delivery, prevention of neonatal HSV infection currently rests both on preventing primary HSV infection during pregnancy by identifying women at high risk for genital HSV and defining a management strategy for them, as well as on recognizing clinical manifestations of genital herpes

in women near delivery. Whitley et al.⁶⁶ analyzed the risk profile of mothers of neonates acquiring HSV and found that 57% had a history of genital herpes, a sex partner with genital lesions suggestive of herpes, or signs or symptoms of genital herpes during pregnancy. Asymptomatic intrapartum shedding of HSV is not predictable from antepartum cultures for HSV among women with a history of genital HSV⁶⁹ and these cultures are no longer recommended.

A rapid test for HSV shedding would allow timely detection of asymptomatic shedding and testing of suspicious but atypical genital lesions, thus targeting cesarean delivery for those actually shedding virus; unfortunately, none of the currently licensed rapid tests has adequate sensitivity for this use.⁷³ PCR testing has enhanced sensitivity to detect asymptomatic shedding, but this method has not been adapted for routine clinical use, and the risk of neonatal infection with low DNA copy numbers detectable by PCR has not been established.^{74,75}

Clinicians should solicit and record in the prenatal record the presence or absence of a history of genital herpes in the patient or her partner(s) and should assess her current sexual behavior. Women with a positive history of genital HSV antedating pregnancy should be counseled to report any prodromal symptoms or lesions present at the onset of labor. For women with recent recurrences, the option of prophylactic antiviral therapy to reduce the risk of recurrence and the need for cesarean delivery can be discussed. A recent meta-analysis including five randomized trials of the use of acyclovir from 36 weeks of gestation until delivery found significant reductions in clinical HSV recurrences at delivery, cesarean delivery for HSV, detection of HSV by culture at delivery, and detection of HSV among asymptomatic women at delivery among women receiving acyclovir compared to placebo or no treatment.⁷⁶ Overall, use of acyclovir was associated with a 75% reduction in symptomatic recurrences at delivery and a 70% reduction in cesarean delivery for genital HSV. None of 339 acyclovir-treated women had positive genital cultures for HSV at delivery compared to 15(5%) of 293 women not receiving acyclovir (OR 0.61, 95% CI 0.43–0.86). In one study that included PCR testing, HSV was detected by PCR within 2 days of delivery in 1 (2%) of 62 women receiving acyclovir; the subject had lesions at the time.⁷⁷ The dosage of acyclovir used in these studies was either 200 mg 4 times daily or 400 mg 3 times daily. One study included only women with first episode genital HSV during pregnancy, two included women with documented recurrent disease, and two did not differentiate between recurrent or primary infections. Based on a previous study attempting to evaluate treatment of new genital HSV acquired during pregnancy, the majority of women with their first symptomatic episode of genital HSV during pregnancy have recurrent disease, which was previously asymptomatic.⁵⁷ No cases of neonatal HSV occurred in any of the

studies but numbers were inadequate to assess any change in the risk. Based on these studies, acyclovir reduces the risk of HSV recurrences and cesarean delivery for HSV among women with symptomatic episodes during pregnancy. Whether or not acyclovir prophylaxis is beneficial for women with genital HSV is uncertain but no symptomatic recurrences in pregnancy has not been studied.

For women with a first symptomatic episode of HSV infection in pregnancy, attempts should be made to determine whether the episode represents recurrent or true first-episode infection. Several assays are now available that detect antibodies to the HSV-1 glycoprotein G (gG1) and HSV-2 glycoprotein G (gG2), allowing differentiation of the antibody response to the specific HSV types isolated from the genital tract.⁵⁸ If reliable testing for type-specific antibody is available, then women with homologous antibody to the HSV strain isolated from the genital tract may be managed as discussed earlier for recurrent disease. Women with primary or first-episode infections, lacking antibody to the genital HSV strain detected in the third trimester of pregnancy should be offered cesarean delivery, ideally before membrane rupture, regardless of symptoms because of the high risk of asymptomatic shedding of high titer HSV in the genital tract and lack of fully developed antibody response.⁵⁸

The most difficult cases to prevent are those related to acquisition during pregnancy. Negative history in the patient (although insensitive for HSV-2-seropositivity), coupled with positive history in the partner (though nonspecific), or risky sexual lifestyle should prompt advice on use of condoms for any intercourse during pregnancy. Women with partners with symptoms or history suggestive of oral HSV infection should avoid oral-genital contact during pregnancy to try to prevent acquisition of genital HSV-1 infection. Women at high risk for primary or recurrent infection should be observed carefully for clinical evidence of genital lesions and, in the absence of herpetic lesions during labor, should be delivered vaginally unless there are other indications for cesarean section. If recurrent herpetic lesions are present in the genital tract at the time of rupture of the membranes or during labor, cesarean section may reduce the risk of neonatal infection and ideally should be performed within 4–6 hours after membrane rupture.

Given the high risk of transmission to the neonate with acquisition of genital HSV during pregnancy, the fact that only about one-quarter to one-third of women with established genital HSV are aware of their infections, and the availability of type specific serologies with reasonable sensitivity and specificity, some experts advocate the use of routine serologic screening for HSV infection in early pregnancy.⁵⁸ Identification of women with HSV-2 antibodies but no history of genital HSV allows education regarding signs and symptoms of recurrence that may identify previously unrecognized outbreaks and increase detection of prodrome or

lesions at the onset of labor. In addition, the risks and benefits of antiviral prophylaxis in late pregnancy can be discussed for women with recurrences identified during pregnancy, and the option of suppressive therapy after delivery to prevent partner transmission can be offered. For women who are seronegative for antibodies to HSV-2, the concern regarding acquisition of genital HSV can be discussed and partner testing offered to assess risk of acquisition. It is estimated that about 20% of couples will be at risk for transmission to the woman during pregnancy.⁵⁸ If the partner is found to be HSV-2 positive, practices to reduce risk of transmission to the pregnant woman including abstinence, condom use, or partner suppression with antivirals can be discussed. The efficacy of these measures for prevention of acquisition of genital HSV during pregnancy and for prevention of neonatal HSV has not been evaluated. If the partner is HSV-1 seropositive and the pregnant woman is not, then avoidance of oral-genital contact in pregnancy is recommended. In addition, since the male HSV-1 infection may be genital if he is HSV-2 seronegative, avoidance of genital-genital contact is also recommended to prevent genital HSV-1 infection. Again, the acceptability and efficacy of these measures in prevention of neonatal HSV infection have not been assessed. If the partner is not able to be tested, seronegative women can be counseled regarding abstinence and condom use to attempt to decrease the risk of primary infection in pregnancy. In addition, symptoms suggestive of genital HSV infection including genital sores and recurrent irritation can be discussed. Given the expense of routine HSV serology in pregnancy and the unproven benefits of subsequent interventions, routine testing is not recommended currently.⁷⁸ However, type-specific maternal serology is indicated for women with first-episode genital HSV in pregnancy and may be useful for women with histories suggestive of genital HSV or with negative histories with a partner with a history suggestive of genital HSV. Further evaluation of HSV serologic testing in pregnancy is needed before routine implementation.

Another key factor in limiting the morbidity and mortality of neonatal HSV infection is early diagnosis and treatment. Despite advances in antiviral therapy, both mortality and long-term morbidity remain high for infants with systemic infection. Parents should be educated about nonspecific signs such as poor feeding or irritability that require notification of the infant's provider, and providers must keep neonatal HSV in the differential diagnosis of infants with illness in the first few weeks of life, regardless of maternal history regarding genital HSV.

Management of pregnant women with HSV lesions and early preterm rupture of the membranes must be individualized. If the pregnancy is at or beyond 34 weeks' gestation, then delivery by cesarean section as soon as possible is indicated. Before this time, risks of prematurity versus risks of in utero or neonatal infection based on gestational age, maternal anti-

body status, and other clinical factors must be weighed. Consideration should be given to the use of intravenous or oral acyclovir in the mother to shorten the maternal course and possibly decrease the risk of neonatal infection. Over 30 cases of use of this approach without cases of neonatal HSV have been reported but the safety remains to be defined.^{79,80}

Although primary genital HSV infection in early pregnancy may cause spontaneous abortion, congenital infection is considered uncommon. For this reason, therapeutic abortion is not recommended for pregnancies complicated by primary infection.

■ FUTURE DIRECTIONS IN MANAGEMENT OF HERPES DURING PREGNANCY

Strategies aimed at decreasing recurrences among women entering pregnancy with history of genital herpes or HSV-2 seropositivity will only eliminate about half the cases of neonatal HSV. At least 50% are related to acquisition of HSV, especially late in pregnancy.⁵⁸ Strategies to decrease exposure and seroconversion in pregnancy would include development of a vaccine to be administered to teenagers before the onset of sexual activity, assessment of ongoing high-risk sexual exposures, and serotesting to identify discordant couples with an HSV-2-seronegative pregnant woman with a seropositive partner, as discussed above. Further evaluation of the use of serotesting and efficacy of interventions is required before routine implementation. A vaccine against HSV-1 and HSV-2 infection could eliminate the risk of primary genital infection during pregnancy but such a vaccine is not currently available. An HSV-2 glycoprotein-D-subunit vaccine showed 74% efficacy in preventing acquisition of genital HSV-2 among women who were both HSV-1 and HSV-2 seronegative at enrollment but no efficacy in women who were seropositive for HSV-1 at enrollment or among men regardless of serostatus.⁸¹ Further trials are underway and vaccine development continues.

HUMAN PAPILLOMAVIRUS INFECTION

From the 1960s through the mid-1980s, the number of initial office visits to physicians in the United States for condylomata acuminata, or genital warts, increased dramatically.⁸² Genital HPVs, the causative agents of genital warts and cervical, vaginal, and vulvar intraepithelial neoplasia and cancer, are of concern in pregnancy for three reasons: (1) warts may rapidly enlarge with advancing gestation and mechanically obstruct labor or bleed during delivery, (2) a common form of therapy, podophyllin application, is contraindicated during pregnancy, and (3) perinatal exposure may result in laryngeal papillomas or genital warts in infancy or childhood. The worsening of cervical intraepithelial neoplasia

(CIN) frequently observed during pregnancy may also be due to accelerated HPV replication.

■ EPIDEMIOLOGY

HPV infection is common during pregnancy. Approximately 1 percent of sexually active adults are estimated to have genital warts, with a range of 0.6–13%, depending on age and sexual risk factors.⁸³ Rates are highest in those 18–28 years old, peak childbearing years. During pregnancy, genital warts may enlarge, with pronounced vascularity. During the puerperium, regression often follows. The responsible mechanism is unknown but may relate to depression of maternal immunocompetence during pregnancy.

In studies of HPV DNA detection during pregnancy, the prevalence has ranged from 5.2 to 65%, with most studies detecting HPV DNA in 30–40% of pregnant women.^{84–95} The majority of studies,^{86,89,91,92,95} but not all,^{84,90} that have compared the detection of HPV DNA among pregnant to non-pregnant women have found increased detection during pregnancy, even when adjusting for age and sexual exposures. These findings are consistent with animal studies showing up regulation of HPV with pregnancy and with high levels of estrogen and progesterone seen in pregnancy.⁹⁶ Thus, genital HPV infection is common during pregnancy.

Infection with genital types of HPV in children may be manifest as genital warts or as laryngeal papillomas. Neonatal exposure to HPV probably occurs most commonly during birth by aspiration of contaminated cervical, vaginal, or vulvar material although some studies have detected HPV in the amniotic fluid without rupture of membranes, and rare cases of genital condylomata present at birth have been reported.^{97,98} Studies on the risk of perinatal transmission are summarized below.

Genital warts in young children may be secondary to perinatal transmission of genital HPV, sexual abuse, exposure to non-genital HPV types through autoinoculation or caregiver warts, or fomite transmission.⁹⁹ The incubation period for development of warts after perinatal exposure is unknown but is felt to range from 1 month to several years. The evaluation for possible exposure through sexual abuse is discussed in Chapter 87.

Laryngeal papillomatosis, a form of recurrent respiratory papillomatosis (RRP), is the most frequent tumor of the larynx in children. There is a bimodal age distribution, with peaks in children between 2 and 5 years of age and in young adulthood. Twenty-eight percent of childhood cases were detected in infants under 6 months of age.¹⁰⁰ Studies of cellular DNA from genital warts and from laryngeal papillomas have shown that HPV types 6 and 11 account for the majority of genital warts and laryngeal papillomas.^{101,102} While malignant transformation of respiratory papillomas is rare, these tumors frequently recur, requiring multiple ablative procedures and potentially leading to hoarseness, respiratory distress, and rarely, death. In one survey, children with RRP

underwent an average of 5.1 surgeries annually for treatment of recurrences while in three other studies, the lifetime number of surgeries was 13.7.^{103,104} The rate of RRP is low with an annual incidence of 0.4–0.6/100,000 children in Danish studies^{105,106} and a range of 0.36–4.5/100,000 in the United States.^{107,108} A rate of 4.7/100,000 births was found in a study of Danish births over a 20-year period.¹⁰⁹ In this study, the risk of RRP among infants born to women with genital warts at delivery was estimated to be 6.9/1000 births.

History of condylomata acuminata can be obtained from 37% to over 50% of mothers whose infants develop laryngeal papillomas.^{109–112} Subclinical genital HPV infection in the mother is presumably responsible for most of the remainder. Perinatal transmission during vaginal delivery has been the presumed mode of spread, since children born by cesarean section have had a lower risk of acquiring RRP in some studies.^{112,113} A more recent study did not find cesarean delivery to be protective for RRP but did find a doubling a risk with labor longer than 10 hours.¹⁰⁹ Other risk factors for RRP in one or more studies were young maternal age and first births, suggestive of primary infection.

■ RISK OF PERINATAL TRANSMISSION

The reported risk of transmission of HPV from mother to infant has varied considerably in different populations studied by various methods. Detection of HPV DNA from infant oral or genital specimens in the first few days of life has ranged from 3.7% to 72% among infants born to women testing positive for HPV DNA during pregnancy and 0.1–20% among infants born to women without HPV DNA detected during pregnancy.^{85,87,88,93,94,97,114–118} Even in studies with high detection rates, the concordance between maternal and infant HPV types is at best about 60%. In a recent large study, the only one to date to use sequencing methods to evaluate concordance between infant and parental HPV types, HPV DNA was detected in 9(1.6%) of 574 infants, including 6(3.7%) of 164 with maternal HPV DNA detection and 3(0.1%) of 410 without genital HPV DNA.⁹³ Only one mother/infant pair was found to have concordant DNA types. These low rates of HPV DNA detection in the neonatal period in this study are consistent with the larger of the previous studies.^{87,115,118} Studies following infants beyond the neonatal period have yielded similar varying rates of HPV DNA detection, with rates varying from 0% to 79% among children born to mothers with genital HPV detected during pregnancy and from 0% to 50% among those without genital HPV detection.^{85,93,116–118} In most cases, the HPV detection rate was not related to detection of genital HPV infection in the mother during pregnancy. Thus far, the only clinical manifestations of perinatal HPV transmission appear to be cases of RRP and infant genital warts, both rare occurrences compared to the frequency of genital warts in reproductive age women. No long-term

consequences of perinatal exposure to high-risk HPV types have been documented, although continued evaluation of the role of HPV in oral lesions is needed.

■ CASE DETECTION AND MANAGEMENT

All pregnant women should have Pap smears to detect CIN, and those with active or past genital warts should be observed to detect recurrence or excessive growth of wart lesions. Pregnant women with visible genital warts should be offered treatment to decrease symptoms, risk of bleeding at delivery, and potentially, risk of transmission, although no studies of treatment to prevent transmission have been reported. The conventional techniques for treating genital warts in pregnancy include bichloroacetic or trichloroacetic acid application, electrocoagulation, cryotherapy, laser vaporization, or surgical excision. Since both maternal and fetal deaths have resulted from podophyllin treatment of large vascular warts, this drug, including the patient-applied form, podofilox, should not be used during pregnancy.¹¹⁹ The safety of imiquimod cream and interferon have not been evaluated in pregnancy, so these agents are not recommended.¹²⁰

Cesarean section is not currently recommended to prevent neonatal exposure to HPV, even among women with visible genital warts.^{120,121} While the rate of RRP was lower among infants born by cesarean delivery in some studies, this finding was not consistent.^{109,112,113} HPV detection among infants born by cesarean delivery without labor has been reported, and no controlled studies have evaluated the ability of cesarean delivery before labor to prevent RRP. Although cesarean delivery is not routinely recommended for women with genital warts in pregnancy, women with genital warts persisting into the third trimester should be informed of the risk of RRP in the infant estimated at about 7/1000, the lack of data as to whether cesarean delivery decreases this risk, and the risks to her from cesarean versus vaginal delivery. Cesarean delivery may be necessary in rare instances where extensive lesions obstruct the vaginal outlet.

■ FUTURE DIRECTIONS IN MANAGEMENT OF HPV DURING PREGNANCY

Recent results from trials of multivalent vaccines for HPV suggest that they are effective in decreasing acquisition of vaccine strains of HPV and preventing development of CIN from high-risk HPV types included in the vaccine.¹²² A vaccine including antigens from HPV types 6, 11, 16, and 18 is undergoing trials.¹²³ If protection from HPV types 6 and 11 infection is similar to that seen for types 16 and 18, implementation of preventive HPV vaccines in adolescence before onset of sexual activity could theoretically eliminate the risk of maternal genital warts and transmission of HPV 6 and 11 to infants.

HEPATITIS B

Hepatitis B is a small DNA virus containing three principal antigens: hepatitis B surface antigen (HBsAg), hepatitis B core antigen (HBcAg), and hepatitis Be antigen (HBeAg). Core antigen is present only in hepatocytes. Detection of HBeAg in blood indicates active viral replication and extremely high viral levels and infectiousness.

Acute HBV infection occurs in 1–2 per 1000 pregnancies, and chronic infection is found in 5–15 per 1000 pregnancies in the United States.¹²⁴ Risk factors for HBV infection include injection drug use, multiple sexual partners, history of other sexually transmitted diseases, work in a health care or public safety field, work or residence in an institution for the developmentally disabled, and receipt of clotting factor concentrates. Higher risks of infection are found among certain ethnic groups such as Native Alaskans and in immigrants from many developing countries. Despite the increased prevalence of HBV infection in patients with risk factors, screening in pregnancy based on risk factors alone will miss up to 75% of women with HBV infection.¹²⁵

Clinical manifestations and natural history of HBV infection are described in Chapter 29. Symptoms of acute HBV infection, if present, are similar in pregnant and nonpregnant individuals and include malaise, fatigue, anorexia, nausea, and right upper quadrant pain. Signs include jaundice, hepatomegaly, and dark urine. There is no evidence that pregnancy worsens the course of acute viral hepatitis. However, pregnant women with the signs and symptoms listed above, especially women in the third trimester, should be evaluated carefully for indications of preeclampsia (hypertension, proteinuria, edema) or acute fatty liver of pregnancy, since delivery is indicated if either of these is present.¹²⁴ Transaminase levels are usually less elevated (200–400 $\mu\text{m}(\text{mL})$ range) with preeclampsia or acute fatty liver than with acute HBV (over 1000 $\mu\text{m}(\text{mL})$). The diagnosis of acute HBV can be confirmed by the presence of HBsAg and anti-HBc IgM antibody in the serum (see Chapter 29). In pregnant women with hepatitis, testing acute and convalescent sera for CMV seroconversion is important because of the potential for fetal CMV infection. Pregnant women with acute liver disease should be evaluated for coagulopathy and hypoglycemia. Hospitalization is indicated for encephalopathy, coagulopathy, severe debilitation, or inability to maintain adequate nutrition.

With acute HBV in pregnancy, the risk of perinatal transmission depends on the stage of gestation at time of infection. First-trimester infection is associated with transmission to the fetus in up to 10% of cases; third-trimester acute infection is associated with an 80–90% risk of transmission.¹²⁶ Since chronic HBV infection is more common than acute infection during pregnancy, 85–95% of cases of perinatal transmission of HBV are related to intrapartum exposure.

With chronic infection, the risk of perinatal transmission is 10–20% among women who are HBsAg-positive and HBeAg-negative but rises to 50–90% among HBeAg-positive women in the absence of infant immunization.^{127–129} Because of the high risk of perinatal transmission of hepatitis B, the 25% risk of death in adulthood from chronic liver disease after infection during infancy, and the 85–95% efficacy of passive plus active immunization of exposed infants, all pregnant women should be screened at the first prenatal visit for HBsAg.¹³⁰ Sexual partners and children of HBsAg-positive women should be offered testing and vaccination. Determination of HBeAg status is important for care and follow-up of the mother but does not change the management of the infant. All infants born to HBsAg-positive women should receive hepatitis B immune globulin (HBIG), 0.5 mL IM, and their first dose of hepatitis B vaccine (0.5 mL) at separate sites.¹³¹ Vaccine doses should be repeated at 1 and 6 months of age. Infants born to HBsAg-positive mothers should be tested for HBsAg and antibody to HBsAg at 9–15 months of age to assess infection and immune status.¹³² Infants born to HBsAg-negative mothers should receive vaccine on the same schedule or starting within 2 months of birth.

Both passive and active immunization against hepatitis B are safe in pregnancy. If a nonimmune pregnant woman has been exposed to HBV, HBIG should be given in standard doses followed by vaccine. Nonimmune pregnant women in high-risk groups for HBV should also be offered vaccination.

Although the combination of HBIG and vaccination in exposed infants prevents the majority of perinatal transmission, prudence suggests minimizing exposure to maternal blood and secretions during labor, as is currently recommended for HIV-seropositive women. Scalp electrodes or blood sampling and instrument deliveries should be avoided if possible. Artificial rupture of the membranes should be delayed as long as possible. Infants should be washed thoroughly before receiving shots or drawing blood.

The combination of active and passive immunization in neonates fails to prevent infant infection in 5–15% of infants.¹²⁸ Failure of prophylaxis is associated with HBeAg positivity and high HBV DNA levels in the pregnant woman but not maternal transaminases levels.^{133,134} It is unclear if failure of newborn prophylaxis represents in utero infection or inadequate immune globulin dosing. In an effort to reduce the risk of failure of neonatal prophylaxis, some investigators have advocated use of HBIG in the mother during the third trimester of pregnancy or short-term use of lamivudine in the mother to reduce the level of hepatitis B viremia. A small study ($n = 112$) from China found a decreased rate of markers of HBV infection among newborns of HbsAg-positive women who received monthly injections of HBIG beginning at 28 weeks of gestation compared to those not receiving HBIG, but the infection rate after 9 months was not reported.¹³⁵ Lamivudine use has been reported to decrease the risk of

failure of neonatal prophylaxis among infants born to women with high HBV DNA levels before therapy compared to historical controls^{136,137} but randomized studies are lacking. In addition, the impact of short-term lamivudine on the course of maternal HBV infection has not been evaluated. Further evaluation of these interventions is required before they can be recommended routinely. Interferon, another therapy for HBV, is not recommended for use in pregnancy.¹²⁰

The rate of HBV infection in the infant is not increased with breast-feeding when the infant receives HBIG and HBV vaccine at birth.^{138,139} Likewise, mode of delivery does not affect the rate of immunization failure.¹⁴⁰ HBV DNA has not been detected in the amniotic fluid before labor, and the risk of transmission of HBV to the fetus with amniocentesis appears to be low.¹⁴¹ However, use of amniocentesis in HBsAg-positive women should be minimized by exhausting noninvasive means of testing first. In addition, HBeAg-positive women should be counseled that their risk of transmission may be higher for them.

Ultimately, prevention of HBV infection in pregnancy relies on implementation of immunization recommendations. The rate of HBV infection in pregnancy has been decreasing over time as a result of newborn and adolescent immunization programs.¹⁴² The rate of acute HBV infections among children and adolescents in the United States has decreased by 89% between 1990 and 2002 as a result of immunization.¹⁴³ In countries where HBsAg testing and HBIG are not routinely available, implementation of routine newborn immunization still leads to a significant reduction in transmission and reduced population levels.¹⁴⁴

CONCLUSION

Viral STIs can have a significant impact on pregnant women and newborns, with sequelae of perinatal transmission being lifelong, as in cases of herpes encephalitis or CMV-associated hearing loss. Current management strategies are unable to prevent all perinatal transmission or sequelae but reduce transmission to varying degrees. Ultimately, vaccine development may make all of the viral STIs discussed here rare in pregnancy and virtually eliminate perinatal transmission.

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HISTORY

■ EARLY OBSERVATIONS

Congenital syphilis is the oldest recognized congenital infection. The transmission of syphilis to infants has been described in the earliest medical writings on “the French disease” (*morbus gallicus*). Among the first treatises on syphilis was that of Garpar Torella, written in 1497—within 4 years of the first known outbreaks of syphilis in Spain. Torella noted that syphilis was “often seen” in nursing children, first appearing on the face or in the mouth. Although early writers clearly recognized the possibility of congenital transmission,^{1–3} they usually presumed that the wet nurse was the source of infection. The first measure advocated for the prevention of congenital syphilis was proscription of the use of wet nurses who had “the French disease,” even if apparently cured. Ambroise Paré, the eminent French surgeon, displayed the same prejudice in a chapter on syphilis among his collected works.⁴ Paré described a good family of Paris, all of whom allegedly were infected from a syphilitic wet nurse, even the nursing child’s two siblings. He concluded by advocating that the nurse be whipped, naked, through the streets of the city.

The German alchemist and physician Paracelsus was the first to state (in 1529) that congenital syphilis is a hereditary illness that passes from father to son.⁵ In 1565, Simon de Vallembert described a case of “hereditary syphilis” in the first French text on pediatrics.⁶ After apparent recovery from syphilis, a goldsmith of Tours fathered several afflicted children over a 14-year period, although their mother remained unaffected.

In the novel *Moll Flanders*,⁷ Daniel Defoe demonstrated that a basic understanding of syphilis transmission from adult to neonate had been achieved by the eighteenth century. Recalling an encounter with a drunken baronet who had paid for her services, Moll imagines the baronet’s regret on arriving home to his family:

How would he be trembling for fear he had got the pox ... how would he, if he had any principles of honour, abhor the thought of giving any ill distemper, if he had it,

as for aught he knew he might, to his modest and virtuous wife, and thereby sowing the contagion in the life-blood of his posterity!

In spite of lingering misconceptions about its mechanisms of transmission, several important empirical observations regarding congenital syphilis were made during the nineteenth century, which, in that simpler time, were accorded the status of “laws.” Colles’s law (1837) stated that syphilitic infants could transmit the disease to previously healthy wet nurses but never to their own mothers.⁸ Profeta’s law (1865) stated that a healthy infant born to a syphilitic mother is immune to the disease. Kassowitz’s law (1876) stated that the toll of the mother’s syphilis diminishes with successive pregnancies. Both Paul Diday (1854) and Jonathan Hutchinson (1863) had made this same observation.^{9,10} Although neither Colles nor Profeta understood the basis for their observations, their laws illustrated the principle that infection with syphilis confers immunity to reinoculation. The essential character of congenital syphilis finally was clarified in 1906 with Wasserman’s development of a serologic test that made it possible to demonstrate that transmission of syphilis to a fetus required an infected, albeit sometimes asymptomatic, mother.¹¹

■ EARLY CLINICAL DESCRIPTIONS

Actual clinical descriptions of congenital syphilis were sparse during the sixteenth through the eighteenth centuries. Lenoir, in 1780, established a lying-in hospital in Paris for syphilitic mothers, the first facility for specialized care of neonates and high-risk pregnancies. Bertin wrote his classic monograph (1810) on congenital syphilis based upon the large accumulated experience at this institution.¹² He recognized several cutaneous lesions; mucous membrane lesions involving eyes, nose, urethra, and anus; adenopathy; and bone lesions, including epiphysitis. Bertin and others recognized the importance of the skeletal examination, although many later authorities, including Trousseau and Diday, considered skeletal lesions rare in congenital syphilis. Diday’s major text, originally published in 1854,⁹ described most of

the cutaneous and visceral manifestations of congenital syphilis known today and characterized the general appearance of the infant as that of “a little, wrinkled, pot-bellied old man with a cold in his head.”⁵ Jonathan Hutchinson’s writings dominated nineteenth-century British clinical descriptions of congenital syphilis just as Diday’s dominated French literature.^{5,13,14} His 1857 presentation before the Pathological Society of London of the characteristic dental malformations, the first description of late sequelae of infant syphilis, was received with “expression of incredulity.” Hutchinson is best known for this work as well as for his association of the dental deformities of late congenital syphilis with interstitial keratitis and deafness (Hutchinson’s triad).^{5,13,14}

Working without the benefit of x-rays, Parrot¹⁵ and Wegner¹⁶ provided clear descriptions of the osteochondritis of congenital syphilis; Parrot went so far as to declare that every bone of the infantile syphilitic skeleton is affected. His name is applied to both the cranial nodes (“hot cross bun” skull) and the pseudoparalysis that he described. Unfortunately, Parrot also mistakenly believed that rickets was a later lesion of congenital syphilis, an error subsequently corrected by the American Robert Taylor.¹⁷ Between 1900 and 1907 a succession of bright young radiologists proved that bony lesions were the most sensitive indication of clinical disease and that these lesions could be demonstrated in infants without other clinical manifestations.

The risks of delivering a congenitally infected infant were well described in the landmark Oslo study of untreated syphilis conducted from 1891 to 1910. Boeck observed that 26% of babies born to syphilitic mothers remained free of disease or recovered spontaneously with conversion to seronegativity, 25% were seroreactive but remained clinically unaffected, and 49% displayed manifest disease.¹⁸

■ MILESTONES IN PREVENTION

Fournier, a student of Diday, wrote a detailed treatise on the prevention of congenital syphilis¹⁹; his concepts influenced premarital counseling for almost a century. Before marriage or resumption of intercourse, he required (1) that the syphilitic patient have no active lesions, (2) that the patient wait 3–4 years after onset of disease, (3) that the patient wait at least 18–24 months after the last sign of disease, (4) that the form of syphilis not be grave, and (5) that an “adequate” course of potassium iodide and mercury be completed (3–4 years). After 1906, serological testing for syphilis was added as a further premarital requirement. This practice has since been abandoned by most states in the United States as the detection rate of syphilis through premarital screening has been very low.^{20,21}

Several observations made in rapid succession during the early twentieth century became cornerstones of strategies to curtail the spread of congenital syphilis.⁵ The experimental

transmission of syphilis to apes by Roux and Metchnikoff⁵ and the microscopic demonstration of *Treponema pallidum* by Schaudinn and Hoffmann⁵ established the microbiologic etiology of venereal syphilis. Wassermann’s development of a complement fixation test using syphilitic fetal liver as a source of antigen enabled physicians, for the first time, to identify individuals with asymptomatic syphilitic infection.⁵ Within a year Levaditi⁵ demonstrated both the presence of spirochetes in syphilitic fetal tissue and the suitability of uninfected liver as an antigen source for the Wassermann test. It was soon recognized that identification of cases of maternal syphilis with the Wassermann test and treatment of the mother with arsenicals could prevent neonatal syphilis. With the introduction of penicillin in 1943 by Mahoney,⁵ all of the essential clinical tools for the control of congenital syphilis were available.

EPIDEMIOLOGY

■ GENERAL TRENDS

The introduction of penicillin as syphilotherapy resulted in a dramatic decline in acquired and congenital syphilis incidence in the United States and Europe. The incidence of syphilis began to rise again in 1959 despite the fact that inexpensive therapy was readily available. It was not until 1978 that the incidence again reached the 1957 low of 3.8 cases per 100,000 live births. From 1986 through the early 1990s, there was a dramatic increase in the number of cases of congenital syphilis, partly reflecting the increases in primary and secondary syphilis among inner-city heterosexual minorities during this same period²² and partly reflecting a revision of the surveillance definition.^{23–25} Interestingly, during this same period, syphilis incidence rates decreased steadily in other industrialized countries.^{26,27} Over the past 15 years, however, there has been a decrease in congenital syphilis in the United States and other industrialized countries. However, as with HIV, sub-Saharan Africa continues with an epidemic of congenital syphilis. Globally, congenital syphilis affects over 500,000 infants every year and is the cause of an estimated additional 500,000 miscarriages and stillbirths each year.^{28,29} In fact, the true impact of congenital syphilis is unknown because, according to statistics from the World Health Organization (WHO), only 68% of women in developing countries receive prenatal care. Moreover, many of these women seek prenatal care too late in their pregnancy, and only a few countries track syphilis in pregnancy.²⁸

■ INCIDENCE AND PREVALENCE PRIOR TO PENICILLIN

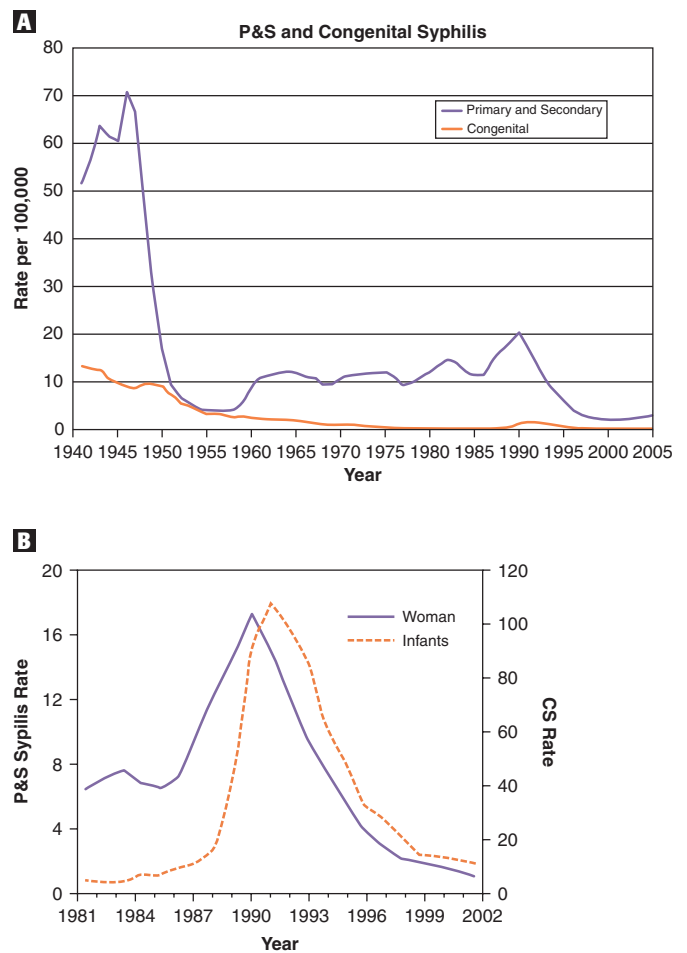
Osler observed in 1917 that syphilis accounted for 20% of all stillbirths and 18–22% of infant deaths in the United States.³⁰ In Edinburgh, in 1922, Browne found that 35 of 153 neonatal

deaths were syphilitic in origin.³¹ The overwhelming importance of perinatal syphilis in that period was a reflection of the prevalence of the disease in adults; 10% of women of the “hospital class” and 4.5% of umbilical cord blood samples in Glasgow’s Royal Maternity & Women’s Hospital had reactive Wassermann tests.³² School examinations in 1922 and 1923 in Plymouth, England, indicated an 8% prevalence of manifest congenital syphilis among school-age children. Between 1922 and 1937, the prevalence of syphilis declined steadily, with prenatal seropositivity falling to 1.8% in Glasgow and from 12% to 4% in Kansas City.³³ A 1936 U.S. Public Health Service survey indicated, however, that 2% of U.S. children and 5.6% of U.S. infants were syphilitic, with striking disparities between whites and African Americans (1.7% vs. 12.2%) and between public and private patients (5.3% vs. 1%). Investigations of families of an index case revealed latent or manifest syphilis in about one fourth of family members.³⁴ A major upsurge in syphilis incidence during World War II in Europe and the United States was associated with a corresponding two- to threefold increase in the number of cases of congenital syphilis.³⁵ However, this effect was blunted somewhat in areas such as Glasgow where comprehensive prenatal screening programs were well established.³⁴

■ CURRENT INCIDENCE AND DEMOGRAPHICS IN THE UNITED STATES

Syphilis is the only congenital infection with national surveillance data. Infections during the perinatal period comprise the vast majority of new cases of congenital syphilis. Consequently, the incidence of congenital syphilis closely follows that of primary and secondary syphilis among women in the peak childbearing age group (15–29 years) (Fig. 82-1); this is also the peak age group in which early syphilis occurs. From 1970 to 1979, men with male sexual partners accounted for an increasing share of syphilis morbidity, and the ratio of male to female cases of infectious syphilis rose during those same years, peaking at 3.5:1 in 1980 (Fig. 82-2A).²⁷ Congenital syphilis rates, accordingly, declined steadily during this period (Figs. 82-1 and 82-3). With changing sexual behavior among men who have sex with men (MSM) in response to the threat of human immunodeficiency virus (HIV), the male-to-female ratio of early syphilis cases started decreasing in 1980; by 1993 the ratio had fallen to 1.1:1, reflecting the fact that new cases were occurring predominantly in heterosexuals (Fig. 82-2).

During this same period congenital syphilis rates increased markedly (Figs. 82-1 and 82-3). Two factors are responsible for the dramatic increase in congenital syphilis observed in the United States from 1990 through 1994. The first was the adoption in 1989 of revised reporting guidelines that broadened the surveillance definition for congenital syphilis (Table 82-1).^{25,36} Previous criteria for reporting



*Per 100,000 Live-born Infants
†Per 100,000 Population

FIGURE 82-1. A. Annual incidence of infant congenital syphilis compared to that of primary and secondary syphilis, United States, 1940–2005. (Source: CDC, STD Surveillance 2005, Table 1.) **B.** Annual incidence of infant congenital syphilis compared to that of women with P&S. U.S. 1996–2005. The trend for congenital syphilis follows that of women with P&S. (Source: CDC, STD Surveillance 2005, Fig. 37.)

cases of congenital syphilis were based on a clinical case definition; only infants who had clinically apparent disease or laboratory findings suggestive of congenital syphilis were reported.²⁵ A *confirmed* case represented an infant or stillbirth in whom *T. pallidum* was identified by either dark-field microscopy or specific stains in specimens from lesions. A *probable* case was that of an infant or stillbirth who had a reactive test for syphilis and an abnormal physical examination, abnormal long-bone radiograph, abnormal cerebrospinal fluid (reactive CSF-VDRL and/or elevated CSF cell count or protein without other cause), a nontreponemal serologic test titer fourfold higher than the mother’s, a rising nontreponemal test titer during follow up, or a persistently reactive treponemal test beyond 1 year of age. Although relatively specific, two problems with this definition were that it did not include infected live-born infants without evidence of congenital syphilis and it

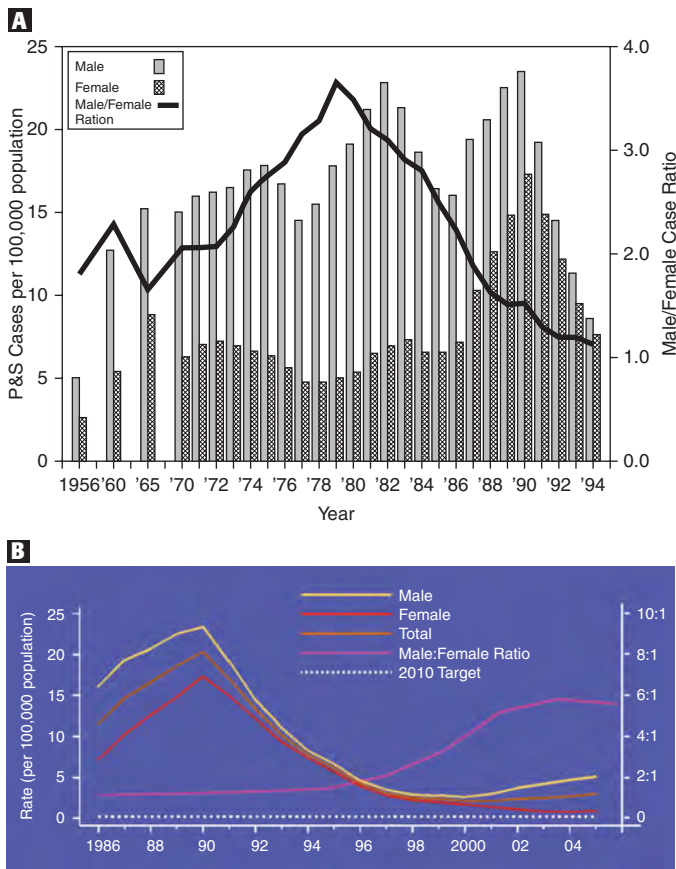


FIGURE 82-2. Incidence rates of early infectious syphilis for men and women, with the male-to-female case ratio, in the United States, **A**, from 1956 to 1994 (courtesy of Kathy Dry, Division of STD Prevention, NCHSTP, CDC, Atlanta) and **B**, from 1986 to 2004 (Source: Adapted from CDC, STD Surveillance 2005, Figs. 27 and 33).

depended in many cases upon follow-up serologic data to make a diagnosis (Table 82-1). The new surveillance case definition includes all infants with clinical evidence of active syphilis, as well as normal appearing neonates and stillbirths delivered to women with untreated or inadequately treated syphilis (Table 82-1).^{23,25} Use of these guidelines increases the sensitivity for reporting cases of congenital syphilis, albeit by including at-risk but truly uninfected cases. Studies have shown that the revised surveillance definition results in a four- to fivefold increase in the number of reported cases.^{24,36,37}

The second factor responsible for the upsurge in congenital syphilis cases during that time was the near-epidemic increase in the incidence of primary and secondary syphilis among young females in the United States (Figs. 82-1 and 82-2A), particularly among inner-city minorities in New York, California, Florida, Texas, and Michigan and among rural blacks throughout the Southeast.^{23,27,38-40} A major contributor to the increase in urban areas was the use of crack cocaine and the exchange of illegal drugs for sex among multiple sexual partners.^{22,41-43} The use of spectinomycin, which is not effective against incubating syphilis,^{44,45} for the

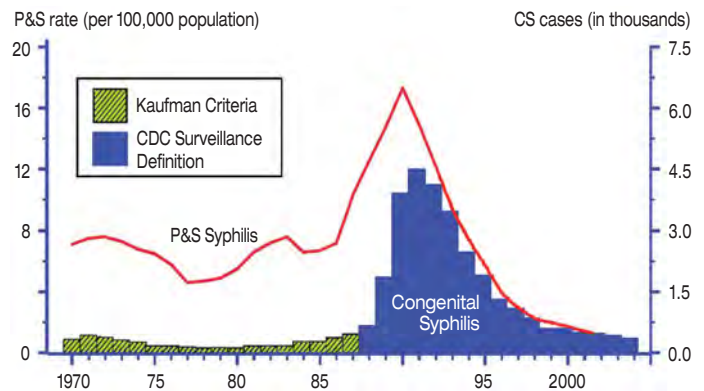


FIGURE 82-3. Reported cases of congenital syphilis in infants younger than 1 year of age and rates of primary and secondary syphilis among women, United States, 1970–2004. Note: The surveillance case definition for congenital syphilis changed in 1988. (Source: CDC, STD Surveillance 2005, Fig. 5.)

treatment of penicillinase-producing *Neisseria gonorrhoeae* also may have been contributory.

While rates of primary and secondary syphilis in the United States continued to decline through the 1990s, increasing rates of syphilis were observed once more in males in 2001 with a concomitant rise in the male-to-female rate ratio of syphilis to 5.7:1 in 2005⁴⁶ (Fig. 82-2B). The syphilis epidemic among MSMs is attributed in part to waning safer sexual behaviors associated with the widespread use of highly active antiretroviral therapy (HAART) and diminished concern among MSMs about the potential seriousness of HIV infection.

Fortunately, despite the syphilis epidemic in males there have been substantial decreases in the incidence of both infectious syphilis in females and congenital syphilis over the past one and one-half decades (Figs. 82-1 and 82-2).⁴⁷ In fact there has been a consistent downward trend in the rates of both primary and secondary syphilis in women and congenital syphilis since 1991.⁴⁸ These decreases have been attributed to (1) the implementation in the early 1990s of innovative, community-based outreach methods that facilitate identification and serologic testing of persons at high risk for syphilis by focusing on sex-for-drugs locations rather than on contact tracing of named sexual partners of persons with early syphilis^{49,50} and (2) the initiation of the National Syphilis Elimination Plan launched by the Centers for Disease Control and Prevention (CDC) in 1999 with the goal of eliminating primary and secondary syphilis in the United States, thereby decreasing syphilis infection in females and preventing congenital syphilis.⁴⁸

Consistent with the risk factors noted in the early 1990s,^{47,51,52} over the last decade women who deliver syphilitic babies are more likely than the general population to be racial/ethnic minorities (black and Hispanic), younger in age (<30 years), unmarried, drug using (specifically cocaine), and living in a high syphilis morbidity areas.⁵³⁻⁵⁶ Of the 329 cases of congenital syphilis in infants less than 1 year of age reported to the CDC in 2005, 46% (151) of mothers

Table 82-1. Summary of the Modified Kaufman and Revised Centers for Disease Control and Prevention (CDC) Criteria for Congenital Syphilis Surveillance

Kaufman Criteria	Revised CDC Criteria ^a
Definite <i>Treponema pallidum</i> by dark-field or histologic examination	Confirmed A case that is laboratory confirmed
Probable Rising Venereal Disease Research Laboratory (VDRL) titer over 3 mo or a reactive serologic test for syphilis (STS) that does not revert to nonreactive within 4 mo One major or two minor criteria ^d and either a reactive STS or fluorescent treponema antibody (FTA) test One major and one minor criteria on radiographs of long bones	Probable A condition affecting an infant whose mother had untreated or inadequately treated ^b syphilis at delivery, regardless of signs ^c in the infant, or an infant or child who has a reactive treponemal test for syphilis and any one of the following: <ul style="list-style-type: none"> • Any evidence of congenital syphilis on physical exam • Any evidence of congenital syphilis • A reactive cerebrospinal fluid (CSF) venereal disease research laboratory (VDRL) • An elevated CSF cell count or protein (without other cause)^e • A reactive fluorescent treponemal antibody absorbed-19S-IgM antibody test or IgM enzyme-linked immunosorbent assay
Possible A reactive STS or FTA test without clinical criteria	Syphilitic stillbirth A fetal death occurring after 20-wk gestation or weighing ≥ 500 g, in which the mother had untreated or inadequately treated syphilis at delivery

^aRevised in 1990 and 1996.

^bInadequate therapy defined as nonpenicillin therapy or penicillin given ≤ 30 days prior to delivery.

^cSigns in infants and children (< 2 years old) are snuffles, hepatosplenomegaly, characteristic skin rash, condylomata lata, anemia, jaundice (nonviral hepatitis, pseudoparalysis, or edema (nephrotic syndrome and/or malnutrition)).

^dMajor criteria: condylomata lata, osteochondritis, periostitis, snuffles, hemorrhagic rhinitis. Minor criteria: fissures of lips, cutaneous lesions, mucous patches, hepatomegaly, splenomegaly, generalized lymphadenopathy, central nervous signs, hemolytic anemia, CSF cell count ≥ 20 , CSF protein ≥ 100 .

^eCSF cell count ≥ 5 or CSF protein ≥ 40 .

Source: Thompson BL, Matuszak D, Dwyer DM, Nakashima A, Pearce H, Israel E. Congenital syphilis in Maryland, 1989–1991: The effect of changing the case definition and opportunities for prevention. *Sex Transm Dis* 1995; 22(6): 364–369; Committee on Infectious Diseases AAoP. *Red Book: 2003 report of the Committee on Infectious Diseases*, 26th edn. Elk Grove Village, IL: American Academy of Pediatrics, 2003; Marriage Laws in the USA: Blood tests required or waiting periods? *Directory of Continuing Medical Education Courses*, 2007.

were black, 37% (122) were Hispanic, 9% (30) were white, 4% (13) were Asian/Pacific Islander, and 4% (13) were other or unknown. The decrease in congenital syphilis cases and racial/ethnic distribution is demonstrated when comparing surveillance data from the last decade. Of the 3209 cases of congenital syphilis reported to the CDC in 1993, 71% (2278) were black, 20% (642) were Hispanic, 5% (160) were white, and 4% (128) were other or unknown.⁵⁷ Over the past 50 years a number of studies have identified inadequate prenatal care as the leading predisposing factor.^{24,35,52,58,59}

While public health efforts have been successful in increasing syphilis screening in some populations over the last decade, lack

of prenatal care continues to be the major risk factor consistently associated with congenital syphilis.^{53,54,60,61} In 2002 almost 75% of mothers with reported congenital syphilis cases had no or inadequate treatment for syphilis before or during pregnancy and inadequate prenatal care.^{62,63} Of the 451 cases of congenital syphilis reported 64% (288) of mothers received prenatal care; 29% (130) received no prenatal care; and the prenatal care status was unknown for 7% (33). Of the 288 women who reported timing of their first prenatal care visit, approximately one third sought prenatal care in their first trimester (86) and another one third in their second trimester (93). As many as 20% (59) did not receive prenatal care until their third

trimester, and almost one third of these women (18) received care less than 30 days before delivery.⁶² For pregnant women overall in the United States health disparities are evident in those who are likely to seek prenatal care and those who are not. In 2001 black and Hispanic women were twice as likely to receive late or no prenatal care when compared to white women.^{53,60,64} Similarly, in surveillance data from 2004, of the women who began prenatal care in the first trimester of pregnancy 85% were white, 76% were black, and 77% were Hispanic, whereas of women who began prenatal care late in the third trimester or received no prenatal care at all, 3.2% were white, 5.7% were black, and 5.4% were Hispanic.

■ GLOBAL BURDEN OF CONGENITAL SYPHILIS

The regions of the world with the highest distribution of syphilis are South America, sub-Saharan Africa, China, and Southeast Asia. Globally syphilis infection is more common among poor populations with fewer resources; lack of access to healthcare; multiple sexual partners; and marginalization from society.⁶⁵ In Eastern Europe, Russia, and China, countries experiencing marked economic and social reforms, syphilis and congenital syphilis are on the rise.^{65–67} During the Soviet era prenatal care was free and congenital syphilis was rare. This has changed over the past two decades with fewer women accessing adequate prenatal care; the number of cases of congenital syphilis rose 26-fold from 15 in 1991 to 730 in 1999.^{67,68} Similarly, under Communist rule in China, the syphilis epidemic of the 1950s was halted in the 1960s and syphilis was virtually eradicated due to government-initiated population screening, free treatment, and ban on prostitution.⁶⁹ However, in the era of decreased governmental power, enhanced personal wealth, social freedom and geographic mobility, syphilis and congenital syphilis have reached epidemic proportions.⁶⁹ In a case–control study of women attending antenatal clinics in Southern China, infection with syphilis was associated with being unmarried, lower education level, multiple sexual partners, a sexual partner who had traveled within the past 12 months, a history of induced abortion, and prior STD.⁷⁰ Notably, from national surveillance data, the incidence of congenital syphilis has increased by 72% yearly from 0.01 cases per 100,000 live births in 1991 to 19.7 cases per 100,000 in 2005.⁶⁹

■ SUB-SAHARAN AFRICA

An estimated 4–15% of women attending antenatal clinics are infected with syphilis in sub-Saharan Africa.⁷¹ Lack of prenatal care, not accessing care until late in pregnancy, and lack of screening despite prenatal care perpetuate the epidemic of congenital syphilis in Africa. Congenital syphilis is estimated to result in 20–30% of all perinatal deaths in sub-Saharan Africa. Yet surveillance in 22 countries found only 38% of women accessing antenatal care were screened for syphilis despite

recommendations for universal screening.⁷² As congenital syphilis is readily preventable with treatment of maternal syphilis early in pregnancy and as antenatal screening and treatment have proven cost-effective,^{71,72} even in settings with low prevalence^{73,74} more needs be done to overcome obstacles that prevent pregnant women from receiving care.

Syphilis during pregnancy

With the onset of intensive HIV research activity over the past 20 years, many seroprevalence surveys undertaken included serologic examination for syphilis. In the early 1990s the surveys in sub-Saharan Africa that estimated rates of active syphilis (reactive results for both *T. pallidum* hemagglutination [TPHA] and rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] tests) in pregnant women, the median reported prevalence was 6%, with areas in Kenya, Cameroon, Tanzania, Gabon, and Malawi all reporting rates of greater than 10%.⁷⁵ More recently over the past decade, in Nairobi, Kenya, the seroprevalence for syphilis was 6.5% in pregnant women at an antenatal screening clinic and 3% in women presenting to hospital for delivery.^{76,77} In a syphilis prevalence study of pregnant women in antenatal clinics in Gaborone, Botswana, 11% of the women were TPHA reactive and 5% had active syphilis.⁷³ In South Africa the antenatal prevalence of syphilis has trended downwards over the past decade from a high of 11.2% in 1997 to a low of 1.6% in 2004 while the prevalence rates between 2001 and 2005 have fluctuated in the range of 1.6–3.2%.⁷⁸

These numbers demonstrate that syphilis during pregnancy is prevalent throughout much of Africa. In Nairobi, Kenya, risk factors for syphilis seroreactivity include fewer years of education, history of preterm delivery, three or fewer antenatal visits, maternal HIV infection, more than one sexual partner in the past year, and a history of genital ulcer disease.⁷⁹ In a recent study in Mwanza, Tanzania, RPR-reactive women at delivery were more likely than RPR-nonreactive women to have no education or a lower level of education; more likely to have two or more sexual partners in the past year; more likely to be infected with *Trichomonas vaginalis* at recruitment; and more likely to be diagnosed with HIV, placental malaria, and anemia at the time of delivery.⁸⁰

One potential problem with the use of serologic tests when screening for syphilis and when estimating prevalences of syphilis is that these tests cannot distinguish between infection by *Treponema pallidum* and endemic treponematoses, which are not sexually transmitted. For example, yaws, caused by a subspecies of *T. pallidum*, (subsp. *pertenue*), is a nonvenereal infection occurring mainly in poor communities with overcrowding and poor sanitation in tropical areas of Africa.^{81,82}

Syphilis and pregnancy outcomes

Over two decades ago the most common outcome of syphilis during pregnancy was spontaneous abortion/stillbirth during

the second and early third trimester; the precise magnitude of this problem is difficult to measure because many African women did not receive prenatal care until the third trimester.⁸³ Furthermore, compliance with syphilis treatment was poor; only 10% of women completed their prescribed treatment at a teaching hospital.⁸⁴ During the same time period, an estimated 5% of all pregnancies were lost each year as a result of syphilis-induced abortions (75,000 pregnancy losses) in Ethiopia.⁸⁵ In an even earlier study from Ethiopia, pregnant women who were seroreactive for syphilis were five times more likely to have a spontaneous abortion or stillbirth than women who were sero-nonreactive.⁸⁶ In Zambia, 19% of miscarriages were attributed to syphilis.⁸³ The spontaneous abortion rate among pregnant African women with syphilis in the 1980s was estimated to be as high as 50%.⁸⁷ A case-control study from Zambia demonstrated a 28-fold increased risk in stillbirths among women with high-titer RPR card test seroreactivity.⁸⁸ In the University Teaching Hospital in Lusaka, Zambia, 42% of stillbirths were attributed to syphilis during pregnancy.⁸³ In Zambia, congenital syphilis was implicated in 20–30% of total perinatal infant deaths (50 per 1000 births).⁸⁹ In 1977, syphilis was the fourth most common cause of perinatal death in Ethiopia, accounting for 10% of the approximately 70 perinatal deaths per 1000 births; syphilis also caused nearly 5% of all post-neonatal infant deaths.⁹⁰ In absolute numbers, during this period, each year 15,000 fetal and infant deaths in Ethiopia were directly attributable to syphilis.⁸⁵

Over the past decade, syphilis has continued to be responsible for a significant proportion of adverse pregnancy outcomes. In 1997 Nairobi, Kenya, women untreated with syphilis were four times as likely to have an adverse outcome (e.g., low birth weight <2500 g or stillbirth) than mothers who had nonreactive serologies at delivery. Treatment for syphilis prior to delivery decreased the rate of adverse outcomes from 26% to less than 15%.^{76,79} In an analysis of four studies of maternal syphilis in Tanzania, women with high titer RPR tests (>1:8) were 18 times more likely to have a stillbirth, three times more likely to have an infant with low birth weight, and 6 times more likely to have preterm birth when compared to women who were serologically nonreactive.^{80,91} More recently (2000–2004), in a study of HIV-positive pregnant women in Blantyre, Malawi, 8%(92) were positive for syphilis. Maternal syphilis was associated with increased in utero, intrapartum and postpartum mother-to-child transmission (MTCT) of HIV.⁹²

Incidence of congenital syphilis

Compared with data from Africa on acquired syphilis during pregnancy in the 1980s and earlier, much less information was available on congenital syphilis. A study in Zambia established that nearly 1% of the babies delivered at the University Teaching Hospital in Lusaka had signs of congenital infection at

birth, and as many as 6.5% were seroreactive at birth and thus considered at risk.⁹³ In another study from Zambia, seroreactivity among infants under 6 months of age was 2.9%.⁸⁹ Half the seroreactive infants had two or more clinical features suggestive of early congenital syphilis and, of these, 60% required hospitalization. Further confirmation of the incidence and morbidity associated with early congenital syphilis in Zambia comes from two treatment studies. Early congenital syphilis was diagnosed in 9% of admissions to one nursery ward and in 8% of admissions to the intensive care unit.⁹⁴

Syphilis remains the leading cause of perinatal mortality in sub-Saharan Africa, resulting in 21% of all perinatal deaths.^{28,87} Estimating the incidence of congenital syphilis in sub-Saharan Africa over the past decade continues to be challenging as few countries track the number of affected infants. Many women in African countries do not have access to prenatal care or receive care too late to prevent congenital syphilis, and many syphilitic pregnancies result in spontaneous abortion or stillbirth prior to the mothers being screened for syphilis.²⁹ In 1995, it was estimated that worldwide there were more than 1 million cases of syphilis in pregnancy. However, as of 2001, in sub-Saharan Africa alone, it was estimated that 2,300,000 women were infected with active syphilis during pregnancy and of these 1,640,000 were estimated to be undetected and, therefore, untreated and infectious. Using these estimates 328,000 (20%) pregnancies would result in spontaneous abortion; 246,000 (15%) in perinatal death; 328,000 (20%) in low birth weight and 328,000 (20%) in congenital infection totaling 1,230,000 pregnancies affected by congenital syphilis. The overall impact of syphilis in pregnancy rivals, and may even exceed, that of HIV infection in Africa, which is estimated at 720,000 pregnancies.^{28,71,87}

Estimates of the incidence of congenital syphilis in South Africa have been possible, however, since 1991 when congenital syphilis became a reportable disease. From 1991 to 2001 there were a total of 5662 cases and 115 deaths of congenital syphilis in that country. This number peaked in 1993 at 903 cases and then steadily declined thereafter to a low of 139 cases in 2001.⁷⁸ From 2001 to 2005, the number of congenital syphilis cases continued to decline with only one reported case in 2005. This success may be attributable to public health interventions in the syndromic management of sexually transmitted infections and increased antenatal visits with screening and management of syphilis in pregnancy.⁷⁸

PATHOGENESIS AND PATHOLOGY

■ TRANSMISSION OF SYPHILIS DURING PREGNANCY

Although a mother can transmit syphilis to her infant at the time of delivery,^{95,96} the vast majority of cases are believed to arise from in utero infection. In fact, no form of syphilis better exemplifies the remarkable invasiveness of *T. pallidum*

Table 82-2. Prospective Observations of Obstetric Events in Syphilitic Women

Event	150 Syphilitic Women	150 Controls
Pregnancies	1001	826
Miscarriages	9.2%	7.4%
Stillbirths	8.0%	2.1%
Infant deaths	22.9%	11.4%
Infant syphilis	21.0%	0.0%
Healthy child	38.9%	79.1%

Source: Harman N. *Staying the Plague*. London: Methuen, 1917.

than congenital syphilis. Also noteworthy is that *T. pallidum* subsp. *pallidum* is the only pathogenic treponemal subspecies with the capacity to regularly traverse the placenta⁶⁵; this fact is even more extraordinary given the remarkably similar genomes of the pathogenic treponemes.^{97–99} Studies with cultured human umbilical vein endothelial cells have documented that *T. pallidum*, but not nonpathogenic treponemes, efficiently penetrates endothelial cells via intercellular junctions,^{100,101} and it is likely that a similar, if not identical, process underlies the traversal of maternal and fetal tissues in utero.^{100,101} The finding of spirochetes in the placenta and umbilical cord in association with typical histopathologic changes supports transplacental invasion during maternal spirochetemia as the major route of transmission.^{102–106} Alternatively, but less likely, *T. pallidum* may gain access to the fetal circulation by first traversing the fetal membranes and infecting the amniotic fluid.^{107–110}

The risk of congenital syphilis is directly related to the stage of maternal syphilis during pregnancy and the duration of exposure of the infant in utero. It is extremely high during the first 4 years after acquisition, when spirochetemia is common, and then decreases during late syphilis, when spirochetemia becomes a rare event. Harman (in 1917) followed obstetric events in 150 syphilitic women and 150 healthy women of similar social status (Table 82-2).¹¹¹ Sixty-one percent of the pregnancies of the syphilitic women resulted in adverse outcomes or the birth of an infected child, compared to a complication rate of 20.4% in healthy women. In 1951, Ingraham reported that following untreated maternal early syphilis of 4 years or less duration, 41% of infants were live born with congenital syphilis, 25% were stillborn, 14% died in the neonatal period, 2% were premature but without evidence of congenital syphilis, and only 18% were normal full-term living infants.¹¹² In contrast, only 2% of infants born to mothers with untreated late syphilis of over 4 years duration had congenital syphilis.¹¹² Subsequently, in 1952, Fiumara and colleagues reported that

Table 82-3. Outcome of Pregnancy in Relation to Stage of Maternal Syphilis

Outcome	Primary and Secondary %	Early Latent %	Late Latent %	Normal %
Prematurity	50%	20%	9%	8%
Perinatal death	0	20%	11%	1%
Congenital syphilis	50%	40%	10%	0
Healthy child	0	20%	70%	90%

Data from Fiumara NJ, Fleming WL, Downing JG, Good FL. The incidence of prenatal syphilis at the Boston City Hospital. *N Engl J Med* 1952; 247(2): 48–52.

among infants born to mothers with primary or secondary syphilis, approximately half of the infants were premature, stillborn, or died in the neonatal period; the other 50% developed congenital syphilis (Table 82-3).⁵⁸ With early latent syphilis, the transmission rate decreased to approximately 40%, while 20% were premature, 4% died in the neonatal period, and 10% were stillborn; 20% of infants were normal and full term (Table 82-3). With late latent syphilis, approximately 10% of infants had congenital syphilis and another 10% were stillborn, but there was no increase in premature births or neonatal deaths beyond the expected rate among women without syphilis (Table 82-3).⁵⁸ Sánchez et al.¹¹³ documented similar rates in a small cohort of 19 infants. In that series, two of two infants born to mothers with primary syphilis had laboratory evidence of infection (reactive serum IgM immunoblot, positive serum/CSF polymerase chain reaction, or positive rabbit infectivity testing) as did six of six infants born to mothers with secondary syphilis. In contrast, only 6 of 11 (55%) infants born to mothers with early latent infection had evidence of infection. In accordance with the above data, experts have more recently pointed out that there are actually two general scenarios that need to be considered when assessing fetal risk for congenital syphilis.^{114,115} One occurs when an infected woman becomes pregnant, the other when a pregnant woman becomes infected. The latter tends to be associated with overall worse outcomes for the infant as it always involves the early, spirochetemic stages of disease in which the likelihood of transmission to the fetus is high. Hollier et al.¹¹⁶ proposed a continuum of fetal involvement that begins with hepatic dysfunction and placental involvement in maternal primary syphilis and progresses to infection of the amniotic fluid, hematologic abnormalities, and, finally, severe multiorgan disease and marked fetal abnormalities in mothers with secondary and early latent disease.

In the past, it was a commonly held obstetric principle that infection of the fetus does not occur before 18 weeks.

In 1938, Beck and Dailey proposed that the prominence of the Langhans' cell layer of the cytotrophoblast prior to mid-gestation explained the rarity of early transplacental infection, and its regression thereafter left the fetus vulnerable to spirochetal invasion.¹¹⁷ This belief was supported by Dippel's series and his review of more than 200 fetal autopsies culled from the literature.¹¹⁸ He found no cases of infected abortuses prior to 18 weeks, and the proportion of abortuses that were infected rose steadily with advancing gestation to a peak at 8 months. Dippel also noted that only 19% of syphilitic abortuses showed delayed regression of the Langhans' layer, whereas 50% of uninfected abortuses had an intact Langhans' layer.¹¹⁸ This theory, however, was disproved by electron microscopic demonstration of the persistence of the Langhans' cell layer throughout pregnancy and by the detection of spirochetes by silver staining and immunofluorescent techniques in fetal tissue from spontaneous abortions at 9 and 10 weeks of gestation.^{102,119} Nathan and coworkers demonstrated spirochetes in amniotic fluid as early as 17 weeks of pregnancy, further proving that *T. pallidum* can gain access to the fetal compartment early in gestation.¹⁰⁷ It is now believed that congenital syphilis can occur following maternal infection at any time in gestation, with the risk of fetal infection increasing as the stage of pregnancy advances. Failure to appreciate syphilis as a cause of first-trimester stillbirth is due to the fetus's inability to mount a characteristic histopathologic response within the first 18–20 weeks of gestation.¹²⁰

■ HISTOPATHOLOGY

General features

Congenital syphilis can involve almost any and every fetal organ, with liver, kidneys, bone, pancreas, spleen, lungs, heart, and brain being the most frequently affected.¹²¹ As with acquired syphilitic infection, the fundamental histologic lesion of congenital syphilis is an obliterative endarteritis typically consisting of mononuclear and plasma cell infiltrates surrounding blood vessels with intimal hyperplasia (of larger vessels) and swollen, hyperplastic endothelial cells.^{122–124} Based upon our current understanding of endothelial cell biology¹²⁵ as well as immunohistochemical analyses of cutaneous biopsies from patients with secondary syphilis,¹²⁶ it is reasonable to presume that the endothelial cells in these lesions are activated and expressing adhesion receptors, cytokines, and other molecules that initiate and sustain the inflammatory response.¹²⁵ Moreover, studies have shown that both motile *T. pallidum* and *T. pallidum* lipoproteins can activate vascular endothelium.¹⁰⁰

Fibrosis and gummas are also frequently observed in congenitally infected tissues. Fibrosis may be relatively fine in character, consisting primarily of collagen deposition about

affected blood vessels, or it may substantially distort and replace the parenchyma in affected organs, such as the liver, pancreas, bone, and lung.¹²¹ Microscopic gummas are common, especially in skin, mucous membranes, bone, and liver. They typically consist of a thin peripheral rim of mononuclear cell infiltration, central coagulation (“gummy” necrosis), and fibrosis, but any of these three features may predominate. Unlike the staged histopathology of acquired syphilis, a distinctive feature of congenital syphilis is that these tissue reaction patterns may be present, to various extents, as part of a single syndrome.

Placenta and umbilical cord

Inflammatory changes in the placenta are often more striking than those of the fetus. Grossly, the infected placenta is large, thick, and pale, weighing up to one third of fetal weight.^{102,127,128} Microscopic changes include (1) focal proliferative villitis with necrosis and focal infiltrations of maternal lymphocytes and plasma cells, (2) endothelial and adventitial proliferation of villous vessels leading to obliteration, (3) villi which are immature, large, clubbed, and crowded, (4) extensive stromal hyperplasia and deposition of granulation tissue, and (5) occasionally, multiple small (“miliary”) gumma (Fig. 82-4).^{102,106,128–130} Although there are no absolute pathologic placental findings associated with congenital syphilis, enlarged hypercellular villi, proliferative vascular changes, and acute or chronic villitis have long been considered as the “syphilis triad”, findings which, together, are strongly suggestive of congenital syphilis.^{102,106,128–131} Spirochetes can often be visualized by silver stain or with more specific immunohistochemical methods (Fig. 82-4). The umbilical cord also may be involved. A deeply seated inflammatory process within the matrix of the umbilical cord, termed *necrotizing funisitis*, has been described,¹⁰⁴ although there is disagreement as to whether this lesion is specific for syphilis.¹⁰⁵ Macroscopically, the umbilical cord resembles a “barber pole”; the edematous portions have a spiral-striped zone of red and pale blue discoloration interspersed with streaks of chalky white (Fig. 82-5). On cross-section, abscess-like foci of necrosis located within Wharton's jelly are centered around the umbilical vessels (Fig. 82-5).

Skeletal system

Characteristic bony lesions are present in 97% of autopsied infants by 6 months of age.¹²⁴ Membranous bones are less involved than endochondral (long) bones, in which the pathological process is concentrated at the metaphyseal-epiphyseal junction. Grossly, an irregular yellow line is found at the zone of provisional calcification.¹³² When membranous bone is involved, it is generally a periostitis, which leads to localized exostosis and osteoporosis. A perivascular inflammatory infiltrate, found in both types of bone, erodes the

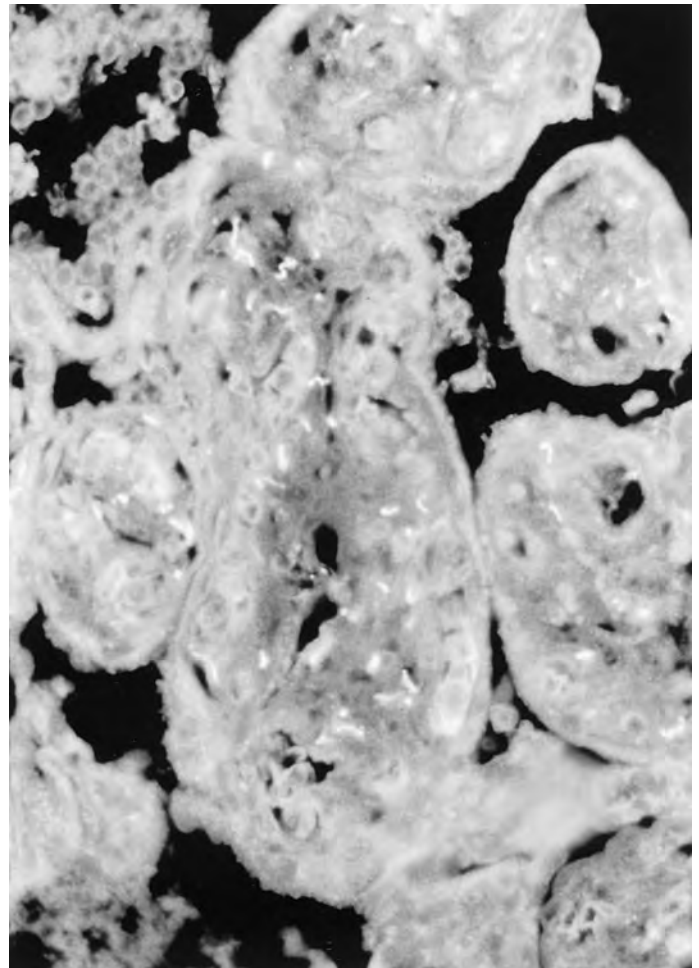
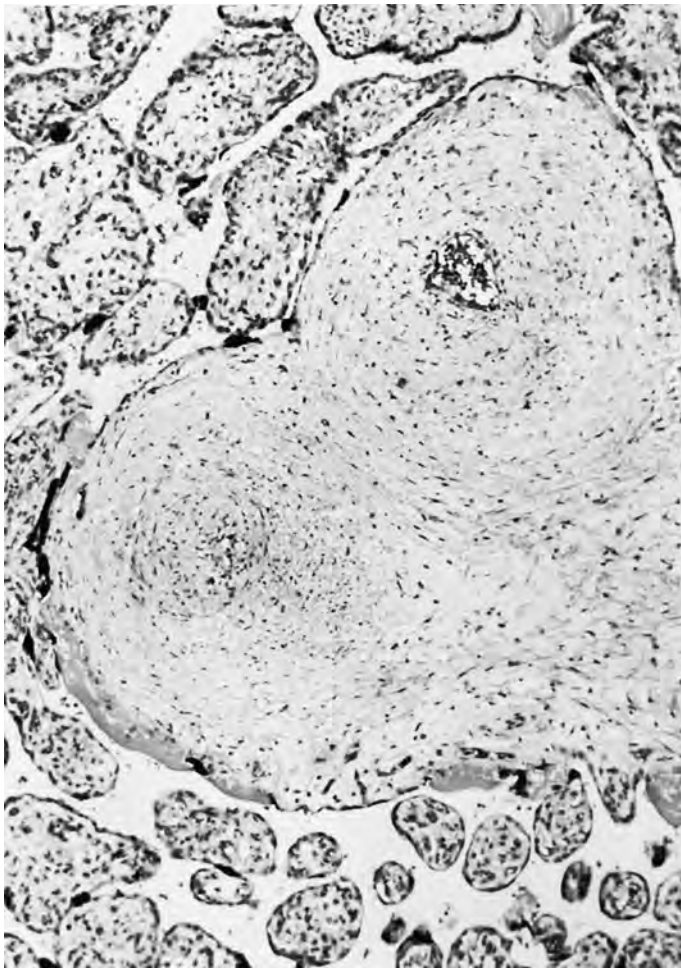


FIGURE 82-4. Syphilitic placentitis. (Left) Blood vessels within the enlarged, clubbed villi exhibit endothelial and adventitial proliferation resulting in near vascular obliteration ($\times 150$). (Courtesy of G. Wendel.) (Right) Detection of *T. pallidum* by indirect immunofluorescence with rabbit anti-*T. pallidum* antiserum. (Courtesy of S. Norris.)

trabeculae and eventually gives way to fibrosis.^{133,134} A debate persists regarding the relative importance of inflammatory and trophic influences (“syphilitic dystrophy”) on the production of these lesions.^{135,136} Caffey attributes the transverse striping of the metaphyses to nutrition and argues that any severe disease of the fetal and neonatal period may produce it.¹³⁵ Others have made careful pathoradiologic correlations, describing the sequential development of an “osteochondritis.”^{137,138} When fully developed, the epiphyseal plate is destroyed, the end of the diaphysis is destroyed, and fragments of bone and cartilage separate to produce a “pseudo-Charcot’s joint.” The diaphysis acquires a worm-eaten appearance resembling fibrocystic disease. Marrow is trapped between thick layers of periosteum, and islands of cartilage are trapped within metaphyseal bone. Epiphyseal ossification centers are usually spared.

In surviving infants, healing occurs over the first 6 months, usually without residual lesions, and seems little influenced by penicillin.^{139,140} This suggests that much of the pathogenesis of these lesions may be trophic rather than directly infectious and that the severely ill infant who comes to

autopsy may not be representative of the survivors whom radiologists and clinicians most commonly encounter. Marked inflammation and exuberant fibrosis may be hallmarks of more profoundly affected infants.

Liver, spleen, pancreas, intestines, and lungs

Liver involvement typically takes the form of inflammation confined to the portal triads with rings of collagen deposited about portal ducts and blood vessels. In some cases, focal inflammation and scarring irregularly replace hepatic parenchyma. In the most severe cases, the inflammatory infiltrates produce a diffuse hepatitis with separation of liver plates and, eventually, extensive scarring. Though not specific for syphilis, excessive extramedullary hematopoiesis within hepatic sinusoids and portal triads often accompanies these changes. Diffuse gumma also may be seen. Silver stains of hepatic tissue often show heavy infiltration with treponemes even in the absence of pronounced histologic abnormalities. Splenic sinusoids are widened and crammed with masses of blood-forming cells, explaining the characteristic splenomegaly. Deposition of granulation tissue about splenic blood vessels can be severe enough to cause “onion

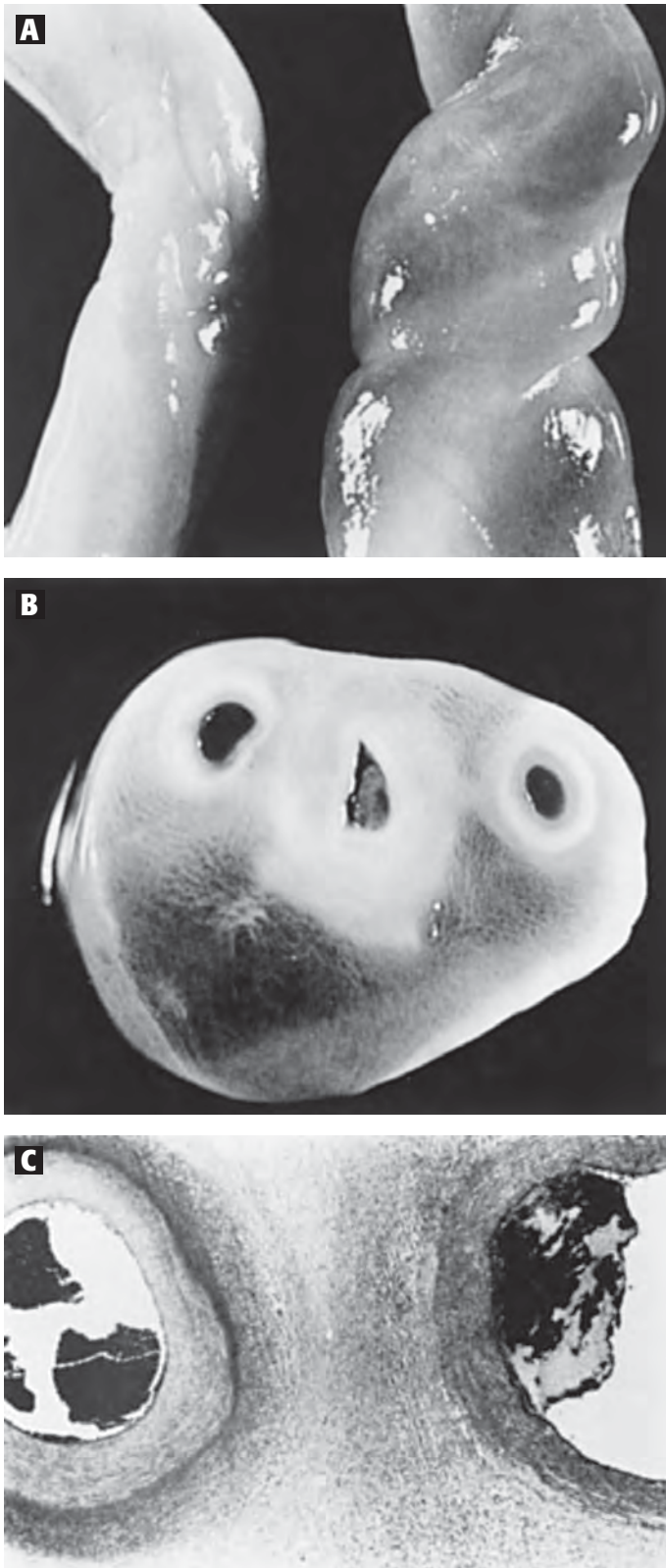


FIGURE 82-5. Necrotizing funisitis. **A.** Umbilical cord in congenital syphilis. A normal segment is at the left of the segment with necrotizing funisitis. **B.** Cross section showing opaque white lesions surrounding blood vessels and venous thrombosis. **C.** Histological section showing perivascular inflammation and necrosis corresponding to white lesions surrounding blood vessels. (From Fojaco RM, Hensley GT, Moskowitz L. Congenital syphilis and necrotizing funisitis. *JAMA* 1989; 261(12): 1788–1790.)

skinning.” Pancreatitis, which may be intense, consists of isolation and obliteration of ductules as well as acini by inflammatory infiltrates and perivascular deposition of rings of collagen.¹²¹ In the gastrointestinal tract, mucosal and submucosal infiltration with mononuclear and plasma cells is associated with a striking fibrotic response and increase in the width of the submucosa. Though now rare,¹²¹ the classical “pneumonia alba” of congenital syphilis is characterized by grossly enlarged, firm, yellowish-white lungs; these changes are due to an intense obliterative fibrosis in the interalveolar septae.¹²⁴

Nervous system

Meningeal involvement is grossly apparent as a discoloration and thickening of the basilar meninges, especially around the brainstem and optic chiasm.¹²⁴ The microscopic¹²⁴ changes consist of endarteritis with various degrees of infarction and neuronal damage. Fibrosis during healing may result in obstructive hydrocephalus and/or entrapment of cranial nerves. Parenchymatous forms of late congenital neurosyphilis (e.g., general paresis, tabes dorsalis), now extremely rare, are pathologically indistinguishable from those of acquired syphilis in adults.¹⁴¹

Kidneys

An epimembranous glomerulopathy is associated with two different forms of immune complex injury. One involves deposition of IgA, IgG, and IgM with complement and the other involves immune complex deposition without complement along the glomerular basement membrane.¹⁴² Elution studies have demonstrated that the complexes consist of treponemal antigens and antitreponemal antibodies.¹⁴³ Interstitial perivascular infiltrates consisting of mononuclear and plasma cells also are present.

Teeth

The late dental consequences of neonatal syphilis are abnormalities of form, structure, and size. There is apical notching, the amelodentinal junction is irregular, enamelization is defective, and the affected teeth are small. The pathogenesis of dental stigmata has been a long-standing controversy. Although Hutchinson himself at first regarded the changes as a part of the syndrome of mercurial stomatitis, he subsequently attributed them to trophic changes.^{13,14,127} Early difficulty in confirming the presence of spirochetes in developing dental tissue contributed to the notion that hypoplasia and malformation were due to the general nutritional state of syphilitic infants, to local impairment of nutrition due to endarteritis, or even to rickets.¹⁴⁴ Indeed, as Hutchinson emphasized, it is the first (6 year) molars and central incisors of the permanent set that are specifically affected. These begin to calcify just before and just after birth, respectively. Therefore, perinatal injury would be expected to produce malformation of these teeth, particularly

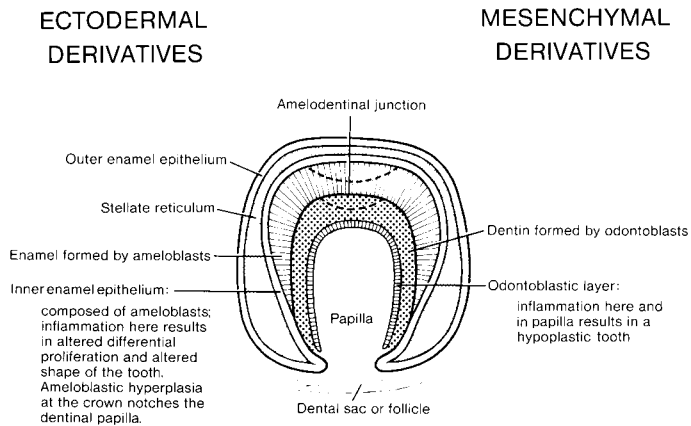


FIGURE 82-6. Development of the permanent incisor, illustrating the effect of treponemal infection or morphogenesis.

if a disturbed process of calcification is the major mechanism of pathogenesis. From 1932 to 1953, however, a series of observations suggested that direct treponemal invasion of the developing permanent tooth and the resulting inflammation are the cause of dental stigmata.¹⁴⁵

The tooth is formed by mesenchymal protrusion into an ectodermal tooth bud, which invaginates to receive it (Fig. 82-6). A dental papilla of mesenchymal origin gives rise to an outer layer of odontoblasts that ultimately produce dentin abutting the ectodermal enamel organ. An enamel epithelium on the inner aspect of the enamel organ consists of ameloblasts that ultimately produce a layer of enamel rods, lining the outer aspect of the dentin. Interactions between ameloblasts and the underlying mesenchymal odontoblasts initiate the apposition of enamel and dentin. This is followed by calcification of both enamel and dentin and finally by eruption. When the jaws of newborn infants dying of congenital syphilis are examined, the tooth germs of the permanent teeth are inflamed and spirochetes can be found throughout the enamel organ and dental papilla. There is endarteritis and perivascular inflammation in the dental papilla, and spirochetes are found in vessel walls. This results in a complex pathological process culminating in a failure to lay down enamel at the center of the notch and an irregular amelodentinal junction in the mature tooth. Radiographs of syphilitic incisors suggest that the irregular amelodentinal junction is the internal counterpart to the external deformity. The impaired growth of the dental papilla, on the other hand, is the precursor of the small size of the incisors and first molars.

CLINICAL MANIFESTATIONS

■ PREMATURETY AND INTRAUTERINE GROWTH RETARDATION

Intrauterine growth retardation, a commonly cited feature of congenital syphilis, is thought to reflect inadequate nutrition of the fetus as a result of syphilitic placentitis.¹⁴⁶⁻¹⁴⁸ Previously,

there were no clear criteria for distinguishing between premature infants and those who are small for gestational age. Furthermore, Naeye's study of 36 syphilitic perinatal deaths seemed to show that, in contrast to rubella and cytomegalovirus infection, syphilis did not affect fetal growth.⁹⁰ The difficulty in sorting out the contribution of syphilis to fetal-growth retardation is compounded by the fact that gestational syphilis disproportionately affects the same population in which other causes of fetal-growth retardation, such as maternal use of intravenous drugs and poor nutritional status, are prevalent. Controlled studies, however, strongly support the association between intrauterine infection with *T. pallidum* and prematurity, low birth weight, and small size for gestational age.^{149,150}

■ EARLY CONGENITAL SYPHILIS

Similar to acquired syphilis in adults,^{151,152} congenital syphilis traditionally is divided into early and late disease. Those features that typically appear within the first 2 years of life comprise early congenital syphilis, while those that occur after 2 years of age, most often near puberty, comprise late congenital syphilis. In current practice, the vast majority of cases present within the perinatal period.

The clinical manifestations of early congenital infections are a consequence of active infection with *T. pallidum* and the resultant inflammatory response induced in various organs and tissues. The severity of these manifestations is extremely variable, ranging from life-threatening involvement of multiple organs and body systems, as is seen in fetal hydrops, to radiologic or laboratory abnormalities in an otherwise normal-appearing newborn.¹⁴⁷ Indeed, most infected infants are entirely asymptomatic at birth.^{34,153-156} In a study from Detroit, only 16 (22%) of 72 infants born to mothers with untreated syphilis had clinical, laboratory, or radiologic evidence of congenital syphilis.¹⁴⁹ When syphilis is not identified in normal appearing infants, the diagnosis is delayed until the patient presents weeks later with such nonspecific complaints as rhinitis, pneumonia, or failure to thrive.^{37,95,157,158} In two thirds of untreated cases, the clinical signs of early congenital syphilis begin to appear in the third to the eighth week of life; in nearly all cases, the signs appear within 3 months.^{158,159}

Neonates born with manifest syphilis are often severely affected and carry a worse prognosis. Among these are the infants who display the classic picture of marasmic syphilis: the "wizened, pot-bellied, hoarse old man with withered brown skin and runny fissured nose ... senescent decrepitude in miniature."³⁴ In an earlier era, a number of signs were very suggestive of syphilis, especially when seen together (e.g., snuffles, certain skin eruptions, pseudoparalysis, and epitrochlear lymphadenopathy).¹⁵⁵ Marfan (as cited by Stokes) considered snuffles, palmar and plantar bullae, splenomegaly, pseudoparalysis, and cutaneous syphilids to

form a diagnostic pentad¹⁵⁸; Bueno suggested that the first three of these signs comprise a triad.¹⁶⁰ None can be considered entirely pathognomonic, however.

Mucocutaneous lesions

Among those infants who have clinical evidence of congenital syphilis, 15–60% will manifest mucocutaneous lesions consisting of rash and/or rhinitis (Table 82-4). Nasal discharge is the earliest sign of congenital syphilis, occurring 1–2 weeks before the rash (Fig. 82-7). It was reported in 68–86% of older series,^{140,144,159} but has become much less common over time (Table 82-4).^{161,162} The discharge, which contains spirochetes in high concentration, is initially watery and indistinguishable from that of viral or allergic rhinitis, but then it becomes progressively thicker and purulent and then hemorrhagic. Resulting nasal obstruction interferes with feeding. Ulceration leads to deeper involvement, including chondritis with necrosis, and eventually to the septal perforation or saddle-nose deformity of late congenital syphilis. Extension into the throat produces laryngitis and either a hoarse or an aphonic cry.

As with secondary syphilis in adults, there are myriad cutaneous lesions in congenital syphilis. The most common lesion is a large round pink macule that fades to a dusky or coppery hue, lasts 1–3 months without treatment, and leaves a residual pigmentation.^{34,158} These lesions are typically distributed over the back, perineum, extremities, palms, and soles, sparing the anterior trunk; they develop slowly over a period of weeks. They may be covered with a fine, silvery scale and may mingle with indurated plaques of similar size and color. The corymbiform lesion consists of a grouped papule around a large central plaque, like a “hen and chicks”; annular lesions occur but are less common than in acquired secondary syphilis.³³ The vesicu-

lobullous eruption, known as *pemphigus syphiliticus*, is highly distinctive when present.¹⁵⁸ Intraepidermal edema leads to spongiotic midepidermal blisters that are most prominent on the palms and soles; the blister fluid teems with spirochetes.¹²⁴ When the bullae rupture, they leave a macerated, dusky red surface that readily dries and crusts (Fig. 82-8). Even in the absence of frank bulla formation, desquamation is common and may be generalized or confined to the periungual areas of fingers and toes. Palmar and plantar desquamation is preceded by subcutaneous edema underlying a shiny erythema and sometimes accompanied by shedding of the nails.^{1,34} Paronychia also leads to narrow, atrophic nails, producing a claw-nail deformity, particularly of the fourth and fifth digits. Hair may be brittle and sparse; infantile alopecia, especially affecting the eyebrows, is considered very suggestive of syphilis.³⁴

The face, perineum, and intertriginous sites are particular targets of syphilitic lesions that may be eczematoid, impetiginous, or even gangrenous (Fig. 82-9 A,C).^{1,34,158} The facial eruption preferentially affects the middle third of the face, from the medial portions of the supraorbital ridges to the chin¹⁶³ (Fig. 82-9B). At the nares, lips, and anus, the initial lesions may be indistinguishable from the mucous patches of secondary syphilis but then become deeply fissured and hemorrhagic, leading to Parrot’s radial scars of late congenital syphilis, known as rhagades.³⁴ Mucous patches are also found on the tongue and palate.

Condylomata lata affect the same mucocutaneous and intertriginous areas and are raised, flat, moist verrucae that are seen in recurrences of untreated congenital syphilis.³⁴ They are seen typically toward the end of the first year of life,¹ and, together with the furuncle of Barlow, may be regarded as an intermediate manifestation between early and late congenital syphilis. The syphilitic furuncle is a deep violaceous

Table 82-4. Clinical Presentations of Early Congenital Syphilis

Total Number						Skin		X-Ray	Abnormal Bone		Ref.
	Hepatomegaly	Splenomegaly	Anemia	Jaundice	Rash	Petechiae	Snuffles		Lympha- denopathy	Pseudo- paralysis	
15	13/15	15/15	13/15	6/15	11/15	8/15	—	6/7	—	—	151
18	17/18	14/18	7/8	6/18	6/18	—	3/18	13/15	—	1/18	147
102	21/102	21/102	13/102	21/102	21/102	—	11/102	43/102	—	16/102	122
16	16/16	16/16	8/16	7/16	8/16	4/16	8/16	11/16	6/16	—	109
21	12/21	12/21	—	—	12/21	—	11/21	21/21	—	21/21	140
6	2/6	4/6	4/6	1/6	2/6	—	1/6	—	1/6	3/6	153
10	10/10	10/10	—	—	5/10	—	2/10	—	—	—	152
24	18/24	12/24	15/22	13/24	9/22	10/23	9/21	14/17	—	—	154
Total(%)	109/212(51)	104/212(49)	60/179(34)	54/181(30)	74/210(35)	22/54(41)	45/194(23)	108/178(61)	7/22(32)	41/147(28)	



FIGURE 82-7. The face of a newborn infant displaying pathologic morphology indicative of “congenital syphilis” with striking mucous membrane involvement. (Used with permission of the American Academy of Pediatrics. Red Book Online Visual Library, 2006. Image 128-42. Available at <http://aapred-book.aappublications.org/visual>; accessed on June 15, 2007.)



FIGURE 82-8. Newborn with congenital syphilis with cutaneous ulceration (luetic gumma). These lesions are highly infectious. (Used with permission of the American Academy of Pediatrics. Red Book Online Visual Library, 2006. Image 128-11. Available at <http://aapredbook.aappublications.org/visual>; accessed on June 15, 2007.)



FIGURE 82-9. **A.** Erythematous macules and papules with scales. (Source: Lugo A et al. Congenital syphilis. *Pediatr Dermatol* 2006; 23(2): 122.) **B.** Erythema and desquamation in the perioral area. (Source: Lugo A et al. Congenital syphilis. *Pediatr Dermatol* 2006; 23(2): 122.) **C.** Scaling, annular rash of congenital syphilis. (Courtesy of C. Ginsburg.)

nodule, usually on the upper outer thigh, that occurs after 9 months and before 3 years of age.³⁴ Furthering the analogy between congenital and secondary syphilis is a recent report of diffuse alopecia in an infected neonate.¹⁶⁴

Reticuloendothelial system

Syphilis was once the most common cause of hepatosplenomegaly in infancy.¹⁶⁵ The majority of infants with clinical evidence of early congenital syphilis will manifest hepatosplenomegaly (Table 82-4).^{121,136,154,161,166–168} Hepatosplenomegaly may occur as an isolated manifestation,¹⁶¹ but splenomegaly without hepatic enlargement occurs rarely, if ever. Both hepatic and splenic enlargement are caused by subacute inflammation and by compensatory extramedullary hematopoiesis.^{121,169} Hypersplenism also may contribute to spleen size.^{158,170} Up to one third of infants with hepatic involvement will manifest both direct and indirect hyperbilirubinemia as well as elevated transaminase, γ -glutamyltransferase, and alkaline phosphatase levels.^{116,171} For unknown reasons, the liver dysfunction may actually worsen with the initiation of penicillin therapy, before gradually improving weeks to months later.¹⁷¹ On occasion, the liver abnormalities may require as long as a year to resolve; permanent hepatic sequelae (e.g., cirrhosis) are rare, however. Generalized lymphadenopathy is found in 20–50% of cases.^{140,162,168,172} The nodes are firm, rubbery, and nontender. Epitrochlear adenopathy, found in 20% of those with adenopathy, is considered especially characteristic of congenital syphilis.^{147,158,162,173}

Skeletal involvement

Among syphilitic infants under 1 year of age studied by Nabarro,³⁴ more than 30% had physical evidence and more than 80% had radiographic evidence of osteochondritis. In an unpublished series from Texas, 70% of infants with probable or definite congenital syphilis had osteochondritis,¹⁷⁴ a figure similar to those in other reports (Table 82-4). The majority of affected infants do not have any symptomatology from skeletal involvement; on occasion, however, the bony lesions may be painful or have superimposed fracture resulting in pseudoparalysis of the affected limb, termed *pseudoparalysis of Parrot*.¹⁴⁷ The physical signs of skeletal syphilis in infants are limited to the signs of epiphysitis. Epiphyses of the radius, femur, humerus, and fibula, in descending order of frequency, are involved. There may be periarticular swelling, and the end of the bone is tender on passive motion of the adjacent joint. When the proximal humerus is affected, the arm hangs in flaccid immobility, internally rotated with the forearm in pronation. Pain elicited by passive motion of the shoulder, however, and development of the condition after birth distinguishes this pseudoparalysis from intrapartum brachial plexus injury. When the femur is involved, the leg is held in rigid flexion. Dactylitis (tender, fusiform swelling of the fingers) was observed in 2–6% of older series,¹⁴⁴ but is now uncommon, probably because it was typically seen in recurrences of untreated congenital syphilis.³⁰ Osteitis of the skull, particularly of the central margins of the occipital and parietal bones, produces

softening (craniotabes) that indents or yields on pressure “like stiff parchment.”^{34,158} Parrot’s nodes are focal, bilateral, frontoparietal swellings, typically separated by a cruciform furrow.

Roentgenographic methods have been used diagnostically in congenital syphilis for more than 80 years. Because the radiographic changes are relatively specific, x-ray formerly rivaled serology in importance for diagnosis and is still highly useful in distinguishing active infection from transplacental transfer of maternal antibodies.¹⁵⁵ The proliferative and destructive changes in bone tissue produce a “celery stick” appearance of increased density alternating with rarefaction on x-ray.^{138,175} Radiographic changes are most readily observed in the areas of rapid bone growth, such as in the provisional zone of calcification and in the periosteum (Fig. 82-10). Syphilitic osteochondritis requires approximately 5 weeks to become roentgenographically demonstrable, while periostitis, multiple layers of new periosteal bone formation in response to diaphyseal inflammation, requires 16 weeks. This corresponds to the clinical observation that osteochondritis is usually manifest perinatally, whereas periostitis sometimes is not seen until 4–5 months later.¹⁵⁵ When both lesions are present perinatally, it suggests that the infant was infected during the second trimester¹⁷⁶; the combination of these lesions makes a diagnosis of syphilis very likely. When periostitis is present by itself, it usually means that an earlier osteochondritis has already healed. Although single bone lesions can occur,¹⁷⁷ such a finding should suggest another diagnosis.

A skeletal survey is required to evaluate infants for congenital syphilis. Widespread lesions involve multiple, symmetrical sites of the long bones and occasionally involve the cranium, spine, and ribs. The tibia and ulna are most commonly followed by fibula, radius, humerus, and femur. Lower extremities are more commonly affected than upper extremities; the femur is more often affected distally, the tibia and humerus proximally.³⁴ The earliest changes occur in the metaphysis, consisting of a transverse sawtooth radiodense band below the epiphyseal plate; this widened and enhanced zone of provisional calcification is accompanied by an underlying zone of osteoporosis, evident as a radiolucent band. A series of alternating dense and lucent bands may extend into the diaphysis.¹³³ This process may be followed by radiolucent mottling and finally by fragmentation of the metaphysis itself. Focal defects with cortical destruction may be seen on the lateral aspect of the metaphysis; in the tibia, such lesions occur on the medial aspect of the proximal metaphysis and are usually bilateral, giving rise to the distinctive “cat bite” or Wimberger’s sign in 21% of cases of infant syphilis.¹⁷⁸ Erosion of the sigmoid notch of the ulna may be of similar significance.¹³⁹ Though also seen in hyperparathyroidism, infantile generalized fibromatosis, and bacterial osteomyelitis, the “cat bite” sign is most suggestive of syphilitic osteitis. Later, longitudinal lines of rarefaction may also

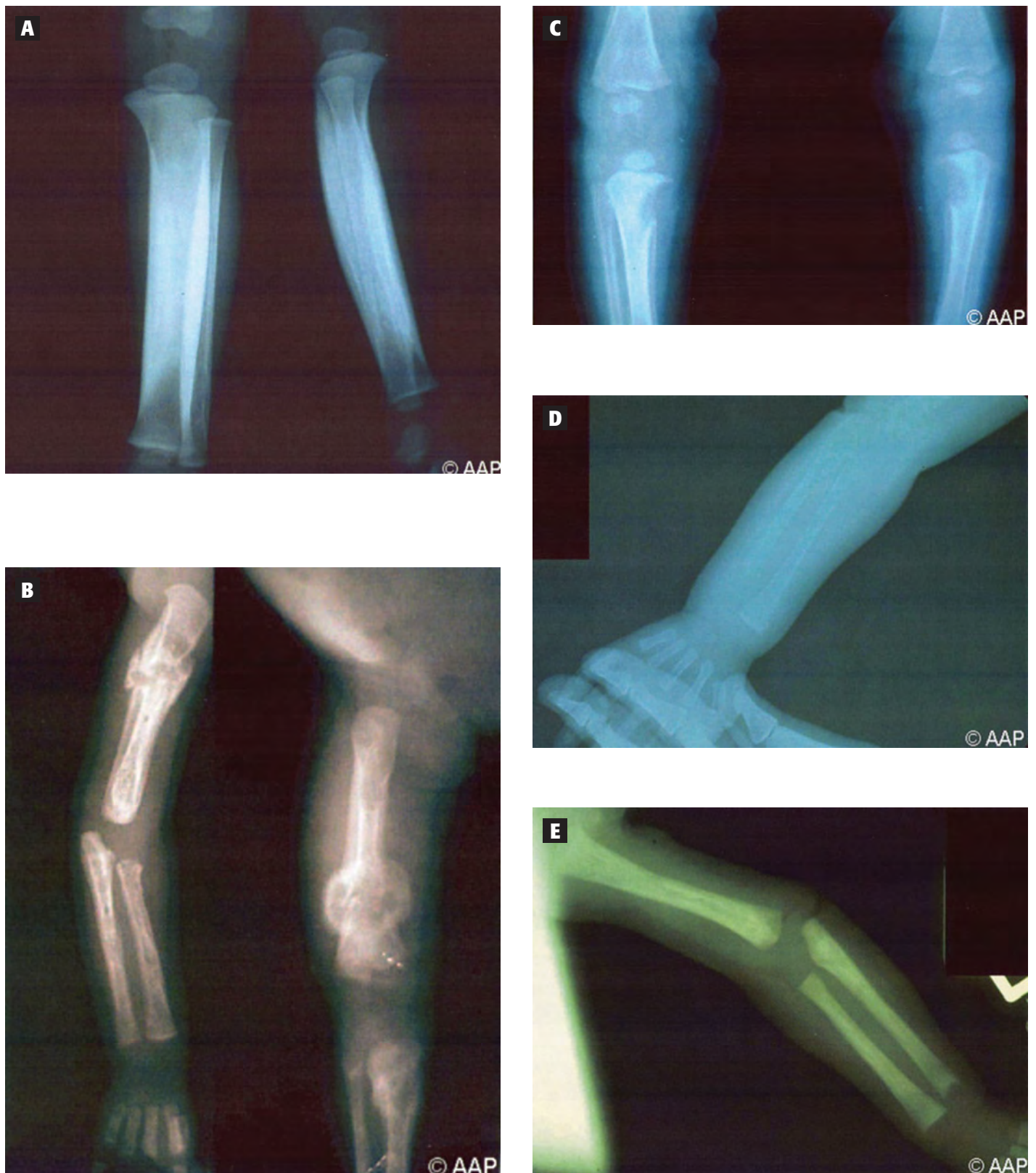


FIGURE 82-10. **A.** A 4-year-old child with diaphyseal cortical thickening secondary to congenital syphilis (a late finding). **B.** Congenital syphilis with a pathologic fracture of the proximal humerus and the distal femur. **C.** Congenital syphilis with proximal tibial metaphysitis (Wimberger's sign). **D.** Congenital syphilis with metaphyseal destruction of distal humerus, radius, and ulna. **E.** Neonate with congenital syphilis with metaphyseal osteomyelitis. Note radiolucent distal radius and ulna with cupping of the distal ulna. (Used with permission of the American Academy of Pediatrics. Red Book Online Visual Library, 2006. Images 128-17, 16, 15, 14, 13, respectively. Available at: <http://aapredbook.aappublications.org/visual>; accessed on June 15, 2007.)

extend into the diaphysis; in serial array, these linear lucencies resemble a “celery stick,” a sign also seen in rubella and cytomegalovirus infection.¹³³ Irregular, patchy focal lucencies may appear in the diaphysis, sometimes containing sequestra that invite confusion with suppurative osteomyelitis.¹⁷⁹ The epiphysis is relatively spared of radiographic changes, except that it may separate as a result of minor trauma.

Fractures through the degenerating metaphysis occur readily, followed by exuberant callus formation, resulting in a cap over the metaphysis called the “bucket handle” sign.¹⁷⁸ Periostitis is found in 71% of cases of infant syphilis and consists of multiple layers of periosteal new bone formation (“onion peel periosteum”) in response to diaphyseal inflammation¹⁷⁸; when exuberant, this process leads to hypertrophic “periosteal cloaking” of the bone, with layers of marrow trapped between layers of subperiosteal bone, thus encasing the entire shaft and producing a radiographic “sarcophagus sign” (Fig. 82-10).

Hematologic manifestations

The major hematologic features of early congenital syphilis are anemia, leukocytosis or leukopenia, and thrombocytopenia. Whitaker et al. found anemia to be the most common laboratory finding in 24 out of 25 cases (96%).¹⁷⁰ The anemia of congenital syphilis is Coombs’ test-negative, normochromic, and normocytic or macrocytic with polychromasia, and often striking reticulocytosis and erythroblastosis.³⁴ Severe anemia may be associated with replacement of marrow by granulation tissue in syphilitic osteitis or with maturation arrest in the erythroblastoid line.^{34,180} Autoimmune hemolysis, however, is a more common mechanism,^{170,181} and it may be associated with cryoglobulinemia, macroglobulinemia, or circulating immune complexes.^{142,143,182,183} Hemolysis may persist for some time following treatment and can be sufficient, if prolonged or complicated by bleeding, to lead to iron-deficiency anemia.

Neutrophilic leukocytosis occurs in over 70% of cases, and congenital syphilis is one of the classic causes of leukemoid reactions in infancy.¹⁸⁴ Leukopenia and monocytosis also have been described.¹⁸⁵ Thirty percent of babies with syphilis develop significant thrombocytopenia.^{166,170} Bleeding complications occur in 60% of those who are thrombocytopenic. Thrombocytopenia is believed to be due to diminished platelet survival mediated by immune complexes or hypersplenism.^{166,170}

Nephropathy

Syphilitic nephrotic syndrome in infancy is an uncommon complication that has, nevertheless, been recognized since the end of the nineteenth century.¹⁶³ Nephrosis was found in 5% of cases of infant syphilis at the Hospital for Sick Children, in London, between 1917 and 1939,³⁴ which is similar to more recent series^{133,181}; glomerulonephritis, with hematuria and cylindruria, is less common.¹⁸⁶ Evidence of

nephrotic syndrome appears at 2–3 months of age with the onset of edema, ascites, hypoproteinemia, and proteinuria.

Central nervous system involvement

Neurologic involvement in congenital syphilis ranges from asymptomatic central nervous system (CNS) invasion by *T. pallidum* to acute syphilitic leptomeningitis. Traditionally, asymptomatic involvement of the CNS is inferred from abnormal CSF indices (e.g., pleocytosis, elevated protein content, or reactive CSF-VDRL test). In 1949, Platou reported a 60% incidence of congenital neurosyphilis based upon diagnostic criteria consisting of >5 wbc/mm³, a protein content >45 mg/dL, and a reactive CSF-VDRL test.¹⁴⁰ These criteria are relatively insensitive and nonspecific, however; in neonates, as many as 25–32 wbc/mm³ and a protein content as high as 170 mg/dL in CSF can be within the normal range.^{187,188} Furthermore, the significance of a reactive CSF-VDRL test in the absence of other diagnostic evidence of congenital syphilis is suspect, inasmuch as nontreponemal IgG antibodies can pass from the serum to the CSF.^{189,190} Investigators have analyzed neonatal CSF utilizing immunoblotting for *T. pallidum*-specific IgM antibodies and rabbit infectivity testing (RIT)¹⁹¹ to arrive at a more precise estimate of the frequency of asymptomatic CNS involvement. Both of these modalities indicated that the likelihood of CNS involvement correlates with the degree of clinical severity. Among infants with clinical and laboratory evidence of congenital syphilis, CNS involvement by IgM immunoblotting ranged from 44% (11 of 25) to 82% (14 of 17).^{113,189,192,193} In contrast, only 10–20% of normal-appearing infants with congenital infection had detectable IgM antibodies in CSF.¹⁹³ By RIT, the prevalence of CNS invasion by *T. pallidum* was 86% (6 of 7) in infants with symptomatic congenital syphilis, but only 8% (1 of 12) among infants with normal physical examination and laboratory evaluation.¹¹³ More recently, researchers have studied the use of PCR to detect CNS involvement in infants. In a comparison of the diagnostic accuracy of IgM immunoblotting and PCR assay of serum and CSF with the CSF RIT, PCR and IgM immunoblotting of serum and blood best predicted CNS infection with sensitivities of 94% (16 of 17) and 100% (17 of 17), respectively.^{194,195}

The neurosyphilitic syndromes described in early congenital syphilis essentially represent diverse clinical expressions of a single pathogenic process—basilar meningitis and meningovascular syphilis. Acute syphilitic leptomeningitis, with meningismus, bulging fontanelles, and intractable vomiting, carries a grave prognosis.¹⁴⁷ Patients who survive this syndrome untreated or inadequately treated are usually left with obstructive hydrocephalus, seizure disorders, and impaired intellectual development. Cerebrovascular accidents occur in the neonatal period, probably as a combined consequence of cerebral arteritis and thrombocytopenia.¹⁶⁶ Untreated neurosyphilis can lead to a chronic meningovascular

process which results in hydrocephalus, cranial nerve palsies, and cerebral infarction late in the first year. Hypopituitarism manifested by persistent neonatal hypoglycemia has been observed among some infants with congenital syphilis.¹⁹⁶ Autopsy specimens have demonstrated interstitial inflammation, fibrosis, and occasionally focal necrosis of the anterior lobe.^{121,196} The neurohypophysis is usually normal. Magnetic resonance imaging (MRI) of the pituitary, combined with evaluation of pituitary function, has aided in its diagnosis.

Ocular involvement

Three ocular lesions are associated with early congenital syphilis: chorioretinitis, glaucoma, and uveitis. Syphilitic chorioretinitis typically produces a “salt and pepper” pattern of pigmentary patches at the periphery of a granular fundus.¹⁹⁷ Proptosis, blepharospasm, corneal clouding and edema, and excessive tearing should suggest the possibility of glaucoma. Uveitis usually occurs as an extension of choroiditis. Interstitial keratitis and optic neuritis have been described in infantile syphilis,³⁴ but they are generally regarded as lesions of late congenital syphilis.

Other manifestations

Syphilitic pneumonitis (pneumonia alba) is uncommon. Radiographically it produces bilateral, streaky infiltrates that can progress to widespread consolidation and may be confused with respiratory distress syndrome (Fig. 82-11).^{34,198} Diarrhea in early congenital syphilis may be due to either pancreatitis with malabsorption or direct involvement of the intestinal mucosa. Rectal bleeding and obstruction due to severe ileitis also have been reported.¹⁹⁹ Approximately 10% of infants dying of syphilis have myocarditis.²⁰⁰ The clinical importance of myocardial involvement in living infants is unknown; there is no convincing evidence of myocardial sequelae in surviving adolescents and adults with congenital syphilis.

■ LATE CONGENITAL SYPHILIS

The malformations or stigmata of late congenital syphilis represent the delayed consequences of the localized inflammatory processes established at sites of treponemal infection during the early stage of disease.^{148,201,202} Thus, late congenital syphilis can be prevented simply by appropriate treatment of early infection. Late congenital syphilis in the child or adolescent corresponds to tertiary syphilis in the adult, and, as with tertiary syphilis, late congenital syphilis is not infectious. Although the cardiovascular system is usually spared in the child, other target organs (e.g., bone and soft tissue, eyes, ears, and the CNS) are similar in late adult and congenital syphilis. Moreover, in both instances, gummatous (i.e., granulomatous) lesions tend to supplant the mononuclear and plasmacytic perivascular infiltrates of early syphilis.

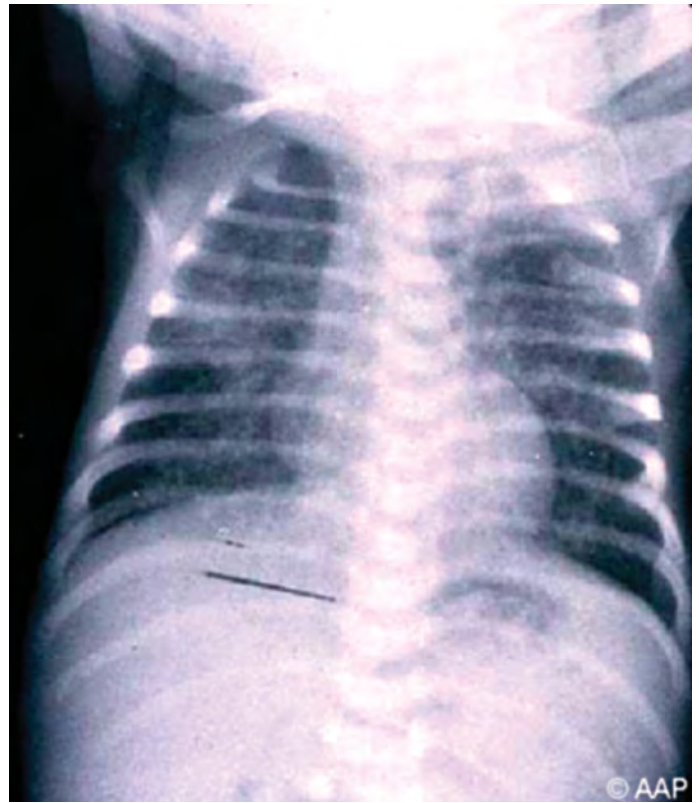


FIGURE 82-11. Congenital syphilis with pneumonia alba. The infant survived with penicillin. (Used with permission of the American Academy of Pediatrics. Red Book Online Visual Library, 2006. Image 128-05. Available at <http://aapredbook.aappublications.org/visual>; accessed on June 15, 2007.)

Malformations (stigmata)

Chondritis and focal osteitis in infancy may lead to the craniofacial malformations that classic writers on congenital syphilis found so fascinating. The most common is frontal bossing, which occurs in some form in 30–87% of symptomatic cases.^{144,158,202,203} Involvement of the parietal bone produces squaring of the cranium or occasionally a “hot cross bun” deformity. Other variations of this malformation include supraorbital thickening (olympian or beetled brow), a high cranium or “tower skull,” and, with parietal bossing alone, a sloping skull.³³ Robinson attributed the absence of bossing among his own cases to the disappearance of rickets.²⁰⁴ By ascribing cranial bossing to associated, unrecognized rickets, he revived the nineteenth century confusion between rickets and congenital syphilis. Since bossing was common in the only other modern series of cases,²⁰² the controversy may outlive the disease.

Deep necrotizing nasal chondritis in infancy produces a collapsed saddle-nose deformity in 10–30% of patients with late congenital syphilis.^{158,162} Involvement of adjacent structures may also lead to a short maxilla and a high palatal arch. The resulting facies has a flat, “dished out” look, with a relatively prominent mandible. Circumoral radiating furrows (rhagades) complete the syphilitic facies in 5–10%. Laryngeal scarring may leave the child hoarse.³⁴

Sequelae of periostitis of long bones affect primarily the tibia, clavicle, and scapula, in that order. Anterior bowing of the tibia (saber shin) occurred in 30–40% of older series but is now uncommon (Fig. 82-12).^{202,204} Particularly in these children, recurrent acute periostitis of the tibia, ulna, fibula, or femur sometimes followed trauma or febrile illness, and it might be heralded by local tender nodules resembling erythema nodosum.³⁴ Thickening of the clavicle in its medial third is called Higouménaki's sign and occurs preferentially on the side of the patient's handedness.¹⁵⁸ Robinson doubted its authenticity as a sign of syphilis.²⁰⁴ Affected scapulae assume a scaphoid shape, concave medially.

Teeth. Syphilis affects morphodifferentiation and apposition, rather than the later stage of calcification as in rickets. There are no consistent abnormalities in deciduous teeth, but when affected they are misshapen and hypoplastic. The permanent teeth that develop later than the central incisors and first molars are much less commonly affected. If the mesenchymal progenitor cells have been destroyed in the newborn period, later developing permanent teeth may be missing. Hutchinson described small canines and incisors that were widely spaced and peg- or screwdriver-shaped.¹³ They were tapered from the gingival bases toward a notched biting edge and were rough, dull, and dirty gray in color due to insufficient enamel (Fig. 82-13A). These changes most often affect the upper central incisors but they may also affect the upper, lower, and lateral incisors. They are changes of the permanent, not the deciduous, teeth, although the latter are believed to be more prone to caries than normal in late congenital syphilis. In the first year of life, the diagnosis can be made by x-ray of the unerupted central incisors.²⁰⁵ Variations of the classic Hutchinson tooth also occur. The lower incisors may have parallel sides and lack a notch but are otherwise small, round, and spaced, resembling little tombstones or top hats projecting from the gum.³⁴ The upper incisors are sometimes pointed (cannibal teeth) rather than notched.¹ Henry Moon described more completely the molars whose peculiar “tubercular projections” Hutchinson had mentioned; the characteristic 6-year (first lower) molars are dome-shaped with diminutive cusps arrayed in a tight circle at the top of the dome (Fig. 82-13B).²⁰⁶ Moon's molars have been variously likened to a mulberry, a *bouton de fleur*, a cow's udder, or a string purse. Poorly enamelized, they are highly prone to decay and are rarely present beyond puberty; they are strongly indicative of congenital syphilis when found.

Inflammatory lesions

Inflammatory lesions produce a variety of clinical manifestations, as described below.

Interstitial keratitis. Interstitial keratitis, when accompanied by neural deafness and typical dental abnormalities,



FIGURE 82-12. Tibial thickening (saber shin) due to periostitis in late congenital syphilis; one of Hutchinson's cases. (From Hutchinson J. *Syphilis*. London: Cassell, 1909.)

forms Hutchinson's triad. Taken alone, keratitis is the most common late manifestation (20–50%) and is bilateral either simultaneously or sequentially in more than 75% of individuals.^{158,204,207} The onset, between 5 and 16 years of age, is heralded by unilateral photophobia, pain, excess tearing, and blurred vision. Neovascularization may be so marked as to give the cornea a “salmon patch” appearance. The second eye is involved within 2 months in 80–90% of patients. Keratitis occurs more commonly in females than males and pursues a self-limited, sometimes relapsing, course that ends in corneal clouding (syphilitic nebulae) (Fig. 82-14) or secondary glaucoma. Chorioretinitis and iritis may be found, but less commonly than in congenital syphilis of infancy. Deafness is the least common of Hutchinson's

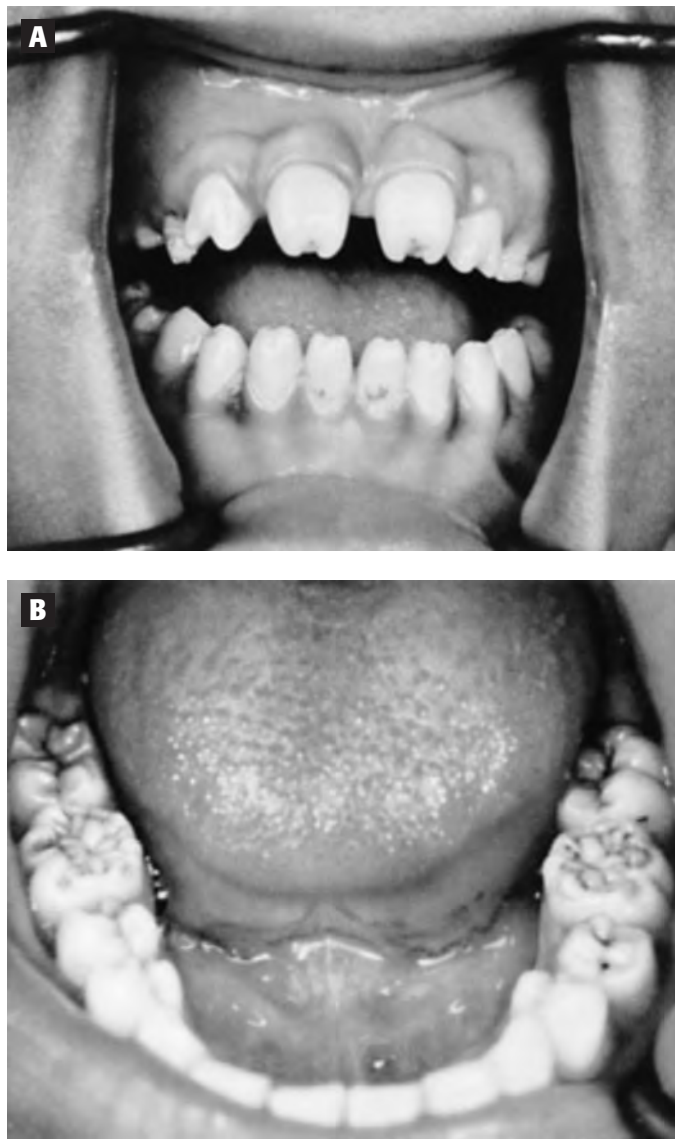


FIGURE 82-13. A. Hutchinson's teeth: The upper and lower incisors are conical, tapered toward the apex, and notched; the canine teeth are hypoplastic and poorly enamelized. **B.** Mulberry molars: the 6-year molars are dome-shaped with a circle of small knob-shaped cusps at the apices. (From Robinson HBG and Miller AS, *Color Atlas of Oral Pathology*. Philadelphia: Lippincott, 1990.)

triad. The primary lesion is osteochondritis affecting the otic capsule and leading to cochlear degeneration. The ossicles occasionally may be affected, so that an associated conduction defect does not exclude syphilis as a cause of sensorineural hearing loss. Karmody and Schuknecht distinguished between the abrupt onset of bilateral deafness without vertigo in childhood and a more gradual asymmetric pattern in adults associated with tinnitus and vertigo.²⁰⁸ Congenital leucic involvement of the otic capsule leads to fibrous adhesion between the medial surface of the stapedial foot plate and the membranous labyrinth (vestibulofibrosis). The result is Hennebert's positive "fistula sign without a fistula"; this consists of nystagmus and vertigo, despite an intact tympanic membrane, when

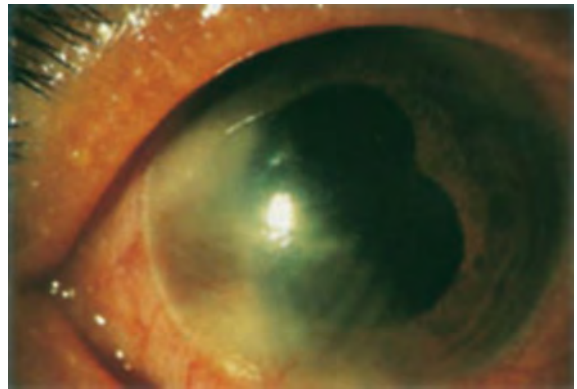


FIGURE 82-14. Congenital interstitial keratitis causing blindness. (Source: EyeNet, American Academy of Ophthalmology, January 2004, R. Trubo [BCSC, section 9]. Available at www.aao.org/aao/news/eyenet/comprehensive/comprehensive_jan_2004.htm)

positive and negative pressures are alternately applied to the external canal. Once considered a classic sign of syphilis, Hennebert's sign also occurs in Ménière's disease and vestibular Schwannoma.²⁰⁹ Hearing loss begins at high frequencies and often progresses to complete bilateral loss of cochlear and vestibular function.

Clutton's joints. Between the ages of 8 and 15, 1–3% of children with congenital syphilis develop symmetrical, painless swelling of the knees (occasionally elbows), with preservation of mobility, often following trauma.^{210,211} Adjacent bone erosion (von Gie joint) is rarely seen. Synoviocentesis reveals 10,000–30,000 leukocytes, predominantly lymphocytes. This hydrarthrosis is believed to be due to perisynovitis and resolves spontaneously over several months.

Palatal deformations. Gummata of the palate, throat, and nasal septum begin in late childhood or even adulthood as a gray, sharply defined "raucous patch." These lead painlessly to perforation of the septum and of the soft palate, usually in the midline. Deep ulcers of the throat and tongue occur in a similar fashion.

Neurosyphilis. As many as one fourth to one third of patients over the age of 2 years have asymptomatic neurosyphilis.¹⁶² Symptomatic neurosyphilis, on the other hand, is quite rare, is usually delayed until adolescence, and fits the adult patterns of tabes dorsalis, syphilitic encephalitis (general paresis), and local gummata.¹⁴¹ Juvenile paresis is the most common of these, occurring in 1–5% of congenital syphilitics, and is generally more severe than the acquired variety.^{34,162,204} It typically begins around puberty with deteriorating school performance, bizarre behavior, emotional inappropriateness, and inattention. Over the ensuing 6–12 months, the child develops ataxis, tremor, and dysarthria; half of these patients have seizure disorder, and nearly all have pupillary findings.^{212,213} Sequelae of untreated neurosyphilis in infancy, including hydrocephalus, convulsive disorders, and cranial neuropathies, were once common.

Paroxysmal cold hemoglobinuria. Late congenital and acquired syphilis were once the leading cause of paroxysmal cold hemoglobinuria.²¹⁴ Only half of these syphilitic patients had other manifestations of disease. About 8 hours following immersion of hands or feet into ice water (Rosenbach test) or other cold exposure, the patient experiences a myalgic, shaking chill and voids dark red or black urine. Many of the syphilitic cases have associated Raynaud's phenomenon.³⁴ The Coombs' test, Donath–Landsteiner (cold hemolysin) test, and VDRL are all positive. In the syphilitic cases, the attacks cease following penicillin therapy.

DIAGNOSIS

■ ANTEPARTUM DIAGNOSIS AND STILLBIRTHS

Ultrasonography can be used to diagnose fetal syphilis. The sonographic findings of nonimmune fetal hydrops due to syphilis include skin thickening, placental thickening, serous cavity effusions, hepatosplenomegaly, and hydramnios.^{107,215–218} At Parkland Memorial Hospital, hepatomegaly was found to be a reliable sonographic sign of fetal infection and correlated with detection of treponemes in amniotic fluid by RIT.²¹⁹ Hill and Maloney also reported noncontinuous gastrointestinal tract obstruction in association with hepatosplenomegaly and placentomegaly in a syphilitic fetus.²¹⁷

As noted earlier, stillbirth is a common outcome of gestational syphilis. According to CDC criteria, a syphilitic stillbirth is defined as a death of a fetus weighing >500 g or having a gestational age >20 weeks in which the mother had untreated or inadequately treated syphilis (Table 82-1).^{26,220,221} Whenever possible, this diagnosis should be supported by long-bone radiography or xeroradiography or confirmed by detection of spirochetes in fetal tissues at autopsy.^{25,222}

■ DIAGNOSIS IN THE LIVEBORN INFANT

As noted above, in 1990 and 1996 the CDC issued revised criteria for congenital syphilis surveillance (Table 82-1).^{201,220,221} Although intended primarily to help assess the public-health impact of congenital syphilis, these same guidelines also are used by practicing clinicians to determine which infants need further evaluation and treatment. The strength of these criteria lies in their recognition that the diagnosis of congenital syphilis is problematic for three reasons: (1) *T. pallidum* is noncultivable and often difficult to demonstrate in clinical specimens, (2) serologic analysis of the infant is complicated by the presence of transplacentally acquired maternal antibodies (i.e., absence of a serologic “gold standard”), and (3) a majority of live-born, infected infants have no evidence of infection.^{25,222}

■ CONFIRMED CONGENITAL SYPHILIS

A confirmed diagnosis of congenital syphilis requires laboratory demonstration of *T. pallidum* (Table 82-1). In current

practice, this involves detection of live treponemes in body fluids by dark-field microscopy or visualization in body fluids and tissue specimens by silver staining, immunofluorescence, or immunocytochemistry. Dark-field microscopy or immunofluorescence should be performed whenever nasal discharge, mucous patches, vesiculobullous lesions, or condylomata are present. Treponemes abound in such lesions, so definitive diagnosis can be achieved in most cases that exhibit these signs. Unfortunately, conventional methods for detection of *T. pallidum* in clinical specimens are insensitive and/or inapplicable because they require an invasive procedure. For this reason, a confirmed diagnosis is achieved only in the small proportion of infants with florid infection. As is now well recognized, PCR technology has the potential to dramatically improve the ability of clinicians to detect *T. pallidum* DNA in clinical specimens.^{194,223} Researchers have demonstrated the usefulness of the PCR testing of amniotic fluid, placental tissue, skin lesions, serum, blood, and CSF in confirming the clinical diagnosis of suspected and asymptomatic congenital syphilis.^{194,195,224}

Histopathologic examination of the products of conception

Since the earliest descriptions of syphilitic placentitis, pathologic examination of placentas and umbilical cords has been recognized as a readily available and yet underutilized tool for diagnosing congenital syphilis in at-risk infants.^{225,226} Placentas from infants with clinical and/or laboratory evidence of congenital syphilis have very high incidence of histopathological abnormalities, including presence of spirochetes by silver staining.^{149,150} Immuno-histochemical methods can facilitate detection of *T. pallidum* in placental tissues.^{131,226} Positive PCR testing of placental tissue for *T. pallidum* was significantly associated with placental histological features of congenital syphilis and suggested as useful in identifying cases in the absence of placental changes²²⁷; these same authors concluded that PCR testing also can be useful when distinctive histopathologic changes are absent in placentae. Stoll and coworkers emphasized the importance of a multidisciplinary approach involving close cooperation among obstetricians, neonatologists, and pathologists to assure that placentas are obtained for routine pathologic evaluation.¹⁵⁰

Presumptive diagnosis

Congenital syphilis is diagnosed presumptively in the absence of direct demonstration of *T. pallidum* in clinical specimens. The descriptor “presumptive” encompasses a wide spectrum ranging from the floridly symptomatic infant, in whom the diagnosis is essentially certain, to normal-appearing infants without clinical or laboratory evidence of infection.

When a child is born to a woman with reactive syphilis serologies, physical examination should be performed and

the infant's nontreponemal test titer should be compared to the mother's. (Treponemal tests generally are not performed on the neonate because they are not titered and infant reactivity merely reflects the transplacental passage of maternal antitreponemal antibodies.) The CDC no longer recommends obtaining umbilical cord blood because of the potential for contamination with maternal blood. Moreover, there also has been concern that RPR testing of umbilical cord blood is prone to false-positives due to contamination with Wharton's jelly.¹⁴⁷ A guide for the interpretation of maternal and infant syphilis serologies and an algorithm for the evaluation of infants born to mothers with reactive syphilis serologies are presented in [Table 82-5](#) and [Fig. 82-15](#), respectively.^{57,228} A diagnosis of congenital syphilis can be made with confidence if the mother has reactive nontreponemal and treponemal serologies and the infant manifests classic signs of disease. Congenital syphilis also is highly likely when the infant's nontreponemal antibody titer is fourfold or greater than the mother's serum, even in the absence of physical findings. In both of the above instances, infants should undergo further evaluation consisting of lumbar puncture with CSF analysis and complete blood cell count to deter-

mine the extent of disease and establish a baseline for follow-up. Other tests such as long bone radiographs, liver function tests, and audiologic and ophthalmologic examination should be performed as clinically indicated. Most commonly, the maternal and infant serologic titers are similar or the infant's titer is lower than the mother's.^{57,149} Further evaluation is dependent on the maternal stage of disease and treatment status and the infant's physical findings. The following are the most frequently encountered scenarios ([Fig. 82-15](#)):

1. The mother was treated *before* pregnancy and her nontreponemal test titer is decreasing appropriately or she is known to be serofast. No further evaluation is required if the infant is asymptomatic.
2. The mother was treated for early syphilis *during* pregnancy more than 4 weeks prior to delivery and her nontreponemal titer decreased fourfold or more prior to delivery. No further evaluation is necessary if the infant is asymptomatic, particularly if follow-up can be assured.
3. The mother was treated appropriately for early syphilis *during* pregnancy more than 4 weeks prior to delivery but her titer did not decrease at least fourfold. Full diagnostic evaluation of the infant (CSF analysis, complete blood

Table 82-5. Guide for Interpretation of Syphilis Serologic Test Results of Mothers and Their Infants

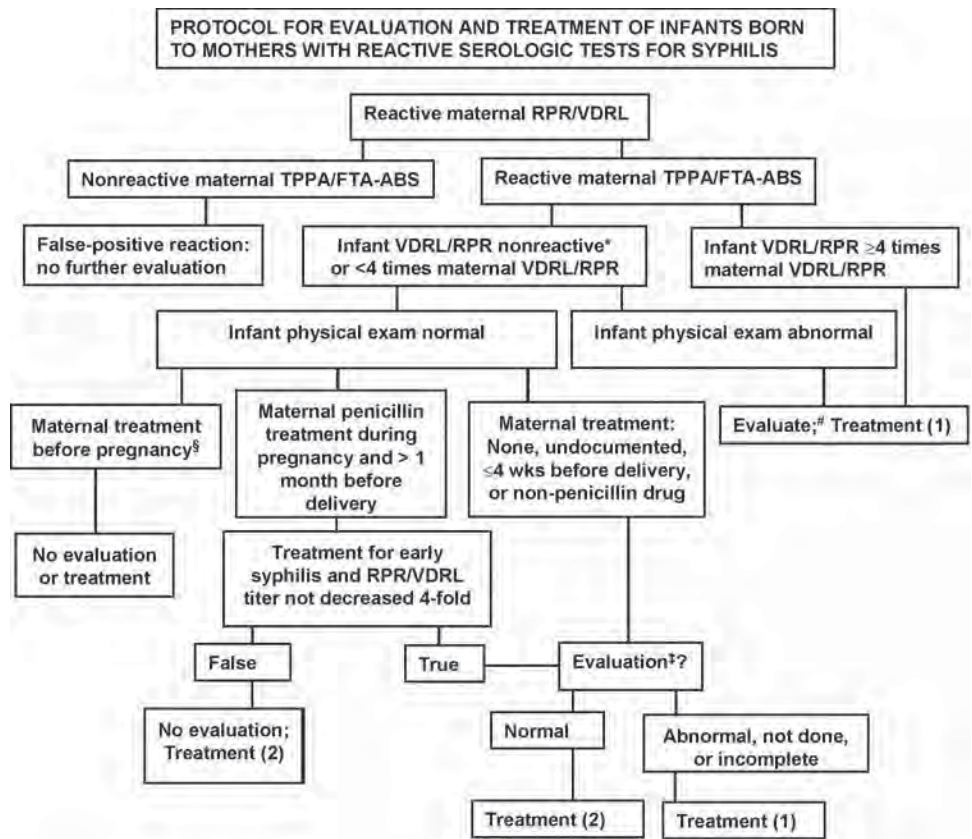
Nontreponemal Test Result (eg, VDRL, RPR, ART)		Treponemal Test Result (eg, TP-PA, FTA-ABS)		Interpretation ¹
Mother	Infant	Mother	Infant	
–	–	–	–	No syphilis or incubating syphilis in the mother or infant or prozone phenomenon
+	+	–	–	No syphilis in mother or infant (false-positive result of nontreponemal test with passive transfer to infant)
+	+ or –	+	+	Maternal syphilis with possible infant infection; mother treated for syphilis during pregnancy; or mother with latent syphilis and possible infant infection ²
+	+	+	+	Recent or previous syphilis in the mother; possible infant infection
–	–	+	+	Mother successfully treated for syphilis before or early in pregnancy; or mother with Lyme disease (ie, false-positive serologic test result); infant syphilis unlikely

VDRL, indicates Venereal Disease Research Laboratory; **RPR**, rapid plasma reagin; **ART**, automated reagin test; **TP-PA**, *Treponema pallidum* particle agglutination test, **FTA-ABS**, fluorescent treponemal antibody absorption; +, reactive; –, nonreactive.

¹Table presents a guide and not a definitive interpretation of serologic test results for syphilis in mothers and their newborn infants. Maternal history is the most important aspect for interpretation of test results; Factors that should be considered include timing of maternal infection, nature and timing of maternal treatment, quantitative maternal and infant titers, and serial determination of nontreponemal test titers in both mother and infant.

²Mothers with latent syphilis may have nonreactive nontreponemal test results.

FIGURE 82-15. Approach for evaluation of infants born to mothers with reactive serologic tests for syphilis. Infants of HIV-Ab mothers do not require different evaluation or treatment. *Infant's VDRL may be nonreactive due to low maternal VDRL titer or recent maternal infection. If the mother has untreated or inadequately treated syphilis and infant's physical exam is normal, some experts would not perform diagnostic evaluation but would treat infant with a single IM injection of benzathine penicillin (50,000 U/kg). #Evaluation consists of CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; and other tests as clinically indicated (eye exam, long-bone films, chest x-ray, liver function tests, cranial ultrasound, auditory brainstem response). §Women who maintain a VDRL titer $\leq 1:2$ beyond 1 year following successful treatment are considered serofast. †CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; long bone films. Treatment: (1) Aqueous penicillin G 50,000 U/kg IV q12h (≤ 1 week of age), q8h (>1 week) for a total of 10 days, or procaine penicillin G 50,000 U/kg IM single daily dose $\times 10$ days. (2) Benzathine penicillin G 50,000 U/kg IM $\times 1$ dose.



count, and other tests as indicated: long-bone radiographs, chest radiograph, liver function tests, cranial ultrasound, ophthalmologic exam, and auditory brain stem response) should be performed to determine appropriate therapy.

- The mother was untreated, treated during pregnancy with an antimicrobial other than penicillin, or treated appropriately less than 4 weeks prior to delivery. These all constitute inadequate therapy for the fetus, and the infant should be fully evaluated as in scenario 3 above.
- The mother was treated *during* pregnancy for late latent syphilis and maintained a low, stable titer through delivery. The infant does not require further evaluation if asymptomatic.

Evaluation for *T. pallidum*-specific IgM antibodies. Serodiagnosis of congenital syphilis poses a difficult problem because of the presence of transplacentally acquired maternal IgG in newborn sera. IgM, on the other hand, does not cross the placenta and is actively synthesized by the third-trimester fetus in response to infection. An early approach to the diagnosis of congenital syphilis was the measurement of serum IgM levels at or shortly after birth. In addition to lacking sensitivity,²²⁹ however, elevated total IgM levels are nonspecific and may result from intrauterine infection with other common pathogens including cytomegalovirus, *Toxoplasma gondii*, and rubella.²⁵ In 1968, Scotti and Logan described an indirect immunofluorescence test for the detection of IgM antibody against *T. pallidum*

(fluorescent treponemal antibody–absorption [FTA-ABS] IgM test) as a means of distinguishing infant from maternal antibody.²³⁰ Unfortunately, despite some early successes,^{156,231} the FTA-ABS IgM test has been shown to lack both sensitivity and specificity and has fallen into disuse.²³² Chromatographic separation of IgM in neonatal sera to remove maternal blocking antibodies and rheumatoid factor has been used to improve the performance of the FTA-ABS test; this improved version of the FTA-ABS IgM test has been designated the FTA-ABS-19S-IgM test.²³³ Though more sensitive than the original FTA-ABS IgM test,^{150,169} the FTA-ABS-19S-IgM test is technically demanding and available at only a handful of centers and, therefore, is no longer recommended. Stoll et al.^{150,169} evaluated a commercial IgM capture enzyme-linked immunosorbent assay (ELISA) for *T. pallidum*-specific antibodies but found a sensitivity of only 88% among infants with clinical and laboratory findings consistent with congenital syphilis. Both the FTA-ABS-19S-IgM test and the IgM capture ELISA appear to have poor sensitivity for detecting infection in at-risk infants with normal clinical and laboratory findings.^{150,169} Currently, no commercially available IgM test is recommended for evaluation of infants for congenital syphilis.²³⁴

Novel molecularly based diagnostic tests for asymptomatic neonates

The major dilemma in the diagnosis of early congenital syphilis is to differentiate normal-appearing, infected infants

from uninfected at-risk infants with reactive serologies due to transplacentally acquired maternal antibodies. Unfortunately, none of the currently available serologic tests can do this with high degrees of sensitivity and specificity in asymptomatic neonates. To address this critical issue, several investigators have utilized immunoblotting techniques to detect and characterize the neonatal IgM response to *T. pallidum*.^{113,192,235–239} IgM antibodies directed against *T. pallidum* antigens with apparent molecular masses ranging from 93- to 15-kDa have been detected in sera from infants with clinical and laboratory evidence of congenital syphilis. IgM immunoblot analysis of asymptomatic infants born to mothers with untreated syphilis has documented that as many as 20–42% of at-risk infants possess IgM antitreponemal antibodies and can be considered actively infected. Fractionation of neonatal sera into IgM and IgG components by high-performance liquid chromatography has confirmed that IgM reactivities obtained with whole sera are not due to rheumatoid factor and are not diminished by maternal IgG antibodies.²³⁸ Dobson and colleagues showed that the serum IgM reactivity disappears 1–3 months after appropriate penicillin treatment of neonates, further supporting the validity of IgM antibody detection as a marker for active infection.²³⁵ Sánchez and coworkers found that immunoblot analysis with recombinant forms of two highly immunogenic *T. pallidum* lipoproteins (47-kDa and 17-kDa lipoproteins) appeared to be even more sensitive than immunoblotting with native *T. pallidum* lysates.²⁴⁰ Most recently, Rawstrom and coworkers²⁴¹ reported that IgM immunoblot using *T. pallidum* lysates was a more accurate predictor of neonatal infection than using a maternal RPR titer >1:16.

Detection of *T. pallidum* is the most definitive means of proving that an asymptomatic child has active infection. Given the cost and difficulties inherent in RIT, PCR has emerged as a highly attractive alternative. Grimprel et al.¹⁹⁴ and Sánchez et al.^{113,195} have shown that PCR results for neonatal sera and CSF correlate quite closely with those obtained by RIT. In our experience, virtually all symptomatic at-risk infants have positive PCR and IgM serum studies.¹¹³ In preliminary findings, only 2 of 12 asymptomatic at-risk infants had positive PCR results on serum, while 5 of 12 had *T. pallidum*-specific IgM serum antibodies detectable by immunoblotting.¹¹³ The PCR results presumably reflect low spirochetal burdens and spirochetemia rates in asymptomatic infected infants. Interestingly, one asymptomatic at-risk infant with a negative immunoblot had a positive serum PCR. In a subsequent study conventional (e.g., physical exam findings; radiological evidence; CSF with reactive VDRL, elevated protein or WBCs) and experimental (e.g., IgM immunoblotting and PCR assay) tests were compared with RIT of CSF to diagnose CNS infection in a subset of 76 infants born to mothers with syphilis. Any abnormality of conventional CSF tests resulted in a sensitivity of 82% (14 of 17) and

specificity of 65% (33 of 51). IgM immunoblotting of serum yielded 100% (17 of 17) sensitivity and 66% (39 of 59) specificity, but these findings were not replicated when testing the CSF. PCR assay of serum and blood proved the most useful test with a sensitivity of 94% (16/17) and specificity of 90% (53 of 90). PCR testing of CSF had high specificity, but low sensitivity.¹⁹⁵ These data suggest that a comprehensive strategy involving physical exam, laboratory and radiologic findings, IgM immunoblotting, and PCR of serum will be needed for maximal sensitivity to distinguish infected from uninfected asymptomatic neonates.

■ DIAGNOSIS OF LATE CONGENITAL SYPHILIS

Diagnosis of late congenital syphilis is almost always presumptive and based on the typical clinical findings in association with reactive serologic tests. In the absence of a maternal history of syphilis, serologic testing of the mother can be helpful for distinguishing between acquired and congenital infection.

TREATMENT

A serum concentration of 0.018 mcg/mL is required to ensure adequate killing of the organism and must be maintained for 7 days in early cases and up to 3 weeks in late disease.²⁴² These basic requirements for achieving treponemicidal levels of penicillin have provided the therapeutic rationale for the use of long acting but relatively low dose penicillin formulations, most notably benzathine penicillin G (BPG), for the treatment of early syphilis in all patients, pregnant or not. Indeed, penicillin remains the drug of choice for the treatment of both acquired and congenital syphilis,^{151,234,243} although it is well recognized that there is a modicum of prospective clinical data to support the specific BPG dosing regimens recommended by the CDC.^{114,244,245} In the largest prospective cohort, involving 340 women treated antepartum with 2.4 MU benzathine penicillin G, Alexander et al.²⁴⁶ found that treatment of maternal syphilis prevented congenital transmission in 98% of patients representing all stages of syphilis; congenital transmission was prevented in 95% and 98% of women with secondary and early latent syphilis, respectively. These results, in concert with extensive clinical experience over decades, indicate that BPG regimens, which achieve at best modest serum levels of antibiotic, not only prevent transplacental transmission of *T. pallidum* but also treat infection once it has occurred. In contrast to erythromycin²⁴⁷ and, more recently, azithromycin,²⁴⁸ penicillin resistance has not been confirmed among any *T. pallidum* isolates.

■ TREATMENT DURING PREGNANCY

Pregnant women with reactive serologic tests for syphilis should be counseled concerning the risks of HIV

infection, tested for HIV antibody, and treated with the penicillin regimen appropriate for the stage of syphilis (Table 82-6).^{234,243} Tetracycline and doxycycline are contraindicated in pregnancy because both can result in staining of decidual teeth and impairment of long-bone growth. Moreover, tetracycline use during pregnancy has been associated with hepatic toxicity when there is concomitant renal dysfunction. There has been longstanding caution about the use of erythromycin because of reports of treatment failures in infants whose mothers received erythromycin treatment during pregnancy.^{249–251} Patient noncompliance with erythromycin therapy due to gastrointestinal side effects also is a major problem. Moreover, there remains concern over unpredictable maternal serum levels and erratic transplacental transfer of the drug.²⁵² Insufficient data exist on ceftriaxone or azithromycin to recommend its use in the treatment of syphilis during pregnancy.²³⁴ Indeed, the widespread prevalence of azithromycin-resistant strains of *T. pallidum*,²⁴⁸ combined with recent reports of treatment failures²⁵³ argue that azithromycin also should not be considered as an alternative to penicillin for antepartum treatment of pregnant women with syphilis.

Approximately 5–10% of pregnant women with syphilis report a history of penicillin allergy. Wendel and colleagues have shown that those individuals who are at risk for acute allergic reactions to penicillin can be identified by skin testing; if the skin test is positive, they can undergo oral penicillin desensitization, which makes them temporarily tolerant to a course of parenteral penicillin.²⁵⁴ No serious adverse reactions

were observed, and this regimen is currently recommended so that all pregnant women with syphilis can receive penicillin therapy (Table 82-7).

The Jarisch–Herxheimer reaction commonly occurs after treatment of acquired early syphilis in adults.¹⁵¹ It consists of fever, chills, myalgias, headache, hypotension, tachycardia, and transient accentuation of the cutaneous lesions; it typically begins within several hours of treatment and resolves within 24–36 hours. The etiology is not fully known; however, since *T. pallidum* lacks lipopolysaccharide,^{255,256} the release of treponemal lipoproteins that possess proinflammatory activities from dead or dying organisms has been implicated as the likely inducer of this clinical phenomenon.^{243,257–259} Klein and coworkers have shown that another manifestation of the Jarisch–Herxheimer reaction in pregnant women is uterine contractions, possibly mediated secondarily by prostaglandins.²⁶⁰ By fetal monitoring during the episode, they demonstrated evidence of fetal stress with tachycardia and decelerations, along with a marked decrease in fetal

Table 82-6. Treatment Guidelines for Acquired Syphilis During Pregnancy

Stage of Infection	Regimen
Primary	Benzathine penicillin G, 2.4 mU IM × 1
Secondary	
Early Latent (≤1 yr)	
Late Latent (>1 yr) unknown duration	Benzathine penicillin G, 2.4 mU IM q wk × 3
Neurosyphilis	Aqueous crystalline penicillin G 3-4 mU IV q4h × 10–14 d* or Procaine penicillin G 2.4 mU IM q day and probenicid 500 mg PO qid × 10–14 d*

*Some authorities recommend following this regimen with benzathine penicillin 2.4 mU IM q wk × 3.

Source: CDC. *Sexually Transmitted Diseases Treatment Guidelines*, 2006.

Table 82-7. Protocol for Oral Desensitization of β -Lactam Antibiotic-Allergic Patients

Step	β -Lactam Drug (mg/mL)	Amount ^a (mL)	Dose ^{a,b} (mg)	Cumulative Dose (mg)
1	0.5	0.1	0.05	0.05
2	0.5	0.2	0.10	0.15
3	0.5	0.4	0.20	0.35
4	0.5	0.8	0.40	0.75
5	0.5	1.6	0.80	1.55
6	0.5	3.2	1.60	3.15
7	0.5	6.4	3.20	6.35
8	5.0	1.2	6.00	12.35
9	5.0	2.4	12.00	24.35
10	5.0	4.8	24.00	48.35
11	50.0	1.0	50.00	98.35
12	50.0	2.0	100.00	198.35
13	50.0	4.0	200.00	398.35
14	50.0	8.0	400.00	798.35
15	Observe patient for 30 min; then administer 1 g of same agent intravenously.			

^aDrug suspension diluted in 30 mL of water for ingestion.

^bInternal between doses: 15 min.

From Sullivan TJ. Drug allergy. In: Middleton E, Reed C, Ellis E, et al, eds. *Allergy: Principles and Practice*, 4th ed. St. Louis: CV Mosby; 1993: 1523–1534.

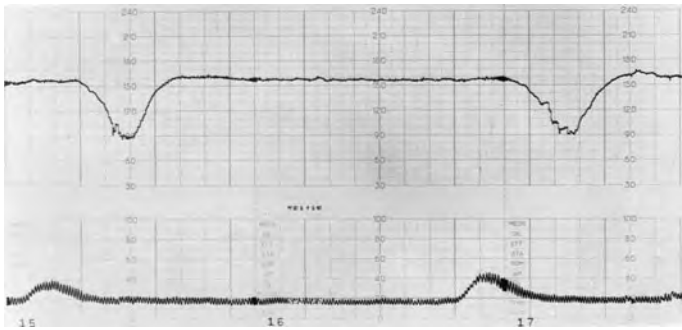


FIGURE 82-16. Fetal heart rate pattern, uterine contractions, and late decelerations occurring during a maternal Jarisch–Herxheimer reaction. Maternal blood pressure was 110/72 mm Hg, temperature 37.2 °C, and pulse 84 beats per minute. (From Klein VR, Cox SM, Mitchell MD, Wendel GD, Jr. The Jarisch–Herxheimer reaction complicating syphilotherapy in pregnancy. *Obstet Gynecol* 1990; 75(3 Pt 1): 375–380.)

activity (Fig. 82-16). For this reason, we sonographically evaluate the fetuses of all third-trimester early syphilis patients prior to initiating therapy. If hepatomegaly or other signs of hydrops are detected, the patient is hospitalized for fetal monitoring during the first 24 hours following the administration of penicillin therapy. If there is evidence of fetal compromise prior to the initiation of therapy, the infant is first delivered by caesarian section and then mother and infant are treated.²⁵⁹

Concern also exists that presumably adequate maternal treatment for syphilis in the final 4 weeks of pregnancy may be inadequate fetal therapy.²⁶¹ A possible explanation is that altered penicillin pharmacokinetics leading to lower serum and CSF levels of penicillin in both the mother and fetus may occur due to increases in renal clearance and plasma volume that are normal adaptations as pregnancy progresses.²¹⁹ Moreover, maternal treatment in the final weeks of pregnancy may not allow sufficient time for the fetus to be adequately treated, thus necessitating penicillin therapy for the newborn infant.²⁶² Because currently available methodologies for diagnosis of congenital syphilis do not accurately identify infants with active infection, the majority of these so-called “treatment failures” probably reflect resolving abnormalities from treated fetal infection. It is well known that the clinical and laboratory abnormalities seen in infants infected with *T. pallidum* may require months for complete resolution, even after prolonged intravenous penicillin therapy. Nonetheless, some treatment failures do occur, as evidenced by autopsy findings of stillborn infants and well documented clinical treatment failures,^{55,263} suggesting that currently recommended regimens may be inadequate when fetal treponemal burdens are large.

■ TREATMENT OF THE INFANT

Given the current absence of a diagnostic “gold standard” and the fact that untreated congenital syphilis is potentially

devastating, CDC guidelines recommend treatment of all infants who fit the surveillance-case definition to avoid undertaking the difficult task of determining which at-risk asymptomatic infants are truly infected.²³⁴ Treatment, therefore, is required for infants with proven or highly probable disease: (1) an abnormal physical exam which is consistent with congenital syphilis; (2) a quantitative nontreponemal serologic test that is fourfold higher than the mother’s titer; or (3) a positive darkfield or fluorescent antibody test of body fluids. Treatment is also recommended for infants with a normal physical exam and a quantitative nontreponemal serologic titer that is less than fourfold the mother’s if (1) the mother was inadequately treated or is lacking documentation of treatment; (2) the mother was treated with erythromycin or another medicine other than penicillin; or (3) the mother received treatment less than 4 weeks prior to delivery. Furthermore, treatment should be considered for low-risk infants when follow-up is uncertain. Treatment should not be delayed until a definitive clinical or serologic diagnosis is made.

Infants 4 weeks of age or less who have confirmed or presumptive disease should be treated for 10–14 days with either (1) aqueous crystalline penicillin G, 50,000 U/kg administered intravenously every 12 hours for the first 7 days of life and every 8 hours beyond 1 week of age for a total of 10 days or (2) aqueous procaine penicillin G, 50,000 U/kg administered intramuscularly once daily (Table 82-8) for 10 days.²³⁴ In our experience, 10 days of either form of penicillin is sufficient. All patients who received aqueous crystalline penicillin G, but only 82% of those who received procaine, had treponemal levels in the CSF at the time of testing.²⁶⁴ Although the significance of this finding is uncertain given that both regimens are curative,¹¹³ some authorities believe that the aqueous crystalline penicillin G regimen is the preferred therapy, particularly in extremely ill infants or infants with neurosyphilis.⁵⁷

An infant with normal physical examination, CSF, radiographic, and laboratory studies and whose nontreponemal test titer is the same or less than the maternal titer can be treated with a single intramuscular injection of benzathine penicillin G (50,000 U/kg) under the following circumstances (Table 82-8)^{234,265}: (1) the mother received erythromycin during pregnancy; (2) the mother was treated with the appropriate regimen 30 days or less prior to delivery; (3) the mother received the recommended penicillin therapy for the stage of infection during the pregnancy, but the nontreponemal titer has not yet decreased fourfold; and (4) the mother has untreated syphilis or her treatment status is undocumented.

After the neonatal period, older infants (>4 weeks of age) and children diagnosed with syphilis should have a CSF examination to exclude neurosyphilis and maternal medical records should be reviewed to assess whether the child has congenital or

Table 82-8. Treatment of Congenital Syphilis

Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. In communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history should also be obtained at 28-week gestation and at delivery.

Scenario 1. Infants with proven or highly probable disease and

1. an abnormal physical examination that is consistent with congenital syphilis,
2. a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer,^a or
3. a positive darkfield or fluorescent antibody test of body fluid(s).

Recommended evaluation

- CSF analysis for VDRL, cell count, and protein.^b
- Complete blood count (CBC) and differential and platelet count.
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver-function tests, cranial ultrasound, ophthalmologic examination, and auditory brainstem response).

Recommended regimens

Aqueous crystalline penicillin G 100,000–150,000 units/kg/d, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

OR

Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 d

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding the use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis. The use of agents other than penicillin requires close serologic follow-up to assess adequacy of therapy. In all other situations, the maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the infant.

Scenario 2. Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

1. mother was not treated, inadequately treated, or has no documentation of having received treatment;
2. mother was treated with erythromycin or other nonpenicillin regimen,^c or
3. mother received treatment <4 week before delivery.

Recommended evaluation

- CSF analysis for VDRL, cell count, and protein.
- CBC and differential and platelet count.
- Long-bone radiographs.

A complete evaluation is not necessary if 10 days of parenteral therapy is administered. However, such evaluations might be useful; a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC, platelet count, and bone radiographs) may be performed to further support a diagnosis of congenital syphilis. If a single dose of benzathine penicillin G is used, then the infant must be fully evaluated (i.e., through CSF examination, long-bone radiographs, and CBC with platelets), the full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is rendered uninterpretable because of contamination with blood, then a 10-day course of penicillin is required.^d

Recommended regimens

Aqueous crystalline penicillin G 100,000–150,000 units/kg/d, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days

(Continued)

Table 82-8. (Continued)

OR

Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days

OR

Benzathine penicillin G 50,000 units/kg/dose IM in a single dose

Some specialists prefer the 10 days of parenteral therapy if the mother has untreated early syphilis at delivery.

Scenario 3. Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

1. mother was treated during pregnancy, treatment was appropriate for the stage of infection, and treatment was administered >4 week before delivery and
2. mother has no evidence of reinfection or relapse.

Recommended evaluation

No evaluation is required.

Recommended regimenBenzathine penicillin G 50,000 units/kg/dose IM in a single dose^e**Scenario 4. Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the**

1. mother's treatment was adequate before pregnancy, and
2. mother's nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL <1: 2; RPR <1: 4).

Recommended evaluation

No evaluation is required.

Recommended regimen

No treatment is required; however, some specialists would treat with benzathine penicillin G 50,000 units/kg as a single IM injection, particularly if follow-up is uncertain.

^aThe absence of a fourfold or greater titer for an infant does not exclude congenital syphilis.^bCSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age and are higher in preterm infants. Values as high as 25 white blood cells (WBCs)/mm³ and/or protein of 150 mg/dL might occur among normal neonates; some specialists, however, recommend that lower values (i.e., 5 WBCs/mm³ and protein of 40 mg/dL) be considered the upper limits of normal. Other causes of elevated values should be considered when an infant is being evaluated for congenital syphilis.^cA woman treated with a regimen other than those recommended in these guidelines for treatment should be considered untreated.^dIf the infant's nontreponemal test is nonreactive and the likelihood of the infant being infected is low, certain specialists recommend no evaluation but treatment of the infant with a single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis, after which the infant should receive close serologic follow-up.^eSome specialists would not treat the infant but would provide close serologic follow-up in those whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis or remained stable or low for late syphilis.Source: CDC. *Sexually Transmitted Diseases Treatment Guidelines, 2006*.

acquired syphilis. Any child thought to have congenital syphilis (or having neurologic involvement) should receive aqueous crystalline penicillin G administered as 50,000 U/kg IV every 4–6 hours for 10 days. Some specialists recommend giving one dose of benzathine penicillin G 50,000 units/kg IM after the 10-day course of IV treatment.²³⁴ Procaine penicillin for this age group has not been fully evaluated and, therefore, is not recommended. Children with acquired syphilis who have a normal

CSF examination can receive IM benzathine penicillin G 50,000 U/kg per dose as dictated by the stage of infection; the amount of penicillin should not exceed that recommended for adults.²³⁴ The CDC 2006 STD guidelines for evaluation and treatment of older infants and children for syphilis are similar but different in evaluation (e.g., long-bone radiographs, chest radiograph, liver function tests, etc.), dosage, and duration (see [Table 82-9](#)).²¹⁶

Table 82-9. Evaluation and Treatment of Older Infants and Children for Syphilis

Children who are identified as having reactive serologic tests for syphilis after the neonatal period (i.e., aged >1 mo) should have maternal serology and records reviewed to assess whether the child has congenital or acquired syphilis.

Recommended evaluation

- CSF analysis for VDRL, cell count, and protein.
- CBC, differential, and platelet count.
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, abdominal ultrasound, ophthalmologic examination, and auditory brain stem response).

Recommended regimen

Aqueous crystalline penicillin G 200,000–300,000 units/kg/d IV, administered as 50,000 units/kg every 4–6 h for 10 d

If the child has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL test result is negative, some specialists would treat with up to 3 weekly doses of benzathine penicillin G, 50,000 U/kg IM.

Source: CDC. *Sexually Transmitted Diseases Treatment Guidelines, 2006.*

Infants born to women coinfecting with syphilis and HIV may be at higher risk of acquiring infection with both syphilis and HIV.^{266,267} It is not known whether infants coinfecting with syphilis and HIV respond to treatment for congenital syphilis differently from those infants not infected with HIV. Nonetheless, there are no data to support more aggressive or prolonged penicillin therapy beyond the regimens recommended for infants not exposed to maternal HIV infection. The necessity of serologic follow-up of these high-risk infants cannot be over emphasized.²³⁴

Less than 1% of infants who are treated for presumed congenital syphilis develop, within several hours of initiation of penicillin therapy, a Jarisch–Herxheimer reaction, consisting of fever, tachypnea, tachycardia, hypotension, accentuation of the cutaneous lesions, and/or death due to cardiovascular collapse.¹⁴⁷ Other than supportive care, there is no specific treatment or prophylaxis.

■ FOLLOW-UP MANAGEMENT

Infants who have reactive serologic tests for syphilis should have serial quantitative nontreponemal tests performed until nonreactivity is documented or the titer has decreased fourfold.^{147,234,262} Follow-up for these infants can be incorporated into routine pediatric well-child care at 2, 4, 6, 12, and 15 months.²²⁸ Among infants with congenital syphilis, nontreponemal serologic tests become nonreactive within 6–12 months after appropriate treatment.²⁶⁵ If the nontreponemal serologic titers remain stable or increase after 6–12 months the child should be reevaluated for syphilis, including CSF examination and treated with parenteral penicillin G for 10 days.²³⁴ Uninfected infants usually become sero-nonreactive by 6 months of age. A reactive *treponemal*

test beyond 18 months of age, when all passively transferred maternal antibody has been cleared, confirms the diagnosis of congenital syphilis.²⁶⁵

Infants with initial abnormal CSF findings should have a repeat CSF analysis performed every 6 months after therapy until normal.^{228,234} A reactive CSF VDRL test, unexplained persistent pleocytosis, or abnormal protein at retesting is an indication for retreatment.²³⁴

PREVENTION AND CONTROL

■ DETECTION OF SYPHILIS DURING PREGNANCY

The mainstay of prevention of congenital syphilis involves identifying and treating infected pregnant women; penicillin therapy during pregnancy is 98-percent effective in preventing congenital infection.^{140,268} Maternal treatment regimens and follow-up are discussed in detail in the 2006 CDC STD Treatment Guidelines. The obstetrician must be alert to the signs and symptoms of syphilis in the pregnant woman. In addition to looking for evidence of active syphilis during prenatal visits, syphilis serologic testing should be performed at the mother's first prenatal visit and repeated in high-risk populations, at 28 weeks gestation and at delivery.^{269,270} Repeat testing of high-risk populations is essential to identify women with incubating syphilis as well as women infected later in pregnancy. False-negative nontreponemal tests also may result from the prozone phenomenon that occurs when an excess of nontreponemal antibodies prevents the flocculation reaction required for a reactive test. Experienced laboratories routinely dilute serum specimens to identify prozones. Screening tests at delivery should be performed on maternal blood specimens

rather than on umbilical cord blood; nontreponemal test titers in umbilical cord blood are usually lower than the mother's and may even be nonreactive in the face of a low maternal titer.¹⁴⁹

Pregnancy occasionally produces a false-positive nontreponemal test (e.g., a reactive nontreponemal test with a nonreactive treponemal test).²⁷¹ A cautionary note must be sounded here, however, because an isolated low nontreponemal test titer may be seen with very early syphilitic infection and have disastrous consequences for the fetus if untreated.¹⁴⁹ A detailed sexual history, careful physical examination (looking for evidence of primary syphilis), and serologic follow-up of the mother are required to distinguish false-positive reactivity from early infection. Treatment is warranted if follow-up serologic testing cannot be assured. Women who have previously received standard therapy for syphilis may remain seroreactive with a low nontreponemal test titer; these women are designated "serofast." Because it can be difficult to distinguish the serofast state from reinfection, our practice is to re-treat asymptomatic women whose nontreponemal test titers are greater than 1:2 at the first screening. Women considered to be serofast are followed with serial serologic testing and re-treated if the titer increases fourfold or more.

■ PUBLIC-HEALTH STRATEGIES FOR PREVENTION

While the cause of congenital syphilis, strictly speaking, is *Treponema pallidum*, the network of social and economic factors that fosters the transmission of syphilis during pregnancy and then allows it to go undetected and untreated also must be considered as part of its etiology. The lines of public-health defense against congenital syphilis can be seen as a series of demographic circles around the fetal population at risk (Fig. 82-17). The first line of defense is the treatment of

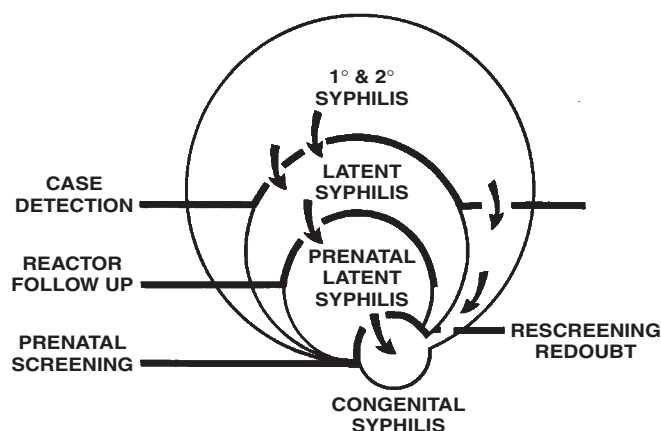


FIGURE 82-17. Sequential lines of defense against congenital syphilis consist of (i) case detection to decrease the population of transmitters of early syphilis, (ii) reactor follow-up to decrease the residual pool of latent syphilis, and (iii) the last line of defense, prenatal screening. In addition, a redoubt is needed to protect the flank (i.e., rescreening to detect acquisition of syphilis during pregnancy).

cases of primary and secondary syphilis and case detection through contact investigations. As noted earlier, this activity is now being supplemented, in many instances, by location-based epidemiologic case finding and treatment. The fewer the total number of cases of primary and secondary syphilis, the fewer the number of cases that joins the pool of early and late latent syphilis, and therefore the fewer the number of latent syphilitics among women in the childbearing age group. The second line of defense is follow-up of reactive serologic tests reported to the health department by clinical laboratories, supplemented by routine screening of high-risk populations. By assuring adequate therapy of cases so detected, this strategy is designed to reduce the pool of women who begin gestation with untreated syphilis. Routine prenatal screening is the last major line of defense against congenital syphilis.

■ ANTENATAL SCREENING AND DECENTRALIZATION OF SCREENING PROGRAMS

Syphilis screening should be performed at the antenatal care site, and women found to be seroreactive should be treated immediately at the same visit.²⁷⁰ On-site testing is recommended by the WHO and may avoid the major difficulties that materialize with laboratory-based testing.

The RPR card test was initially used for on-site testing. In 1990, a syphilis-intervention study in Zambia used this treatment approach in three intervention centers and compared the outcomes to three control centers.²⁷² With on-site testing the adverse outcomes attributable to syphilis were reduced to 28%, an almost two-thirds reduction when compared to 72% in control centers.²⁷² In Maputo, Mozambique, an intervention study of antenatal clinics trained nurse midwives to perform the RPR tests and seroreactive cases were treated on-site and partners were encouraged to receive treatment; the intervention was repeated at 30 weeks gestation. At delivery the perinatal mortality (1.3%) was significantly lower in the intervention group as compared to the control group (3.4%).²⁷³

Screening pregnant women for syphilis has proven cost-effective in the prevention of congenital syphilis.⁷⁴ WHO found that at seroprevalences of 15%, 10%, and 1%, respective expenditures of only \$9.30, \$12, and \$70 would avert one adverse outcome.²⁷⁰ In Nairobi, Kenya, a decentralized clinic-based syphilis control program was implemented in 1992 where pregnant women were screened with the RPR card test by antenatal clinic nurses and treated on-site if RPR-reactive. There was a 6.5% (860) prevalence of RPR-reactivity of which over 87% (751) of these women were treated at their first visit and almost 50% (428) of their partners were treated as well. An estimated 413 cases of congenital syphilis would have been prevented with this program at a cost of U.S.\$50 per case.⁷⁷

Decentralization of screening programs has found to be successful in other countries as well. In rural Haiti, prior to

1996 and decentralization of antenatal screening for maternal syphilis, testing was done at a community hospital, followed by sending specimens to an off-site laboratory for testing and requiring women to return for their results and treatment at a follow-up visit. During this time 41% (14/34) of seropositive women did not receive treatment. After decentralization with laboratory installation and personnel training in 12 local dispensaries, 100% (50/50) of seropositive women were treated. The rate of congenital syphilis dropped by 75% (from 550 to 137 cases per 100,000 live births) within 3 years of the intervention.²⁷⁴

More recently, the syphilis immunochromatographic strip (ICS) test has been studied in the field as an on-site screening test for syphilis. Studies find that the ICS test outperforms the RPR test and is also cost-effective.^{275–279} In Bolivia public health personnel were trained and ICS tests were introduced into antenatal clinics in urban maternity hospitals and rural clinics resulting in over 11,500 women tested of which 5% were seropositive and over 93% were treated.²⁸⁰ In 1992 the Mozambique National Health System prioritized antenatal syphilis screening when only 5% of women in two targeted provinces were screened. Due to their efforts over the past decade annual antenatal screening has increased to 60–95%.

The successful scaling up of antenatal screening programs in one of the world's poorest countries is attributable to (1) the widespread utilization of the rapid ICS test to allow screening in areas without laboratories and where women were previously left unscreened; (2) across the broad strengthening of the health-care delivery system; and (3) continuous monitoring to assess the implementation of changes in health-care delivery.²⁸¹

■ NEXT STEPS

An estimated 1.5 million cases of congenital syphilis occur annually worldwide which significantly overshadows the estimated 530,000 children infected with HIV each year.^{282,283} In fact, “on-site antenatal syphilis screening and treatment is just as cost-effective as prevention of maternal-to-child HIV transmission.”^{74,284}

From the public health viewpoint, congenital syphilis can be regarded as a “sentinel health event” whose occurrence reflects a failure of delivery systems for prenatal care as well as syphilis control programs.⁵⁷ The tragedy of congenital syphilis is that it is a completely preventable disease. In 2004 WHO proposed a strategy for the prevention and ultimately the elimination of congenital syphilis worldwide. Specifically, the goal is to prevent mother-to-child transmission with early antenatal care for all women; the treatment of all sexual partners of infected women and the treatment of all newborns born to seropositive women.²⁸³ As outlined by Schmid et al.,²⁸³ the four pillars of the WHO Strategy are (1) to ensure sustained political commitment and advocacy for the

elimination of congenital syphilis; (2) to increase access and quality of health services for pregnant women and newborns; (3) to screen and treat all pregnant women; and (4) to establish surveillance, monitoring and evaluation systems. In an analysis of 14 countries representing low, middle, and high prevalences of congenital syphilis and with existing maternal or congenital syphilis control policies, most did not meet all of the elements of the WHO elimination strategy and there was varying discrepancy between outlined objectives, actual implementation, and effectiveness of the programs.^{284,285}

There is a preponderance of evidence that with the appropriate commitment of resources to high-risk populations, the prevention of the morbidity and mortality caused by syphilis in pregnancy is within the grasp of the international health community and that the devastating effects of congenital syphilis can be eliminated.

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INFECTIONS DUE TO *NEISSERIA GONORRHOEAE* IN INFANTS AND CHILDREN

■ HISTORY

Gonococcal ophthalmia neonatorum was recognized as a distinct infectious disease related to a maternal genital infection in 1881 when Credé published his report of the effectiveness of eye prophylaxis in the form of a single drop of 2% silver nitrate. Following the introduction of this prophylaxis to all babies the rates of ophthalmia fell from 14 of 187 births (7%) to 1 of 200 births (0.5%).¹ One year later Königstein claimed to have recovered identical bacteria from infected eyes and the mother's genitals.² Gonococcal ophthalmia neonatorum used to be a major cause of blindness. The decrease in the rates of blind children with a history of ophthalmia neonatorum demonstrated the efficacy of ocular prophylaxis most impressively.³ During the second half of the twentieth century the link between gonococcal infections in prepubertal children beyond the neonatal age period and sexual abuse became increasingly recognized.

■ EPIDEMIOLOGY

*Epidemiology of genital infection due to *N. gonorrhoeae* in children and adolescents*

CDC surveillance data from the 50 states in 1998 found that the highest incidence of gonococcal disease was reported in adolescent females, ages 15–19 years, with 761.4 cases per 100,000 population (up from 683.2 in 1997).⁴ A similar increase in the number of infections in males also occurred during the teens and early adult years with a peak rate of 564.0 cases per 100,000 population among men aged 20–24 years.⁴ Rates have been much higher in some states and populations. The overall rate in African American females, ages 15–19 years in 1995 was 4433 per 100,000 population.⁴ Some special risk populations demonstrate an extremely high prevalence such as sexually active female adolescents seen at

an inner city clinic in the United States (6%), adolescents entering shelters in Korea (15.4%), adolescents in 14 U.S. juvenile detention centers (5.1% in females and 1.3% in males), or patients visiting a sexually transmitted disease clinic in Amsterdam, The Netherlands (male 10.5%, female 5.9%).^{5–8} Van Duynhoven et al. found that being a teenager carried the highest risk of having a positive *N. gonorrhoeae* culture compared to all other age groups.⁸ Coinfections with other sexually transmitted organisms, especially *Chlamydia trachomatis*, are also frequent.⁷

Data on the prevalence of symptomatic gonococcal infection in preadolescent children and early adolescent youths are limited to a few studies and case reports. Incidence rates as high as 11 per 100,000 for the age group 1 month through 9 years per year have been reported from *N. gonorrhoeae* infection surveillance data in Florida, which is derived from mandatory reports of laboratory-confirmed episodes.⁹ In that study 854 episodes were reported in 849 children aged 1 month through 12 years all of which were assumed to be acquired by sexual abuse. Since there are no screening studies in these age groups and diagnosis and reporting mostly rely on tests performed in symptomatic children, the true incidence of gonococcal infection remains unknown. Presenting complaints of symptomatic children who are subsequently established to have *N. gonorrhoeae* infection are primarily vaginal or urethral discharge, but symptoms resolve spontaneously and may also be absent. Some infected children present for evaluation of sexual abuse or assault, and a number of children have a variety of complaints not related to the genitalia. Despite occasional reports of nonsexual transmission most of which fail to appropriately address the possibility of sexual abuse, it has been recognized that close sexual contact with an infected individual is the main risk factor for transmitting *N. gonorrhoeae* in children.^{10–13} The recognition of gonococcal infection in children after the newborn period and before the onset of puberty is particularly important because it is considered an indicator of sexual abuse.¹⁴ Consequently, cultures for *N. gonorrhoeae* should be obtained if child abuse is seriously suspected.

The most recent prevalence rates of gonococcal infections in an American and a British cohort of sexually abused children were 1.2% and 1.9%, respectively.^{15,16} The highest number of infections in one study was reported in the 3-year-old age group, and the occurrence of multiple sites of infection is common.¹⁷ In a cohort of 567 prepubertal girls from Rwanda referred for sexual abuse or vulvovaginitis, the most common cause of vaginal discharge was *N. gonorrhoeae* (35.9%).¹⁸ In a prospective patient series of children between 1 and 12 years presenting to the emergency department with symptoms of vaginitis, 9% were culture-positive for *N. gonorrhoeae*.¹⁹ On the other hand, about 20% of children with positive genital cultures have been reported to be asymptomatic in one study.²⁰ Recently Ingram et al. have proposed a risk assessment algorithm that may help limit unnecessary testing in abused children while correctly identifying all children with *N. gonorrhoeae* infections.^{15,21} Identification of infection in children should also lead to a search for contacts within the child's epidemiologic unit.²² When such contact investigations are performed, the results frequently include identification of significant numbers of adults, often family members, and other children who are also infected.²³ Since sexual abuse of children is usually a chronic and recurring condition, as opposed to rape by a stranger, children may present with recurrent gonococcal infections if they remain unprotected. The special considerations involved in the management of sexually abused children are discussed in detail in the separate chapter on sexual abuse (see Chapter 87).

Epidemiology of conjunctival infections due to *N. gonorrhoeae*

The main population at risk for gonococcal conjunctivitis is neonates born to mothers with genital infection. The transmission rate in unprophylaxed neonates born to infected mothers may be as high as 42%.²⁴ Signs of infection usually appear from 2 to 5 days after birth, but infection in utero may also occur usually in the context of premature rupture of membranes.²⁵ Ocular prophylaxis and the availability of antibiotic therapy for ophthalmia neonatorum have led to a decrease in the proportion of new entrants to schools for the blind attributable to ophthalmia neonatorum to 1% by 1950 and to less than 0.1% by 1959.³ Since then, periods of regional and national resurgences of gonorrheal infections in adults in the United States were reflected in increases of gonorrheal ophthalmia neonatorum.^{26,27} Public health programs in the United States and many other industrial countries were established, encouraging the routine screening of sexually active women for gonorrhea at the time of the first antenatal visit and again in the third trimester for those women still at risk.²⁸ While these efforts have led to overall falling rates of maternal gonorrhea and gonococcal ophthalmia neonatorum in the developed countries, data from developing countries (mostly from Africa) have demonstrated that *N. gonorrhoeae* remains a significant pathogen in the absence of

a public health approach toward prevention of ophthalmia neonatorum.^{24,29,30} Recognition of gonorrhea early in pregnancy identifies a population at risk that should be followed sequentially throughout pregnancy, since reinfection rates may be high.^{31,32} Even in the presence of active prenatal screening programs, poor prenatal care and maternal substance abuse can be risk factors for higher infection rates in pregnant women and neonates.^{32,33} Hammerschlag et al. reported that seven of eight infants with *N. gonorrhoeae* conjunctivitis seen in an inner-city hospital over a 2-year period were born to women with no prenatal care, five of whom were "crack" cocaine abusers.³² None of the infants who were born to women diagnosed with and treated for *N. gonorrhoeae* infection during their prenatal care (248 of 9128) developed gonococcal ophthalmia. Active screening and treatment of pregnant women have reduced the incidence of gonococcal ophthalmia in the United States to the point where any additional effect from prophylaxis is hard to discern. The most recent data concerning the relative frequency of microbiologic etiologies of conjunctivitis in early infancy in the United States were presented in a study published from Seattle in 1992.³⁴ This case-control study identified, in order of prevalence, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Neisseria cinerea*, *Klebsiella pneumoniae*, and *C. trachomatis* but not *N. gonorrhoeae*. It should be noted that this population had extremely low rates of maternal *N. gonorrhoeae* and *C. trachomatis* infections. In developed countries *N. gonorrhoeae* is among the least common causes of neonatal conjunctivitis.

All current studies of gonococcal ophthalmia have been performed outside the United States. A case-control study from Nigeria found only one of 122 neonates with ophthalmia neonatorum to be positive for *N. gonorrhoeae*.³⁵ Unfortunately, it was not stated whether mothers were tested and treated for gonorrhea during pregnancy, and transport of swabs from clinic sites to the microbiology laboratory may have decreased the sensitivity of culture. In a study from Argentina, *N. gonorrhoeae* infection was not detected in 332 consecutive cases of neonatal conjunctivitis; the rates of maternal infection and treatment were not stated.³⁶

Neonatal gonococcal ophthalmia may cause primary disease at other mucous membrane sites or cause systemic disease. The ocular disease serves as a signal that the infant has been infected. While gonococcal conjunctivitis is primarily a neonatal infection it can also occur in older infants and children mainly in the context of sexual abuse, but eye to eye spread in the household and community outbreaks has also been reported.^{37,38}

Epidemiology of gonococcal infections at other sites

Pharyngeal infections can occur in the perinatal period through ingestion of infected amniotic fluid.³⁹ Pharyngeal and anal infections in children beyond the neonatal age period occur mainly in the context of sexual abuse and are frequently coinfections of vaginal or urethral infections.^{17,40}

Disseminated gonococcal infection has been associated with certain host risk factors such as a deficiency in the terminal complement system, which is also associated with recurrent gonococcal and meningococcal infections.⁴¹ While osteomyelitis is very rare and usually occurs only in patients who have had septic arthritis and an adjacent focus, septic arthritis has been the most commonly recognized manifestation of disseminated gonococcal infection in the neonatal period.⁴² In 1905, Holt reported 26 cases of gonococcal arthritis in children, including two infants who developed arthritis within the first month of life.⁴³ One of these children also had ophthalmia neonatorum, most had no recognized focus, and rectal cultures were not taken. Ophthalmia neonatorum has also often been absent in subsequent reported cases of neonatal gonococcal arthritis. The primary focus of infection in most of the 53 infants with gonococcal arthritis reported by Cooperman in 1927 was uncertain; only one had ophthalmia neonatorum.⁴⁴ All of the females were said to have had vulvovaginitis, while several infants had proctitis. Bacteremia in some other cases has been attributed to infection of the mouth, nares, and umbilicus, while the source of bacteremia has been inapparent in many cases reported in the English language since the 1940s.^{45,46} Gonococcal meningitis is a rare occurrence in neonates or children, but a high index of suspicion is warranted in patients with meningitis who present with clinical symptomatology or past history of gonococcal infection (including that of source cases).⁴⁷ As an iatrogenic cause of infection gonococcal scalp abscesses have been attributed to intrauterine fetal monitoring.⁴⁸

■ CLINICAL MANIFESTATIONS

Gonococcal infections in children may produce a variety of syndromes that are age related. Investigation of adult gonococcal disease syndromes has demonstrated that there is a very extensive interaction and accommodation between

gonococcal surface structures and the host milieu.⁴⁹ In contrast, there have been no studies of gonococcal infections of infants or prepubertal children to investigate host-microbe interactions and consequently nothing is known.

Perinatal N. gonorrhoeae infection

Gonococcal infections present several unique problems during pregnancy, most of which are covered in a separate chapter (Chapter 80). A demonstration of ascending infection of the fetus prior to delivery is found in a report of an infected stillborn infant who was found at autopsy to have multiple submucosal foci of the esophagus and upper respiratory tracts containing gram-negative diplococci.⁵⁰ The location of the lesions indicated that infection had been contracted in utero during swallowing and respiration. Chorioamnionitis of the placenta was an accompanying finding. Six studies have reviewed the effects of untreated gonococcal disease of the mother on the health of the fetus and infant (Table 83-1). Rates of premature delivery, perinatal distress, and perinatal deaths were higher in infants born to mothers with untreated gonococcal infections at the time of delivery compared to mothers without infection and mothers with infections treated during pregnancy.^{51,53,55,56}

Neonatal gonococcal ophthalmia

Conjunctival infection caused by *N. gonorrhoeae* in the newborn usually produces an acute purulent conjunctivitis that appears from 2 to 5 days after birth. The initial course is occasionally indolent, however, and onset can occur later than 5 days after birth, perhaps because of partial suppression of infection by ophthalmic prophylaxis, small inoculum size, or strain-to-strain variations in gonococcal virulence.^{57,58} Ocular gonococcal infection without signs of inflammation has been described in a neonate whose conjunctiva and nasopharynx were cultured at 2 and 3 weeks of age as part of

Table 83-1. Outcome of Pregnancy in Mothers Who Were Infected with *N. gonorrhoeae* at Delivery

Outcome	Charles ⁵¹ (n = 14)	Sarrell ⁵² (n = 37)	Israel ⁵³ (n = 39)	Amstey ⁵⁴ (n = 222)	Edwards ⁵⁵ (n = 19)	Handsfield ³⁹ (n = 12)
Normal or term infant	—	13 (35%)	30 (77%)	142 (64%)	7 (37%)	—
Aborted	—	13 (35%)	1 (2%)	24 (11%)	—	—
Perinatal death	—	3 (8%)	1 (2%)	15 (8%)	2 (11%)	—
Premature	—	6 (17%)	5 (13%)	49 (22%)	8 (42%)	8 (67%)
Perinatal distress	—	—	2 (5%)	—	2 (10%)	—
Premature rupture of membranes	6 (28%)	8 (21%)	—	52 (26%)	12 (63%)	9 (75%)

the follow-up for a maternal infection at the time of delivery.⁵⁹ Permanent corneal damage following gonococcal ophthalmia neonatorum was usual in the preantibiotic era. The infant typically develops tense edema of both lids, followed by chemosis and a progressively purulent and profuse conjunctival exudate, which literally pours or squirts out of the lids when they are separated. If treatment is delayed, the infection extends beyond the superficial epithelial layers, reaching the subconjunctival connective tissue of the palpebral conjunctivae and, more significantly, the cornea. Corneal complications include ulcerations that may leave permanent nebulae or may cause perforation and lead to anterior synechiae, panophthalmitis (rarely), and loss of the eye. While 1% silver nitrate is no longer manufactured or used in the United States, it is still used in many parts of the world and associated with a mild chemical conjunctivitis, which can be easily distinguished from gonococcal conjunctivitis. Evidence of epithelial desquamation and polymorphonuclear leukocytic exudate appears usually within 6–8 hours and disappears usually within 24–48 hours.

Other manifestations of neonatal gonococcal infection

Besides ophthalmia neonatorum and the systemic complications of gonococcemia such as arthritis, other localized forms of neonatal gonococcal infection such as vaginitis, rhinitis, anorectal infection, funisitis, and urethritis have been reported.^{60–63} *N. gonorrhoeae* may be an indirect or a direct cause of early neonatal sepsis in the absence of gonococcal arthritis. As noted, intrapartum gonococcal infection has been associated with premature delivery and premature rupture of membranes, which may lead to amniotic fluid infection with a variety of vaginal organisms capable of causing neonatal sepsis. *N. gonorrhoeae* has been isolated from blood of newborn infants with clinical sepsis without arthritis.⁶⁴ A small number of gonococcal infections become disseminated, with arthritis being the most common manifestation. The onset of clinical evidence of gonococcal arthritis in the newborn usually occurs from 1 to 4 weeks after delivery. One cannot distinguish between perinatal and postnatal acquisition of infection in most cases. The pustular and necrotic skin lesions that characteristically appear during gonococcemia in the adult have not yet been described in the newborn. The natural history of gonococcal arthritis in the infant is uncertain. Of the 53 cases in newborns that were presumably infected by a single epidemic strain of *N. gonorrhoeae*, described by Cooperman, none had a fatal outcome and permanent impairment of function was uncommon, even without antibiotic therapy.⁴⁴ In contrast, 14 of 26 cases that occurred in a series of outbreaks described by Holt were fatal.⁴³

Infants with neonatal gonococcal arthritis share several important characteristics with neonates whose arthritis is of other etiologies. Polyarticular involvement is the norm.⁴⁴ The

primary presentation is refusal to move the involved limb, leading to the appearance of paralysis. Infants with bacterial infections of the hips have a high incidence of subsequent development of aseptic necrosis of the head of the femur, and the physician must examine the child with particular care for this condition. If the infant with gonococcal disease fails to show normal spontaneous movement of a leg, a full workup, often including arthrocentesis, is indicated.

Genital infections in children

Gonococcal vaginitis is the most common form of gonorrhea in children beyond the neonatal period. In contrast to adults, in prepubertal girls the nonestrogenized alkaline vaginal mucosa may be colonized and infected with *N. gonorrhoeae*. Gonococcal vaginitis is often a mild disease, perhaps because it is restricted to the superficial mucosa. The majority of symptomatic children have minor crusting discharge that may discolor the underwear and vaginal pruritus; other signs may be minimal to absent, or they may point to systemic infection.^{10,18} Dysuria and polymorphonuclear leukocytes in the urine may accompany this infection. While pelvic inflammatory disease (PID) and salpingitis in women and teenagers are discussed in a separate chapter, it is important to recognize that vaginal infection of females who are adolescent or younger may also progress to involve the fallopian tubes or may disseminate to the pelvis, leading to perihepatitis and PID. Less than 10% of girls with gonorrhea have signs compatible with peritonitis, including fever, diffuse abdominal pain, leukocytosis, and decreased bowel sounds—findings that are similar to those of appendicitis. For these reasons, a perineal examination for vaginal irritation, discharge, or both is important prior to abdominal surgery in young girls. During the examination of patients, it should be kept in mind that gonococcal infections in sexually abused children can occur in other sites, including the pharynx and rectum.^{17,40} Gonococcal urethritis in prepubertal males is much less common than is vaginitis in girls. When recognized, the disease is usually symptomatic and resembles gonococcal urethritis in the adult male. As with vaginitis, asymptomatic pyuria is a presentation with which the pediatrician should be familiar.⁶⁵ In children with gonococcal infection of the genitourinary tract, concomitant anorectal and tonsillopharyngeal colonization is common. This colonization is usually asymptomatic, as in adults, but it may also cause symptoms.^{40,66}

Other forms of gonococcal disease in children

Gonococcal arthritis in older children resembles that of adults and may be accompanied by cutaneous lesions.⁶⁷ Multiple septic involvement of joints is not as common as in the newborn period, although a migratory polyarthritis may be part of the prodrome.⁶⁸ More typically a single, severely affected joint and myositis, and tenosynovitis predominate.⁶⁷

Each patient must be evaluated for the need for drainage of an involved joint. Since complete response to medical therapy may not occur for several days, most physicians attempt to avoid an open drainage procedure and manage the pyarthrosis with needle aspirations if possible. An exception is purulent arthritis of the hips in which early drainage may be necessary to prevent necrosis of the femoral head. Other complications of gonorrhea are rarely, if ever, reported in the pediatric literature. Gonococcal sepsis, meningitis, Waterhouse-Friderichsen syndrome, endocarditis, myocarditis, and hepatitis may occur in children and may be fatal.^{46,47,69-71} However, the pediatric experience with these conditions is limited to case reports and too minimal for comment.

■ DIAGNOSIS OF *N. GONORRHOEAE* INFECTION IN INFANTS AND CHILDREN

The microbiologic diagnosis of gonococcal infection and disease in infants and children must be made using techniques that are highly specific.²⁸ This is because the societal response to such infections, in addition to the medical implications, also often includes considerations of abuse and neglect. Child abuse and evaluations for sexually transmitted diseases are discussed in detail in Chapter 87. Because of the medical/legal issues involved, as well as special aspects of the diseases in the young, the following principles and approaches should be observed.

Only standard culture systems for the isolation of *N. gonorrhoeae* should be used for testing for *N. gonorrhoeae* in infants and children.²⁸ Nucleic acid amplification tests (NAATs) routinely used in sexually active adults, have not been adequately evaluated in children and are not approved for diagnosis. The performance of *N. gonorrhoeae* NAATs in low-prevalence adult populations has not been good with a significant number of false-positive test results.⁷² False-positive results from commensal *Neisseria* spp. have been reported, which may be the result of horizontal genetic exchange between members of the genus *Neisseria*.⁷³ In addition, polymerase chain reaction (PCR) targeting the *cppB* gene may miss isolates lacking that gene.⁷⁴ These performance issues with NAATs in adults should lead to caution in applying molecular detection tests in children.

Culture remains the gold standard. However, in order to achieve satisfactory results from cultures, specimens for culture from children may require particularly meticulous handling. First, specimens should immediately be placed into prewarmed media. Second, in many pediatric gonococcal infections the *N. gonorrhoeae* organisms are sparse or are a minority of the flora. It appears to improve isolation rates when two separate chocolate agar plates (one with inhibitory antibiotics, one without) are used rather than a biplate. The larger surface area provided by full-sized plates appears to enable technicians to recognize colonies more completely.

Third, plates must be promptly introduced into a 36°C incubator with enhanced CO₂ environment, such as a candle jar. This implies that the clinician must arrange for the appropriate triage of specimens, often to distant laboratories and through inclement weather. The difficulty involved with such processing in remote areas without a laboratory capable of performing *N. gonorrhoeae* is pointed out in a report by Lindsay and coworkers.⁷⁵ It highlights the need for continued availability of capabilities for cultural diagnosis in regional laboratories. The clinician should have a policy regarding the identification of specimens and establish a chain of custody so that results can be supported in court procedures when/if issues of the child's safety are being considered. The identification of *N. gonorrhoeae* from a pediatric specimen should be confirmed with at least two tests that employ different principles. Currently used identification models are biochemical, serologic, and enzyme substrate. The standard biochemical tests demonstrate utilization of glucose, but not maltose, sucrose, or lactose and a positive oxidase test. There have been reports of the misidentification of related organisms as *N. gonorrhoeae*.⁷⁶⁻⁷⁸ Because of the societal responses, such occurrences bring the child into risk of loss of home and into social chaos. Preservation of isolates will enable additional or repeated testing. Finally, the diagnosis of gonococcal infection or disease in a child requires an evaluation for the source of infection and of other children who may also have been exposed to the perpetrator.

A clinician who is examining a prepubertal child for a possible sexually transmitted disease (STD) should be aware that contrary to adults, it is not necessary to obtain a specimen from the cervical canal in order to provide culture material from a prepubertal child for gonorrhea. A specimen from the vaginal canal suffices.

Conjunctival exudate can be directly examined by Gram stain for the presence of gram-negative intracellular bean-shaped diplococci suggestive (but not definitive) of *N. gonorrhoeae*, for gram-negative coccobacilli typical of *Hemophilus* spp. or for gram-positive cocci suggestive of infection with gram-positive pathogens. The presence of one or more polymorphonuclear leukocytes per oil-immersion field in a conjunctival smear supports the diagnosis of conjunctivitis. Detection of typical gram-negative diplococci by Gram stain warrants the presumptive diagnosis of gonococcal conjunctivitis, although other *Neisseria* spp. have also been associated with purulent ophthalmia neonatorum.⁷⁹ If infection with *N. gonorrhoeae* is suspected because of maternal risk factors, the diagnosis should be confirmed by culture and tests for antibiotic susceptibility should be performed. A definitive diagnosis is important because of the public health and social consequences of a diagnosis of gonorrhea. Cultures for *N. gonorrhoeae* should also be obtained from the oropharynx and anal canal, since concomitant infection of these sites has been demonstrated in association with gonococcal ophthalmia neonatorum.

Detection of gonococcal infection in neonates who have sepsis, arthritis, meningitis, or scalp abscesses requires cultures of blood, CSF, and joint aspirate. Specimens obtained from the conjunctiva, vagina, oropharynx, and rectum that are cultured on gonococcal selective medium are useful for identifying the primary site(s) of infection, especially if inflammation is present. Positive Gram-stained smears of exudate, CSF, or joint aspirate provide a presumptive basis for initiating treatment for *N. gonorrhoeae* but should be confirmed with definitive tests on culture isolates.

A new development is the typing of *N. gonorrhoeae* isolates using molecular methods such as pulsed-field gel electrophoresis (PFGE), or lip gene sequencing. A recent report by Di Matteo and coworkers illustrates the use of molecular typing in a case of sexual abuse showing different patterns of the isolates from the child victim and the supposed perpetrator.⁸⁰ However, this forensic application will need to be evaluated in adult and pediatric populations before its use can be recommended.

■ TREATMENT

General

Recommendations for therapy of childhood gonorrhea are based on guidelines from the 2006 STD treatment guidelines from the Centers for Disease Control.²⁸ Treatment recommendations are summarized in [Table 83-2](#). Pediatric patients encompass children from birth to adolescence. When a child is postpubertal or weighs more than 45 kg (100 lb.), he or she should be treated with dosage regimens recommended for adults (see Chapter 35). Ceftriaxone remains the preferred drug for treatment of gonococcal infection in children. Clinician should be aware of the emergence and continuing spread of quinolone-resistant *N. gonorrhoeae* (QRNG) in some areas in the United States (20% in Hawaii 2001).⁸¹ The Gonococcal Isolate Surveillance Project (GISP), the nationwide program for monitoring trends in resistance, performs and releases regular reports on susceptibility testing on clinical isolates.⁸²

Management of asymptomatic infants born to a mother with untreated gonococcal infection

The asymptomatic infant born to a mother with untreated gonorrhea should have orogastric and rectal cultures taken routinely. It is recommended that the child receive ceftriaxone, 25–50 mg/kg (up to 125 mg) IV or IM as a single dose.²⁸ Both mother and infant should be tested for chlamydial infection.

Gonococcal ophthalmia

The patient should be hospitalized until the infection has been controlled. Single dose ceftriaxone was found to be effective treatment even in the presence of penicillinase-producing *N. gonorrhoeae*.^{40,83} The currently recommended therapy by

Table 83-2. Recommendations for Treatment of Gonococcal Infections in Children Who Weigh <45 kg

Neonatal Infection (Ophthalmia Neonatorum)
Ceftriaxone 25–50 mg/kg (maximum 125 mg) IV or IM in a single dose
Neonatal infection (Disseminated and gonococcal scalp abscesses)
Ceftriaxone 25–50 mg/kg/d (maximum 125 mg) IV or IM in a single daily dose for 7 d, 10–14 d for meningitis
OR
Cefotaxime 25 mg/kg/dose IV or IM every 12 h for 7 d, 10–14 d for meningitis
Prophylactic treatment of neonates whose mothers have gonococcal infection
Ceftriaxone 25–50 mg/kg (maximum 125 mg) IV or IM in a single dose
Children with uncomplicated vulvovaginitis, cervicitis, urethritis, pharyngitis, proctitis
Ceftriaxone 125 mg IM in a single dose
Complicated infection in children (bacteremia, arthritis, meningitis, peritonitis)
Ceftriaxone 50 mg/kg (maximum 1 g) IM or IV in a single dose daily for 7 d (for meningitis increase maximum dose to 2 g, duration of treatment to 10–14 d)

Adapted from Centers for Disease Control and Prevention. 2006 STD Treatment Guidelines. *MMWR*, in press.

both the CDC and WHO is ceftriaxone, 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg. Topical antimicrobial therapy is not beneficial in the presence of systemic treatment.⁸³ Recently, Hoosen et al. reported 100% cure rates in 21 neonates in South Africa with culture-proven *N. gonorrhoeae* conjunctivitis using a single “low dose” of 62.5 mg ceftriaxone.⁸⁴ Alternatives for the treatment of gonococcal conjunctivitis when ceftriaxone is not available are cefotaxime 25 mg/kg IM in a single dose or kanamycin 25 mg/kg (maximum 75 mg) IM in a single dose ([Table 83-2](#)).^{28,85–89} There is also some experience with spectinomycin, which is recommended as another alternative at a single IM dose of 25 mg/kg (maximum of 75 mg) by the WHO, but it does not achieve adequate cure rates for pharyngeal infections.^{85,90}

Complicated infection in newborns

Arthritis, abscess, meningitis, and septicemia should be treated by hospitalization and administration of ceftriaxone, 25–50 mg/kg/day IV or IM in a single daily dose for at least 7 days.²⁸ Meningitis should be treated for at least

10–14 days.²⁸ Cefotaxime can also be used at a dose of 25 mg/kg IV or IM every 12 hours for 7 days, for 10–14 days, if meningitis is documented.²⁸

Childhood disease beyond infancy

Children who weigh less than 45 kg and have uncomplicated localized gonococcal disease (vulvovaginitis, urethritis, pharyngitis, proctitis, conjunctivitis) may receive ceftriaxone, 125 mg IM in a single dose, or spectinomycin, 40 mg/kg (maximum 2 g) IM in a single dose.^{28,91} Because spectinomycin is unreliable in eradicating pharyngitis, eradication of infection needs to be documented if ceftriaxone cannot be used.⁹² A high index of suspicion is key to the management disseminated gonococcal disease. Children who weigh less than 45 kg and have disseminated gonococcal disease (bacteremia, arthritis, meningitis, perihepatitis) may receive ceftriaxone, 50 mg/kg IM or IV in a single daily dose for 7–14 days.²⁸ Note that only parenteral cephalosporins are recommended for therapy in children; cefixime has been used to treat gonococcal infections in children, but there is no published data in regards to safety and efficacy in children (cefixime is no longer manufactured in the United States at the time of preparation of this chapter, Lupin Pharmaceuticals has received FDA approval for a generic version including a suspension). Quinolones are not approved for this indication in children, and concerns about increases in prevalence of QRNG may limit their usefulness in parts of the United States and other countries. Ceftriaxone is the treatment of choice for genital infections in pediatric patients (Table 83-2). It should be kept in mind that coinfection with *C. trachomatis* is common in children as well as adolescents or adults and the microbiologic evaluation needs to reflect this. Optimal therapy for known or possible coinfection with both pathogens has not been explored in children. See the separate chapter on PID (see Chapter 56) for considerations in the treatment of gonococcal cervicitis and salpingitis in adolescents.

■ PREVENTION OF NEONATAL GONOCOCCAL DISEASE

Prevention of ophthalmia neonatorum is a principal goal of medical care of the newborn and remains an important focus in the fight against childhood blindness in low-income countries.⁹³ The most effective method is the prevention and treatment of the disease in the mother so that exposure of the newborn does not occur. All pregnant women at risk should have endocervical culture examinations for gonococci as an integral part of prenatal care at the first prenatal visit followed by appropriate antibiotic therapy. A second culture late in pregnancy (third trimester) should be obtained from women who are at high risk of gonococcal infection. This approach, while effective, is also costly and may not be feasible in resource-poor countries where eye prophylaxis is the most common intervention to prevent ophthalmia

neonatorum. Credé's topical use of silver nitrate was one of the most successful strategies in preventive medicine resulting in reports of low rates of ophthalmia neonatorum in the presence of prophylaxis. A review of 24 studies conducted from 1930 to 1979 showed an overall risk estimate of 0.06%.⁹⁴ Because of reports of failure and the high incidence of chemical conjunctivitis with silver nitrate and the importance of eye contact in mother–infant bonding, interest developed in the use of other agents.^{95,96} Alternatives were studied in several prospective trials. Alternating regimens of silver nitrate and erythromycin ophthalmic ointment at hospitals in St. Louis and Chicago showed no gonococcal isolates during the use of either regimen but a higher number of side effects with silver nitrate.^{95,96} A randomized prospective trial of silver nitrate versus erythromycin for prophylaxis of ophthalmia neonatorum in Seattle, WA, found no gonococcal infections in either group.⁹⁷ Lund et al. compared the incidence of gonococcal ophthalmia neonatorum before and after introduction of prophylactic agents in South Africa and reported decreased incidences of similar magnitude in hospitals using silver nitrate or erythromycin ophthalmic ointment.⁹⁸ Tetracycline ophthalmic ointment reduced the incidence of gonococcal ophthalmia among exposed infants in Kenya compared to historic controls by similar or slightly greater amounts than silver nitrate.⁹⁹ This effect was seen despite a high percentage of tetracycline resistant gonococci in the study indicating that the high local concentration may be sufficient to eradicate the low inoculum received during birth.⁹⁹ The frequency of gonococcal ophthalmia was similar with each of the three prophylactic regimens used in a study by Hammerschlag et al., in Brooklyn, NY, comparing silver nitrate drops, erythromycin ophthalmic ointment, and tetracycline ophthalmic ointment.³³ However, only 3% (11 of 389) of the enrolled mothers had positive cultures for *N. gonorrhoeae* at some point during pregnancy and were treated.⁹⁷ A study of 2.5% povidone-iodine solution as prophylaxis against ophthalmia neonatorum in Kenya found that it reduced the overall incidence of conjunctivitis, but the true effectiveness in preventing gonococcal ophthalmia could not be estimated as the rate of gonococcal infections in the mothers, and thus the number of exposed neonates was unknown.¹⁰⁰ Povidone-iodine is not currently recommended as an alternative to the established prophylactic agents.²⁸ Bacitracin ointment (not effective) and penicillin drops (sensitizing) should not be used. Chemical prophylaxis of the newborn conjunctivae provides excellent but not perfect protection and does not provide effective therapy for an established infection. The main reasons cited for failure of prophylaxis are prematurity, prolonged rupture of the membranes, and infection before birth.^{101,102} Prophylaxis with ophthalmic ointments containing antimicrobial agents is not completely without adverse effects, for example the potential selection of resistant bacteria.¹⁰³

Most state health departments in the United States require ocular prophylaxis of some form. Silver nitrate 1% aqueous solution is no longer available in the United States. The remaining recommended agents are 1% tetracycline ophthalmic ointment in a single application, or 0.5% erythromycin ophthalmic ointment in a single application.²⁸ Prophylaxis should be administered as soon as possible after birth as delay has been associated with increased risk of gonococcal ophthalmia (four- to fivefold with delay ≥ 4 hours).¹⁰⁴ It should be noted that in countries with a very low prevalence of gonococcal infections in pregnant women and/or a prenatal screening program, the effect of universal eye prophylaxis may not be discernible and the approach may not be cost-effective.^{94,105} Therefore, some such countries have adopted a strategy of diagnosing and treating ophthalmia neonatorum in those infants who develop symptoms instead of universal prophylaxis. However, ocular prophylaxis remains an inexpensive preventive tool, which is safe, easy to administer, and effectively prevents most cases of gonococcal ophthalmia.

CHLAMYDIA TRACHOMATIS INFECTIONS IN INFANTS AND CHILDREN

■ HISTORY

At the turn of the twentieth century, there was no screening of expectant mothers for STDs, no instillation of prophylactic eye drops, and no antibiotic treatment for established infections. In this period, the term *ophthalmia neonatorum* was for all practical purposes synonymous with gonococcal conjunctivitis. As neonatal conjunctivitis came under control with silver nitrate prophylaxis, the importance of another form of ophthalmia neonatorum, termed *inclusion blennorrhoea*, was noted. The relationship between maternal genital infection and conjunctivitis of the newborn associated with inclusion bodies within epithelial cells was established by Lindner, Halberstader, Von Prowazek, and others.¹⁰⁶ In 1967, Schachter and colleagues further emphasized the relationship of sexual transmission of the infection in the parents of infants with inclusion conjunctivitis.¹⁰⁷ Respiratory infection in infants due to *C. trachomatis* was probably first reported in 1941 by Botsztejn, who described an entity he called *pertussoid eosinophilic pneumonia*.¹⁰⁸ The syndrome of infantile chlamydial pneumonia was further characterized by Beem and Saxon in 1977.¹⁰⁹

■ EPIDEMIOLOGY

C. trachomatis infection is acquired by the infant from his or her mother during parturition.^{110,111} This is based on a number of well-controlled prospective studies of maternal-infant infection conducted in the 1970s and 1980s, where infection occurred only in those infants born to infected mothers.

There is no convincing evidence of horizontal transmission from mother-to-infant, other family members-to-infant, or from infant-to-infant after delivery. Infection after cesarean delivery or through intact membranes is rare but may occur.¹¹² In the former, there has usually been early rupture of the amnionic membranes. The overall risk of acquiring infection in an infant born to a mother with active chlamydial infection at any anatomical site has been approximately 50–75% in various studies.^{110,111} Infants are often infected at more than one site, including the conjunctiva, nasopharynx, rectum, and vagina. The most frequent clinical manifestation of neonatal chlamydial infection, inclusion conjunctivitis, has been reported to occur in 15–37% of infants born to mothers with untreated cervical chlamydial infection.^{110–112} The most frequent site of infection, however, is the nasopharynx, with 78% of infected infants having positive nasopharyngeal cultures in one study.¹¹² Approximately one-half of infants with inclusion conjunctivitis will also be infected in the nasopharynx. Only a minority of infants with nasopharyngeal infection actually go on to develop chlamydial pneumonia; Hammerschlag et al. found that only 4 of 12 (33%) infants with isolated nasopharyngeal infection subsequently developed pneumonia.¹¹² The overall risk of developing pneumonia among infants born to chlamydia-positive mothers has been reported to range from 1% to 22%.^{110,111}

Data on the risk of acquiring rectal or vaginal infection are more limited. Bell and colleagues demonstrated that perinatally acquired *C. trachomatis* infection may persist for months to years.¹¹³ Twenty-two infants born to women with culture-documented chlamydial infection were followed, and positive cultures from the nasopharynx and oropharynx in the infants were detected as late as 28.5 months after birth. Rectal and vaginal infection persisted for at least 1 year. This can become an important confounding variable when young children are tested for the presence of *C. trachomatis* during evaluation for suspected sexual abuse.

■ CONJUNCTIVITIS

Before the introduction of systematic screening and treatment of *C. trachomatis* infection in pregnant women in the 1990s, *C. trachomatis* was the most frequent identifiable infectious cause of neonatal conjunctivitis and the major clinical manifestation of neonatal chlamydial infection in the United States.^{110,111} Screening and treatment have resulted in a dramatic decrease in perinatal chlamydial infections. However, in countries where pregnant women are not routinely screened, including the Netherlands and many developing countries, *C. trachomatis* remains the most frequent cause of neonatal conjunctivitis.^{114–116} The incubation period of *C. trachomatis* conjunctivitis is 5–14 days

after delivery, or earlier if there has been premature rupture of membranes. At least 50% of infants with chlamydial conjunctivitis will also have nasopharyngeal infection. The presentation is extremely variable, ranging from mild conjunctivitis with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva can be very friable and may bleed when stroked with a swab. Eyelid erythema and edema are frequently present. A Gram-stained conjunctival smear may initially reveal a predominance of polymorphonuclear leucocytes (PMNs). Chlamydial conjunctivitis needs to be differentiated from gonococcal ophthalmia in some infants, especially those born to mothers who did not receive any prenatal care, had gonorrhea during pregnancy, and/or abused drugs. There can be overlap in both incubation periods and presentation. Bilateral infections are present in two-thirds of cases. A follicular reaction is not seen because infants less than 3 months of age do not have the requisite lymphoid tissue present in the conjunctiva. Although uncommon, chlamydial neonatal conjunctivitis has been noted to induce the long-term sequelae of corneal neovascularization and scarring. However, Hammerschlag and colleagues did not detect micropannus at 1 year of age in seven infants who had culture-documented neonatal *C. trachomatis* conjunctivitis.¹¹⁷

■ PNEUMONIA

Approximately 70% of infected infants will have positive nasopharyngeal cultures. The majority of nasopharyngeal infections are asymptomatic and may persist for 3 years or more.¹¹³ Chlamydial pneumonia develops in only about 30% of infants with nasopharyngeal infection.¹¹⁷ In those infants who develop pneumonia, the presentation and clinical findings are very characteristic.^{118,119} The children usually present between 4 and 12 weeks of age. A few cases have been reported presenting as early as 2 weeks of age but no cases have been seen beyond 4 months. The infants frequently have a history of cough and congestion with an absence of fever. On physical examination, the infant is tachypneic and rales are heard on auscultation of the chest; wheezing is distinctly uncommon. There are no specific radiographic findings except hyperinflation (Fig. 83-1). Significant laboratory findings include peripheral eosinophilia (>300 cells/cm³) and elevated serum immunoglobulins. If cultured, infants with *C. trachomatis* pneumonia may remain symptomatic and shed the organism from the nasopharynx for protracted periods.¹¹⁷⁻¹¹⁹ Generally, infantile pneumonia due to *C. trachomatis* appears to be self-limited. Most infants can be managed as outpatients although there are a few reports of severe disease requiring hospitalization and assisted ventilation. *C. trachomatis* pneumonia in infants also appears to be associated with few sequelae, although data are limited.

■ OTHER INFECTIONS

Otitis media

Isolation of *C. trachomatis* from middle-ear fluid was first reported by Tipple et al.¹¹⁹ The organism was isolated from the middle-ear aspirates of 3 of 11 infants with chlamydia pneumonia. These infants were all under 3 months of age and had the typical infantile chlamydial pneumonia and what was described as “serous” otitis media. This may not imply a

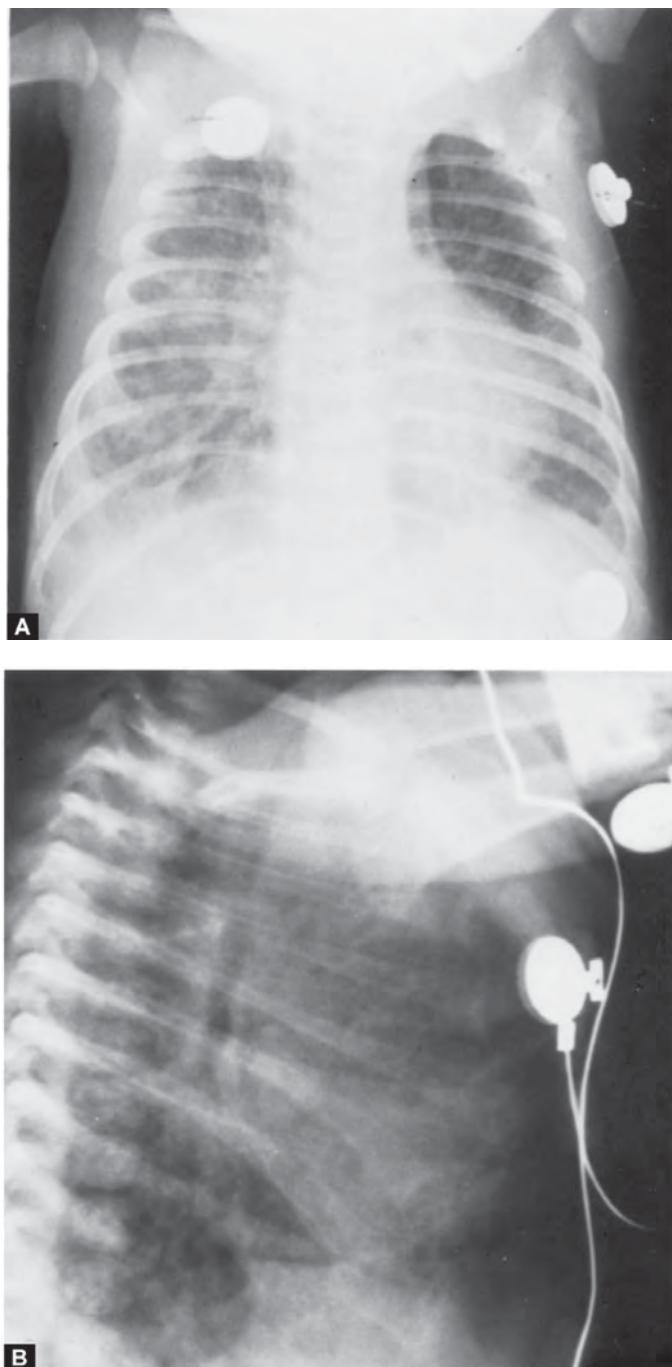


FIGURE 83-1 A, Anteroposterior and B, lateral chest radiographs of a severely ill 1-month-old male infant with chlamydial pneumonitis. Diffuse interstitial infiltrates and hyperaeration with flattened diaphragms are prominent.

causal relationship, as the middle ear is contiguous with the nasopharynx and the organism is present in the mucosa of the nasopharynx. Infants with chlamydial pneumonia have a significant degree of nasal congestion, which can lead to eustachian-tube dysfunction, and thus the presence of serous otitis media may not be directly attributable to the presence of *C. trachomatis* in middle-ear fluid. However, subsequent studies that have examined middle-ear fluids from older infants and children with acute and chronic otitis media have not found convincing evidence of *C. trachomatis* as an etiologic agent of otitis. Four studies examined middle-ear fluids from a total of 337 children ranging in age from 5 months through 12 years.^{120–123} *C. trachomatis* was isolated from ear fluids from five of these children enrolled in two of the studies.^{120,121} Chang et al. isolated *C. trachomatis* from ear aspirates of 3 of 26 (11.5%) children but the age of only 1 of these children, a 10-month-old, was given.¹²⁰ The culture method used was iododeoxyuridine (IUDR)-treated McCoy cells with iodine staining, which should be specific for *C. trachomatis*. In the other study, Dawson and colleagues isolated presumptive *C. trachomatis* from two ear aspirates from 217 Australian aboriginal children.¹²¹ The positive children were 4 and 8 years of age. The researchers used McCoy cells but confirmed the isolates with a fluorescein conjugated genus-specific monoclonal antibody, and thus it is possible that both isolates may have actually been *C. pneumoniae*. Considering that perinatally acquired nasopharyngeal *C. trachomatis* infections may persist for at least 2 years, it is possible that the organism may be isolated from middle-ear fluids beyond early infancy but a causal relationship has not been established. *C. pneumoniae* is a more likely candidate as a cause of otitis media in older children and was isolated from middle-ear fluids of 8% of children presenting with acute otitis media in one study.¹²⁴

Rectogenital infection in older children

C. trachomatis has not been associated with any specific clinical syndrome in older infants and children. Most attention to *C. trachomatis* infection in these children has concentrated on the relationship to child sexual abuse. Isolation of *C. trachomatis* from rectal or genital sites in children without prior sexual activity may be a marker of sexual abuse.^{110,111,125} Although evidence for other modes of spread, such as through fomites, is lacking for this organism, perinatal maternal-infant transmission resulting in vaginal and/or rectal infection has been documented with prolonged infection for periods up to 3 years.¹¹³ This could be an important confounding variable.

Studies have identified rectogenital chlamydial infection in 2–3% of sexually abused children when these children were routinely cultured for the organism.¹²⁵ The majority of those with chlamydial infection were asymptomatic. The association of *C. trachomatis* infection and sexual abuse is covered in detail in Chapter 87. *C. pneumoniae* can be confused with

C. trachomatis in pharyngeal cultures if genus specific monoclonal antibodies are used for culture confirmation.¹²⁶ Asymptomatic nasopharyngeal infection with *C. pneumoniae* occurs in 2–5% of children.^{110,111}

■ DIAGNOSIS

It is difficult to make an etiologic diagnosis of neonatal conjunctivitis on clinical grounds alone. There can be significant overlap in both incubation period and clinical findings with infections due to other organisms, especially *N. gonorrhoeae*. In a high-risk population, gonococcal ophthalmia must be seriously considered. The incubation period for gonococcal conjunctivitis is usually 3–5 days but it can be longer. The incubation period for chlamydial conjunctivitis is approximately 5–14 days. Most cases will present by 2 weeks of age, which is after the infant leaves the hospital. Epidemiologic clues can help the physician decide whether gonococcal ophthalmia needs to be considered. Hammerschlag and colleagues noted that seven of the eight infants who presented with gonococcal conjunctivitis were born to mothers who had not received any prenatal care.³³ Five of these women were abusers of crack cocaine. Another epidemiologic clue is a history of gonorrhea or other STD during pregnancy.

The clinical presentation of *C. trachomatis* pneumonitis in infants is fairly characteristic, and one may be able to make a clinical diagnosis with a degree of certainty.

Laboratory diagnosis of *C. trachomatis* infections in infants and children

The “gold standard” for diagnosis of *C. trachomatis* infections in infants and children remains isolation by culture of *C. trachomatis* from the conjunctiva, nasopharynx, vagina, or rectum. *C. trachomatis* culture has been defined further by the CDC as isolation of the organism in tissue culture and confirmation by microscopic identification of the characteristic inclusions, preferably by staining with a fluorescein-conjugated species-specific monoclonal antibody.²⁸ Enzyme immunoassays (EIAs) have been used by some commercial laboratories as a “screen” for culture confirmation; however, use of EIAs for culture confirmation has been associated with significant numbers of false-positive results, especially with rectal and vaginal specimens.¹²⁷ The CDC has strongly stated that use of EIAs for this indication is not acceptable.^{28,127} Several nonculture tests are approved for diagnosis of chlamydial conjunctivitis in infants, specifically EIAs, and direct fluorescent antibody tests (DFAs). The only EIA and DFA assays still available in the United States are Pathfinder, Chlamydia DFA and EIA Microplate (Bio-Rad Laboratories). These tests appear to perform well with conjunctival specimens with sensitivities greater than or equal to 90% and specificities greater than or equal to 95% compared with culture.^{128,129} Unfortunately, the performance with nasopharyngeal specimens has not been as

good, with sensitivities ranging from 33% to more than 90%. The DNA probe, Pace II (GenProbe, San Diego, CA), which is still used in many laboratories, does not have approval for any site in children, including the conjunctiva.

There are currently three FDA approved, commercially-available NAATs for diagnosis of *C. trachomatis* infection: polymerase chain reaction (PCR), Amplicor (Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (SDA) (ProbeTec, Becton Dickson, Sparks, MD), and transcription mediated amplification (TMA) (GenProbe, San Diego, CA). These assays all have FDA approval for cervical swabs from women, urethral swabs from men, and urine from men and women. These tests also perform very well in adolescents who have very high rates of genital *C. trachomatis* infection. The use of noninvasive specimens such as urine is especially useful in high prevalence populations such as sexually active adolescents. However, data on use of NAATs in infants and children are limited. Preliminary data suggest that PCR is equivalent to culture for detection of *C. trachomatis* in the conjunctiva and nasopharynx of infants with conjunctivitis.¹³⁰ Roblin et al. evaluated Amplicor for the detection of *C. trachomatis* in ocular and nasopharyngeal specimens from 75 infants with suspected chlamydial conjunctivitis.¹³⁰ Amplicor was equivalent to culture for eye specimens with sensitivity and specificity of 92.3% and 100%, respectively. The sensitivity and specificity for nasopharyngeal specimens were 100% and 97.2%. PCR also detected *C. trachomatis* in the urine of 12 of 12 mothers of culture-positive infants.

Use of these EIAs and DFAs for vaginal and rectal specimens in the evaluation of children suspected of being sexually abused has been associated with false-positive tests.^{127,131} Fecal material can give false-positive reactions with any EIA. Common bowel organisms, including *Escherichia coli*, Group B streptococcus, and even some respiratory flora such as Group A Streptococcus can also give false-positive reactions with EIAs. Another potential problem can occur with use of an EIA for respiratory specimens. As the only currently available EIA, Pathfinder®, Chlamydia EIA Microplate (Bio-Rad Laboratories) uses a genus-specific antibody; if used for respiratory specimens, this test will also detect *C. pneumoniae*.¹²⁶ Even though culture is considered the gold standard, culture of *C. trachomatis* is not regulated in any way and sensitivity may vary from laboratory to laboratory. The methods used for culture confirmation became an issue when several large commercial laboratories started using an EIA instead of FA staining and visual identification of inclusions for culture confirmation. This has resulted in at least one “outbreak” of *C. trachomatis* infection in the evaluation of suspected sexual abuse among residents and staff of an institution for the mentally retarded in Ohio in 1990.¹²⁷ All the “positive” cultures, mostly rectal specimens, were subsequently determined to be false-positives

resulting from carryover of fecal material and bacteria in the culture specimens. The major advantage of culture is that it is 100% specific. When cultures are obtained for *C. trachomatis* in the evaluation of suspected sexual abuse, one should pay careful attention to the laboratory used. Unlike Canada, the United States does not have a system of designated reference laboratories to be utilized for evaluation of sexual abuse or assault.

NAATs are currently not approved for detection of *C. trachomatis* in rectogenital sites from prepubertal children and rectal specimens in adults. The major problem with rectal specimens is the presence of inhibitors of DNA polymerase, which can lead to false-negative results. Data on use of NAATs for vaginal specimens or urine from children are very limited and insufficient at this time to allow making a recommendation on their use. There have been three studies published since 1999 evaluating the performance of NAATs and use of urine for detection of *C. trachomatis* and *N. gonorrhoeae* in children being evaluated for suspected sexual abuse.^{132–134} Unfortunately, all are seriously flawed. The major deficiency is the failure to analyze the results by site tested, age, and sex. The majority of the girls in all three studies were postpubertal; some gave histories of consensual sex, which is a major confounding variable. The number of males enrolled (only two of the studies) was small and the data on males were not analyzed separately. Two of the studies used ligase chain reaction (LCx, Abbott Diagnostics), which was withdrawn from the market in 2002.¹³⁴ The CDC currently recommends that NAATs may be used as an alternative to *C. trachomatis* culture only if confirmation is available, which means using second FDA-approved NAAT that targets a different gene sequence from the initial test.²⁸ It is also recommended that all isolates and specimens be preserved for confirmatory testing.

Treatment of chlamydial conjunctivitis and pneumonia in infants

Oral erythromycin suspension (ethylsuccinate or stearate) (50 mg/kg/day for 14 days) is the therapy of choice for the treatment of chlamydial conjunctivitis and pneumonia in infants. It provides better and faster resolution of conjunctivitis as well as treats any concurrent nasopharyngeal infection, which prevents the development of pneumonia. Additional topical therapy is not needed. The efficacy of this regimen has been reported to range from 80–90%; as many as 20% of infants may require another course of therapy.^{110,111,117} Erythromycin at the same dose for 2 weeks is the treatment of choice for pneumonia and does result in clinical improvement as well as elimination of the organism from the respiratory tract.

Treatment with oral erythromycin has been associated with infantile hypertrophic pyloric stenosis in infants less than 6 weeks of age who were given the drug for prophylaxis after nursery exposure to pertussis.^{135,136} Erythromycin is a

motilin receptor agonist. Data on use of other macrolides, including azithromycin or clarithromycin, for the treatment of neonatal chlamydia infection are limited. There are no published studies of clarithromycin, and only one small study that evaluated azithromycin which found that a short course of azithromycin suspension, 20 mg/kg/day orally, one dose daily for 3 days, was as effective as 2 weeks of erythromycin in eradication of *C. trachomatis* from the conjunctivae and nasopharynx of infants with conjunctivitis.¹³⁷

Chlamydial infections in older children may be treated with oral erythromycin (50 mg/kg/day 4 times a day orally to a maximum of 2 g a day for 7–14 days). Children older than 8 years of age may be treated with tetracycline (25–50 mg/kg/day 4 times a day orally for 7 days). Azithromycin, 1 g orally, as a single dose may also be used in children who weigh ≥ 45 kg and/or are ≥ 8 years of age. The first-line treatment for uncomplicated *C. trachomatis* infections in adults and adolescents is azithromycin, 1 g given as a single dose or doxycycline, 100 mg bid, orally for 7 days. Alternative regimens include erythromycin base, 500 mg or erythromycin ethylsuccinate, 800 mg, both orally, qid for 7 days or ofloxacin 300 mg, orally bid for 7 days or levofloxacin, 500 mg orally, once a day for 7 days.

Prevention and control strategies

Since *C. trachomatis* infections are transmitted vertically from mother to infant during delivery, there are several possible options for intervention. One of the first to be considered was neonatal ocular prophylaxis. The results of several prospective studies of mother-to-infant transmission of *C. trachomatis* demonstrated that neonatal ocular prophylaxis with silver nitrate does not prevent the development of chlamydial conjunctivitis.^{110,111} These studies had found that the risk of conjunctivitis among infants born to infected women ranged from 18% to 50%. As erythromycin and tetracycline ophthalmic ointments were also approved and used for ocular prophylaxis, it was suggested that they might also be effective for prevention of chlamydial conjunctivitis. The first such study conducted in 1980 found that not one of 24 infants in Seattle born to *C. trachomatis*-positive women and who received topical erythromycin developed chlamydial conjunctivitis, compared to 33% (12 of 36) of those who received silver nitrate drops.⁹⁷ There was no effect on the incidence of nasopharyngeal infection or on the subsequent development of chlamydial pneumonia. In a subsequent study, Laga et al. in a subsequent study from Nairobi, Kenya, compared tetracycline ointment with silver nitrate drops,⁹⁹ chlamydial ophthalmia developed in 10.1% of the infants born to women with cultures positive for *C. trachomatis* who received silver nitrate drops as prophylaxis compared to 7.2% who received tetracycline ointment. The authors initially concluded that both preparations were efficacious when compared with a historical cohort in which the disease developed

in 31.3% of the infants who were not treated prophylactically and who were born to infected women. Most of the infants in this study were followed only for the first 4 weeks of life, however, and the follow-up rate was less than 50%. When these authors examined a smaller group of infants who were followed for at least 6 months, 23% and 31% of those who received silver nitrate and tetracycline, respectively, ultimately acquired an ocular infection with *C. trachomatis*. What is especially interesting about these results is that many of these ocular infections were detected when the infants were more than 2 months of age and were asymptomatic. This is very different from the experience in the United States, where asymptomatic ocular infection has been uncommon.

In 1989, Hammerschlag et al. compared silver nitrate, erythromycin, and tetracycline as neonatal ocular prophylaxis in a large urban hospital in Brooklyn, New York.³³ The prophylaxis preparations were given within 30 minutes of birth. Chlamydial conjunctivitis developed in 20% (15 of 76) of infants born to infected mothers who received silver nitrate drops, 14% (13 of 92) of those who received erythromycin, and 11% (7 of 62) of those who received tetracycline. There was no effect on the incidence of nasopharyngeal infection and pneumonia. A subsequent study from Taiwan compared silver nitrate, the two antibiotics, and no prophylaxis.¹³⁸ This study, in contrast to previous studies, did not specifically follow infants born to women with culture-documented chlamydial infection but instead followed all infants delivered during the period of the study—for 4 weeks or until they developed conjunctivitis. Again, there was no difference in the incidence of neonatal chlamydial conjunctivitis among the four groups. The incidences of chlamydial conjunctivitis in the tetracycline, erythromycin, silver nitrate, and no prophylaxis group were 1.3, 1.5, 1.7, and 1.6%, respectively. Diagnosis of *C. trachomatis* was by DFA rather than culture. No data were given as to the prevalence of maternal infection with *C. trachomatis* or *N. gonorrhoeae*. Differences in the prevalence of maternal infection among the four groups could lead to different rates of *C. trachomatis* conjunctivitis in the infants that were unrelated to prophylaxis. Respiratory infection was not assessed. A similar study from a clinic in Kenya was reported by Isenberg et al. comparing povidone-iodine, erythromycin ophthalmic ointment, and silver nitrate drops as neonatal ocular prophylaxis.¹⁰⁰ Povidone-iodine was selected because, in vitro, it has a broad antibacterial spectrum; it is also antiviral and is very inexpensive compared to the other prophylaxis agents. As with the study from Taiwan, the pregnant women were not screened for *C. trachomatis* prenatally, and chlamydial conjunctivitis in the infants was diagnosed by DFA. Mothers were told to bring their infants back if conjunctivitis developed. Use of povidone-iodine appeared to result in a 50% reduction in *C. trachomatis* conjunctivitis compared to silver nitrate (5.5% vs. 10.5% of infants) and an approximately 30% reduction

compared to erythromycin (7.4%). There was no difference in the proportions of infants who developed gonococcal ophthalmia. Because of the structure of the study, one cannot be sure if every infant who developed conjunctivitis returned to the clinic. As the prevalence of chlamydial infection among the pregnant women in the population was unknown, the investigators did not know how many cases of chlamydial ophthalmia to expect. The CDC does not recommend the use of providone-iodine,²⁸ and silver nitrate drops are no longer manufactured in the United States. Another approach that has been considered is oral prophylaxis of infants born to mothers with untreated *C. trachomatis* infection with erythromycin or azithromycin.¹³⁹ However, several analyses have found this approach to be very expensive compared to watching and treating the infant when they become symptomatic. In addition, there is the issue of compliance and there are no data on the efficacy of either oral erythromycin or azithromycin for prophylaxis.

The most effective method of control of perinatal *C. trachomatis* infection is screening and treatment of pregnant women. This approach has been validated by a dramatic decrease in perinatal chlamydial infection seen in the United States and the persistence of these infections in countries where screening and treatment of pregnant women is not standard practice, such as the Netherlands, India, and China.^{114–116} Rours and colleagues reported that during the period from 1996 to 2001, *C. trachomatis* was responsible for 61–64% of the cases of neonatal conjunctivitis seen in a large university affiliated hospital in Rotterdam.¹¹⁴ Even though the rate of *C. trachomatis* infection among pregnant women in Rotterdam exceeded 5%, prenatal screening and treatment is not a part of routine prenatal care in the Netherlands.

Reasons for failure of maternal treatment to prevent infantile chlamydial infection include poor compliance and reinfection from untreated or new sexual partners. Even with effective screening, some infected women will be missed, depending on the methods used. There are also women who do not seek prenatal care.

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Herpesvirus Infections in Neonates and Children: Cytomegalovirus and Herpes Simplex Virus

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CONGENITAL AND PERINATAL CYTOMEGALOVIRUS INFECTIONS

Cytomegaloviruses (CMVs) are members of the herpesvirus family known for their ubiquitous distribution in humans and in numerous other mammals. These viruses share a number of biologic attributes in common with herpes simplex virus (HSV) and other members of the herpesvirus family. Both in vivo and in vitro, infection is highly species-specific.¹ The first description of cells containing intranuclear and cytoplasmic inclusions dates from 1881 when Ribbert described them in the kidneys of a still-born infant with congenital syphilis.² In 1954, Smith succeeded in propagating murine CMV in explant cultures of mouse embryonic fibroblasts.³ Utilization of similar techniques led to the independent isolation of human CMV shortly thereafter by Smith, Rowe et al. and Weller et al.⁴⁻⁶ The term CMV was proposed in 1960 by Weller, Hanshaw, and Scott to replace the names cytomegalic inclusion disease (CID) and salivary gland virus, which were misleading, since the virus usually involved other organs and the term salivary gland virus had been used to designate unrelated agents obtained from bats.⁷

The propagation of CMV in vitro led to the rapid development of serologic methods and the ability to isolate the virus from clinical specimens. It quickly became apparent that CMV is a significant human pathogen.⁸ The natural history of human CMV infection is complex. Following primary infection, viral excretion (occasionally from several sites) persists for weeks, months, or years before becoming latent. Asymptomatic episodes of recurrent infection with renewed viral shedding are common, even years after primary infection. Most maternal CMV infections are subclinical. However, although infection may be without consequences for the mother, it can have serious repercussions for the fetus.⁹

■ EPIDEMIOLOGY

General

Humans are the only reservoir for CMV. The infection is endemic and without seasonal variation.¹⁻⁸ Climate does not

affect the prevalence of infection, and there are no known vectors in the natural transmission cycle. Seroepidemiologic surveys have found CMV infection in every human population that has been tested. The prevalence of antibody to CMV increases with age, but the patterns of acquisition of infection vary widely among populations according to geographic, ethnic, and socioeconomic backgrounds. In general, the prevalence of CMV infection is higher in developing countries and among the lower socioeconomic strata of developed nations. These differences are particularly striking during childhood.

The level of immunity among women of child-bearing age also varies widely in different populations. In the United States and eastern Europe, seropositivity rates in young women range from less than 50% to 85%.⁹ In contrast, in the Ivory Coast, Japan, and Chile the rate of seropositivity is greater than 90% by the end of the second decade of life.¹⁰⁻¹² Prospective studies of pregnant women in the United States indicate that the rate of CMV acquisition for childbearing age women of middle to higher socioeconomic background is approximately 2% per year, whereas it is 6% among women of lower socioeconomic status.¹³

The modes of transmission from person to person are incompletely understood.⁸ The following features of CMV infection make it difficult to study the modes of acquisition. In the majority of individuals, CMV infections are subclinical, including those acquired in utero and during the perinatal period. Virus excretion persists for years following congenital, perinatal, and early postnatal infections. Prolonged viral shedding is also a feature of primary infection in older children and adults. These infected persons continue to expose other susceptible people. Since non-primary infections (reactivated infection or reinfection) are fairly common, intermittent excretion of virus can be anticipated in a significant proportion of seropositive adults. Clearly, a large reservoir of CMV exists in the population at all times. Transmission occurs by direct or indirect person-to-person contact. Sources of virus include urine, oropharyngeal secretions, cervical and vaginal secretions, semen, milk, tears, blood, and transplanted organs.^{14,15}

The spread of infection requires close or intimate contact with infected secretions or infected blood and organs. Sexual contact contributes the most to the spread of CMV. Higher rates of seropositivity have been observed among males and females with multiple sex partners and histories of sexually transmitted diseases.^{14,16–21}

Certain child-rearing practices influence the spread of CMV among children. Because seropositive women often excrete CMV in breast milk, the incidence of perinatal CMV infection is high where breast feeding is a common practice.¹⁵ In 1971, Weller suggested that the high rate of seropositivity among Swedish children was probably due to the frequent use of day care centers.¹ Swedish children had a rate of infection that was three to four times higher than that observed in London or Rochester, New York. High rates of CMV infection among children attending day care centers were later confirmed in the United States.^{22–24} Pass et al. reported that in a group of 70 children of middle- to upper-income background whose ages ranged from 3 to 65 months, the rate of CMV excretion in urine and saliva was 50%.²⁴ The lowest rate of excretion (9%) occurred in infants less than 1 year of age, and the highest rate (88%) among toddlers in their second year of life. Infants younger than 12 months in group day care who excrete CMV are more likely to have acquired CMV congenitally or perinatally from contact with maternal cervical secretions or breast milk. Twelve children whose mothers were seronegative excreted CMV, which indicated that their infection was not perinatally acquired. These findings have been confirmed by other investigators.^{22,23,25,26}

The high rate of CMV infection among children in group day care is caused by horizontal transmission from child to child. The route of transmission that appears most likely is the transfer of virus that occurs through saliva on hands and toys.^{27,28} The strongest evidence supporting child-to-child transmission was obtained by Adler who used restriction enzyme digestion patterns of CMV DNA to show the identity of isolates obtained from infected children attending day care.²⁹ His findings support that CMV is efficiently transmitted from child to child in the day care setting, and that it is not unusual to find excretion rates as high as 20–40% in young toddlers. In many instances, these rates of infection are substantially higher than the seroprevalence rates for the parents of the children and young adults in the cities where the studies were done. No data demonstrate CMV transmission via respiratory droplets.

An important issue is whether children excreting CMV are a source of infection for susceptible child care personnel and parents, particularly women of childbearing age. This mode of transmission has been confirmed by restriction endonuclease mapping of CMV DNA.^{30,31} Seroepidemiologic studies suggest that parents often acquire CMV from their children who became infected outside the family.^{32–34} Adler and Pass et al. have presented compelling evidence linking the acquisition of CMV by children in day care with subsequent infection of

their mothers and caretakers. Pass et al. followed seronegative parents whose children attended a day care center and a similar control population of parents whose children did not attend day care.²⁶ The groups were followed for a mean of 17 and 21 months, respectively. Fourteen of 67 seronegative parents with children in day care centers acquired CMV as compared with none of 31 susceptible parents whose children did not attend day care. More significantly, all 14 parents of the day care group who seroconverted had a child who shed CMV in saliva or urine. In fact, seroconversion occurred in 14–48 parents of children who shed CMV, compared with none of 21 whose children did not excrete CMV. The highest risk of seroconversion (45%) was for parents with a child shedding CMV who was younger than 18 months at enrollment. In 2 of the 14 cases, DNA analysis indicated the child as the source of CMV infection. In a subsequent study, this group of investigators also demonstrated by means of restriction enzyme analysis that infections acquired by a mother from a child can be transmitted to her fetus.²⁶ Similarly, Adler observed that of 18 seronegative mothers whose children shed CMV strains associated with day care, 6 seroconverted and excreted CMV strains identical to the strains shed by their children.³⁵ On an average, these mothers became infected within 4.2 months (range, 3–7 months) after the child's infection.

In assessing the risk to caretakers working with young children in day care centers, Adler reported an annual seroconversion rate of 11% among 202 seronegative women employed at 33 day care centers in Richmond, Virginia.³⁶ This rate was significantly higher than the 2% annual rate of 229 female hospital employees matched for age, race, and marital status. Restriction endonuclease DNA patterns of 17 of 31 isolates of CMV obtained from day care workers were compared with the patterns of isolates shed by the children cared for by these women. Nine of the 17 isolates were identical to the isolates shed by one or more children. These observations provide evidence that susceptible women who work with children in day care have an occupational risk of acquiring CMV.

From the data generated from these studies, approximately 50% of susceptible children between the ages of 1 and 3 years who attend group day care will acquire CMV from their playmates and become an important potential source of infection for susceptible parents and caretakers. Of particular concern is the risk to seronegative mothers who have children in group day care and who become pregnant.

Fomites may also play some role in transmission because CMV has been both shown to retain infectivity for hours on plastic surfaces and isolated from randomly selected toys and surfaces in a day care center.^{27,28}

Maternal infection and vertical transmission

Maternal CMV infection is the origin of congenital infections and of most perinatal infections. As used here, vertical transmission implies mother-to-infant transmission.

Congenital infection

Congenital infection is the result of transplacental transmission. In the United States, congenital CMV infection occurs in between 0.2% and 2.2% (average 1%) of all newborn infants. The natural history of CMV infection during pregnancy is particularly complex and has not been fully explained. With infections such as rubella and toxoplasmosis, transmission in utero occurs only as a result of a primary infection acquired during pregnancy, whereas the in utero transmission of CMV can occur as a consequence of either primary or non-primary infections.³⁷ Far from being a rare event, congenital infection resulting from non-primary CMV infection has been shown to be quite common, especially in highly immune populations. The initial clue was provided by three independent reports of congenital CMV infections that occurred in consecutive pregnancies.^{38–40} In all three instances, the first infant was severely affected or died and the second born in each case was subclinically infected. More convincing evidence came from a prospective study of women known to be seroimmune before conception.³⁷ The rate of congenital CMV infection was 1.9% among 541 infants born to these seropositive women. These infants were not infected as a result of primary maternal CMV infection since all of the mothers were known to have been infected with CMV from one to several years before the onset of pregnancy. This unique characteristic (intrauterine transmission in immune women) accounts for the high incidence of congenital CMV infection in populations with the highest rate of seropositivity.⁴¹

The phenomenon of intrauterine transmission occurring in the presence of humoral immunity had been attributed to reactivation of endogenous virus. However, in 2001, Boppana et al. utilized serologic studies of immune mothers to prove that maternal reinfection accounted for a significant number of babies with congenital infection.⁴²

Although it seems likely that the route of and risk factors for reinfection are the same as those for primary infection, this has not been established. Additionally, the sites from which CMV reactivates to produce congenital infection are not known. Although CMV excretion is a relatively common event during and after pregnancy, simple isolation of virus from the cervix or urine or both is a poor indicator of the risk of intrauterine infection.^{43,44}

Virus can be shed at variable rates from single or multiple sites following primary or non-primary infections in both pregnant and nonpregnant women. Pregnancy per se has no discernible effect on the overall prevalence of viral shedding. However, gestational age influences the rate of CMV excretion, being significantly lower in the first trimester.⁴⁵

The rates of CMV excretion in the genital and urinary tracts of women are inversely related to age after puberty.⁴⁶

Perinatal infection

In contrast to the poor correlation between CMV excretion during pregnancy and congenital infection, a good correlation exists between maternal shedding in the genital tract and/or breast milk and perinatal acquisition. In one study, the two most efficient sources of transmission in the perinatal period were infected breast milk (which resulted in a 63% rate of perinatal infection) and the infected genital tract, particularly in late gestation, which was associated with transmission in 57% of the cases (natal infection).¹⁵ Viral shedding from the pharynx and urinary tract of the mother late in gestation and during the first months postpartum has not been associated with perinatal transmission.

There is considerable variability in perinatal transmission of CMV throughout the world. The age of the mother and her prior experience with CMV, which in turn influence the frequency of viral excretion into the genital tract and breast milk, certainly are important factors. Younger seropositive women who breast feed are at a greater risk for transmitting virus in early infancy, especially in lower socioeconomic groups. In Japan, Guatemala, Finland, and Thailand, the rates of CMV excretion during the first year of life are extremely high (39–56%), and the practice of breast feeding is almost universal. The majority of these women of childbearing age is seroimmune for CMV.

Sexual transmission

In general, in developing areas of the world, 90–100% of the population is infected during childhood, even as early as 5 years of age. Sexual transmission in these populations plays a minor role as a source of primary CMV infection, and its importance in reinfection is unclear. In developed countries, infection is acquired at a lower rate and in some population groups an increase in prevalence of infection occurs only after puberty.

Several lines of evidence indicate that sexual transmission of CMV is at least partly responsible for this increase in seroprevalence. CMV is frequently recovered from semen and cervical secretions.^{14,16–21} Increased seroprevalence of CMV and excretion of virus has been found in women attending sexually transmitted disease clinics and in young male homosexuals. Chretien et al. reported a cluster of cases with CMV mononucleosis that occurred in sex partners, but not in persons who shared living quarters but did not engage in sexual contact.⁴⁷ Handsfield et al. showed that, in two pairs of sex partners with CMV infections attending a sexually transmitted disease clinic, strains of virus were identical by restriction endonuclease analyses of DNA.⁴⁶ Evidence has also been provided for sexual transmission in less promiscuous populations.^{16,18} Among the many variables investigated, a significant correlation was found between seropositivity to CMV and greater numbers of lifetime sexual partners and past or present

infection with *Chlamydia trachomatis*. Although the evidence for sexual transmission of CMV is compelling, the fact that CMV is frequently shed in saliva indicates that oral contact may also be an important route of transmission.

Transmission via transfusion of blood and blood products

CMV infection is an important hazard of blood transfusion and organ transplant. In compromised hosts, such as small premature newborns and stem cell transplant recipients, transfusion-acquired CMV has been associated with serious morbidity and even fatal infection. The association between the acquisition of CMV infection and blood transfusion was first suggested in 1960 by Kreel et al., who described a syndrome characterized by fever and leukocytosis occurring 3–8 weeks after open heart surgery.⁴⁸ Reports that followed expanded the syndrome to include fever, atypical lymphocytosis, splenomegaly, rash, and lymphadenopathy.^{49–56} The term *postperfusion mononucleosis* was then proposed. Prospective studies incriminated blood transfusion as the major risk factor and demonstrated that while the clinical syndrome occurred in approximately 3% of the patients receiving transfusion, inapparent acquisition of CMV infection occurred in 9–58%. It has been estimated that blood donors capable of transmitting CMV range from 2.5% to 12%. In a study of seronegative children receiving blood for cardiac surgery, the risk of acquiring CMV was calculated to be 2.7% per unit of blood.⁵⁰ Notably, the risk of acquisition of CMV by seronegative patients increases significantly and directly with total volume of blood transfused.⁵⁷ Seronegative immunocompromised patients who receive prophylactic white blood cell transfusions from multiple donors (of whom 50% are expected to be seropositive) are also at increased risk of acquiring CMV.⁵⁷

The observation that two newborn infants who received large volumes of fresh blood subsequently developed symptomatic CMV infections led McCracken et al. to suggest an association between blood transfusion and clinically apparent postnatal CMV infection.⁵⁸ Subsequent reports indicated an association between postnatal CMV infection and exchange transfusions.⁵⁹ With exchange transfusions, the probability of a seropositive infant receiving seropositive blood becoming infected is 20%, whereas for a seronegative infant receiving seropositive blood, the probability increases to 50%. This remarkably high incidence after exchange transfusions is most likely owing to the fact that infants who receive the transfusions usually receive large volumes (150–200 mL/kg) of fresh whole blood from a single donor. Intrauterine transfusions were implicated by King-Lewis and Gardner as the source of CMV in two pregnant women who subsequently seroconverted and whose infants developed viremia between 2 and 8 weeks of life.⁶⁰

Two prospective studies have proven that seropositive blood is the source of acquired CMV in neonates undergoing multiple transfusions. In the study of Yeager et al., 10 of

74 infants of seronegative mothers who were exposed to one or more seropositive blood donors acquired CMV.^{61,62} The risk of infection increased to 24% for patients who received more than 50 mL of packed red cells from at least one seropositive donor. The use of solely seronegative blood completely eliminated the acquisition of CMV by infants. A subsequent study by Adler confirmed these findings and proved further that significant risk factors for transmission of CMV and subsequent disease included transfusions from multiple seropositive donors, lack of passively acquired maternal antibody to CMV, and low birth weight (<1250 g).^{49,63}

Transmission to hospital workers

Because hospital workers are often women of childbearing age, there has been concern about occupational risk through contact with patients shedding CMV. Yeager reported a higher seroconversion rate for neonatal (4.1%/year) and pediatric nurses (7.7%/year) than for non-nurse hospital employees (0%), but these differences were not statistically significant.⁶⁴ Friedman et al. noted higher seroconversion rates in a pediatric hospital among workers with patient contact compared with those without such contact.⁶⁵ Although the difference in rates was not statistically significant, when “high-risk” employees (intensive care nurses and an IV team) were compared with others, a significantly higher rate of CMV infection was found in the former. Dworsky studied nurses in newborn nurseries and other health-care workers and found no difference when the seroconversion rate in these women was compared with that of a large group of pregnant women in the community.³² Balfour and Balfour measured incidence of CMV infection among transplant/dialysis nurses, neonatal intensive care nurses, student nurses, and a control group; neither the initial rate of seropositivity nor the annual seroconversion rate differed significantly among any of the groups.⁶⁶ Their annualized seroconversion rate of 1.84% was very close to rates determined for middle-income pregnant women in Birmingham, Alabama.¹³

The risk for hospital personnel is a function of the prevalence of CMV excretion among patients, the prevalence of seronegative health-care workers, and the degree of their exposure to infected patients. In general, among hospitalized infants and children, viremia occurs in approximately 1% of newborn infants, 13% of premature infants hospitalized for 1 month or longer, and 5–10% of older infants and toddlers. The rate of viral excretion in premature infants depends on the rates of perinatal transmission from mother to infant, breast feeding practices, and blood transfusion policies. In toddlers and older children, viral excretion depends on factors like crowding, socioeconomic status, and childrearing practices (breast feeding, attendance at day care centers). On the other hand, age, race, and, to some extent, sex influence the prevalence of seronegative hospital personnel.

Working with hospitalized children inevitably leads to contact with a child shedding CMV. However, workers who develop primary infection should not assume that occupational exposure or contact with a specific patient was the source of infection.^{67–69} Two case reports illustrate this point well. Yow et al. and Wilfert et al. described health-care workers who acquired CMV while pregnant and after attending a patient known to be excreting CMV.^{70,71} In each of these reports, restriction endonuclease analysis of DNA from CMV isolates indicated that the source of CMV for the worker and her aborted fetus was not the patient under suspicion. Adler et al. used restriction enzyme methods to study CMV strains from 35 newborns and a nurse who seroconverted.⁶⁷ All 35 strains were different, supporting the conclusion that nosocomial spread of CMV to workers or among newborns had not occurred. Although hospital workers, particularly those who attend children or immunocompromised patients, will likely have occupational exposure to CMV, there is no convincing evidence that their risk of infection is increased. There is little information about the risk of CMV acquisition by house officers and medical students. In one study, the annual rate of seroconversion for 25 seronegative pediatric residents was 2.7%, which differed little from nursery nurses (3.3%) but was higher than the risk (0.6%) for 89 serosusceptible students completing their clinical rotations.⁶⁶

■ PATHOGENESIS

Of the women who acquire CMV infection during pregnancy, 30–40% transmit the virus to their fetuses.¹³ The risk for those mothers with non-primary infection (reactivation or reinfection) is unknown. Acute and/or long-term morbidity occurs in a small number (5–15%) of infected offspring.

Although not clearly established, intrauterine infection is assumed to result from maternal viremia with subsequent placental infection and hematogenous dissemination to the fetus. Since intrauterine transmission occurs in only 30–40% of pregnant women with primary CMV infection, a mechanism(s) that is not understood, but is generally referred to as the placental barrier, must operate to prevent fetal infection.

Boppana and Britt examined CMV-specific antibody responses after primary maternal infection to determine if specific deficits in antibody response were associated with *in vitro* uterine transmission.⁷² They reported that anti-glycoprotein B IgG antibodies were significantly higher at delivery in women who transmitted the infection compared to the nontransmitters. This observation suggests that the amount of antiviral antibody was not reflective of protection from transmission. They also examined the qualitative antibody response and found lower neutralizing antibody titers in transmitters, suggesting an association between neutralizing activity and *in utero* transmission. They also found that a higher antibody avidity index (≥ 2.0) occurred in the majority

of nontransmitters but in less than 20% of transmitters. Antibody avidity correlated with neutralizing titers, suggesting that antibody affinity maturation is critical for production of high levels of neutralizing antibodies during primary CMV infection. This defect in affinity maturation may indicate that subtle abnormalities in cellular immune mechanisms were present in this group. Previous studies of pregnant women suggested that abnormalities in CMV-specific T-lymphocyte responses occurred in some women. Gehrz showed a transient reduction of the blastogenic response during the second and third trimesters.⁷³ The defect was not generalized, moreover none of the women with the defect excreted CMV, nor did they transmit the infection *in utero*. Stern showed that women with recently acquired infection who had depressed blastogenic responses had a greater risk of delivering a congenitally infected infant.⁷⁴

In immune pregnant women with non-primary infection, it is difficult to postulate that congenital infection results from cell-free virus in plasma causing placental infection with subsequent spread to the fetus.⁷⁵ In this circumstance, the virus could evade the immune system within leukocytes, or local reactivation of infection within the endometrium, myometrium, or cervical canal could occur.

Once intrauterine infection has occurred, the incidence of harmful effects is higher than at any other time in life, with the exception of severely immunocompromised patients. The clinical manifestations of congenital CMV infection are very different from the signs and symptoms associated with infection acquired at delivery or soon after, even in immature infants, suggesting the importance of the intrauterine environment.

Why some infants are severely affected and others remain free of symptoms is not clear. The most obvious, but not necessarily the most important, pathogenic mechanism is continuous viral replication in affected organs. Longitudinal studies of infants with congenital and perinatal infections have demonstrated that excretion of CMV into urine and saliva persists for years. Likely, chronic viral replication occurs at other sites that are less accessible to virologic examination. Many cells are susceptible to the direct cytotoxic effect of CMV, but differences in the intrinsic susceptibility of various tissues to CMV-mediated injury may determine the frequency with which different organs are involved during the course of CMV infection. Another possible factor is vasculitis, which may occur *in utero* or after birth. Infants with symptomatic congenital CMV infection and who die soon after birth usually have disseminated intravascular coagulopathy.⁷⁶ Proliferating endothelial cells within inflamed tissue are susceptible to CMV infection. Injury mediated by immunologic factors also has been studied. The humoral immune system of infected infants is generally felt to be intact and respond normally to antigenic stimulation.^{41,77} Hayashi et al. have reported, however, that compared to

healthy perinatally infected infants and infected adults, congenitally infected infants had a much less vigorous CMV-specific CD4⁺ and CD8⁺ T-cell response.⁷⁸

Perinatal infection results mainly from non-primary (mostly reactivated) infection in immune women. However, transplacental maternal antibody protects only 50% of exposed infants from becoming infected.⁷⁹ The ensuing infection, although chronic, remains subclinical in the vast majority of infants, indicating that the passive transfer of maternal antibody is more protective for virulence than for transmission. Studies show transfusion-acquired infection is more virulent in seronegative than in seropositive infants irrespective of underlying diseases or gestational age.

Congenitally and perinatally infected infants have also been noted to have impaired specific cell-mediated immunity as assessed by the lymphocyte transformation response (LTR) to CMV antigen.^{80–83} This test measures only the recognition, not the effector function, of T lymphocytes and does not require other techniques like the use of syngeneic target cells. Another defect consistently observed is the inability of the lymphocytes of these infants to induce interferon production *in vitro* when challenged with CMV antigens. The impairments are not a reflection of a generalized disturbance, since it is restricted to a blastogenic response to CMV and is highly virus specific. CMV-infected patients who have antibodies to HSV, for example, have a normal blastogenic response to this virus. Infants with impaired LTRs respond normally to both killed and live vaccines. The impairment has no relation to the clinical presentation and outcome, but it is more intense and longer lasting in patients with symptomatic CMV infection. As patients grow older, the impairment disappears together with viral replication. Subtle alterations of host defense mechanisms could contribute to disease, in conjunction with persistent viral replication.

Nature of maternal infection

The impact of the type of the maternal infection on the pathogenesis of congenital CMV infection is in question. Fowler et al. demonstrated that primary infections are more likely to be transmitted to the fetus and are likely to cause more fetal injury than non-primary infections.⁸⁴ Intrauterine transmission following primary infection occurs in approximately 30–40% of cases. Current information suggests that gestational age has no apparent influence on the risk of transmission of CMV *in utero*. However, several studies suggest that infection at an earlier gestational age produces the worst outcome.

Congenital infection also results from non-primary infection, representing either reactivation of infection or reinfection with the same or a different strain of CMV during pregnancy. The risk of congenital CMV infection resulting from a non-primary infection during pregnancy ranges from a high of

1.5% for an American population of low socioeconomic background to 0.19% for women of middle or upper socioeconomic extraction in the United States or from Britain and Sweden.^{13,70,85} On the basis of early studies, it was widely thought that though congenital infection occurs in the setting of non-primary maternal infection, symptomatic infection is rare.^{84,86} However, in 1999, Boppana et al. challenged that dogma with a study that demonstrated that 8 of 47 infants with symptomatic congenital CMV infection (8 of 20 in whom preconceptional status could be confirmed) were born to mothers with preexisting immunity.⁸⁷

In non-primary infection, preexisting immunity partially inhibits the occurrence of viremia. Maternal IgG antibodies are transmitted to the fetus but their precise role has not been elucidated. Conceivably, cellular immunity may be more important than humoral immunity.

Level of viremia at birth

Recent studies conducted by the Collaborative Anti-Viral Study Group and by Boppana et al. suggest that the level of viremia at or near birth in congenitally infected infants may predict hearing loss, in both symptomatic and asymptomatic infections.^{88,89} As this relationship is understood further by future study, it may help identify those patients in whom closer follow-up is warranted and those in whom the benefits of antiviral therapy are most likely to outweigh the risks.

Perinatal infection

Naturally acquired perinatal CMV infections result from exposure to infected maternal genital secretions at birth or to breast milk during the first months of postnatal life. The presence of CMV at these sites may result from either primary or non-primary maternal infection. Iatrogenic CMV infections are acquired predominantly from transfusions of blood or blood products and breast milk from CMV-infected donors. Exposure to CMV in the maternal genital tract has resulted in a 30–50% rate of perinatal infection. During delivery the infant is exposed to genital secretions that may contain high titers of CMV. The transmission from mother to infant via breast milk occurs in 30–70% if nursing lasts for over 1 month. Following ingestion, CMV infection is presumably established at a mucosal surface (buccal, pharyngeal, or esophageal mucosa) or in the salivary glands for which CMV has a special tropism.

Transmission of CMV by blood transfusion is more likely to occur when larger quantities of blood are transfused. The failure to isolate CMV from the blood or blood elements of seropositive healthy blood donors suggests that the virus exists in a latent state, presumably within leukocytes. Presumably, following transfusion, when infected cells encounter the allogeneic stimulus, CMV becomes reactivated.

CLINICAL MANIFESTATIONS

■ CONGENITAL INFECTION

Symptomatic infection

Acute Manifestations. CID is characterized by involvement of multiple organs, in particular, the reticuloendothelial and central nervous systems (CNS), with or without ocular and auditory damage. Weller and Hanshaw defined the abnormalities found most frequently in infants with symptomatic congenital infection as hepatomegaly, splenomegaly, microcephaly, jaundice, and petechiae.⁹⁰ As illustrated in [Table 84-1](#), a combination of petechiae, hepatosplenomegaly, and

jaundice is the most frequently noted presentation. In addition, the magnitude of the prenatal insult is reflected in the occurrence of microcephaly with or without cerebral calcifications, intrauterine growth retardation, and prematurity.⁹¹ Inguinal hernia in males and chorioretinitis with or without optic atrophy are less common. Occasionally clinical findings include hydrocephalus, hemolytic anemia, and pneumonitis. Among the most severely affected infants, mortality may be as high as 30%. Most deaths occur in the neonatal period. Neonatal mortality is usually secondary to multiorgan disease with severe hepatic dysfunction, disseminated intravascular coagulation, and secondary bacterial infections. When death occurs after the first month but during the first year, it is usually due to progressive

Table 84-1. Clinical and Laboratory Findings in 106 Infants with Symptomatic Congenital CMV Infection in the Newborn Period

Abnormality	Positive/Total Examined (%)
Prematurity (< 38 wk)	36/106 (34)
Small for gestational use	53/106 (50)
Petechiae	80/106 (76)
Jaundice	69/103 (67)
Hepatosplenomegaly	63/105 (60)
Purpura	14/105 (13)
Neurologic findings One or more of the following:	72/106 (68)
Microcephaly	54/102 (53)
Lethargy/hypotonia	28/104 (27)
Poor suck	20/103 (19)
Seizures	7/105 (7)
Elevated alanine aminotransferase (> 80 U/L)	46/58 (83)
Thrombocytopenia	
< 100 × 10 ³ /mm ³	62/81 (77)
< 50 × 10 ³ /mm ³	43/81 (53)
Conjugated hyperbilirubinemia	
Direct serum bilirubin > 4 mg/dL	47/68 (69)
Hemolysis	37/72 (51)
Increased cerebrospinal fluid protein (> 120 mg/dL) ^a	24/52 (46)

From Boppana S. et al. Symptomatic congenital cytomegalovirus infection: Neonatal morbidity and mortality. *Pediatr Infect Dis J* 1992; 11: 93–9, with permission.

^aDeterminations in the first week of life.

liver disease with severe failure to thrive. Death after the first year is usually restricted to the severely neurologically handicapped children and is the consequence of malnutrition, aspiration pneumonia, and overwhelming infections.

Hepatomegaly. This sign, along with that of splenomegaly, is probably the most common abnormality found in the newborn period in infants born with symptomatic congenital CMV infection. Liver function tests are often abnormal but usually not markedly so. The persistence of hepatomegaly is variable. In some infants, liver enlargement disappears by the age of 2 months. In others, significant enlargement persists throughout the first year of life. However, massive hepatomegaly extending beyond the first 12 months of life is uncharacteristic of CID.

Splenomegaly. Enlargement of the spleen is especially frequent in congenital CMV infections and may be the only abnormality present at birth. In some instances, splenomegaly and a petechial rash coexist as the only manifestations of the disease. Occasionally, the enlargement is such that the spleen may be felt 10–15 cm below the costal margin. Splenomegaly usually persists longer than hepatomegaly.

Jaundice. Jaundice is a common manifestation of CID. The pattern of hyperbilirubinemia may take several forms, ranging from high levels on the first day to undetectable jaundice on the first day with gradual elevation of the bilirubin level to clinically apparent jaundice. In some instances, jaundice is a transient phenomenon, beginning on the first day and disappearing by the end of the first week. More often, however, it tends to persist beyond the time of physiologic jaundice. Occasionally, transient jaundice may occur in early infancy with pronounced elevation of bilirubin levels during the third month. Bilirubin levels are high in both the direct and indirect components. Characteristically, the direct component increases after the first few days of life and may constitute as much as 50% of the total bilirubin level. Rarely, the indirect bilirubin rises high enough to require exchange transfusion.

Petechiae and Purpura. There is evidence that CMV has a direct effect on the megakaryocytes of the bone marrow that results in a depression of the platelets and a localized or generalized petechial rash. In some patients, the rash is purpuric in character, not unlike that observed in the expanded rubella syndrome. Unlike the latter infection, however, pinpoint petechiae are a more common manifestation of congenital CMV infection. The rash usually appears within a few hours of birth; it may be transient, disappearing within 48 hours. The petechiae may be the only clinical manifestation of CMV infection. More often, however, enlargement of the liver and spleen is coassociated. The petechiae may persist for weeks after birth. Crying,

coughing, the application of a tourniquet, a lumbar puncture, or restraints of any kind may result in the appearance of petechiae even months after birth. Platelet counts in the first week of life range from <10,000 to 125,000, with a majority in the 20,000–60,000 range. Some infants with petechial rashes do not have associated thrombocytopenia.

Microcephaly. Microcephaly, usually defined as a head circumference of less than the fifth percentile occurs in approximately 50% of patients with symptomatic congenital infection. Not all infants remain microcephalic. This is especially true if the head measurement is close to the fifth percentile in an infant of low birth weight. If intracranial calcifications are present, brain growth is invariably impaired.

Ocular Defects. The principal abnormality related to the eye in CMV infection is chorioretinitis, with strabismus and optic atrophy being uncommon. Microphthalmia, cataracts, retinal necrosis and calcification, blindness, anterior chamber and optic disk malformations, and pupillary membrane vestige have also been described in association with generalized congenital CID. Chorioretinitis occurs in approximately 14% of infants born with symptomatic congenital infection. CMV chorioretinitis cannot be differentiated from the lesions produced by toxoplasmosis on the basis of location or appearance. Both *Toxoplasma gondii* and CMV can induce central retinal lesions. Chorioretinitis caused by CMV differs from that caused by toxoplasmosis in that it rarely progresses postnatally, becoming inactive in early infancy.

Pneumonitis. Pneumonitis, a common clinical manifestation of CMV infection following bone marrow and renal transplantation in adults, is not usually a part of the clinical presentation of congenital CMV infection in newborn infants. Diffuse interstitial pneumonitis occurs in <1% of congenitally infected infants, even when the most severely affected cases are considered. CMV-associated pneumonitis is more likely to develop in infants with perinatally acquired CMV infections.

Deafness. Sensorineural deafness is the most common handicap caused by congenital CMV infection. Medearis first directed attention to the presence of deafness in symptomatic congenitally infected infants.⁹² Subsequent reports confirmed this association and provided evidence that CMV can also cause sensorineural hearing loss in children with subclinical infection.⁹³

Because hearing is not commonly assessed within the first month of life, it is difficult to say how many congenitally infected infants, whether symptomatic or not, are born with hearing impairments. This handicap, however, becomes significant in infancy and early childhood. In general, the frequency and severity of the hearing impairment is worse in patients with symptomatic infection.⁹¹ Of

104 surviving patients with symptomatic CMV infection we have prospectively followed over the past 20 years, 100 have had adequate audiometric evaluations and 58 of them (58%) suffer from some degree of hearing impairment.⁹¹ Among the 330 patients with subclinical infection, 299 have received at least one adequate audiometric evaluation and 22 (7.4%) manifest some degree of hearing loss. The sensorineural hearing loss is bilateral in over half the cases and of significant magnitude (50–100 dB) to produce serious difficulties with verbal communication and learning.

Long-Term Outcome. The long-term clinical manifestations of symptomatic congenital CMV infection are highly variable. It is clear that the infection is usually not recognized in infants, especially when it is marked by minor signs such as failure to thrive, mild splenomegaly, and neonatal jaundice. In some cases, psychomotor retardation, neurologic dysfunction, hearing loss, and other delayed complications may take years to identify. The medical significance of congenital CMV derives primarily from the adverse effects that this infection has on the developmental potential of children. The likelihood of survival with normal intellect and hearing following symptomatic congenital CMV infection is small. The most common long-term complications are hearing loss, mental retardation, microcephaly, chorioretinitis, optic atrophy, seizures, paraparesis, diplegia, language delay, and learning disabilities (Table 84-2).⁹⁴

Asymptomatic infection. As indicated in the previous section, nearly 90% of infants with congenital CMV infections have no early clinical manifestations and their long-term outcome is much better. Nevertheless, anywhere from 5% to perhaps as many as 15% are at risk for developing a multitude of developmental abnormalities, such as sensorineural hearing loss, microcephaly, motor defects such as spastic diplegia or quadriplegia, mental retardation, chorioretinitis, and dental defects. These abnormalities usually become apparent within the first 2 years of life. Table 84-2 summarizes our prospective longitudinal study of 330 patients with asymptomatic congenital infection and followed by using serial clinical, psychometric, audiometric, and visual assessments.⁹⁵ Follow-up studies of patients with inapparent congenital CMV infection have also been done by Kumar et al., Saigal et al., Melish and Hanshaw, and Pearl et al.^{96–99} In general their findings resemble the data in Table 84-2.

In summary, these observations underscore the need for longitudinal follow-up of patients with congenital CMV infection regardless of its clinical presentation at the outset. Careful assessments of perceptual functions (hearing, visual acuity), psychomotor development, and learning abilities must be made in order to recognize the full impact of CMV. With early identification of a problem, corrective measures can be instituted to reduce psychosocial and learning problems.

Table 84-2. Sequelae in Children After Congenital CMV Infection

Sequelae	Percent Symptomatic (No.)	Percent Asymptomatic (No.)
Sensorineural hearing loss	58.0 (58/100)	7.4 (22/299)
Bilateral hearing loss	37.0 (37/100)	2.7 (8/299)
Speech threshold moderate to profound (60–90 dB) ^a	27.0 (27/100)	1.7 (5/299)
Chorioretinitis	20.4 (19/93)	2.5 (7/281)
IQ < 70	55.0 (33/60)	3.7 (6/159)
Microcephaly, seizures, or paralysis	51.9 (54/104)	2.7 (9/330)
Microcephaly	37.5 (39/104)	1.8 (6/330)
Seizures	23.1 (24/104)	0.9 (3/330)
Paresis/paralysis	12.5 (13/104)	0.0 (0/330)
Death ^b	5.8 (6/104)	0.3 (1/330)

Adapted from Pass RR, Fowler KB and Boppana S. Progress in cytomegalovirus research. In: Landini MP (ed), *Proceedings of the Third International Cytomegalovirus Workshop*, Bologna, Italy, June 1991. London, Excerta Medica, 1991, pp. 3–10.

^aFor the ear with better hearing.

^bAfter newborn period.

Perinatal infection

In order to establish the diagnosis of perinatal CMV infection, one must first exclude congenital infection by showing absence of viral excretion during the first 2 weeks of life. The incubation period of perinatal CMV infection ranges between 4 and 12 weeks. Although the quantity of virus excreted by infants with perinatal infection is less than with intrauterine acquisition, the infection is also of a chronic nature, with viral excretion persisting for years. The vast majority of otherwise healthy infants with naturally acquired perinatal infections remain asymptomatic and the infection does not appear to have an adverse effect on growth, perceptual functions, or motor or psychosocial development.

CMV has been incriminated as a cause of pneumonitis in infants younger than 4 months.^{92,100,101} CMV-associated pneumonitis is clinically and radiographically indistinguishable from other causes of afebrile pneumonia in this age group.

In premature and sick term infants, naturally acquired CMV infection may pose a greater risk. Yeager et al. found that premature infants weighing less than 1500 g at birth who acquired CMV from a maternal source often developed hepatosplenomegaly, neutropenia, lymphocytosis, and thrombocytopenia coinciding with the onset of virus excretion.¹⁰² Frequently, these patients required longer treatment with oxygen. In a later prospective study, Paryani et al. suggested that there may be a propensity for an increased incidence of neuromuscular impairments, particularly in premature infants with onset of CMV excretion during the first 2 months of life.¹⁰³ However, sensorineural hearing loss, chorioretinitis, and microcephaly occurred with similar frequency in both groups.

Transfusion-acquired perinatal CMV infection can cause significant morbidity and mortality, particularly in premature infants with a birth weight of less than 1500 g born to CMV seronegative mothers.^{59–63} The syndrome of posttransfusion CMV infection in premature newborn infants has been characterized by Ballard and coworkers and consists of deterioration of respiratory function, hepatosplenomegaly, unusual gray pallor with disturbing septic appearance, both an atypical and absolute lymphocytosis, thrombocytopenia, and hemolytic anemia.¹⁰⁴ The syndrome was more severe in low-birth-weight infants and occurred approximately 4–12 weeks posttransfusion, at a time when the infants were progressing satisfactorily. Although the course of the disease was generally self-limited (lasting 2–3 weeks), death occurred in 20% of the sick infants. Subsequent work by Yeager and Adler has confirmed these observations.^{49,62} Yeager demonstrated that the risk of infection is related to the serologic status of the donor and that these infections could be prevented by transfusing seronegative newborns with blood from seronegative donors.

TREATMENT AND PREVENTION

Antiviral therapy

Recently, Kimberlin and the National Institutes of Health Collaborative Antiviral Study Group (CASG) reported the results of a Phase III study evaluating the use of ganciclovir at 6 mg/kg per dose every 12 hours for 6 weeks versus no treatment in infants with symptomatic congenital CMV infection.¹⁰⁵ Primary endpoints included maintenance of normal hearing or improvement of hearing as measured by brainstem evoked response testing between the baseline and 6-month follow-up visit. Forty-two subjects were fully evaluable for the primary endpoint, 25 of whom received the study drug and 17 of whom received no treatment. The investigators reported analysis of hearing data in both a functional “best ear” approach, where patient’s hearing was judged based on the hearing in the best ear, as well as a more biological analysis, or “total ear” approach, where hearing data from each ear was included in the analysis. By best ear analysis, 84% of ganciclovir recipients had improvement of hearing or maintained normal hearing between the baseline and 6-month follow-up visit versus 59% of the no-treatment group ($P = 0.086$). By total ear analysis, 69% of ganciclovir recipients had improvement of hearing or maintained normal hearing between the baseline and 6-month follow-up visit versus 39% of the no-treatment group ($P = 0.011$).

The primary toxicity observed in the study was neutropenia, observed 63% of the time in patients receiving study drug versus 21% of patients in the control group. Half of the ganciclovir-receiving patients who developed neutropenia required dosage adjustment, and only 4 required discontinuation of the study drug.

Despite the results of this study, it is difficult to recommend a global approach to antiviral treatment with ganciclovir in congenital CMV infection. The study subjects all had symptomatic disease with CNS manifestations, which may or may not be the group most likely to benefit from antiviral therapy. The data suggest that antiviral therapy affords some benefit in hearing protection, but the requirement for 6 weeks of intravenous access and the administration of a potentially toxic drug make the issue problematic. Consultation with a pediatric infectious diseases specialist familiar with the issues is recommended prior to initiating treatment with ganciclovir in the setting of symptomatic congenital CMV.

Additional studies are ongoing by the CASG to evaluate the use of valganciclovir (the valine-ester prodrug of ganciclovir), which can be administered orally, in patients with symptomatic congenital CMV. Factors that confound the evaluation of clinical efficacy of antiviral therapy include the wide spectrum of disease resulting from symptomatic congenital CMV infection, the unpredictable natural course of

the disease, and the fact that many patients incur irreversible damage before birth.

Vaccines

In 1999, the Institute of Medicine assigned the highest priority to the development of a vaccine effective against CMV. A number of candidate vaccines have been evaluated clinically are currently undergoing testing or are in the preclinical phase. Several live attenuated vaccines have undergone clinical testing, the AD169 vaccine (no longer in clinical trials), the Towne vaccine, and a series of four vaccines based on Towne strain and Toledo strain chimeras.^{106–111}

The only candidate to undergo efficacy trials in humans has been the Towne vaccine. Immunization of susceptible kidney transplant recipients with Towne strain CMV vaccine significantly reduced the morbidity of primary CMV infection, although it did not prevent acquisition of infection. No evidence of reactivation of vaccine virus was found when the patients were immunosuppressed.¹¹² Healthy CMV-negative adult males who were vaccinated with Towne strain vaccine were protected against low-dose challenge with Toledo strain CMV (a nonattenuated, wild-type clinical isolate), but not against high-dose challenge.¹¹⁰ In healthy CMV-seronegative women with children in day care (where women are at high risk of exposure via their children) Towne vaccination failed to protect women from CMV infection.¹¹³

Despite the evidence that the Towne vaccine is safe and immunogenic, and may provide some protection against CMV disease in some situations, it does not appear to provide sufficient protection. One explanation is that it may be overattenuated. Four genetic recombinant viruses have been constructed as chimeras of the Towne and Toledo strains and appear to be well-tolerated, but have not been tested in seronegative individuals.^{111,114}

An important objective for the development of a CMV vaccine is to prevent the serious consequences of congenital infection. A candidate vaccine should be able to prevent primary infection in pregnant women without inducing latent infection. Although the AD169 and the Towne strain vaccines have not been shown to reactivate, the possibility that reactivations might occur during pregnancy with transmission to the fetus raises concern about the use of live, attenuated viruses, even in vaccine trials.

A more attractive approach is to use a subunit vaccine that contains surface glycoproteins or other structural or regulatory proteins. The best-studied candidate is glycoprotein gB, the most abundant protein complex of the viral envelope, which is exposed on the surface of infected cells and contains the majority of viral neutralizing epitopes. Immunogenicity and safety of gB when administered with a novel adjuvant (MF59) appears promising, when administered to seronegative adults or to toddlers.^{115,116} A Phase III efficacy study

evaluating a gB/MF59 vaccine in young, CMV-negative, postpartum women is ongoing.^{117,118} The results of this trial may help identify the potential for vaccination to be effective in preventing congenital CMV infection.

Other vaccine constructs in early clinical or preclinical evaluation include other purified subunit vaccines, vectored subunit vaccines (primarily a canarypox vector known as ALVAC and an attenuated alphavirus vector based on the Venezuelan equine encephalitis virus), DNA vaccines, peptide vaccines, and dense-body (enveloped, replication-defective particles formed during CMV replication in cell culture) vaccines.¹¹⁴

Prevention of congenital infection

CMV is not very contagious and its horizontal transmission requires close direct contact with infected material, namely, secretions that contain the virus and, less likely, fomites. With the exception of a few small studies that were designed to prevent infection via blood and blood products and transplanted organs, no broad-based strategies for preventing the transmission of this virus have been tested. Although there are still no effective means of preventing congenital CMV infection, or most perinatally acquired CMV infections, a few common sense recommendations can be made.

An average of 2% of susceptible pregnant women acquire CMV infection during pregnancy in the United States; the majority have no symptoms and only 40% of the episodes result in fetal infection. With no proven effective antiviral therapy and a low risk of fetal morbidity, serologic screening of pregnant women searching for primary CMV infections during pregnancy is of limited value. Nigro et al. recently reported the results of a trial of hyperimmune globulin in 68 pregnant women with either known CMV DNA in their amniotic fluid or known recent primary CMV infection which suggests the possibility that hyperimmune globulin may be efficacious in the treatment and prevention of congenital CMV infection in this setting.¹¹⁹ The nature of this study and the way it was conducted make it difficult to generalize. We do not advocate the use of hyperimmune globulin at this time. Additional studies will be needed to validate the results of the Nigro study.

Primary CMV infection should be suspected in pregnant women with symptoms compatible with a heterophil-negative mononucleosis-like syndrome. At present the sensitivity of intrauterine diagnosis before the twenty-second week of gestation is only 50%.^{120–124} Thus, there is inadequate information to serve as a basis for recommendations regarding termination of pregnancy after a primary CMV infection. Similarly, there is no information regarding how long conception should be delayed after primary infection.

The data on which to base recommendations for prevention of congenital CMV infection after non-primary maternal

infection are even more inadequate.^{74,125–128} At present, there are no techniques for identifying women with reactivation of CMV that result in intrauterine transmission. Since the risk of transmission is very low and the risk of fetal disease even lower, women known to be seropositive before conception do not need to be virologically or serologically tested, nor do they need to be unduly worried about the very low risk of transmitting the virus to the fetus.

The principal sources of CMV infection among women of childbearing age are exposure to children excreting CMV and sexual contacts. Sexual transmission of CMV can probably be prevented by barrier methods (condoms, spermicides) that reduce the transmission of more common sexually transmitted infections, although no data have been published to specifically assess the effectiveness of such methods for CMV. Concerning the risk from exposure to children, those at greatest risk are susceptible pregnant mothers of CMV-infected children who attend day care centers. Hand washing and simple hygienic measures that are routine for hospital care can be recommended, but it is unrealistic to expect many mothers to comply.

Although hospital workers do not appear to be at increased risk for CMV infection, personnel who work in day care centers certainly are. In hospitals, vigorous adherence to routine infection control procedures such as hand washing and gloving should make nonparenteral acquisition of CMV less likely than in the community. Since the majority of patients who shed CMV are asymptomatic and unrecognized, universal precautions should be emphasized to prevent transmission from unrecognized infected patients as well as from known CMV-excreting patients. In the day care setting, where hygiene is difficult at best, preventive measures may be more difficult to implement. Although there is still debate about the need for routine screening of female hospital personnel and day care workers, we believe it should be recommended for potentially childbearing women whose occupation exposes them to CMV. Those found seropositive can be strongly reassured. Those found to be serosusceptible should be provided with information and reassured that common sense measures, such as hand washing and avoiding contact with secretions, should reduce the risk of acquisition of CMV. Attempts to identify all CMV-excreting patients or children in the workplace so that seronegative workers can avoid contact with them is totally unreasonable.

NEONATAL HSV INFECTIONS

■ HISTORY

Infections caused by HSVs have been recognized since the era of the ancient Greeks. Greek scholars defined the word *herpes* to mean to creep or crawl in reference to the visualized skin

lesions. The Greek historian Herodotus associated mouth ulcers and lip vesicles with fever and called this event *herpes febriles*.¹²⁹ Genital herpetic infections were first described by a physician to the eighteenth century French court, Astruc.¹³⁰ Over the ensuing two centuries, the infectious nature of HSV was delineated. The transmissibility of these viruses was unequivocally established by passage of virus from lip and genital lesions of humans to either the cornea or the scarified skin of the rabbit.¹³¹

Only 50 years ago, the first written descriptions of neonatal HSV infections were attributed nearly simultaneously to Hass, when he described the histopathologic findings of a fatal case, and to Batignani, who described a newborn child with HSV keratitis.^{132,133} Subsequently, histopathologic descriptions of the disease demonstrated a broad spectrum of involvement in newborns.

In the mid-1960s, Nahmias and Dowdle demonstrated two antigenic types of HSV.¹³⁴ The differentiation of HSV into two types resulted in the development of viral typing methods, which were critical in clarifying the epidemiology of these infections. HSV infections “above the belt,” primarily of the lip and oropharynx, were found in most cases to be caused by HSV-1. Those infections “below the belt,” particularly genital infections, were usually caused by HSV-2. However, this distinction more recently has become less clear. With the finding that both genital herpes infections and neonatal HSV infections were most often caused by HSV-2, a natural cause-and-effect relationship developed between these two disease entities. This causal relationship was strengthened by the finding of viral excretion in the maternal genital tract at the time of delivery, suggesting that acquisition of the virus by the infant occurs by contact with infected genital secretions during birth.

Over the past 20 years, our knowledge of the epidemiology, natural history, and pathogenesis of neonatal HSV infections has expanded greatly (see Chapter 24). The development of antiviral therapy represents a significant advance in the management of infected children, providing the opportunity to decrease mortality and improve the morbidity associated with these infections. Of all the herpesvirus infections, neonatal HSV infection represents the one that should be most amenable to prevention and treatment because it is acquired most often at birth rather than early in gestation. As our knowledge of the epidemiology of HSV infections has increased, it has become apparent that there are modes of infection other than contact with infected maternal genital secretions during delivery. Postnatal acquisition of HSV-1 has been documented from nonmaternal sources. The changing presentation of neonatal HSV infection, particularly the increasing difficulty of diagnosing infection, and the success of antiviral therapy, will be stressed.

■ EPIDEMIOLOGY OF NEONATAL HSV INFECTION

Nature of infection

Transmission of HSV most often occurs in association with intimate, personal contact.¹³⁵ Virus must come in contact with mucosal surfaces or the abraded skin of a susceptible individual for infection to be initiated. After viral replication at the site of infection, either an intact virion or the nucleocapsid is transported by neurons to the ganglia where latency is established. Infection with HSV-1, generally limited to the oropharynx, can be transmitted by respiratory droplets or through direct contact of a susceptible individual with infected secretions (such as virus-containing labial vesicular fluid). Acquisition often occurs during childhood.

Primary HSV-1 infection in the young child is usually asymptomatic. If present, clinical illness is manifested by gingivostomatitis. Primary infection in young adults has been associated with pharyngitis and with a mononucleosis-like syndrome. Like other herpesvirus infections, seroprevalence studies have demonstrated that acquisition of HSV-1 infection is related to socioeconomic factors. Antibodies, indicative of past infection, are found early in life among individuals of lower socioeconomic groups and are presumed to be the consequence of crowded living conditions that provide a greater opportunity for direct contact with infected individuals.

As many as 75–90% of individuals from lower socioeconomic populations develop antibodies by the end of the first decade of life. In comparison, in middle and upper socioeconomic groups only 30–40% are seropositive by the middle of the second decade of life.^{136–139} A declining seroprevalence of HSV-1 may account, in part, for the increased clinical awareness of HSV-2 infections, since HSV-1 antibodies may be partially protective against type 2 infection.^{140,141}

Because infections with HSV type 2 are usually acquired through sexual contact, antibodies to this virus are rarely found until adolescence. Thereafter, progressive increase in seroprevalence of HSV type 2 develops in all populations.¹⁴² The risk of acquisition of infection with HSV-2 appears related to both socioeconomic factors and the number of sexual partners. Utilizing nonspecific serologic assays, as many as 50–60% of lower socioeconomic populations have antibodies to HSV-2. In contrast, 10–20% of individuals in higher socioeconomic groups are seropositive.^{143,144} Utilizing a type-specific assay for HSV-2 (glycoprotein (g) G-2), antibodies were detected in 35% of middle-class women receiving care through an Atlanta health maintenance organization.¹⁴⁵ Similarly, there are differences in seroprevalence between blacks and Caucasians of childbearing age, 65% versus 35% overall, respectively.¹⁴⁶

Maternal infection

The epidemiology and clinical nature of genital HSV infection do not appear to be greatly influenced by pregnancy. Infection during gestation can manifest in a variety of ways. The most serious but fortunately uncommon problem encountered with HSV infections during pregnancy is that of widely disseminated disease. Infection has been documented to involve multiple visceral sites, in addition to cutaneous dissemination.^{147–152} In a limited number of cases, dissemination after primary oropharyngeal or genital infection has led to such severe manifestations of disease as necrotizing hepatitis with or without thrombocytopenia, leukopenia, disseminated intravascular coagulopathy, and encephalitis. Although only a small number of patients have suffered from disseminated infection, the mortality among these pregnant women is reported to be greater than 50%. Fetal deaths have also occurred in more than 50% of cases, although mortality did not necessarily correlate with the death of the mother. Surviving fetuses were delivered by cesarean section either during the acute illness or at term and none had evidence of neonatal HSV infection.

Localized genital infection is the most common form of HSV infection during pregnancy. Overall, prospective investigations utilizing cytologic and virologic screening indicate that genital herpes occurs with a frequency of about 1% at any time during gestation.¹⁵³ Most of these infections are recurrent, although a few are primary. Those factors that influence the frequency of both primary and recurrent infection in pregnancy are not well defined.

Maternal primary infection prior to 20 weeks' gestation has been associated with spontaneous abortion.^{154,155} Although the original estimate of spontaneous abortion following a symptomatic primary infection during gestation was thought to be as high as 25%, it is likely that this calculation is erroneously high because of the very small number of women followed. Unfortunately, precise data, indicating the true risk of spontaneous abortion following primary infection during gestation, are not available. Infection that develops later in gestation was not associated with the termination of pregnancy.^{155–157} The frequency of HSV recurrences during gestation should be of concern for women with a known history of infection. Transmission of infection to the fetus is most frequently related to the actual shedding of virus at the time of delivery. Since HSV infection of the fetus is usually the consequence of contact with infected maternal genital secretions at the time of delivery, the determination of viral excretion at this time is of utmost importance. The actual incidence of viral excretion at delivery ranges from 0.39% to 1.0%.^{135,153,158–162} Utilizing polymerase chain reaction (PCR) detection of viral DNA, the prevalence of viral shedding is even higher—as much as four- to fivefold.¹⁶³ Several

prospective studies have evaluated the frequency and nature of viral shedding in pregnant women with a known history of genital herpes. In a predominantly white, middle-class population, documented recurrent infection occurred in 84% of pregnant women.¹⁶² Moreover, asymptomatic viral shedding occurred in at least 12% of the recurrent episodes. Viral shedding from the cervix occurred in 0.56% of symptomatic and 0.66% of asymptomatic infections, data similar to the nonpregnant state.^{158,160} The incidence of cervical shedding in asymptomatic pregnant women has been reported to be as high as 3%.¹⁵⁷ However, the observed rate of shedding among asymptomatic pregnant women has varied more than that among nonpregnant women (0.2–7.4%), depending on the study population and trial design.^{157,158,160,164–167} Overall, these data indicate that the frequency of cervical shedding is low, rendering the risk of transmission of virus to the infant similarly low when the infection is recurrent in nature.¹⁵³ The frequency of shedding does not appear to vary by trimester during gestation.^{157,168} Overall, no increased incidence of premature onset of labor is apparent in these prospective studies. Regardless, given the high seroprevalence of infection, a significant degree of protection for the fetus must exist or else the incidence of neonatal disease should be significantly higher. Importantly, most infants who develop neonatal disease are born to women who are completely asymptomatic at the time of delivery and have neither a past history of genital herpes nor a sexual partner reporting a genital vesicular rash.^{153,167–169} These women account for 60–80% of all women whose infected children develop infection.

Only 27% of women delivering children who developed neonatal HSV infection have had either a history of or evidence of recurrent lesions indicative of HSV infection during the current pregnancy.¹⁶⁹ Furthermore, only half of these women reported genital HSV infection in their sexual partners. The majority of women were without signs or symptoms of genital herpetic infection.

Factors that influence transmission of infection to the fetus

The type of maternal genital infection at the time of delivery influences the incidence of neonatal herpes.^{159,170} The duration and quantity of viral excretion and the time to total healing vary with primary, initial (first episode at the nonprimary site), and recurrent (HSV-1 and -2) maternal genital infection (see Chapter 21).^{171,172} Primary infection is associated with larger quantities of virus replicating in the genital tract (>10⁶ viral particles/0.2 mL of inoculum) and a period of viral excretion which may persist for an average of 3 weeks. In contrast, virus is shed for an average of only 2–5 days and at lower concentrations (approximately 10²–10³/0.2 mL of inoculum) in women with recurrent genital infection. The difference in the natural history of primary and recurrent disease is likely a major factor that influences the frequency of

transmission and, perhaps, the severity of neonatal disease. In 2003, Brown and colleagues reported the results of their study of over 58,000 pregnancies in the Seattle, Washington, area over 17 years, in which they performed cultures for HSV within 48 hours of delivery on nearly 40,000 women without evidence of genital HSV.¹⁷⁰ Of these, 202 women were asymptotically shedding HSV and 121 of them had HSV serology available, allowing their infection to be classified as first episode primary, first episode nonprimary, or recurrent HSV infection. Fifty-seven percent of babies delivered to mothers with first episode primary infection developed neonatal HSV disease. In comparison, 25% of babies delivered to mothers with first episode nonprimary infection and 2% of babies delivered to mothers with recurrent HSV infection developed neonatal HSV disease.¹⁷⁰

Paralleling the type of maternal infection, the mother's antibody status to HSV at delivery appears to be an additional factor that also influences the severity of infection as well as the likelihood of transmission. Transplacental maternal neutralizing antibodies appear to have a protective, or at least an ameliorative, effect on acquisition of infection for babies inadvertently exposed to virus.^{161,170,173,174} Maternal primary infection late in gestation may not result in significant passage of maternal antibodies across the placenta to the fetus. The distinction between symptomatic and asymptomatic disease whether primary, initial, or recurrent remains poorly defined at present in relation to the risks of transmission of infection to the infant.

The duration of ruptured membranes is also a risk factor for acquisition of neonatal infection. Observations by Nahmias and colleagues indicate that prolonged rupture of membranes (>6 hours) increases the risk of acquisition of virus, probably the consequence of ascending infection from the cervix.^{153,155}

On the basis of this observation, it has been recommended for more than three decades that women with active genital lesions be delivered by cesarean section. In the 2003 Seattle study, cesarean delivery was finally proven to reduce transmission of HSV to the neonate.¹⁷⁰ Of 202 deliveries where HSV was isolated, neonatal HSV occurred in 1 infant of 85 delivered by cesarean section (1.2%) versus 9 infants with neonatal HSV of 117 delivered vaginally (7.7%). Importantly, however, neonatal infection still occurs in cases managed according to these recommendations.^{169,170,175}

Fetal scalp monitors are a site of inoculation of virus and may increase the risk of neonatal HSV infection.^{176,177} Such devices are contraindicated in women with a history of recurrent genital HSV infections.

Incidence of newborn infection

The estimated incidence of neonatal HSV infection is approximately 1 in 2000 to 1 in 5000 deliveries per year.^{153,170} Neonatal HSV infection occurs far less frequently than

genital HSV infections in the adult childbearing population. Several countries do not appear to recognize a significant number of cases of neonatal HSV infection in spite of the high prevalence of antibodies to HSV-2. Serologic studies in central Africa indicate that women have a high frequency of antibodies to HSV-2, but the first case of neonatal herpes was reported only relatively recently.^{178,179} The United Kingdom presents a similar dilemma. Genital herpetic infection is relatively common in the United Kingdom, but very few cases of neonatal HSV infection are recognized in that country. This may reflect a low number of primary HSV infections in pregnant women. Overall, the United States has approximately 4 million deliveries a year and an estimated 1500 cases of neonatal infection, though the local incidence within the United States varies considerably.^{180,181}

Time of transmission of infection

HSV infection of the newborn can be acquired at one of three times: in utero, intrapartum, or postnatally. The mother is the source of infection for the first two routes of transmission. For postnatal acquisition of HSV infection, the mother may be the source of infection from a genital or nongenital site, or other environmental or patient sources of virus can lead to infection of the child. Nevertheless, a maternal source should be suspected when herpetic lesions are discovered promptly after the birth or when the baby's illness is caused by HSV-2. Although intrapartum transmission accounts for 80–90% of cases, the other two routes must be recognized and identified in a child with suspect disease for both public health and prognostic purposes.

Although it was originally presumed that intrauterine infection resulted in either a totally normal baby or premature termination of gestation, intrauterine acquisition of infection can lead to the clinical evidence of congenital infection.^{155,158,182–184} Utilizing stringent diagnostic criteria (namely, identification of infected babies within the first 48 hours of life who have virologic confirmation of infection) and excluding other pathogens with similar clinical findings such as congenital CMV infection, rubella, syphilis, or toxoplasmosis, over 100 babies have been identified in the world's literature to date with symptomatic congenital disease.¹⁸² The manifestations of disease in this group of children range from significant neurologic abnormalities to simply the presence of skin vesicles at the time of delivery.

Intrauterine infection can occur as a consequence of either transplacental or ascending infection. Examination of the placenta in cases of neonatal herpes thought to be the consequence of in utero transmission has helped to clarify the route of transmission. A placenta showing evidence of necrosis and inclusions in the trophoblasts suggests a transplacental route of infection and can result in a baby with hydranencephaly at birth or may be associated with spontaneous abortion following intrauterine herpes simplex

viremia.^{185–187} Virus has been isolated from the products of conception in such circumstances.¹⁸⁶ Histopathologic evidence of chorioamnionitis, suggestive of ascending infection, has been identified as an alternative route for in utero infection as compared with transplacental spread.

Risk factors associated with intrauterine transmission are not known. However, both primary and recurrent maternal infection can result in infection of the fetus in utero. Although it might be convenient to assume that only primary maternal infection is associated with transmission of virus in utero, it has been documented that women with recurrent genital infection can transmit HSV to the fetus as well, leading to disease.

The second, and most common, route of infection is that of intrapartum contact of the fetus with infected maternal genital secretions. Approximately 80–90% of infected babies acquire HSV infection by this route. Those factors that favor intrapartum transmission of infection have been described in the preceding text.

The third route of transmission is postnatal acquisition. Even though HSV-1 has increasingly been associated with genital lesions, postnatal transmission of HSV has been suggested because 15–20% of neonatal HSV infections are caused by this virus type.¹⁵³

In fact, more recent data from the National Institutes of Allergy and Infectious Diseases (NIAID), Collaborative Antiviral Study Group, indicate that the proportion of babies with neonatal herpes simplex infections owing to HSV-1 has increased to nearly 30%.¹⁶⁹ This observation, in light of the recognition that genital HSV-1 infections appear to account for only approximately 5–15% of all genital HSV infections, creates greater concern for postnatal acquisition of infection. However, data recently suggest an increasing number of genital herpes cases caused by HSV-1 in the United States, as occurs in Japan.

Relatives and hospital personnel with orolabial herpes may be a reservoir of virus for transmission to the newborn. The documentation of postnatal transmission of HSV has focused attention on such sources of virus for neonatal infection.^{188–195} Postnatal transmission from mother to child has been documented. Maternal–infant postpartum transmission has been reported as a consequence of nursing on an infected breast.^{189,191,194} Furthermore, father-to-baby transmission has been documented.^{188,195}

Many individuals asymptotically excrete HSV from the oropharynx and, therefore, represent a potential source of infection for the newborn. The occurrence of fever blisters in various groups of adults has ranged from 16% to 46%.^{196,197} Population studies in two hospitals indicated that 15–34% of hospital personnel had a past history of nongenital herpetic lesions.^{198–200} In both hospitals surveyed, at least 1 in 100 individuals had a recurrent cold sore each week. No cases of neonatal HSV infection were documented

in these nurseries.^{199,201} However, the demonstration in other studies of identical viruses (utilizing restriction endonuclease analyses of viral DNA) in babies with different mothers leaves little doubt of the possibility of spread of virus in a high-risk nursery.^{190,193} The sources of virus and vectors for transmission have been inadequately studied. The potential legal implications for HSV infections acquired in a nursery are obvious. There is significant variation in the United States regarding both the concern for nosocomial transmission of infection in the hospital as well as infection control policies for its prevention.

Various individuals and committees have recommended that personnel with cold sores not work in the nursery. If such a policy were followed, the estimated medical costs would be nearly 20 million dollars annually in the United States if calculated just on the basis of estimates of lost work days.¹⁹⁸ Likely, vigorous hand washing procedures and continuing education of personnel in newborn nurseries has helped contribute to the low frequency of transmission in this environment. The existence of a herpetic whitlow in staff providing patient care should preclude direct patient contact, irrespective of nursing unit.

■ IMMUNOLOGIC RESPONSE TO HSV INFECTION

The host response to HSV in newborns must be distinguished from that of older individuals. Impairment of host defense mechanisms has been implicated as a cause of the increased severity of some infectious agents in the fetus and the newborn. Factors that must be considered in defining host response include the mode of transmission of the agent (viremia versus mucocutaneous infection), time of acquisition of infection, and the potential of increased virulence of certain strains, although this last point remains purely speculative. Two broad issues are of relevance: Protection of the fetus by transplacental antibodies and definition of host response of the newborn.

Host responses to HSV infection influence the likelihood of disease, severity of infection, and the development, maintenance, and reactivation of HSV.^{202–204} Clearly, humoral immune responses do not prevent either recurrences or exogenous reinfection. Thus, not surprisingly, transplacentally acquired antibodies from the mother are not totally protective against newborn infection. The key issue, then, is to what extent these antibodies protect and whether specific antibody classes confirm greater protection than others. Transplacentally acquired neutralizing antibodies seem to either prevent or ameliorate infection in exposed newborns.^{173,174} Nevertheless, the presence of antibodies at the time of clinical presentation with disease does not appear to influence the subsequent outcome.^{167,169,205}

Infected newborns produce IgM antibodies, as detected by immunofluorescence, specific for HSV within the first 3 weeks

of infection. These antibodies increase rapidly in titer during the first 2–3 months of life and persist for as long as 1 year. The most reactive immunodeterminants include the viral surface glycoproteins, particularly gD and gB. Humoral antibody responses have been studied using immunoblot technology.^{205,206} These studies indicate that the severity of infection correlates directly with the number of antibody bands to defined polypeptides. Children with more limited infection, namely, infection of the skin, eye, and/or mouth, have fewer antibody bands as compared with those children who have disseminated disease. The quantity of neutralizing antibodies in babies with disseminated infection is lower.²⁰⁶

Cellular immune responses have been considered important in the resolution of primary herpetic infections. Newborns with HSV infections have a delayed T-lymphocyte proliferative response compared with older individuals.²⁰⁶ Most infants studied in a recent evaluation had no detectable T-lymphocyte responses to HSV 2–4 weeks after the onset of clinical symptoms, as noted previously by other investigators.^{80,206,207} The delayed response to T-lymphocyte antigens in children who have disease localized to the skin, eye, or mouth at the onset of disease may be an important determinant of the frequency of disease progression.^{206,208}

Infected newborns have decreased production of alpha interferon in response to HSV antigen when compared to adults with primary HSV infection.²⁰⁶ The importance of alpha interferon in the maturation of host responses, particularly the elicitation of natural killer cell responses, remains to be defined. Infected babies have decreased gamma interferon production during the first month of life.^{206,209,210} Taken together, the data indicate that the newborn has a delayed cell-mediated immune response and lymphokine generation.

Antibodies plus complement and antibodies with killer lymphocytes, monocytes, macrophages, or polymorphonuclear leukocytes will lyse HSV-infected cells *in vitro*.²¹¹ Antibody-dependent cell-mediated cytotoxicity is an important component of the development of host immunity to infection.²¹² However, the total population of killer lymphocytes in the newborn is lower than that in older individuals. Thus, certain cell-mediated immune factors do appear relevant in neonatal disease. Both the type and quantity of antibodies present as well as the immaturity of monocyte and macrophages of human neonates are of greater importance than in adults.^{211,213–219} These findings are supported by animal model data.^{211,213,214}

■ NEONATAL HSV INFECTION

Pathogenesis

Following direct exposure, the newborn will either limit viral replication to the portal of entry (namely, the skin, eye, or

mouth) or viral replication will progress and cause more serious disease, including involvement of the brain (causing encephalitis) or multiple other organs. Host mechanisms responsible for control of progression of viral replication at the site of entry are unknown. For CNS disease, intraneuronal transmission of viral particles provides a privileged site that may be immune to circulating humoral and cell-mediated defense mechanisms. Thus, transplacental maternal antibodies may be of less value under such circumstances. In contrast, disseminated infection may be the consequence of viremia or secondary to extensive cell-to-cell spread as occurs with pneumonitis following aspiration of infected secretions.

Clinical presentation

The clinical presentation of babies with neonatal HSV infection is a direct reflection of the site and extent of viral replication. Neonatal HSV infection is almost invariably symptomatic and frequently lethal. Although reported cases of asymptomatic infection in the newborn exist, they are most uncommon, and long-term follow-up of these children to document absence of subtle disease or sequelae has not been carefully performed. Classification of newborns with HSV infection is mandatory for prognostic and therapeutic considerations. Babies with congenital infection should be identified within the 48–72 hours following birth. Babies who are infected in utero or postnatally can be divided into three categories: (1) disease localized to the skin, eye, or mouth; (2) encephalitis with or without skin, eye, and/or mouth involvement; and (3) disseminated infection which involves multiple organs, including CNS, lung, liver, adrenals, skin, eye, and/or mouth. Prospectively acquired data obtained through the NIAID Collaborative Antiviral Study Group will be reported here.^{220,221}

Intrauterine infection

In the most severely afflicted group of babies, intrauterine infection is apparent at birth and is characterized by a triad of findings, including skin vesicles or skin scarring, eye disease, and the far more severe manifestations of microcephaly or hydranencephaly. Often chorioretinitis alone or in combination with other eye findings, such as keratoconjunctivitis, is a component of the clinical presentation. Serial ultrasound examination of the mothers of those babies infected in utero has demonstrated the presence of hydranencephaly. Chorioretinitis alone can be a presenting sign and should alert the pediatrician to the possibility of this diagnosis, albeit HSV infection is a less common cause than other congenital infections. Severe disease can follow acquisition of infection virtually at any time in gestation. The frequency of occurrence of these manifestations has been estimated to be between 1 in 100,000 and 1 in 200,000 deliveries.¹⁸²

A small group of children will have skin or eye lesions that are present at the time of delivery. These children are frequently

born to women who have had prolonged rupture of membranes, sometimes for as long as 2 weeks prior to delivery. The babies have no other findings of invasive multiorgan involvement, including chorioretinitis, encephalitis, or evidence of other diseased organs. The prognosis for successful antiviral therapy in this group of babies is far better than in the children who are born with hydranencephaly.

Disseminated infection

Table 84-3 summarizes the disease classification of 186 babies with neonatal HSV treated with acyclovir from two studies by the NIAID Collaborative Antiviral Study Group.²²⁰ Babies with disseminated infection have the worst prognosis in terms of both mortality and morbidity. Children with disseminated infection usually present to tertiary care centers for therapy between 9 and 11 days of life. However, signs of infection are usually present on an average for 4 to 5 days earlier. Prior to antiviral therapy, this group of babies accounted for approximately one-half to two-thirds of all children with neonatal HSV infection. The principal organs involved following disseminated infection are the liver and adrenals. However, infection can involve multiple other organs including the larynx, trachea, lungs, esophagus, stomach, lower gastrointestinal tract, spleen, kidneys, pancreas, and heart. Encephalitis appears to be a common component of this form of infection, occurring in about 60–75% of children. Constitutional signs and symptoms include irritability, seizures, respiratory distress, jaundice, bleeding diatheses, shock, and frequently the characteristic vesicular exanthem that is often considered pathognomonic for infection. The vesicular rash, as described in the following, is particularly important in the diagnosis of HSV infection. However, 20–40% of children having disseminated infection never develop skin vesicles during the course of illness.^{169,220} In the absence of skin vesicles, the diagnosis becomes exceedingly difficult, since other clinical signs are often vague and nonspecific, mimicking those of neonatal sepsis. Mortality in the absence of therapy exceeds 80%; all but a few survivors are impaired. The most common cause of death in babies with disseminated disease is either HSV pneumonitis or disseminated intravascular coagulopathy.

Evaluation of the extent of disease is imperative, as with all cases of neonatal HSV infection. The clinical laboratory should be utilized to define hepatic enzyme elevation (SGOT and GGT), direct hyperbilirubinemia, neutropenia, thrombocytopenia, and bleeding diatheses among others. Cerebrospinal fluid (CSF) examination and use of noninvasive neurodiagnostic tests, as defined in the following, will help assess the extent of brain disease. In addition, chest roentgenograms, abdominal x-rays, electroencephalography, and computed tomography of the head all can be judiciously and serially employed to determine the extent of disease. The radiographic picture of HSV

Table 84-3. Clinical Characteristics of Infants Enrolled in NIAID Collaborative Antiviral Studies

Time Frame: 1989–1997	Disease Classification			
	SEM ^a (n = 10)	CNS ^b (n = 28)	Disseminated (n = 41)	Total (n = 79)
Number premature	2 (20%)	10 (36%)	17 (41%)	29 (37%)
Mean age at study enrollment (days ± SE ^c)	12.0 ± 2.2	19.7 ± 1.6	11.4 ± 0.8	
Mean time (days ± SE) between earliest HSV symptom and enrollment	5.7 ± 1.3	7.4 ± 1.3	5.6 ± 0.7	
Time Frame: 1981–1997	SEM (n = 64)	CNS (n = 63)	Disseminated (n = 59)	Total (n = 186)
Skin Vesicles				
Number of patients	53 (83%)	40 (63%)	34 (58%)	127 (68%)
Duration of symptoms (days ± SE)	3.8 ± 0.5	6.1 ± 1.0	3.7 ± 0.6	4.5 ± 0.4
Lethargy				
Number of patients	12 (19%)	31 (49%)	28 (47%)	71 (38%)
Duration of symptoms (days ± SE)	3.3 ± 0.7	4.6 ± 0.7	3.4 ± 0.7	3.9 ± 0.4
Fever				
Number of patients	11 (17%)	28 (44%)	33 (56%)	72 (39%)
Duration of symptoms (days ± SE)	4.6 ± 1.5	3.1 ± 0.4	4.6 ± 0.6	4.0 ± 0.4
Conjunctivitis				
Number of patients	16 (25%)	10 (16%)	10 (17%)	36 (19%)
Duration of symptoms (days ± SE)	6.5 ± 1.5	4.1 ± 1.3	5.9 ± 1.9	5.7 ± 0.9
Seizure				
Number of patients	1 (2%)	36 (57%)	13 (22%)	50 (27%)
Duration of symptoms (days ± SE)	7.0	2.9 ± 0.5	2.5 ± 0.7	2.9 ± 0.4
DIC^d				
Number of patients	0 (0%)	0 (0%)	20 (34%)	20 (11%)
Duration of symptoms (days ± SE)	–	–	1.5 ± 0.3	1.5 ± 0.3
Pneumonia				
Number of patients	0 (0%)	2 (3%)	22 (37%)	24 (13%)
Duration of symptoms (days ± SE)	–	9.0 ± 6.0	4.0 ± 0.8	4.5 ± 0.9

Data from Kimberlin DW et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. *Pediatrics* 2001; 108: 223–9.

^aSEM, skin, eye, mouth disease; ^bCNS, central nervous system; ^cSE, standard error; ^dDIC, disseminated intravascular coagulation.

lung disease is characterized by a diffuse, interstitial pattern that progresses to a hemorrhagic pneumonitis. Not infrequently, pneumotosis intestinalis can be detected when gastrointestinal disease is present.

Encephalitis

Infection of the CNS occurs alone or in combination with disseminated disease and presents with the findings indicative of encephalitis in the newborn. Overall, nearly 90% of babies with dissemination or encephalitis have evidence of acute

brain infection. Brain infection can occur either as a component of multiorgan disseminated infection or as encephalitis with or without skin, eye, and mouth involvement. One-third of all babies with neonatal HSV infection have only encephalitis. The pathogenesis of these two forms of brain infection is likely different. Babies with disseminated infection probably seed the brain by a blood-borne route, resulting in multiple areas of cortical hemorrhagic necrosis. In contrast, babies who present with encephalitis alone are likely to develop brain disease as a consequence of retrograde axonal transmission of

virus to the CNS. Two pieces of data support this contention. First, babies with disseminated disease have documented viremia and are hospitalized earlier in life (at 9–10 days vs. 16–17 days) than those with encephalitis. Second, babies with encephalitis are more likely to receive transplacental neutralizing antibodies from their mothers, which may not prevent intraneuronal transmission of virus to the brain.

The clinical manifestations of encephalitis include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanelle, and pyramidal tract signs. Although babies with encephalitis alone can have skin vesicles in association with brain infection, 30–40% do not develop skin vesicles at any time in the disease course.^{169,220,222–224} Cultures of CSF yield HSV in 25–40% of all cases. Anticipated findings on CSF examination include pleocytosis and proteinosis (as high as 500–1000 mg/dL). Although a few babies with CNS infection proven by brain biopsy have been reported to have no abnormalities of their CSF, this occurs very rarely. Serial CSF examination is useful diagnostically as the infected child with brain disease will demonstrate progressive increases in the CSF protein content. The importance of CSF examinations in all infants is underscored by the finding that even subtle changes have been associated with significant developmental abnormalities. Furthermore, as discussed in diagnosis, CSF provides an essential biologic specimen for diagnostic evaluation by PCR.^{225,226}

Electroencephalography and computed tomography can be very useful in defining the presence of CNS abnormalities.^{220,227} Death occurs in 50% of babies with localized CNS disease who are not treated and is usually related to brain-stem involvement. With rare exceptions, survivors are left with severe neurologic impairment.^{222,224}

The long-term prognosis, following either disseminated infection or encephalitis, is poor. As many as 50% of surviving children have some degree of psychomotor retardation, often in association with microcephaly, hydranencephaly, porencephalic cysts, spasticity, blindness, chorioretinitis, or learning disabilities. It is thought that visceral or CNS damage can be progressive after initial clearance of the viral infection, a possibility suggested by long-term assessment of children with skin, eye, or mouth disease and more recently, in a group of babies with more severe disease.^{153,169,228,229}

Despite the presumed difference in pathogenesis, the clinical manifestations of encephalitis alone are virtually identical to those that occur with brain infection in disseminated cases. Only two of three babies with encephalitis will develop a vesicular rash characteristic of HSV infection. Thus, a newborn with pleocytosis and proteinosis of the CSF but without a rash can easily be misdiagnosed as having a bacterial or other viral infection unless HSV infection is carefully considered. In such circumstances, a history of genital lesions in the mother or her sexual partner may be very important in suggesting HSV as a cause of illness.

Skin, eye, and/or mouth infection

Infection localized to the skin, eye, and/or mouth is associated with lower mortality, but it is not without significant morbidity. When infection is localized to the skin, the presence of discrete vesicles remains the hallmark of disease. Clusters of vesicles often appear initially on the presenting part of the body that was in direct contact with the virus during birth. With time, the rash can progress to involve other areas of the body as well. Vesicles occur in 90% of children with skin, eye, and/or mouth infection. Children with disease localized to the skin, eye, or mouth generally present at about 10–11 days of life. Those babies with skin lesions invariably will suffer from recurrences over the first 6 months (and longer) of life, regardless of whether therapy was administered or not. Although death is not associated with disease localized to the skin, eye, and/or mouth, up to 30% of these children eventually develop evidence of neurologic impairment.^{156,169,227}

Vesicles usually erupt from an erythematous base and are usually 1–2 mm in diameter. They can progress to larger bullous lesions greater than 1 cm in diameter. Although discrete vesicles on various parts of the body are usually encountered, crops and clusters of vesicles have also been described. For most babies with neonatal HSV infection localized to the skin, eye, and/or mouth, the vesicular skin rash involves multiple and often distant cutaneous sites. However, a limited number of babies have had infection of the skin limited to one or two vesicles and no further evidence of cutaneous disease. This group of babies warrants careful evaluation because many have developed encephalitic involvement when antiviral therapy was not administered. Other manifestations of skin lesions have included a zosteriform eruption.

Infections involving the eye may manifest as keratoconjunctivitis or, later, chorioretinitis. The eye can be the only site of HSV involvement in the newborn.²⁰² These children present with keratoconjunctivitis or, surprisingly, evidence of microphthalmia and retinal dysplasia. In the presence of persistent disease and no therapy, chorioretinitis can result, caused by either HSV-1 or -2.^{230–232} Keratoconjunctivitis, even in the presence of therapy, can progress to chorioretinitis, cataracts, and retinal detachment. Cataracts have been detected on long-term follow-up in three infants with proved perinatally acquired HSV infections.²³³

Localized infection of the oropharyngeal cavity is found in approximately 10% of neonates with HSV infection. Long-term neurologic impairment including spastic quadriplegia, microcephaly, and blindness has been encountered in children whose disease appeared localized to the skin, eye, and/or mouth. Important questions regarding the pathogenesis of delayed-onset neurologic debility are raised by such clinical observations. Despite normal clinical examinations, neurologic impairment develops between 6 months and 1 year of life. The clinical presentation occurs in a manner similar to

that associated with congenitally acquired toxoplasmosis or syphilis. As noted in the following, two factors appear to predict neurologic outcome in babies with disease localized to the skin, eye, or mouth. These are (1) frequency of recurrent skin lesions over the first 3 months of life and (2) detection of HSV DNA by PCR in the CSF at the end of therapy.

Subclinical infection

Although it has been suggested that two newborns had evidence of HSV infection proved by culture isolation of virus but without evidence of symptoms, it has been difficult to document such cases through the serial evaluation in over 1000 infants evaluated in multiple centers around the United States. Because of the propensity of the newborn to develop disease, any evidence of infection should be considered potentially serious and an indication for antiviral therapy.

■ DIAGNOSIS

Clinical evaluation

The clinical diagnosis of neonatal HSV infection has become increasingly difficult because of the apparent decrease in the incidence of skin vesicles as an initial component of disease presentation. A variety of other disease conditions of the newborn can masquerade as neonatal HSV infections, including hyaline membrane disease, intraventricular hemorrhage, necrotizing enterocolitis, and various ocular or cutaneous disorders. Bacterial infections of newborns can mimic neonatal HSV infection. It is not uncommon for some babies infected by HSV to also experience a concomitant bacterial infection, particularly those caused by the group B streptococcus, *Staphylococcus aureus*, *Listeria monocytogenes*, and gram-negative bacterial infections.

As with other vesicular rashes, alternative causes of such exanthems should be excluded. Such diseases include varicella-zoster virus infection, enteroviral disease, and disseminated CMV infection. With the aforementioned clinical findings in a child presenting to the hospital during the first 3 weeks of life, consideration of neonatal HSV infection is necessary. The presence of skin vesicles provides a natural site for attempted isolation of virus in order to rapidly determine if the etiology of the vesicular rash is HSV as opposed to varicella-zoster virus. Simultaneously, serologic specimens and other virologic cultures should be obtained to exclude other common causes of perinatal infection, including toxoplasmosis, CMV infection, rubella, and syphilis. Such cutaneous disorders as erythema toxicum, neonatal melanosis, or acrodermitis enteropathica often confuse physicians who suspect neonatal HSV infections. Lesions associated with these diseases can be rapidly distinguished from those caused by HSV by the presence of eosinophils on a Wright stain of a tissue scraping and by appropriate viral cultures.

The most difficult clinical diagnosis to make is that of HSV encephalitis, as nearly 40% of children with CNS infection will not have a vesicular rash at the time of clinical presentation. HSV infection of the CNS should be suspected in the child who has evidence of acute neurologic deterioration with the onset of seizures and in the absence of intraventricular hemorrhage and metabolic causes. Serial increases in CSF fluid cell counts and protein concentrations, negative bacterial cultures of the CSF, and negative CSF antigen studies help suggest the diagnosis of HSV infection of the CNS. A maternal genital culture or history of genital herpes in either the mother or a sexual partner reinforces the suspicion of neonatal HSV infection. As noted previously, noninvasive neurodiagnostic studies can be used to define the sites of involvement.

Laboratory assessment

Every effort should be made to confirm infection by viral isolation, the definitive diagnostic method. If skin lesions are present, a scraping of skin vesicles should be transferred in appropriate virus transport media to a diagnostic virology laboratory. Clinical specimens should be shipped on ice for inoculation into appropriate cell culture systems. Shipping of specimens and their processing should be expedited. In addition to skin vesicles, other sites from which virus may be isolated include the CSF, stool, urine, throat, nasopharynx, and conjunctivae. It may also be useful in infants with evidence of hepatitis or other gastrointestinal abnormalities to obtain duodenal aspirates for HSV isolation. The virologic results of the cultures from these sites along with clinical findings should be used in conjunction with clinical findings to establish a disease classification. Typing of an HSV isolate may be done by one of several techniques.

Over the past several years, PCR detection of HSV-DNA in CSF has become the diagnostic method of choice for CNS disease, replacing brain biopsy. It has proved both sensitive and specific when properly performed.^{226,234-237}

The serologic diagnosis of HSV infection is not of great clinical value. Therapeutic decisions cannot await the results of serologic studies. Further, the inability of the commonly available serologic assays to distinguish between antibodies to HSV-1 or HSV-2 as well as to denote the presence of transplacentally acquired maternal IgG, as opposed to endogenously produced antibodies, makes the assessment of the neonate's antibody status difficult during acute infection. Serial antibody assessment may be useful if a mother without a prior history of HSV infection has a primary infection late in gestation and transfers very little or no antibody to the fetus.

■ TREATMENT OF NEONATAL HSV INFECTIONS

Background

Since most babies acquire HSV infection at the time of delivery or shortly thereafter, successful antiviral therapy should

decrease mortality and improve long-term outcome. Inherent in this presumption is the recognition that diagnosis shortly after the onset of clinical illness is essential, as is the case with other perinatally acquired infections. Children presenting with disease localized to the skin, eye, and/or mouth progress to either involvement of the CNS or disseminated infection in approximately 70% of cases when no therapy is administered.¹⁶⁷ When such occurs, the likelihood of an adequate outcome, even with established drugs, is not optimal as many of these children will either die or be left with significant neurologic impairment. Such factors must be considered in the development of any treatment strategy.

Antiviral therapy

Vidarabine was the first drug proven effective for treatment of infants with disseminated or localized CNS disease, being associated with a decline in mortality rate from 75% to 40%.²²⁹ However, vidarabine has been replaced by acyclovir as the treatment of choice for neonatal HSV infection. When outcome was examined according to each of the three disease classifications, the best therapeutic result was achieved in babies with either encephalitis or skin, eye, and/or mouth infection.

Acyclovir is the treatment of choice for neonatal HSV infections of the CNS. It is a selective inhibitor of HSV replication, representing one of the most important advances in antiviral therapy. Acyclovir is a synthetic acyclic purine nucleoside analog which selectively inhibits HSV-1 and HSV-2.^{238,239} Acyclovir is converted to its monophosphate derivative by virus-encoded thymidine kinase, an event that does not occur to any significant extent in uninfected cells. Subsequent di- and triphosphorylation is catalyzed by cellular enzymes and results in acyclovir triphosphate concentrations 40- to 100-fold higher in HSV-infected cells than in uninfected cells. Acyclovir triphosphate inhibits viral DNA synthesis by competing with deoxyguanosine triphosphate as a substrate for viral DNA polymerase.^{240,241} DNA synthesis is then terminated because acyclovir triphosphate lacks the 3' hydroxyl required for DNA chain elongation. The viral polymerase has greater affinity for acyclovir triphosphate than cellular DNA polymerase, resulting in little incorporation of acyclovir into cellular DNA. In vitro, acyclovir is active against HSV-1 (average ED₅₀ = 0.04 µg/mL), HSV-2 (0.10 µg/mL), and varicella-zoster virus (0.50 µg/mL).

Acyclovir has been established as efficacious for the treatment of primary genital HSV when administered by intravenous, oral, and topical routes.^{242–245} Furthermore, the oral and intravenous administration of acyclovir to the immunocompromised host decreases both the frequency of reactivation following immunosuppression and disease duration.^{246,247} Acyclovir is superior to vidarabine for the treatment of HSV encephalitis.²⁴⁸ Because this compound is a selective inhibitor of viral replication, it has a low frequency of side effects.

Acyclovir has become a preferred treatment for all serious HSV infections.

In the treatment of neonatal HSV infections, intravenous acyclovir at standard dosing of 30 mg/kg/day for 10–14 days was been shown to be as effective as vidarabine treatment; but not superior.²⁴⁹ A subsequent study performed by the NIAID CASG evaluating the use of higher-dose acyclovir (60 mg/kg/day) for 21 days demonstrated clear superiority and has become the standard of care.²⁵⁰ The mortality rate of infants with encephalitis or disseminated infection in this study was 6% and 31%, respectively. This represents a decrease from 20% to 61% for patients receiving standard dosing of acyclovir in the earlier CASG trial, respectively. However, despite the clear benefit in mortality, particularly among those infants with disseminated disease, high-dose acyclovir did not show a statistically significant improvement in morbidity at 12 months of life.²⁵⁰ There was, however, a borderline significant trend toward improved morbidity when potentially confounding factors were controlled for in a logistic regression model. The most important toxicity of high-dose acyclovir is neutropenia. It is recommended to monitor neutrophil counts twice weekly during high-dose acyclovir therapy. It is prudent to monitor renal function as well, though our experience indicates very low rates of immediate renal toxicity during therapy with acyclovir in this population.

To improve outcome, more active drugs that have greater activity in the CNS must be developed. Importantly, therapy must prevent progression of infection to the CNS or disseminated disease. Ideally, prevention of neonatal HSV infection, including CNS involvement, by either immunization of the mother at risk or immunoprophylaxis and therapy of the newborn delivered to the mother with asymptomatic primary or initial infection would be far more desirable.

Recognizing that disease is often present in these babies for 4 or 5 days prior to diagnosis, a window for administration of therapy earlier in life does exist. This point must be reiterated as earlier therapeutic intervention for any microbial infection will lead to improved outcome, particularly when a vital organ such as the brain is involved. Furthermore, when therapy is instituted early, fewer children will progress from localized skin involvement to more serious forms of infection. Therapy decreases the frequency of progression.

Infants with ocular involvement caused by HSV should receive topical antiviral medication in addition to parental therapy. At the present time, few safety and tolerance data are available for topical ophthalmic antiviral drugs. In older patients, viroptic (trifluorothymidine) has the greatest antiviral activity and is the treatment of choice for HSV infection of the eyes. Vidarabine ophthalmic and Stoxil (idoxuridine) have been utilized for a longer period of time. There is more experience regarding their safety in both adults and children, but they are less active.

During the course of therapy, careful monitoring is important in order to assess therapeutic response. Even in the absence of clinical evidence of encephalitis, the CNS should be examined serially for prognostic purposes. Evaluation of certain hepatic (increased SGPT or SGOT) and bone marrow parameters (decreased platelets) may indicate viral involvement of these organs or drug toxicity.

As for all drugs, a consideration of the therapeutic index or a ratio of efficacy to toxicity is important. Experience with acyclovir has indicated little toxicity when used appropriately. However, the possibility of both acute and long-term toxicity should be considered in any child receiving parenteral antiviral therapy and assessed by serially evaluating bone marrow, renal, and hepatic function. The potential for long-term harm from acyclovir appears low. Since these compounds act at the level of DNA replication, physicians responsible for follow-up of these children should be aware of the possibility of mutagenic or even teratogenic effects that may not appear until decades later. A recent topic of debate is the possibility of the development of viral resistance to a drug; the clinical significance remains to be defined, although it has occurred in the newborn.²⁵¹

Continuing discussion surrounds the administration of oral acyclovir following intravenous therapy. Oral therapy appears to decrease the frequency of cutaneous recurrences but has been associated with absolute neutropenia. Since the child with neonatal HSV infection, particularly with skin vesicles, will excrete virus in large quantities, isolation of the newborn is important in order to decrease the potential for nosocomial transmission of infection.

Factors predictive of neurologic outcome

Table 84-4 summarizes the risk factors for mortality and morbidity even with therapy of neonatal HSV infection.²⁵² Mortality is best predicted by disease classification, level of consciousness, and disseminated intravascular coagulopathy for the entire study population. As it relates to morbidity, disease classification, virus type (HSV-2), and the presence of seizures predict a poor neurologic outcome.

Notably, for babies with disease localized to the skin, eye, or mouth, risk of neurologic impairment increases with the frequency of recurrent cutaneous lesions within 3 months of the completion of therapy. Additionally, infection caused by HSV-2 appears more likely to cause neurologic impairment.

Other therapeutic approaches

At present, there is no indication that administration of immune globulin or hyperimmune globulin is of value in therapy of neonatal HSV infection. Although a series of studies have suggested that high levels of transplacental neutralizing antibodies will ameliorate neonatal HSV infections at the time of presentation with clinical disease, the presence or absence of antibodies does not influence the subsequent

Table 84-4. Prognostic Factors Identified by Multivariate Analyses for Neonates and HSV Infection^a

	Relative Risk	
	Mortality	Morbidity
Total group (<i>n</i> = 202)		
Extent of disease		
Skin, eyes, or mouth	1.0	1.0
CNS	5.8 ^b	4.4 ^b
Disseminated	3.3 ^b	2.1 ^b
Level of consciousness		
Alert or lethargic	1.0	NS
Semicomatose or comatose	5.2 ^b	NS
Disseminated intravascular coagulopathy	3.8 ^b	NS
Prematurity	3.7 ^b	NS
Virus type		
HSV-1	2.3 ^c	1.0
HSV-2	1.0	4.9 ^b
Seizures	NS	3.0 ^b
Infants with disseminated disease (<i>n</i> = 46)		
Disseminated intravascular coagulopathy	3.5 ^b	NS
Level of consciousness		
Alert or lethargic	1.0	1.0
Semicomatose or comatose	3.9 ^b	4.0 ^b
Pneumonia	3.6 ^b	NS
Infants with CNS involvement (<i>n</i> = 71)		
Level of consciousness		
Alert or lethargic	1.0	NS
Semicomatose or comatose	6.1 ^b	NS
Prematurity	5.2 ^b	NS
Seizures	NS	3.4 ^b
Infants with infection of the skin, eyes, or mouth (<i>n</i> = 85)		
No. of skin vesicle recurrences		
< 3	NA	1.0
≥ 3	NA	21 ^b
Virus type		
HSV-1	NA	1.0
HSV-2	NA	14 ^{b, d}

^aCNS denotes central nervous system, NS not statistically significant ($p > 0.05$), and NA not applicable. (No baby with disease confined to the skin, eyes, or mouth died).

^b $p < 0.01$.

^c $p < 0.05$.

^dBecause of the correlation between virus type and skin-vesicle recurrence, virus type was not significant in the multivariate model; however, it was significant as a single factor. (Adapted, with permission, from Whitley RJ et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. *N Engl J Med* 1991; 324: 450-454.)

course of infection.^{169,173,174} Moreover, at present no other form of therapy is useful for treating neonatal HSV infection. Various experimental modalities including BCG, interferon, immune modulators, and immunization have been used, but none have produced demonstrable effects.

■ LONG-TERM MANAGEMENT OF HSV-INFECTED BABIES

With the advent of antiviral therapy, an increasing number of newborns who suffer from HSV infection survive and require careful long-term follow-up. Three areas of follow-up warrant attention from a medical standpoint. First, it is not infrequent that parents of children with neonatal HSV infection have significant guilt feelings. A once stable marriage can suffer and require interventive support from psychologists, psychiatrists, or marriage counselors. The family physician or pediatrician in this situation can provide support to the family. Second, the most common complications of neonatal HSV infection include neurologic and ocular sequelae which are detected only on long-term follow-up. Therefore, these children should receive serial long-term evaluations from qualified pediatric specialists in these areas, including neurodevelopmental, ophthalmologic, and hearing assessments. Third, skin vesicles will recur with time. These vesicles provide a potential reservoir for transmission of infection to other children who have direct contact with these infants. The increasing use of day care for children in this country, including children surviving neonatal HSV infections, has stimulated many questions concerning how these children should receive care. Certainly, there is some risk that children with recurrent HSV skin lesions will transmit the virus to other children in this environment. The most reasonable recommendation in this situation appears to be simply to cover the lesions to prevent direct contact with them. More likely, HSV-1 is present in the day care environment in the children with symptomatic or asymptomatic gingivostomatitis. In both cases, virus is present in the mouth and pharynx, so that the frequent exchange of saliva and other respiratory droplets that occurs among children in this setting makes this route of transmission much more likely. Education of day care workers and the general public concerning herpesvirus infections, their implications, and the frequency with which they occur would do much to calm fears and correct common misconceptions concerning infections with this virus.

■ PREVENTION OF NEONATAL HSV INFECTION

Background

In spite of the progress that has been made over the last 25 years in the development of antiviral therapy for treatment of neonatal HSV infection, the best approach is that of prevention. It is not surprising that because of the attention of the lay

press to the devastating outcome of neonatal herpes, many women with known genital herpetic infection elect to be delivered by cesarean section rather than undergo the potential risks of exposure of the fetus to the virus at the time of vaginal delivery. As a consequence, an unnecessarily high frequency of cesarean infections is believed to occur in these individuals. All individuals involved in the care of pregnant women and their offspring should individualize the care of mother and child to optimize patient management. Cultures obtained for HSV earlier in gestation prior to delivery do not predict neonatal infection and, therefore, are not indicators.^{253–255}

For women with known shedding of HSV at delivery (i.e., genital lesions), cesarean section has been shown to be efficacious in the prevention of neonatal HSV infections. For women with a past history of genital HSV infection, a careful vaginal examination at presentation to the delivery suite is of paramount importance. Although visualization of the cervix is often difficult, speculum examination for documentation of recurrent lesions is extremely important and should be attempted in these women. A culture for HSV obtained at the time of delivery may be of great importance in establishing whether transmission of infection to the fetus is likely.

The fact that predelivery cultures not only fail to predict the woman who excretes virus at delivery but are also an unnecessarily large health care cost burden places their value in further question. Thus, alternative management approaches will have to be developed.²⁵⁴

Clearly, identifying the woman who excretes HSV at delivery and then optimizing either prophylactic protocols with safe and acceptable antivirals or delivery by cesarean section is the optimal way to manage genital infection at the time of delivery. Unfortunately, at present isolation of virus in tissue culture or standard HSV PCR are the only commonly available tests capable of documenting the excretion of virus. Alternative, rapid non-culture-based diagnostic approaches are not currently available, though there are ongoing efforts to develop them, in order to expedite identification of women at risk for delivering an infected baby.²⁵⁶

An alternative strategy is evolving for women with a history of recurrent genital herpes. The administration of acyclovir during the last 4 to 6 weeks of gestation has resulted in a lower frequency of cesarean sections and viral shedding.²⁵⁷ However, a recent study demonstrated similar rates of viral shedding and lesions in a cohort of women receiving valacyclovir in the last 4 weeks of pregnancy as compared to those receiving placebo.²⁵⁸ In a registry of neonates exposed to acyclovir in utero, no significant teratogenic effects to the newborn were seen.²⁵⁹ However, the study was not powered to detect rare defects, or those presenting after the perinatal period.

For infections that occur in the first half of gestation, no specific recommendations regarding the termination of pregnancy can be made at this time. It appears that the frequency of infection acquired in utero is approximately 1 in 200,000 deliveries

and can occur as a consequence of either maternal primary or recurrent infection. Nevertheless, detailed prospective studies to document this occurrence have yet to be performed. Thus, no specific recommendation regarding termination of pregnancy with such findings can be made.

Serious forms of neonatal HSV infections will continue to be associated with significant mortality and morbidity, even with acyclovir therapy. As a consequence, some investigators have suggested that acyclovir may be useful in preventing the occurrence of neonatal HSV infections in infants who are delivered unknowingly through an infected birth canal. Since the incidence of neonatal HSV infection following maternal recurrent disease is low, the risks and costs will likely outweigh the benefits. However, with a suspected maternal primary infection and a vaginal delivery intravenous acyclovir therapy may be indicated. However, it must be recognized that the women who are at greatest risk for delivering babies who develop neonatal HSV infection are those least likely to have a history of recurrent genital HSV infection or to have a recognized primary case.

Management of high-risk women and their offspring

Infants delivered either vaginally or by cesarean section when membranes are intact to mothers who have no evidence of active genital herpetic infection are at low risk for acquiring neonatal HSV infection. These children need no special evaluation in the nursery other than initial isolation until results of maternal genital cultures are available. With negative maternal genital cultures, these children can be discharged at the time the mother leaves the hospital.

Infants delivered vaginally to mothers with active genital herpes should be evaluated with viral cultures obtained between 24 and 48 hours after delivery. Sites from which virus should be sought include eye, oronasopharynx, and suspect lesions. These recommendations should serve only as guidelines until formal data are available. If any site is positive, a thorough virologic and clinical examination must be performed and therapy instituted. Other sites to be considered for viral isolation include the CSF, urine, and buffy coat of the blood. In addition, neurodiagnostic evaluation by electroencephalogram and a computed tomographic scan, if indicated, is essential.

Postnatal infection

Isolation of mother from baby. An issue of frequent concern is whether the mother with active genital HSV infection at delivery should be isolated from her child after delivery. Women with recurrent orolabial HSV infection as well as cutaneous herpes simplex infections at other sites (breast lesions) are at similar risk for transmission of virus to their newborn. The risks presented to the newborn by other family members, medical personnel, and friends remain unknown but are low and do not justify removal of personnel from the nursery at this

time. Since transmission occurs by direct contact with the virus, appropriate precautions by the mother, including careful hand washing before touching the infant, should prevent the necessity of separation of mother and child. Similarly, breastfeeding is contraindicated only if the mother has vesicular lesions involving the breast. We do not isolate babies born to infected women unless they themselves become infected. Hospitalization is not prolonged in the uninfected child.

Parental education

At the time of discharge, it is essential to educate parents with known recurrent herpetic infection regarding the possibility that their child may become infected. The parental stigma of a diagnosis of genital herpes and the monitoring procedures associated with evaluating the newborn can create excessive fear and anxiety in the family. The parents and responsible family members must be educated in order to relieve anxiety and provide prompt access to the health-care delivery system should evidence of infection appear. Information regarding infection should include an overview of HSV infection, the risks associated with transmission of infection to the newborn, the necessity for monitoring, the anticipated consequences of positive and negative viral cultures, planned approaches to treatment, and the potential for postnatal acquisition of infection at home.

Hospital staff

At many institutions, a policy that requires transfer or provision of medical leave for nursing or other personnel in nurseries with a labial HSV infection is impractical and causes an excessive burden in those attempting to provide adequate care. Temporary removal of personnel with cold sores has been advocated on some clinical services. As noted previously, individuals with herpetic whitlows carry a high risk of viral shedding. These individuals should be removed from care of newborns at risk for acquiring neonatal HSV infection since even gloves may not prevent transmission of infection. Education regarding the risk of transmission of virus and the importance of hand washing when lesions are present should be repeatedly emphasized to health-care workers. In addition, hospital personnel should wear masks when active lesions are present.

SUMMARY

Neonatal HSV infection remains a life-threatening infection for the newborn in the United States today. With an increasing incidence of genital herpes and an increase in the incidence of neonatal HSV infections, it is important that pediatricians, neonatologists, obstetricians, and family practitioners continue to maintain a high index of suspicion in infants whose symptoms may be compatible with HSV infections so that

early identification leads to prompt treatment. We hope that over the next decade, the development of safe and efficacious vaccines as well as a better understanding of factors associated with transmission of virus from mother to baby will allow ultimate prevention of neonatal HSV infection.

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Lynne M. Mofenson

INTRODUCTION

An estimated 39.5 million people are living with HIV infection; in 2006 alone, there were 4.3 million new infections and 2.9 million deaths due to HIV. The HIV epidemic is increasingly affecting women and girls; globally, just under half of all people living with HIV are female.¹ In sub-Saharan Africa, women make up 59% of all persons infected with HIV and 76% of youth aged 15–24 years.¹ The predominant mode of HIV acquisition in women is heterosexual contact, and the majority of women are of childbearing age. Thus, the combination of pregnancy and HIV infection is increasingly common.

An estimated 2.3 million children are infected with HIV, predominantly through mother-to-child transmission (MTCT). In 2006, an estimated 530,000 children were newly infected with HIV; about 90% of such infections occurred in sub-Saharan Africa.¹ Prior to the development of effective interventions to reduce MTCT, the estimated rates of transmission ranged from 15% to 25% in nonbreastfeeding women in the United States and other resource-rich countries and 25–40% in breastfeeding women in resource-limited countries. In the last decade, there has been impressive success in the United States and other resource-rich countries in reducing incident pediatric HIV-1 infections and a concomitant dramatic decrease in the incidence of new cases of pediatric AIDS. In 1994, Pediatric AIDS Clinical Trials Group (PACTG) protocol 076 showed that administration of zidovudine (ZDV) to the HIV-infected woman during pregnancy and labor and to her newborn decreased the risk of perinatal HIV transmission.² With the implementation of recommendations for universal prenatal HIV counseling and testing, antiretroviral prophylaxis, elective cesarean delivery, and avoidance of breastfeeding, perinatal HIV infection has dramatically diminished to less than 2%.³

Clinical trials have also identified effective, simple, and less expensive antiretroviral prophylaxis regimens more relevant to resource-limited countries. However, implementation of these regimens has been slow, and postnatal transmission of HIV through breastfeeding remains a significant problem in

such settings, where it is estimated that 1750 infants with HIV infection continue to be born every day.

The obstetrician has a key role in educating women to prevent HIV acquisition, providing state-of-the-art care to HIV-infected women who become pregnant to optimize their health, and in prevention of MTCT. This chapter will discuss HIV testing in pregnancy: the potential impact of pregnancy on HIV infection and maternal health, the potential impact interaction between HIV and pregnancy, MTCT and prevention of MTCT, and the general approach to care and treatment of the HIV-infected woman during pregnancy, including antiretroviral therapy for treatment of the mother and prevention of MTCT. This chapter will focus on management of the HIV-infected pregnant women in the United States and other resource-rich countries but will also briefly discuss management in resource-limited settings.

HIV TESTING IN PREGNANCY

Identification of HIV infection during pregnancy is important both from the maternal health perspective and for prevention of MTCT. Ideally, all women should be screened prior to pregnancy to allow informed decisions regarding pregnancy and optimize maternal health status prior to pregnancy for those women who wish to become pregnant. If not screened prior to pregnancy, all women should be screened for HIV during an initial prenatal visit, as antiretroviral therapy to prevent MTCT is most effective when it is initiated early in pregnancy. The Centers for Disease Control and Prevention (CDC), the American College of Obstetricians and Gynecologists (ACOG), and the American Academy of Pediatrics (AAP) recommend universal and routine offering of HIV testing with patient notification (“opt out”) to all pregnant women in the United States.^{4–6} Universal antenatal HIV screening has been shown to be cost effective even in settings with very low HIV seroprevalence in pregnant women.⁷ Data indicate that use of “opt-out” testing policies can improve uptake rates of testing and is recommended.^{5,8,9} “Opt-out” testing with patient notification means that the

HIV test is part of the routine battery of standard antenatal tests, and women are informed that the HIV test is being done and that they may refuse the test. Universal incorporation of HIV testing as part of routine prenatal testing avoids stigmatization based on perceived risk behavior or ethnic group, reduces the cost of testing, and deals with potential geographic shifts in epidemiology.

The use of enzyme immunoassay followed by confirmatory western blot or immunofluorescent assay remains the standard method for diagnosis of HIV infection in pregnant and nonpregnant women, with sensitivity and specificity above 99%.¹⁰ The diagnostic accuracy of standard HIV testing is similar for pregnant and nonpregnant persons, although indeterminate Western blots may occur slightly more frequently in pregnancy.¹¹

Repeat HIV testing is recommended in the third trimester for women with initially negative HIV antibody tests who are at high risk of HIV infection (e.g., history of sexually transmitted infection, illicit drug use or exchange of sex for money or drugs, multiple sex partners during pregnancy or a sex partner known to be HIV positive or at high risk, or signs/symptoms suggestive of acute HIV infection), who are in health-care facilities where the seroprevalence of HIV in childbearing-aged women is high (>0.5%), or who have declined testing earlier in pregnancy.^{5,12} There are data suggesting that the risk of HIV acquisition may be significantly higher during pregnancy than in the postpartum period. The Rakai Community Cohort Study in Uganda found that the HIV incidence rates were 2.3 per 100 person years during pregnancy, 1.3 per 100 person years during breastfeeding, and 1.1 per 100 person years in the nonpregnant, nonlactating women.¹³

Women who present in labor without prenatal care are at increased risk of HIV infection. The CDC has reported that 15% of HIV-infected women had no prenatal care, with women who used illicit drugs being at greatest risk of lacking care.¹⁴ Data from several studies indicate that 40–85% of infants infected with HIV in recent years were born to women whose HIV infection status was unknown prior to delivery.⁵ Starting antiretroviral therapy during labor and delivery or even providing it to the newborn within hours after birth can significantly reduce MTCT.^{15–17} To maximize this benefit, routine offering of rapid HIV testing to women whose HIV status is unknown during labor and delivery has been shown to yield accurate and timely results; be feasible, acceptable to women,¹⁸ and cost effective¹⁹; and is recommended by the CDC, ACOG, and AAP.^{4–6,20} Rapid HIV antibody tests that can provide results in 5–20 minutes are now commercially available. While a positive rapid test needs to be confirmed by a supplemental test such as Western blot, because of the importance of rapid initiation of antiretroviral prophylaxis to prevent MTCT, if a rapid test is positive, antiretroviral prophylaxis can be initiated in the mother and the infant while the results of the confirmatory test are

pending.^{5,20} If the confirmatory test turns out to be negative, then treatment of the infant can be discontinued.

EFFECT OF PREGNANCY ON HIV DISEASE

Data on the impact of pregnancy on progression of HIV disease are mixed, with results differing in resource-rich and resource-limited countries. CD4 lymphocyte count tends to drop during pregnancy in both HIV-infected and HIV-uninfected pregnant women, although the absolute number is significantly lower in HIV-infected pregnant women^{21–25}; CD4 lymphocyte percentage tends to be more stable. Theoretically, the drop in CD4 count could allow enhanced viral replication and disease progression, and antigenic stimulation by fetal tissues during pregnancy could lead to T-cell activation and viral replication.

Reports from resource-limited countries suggest a possible increased progression in HIV disease and HIV-related mortality during pregnancy.^{26,27} However, it is difficult to interpret these reports because sample sizes are small and subject to selection bias related to the indications for testing.^{28,29} However, larger studies from Europe and United States do not show clearly that pregnant women have more rapid progression to an AIDS-defining illness or death than nonpregnant women.^{30–32} Thus, at least in resource-rich countries, pregnancy does not appear to accelerate HIV progression or maternal mortality when appropriate care and access to medication are ensured. Additionally, no clear benefit from pregnancy termination on maternal health of HIV-infected women has been shown.³²

A small, nonsignificant decline in HIV RNA levels during pregnancy with a modest but significant increase in HIV RNA levels (approximately 0.2–0.5 log copies/mL) in the first 3 months postpartum has been reported in infected women, both in those receiving no therapy and also in those receiving and continuing therapy postpartum.^{33–35} These data suggest that this increase may be related to physiologic changes during pregnancy that reverse postpartum. However, the clinical significance of this finding is unclear.

EFFECT OF HIV ON FERTILITY AND PREGNANCY OUTCOME

A reduction in fertility has been noted in HIV-infected compared to HIV-uninfected women in the United States, although specific rates of miscarriage, abortion, ectopic pregnancy, and stillbirth among HIV-infected women do not appear to be significantly different from those in HIV-uninfected women.³⁶ Similar reductions in fertility have been reported in studies from Africa, with the greatest decrease in fertility being observed in women with more advanced HIV disease.^{37–40} However, higher pregnancy rates have been reported in women in the highly active antiretroviral therapy

(HAART) era than the pre-HAART era, as rates of immune suppression and disease progression decrease and survival lengthens secondary to therapy, and more women may be choosing to become pregnant.⁴¹

The data on the effect of HIV (and HIV-related therapies) on pregnancy outcome, such as prematurity, low birth weight, and stillbirth, are mixed. Controlled studies in resource-rich countries prior to routine antiretroviral use have generally not shown an increase in the frequency of prematurity, low birth weight, or intrauterine growth restriction associated with HIV infection.³² However, the rates of these adverse outcomes in both the HIV-infected and the control groups in these studies were relatively high, possibly due to high rates of coexisting conditions that have traditionally been shown to be independently associated with such outcomes in both groups. Studies that have evaluated risk factors for preterm birth and low birth weight in HIV-infected pregnant women have found that they are similar to those identified among uninfected women, including previous adverse outcomes, hypertension, minority race/ethnicity, smoking, cocaine or opiod use, multiple gestation, bleeding during pregnancy, and *Trichomonas vaginalis* infection.^{42,43}

In contrast, controlled studies in resource-limited countries, where the rates of adverse outcomes even in the absence of HIV infection are high, have generally shown higher frequencies of adverse outcomes in HIV-infected women compared to those without HIV infection.^{29,44} HIV-infected women with more advanced disease and/or immunosuppression generally had higher rates of adverse outcomes.

The data concerning the effect of antiretroviral therapy, and particularly combination antiretroviral therapy, on pregnancy outcome are also mixed and appear to differ between Europe and the United States.^{45–47} It is important to note that the contribution of maternal HIV disease stage and other covariates that might be associated with risk for adverse pregnancy outcome in many of these studies is unclear; as discussed earlier, studies have shown elevated preterm birth rates in HIV-infected women who have not received any antiretroviral therapy.^{29,44,48} This is discussed further in the section on antiretroviral therapy in this chapter.

No studies have indicated that there is an increase in the frequency of birth defects related to HIV infection itself.³² Issues related to antiretroviral therapy and congenital birth defects are discussed in the section on antiretroviral therapy in this chapter.

MOTHER-TO-CHILD HIV TRANSMISSION

MTCT of HIV is the most common mode of acquisition of HIV infection in children worldwide. The risk of MTCT varies geographically, with rates in the absence of intervention ranging between 15–25% in resource-rich and 25–40% in resource-limited countries. Although there may be variation in

various risk factors for MTCT in different geographic areas, breastfeeding practices likely account for the majority of differences in MTCT rates between resource-rich and resource-limited countries. In countries like the United States, where formula feeding is accessible, affordable, safe, and sustainable, complete avoidance of breastfeeding by HIV-infected women is recommended, thereby preventing postnatal infection. However, in resource-limited settings, clean water and a sustainable source of formula may not be available or affordable, formula feeding may not be a socially acceptable practice (or would identify a woman as HIV infected), and early infant mortality due to infectious diseases may be high and hence the early protective effect of breastfeeding against diarrheal and respiratory infections during the early months of life is important.⁴⁹ In such settings, breastfeeding is nearly universal, and interventions to make breastfeeding safer in terms of HIV transmission are critically needed.

■ RISK FACTORS FOR HIV MTCT

HIV can be transmitted throughout pregnancy, during labor and delivery, and postpartum through breast milk. Different risk factors may influence HIV-1 transmission during each of these time periods, and different approaches may be required for prevention of transmission during each period. However, maternal plasma HIV-1 viral load has consistently been a strong independent predictor of transmission risk regardless of timing of transmission or antiretroviral use.^{3,50,51} Therefore, it would be expected that interventions that reduce viral load might reduce the risk of transmission during each of these periods. [Table 85-1](#) lists key factors during pregnancy, labor and delivery, and breastfeeding that increase risk of HIV MTCT, which are discussed in more detail below.

In utero and intrapartum transmission

In the absence of breastfeeding and antiretroviral prophylaxis, the majority of MTCT of HIV occurs during the intrapartum period; in utero transmission proportionally accounts for 25–30% and intrapartum transmission for 65–70% of transmission.⁵²

While HIV transmission can occur at any time during pregnancy, the majority of in utero transmission is thought to occur late in pregnancy.^{53,54} During pregnancy, the placenta provides an important physical and immune barrier between maternal and fetal circulations, and also apparently against in utero HIV-1 infection, as the absolute rate of in utero transmission is only 5–10%.⁵² The exact mechanisms of in utero transmission are not known, but factors that disrupt placental integrity, such as chorioamnionitis, might be expected to play a role.^{55,56} Viral characteristics, such as viral subtype or cellular tropism, and host genetic factors, such as HLA or chemokine receptor genotype, have been reported in some studies to influence in utero transmission.^{57–62}

Table 85-1. Key Risk Factors Influencing the Risk of Mother-to-Child HIV Transmission

Risk factors during pregnancy

- High maternal viral load in plasma
- Low maternal CD4 count
- Advanced maternal HIV disease (e.g., AIDS and wasting)
- Placental infection (e.g., sexually transmitted diseases and malaria)
- Viral characteristics (e.g., tropism, chemokine receptor usage, and viral subtype)
- Host genetic factors (maternal/infant HLA)?

Risk factors during labor and delivery

- High maternal viral load in genital secretions
- Vaginal delivery
- Prolonged duration of membrane rupture
- Chorioamnionitis
- Invasive delivery procedures (e.g., fetal scalp electrodes)
- Prematurity and low birth weight

Risk factors during breastfeeding

- High maternal viral load in plasma and/or breast milk
- Low maternal CD4 count
- Advanced maternal HIV disease (e.g., AIDS or wasting)
- Duration of breastfeeding
- Clinical or subclinical mastitis or breast abscess
- Cracked or bleeding nipples
- Infant oral disease (e.g., thrush or mouth sores)
- Mixed infant feeding (i.e., breast milk plus other liquids, nonhuman milk or foods)

There are several mechanisms by which intrapartum transmission can occur: by direct access of cell-free or cell-associated virus to the infant systemic circulation through maternal–fetal transfusions that occur during uterine contractions in labor or by the infant swallowing HIV in genital tract fluids during delivery, with viral passage through the infant’s gastrointestinal mucosa to underlying lymphoid cells, followed by systemic dissemination. Consistent with the importance of intrapartum viral exposure, genital tract cell-associated and cell-free virus has been shown to be risk factors for MTCT, independent of plasma viral load.^{51,63–65} The proven efficacy of interventions restricted to the intrapartum period to reduce MTCT, such as intrapartum/neonatal antiretroviral prophylaxis or elective cesarean delivery performed prior to labor and rupture of membranes, illustrates the importance of the intrapartum period in transmission.^{15,16,66,67}

The Women and Infants Transmission Study has evaluated risk factors for in utero and intrapartum transmission in 1709 infants with known infection status, born between 1990 and 2000.⁵⁰ Both in utero and intrapartum transmission were associated with maternal antenatal viral load and use of antiretroviral therapy. After controlling for maternal viral load and antiretroviral therapy, low birth weight was significantly

associated with in utero transmission, while maternal age, antenatal CD4⁺ count, year of birth, preterm delivery, birth weight, and duration of membrane rupture were associated with intrapartum transmission.

Postnatal transmission

Breastfeeding substantially increases the risk of HIV transmission; postnatal infection can account for 30–50% of all MTCT in breastfed infants.^{52,68} Antiretroviral regimens that have proven efficacy for prevention of in utero and intrapartum transmission show a significant diminution of efficacy over time in breastfeeding infants.^{16,69,70} Thus, to achieve optimal prevention of MTCT in a breastfeeding setting, additional interventions will be needed to reduce postnatal transmission.

Transmission of HIV through breast milk can occur at any point during lactation. Determining the timing of breast milk transmission has been complicated by the difficulty in distinguishing between intrapartum and early breast milk transmission. Data from several studies that compared transmission among breast- and formula-fed infants suggest that the first 6–8 weeks of life may be a particularly high-risk period.⁷¹ In a randomized trial of breast versus formula feeding in Kenya, the SAINT perinatal study of intrapartum–postpartum regimens

for prevention of MTCT, and an observational study in Uganda, the differences in infection rates between breast- and formula-fed infants by age 6–8 weeks were 6.0%, 5.6%, and 9.5%, respectively, with much lower postnatal transmission rates after this time.^{72–74}

Most studies have focused on postnatal transmission occurring after age 1 month. The largest study was the Breastfeeding and HIV International Transmission Study, an individual patient meta-analysis of data from over 4000 children in nine clinical trials in breastfeeding populations.⁷⁵ Of 539 HIV-infected children with known timing of infection, 225 (42%) had late postnatal transmission (occurring after age 1 month). The overall risk of late postnatal transmission was 8.9 infections per 100 child years of breastfeeding, with the risk being generally constant throughout the breastfeeding period. The cumulative probability of late postnatal infection at age 18 months was 9.3%.

In addition to duration of infant breastfeeding, risk factors for breast milk transmission include high maternal viral load, both in plasma and in breast milk; low CD4 lymphocyte count; breast milk immunologic factors; breast pathology such as clinical and subclinical mastitis, nipple bleeding, cracked nipples, or breast abscess; and infant pathology that may disrupt mucosal integrity, such as thrush.^{68,71} More controversial is the role of infant feeding pattern. Several studies have suggested that exclusive breastfeeding during the first few months of life is associated with lower risk of postnatal transmission than mixed feeding of breast milk combined with nonhuman milk, fluids, or other foods.^{76,77} The largest study, conducted in Zimbabwe, included 2060 HIV-exposed infants who were HIV uninfected at age 6 weeks; the rate of late postnatal transmission was 1.3% at age 6 months and 6.9% at age 18 months in exclusively breastfed infants compared to 4.4% and 13.9%, respectively, in infants with mixed feeding.⁷⁷ It is hypothesized that mixed feeding may result in disruption and damage to the neonatal gut epithelium, thereby making HIV transmission more likely. While this remains controversial, in areas where safe substitutes to breast milk cannot be ensured, exclusive breastfeeding is recommended among HIV-infected women due to its general health benefits in terms of optimally reducing infant morbidity and mortality not related to HIV.⁴⁹

PREVENTION OF MOTHER-TO-CHILD HIV TRANSMISSION

The most effective way to prevent HIV MTCT is through primary prevention of HIV infection among women. Additionally, among women who are HIV infected, prevention of unintended pregnancy through provision of family planning and contraception services is important.

For the woman who is HIV infected and pregnant, the most successful intervention to reduce MTCT is the use of

antiretroviral drugs. Additionally, elective cesarean delivery has proven to be effective in reducing intrapartum MTCT in areas where safe operative delivery is possible. A number of additional nonantiretroviral interventions have also been studied but not yet proven to be effective, such as nutritional supplementation, vaginal virucidal cleansing, and empiric antibiotics to prevent chorioamnionitis. The next two sections of this chapter will review studies of the efficacy of these antiretroviral and nonantiretroviral interventions.

ANTIRETROVIRAL INTERVENTIONS TO REDUCE MOTHER-TO-CHILD HIV TRANSMISSION

One of the seminal achievements in HIV research was the demonstration by PACTG 076 that administration of AZT to the pregnant woman and her infant could reduce the risk of MTCT by nearly 70%.² In PACTG 076, AZT was started at 14–34 weeks' gestation, given intravenously to the mother during labor and administered for 6 weeks to the infant.

Following the results of PACTG 076, in the United States and other countries with higher-level resources, implementation of the AZT regimen coupled with increased antenatal HIV counseling and testing rapidly resulted in significant declines in transmission in these countries.^{3,78,79} Subsequent clinical trials and observational studies demonstrated that combination antiretroviral prophylaxis (initially dual and then triple combination therapy) given to the mother antenatally was associated with further declines in transmission to under 2%.^{3,80,81} It is currently estimated that fewer than 400 infected infants are currently born each year in the United States.⁷⁸ However, while new perinatal HIV infections are becoming rare in resource-rich countries, infections continue to occur, and the birth of an infected infant is a sentinel event, representing missed opportunities and barriers to prevention.^{82,83} Important barriers to eradication of MTCT in the United States include the continued increase of HIV infection among women of childbearing age; delayed or lack of prenatal care, particularly in women using illicit drugs; and lack of full implementation of routine, universal prenatal HIV counseling and testing.⁸³

The complexity and cost of the three-part PACTG 076 regimen significantly limit its applicability and implementation within resource-constrained settings. Thus, researchers began to explore the development of shorter, less expensive prophylactic regimens more applicable to resource-constrained settings. Clinical trials initially focused on shortened AZT-alone prophylaxis regimens and moved to evaluating whether combination antiretroviral regimens, such as short-course AZT combined with lamivudine 3TC, might have improved efficacy over AZT alone. Studies also evaluated whether even simpler, less expensive, single-drug regimens, such as single-dose intrapartum/neonatal nevirapine (NVP), would be

effective and whether combining such regimens with other short-course regimens might result in improved efficacy.

■ MECHANISMS OF ACTION OF ANTIRETROVIRAL PROPHYLAXIS IN REDUCING MTCT

There are a number of mechanisms through which AZT or other antiretroviral drugs can reduce MTCT. An important mechanism is by decreasing maternal viral load in the blood and genital secretions through antenatal drug administration to the mother⁸⁴; it is likely that lowering maternal viral load by antenatal antiretroviral therapy is a critical component of protection, particularly in women with high viral loads. However, antiretroviral drugs have been shown to reduce the risk of transmission even among women with HIV-1 RNA levels <1000 copies/mL.⁸⁵ Additionally, the level of HIV-1 RNA at delivery and receipt of antenatal antiretroviral therapy are each independently associated with the risk of transmission, suggesting that antiretroviral prophylaxis does not work solely through reduction in viral load.³

An additional mechanism of protection is “preexposure” infant prophylaxis provided by administration of antiretroviral drugs that cross the placenta of the mother during labor, resulting in systemic drug levels in the infant at a time of intensive exposure to maternal genital tract virus during passage through the birth canal. Postexposure infant prophylaxis is provided through administration of drug to the infant after birth; this would protect against cell-free or cell-associated virus that might have obtained access to the fetal/infant systemic circulation through maternal–fetal transfusion during uterine contractions occurring in labor, or through systemic dissemination of virus swallowed by the infant during passage through the birth canal.

It is likely that efficacy of antiretroviral drugs in reducing MTCT is multifactorial, and each of these mechanisms is contributory. The efficacy of antiretroviral regimens administered only during labor and to the newborn or only to the newborn in reducing MTCT, as discussed below, demonstrates the importance of the pre- and postexposure components of prophylaxis in reducing MTCT.^{15–17,73,86–88}

■ CLINICAL TRIALS OF SHORT-COURSE REGIMENS FOR PREVENTION OF HIV MTCT

Table 85-2 summarizes the results of the major clinical trials of antiretroviral interventions for the prevention of MTCT, which have built sequentially on each other. A number of simple regimens have been identified that are effective in reducing MTCT. Because the studies involved different patient populations residing in different geographic locations, infected with different viral subtypes and having different infant feeding practices, making direct comparison of results between trials difficult. However, some general conclusions can be drawn from the study results.

Short-term efficacy has been demonstrated for a number of short-course antiretroviral regimens, including those with AZT alone, AZT plus 3TC, single-dose NVP, and, more recently, combining single-dose NVP with either short-course AZT or AZT/3TC.^{15,16,69,70,73,89–92} In general, combination regimens are more effective than single-drug regimens in reducing MTCT, and when it is feasible and affordable, a longer three-part regimen given antenatally, intrapartum, and postpartum is superior in preventing MTCT than a shorter two-part antepartum/intrapartum or intrapartum/postpartum regimen.^{16,92}

Almost all trials have included an oral intrapartum prophylaxis component, with varying durations of maternal antenatal and/or infant (and sometimes maternal) postpartum prophylaxis. MTCT is reduced by regimens with antenatal components starting as late as 36 weeks of gestation and lacking an infant prophylaxis component.^{69,89} However, longer duration of antenatal therapy (starting at 28 weeks’ gestation) is more effective than shorter (starting at 36 weeks’ gestation), suggesting that a significant proportion of in utero transmission occurs between 28 and 36 weeks of gestation.⁹⁰ More prolonged postexposure prophylaxis of the infant does not appear to substitute for longer duration of maternal therapy.⁹⁰

Because some women may lack antenatal care and first present to the health-care system during labor, regimens that do not include maternal therapy during pregnancy have been evaluated; in many resource-limited settings, this may constitute the majority of pregnant women. Regimens that include only intrapartum and postpartum drug administration have also been shown to be effective in reducing MTCT.^{15,16,73} However, intrapartum “preexposure” prophylaxis alone, without continued postexposure prophylaxis of the infant, is not effective.¹⁶ The SAINT trial demonstrated that the two proven effective intrapartum/postpartum regimens (AZT/3TC or NVP) are similar in efficacy and safety.⁷³

In some situations, maternal intrapartum therapy may not be possible, and only infant prophylaxis can be provided. Based on epidemiologic data,¹⁷ in resource-rich countries, the standard prophylaxis regimen in the absence of maternal therapy is 6 weeks of infant AZT. To define the optimal infant prophylaxis regimen in these settings, an ongoing study in infants born to women who have not received antenatal therapy is comparing the standard 6-week infant AZT regimen to 6 weeks of AZT combined with either three NVP doses during the first week of life or 2 weeks of nelfinavir (NFV) and 3TC. In resource-limited settings, administration of even 6 weeks of infant AZT may be difficult to achieve, and single-dose NVP is widely used. In a study in South Africa, administration of a single-dose infant NVP given within 24 hours of delivery was compared with 6 weeks of infant AZT therapy in infants born to mothers who did not receive antenatal or intrapartum therapy; overall MTCT rates were not significantly different.⁸⁸ A trial in Malawi

Table 85-2. Clinical Trials of Antiretroviral Drugs for Prevention of Mother-to-Child HIV-1 Transmission

Study/Reference/ Location/Infant Feeding	Regimen	Antenatal/Intrapartum	Postpartum	Efficacy
PACTG 076 ² United States, France Formula feeding	AZT vs. placebo	Long (from 14 wk) Intravenous intrapartum	Long (6 wk) (Infant only)	MTCT at 18 mo, 7.6% AZT vs. 22.6% placebo (68% efficacy).
Bangkok Short-Course AZT Trial ⁸⁹ Thailand Formula feeding	AZT vs. placebo	Short (from 36 wk) Oral intrapartum	None	MTCT at 6 mo, 9.4% AZT vs. 18.9% placebo (50.1% efficacy).
Thai Perinatal HIV Prevention Trial (PHPT-1) ⁹⁰ Thailand Formula feeding	AZT different length AP and infant PP regimens, no placebo	Long (from 28 wk) Short (from 36 wk) Oral intrapartum	Long (for 6 wk) Short (for 3 d) (Infant only)	Short-short stopped early due to significantly higher MTCT (10.5%). MTCT at 6 mo, 6.5% long-long vs. 4.7% long-short vs. 8.6% short-long (statistical equivalence). However, in utero transmission significantly lower with long vs. short maternal antenatal AZT (1.6% vs. 5.1%).
Ivory Coast Short-Course AZT Trial ^{69,70} Ivory Coast Breastfeeding	AZT vs. placebo	Short (from 36 wk) Oral intrapartum	None	MTCT at 3 mo, 15.7% AZT vs. 24.9% placebo (37% efficacy).
DITRAME/ANRS 049a ⁷⁰ Ivory Coast/Burkina Faso Breastfeeding	AZT vs. placebo	Short (from 36 wk) Oral intrapartum	Short (1 wk) (Mother only)	MTCT at 6 mo, 18.0% AZT vs. 27.5% placebo (38% efficacy); MTCT at 15 mo, 21.5% vs. 30.6% (30% efficacy). MTCT at 24 mo (pooled analysis with other Ivory Coast trial) 22.5% vs. 30.2% (26% efficacy).
PETRA ¹⁶ South Africa, Tanzania and Uganda Breastfeeding (74%) and formula feeding	AZT + 3TC in three regimens (three-part ante/intra/postpartum; two-part intra/ postpartum; intrapartum) vs. placebo	Short (from 36 wk) Oral intrapartum	Short (7 d) (Mother and infant)	MTCT at 6 wk, 5.7% three- part (63% efficacy) vs. 8.9% two- part (42% efficacy) vs. 14.2% intrapartum vs. 15.3% placebo. MTCT at 18 mo, 14.9% three- part vs. 18.1% two-part vs. 20% intrapartum vs. 22.2% placebo.
HIVNET 012 ¹⁵ Uganda Breastfeeding	Intrapartum/postpartum NVP vs. AZT	No antenatal ARV Oral intrapartum: single oral dose NVP 200 mg vs. AZT	Single-dose NVP 2 mg/kg within 72 h of birth vs. short AZT (7 d) (Infant only)	MTCT 15.7% in NVP arm vs. 5.8% in AZT arm (41% efficacy) at 18 mo.
PACTG 316 ⁸¹ (United States, Europe, Brazil, Bahamas) Formula feeding	Intrapartum/postpartum NVP vs. placebo in women already receiving AZT or AZT plus other ARV (77% on combination therapy)	Nonstudy antepartum ARV. Intrapartum: single-dose NVP 200 mg + intravenous AZT	Single NVP dose 2 mg/kg within 72 h of birth + 6 wk AZT (Infant only)	Trial stopped early due to very low MTCT in both arms. MTCT at 6 mo, 1.4% NVP vs. 1.6% placebo.

(Continued)

Table 85-2. (Continued)

Study/Reference/ Location/Infant Feeding	Regimen	Antenatal/Intrapartum	Postpartum	Efficacy
SAINT ⁷⁵ South Africa Breastfeeding (42%) and formula feeding	Intrapartum/ postpartum NVP vs. AZT + 3TC	No antenatal ARV Oral intrapartum: single-dose NVP 200 mg vs. AZT + 3TC	Single NVP dose within 48 h of birth vs. short AZT + 3TC (7 d) (mother and infant)	MTCT at 8 wk, 12.3% NVP vs. 9.3% AZT + 3TC
Thai Perinatal HIV Prevention Trial-2 (PHPT-2) ⁹¹ Thailand Formula feeding	AZT vs. AZT + maternal/ infant single-dose NVP vs. AZT + maternal single-dose NVP only	Long (AZT from 28 wk) Oral intrapartum: AZT + single-dose NVP or placebo	1 wk AZT alone vs. 1 wk AZT + single-dose NVP (infant only)	AZT alone arm stopped early due to significantly higher MTCT: MTCT at 6 mo, 6.3% AZT alone vs. 1.1% with AZT plus maternal/ infant NVP vs. 2.1% with AZT plus maternal NVP alone. Final analysis, MTCT at 6 mo, 2.8% with AZT plus maternal NVP only vs. 1.9% with AZT plus maternal/infant NVP.
DITRAME PLUS/ANRS 1201.0 ⁹² Abidjan, Cote d'Ivoire Breastfeeding (54%) and formula feeding	Open label, AZT boosted by intrapartum/ postpartum NVP	Short (from 36 wk) Oral intrapartum: single-dose NVP 200 mg + AZT	Single-dose NVP, + 1 wk AZT (Infant only)	MTCT at 6 wk, 6.5% (95% CI, 3.9–9.1%). Compared to MTCT in historical control AZT alone (1995–2000) 12.8% (in AZT alone group, breastfeeding rate was 97.6%).
DITRAME PLUS/ANRS 1201.192 Abidjan, Cote d'Ivoire Breastfeeding (66%) and formula feeding	Open label, AZT + 3TC boosted by intrapartum/ postpartum NVP	Short (from 32 wk). Oral intrapartum: single-dose NVP 200 mg + AZT + 3TC	AZT + 3TC for 3 d (Mother only) Single-dose NVP + 1-wk AZT (Infant only)	MTCT at 6 wk, 4.7% (95% CI, 2.4–7.0%). MTCT not significantly different than observed with DITRAME 1201.0 regimen AZT + single-dose NVP ($p = 0.34$).
SIMBA ⁹⁶ Rwanda, Uganda Breastfeeding (median duration 3.3–3.5 mo, upper range 4.9–5.3 mo)	NVP vs. 3TC for 6 mo postnatally in breastfeeding neonates exposed antenatally to AZT + ddl	Short (AZT + ddl from 36 wk). Intrapartum: oral AZT + ddl	AZT + ddl for 1 wk postpartum (Mother only) NVP once then twice daily vs. 3TC twice daily while breastfeeding (Infant only)	MTCT at 6 mo, 7.8%, no difference between the two infant arms. MTCT by age (note median duration of breastfeeding 3.3–3.5 mo): MTCT birth (to 3 d), 5.3%; MTCT 4.28 d, 1.6%; MTCT 1–6 mo, 0.9% Overall, postpartum to 6 mo, 2.4%
NVAZ-1 ⁸⁶ Malawi Breastfeeding	Neonatal single-dose NVP only vs. NVP + AZT	No ARV antepartum or intrapartum (late presenters)	Single-dose NVP immediately after birth + AZT twice daily for 1 wk (Infant only)	Overall MTCT at 6–8 wk, 15.3% NVP + AZT vs. 20.9% NVP only. MTCT at 6–8 wk in babies who were uninfected at birth, 7.7% NVP + AZT vs. 12.1% NVP only (36% efficacy).
NVAZ-2 ⁸⁷ Malawi Breast feeding	Neonatal single-dose NVP only vs. NVP + AZT	No ARV antepartum Intrapartum: single-dose NVP to mother	Single-dose NVP immediately after birth + AZT twice	Overall MTCT at 6–8 wk, 16.3% NVP + AZT vs. 14.1% NVP only. MTCT at 6–8 wk in

Table 85-2. (Continued)

Study/Reference/ Location/Infant Feeding	Regimen	Antenatal/Intrapartum	Postpartum	Efficacy
MASHI ⁹³ Botswana Breastfeeding and formula feeding (randomized)	Factorial design, randomized to mode of infant feeding and maternal/infant single-dose NVP vs. placebo Infant placebo discontinued 08/02 (after PHPT-2 results), study modified to maternal NVP vs. placebo, with all infants receiving single-dose NVP	Short (AZT from 34 wk) Oral intrapartum: AZT + single-dose NVP or placebo	daily for 1 wk (Infant only) Single-dose NVP + 1 mo AZT if formula feeding Single-dose NVP + 6 mo AZT if breastfeeding (infant only)	babies who were uninfected at birth, 6.9% NVP + AZT vs. 6.5% NVP only. <i>Original study</i> (maternal/infant NVP vs. placebo): Added efficacy from NVP in formula but not breastfed infants. MTCT at 1 mo, formula-fed infants, 2.4% NVP/NVP vs. 8.3% PL/PL; breastfed infants, 8.4% NVP/NVP vs. 4.1% PL/PL. <i>Revised study</i> (maternal NVP vs. placebo, all infant NVP): No added efficacy from maternal NVP regardless infant feeding mode. MTCT at 1 mo, 4.3% NVP/NVP vs. 3.7% PL/NVP. <i>Infant feeding:</i> Breastfeeding + AZT higher MTCT than formula. MTCT at 7 mo, 9.1% breastfeeding + AZT vs. 5.6% formula. However, higher infant mortality with formula at 7 mo, 9.3% formula vs 4.9% breastfeeding + AZT 18-mo. HIV-free survival did not differ by arm: MTCT/death at 18 mo, 14.2% formula (33 infected, 46. deaths) vs 15.6% breastfeed + AZT (54 infected, 34 deaths).
South Africa ⁸⁸ Breastfeeding (15%) and formula feeding	Neonatal single-dose NVP vs. neonatal AZT	None	Single-dose NVP within 24 h of birth vs. AZT twice daily for 6 wk (infant only)	Overall MTCT at 6 wk, 11.9% NVP vs. 13.6% with AZT; at 12 wk, 14.3% NVP vs. 18.1% AZT; no significant differences. MTCT at 6 wk in babies who were uninfected at birth, 5.3% NVP vs. 8.2% AZT; at 12 wk 7.9% NVP and 13.1% AZT. Stratified by mode of infant feeding, NVP appeared superior to AZT in breastfed infants ($p = 0.03$) but not formula-fed infants ($p = 0.3$).

MTCT, mother to child HIV-1 transmission; AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; PL, placebo.

compared single-dose infant NVP to combination of single-dose NVP with a week of AZT therapy when no antenatal maternal therapy was received. The addition of 1 week of AZT therapy to infant single-dose NVP reduced the risk of transmission by 36%, compared to infant single-dose NVP alone.⁸⁶ However, when maternal intrapartum NVP was received, thereby providing “preexposure” prophylaxis in addition to postexposure prophylaxis, the infant single-dose NVP alone was as effective as the combined NVP/AZT infant postexposure prophylaxis regimen.⁸⁷

In an attempt to improve the efficacy of short-course regimens but retain a regimen that remains appropriate to the cost limitations existing in resource-limited countries, more recently researchers have evaluated whether the addition of a potent intrapartum intervention—the single-dose NVP regimen—to short-course regimens might increase efficacy. In the setting of short-course antenatal AZT alone or AZT/3TC, the Perinatal HIV Prevention Trial (PHPT)-2 study in nonbreastfeeding women in Thailand, the DITRAME studies in a partially breastfeeding population in the Ivory Coast, and the Mashi study in Botswana (in the formula-fed, but not the breastfed, strata) demonstrated that the addition of single-dose NVP did significantly increase efficacy.^{91–93} However, a clinical trial conducted in nonbreastfeeding women in resource-rich countries, PACTG 316, demonstrated that the addition of single-dose NVP did not appear to offer significant benefit in the setting of potent combination antiretroviral therapy throughout pregnancy and very low viral load at the time of delivery.⁸¹ The relative importance of the maternal and infant components of single-dose NVP in the context of short-course AZT regimens remains unclear; the Thailand PHPT-2 study suggests that the infant NVP dose at day 2 of life may not add significant efficacy to the maternal NVP dose alone; however, the Botswana Mashi study suggests that maternal NVP may not be necessary when infant single-dose NVP is provided at birth.^{91,93}

Although the short-course regimens identified as effective in nonbreastfeeding populations are also effective in breastfeeding populations, efficacy is diminished over time. The reduction in efficacy is greatest with AZT or AZT/3TC short-course regimens and less with single-dose NVP.^{15,16,70} This is likely due to the prolonged half-life of NVP in pregnant women in labor and in neonates, with detectable drug levels that can persist for 2 weeks or longer following a single dose,⁹⁴ thereby providing a much longer period of prophylaxis than do nucleoside analogue reverse transcriptase inhibitors (NRTIs) like AZT, which have much shorter half-lives. Consistent with this hypothesis, a study in breastfeeding mother/infant pairs in Kenya found that single-dose maternal/infant NVP was significantly more likely than antepartum/intrapartum AZT to decrease HIV RNA in breast milk during the first through the third week postpartum and was associated with lower transmission at 6 weeks than the AZT regimen.⁹⁵

In breastfeeding populations, several ongoing and planned trials will assess the effect of antiretroviral prophylaxis provided to the breastfeeding infant and/or the mother during lactation, combined with early weaning. Preliminary results from the SIMBA trial suggest that infant prophylaxis may provide some protection against transmission.⁹⁶ This study compared 6 months of infant prophylaxis with NVP compared to 3TC in the context of maternal antepartum, intrapartum, and 1-week postpartum combination of AZT and didanosine (ddI). However, the study lacked a control group, had high rates of exclusive breastfeeding (85%) that itself may lower postnatal transmission,^{76,77} and a median duration of breastfeeding of only 3.5 months, making interpretation of the results difficult. Several other trials of infant prophylaxis are currently ongoing.

A number of trials will evaluate the effect on the risk of postnatal MTCT of using HAART in breastfeeding women who do not require therapy for their own health; in this case, treatment would be provided solely for reducing breast milk transmission and stopped after weaning.⁹⁷ At the present time, there are no data to address the safety and efficacy of this approach. In a study in Botswana, receipt of HAART by lactating women was associated with suppression of cell-free virus (HIV RNA) in breast milk, but not cell-associated virus (HIV DNA).⁹⁸ The relative importance of cell-free versus cell-associated virus in breast milk with risk of transmission is not known. Additionally, there is very limited information about penetration of antiretroviral drugs into breast milk. If there were differential penetration, some drugs may have low or undetectable levels while other drugs may have high levels, leading to the potential for developing drug-resistant virus in breast milk as well as the potential for toxicity in the infant. In a study in Botswana in lactating women who received AZT, 3TC, and NVP for treatment of advanced HIV infection, the median breast milk concentration of NVP was only 67% compared to that in plasma, while the levels of 3TC in breast milk were three times higher than those in plasma.⁹⁹ Additionally, despite no postnatal infant NVP or 3TC administration, levels of these drugs were unexpectedly high in the infants, nearing levels that might be achieved with therapeutic dosing.⁹⁹ In another study in Zimbabwe that evaluated NVP resistance in plasma and breast milk of women who received single-dose NVP, resistance was more common in breast milk than in plasma.¹⁰⁰ Additionally, the resistance mutations were divergent between breast milk and plasma. These data suggest that the breast milk and plasma are separate compartments and that subtherapeutic NVP levels may persist for different periods in milk and plasma, resulting in different patterns of resistance mutations in the virus in each compartment. Therefore, results from clinical trials are needed before recommendations can be made about the efficacy and safety of HAART to reduce breastfeeding transmission in women who do not require it for their own health.

Recommendations for prevention of MTCT in resource-limited countries are based on the results of these studies¹⁰¹ and are shown in [Table 85-3](#).

■ SHORT-COURSE ANTIRETROVIRAL PROPHYLAXIS AND ANTIRETROVIRAL DRUG RESISTANCE

Because the short-course antiretroviral drug regimens used for prevention of MTCT do not fully suppress viral replication, there are concerns about the potential for development of antiretroviral drug resistance. This is of most concern for prophylaxis regimens using antiretroviral drugs for which a single-point mutation can confer drug resistance, such as NVP or 3TC. Resistance mutations conferring resistance to NVP can confer cross resistance with other drugs in the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, such as efavirenz (EFV).

In the Ugandan HIVNET 012 study of single-dose intrapartum/newborn NVP for prevention of MTCT, 25% of 279 women receiving single-dose NVP developed detectable NVP resistance mutations by 6 weeks postpartum, most commonly the K103N mutation, and 46% of 24 infants who became infected despite prophylaxis had NVP resistance, most commonly the Y181C mutation.^{102,103} In follow-up samples from 12 to 18 months postpartum, resistance mutations were no longer detectable and wild-type virus again predominated in both the mothers and the infants.^{102,103} However, using more sensitive assays, resistance may be detected more frequently than detected with standard resistance assays, and very low levels of resistant virus may persist for a prolonged period.^{104,105} Factors associated with development of NVP resistance following single-dose exposure include delivery maternal viral load and CD4⁺ cell count, viral subtype (rates are higher with subtypes D and C than A), time of sampling following exposure (rates are higher closer to time of exposure), number of maternal doses, and possibly body compartment (rates may be higher in breast milk than plasma).^{100,102,103,106}

Rapid development of genotypic resistance to 3TC has also been observed when 3TC has been given as part of a nonsuppressive dual NRTI regimen with AZT in pregnant women for prevention of MTCT. In a study in France, where 3TC was added to AZT after 32 weeks of gestation, 39% of 132 women had detectable high-level resistance to 3TC (the M184V mutation) at 6 weeks postpartum and 40% of five infants infected despite prophylaxis had 3TC resistance.⁸⁰ Maternal 3TC resistance was only detected in women who had received 3TC for 4 weeks or longer during pregnancy. 3TC resistance was also detected at 1 week postpartum in 12% of women receiving 4 weeks of AZT/3TC for prevention of MTCT in the PETRA study.¹⁰⁷ However, no AZT or 3TC resistance was observed with intrapartum/1-week maternal postpartum AZT/3TC.^{107,108} The transient presence of detectable resistance did not have any deleterious short-term clinical effect

on infected women or their infants, and despite the high prevalence of 3TC resistance in the French study, the overall MTCT rate in this group was only 1.6%.⁸⁰

However, whether the presence of transient drug resistance may be associated with diminished viral response to subsequent 3TC or NNRTI-based therapy is unknown. In a study in Thailand, response to NVP-based HAART was assessed in immunocompromised women with and without prior single-dose NVP exposure.¹⁰⁹ In those women with prior NVP exposure, the median time following receipt of single-dose NVP to initiation of therapy was only 6 months. Rates of maximal viral suppression (HIV RNA levels <50 copies/mL) after 6 months of NVP-based HAART were lower in women with recent prior single-dose NVP exposure (HIV RNA was <50 copies/mL in 49% of women with and 68% without prior single-dose NVP exposure); however, clinical and immunologic responses were not different.¹⁰⁹ However, in a study from Botswana, exposure to single-dose NVP was associated with higher rates of viral failure only among women who started therapy within 6 months of single-dose NVP exposure, but not among women starting therapy 6 months or more after exposure.¹¹⁰ Further research is ongoing to more definitively address this issue.

Research is also ongoing to develop interventions to prevent development of resistance following single-dose NVP exposure. Data from a South African study suggest that combining single-dose NVP with AZT/3TC given intrapartum and for 4 or 7 days postpartum significantly reduced (although it did not eliminate) the risk of resistance.¹¹¹ NVP resistance was detected at 2 and/or 6 weeks postpartum in 60% of 68 women receiving single-dose NVP without postpartum AZT/3TC, 12% of 67 women who received 4 days of AZT/3TC, and 10% of 68 women who received 7 days of AZT/3TC. Resistance can also occur when NVP-based HAART is discontinued, due to the prolonged half-life of NVP; whether this is decreased by staggered discontinuation of drugs is not clear. Several studies have found that NVP resistance occurs in about 15% of women who stop NVP-based HAART postpartum even if AZT/3TC is continued for 5 days following discontinuation of NVP.^{112,113} Given the persistence of NVP levels for up to 21 days after a single dose,⁹⁴ the optimal duration of time following single-dose NVP and the optimal regimen for prevention of resistance require further study. Since 3TC resistance can also be conferred by a single mutation, prolonged duration of a dual NRTI regimen containing 3TC also runs the risk of development of 3TC resistance in addition to NVP resistance.

NONANTIRETROVIRAL INTERVENTIONS TO REDUCE MOTHER-TO-CHILD HIV TRANSMISSION

A number of interventions that do not involve antiretroviral drugs have been evaluated for prevention of MTCT. These include elective cesarean delivery, studied in Europe and the

Table 85-3. World Health Organization Recommendations for Antiretroviral Drug Use in HIV-Infected Pregnant Women in Resource-Limited Settings

Clinical Situation	Recommendation
HIV-infected women of childbearing potential and indications for starting therapy	<ul style="list-style-type: none"> • Antiretroviral regimen choice should follow WHO recommendations. First line regimen for childbearing-age women: AZT + 3TC + NVP. • Avoid drugs with teratogenic potential in women of child-bearing age (EFV) unless adequate contraception can be ensured. Exclude pregnancy before starting treatment with EFV.
HIV-infected women on antiretroviral therapy who become pregnant	<p>Woman:</p> <ul style="list-style-type: none"> • Continue current regimen except discontinue drugs with teratogenic potential (EFV) or with known adverse potential for the pregnant mother (combination d4T/ddl). • Discontinuation of antiretroviral drugs during the first trimester is not recommended. • Continue antiretroviral regimen during intrapartum period and postpartum. <p>Infant:</p> <ul style="list-style-type: none"> • AZT for 1 wk (4 wk of AZT recommended if mother receives <4 wk of antepartum antiretrovirals).
Women first diagnosed with HIV infection during pregnancy with clinical indications for antiretroviral therapy	<p>Woman:</p> <ul style="list-style-type: none"> • Follow guidelines for non-pregnant women except exclude drugs with teratogenic potential (EFV) or with known adverse potential for the pregnant mother (combination of d4T/ddl). First line regimen: AZT + 3TC + NVP. • For severely ill woman, benefit of therapy exceeds theoretical risk of teratogenicity and therapy can be started in the 1st trimester if needed. • Continue antiretroviral regimen during intrapartum period and postpartum. <p>Infant:</p> <ul style="list-style-type: none"> • AZT for 1 wk (4 wk of AZT recommended if mother receives <4 wk of antepartum antiretrovirals).
Pregnant HIV-infected women without indication for antiretroviral therapy	<ul style="list-style-type: none"> • Initiate antiretroviral prophylaxis to reduce the risk of peripartum mother to child transmission: <p>Recommended:</p> <p>Short course AZT + single-dose NVP</p> <p>Woman: AZT starting at 28 wk gestation or as soon as feasible after that; continue with oral AZT during labor plus single-dose NVP at the onset of labor. When possible, intrapartum 3TC plus 1 wk of AZT/3TC should be given to the mother to reduce the risk of NVP resistance. If delivery is imminent, do not give the maternal intrapartum dose but give infant single-dose NVP at birth.</p>

Table 85-3. (Continued)

Clinical Situation	Recommendation
Pregnant women of unknown HIV infection status at time of labor or HIV-infected pregnant women who have not received antepartum antiretroviral drugs	<p>Infant: Single dose NVP plus AZT for 1 wk (4 wk of AZT if mother receives <4 wk antepartum AZT).</p> <p><i>Minimum if lack resources for recommended regimen:</i> Single-dose NVP</p> <p>Woman: Single-dose NVP at onset of labor.</p> <p>Infant: Single-dose NVP.</p> <ul style="list-style-type: none"> • If there is time, counsel and offer HIV rapid test; if positive, initiate intrapartum prophylaxis. If insufficient time to obtain HIV test result while in labor, offer HIV test as soon as possible after delivery, and follow the recommendations in next scenario.
Infants born to HIV-infected women who have not received antepartum and intrapartum antiretroviral drugs	<p>Recommended: Single-dose NVP</p> <p>Woman: Single dose NVP. When possible, intrapartum AZT/3TC plus 1 wk of AZT/3TC should be given to the mother to reduce the risk of NVP resistance. If delivery is imminent, do not give the maternal intrapartum dose but give infant single-dose NVP at birth.</p> <p>Infant: Single-dose NVP. When possible, also give 4 wk of AZT.</p> <p><i>Alternative:</i> PETRA AZT + 3TC</p> <p>Woman: AZT + 3TC during labor and for 1 wk postpartum</p> <p>Infant: AZT + 3TC for 1 wk.</p> <ul style="list-style-type: none"> • Single dose NVP as soon as possible after birth, plus AZT for 4 wk. If 4 wk of AZT cannot be given, at least 1 wk of AZT recommended. • If regimen is started more than 2 days after birth, unlikely to be effective
HIV-infected women who are breastfeeding	<ul style="list-style-type: none"> • If indications for therapy, initiate or continue HAART as per non-pregnant scenario. • If there are not indications for therapy, there are insufficient data regarding the safety and efficacy of use of antiretroviral drugs in lactating women solely to prevent breast milk HIV transmission to recommend use outside of clinical trial setting.

HAART: Highly active antiretroviral therapy; WHO: World Health Organization; D4T: Stavudine; AZT: Zidovudine; 3TC: Lamivudine; NVP: Nevirapine; ARV: Antiretroviral; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NRTI: Nucleoside analogue reverse transcriptase inhibitor; NFV: Nelfinavir; SQV: Saquinavir; RTV: Ritonavir.

Data from World Health Organization. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants in Resource-limited Settings: Towards Universal Access*. Geneva, Switzerland: World Health Organization, 2006.

United States, and a number of interventions more applicable to, and studied in, resource-limited settings, including nutritional supplementation, vaginal virucidal cleansing, treatment and prophylaxis of sexually transmitted diseases

and chorioamnionitis, and passive and/or active immunoprophylaxis. In general, other than elective cesarean delivery, the nonantiretroviral interventions studied to date have not proven effective in reducing MTCT.

■ ELECTIVE CESAREAN DELIVERY

Given that most MTCT occurs during the intrapartum period, it was hypothesized that interventions that prevent infant exposure to infectious maternal blood and secretions in the birth canal during delivery could provide some protection against transmission during this time period. Additionally, cesarean delivery performed prior to onset of labor would also prevent maternal–fetal microtransfusions that occur during uterine contractions.^{114,115}

Several studies, conducted in an era of either no antiretroviral therapy or AZT monotherapy, demonstrate a protective effect of elective cesarean delivery (performed prior to labor and rupture of membranes) in reducing MTCT.^{66,67,116} The largest study was an individual patient data meta-analysis including 8533 nonbreastfeeding mother–child pairs from 15 prospective U.S. and international cohort studies.⁶⁶ After adjusting for the receipt of antiretroviral therapy, maternal disease stage, and infant birth weight, elective cesarean section decreased the likelihood of transmission by approximately 50% (adjusted odds ratio [OR] = 0.43, 95% confidence interval [CI] 0.33–0.56). The combination of elective cesarean section and receipt of AZT during the antepartum, intrapartum, and neonatal periods reduced transmission by about 85% compared to other modes of delivery and no antiretroviral therapy (adjusted OR, 0.13, 95% CI 0.09–0.19). Similarly, in a cohort study from France, elective cesarean delivery combined with ZDV prophylaxis was associated with a fivefold lower rate of transmission than vaginal delivery or emergent cesarean section.¹¹⁶ A protective effect for elective cesarean section was found in a randomized trial of elective cesarean versus vaginal delivery conducted in Europe (MTCT 1.8% in 170 women delivered by elective cesarean section compared to 10.5% in 200 delivered vaginally).⁶⁷

Fewer studies have evaluated the effect of elective cesarean delivery in the HAART era.^{117,118} The European Collaborative Study, involving 29 centers in 10 European countries, examined risk factors for MTCT in the HAART era in 1982 patients who were enrolled from January 1997 through May 2004.¹¹⁷ During this period, receipt of antenatal antiretroviral therapy increased from 5% at the start of the HAART era to 92% during 2001–2003, with concomitant decrease in the rates of MTCT from 5% (1997 to 1998) to <1% (2001 to 2003). In a multivariate analysis including 885 mother–child pairs, MTCT risk was associated with high maternal viral load (adjusted OR 12.1, $p = 0.003$) and elective cesarean section (adjusted OR 0.33, $p = 0.04$). Among the subset of 560 women with undetectable HIV RNA levels, on univariate analysis, elective cesarean delivery was associated with a significant reduction in transmission risk compared with vaginal delivery or emergency cesarean section (OR 0.07, 95% CI 0.02–0.31). However, after

adjustment for antiretroviral therapy (none vs. any), this effect was no longer statistically significant in this subgroup (adjusted OR 0.52, 95% CI 0.14–2.03, $p = 0.36$).

The risks of operative delivery also need to be considered. HIV-infected pregnant women may be at increased risk of developing postpartum complications regardless of the mode of delivery.¹¹⁹ It is known that maternal morbidity and mortality are higher after cesarean than vaginal delivery in women who are not HIV infected. Complications are more frequent when the cesarean section is performed after the onset of labor or membrane rupture, as opposed to elective cesarean delivery. There have been several studies that have suggested that complications from cesarean delivery are higher in HIV-infected than HIV-uninfected women, particularly in women undergoing emergency cesarean delivery. In the European randomized mode of delivery clinical trial, while the overall frequency of postpartum complications was low, postpartum fever was significantly more common in women with operative rather than vaginal delivery.⁶⁷ Similarly, an increased rate of postpartum fever following cesarean compared to vaginal delivery was observed in an analysis of 1200 HIV-infected pregnant women enrolled in the observational Women and Infants Transmission Study and an analysis from another study of HIV-infected women undergoing cesarean delivery solely for prevention of transmission.^{120,121} The difference in postpartum complications was greatest among women with more advanced HIV disease and low CD4 cell counts. In an examination of postpartum morbidity among 497 women enrolled in perinatal trial PACTG 185, endometritis, wound infection, and pneumonia were increased among HIV-infected women delivered by scheduled or urgent cesarean section, compared with HIV-infected women undergoing vaginal delivery, but complication rates were within the range previously reported for similar general obstetric populations.¹²² Thus, overall data indicate that elective cesarean delivery may be associated with a slightly greater risk of complications among HIV-infected than HIV-uninfected women, with the greatest difference being observed among women with immunologic suppression. Whether these differences would be mitigated by routine use of prophylactic antibiotics in women undergoing cesarean delivery to reduce infectious morbidity is unknown; the published studies did not delineate whether prophylactic antibiotics were administered.

Thus, despite the potential benefits of elective cesarean delivery for prevention of MTCT, the risks need to be addressed for each individual patient. In some cases (e.g., when risk of transmission is very low, such as a woman on HAART with undetectable viral load), the risk of operative delivery to the mother may outweigh the potential benefit in reducing HIV transmission to her infant.¹¹⁸

Furthermore, the benefit of cesarean delivery in terms of prevention of MTCT is lost if the procedure is performed after the onset of labor or rupture of membranes.^{66,67,116}

■ NUTRITIONAL SUPPLEMENTATION

The efficacy of nutritional supplementation for prevention of MTCT has been evaluated for vitamin A, micronutrients, and multivitamins. Observational studies evaluating the relationship between maternal vitamin A concentrations and the risk of perinatal HIV transmission have produced conflicting results, with some studies suggesting that low serum retinol concentrations are associated with an increased risk of perinatal transmission, while other reports have shown no such relationship.^{123–126}

Several randomized, placebo-controlled perinatal trials have been conducted to determine whether administration of vitamin A and/or other micronutrients to HIV-infected pregnant women would lower perinatal HIV transmission. Maternal antenatal vitamin A supplementation did not reduce in utero, intrapartum, or early breast milk transmission of HIV, nor did it affect maternal morbidity.^{77,127–131} In one trial, vitamin A supplementation, started at approximately 20 weeks' gestation and continued throughout lactation, actually increased HIV transmission during lactation (relative risk 1.38), while multivitamins had no overall effect but reduced breastfeeding transmission among mothers with low baseline CD4 counts in a post hoc subgroup analysis.¹²⁹ However, this increase in postnatal transmission with vitamin A supplementation has not been observed in other studies.^{77,127}

The effect of vitamin supplementation on fetal health and maternal lymphocyte counts was addressed in a randomized controlled trial of 1075 pregnant women in Tanzania who, at 12–27 weeks of gestation, were assigned to placebo, vitamin A alone, multivitamins excluding vitamin A, or multivitamins including vitamin A; one-third were vitamin A deficient at baseline. Multivitamin supplementation, but not vitamin A supplementation alone, was associated with significant improvement in non-HIV-related pregnancy outcomes including fetal death (5.9% vs. 9.6% in the multivitamin vs. placebo groups, respectively), low birth weight (8.8% vs. 15.8%), severe preterm birth at <34 weeks (6.2% vs. 10.2%), and small for gestational-age infants (10.0% vs. 17.6%).¹³² Additionally, maternal multivitamin supplementation (but not vitamin A supplementation) was reported to improve postnatal growth and decrease morbidity in their infants.^{133,134} Multivitamin but not vitamin A supplementation resulted in significant elevations in maternal CD4, CD8, and CD3 counts during pregnancy and immediately postpartum.¹³² Additionally, multivitamin supplementation modestly decreased longer-term risk of HIV disease progression in the mothers.¹³⁵

These data suggest that while micronutrient and vitamin supplementation do not reduce MTCT, they may provide

some benefit in terms of improving pregnancy outcome and decreasing maternal morbidity in HIV-infected women and infants residing in resource-limited countries where nutrient deficiencies are common. However, in the United States and other resource-rich countries, where prenatal vitamin supplementation is routinely provided and vitamin deficiency is uncommon, additional supplementation is not recommended and could be harmful. As an example, large doses of vitamin A (>10,000 international units per day) in pregnancy can be teratogenic.¹³⁶

■ VAGINAL VIRUCIDAL CLEANSING

Use of a microbicide, 0.25% chlorhexidine, to cleanse the birth canal before vaginal delivery has been shown to reduce the risk of neonatal group B streptococcal sepsis and be safe for the mother and infant¹³⁷; this intervention has also been studied for prevention of MTCT of HIV. A perinatal clinical trial in Malawi evaluated vaginal swabbing with 0.25% chlorhexidine every 4 hours during labor, combined with infant cleansing immediately after birth. The treatment was well tolerated, but no overall reduction in HIV transmission was observed (27% vs. 28% transmission in the treatment and control arms, respectively).¹³⁸ Similarly, in a study of vaginal lavage with 0.2% chlorhexidine (increased to 0.4% later in the study) during labor in Kenya, there was no evidence of a difference in intrapartum HIV transmission between lavage and nonlavage groups (15.9% vs. 17.2%, respectively).¹³⁹ In a West African study of vaginal disinfection with 1% benzalkonium chloride vaginal suppositories, women self-administered a daily vaginal suppository or placebo from week 36 of pregnancy and a single intrapartum dose, and the neonatal was bathed in 1% benzalkonium chloride solution. As in the other studies, no difference in perinatal transmission was observed between treatment and placebo groups (21.2% vs. 21.6%, respectively).¹⁴⁰

In the Malawi study, non-HIV-related maternal and infant outcomes were significantly improved in the chlorhexidine group. In the neonates, hospital admissions due to sepsis were reduced by 57% and mortality from sepsis by 67%; in the mothers, hospitalizations due to sepsis were reduced by 63%.¹⁴¹ The duration of hospitalization was also decreased in the treatment group. Thus, while use of vaginal microbicides does not appear to reduce MTCT, it is inexpensive, easily administered, does not require HIV testing for implementation, and could have potential overall benefit to HIV-infected and HIV-uninfected women and infants in resource-limited settings where perinatal maternal and infant morbidity and mortality are high.

■ TREATMENT AND PROPHYLAXIS OF SEXUALLY TRANSMITTED DISEASES AND/OR CHORIOAMNIONITIS

Some studies have suggested that sexually transmitted diseases may facilitate both heterosexual and MTCT HIV

transmission.^{142,143} As a result, it has been hypothesized that treatment of sexually transmitted infections might provide an effective intervention to decrease both sexual transmission and MTCT. A randomized, controlled, community-based trial of mass sexually transmitted disease treatment was conducted in Rakai, Uganda, to address this hypothesis.^{144,145} In this study, all adults, including pregnant women, in communities randomized to the treatment regimen received single doses of azithromycin, ciprofloxacin or cefixime (in pregnant women), metronidazole, and benzathine penicillin G, to provide protection against gonorrhea, chlamydia, chancroid, syphilis, and trichomoniasis and short-term control of bacterial vaginosis. Although antibiotic therapy was associated with substantial reduction in overall maternal and infant morbidity and in the rate of sexually transmitted diseases compared to the control communities, there were no decreases documented for sexually or MTCT HIV infection.¹⁴⁵

Studies have also suggested that clinical and/or histologic chorioamnionitis is associated with MTCT.⁵⁶ Chorioamnionitis is associated with significant inflammation and activation of immune cells in the placenta, which could lead to breaks in the placental barrier, allowing passage of virus or infected lymphocytes from the mother to the fetus. Thus, prevention of chorioamnionitis has also been proposed as an intervention to reduce MTCT. However, data from a controlled clinical trial in Malawi and Zambia, in which empiric therapy for chorioamnionitis with a short course of antibiotics was given to HIV-infected pregnant women at 20–24 weeks' gestation and again during delivery, found that such therapy did not reduce HIV MTCT or affect infant morbidity and mortality.¹⁴⁶

■ PASSIVE/ACTIVE IMMUNOPROPHYLAXIS

The success of passive and active immunization to prevent perinatal hepatitis B transmission has stimulated evaluation of a similar approach for prevention of MTCT of HIV.¹⁴⁷ A clinical trial conducted in the United States, PACTG 185, examined whether administration of intravenous HIV hyperimmune globulin (HIVIG) combined with AZT prophylaxis would reduce in utero and intrapartum transmission in HIV-infected women who did not breastfeed, compared to intravenous immune globulin without HIV antibody (IVIG). There was no measurable difference in transmission between treatment and control groups overall (MTCT was 4% with HIVIG vs. 6% with standard IVIG); however, there was a suggestion that HIVIG may have had an effect in reducing in utero transmission, as none of the nine infected infants in the HIVIG group had positive HIV cultures at birth compared to five of the 13 (38%) infected infants in the IVIG group.¹⁴⁸

A clinical trial of HIVIG in breastfeeding women and infants in Uganda for prevention of breast milk transmission

is ongoing. A phase I study of HIVIG in Uganda demonstrated that HIVIG was safe but did not have an effect on maternal viral or immune parameters, similar to previous data from PACTG 185.^{149,150} A phase III trial of HIVIG to prevent intrapartum and breast milk transmission is ongoing in Uganda. Ideally, a monoclonal antibody product that did not require manufacture from inactivated plasma from HIV-infected individuals, that was targeted against specific conserved HIV epitopes with cross-clade neutralization capacity, and that could be administered intramuscularly would be desirable. Additional studies are planned to evaluate the safety and pharmacokinetics of monoclonal anti-HIV antibody preparations in pregnant women and newborns.

The safety and immunogenicity of HIV vaccine candidates are also being evaluated in newborns of HIV-infected women.^{151–153} A study of a fowlpox HIV vaccine (ALVAC) in neonates is about to begin in Uganda. Once a promising candidate vaccine is identified, a phase III trial that would potentially combine anti-HIV monoclonal antibodies with HIV vaccine in neonates to prevent breast milk transmission is planned.

MANAGEMENT OF HIV IN PREGNANCY

Care of the HIV-1-infected pregnant woman should involve an ongoing collaboration between the HIV specialist caring for the woman when she is not pregnant, her obstetrician, and the woman herself. [Table 85-4](#) lists the important HIV-related components of antenatal, intrapartum, and postnatal care for HIV-infected women. Important components of an initial evaluation of an HIV-infected pregnant woman include assessment of the status of her HIV disease, recommendations about beginning or altering antiretroviral treatment, and discussion of interventions to reduce the risk of perinatal HIV transmission. Decisions regarding the use of antiretroviral drugs during pregnancy should be made by the woman, following discussion with her health-care provider of the known and unknown benefits and risks of therapy.¹⁵⁴

Initial assessment should include evaluation of the degree of existing immunodeficiency, as determined by CD4 cell count and percent, and an assessment of the need for prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP) or *Mycobacterium avium* complex (MAC), or for treatment of any current HIV-related illnesses. The criteria for initiation of PCP or MAC prophylaxis are the same as in nonpregnant individuals.¹⁵⁵ Trimethoprim–sulfamethoxazole (TMP/SMX) is the recommended PCP prophylactic regimen. Because of theoretical concerns regarding potential for teratogenicity during the first trimester, aerosolized pentamidine may be considered as an alternative to TMP/SMX during this period due to its lack of systemic absorption. The drug of choice for MAC prophylaxis in pregnant HIV-infected women is azithromycin, due to safety in animal studies and anecdotal safety in humans. Experience with rifabutin in pregnancy is limited. Clarithromycin has been

Table 85-4. Important Components of Care in the United States for the HIV-Infected Pregnant Woman in Addition to Routine Obstetrical Care**Antepartum**

History

- History of HIV-related symptoms, hospitalizations
- Antiretroviral drug past or current use, use of other concomitant drugs, use of alternative medicines (e.g., herbal preparations); assess potential drug interactions with current or planned antiretroviral treatment/prophylaxis

Physical examination

- Ophthalmic examination if CD4 cell count $<50/\text{mm}^3$

HIV-related laboratory

- HIV RNA testing at baseline and a minimum of every 3 mo
- CD4 cell count at baseline and every 3 mo
- Antiretroviral drug resistance testing in women on antiretroviral therapy but without virologic suppression, acute infection, or high likelihood of resistant virus (e.g., partner with resistant virus); consideration of antiretroviral drug resistance testing in all women with detectable RNA levels (see text)

Other laboratory

- Tuberculin skin test
- Antibody status for hepatitis B and C, cytomegalovirus, and *Toxoplasma gondii*, if unknown
- Screening for sexually transmitted infections
- Complete blood cell count and renal- and liver-function testing at baseline (and to monitor for antiretroviral drug toxicity; choice of tests, and frequency dependent on antiretroviral drug choice)

Counseling

- Antiretroviral drugs for treatment and/or for prevention of mother to child HIV transmission, adherence counseling, and potential drug side effects
- Discuss risk factors for mother-to-child HIV transmission, need for avoidance of substance abuse, smoking, multiple sexual partners, condom use to avoid sexually transmitted infections, and HIV superinfection
- Discuss mode of delivery
- Discuss recommendation to not breastfeed

Treatment

- Antiretroviral therapy or prophylaxis
- Prophylaxis of opportunistic infections, if needed
- Immunizations (influenza, pneumococcal, hepatitis B, and others if needed)—ideally given immunizations after antiretroviral therapy improves immune function and suppresses virus

Psychosocial support

- General support, mental health and substance abuse treatment if needed; support for adherence to antiretroviral drug regimen

Fetal monitoring

- For women receiving combination antiretroviral therapy, consideration of assessment of fetal anatomy with level II ultrasound and continued assessment of fetal growth and well-being during third trimester

Intrapartum

Antiretroviral therapy

- Continuation of antiretroviral therapy
- Administration of AZT by intravenous continuous infusion

Mode of delivery

- Evaluation of antiretroviral drugs for any interaction with drugs given during labor (e.g., avoid ergot preparations, monitor closely after midazolam use in women on protease inhibitors or EFV)
- Elective cesarean delivery at 38 wk gestation if maternal RNA >1000 copies/mL at 34–36 wk gestation
- If vaginal delivery, avoid artificial rupture of membranes, minimize interval between rupture of membranes and delivery, and avoid use of instruments for delivery
- Avoid invasive monitoring (e.g., fetal scalp electrodes and fetal scalp blood sampling)

Postpartum

Woman

- Decisions about continuation or discontinuation of antiretroviral treatment; adherence counseling if continuing antiretroviral drugs
- Counsel not to breastfeed
- Family planning and contraception services
- Psychosocial support services
- Referral for HIV-related primary care

Infant (see chapter on care of the infant)

- Pediatric referral of HIV-exposed infants to pediatrician with HIV expertise
- Oral AZT for 6 wk
- Initiation of prophylaxis for *Pneumocystis jiroveci* at 4–6 wk of age
- HIV virologic diagnostic testing

demonstrated to be a teratogen in animals and thus should be used with caution in pregnancy. Treatment of serious infections should not be withheld because of pregnancy; regimens should be chosen in consultation between the obstetrician and a specialist in infectious diseases.

Risk of disease progression should be assessed by determination of plasma HIV RNA copy number. While determination of HIV RNA copy number is important for decisions related to maternal treatment, it should not be the determining factor in the decision to begin antiretroviral prophylaxis to reduce MTCT, because antiretroviral drugs reduce transmission regardless of maternal RNA level and transmission may occur when RNA is undetectable.^{3,85}

Decisions regarding initiation of antiretroviral therapy in women not currently receiving therapy or to continue or alter treatment in women currently receiving therapy should be based on the same criteria as for nonpregnant individuals, with the additional consideration of the potential impact of such therapy on the fetus and infant.¹⁵⁴ In nonpregnant HIV-infected individuals, initiation of treatment is recommended for all individuals with CD4 cell count $<200/\text{mm}^3$ or an AIDS-defining illness, and to be considered for individuals with CD4 cell count $<350/\text{mm}^3$ or HIV RNA levels $>100,000$ copies/mL.¹⁵⁶ Standard treatment is three drugs, generally two NRTIs plus an NNRTI or a protease inhibitor (PI),¹⁵⁶ as discussed in more detail in Chapter 73 (“Antiviral Therapy of Human Immunodeficiency Virus Infection”). Recommendations for antiretroviral treatment and prevention of MTCT of women in the United States in different clinical scenarios are shown in Table 85-5 and found in the U.S. Public Health Service guidelines, which can be accessed on the web at <http://AIDSInfo.nih.gov>.¹⁵⁴ Considerations related to specific antiretroviral drug choice in pregnancy are discussed in the next section in this chapter.

For HIV-infected pregnant women who do not require therapy for their own health, antiretroviral drugs are recommended for prevention of MTCT. In the United States and other resource-rich countries, combination therapy with HAART is recommended for all women with HIV RNA levels >1000 copies/mL, along with consideration of elective cesarean delivery if HIV RNA remains >1000 copies/mL at 34–36 weeks’ gestation.¹⁵⁴ For women with HIV RNA levels <1000 copies/mL, the three-part PACTG 076 AZT prophylaxis regimen² can be used alone or in combination with other antiretroviral drugs although many experts would use a 3-drug regimen in such women as well. Long-term follow-up (mean 4.1 years) of women who participated in PACTG 076 found no differences in HIV disease progression, time to AIDS or death, CD4 lymphocyte count, HIV RNA levels, or genotypic AZT resistance in women from the AZT group compared to those in the placebo group.¹⁵⁷

Depending on individual circumstances, provision of support services, mental health services, and drug abuse treatment

may be required; such services may be especially important in promoting adherence to prescribed antiretroviral regimens. Adherence to antiretroviral therapy during pregnancy is particularly important for ensuring viral suppression, important for maternal health as well as prevention of MTCT, and prevention of drug resistance. Adolescent women or women who use alcohol or are substance abusers may be at particularly high risk of adherence problems during pregnancy.^{158,159} These services need to be coordinated with prenatal care, primary care, and HIV specialty care providers. Discussion of long-term permanency planning for care of the child in the event of maternal illness should be initiated. A long-term treatment plan should be developed with the patient and the importance of adherence to prescribed antiretroviral regimens discussed.

General counseling related to prevention of perinatal transmission should include information about what is known about risk factors for transmission, particularly those potentially modifiable by the patient. Cigarette smoking, hard drug use (heroin, cocaine, and/or injection drug use), and/or unprotected sexual intercourse with multiple partners during pregnancy have been associated with an increased risk of perinatal HIV transmission.^{160–164} In addition to improving maternal health, discontinuing cigarette smoking and drug use, and use of condoms with sexual intercourse during pregnancy may independently reduce risk of MTCT.

Plasma viral load and CD4 count should be monitored at least every 3 months during pregnancy and at approximately 34–36 weeks to inform decisions on mode of delivery.¹⁵⁴ Monitoring for potential complications of antiretroviral therapy should be based upon the known side effects of the drugs the woman is receiving. For example, monitoring for hematologic toxicity will be needed in women receiving AZT; women receiving NVP should have frequent monitoring of liver transaminase levels, particularly during the first 18 weeks of therapy, and women receiving PIs may require more frequent monitoring for development of hyperglycemia. Because of the limited data of the effect of combination antiretroviral therapy on the fetus, more intensive fetal monitoring should be considered for women receiving combination therapy during pregnancy, including assessment of fetal anatomy with a level II ultrasound and continued assessment of fetal growth and well-being during the third trimester.

■ CHOICE OF ANTIRETROVIRAL DRUGS IN PREGNANCY

Antiretroviral therapy in pregnancy involves two separate but related goals: treatment of maternal HIV disease and reduction of MTCT. The special circumstances of pregnancy raise additional issues of toxicity to mother and fetus, which affect choice of antiretroviral drug, and of the need for antiretroviral prophylaxis for prevention of MTCT, but these concerns should be dealt with in the context of assuring optimal

Table 85-5. Recommendations for Antiretroviral Drug Use by Pregnant HIV-1-Infected Women and Prevention of Mother-to-Child Transmission in the United States

Clinical Situation	Recommendation
HIV-1-infected woman of childbearing potential but not pregnant and who has indications for initiating antiretroviral therapy	<ul style="list-style-type: none"> • HAART as per U.S. treatment guidelines. • Avoid drugs with teratogenic potential (EFV) in women of childbearing age unless adequate contraception ensured. Exclude pregnancy before starting treatment with EFV.
HIV-1-infected woman with indications for antiretroviral therapy, who is receiving HAART and becomes pregnant	<p>Woman:</p> <ul style="list-style-type: none"> • Continue current HAART regimen except discontinuing drugs with teratogenic potential (EFV) or with known adverse potential for the pregnant mother (combination d4T/ddI). • Discontinuation of antiretroviral drugs during the first trimester is not recommended. • Continue HAART regimen during intrapartum period (AZT given as continuous infusion^a during labor) and postpartum. • Elective cesarean delivery if plasma HIV-1 RNA remains >1000 copies/mL at 34–36 wk gestation. <p>Infant:</p> <ul style="list-style-type: none"> • AZT for 6 wk.
HIV-1-infected pregnant woman with antenatal plasma HIV-1 RNA \geq 1000 copies/mL who is not currently receiving antiretroviral therapy	<p>Woman:</p> <ul style="list-style-type: none"> • HAART (ideally containing AZT after the first trimester). • Due to risk of severe hepatic toxicity with NVP in women with CD4 >250/mm³, use NVP in this situation only if benefit clearly outweighs risk and alternatives not available. • Continue HAART regimen during intrapartum period (AZT given as continuous infusion^a during labor). • Evaluate need for continued therapy postpartum; discontinue HAART unless has indications for continued therapy (if regimen includes drug with long half-life like NNRTI, consider stopping NRTIs 3–7 d after stopping NNRTI although limited data). • Elective cesarean delivery if plasma HIV-1 RNA remains >1000 copies/mL at 34–36 wk gestation. <p>Infant:</p> <ul style="list-style-type: none"> • AZT for 6 wk.
HIV-1-infected pregnant woman with antenatal maternal plasma HIV-1 RNA <1000 copies/mL who is not currently receiving antiretroviral therapy	<p>Woman:</p> <ul style="list-style-type: none"> • HAART (ideally containing AZT after the first trimester), plus AZT given as continuous infusion^a intrapartum. Discontinue HAART postpartum (if regimen includes drug with long half-life like NNRTI, consider stopping NRTIs 3–7 d after stopping NNRTI although limited data). <p>OR</p> <ul style="list-style-type: none"> • AZT given antepartum after the first trimester and as continuous infusion^a during labor.

(Continued)

Table 85-5. (Continued)

Clinical Situation	Recommendation
HIV-1 infected woman who has received no antiretroviral therapy prior to labor	<p>Infant:</p> <ul style="list-style-type: none"> • AZT for 6 wk. • Several effective regimens are available to choose from for women who have had no prior therapy: <ol style="list-style-type: none"> 1. <i>AZT</i> <i>Woman:</i> AZT given as continuous infusion^a during labor. <i>Infant:</i> AZT for 6 wk. <i>OR</i> 2. <i>Combination AZT ± NVP</i> <i>Woman:</i> AZT given as continuous infusion^a during labor, plus single-dose NVP at onset labor. Intrapartum 3TC plus 1 wk postpartum AZT/3TC should be considered to reduce the risk of NVP resistance. <i>Infant:</i> Single-dose NVP (2 mg/kg) plus AZT for 6 wk. 3. <i>PETRA AZT ± 3TC</i> <i>Woman:</i> AZT + 3TC every 12 h during labor. <i>Infant:</i> AZT + 3TC twice daily for 1 wk. <i>OR</i> 4. <i>Single-dose NVP</i> <i>Woman:</i> Single-dose NVP (200 mg). Intrapartum and 1 wk postpartum AZT/3TC should be considered to reduce the risk of NVP resistance. <i>Note:</i> If delivery is imminent (<1 h), do not give the maternal intrapartum NVP as insufficient time to reach adequate level in infant. <i>Infant:</i> Single-dose NVP (2 mg/kg) at 48–72 h of age. <i>Note:</i> If mother did not receive intrapartum NVP, then could give infant NVP at birth and 48–72 h.
Infant born to HIV-1-infected woman who has received no antiretroviral therapy prior to or during labor	<p><i>OR</i></p> <ul style="list-style-type: none"> • AZT given for 6 wk to the infant, started within 6–12 h of birth) <p><i>OR</i></p> <ul style="list-style-type: none"> • Some clinicians may choose to use AZT in combination with additional drugs, but appropriate dosing for neonates is incompletely defined and the additional efficacy of this approach in reducing transmission is not known.

^aAZT continuous infusion: 2 mg/kg AZT intravenously over 1 hour, followed by continuous infusion of 1 mg/kg/h until delivery.

HAART, highly active antiretroviral therapy; AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz.

Adapted from Public Health Service Task Force recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. For most recent guidelines see <http://AIDSInfo.nih.gov>. Accessed on October 17, 2005.

treatment to preserve the mother's health; pregnancy should not be a reason to defer standard therapy when it is needed. Table 85-6 delineates recommendations for use of antiretroviral drugs in pregnancy, including Food and Drug Administration (FDA) pregnancy classification and pharmacokinetic and pregnancy-related toxicity data for individual drugs.

Decisions related to choice of antiretroviral drugs during pregnancy involve weighing competing factors influencing risk and benefit. Maternal risk for disease progression and the gestational age of the pregnancy should be considered in determining the risks and benefits of delaying initiation of antiretroviral drugs until after the first trimester. The proven efficacy of antiretroviral therapy to reduce MTCT regardless of maternal HIV RNA levels means that all HIV-infected pregnant women should be receiving some kind of antiretroviral therapy during pregnancy, whether it is HAART or consideration of AZT alone for the rare antiretroviral-naïve woman who has HIV RNA levels <1000 copies/mL. The choice of antiretroviral drugs includes consideration of pre-clinical, animal, and human studies related to the short- and long-term safety of the particular drug in pregnancy for the woman and her infant. Choice of drug also involves consideration of potential drug interactions between antiretroviral drugs themselves or with other medications the woman is receiving.

The period when the fetus is most susceptible to potential teratogenic effects of the drugs is during the first 10 weeks of gestation, and women who are in the first trimester of pregnancy may wish to consider delaying initiation of therapy until after 10–12 weeks of gestation; discussion should include assessment of the woman's health status and the benefits and risks of delaying initiation of therapy for several weeks. If the clinical or immune status of a woman in the first trimester of pregnancy suggests that she is severely ill, the benefits of early treatment outweigh the potential risk to the fetus. However, use of drugs that are potentially teratogenic, such as EFV (discussed below), should be avoided during the first trimester.

For women who require therapy for their own health and are already receiving treatment when they become pregnant, continuation of treatment is generally recommended as the benefit of therapy to maternal health for women who require therapy outweighs theoretical risk to the fetus. However, if the woman is receiving EFV and her pregnancy is recognized in the first trimester, EFV should be discontinued and another drug substituted due to teratogenicity issues, as discussed below.

Antiretroviral drugs and congenital abnormalities

Data on the risk of congenital abnormalities in infants born to women receiving antiretroviral drugs during pregnancy

has been assessed by observational studies and through the Antiretroviral Pregnancy Registry, an international registry of pregnancies exposed to antiretroviral agents prospectively reported by health-care providers.^{165–167} In the Antiretroviral Pregnancy Register, the prevalence of birth defects in infants with in utero antiretroviral exposure (during the first trimester or anytime during pregnancy) is not significantly different from the rates in the general population. Among infants with first trimester exposure to any antiretroviral, the birth defect rate was 2.9% (95% CI 2.2–3.8%) and for any exposure during pregnancy was 2.4% (95% CI 2.0–2.9%).¹⁶⁷ In CDC population-based birth defects surveillance, the total prevalence of birth defects identified among live births in the United States was 3.1% (95% CI 3.1–3.2%). Similar data have been reported by the Europeans.¹⁶⁵ There are sufficient numbers of cases of exposure in the Registry to AZT, abacavir (ABC), 3TC, stavudine (d4T), ddI, NVP, and NFV in the prospective cases to exclude a twofold or greater increase in birth defects among pregnant women exposed to these drugs in the first trimester compared to the general population.¹⁶⁷ There are insufficient data for meaningful analyses of other individual agents.

In retrospective case reports, significant central nervous system congenital abnormalities have been with first trimester exposure to EFV.¹⁶⁷ In primates, significant central nervous system malformations were observed in three of 20 infant monkeys with in utero EFV exposure at drug levels similar to those seen with human exposure at standard therapeutic doses; the malformations included anencephaly, anophthalmia and microphthalmia, and cleft palate. Central nervous system abnormalities (including myelomeningocele and Dandy–Walker malformation) have been reported in four human infants with first trimester exposure to EFV-containing regimens.^{167–170} Based on these data, EFV has been classified as U.S. FDA Pregnancy Category D (positive evidence of human fetal risk). Pregnancy should be avoided in women receiving EFV-based therapy, and EFV should be used during the first trimester or pregnancy only if the potential benefit justifies the potential risk to the fetus, such as in pregnant women without any other therapeutic options.

Combination antiretroviral therapy and pregnancy outcome

Data are conflicting about the association of combination antiretroviral therapy, particularly therapy containing PIs, and prematurity. Data from European cohorts suggest that use of antenatal antiretroviral therapy including a PI was associated with a 2.5-fold increased risk of premature delivery compared to no treatment, after adjustment for maternal CD4 count and use of illicit drugs, and that risk of preterm delivery was greatest for those women who started PI-based therapy before pregnancy or during the first

Table 85-6. Antiretroviral Drugs in Pregnancy: FDA Pregnancy Class, Pharmacokinetic and Toxicity Data, and Recommendations for Use in Pregnancy

Antiretroviral Drug	FDA Pregnancy Class ^a	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
<i>NRTIs/NtRTIs</i>			Potential maternal and infant mitochondrial toxicity (see text)	NRTIs are recommended for use as part of combination regimens, usually including two NRTIs and an NNRTI or PI. Use of one or two NRTIs alone is not recommended for treatment (AZT alone may be considered for prevention of MTCT in pregnant women with HIV RNA <1000 copies/mL).
<i>Recommended agents</i>				
Zidovudine (AZT)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or d4T use.
Lamivudine (3TC)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with 3TC in pregnancy in combination with AZT, 3TC plus AZT is the recommended dual NRTI backbone for pregnant women.
<i>Alternate agents</i>				
Didanosine (ddI)	B	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together.	Alternate NRTI for dual nucleoside backbone of combination regimens. ddI should be used with d4T only if no other alternatives are available.
Emtricitabine (FTC)	B	Study in progress.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone combination regimens.
Stavudine (d4T)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together.	Alternate NRTI for dual nucleoside backbone of combination regimens. d4T should be used with ddI only if no other alternatives are available. Do not use d4T with AZT due to potential for antagonism.
Abacavir (ABC)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Hypersensitivity reactions occur in 5–8% of nonpregnant persons; rate in pregnancy unknown.	Alternate NRTI for dual nucleoside backbone of combination regimens. Patient with hypersensitivity reaction should not be rechallenged, can be fatal. Patient should be educated regarding symptoms of hypersensitivity reaction.

Table 85-6. (Continued)

Antiretroviral Drug	FDA Pregnancy Class ^a	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
<i>Insufficient data to recommend use</i>				
Tenofovir (TFV)	B	No studies in human pregnancy. Phase I study of single dose in late pregnancy in progress.	Primate studies show decreased fetal growth, reduced fetal bone porosity with in utero exposure; bone demineralization seen with TFV therapy in children; clinical significance unknown.	Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, TFV should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
<i>Not recommended</i>				
Zalcitabine (ddC)	C	No studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity.	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.
NNRTIs				
<i>Recommended agents</i>				
Nevirapine (NVP)	C	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Increased risk of symptomatic, often rash-associated, potentially fatal liver first initiating therapy; unclear if pregnancy increases risk.	NVP should be initiated in pregnant women with CD4+ counts >250 cells/mm ³ only if benefit clearly outweighs risk, due to the increased risk of potentially life-threatening s NVP regimens and are tolerating them well may continue therapy, regardless of CD4 count.
<i>Not recommended</i>				
Efavirenz (EFV)	D	No studies in human pregnancy.	Anencephaly, anophthalmia, cleft palate in three of 20 infant monkeys born to mothers receiving EFV in the first trimester at levels similar to human exposure. There are	Use of EFV should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Use after the second trimester can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.

(Continued)

Table 85-6. (Continued)

Antiretroviral Drug	FDA Pregnancy Class ^a	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Delavirdine (DLV)	C	No studies in human pregnancy.	four reports of central nervous system defects in humans after first trimester exposure; relative risk unclear. Rodent studies indicate potential for carcinogenicity and teratogenicity.	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.
Protease inhibitors		For all PIs studied, lower levels observed in pregnancy than postpartum. With exception of NFV, PIs likely need low-dose RTV "boosting."	Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see text).	
Recommended agents				
Nelfinavir (NFV)	B	Adequate drug levels are achieved in most pregnant women with NFV 1250 mg, given twice daily.	No evidence of human teratogenicity. Well-tolerated, short-term safety in mother and infant. NFV dosing at 750 mg three times daily produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared to other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in nonpregnant adults, NFV-based regimens had a lower rate of viral response compared to LPV/RTV- or EFV-based regimens but similar viral response compared with ATV- or NVP-based regimens.
Lopinavir/ritonavir (LPV/RTV)	C	Preliminary studies of capsule formulation suggest low levels in later pregnancy, may need increased dose (533 mg LPV/133 mg RTV) in third and possibly second trimester; however, by	No evidence teratogenicity well tolerated, short term safety in mother & infant	Specific dosing recommendations for the tablet formulation not established. If used during pregnancy, monitor response to therapy closely. If expected virologic result is not observed, consult with a specialist with expertise in HIV in pregnancy.

Table 85-6. (Continued)

Antiretroviral Drug	FDA Pregnancy Class ^a	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
		2 wk postpartum, standard dose should be used. Pharmacokinetic data on current tablet formulation not yet available.		
<i>Alternate agents</i>				
Indinavir (IDV)	C	Studies show pregnant women receiving IDV 800 mg three times daily have markedly lower levels during pregnancy compared to postpartum, although HIV RNA generally suppressed.	Theoretical concern: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental IDV passage. Use of unboosted IDV during pregnancy is not recommended.	Alternate PI to consider if unable to use NFV or SQV-SGC/rtrv, but would need to give IDV as low-dose RTV-boosted regimen. Optimal dosing for the combination of IDV/RTV in pregnancy is unknown.
Saquinavir-hard gel capsule (HGC) (Invirase)/low-dose ritonavir (SQV/rtv)	B	Adequate drug levels are achieved in pregnant women with SQV-SGC 800 mg boosted with RTV 100 mg twice daily; SQV-SGC no longer available Limited pharmacokinetic data on SQV-hard gel capsule [HGC]/ rtv in pregnancy, suggest 1000 mg SQV-HGC/ 100 mg rtv given twice daily will achieve adequate levels in pregnancy.	Well-tolerated, short-term safety in mother and infant.	Given pharmacokinetic data and moderate experience with use in pregnancy, RTV-boosted SQV-HGC can be considered an alternative for combination regimens in pregnancy.
Ritonavir (RTV)	B	Lower levels during pregnancy compared to postpartum.	Limited experience in human pregnancy.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose rtv "boost" to increase levels of second PI.
<i>Insufficient data to recommend use</i>				
Amprnavir (APV)	C	Limited studies in human pregnancy.	Oral solution contraindicated in pregnant women due to	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use of capsules in pregnancy.

(Continued)

Table 85-6. (Continued)

Antiretroviral Drug	FDA Pregnancy Class ^a	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Fosamprenavir (fos-APV)	C	Limited studies in human pregnancy.	high levels of propylene glycol, which is not be adequately metabolized during pregnancy. Limited experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use in pregnancy.
Atazanavir (ATV)	B	Limited studies in human pregnancy.	Theoretical concern: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental PI passage has been low.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use in pregnancy.
Darunavir	B	No studies in pregnancy.	No experience in pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend in pregnancy.
Tipranavir (TPV)	C	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use in pregnancy.
<i>Fusion inhibitors</i>				
<i>Insufficient data to recommend use</i>				
Enfuvirtide (T-20)	B	No studies in human pregnancy	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use in pregnancy.

A: Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).

B: Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate and well-controlled studies of pregnant women have not been conducted.

C: Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.

D: Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.

X: Studies with animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

^aFood and Drug Administration pregnancy categories.

NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SGC, soft gel capsule; HGC, hard gel capsule.

Modified from Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States. Centers for Disease Control and Prevention. MMWR. For most recent guidelines see <http://AIDSInfo.nih.gov>. Accessed on October 17, 2005.

trimester.^{45,46,171} However, data from U.S. cohorts have not indicated an association of preterm delivery with PI-based HAART use, regardless of time of initiation.^{47,172–174}

An association was also suggested between HAART use and pre-eclampsia in cohorts from the UK and Spain^{175,176} but was not observed in U.S. cohorts.^{172–174} It is hypothesized that there may be an immunologic mechanism for an association of HAART with preterm delivery and pre-eclampsia.¹⁷⁷ Normal immune modulation in pregnancy is associated with an increase in type 2 and decrease in type 1 cytokines, and adverse pregnancy outcome has been associated with poor type 2 cytokine production. HIV disease is accompanied by a shift from a type 1 to type 2 cytokine environment; however, with immune restoration from HAART, there is a resultant increase in type 1 cytokine production, which, it is hypothesized, might induce pregnancy complications such as preterm delivery or pre-eclampsia.¹⁷⁷

Because the available data are conflicting, no definitive conclusions can be drawn about an association of antiretroviral therapy and adverse pregnancy outcome; further evaluation is needed. HIV-infected women receiving antiretroviral therapy should have careful, regular monitoring for pregnancy complications and for potential toxicities.

Antiretroviral drug resistance testing

Antiretroviral drug resistance develops when viral replication continues under the selective pressure of drug exposure, as can occur with suboptimal, nonsuppressive therapy or if plasma drug concentrations are below inhibitory levels, either due to dosing or pharmacokinetic problems or poor/intermittent adherence to therapy. Drug resistance (along with lack of adherence) is a major reason for therapy failure and lack of viral suppression, which both can affect maternal health and the risk of MTCT. Genotypic and phenotypic assays are available to detect antiretroviral resistance. Transmission of drug-resistant virus has been reported, including through MTCT.^{178,179}

Recommendations for antiretroviral drug resistance testing in pregnant women are the same as those for nonpregnant persons: viral failure with persistently detectable HIV RNA levels while receiving therapy or suboptimal viral suppression after initiation of therapy; individuals with a high likelihood of having resistant virus based on community prevalence or resistance, known drug resistance in the woman's partner, or other source of infection; or acute infection.^{154,156} In the case of viral failure, resistance testing should be performed while the patient is receiving the failing drug regimen to maximize the detection of drug resistance, as mutations may fade when drugs are discontinued and selective pressure is no longer being exerted, although they may remain archived in cellular virus and re-emerge when the drug or a cross-resistant drug is administered.¹⁵⁶

Recommendations related to drug resistance testing in antiretroviral-naïve pregnant women with chronic HIV infection has been more controversial. The prevalence of antiretroviral drug resistance in newly infected, therapy-naïve individuals has varied by geographic region; recent studies in the United States and Europe indicate a prevalence of drug resistance among antiretroviral-naïve patients of 8–10%.^{180,181} The prevalence of resistance in pregnant women also varies depending on the characteristics of the population studied and does not necessarily correlate with failure of antiretroviral drug prophylaxis of MTCT.^{182–184} The International AIDS Society recommends that all HIV-infected pregnant women undergo resistance testing when first seen to guide treatment.¹⁸⁵ A recent analysis by the CDC suggests that resistance testing in treatment-naïve, chronically infected nonpregnant individuals may be cost effective and improve clinical outcome if the prevalence of drug resistance is $\geq 1\%$.¹⁸⁶

Nucleoside/nucleotide analogue reverse transcriptase inhibitor drugs

The nucleoside analogue reverse transcriptase inhibitor (NRTI) drugs are generally well tolerated in pregnancy (Table 85-6). All the NRTI drugs have been shown to cross the placenta in humans (AZT, ddI, and 3TC) or animals (ABC, d4T, emtricitabine [FTC], tenofovir [TFV], and zalcitabine [ddC]), although with different cord blood:maternal drug ratios (ranging from 0.5 for ddI to 0.85 for AZT).^{177,187} Pharmacokinetic studies on the NRTI drugs studied to date in pregnant women (which include ABC, AZT, ddI, d4T, and 3TC) have not demonstrated a need for dose modification of the drugs during pregnancy.¹⁸⁷

The efficacy of AZT to reduce MTCT was demonstrated in PACTG 076²; AZT should be included as a component of antiretroviral therapy or prophylaxis whenever possible, given its proven efficacy in reducing MTCT. In addition to antenatal treatment, the PACTG 076 regimen includes intravenous AZT during labor and administration of 6 weeks of AZT to the infant. The NRTI drugs with the greatest clinical experience with use in pregnant women are AZT and 3TC, which are the preferred NRTIs for use in pregnant women (Table 85-6). Alternative NRTI drugs for use in pregnancy include ABC, d4T, ddI, and FTC. There are not yet data on use of FTC in pregnancy, although data on the other NRTI drugs suggest that standard dosing would be appropriate and it has been classified as FDA Pregnancy Category B (no animal safety concerns but no human data).

There are also no data on use of TFV during pregnancy. Studies in infant monkeys with in utero TFV exposure have not demonstrated gross congenital abnormalities but have shown decreased fetal growth and a reduction in fetal bone porosity within 2 months of starting maternal therapy¹⁸⁸; additionally, bone demineralization has been observed in some infected

children receiving chronic TFV-based therapy.¹⁸⁹ The clinical significance of these findings for children with in utero TFV exposure is unknown. Because of the lack of data on use in human pregnancy and concern regarding potential fetal bone effects, TFV should be used as a component of therapy in pregnant women only if there are no other alternatives.

NRTI drugs can bind to mitochondrial DNA polymerase gamma, which can cause mitochondrial dysfunction.^{154,177,190} Manifestations of mitochondrial dysfunction can include lactic acidosis, hepatic steatosis, myopathy, cardiomyopathy, or neuropathy. Whether such toxicities are enhanced in pregnant women is unknown. However, fatal cases of lactic acidosis and hepatic failure have been reported in pregnant women who received the combination of d4T/ddI throughout pregnancy.^{177,190} Use of the dual NRTI combination of d4T/ddI should be avoided in pregnancy and only used when no other alternatives exist. Although this complication has been reported most commonly with long-term use of d4T/ddI, the potential exists with all the NRTI drugs (binding affinity to mitochondrial polymerase gamma is greatest for ddC, followed by ddI, d4T, AZT, 3TC, ABC, and TFV).¹⁹¹ Therefore, clinicians should be alert for symptoms of liver dysfunction and lactic acidosis, which can be nonspecific, in women receiving NRTI drugs. Routine monitoring of blood lactate is not recommended, because an elevated lactate alone is not predictive of the development of lactic acidosis; however, measurement of serum lactate, along with liver enzymes, would be useful in pregnant women receiving NRTI drugs if suggestive symptoms are present.

It has been suggested that mitochondrial dysfunction might develop in infants with in utero exposure to NRTI drugs. Data from a French cohort of over 4300 uninfected, HIV-exposed children found an 18-month incidence of clinical symptoms of mitochondrial dysfunction of 0.26%, and mortality of 0.07%¹⁹²; these findings were only seen in children with perinatal antiretroviral exposure. The children presented with neurologic symptoms, often with abnormal magnetic resonance imaging and/or episode of significant hyperlactatemia, with deficits in mitochondrial respiratory chain complex enzyme function on biopsy of muscle. The same group has also reported an increased risk of simple febrile seizures in the first 18 months of life and persistently lower (but clinically insignificant) neutrophil, lymphocyte, and platelet counts in infants with in utero NRTI exposure.^{193,194} Although the clinical abnormalities and mortality findings have not been duplicated in other cohorts from the United States and Europe to date,^{195,196} the European Collaborative Study has reported similar persistent, although clinically asymptomatic, hematologic abnormalities in uninfected infants with in utero exposure.^{197,198} Further studies to evaluate mitochondrial DNA content and clinical findings in infants with in utero antiretroviral drug exposure are ongoing.

Thus, data are conflicting regarding whether mitochondrial dysfunction is associated with in utero antiretroviral exposure. If the association is confirmed, the risk of severe or fatal mitochondrial disease appears to be extremely rare and must be compared against the clear benefit of antiretroviral prophylaxis in reducing transmission of a fatal infection by 70% or more.^{32,154} Mitochondrial dysfunction should be considered in HIV-exposed, uninfected children with perinatal antiretroviral exposure who present with severe clinical findings, particularly neurologic findings, of unknown etiology. Additionally, all children with in utero exposure to antiretroviral drugs should have long-term follow-up into adulthood for potential toxicities of such exposure.¹⁵⁴

NNRTI drugs

Of the NNRTI drugs, only NVP has been studied in pregnant women; NVP pharmacokinetics during chronic administration in pregnant women are similar to those in nonpregnant women.¹⁸⁷ NVP crosses the placenta, with a cord blood:maternal ratio of approximately 1.0. Data from the Antiretroviral Pregnancy Registry indicate that the prevalence of birth defects with first trimester NVP exposure was 2.1%, similar to the 3.1% total prevalence of birth defects in the U.S. population.¹⁶⁷ NVP is the NNRTI drug of choice in pregnancy, due to extensive clinical experience with this drug in pregnant women (Table 85-6).

However, symptomatic NVP-associated hepatic or serious rash toxicity (Stevens Johnson Syndrome/Toxic Epidermal Necrolysis), while uncommon, can be life threatening, is more frequent in women than in men, and is more likely to be seen in antiretroviral-naïve women with higher CD4 cell count (>250 cells/mm³).^{199–201} It is not known if pregnancy further predisposes women to such toxicities, but cases have been reported in pregnant women.^{202,203} Thus, NVP should not be used as a component of an antiretroviral regimen when antiretroviral therapy is being initiated in women with CD4 cell counts >250 cells/mm³ (e.g., when used solely for prevention of MTCT in women who do not require therapy for their own health) unless there are no other available alternatives.¹⁵⁴ Health-care providers caring for women receiving NVP during pregnancy should be aware of this potential complication and conduct frequent and careful monitoring of hepatic transaminases and clinical symptoms, particularly during the first 18 weeks of therapy. Additionally, transaminase levels should be checked in all women who develop a rash while receiving NVP. Patients who experience clinical hepatotoxicity or severe rash while receiving NVP should have NVP discontinued and should not receive NVP therapy in the future.

The other FDA-approved NNRTI drugs, delavirdine (DLV) and EFV, have not been studied in pregnant women and are teratogenic in laboratory animals. Administration of DLV to pregnant rats at doses producing systemic levels

similar or lower than typical human exposures was associated with ventricular septal defects and increased infant mortality in the offspring.¹⁸⁷ EFV has been discussed previously. As noted previously, if a woman receiving EFV-containing therapy becomes pregnant and this is recognized during the first trimester, EFV should be discontinued and replaced by another drug. If the patient is already in the second or third trimester when pregnancy is recognized, the high-risk exposure has already occurred and some clinicians might opt to continue EFV and evaluate the fetus by ultrasound for defects.²⁰⁴ The exposure and risk should be discussed with the patient, and adequate contraception should be ensured when the woman is postpartum.

PI drugs

The PI drugs that have been studied in human pregnancy (NFV, saquinavir [SQV], indinavir [IDV], ritonavir [RTV], and lopinavir/ritonavir [LPV/r]) have generally been well tolerated (Table 85-6).^{172,187} Gastrointestinal symptoms are the most common side effects of the PI drugs (e.g., nausea, vomiting, and diarrhea). There is minimal transplacental passage of PIs in humans and most infants born to mothers receiving PIs have undetectable PI concentration in cord blood.^{205,206} While the limited transplacental transfer may protect the fetus from potential toxicities from in utero exposure to drug, it also suggests that PI therapy during labor will not provide postexposure prophylaxis to the newborn at the time of birth, in contrast to the NRTI drugs or NVP. No specific teratogenic effects have been noted in animals or observed in the Antiretroviral Pregnancy Registry to date, although with the exception of NFV, the numbers of reported pregnancies remain small.¹⁶⁷

Optimal dosing of PIs in pregnancy remains to be determined; lower serum concentrations have been observed in pregnant compared to nonpregnant women, although in most cases HIV RNA levels in the pregnant women have remained suppressed.^{32,187} There are conflicting data regarding NFV levels in pregnant women; however, data suggest that although levels are variable, standard 1250 mg twice daily dosing should maintain adequate levels in most women.²⁰⁷⁻²¹⁰ Other than NFV, use of nonboosted PIs in pregnancy is not recommended. Given the safety experience and documentation of appropriate dosage, NFV given twice daily or LPV/r are reasonable choices for PI drugs in pregnant women (Table 85-6). Some data suggest that drug levels of LPV/r when given on the no longer available capsule formulation may be lower in pregnant women during the third trimester than postpartum²¹¹; there are not yet data on the currently available tablet formulation of LPV/r. Viral response to treatment should be carefully monitored. There are very limited to no data on the pharmacokinetics of amprenavir (APV), fos-APV, atazanavir (ATV), darunavir (DRV) or tipranavir (TPV) in pregnant women.

Hyperglycemia, new-onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with administration of PI drugs in HIV-infected patients.^{177,212} In addition, pregnancy is itself a risk factor for hyperglycemia; it is unknown if the use of PIs will exacerbate the risk for pregnancy-associated hyperglycemia. Some data suggest that pregnant women receiving a PI have a slightly higher risk of developing gestational hyperglycemia or diabetes than HIV-uninfected or HIV-infected women receiving either no therapy or NRTIs only.^{173,213,214} In one study, infants born to women with an abnormal glucose tolerance test had lower mean birth weight than those born to women with normal tests.²¹⁴ Clinicians caring for HIV-infected pregnant women receiving PIs should be aware of this complication and closely monitor glucose levels. Patients should be educated to recognize the early symptoms of hyperglycemia and to promptly seek health care if such symptoms develop.

PI drugs are metabolized by the hepatic CYP 450 enzyme system and can induce, inhibit, or both induce and inhibit drug metabolism enzymes, leading to the potential for complex interactions of PI drugs with other each other, NNRTI drugs, or other drugs metabolized by these enzymes.¹⁸⁷ Therefore, diligent monitoring of concomitant medications is needed.²¹⁵

MANAGEMENT OF LABOR

The management of the HIV-infected woman during delivery of her infant aims to minimize the risk of MTCT, while not increasing maternal and neonatal morbidity and mortality (Table 85-4). A thorough review of maternal therapies should be done prior to administration of any drugs during labor to avoid any potentially adverse drug interactions. For example, ergot preparations should be avoided and women receiving midazolam should be monitored closely in women receiving PIs or the NNRTIs EFV or DLV because their metabolism may be delayed by such antiretroviral drugs.³²

The potential mode of delivery should be discussed with the woman throughout pregnancy and final decisions should be based on the HIV RNA level at 34–36 weeks of gestation and the wishes of the mother.¹⁵⁴ ACOG recommends that elective cesarean delivery should be discussed and recommended for all HIV-infected pregnant women with viral loads above 1000 copies/mL²¹⁶ (Table 85-5). If the decision is made to perform an elective cesarean delivery, ACOG recommends that it be done at 38 weeks' gestation, due to the potential risk for labor and membrane rupture before the woman would reach 39 weeks' gestation, the standard recommended time for operative deliveries in women without HIV infection. Because of the potential for increased postoperative maternal morbidity in HIV-infected women undergoing operative delivery, clinicians may opt for administering perioperative antibiotic prophylaxis.^{212,217} In the developing world, operative delivery would not be an intervention that could be

routinely implemented safely or easily, due to its expense, invasive nature, and attendant risk of maternal morbidity and mortality.^{218,219}

In women at very low risk of transmission, such as those with low or undetectable viral load, the additional benefit provided by elective cesarean section may be marginal. The Public Health Service has developed four clinical scenarios to assist in the decision about whether or not to perform an elective cesarean delivery to reduce perinatal HIV transmission.¹⁵⁴

Intrapartum management of HIV-infected women should, whenever possible, minimize invasive procedures that might increase MTCT, such as fetal blood sampling and invasive fetal monitoring with procedures that may cause a break in the infant skin, such as scalp electrodes, instrumental delivery, and artificial rupture of membranes. Because duration of membrane rupture is associated with risk of MTCT,²²⁰ in women not undergoing elective cesarean delivery, the interval between rupture of membranes and delivery should be minimized through augmenting labor as needed after spontaneous rupture has occurred.

Intrapartum AZT prophylaxis should be provided regardless of the mode of delivery, as the available data indicate that AZT provides an additional protective effect in women undergoing elective operative delivery.^{66,67,116} Intravenous AZT should begin 3 hours prior to a scheduled cesarean delivery. Other antiretroviral drugs should be continued on schedule during labor or preoperatively to provide maximal virologic effects and to minimize the risk of developing drug resistance. However, d4T may antagonize the effects of AZT and therefore for women on a d4T-containing regimen, d4T should be either given orally without AZT or discontinued before intravenous AZT is administered.

Avoidance of episiotomy may decrease exposure of the infant to maternal blood; the infant should be washed before any blood is drawn, injections given, or other invasive procedures performed. Care of the HIV-exposed infant is discussed further in Chapter 86 (“Pediatric HIV Infection: Managing HIV-Exposed and HIV-Infected Children”).

■ POSTPARTUM CARE

Because of the risk of transmission of HIV through breastfeeding, in areas where there are safe alternatives to breastfeeding, such as the United States and other resource-rich countries, HIV-infected women should be advised not to breastfeed.^{154,212} This recommendation also applies to women receiving antiretroviral therapy. Passage of antiretroviral drugs into breast milk in humans has been evaluated for only a few antiretroviral drugs. AZT, 3TC, and NVP have been detected in breast milk of women receiving the drugs⁹⁹; while the passage of other antiretroviral drugs into breast milk has not been studied in humans, studies in lactating rodents have demonstrated passage of most other antiretroviral drugs into breast milk. However, while HAART has been found to

decrease HIV RNA levels in milk, it does not appear to decrease cell-associated virus.⁹⁸ As discussed previously, the efficacy of antiretroviral therapy for prevention of postnatal transmission of HIV through breast milk and the toxicity of chronic antiretroviral exposure of the infant via breast milk are unknown.

Maternal medical services during the postpartum period need to be coordinated between obstetric and HIV-specialist health-care providers. When combination therapy during pregnancy is required for treatment of the woman’s HIV disease, assurance of continuity of antiretroviral therapy postpartum is critical. Additional support and measures to enhance adherence to treatment may be needed because the physical changes of the postpartum period coupled with the stress and demands of caring for a newborn infant may make adherence more difficult during this period.²²¹

For women receiving antiretroviral drugs solely for prevention of MTCT, an evaluation should be made to determine the need for antiretroviral therapy during the postpartum period. If therapy is not required, antiretroviral drugs can be discontinued. In general, all drugs should be discontinued simultaneously. However, due to the long half-life of the NNRTI drugs⁹⁴ and the potential for single mutation to induce resistance to this class of drugs, some clinicians may continue the dual NRTI component of therapy for a period of time (e.g., 7 days) after discontinuation of the NNRTI in an attempt to reduce the risk of developing resistance. The optimal duration of time is not known; NVP resistance was seen in 15% of women receiving NVP-based HAART who had staggered discontinuation of therapy, with 5 days of dual NRTI therapy continued after stopping NVP.^{112,113}

HIV-infected women should receive comprehensive care and support services in the period following delivery, including HIV-related medical care, psychosocial support, and assistance with family planning and contraception (Table 85-4). Options for contraceptive methods should be discussed. Barrier methods of contraception are recommended to prevent HIV transmission and potential acquisition of HIV superinfection or other sexually transmitted diseases. If hormonal contraception is being considered, potential interaction with antiretroviral and opportunistic infection prophylaxis drugs should be assessed.¹⁵⁴ Several PI and NNRTI drugs as well as rifampin and rifabutin may lower hormonal levels and decrease contraceptive efficacy of oral hormonal contraceptives (see Chapter 78 “Contraceptive Choices and STD/HIV”). Interactions of antiretroviral drugs with injection hormonal contraceptives, such as depot medroxyprogesterone, are under study.

SUMMARY

The care of the HIV-infected pregnant women is challenging for the obstetrician-gynecologist, who has the dual responsibility of assuring the health of the woman and of her child.

While primary prevention of HIV infection in women is the ultimate goal, half of individuals newly infected with HIV are women, and many will become pregnant. The obstetrician must be able to offer state-of-the-art care to maximize the health of the mother and her fetus and infant and to minimize MTCT. Standards of care for the treatment of HIV infection change rapidly, and up-to-date recommendations from the U.S. Public Health Service regarding treatment of HIV infection in pregnancy and prevention of MTCT are available at <http://AIDSInfo.nih.gov>.

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Pediatric HIV Infection: Epidemiology, Treatment, and Complications in the United States and Internationally

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This chapter presents an overview of the epidemiology, spectrum of disease, and current treatment of HIV-1 infection among infants, children, and adolescents—internationally and in the United States.

BACKGROUND: EPIDEMIOLOGY OF PEDIATRIC HIV-1 IN THE UNITED STATES AND WORLDWIDE

The HIV-1 pandemic has had a profound impact on the health and survival of children worldwide. As of December 2004, UNAIDS estimates that 2.2 million children less than 15 years of age were living with HIV.¹ Of these children, the vast majority (1.9 million) reside in sub-Saharan Africa. In addition, in 2004, approximately 640,000 children under 15 years of age were newly infected with HIV, primarily through mother-to-child transmission—either prenatally, at the time of delivery, or through breast-feeding. Unless there is an unexpected abatement in the global spread of HIV, the numbers of HIV-infected and affected infants, children, and adolescents will continue to escalate with increasing numbers of pediatric HIV infections being seen in the Far East as well as Africa.

The health gains in child survival that were hard won in the 1980s and early 1990s based on widespread implementation of interventions including early childhood immunization programs, promotion of breast-feeding, and use of oral rehydration therapy have in many countries been reversed due to HIV disease among both children and their caretakers. In countries such as Botswana, Zimbabwe, and Swaziland, under 5 mortality rates have doubled in recent years. In 2004, WHO/UNAIDS estimated that 510,000 children worldwide died from AIDS related causes.¹ This is occurring in the background of malnutrition, endemic diarrheal and lower respiratory infectious diseases, and malaria as well as high maternal HIV prevalence which place infants and children at increased risk for both HIV-related and other mortality.²

■ EVOLVING U.S. PEDIATRIC HIV EPIDEMIC

In the United States, there has been major progress in the prevention of perinatal HIV transmission since 1994 when the landmark trial, PACTG 076,³ demonstrated that an intensive regimen of zidovudine given to the mother prenatally and intrapartum and followed by 6 weeks of zidovudine to the newborn, could reduce mother-to-child HIV transmission by two-thirds. Today with routine prenatal testing leading to identification of HIV-infected women during pregnancy, use of potent combination antiretroviral (ARV) and obstetrical interventions, avoidance of breast-feeding, mother-to-child transmission rates of 2% or less are being achieved.^{4,5} In 2003, fewer than 200 HIV-infected infants were estimated to have been born in the United States. Elimination of any new perinatal HIV cases in the United States remains a major public health goal.

By the end of 2003, CDC estimated that there were 9419 cumulative AIDS cases reported among children <13 years since the beginning of the epidemic in the United States, the vast majority of whom were children infected through mother-to-child HIV transmission.⁶ Also, by the end of 2003, there were 3927 children <13 years of age living with AIDS. In recent years, the numbers of newly reported perinatal AIDS cases have declined steadily both due to sharp reductions in perinatal HIV transmission since 1994 and potent combination treatment which has slowed the pace of progression to AIDS among HIV-infected children (Fig. 86-1).

With respect to the HIV epidemic among adolescents, at the end of 2003, the estimated number of 13–15-year olds living with AIDS in the United States was 1145 (554 males and 591 females) of whom 989 (86%) were perinatally infected, and the estimated number of 16–19-year olds living with AIDS was 1422 (715 males and 707 females) of whom 672 (47%) were perinatally infected.

The bulk of the pediatric and adolescent HIV epidemic in the United States is represented by an aging population of perinatally infected children with increasing long-term survival due to potent combination ARV treatment, as well as recently

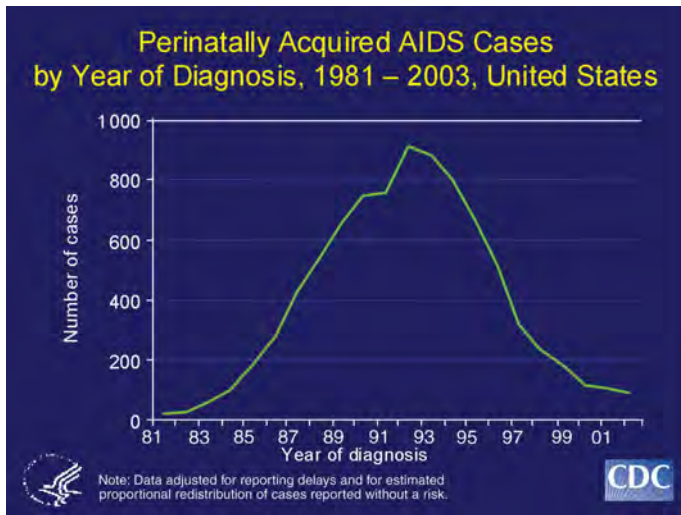


FIGURE 86-1. CDC HIV perinatal AIDS surveillance.

infected adolescents who acquired their HIV from sexual contact and/or illicit drug-related behaviors.

■ DEMOGRAPHICS OF THE PEDIATRIC/ADOLESCENT HIV EPIDEMIC IN THE UNITED STATES

The majority of children <13 years of age in the United States living with AIDS were perinatally infected and are of black non-Hispanic or Hispanic race/ethnicity.⁶ These demographics mirror the HIV epidemic among women in the United States. Equivalent numbers of perinatally infected male and female children <13 years of age are living with AIDS, as are adolescents. Most children with perinatal AIDS live in high prevalence states where the burden of HIV among women is highest.

Emerging adolescent HIV epidemic

The southern region of the United States is seeing an increasing burden of HIV infection among youth. For adolescents aged 13–19 years, 157 of 314 or 50% of the estimated new AIDS cases diagnosed in 2003 were reported in the South. AIDS rates among youth were highest among non-Hispanic blacks followed by Hispanics. About equal numbers of new AIDS diagnoses were seen among male and female teens. AIDS represents one of the top 10 causes of death among blacks aged 10–19 years.⁶

The numbers of behaviorally HIV-infected adolescents living in the United States are likely underestimated due to a number of factors: name-based HIV (non-AIDS) reporting is not done in all states; HIV testing is not usually done as part of routine health care in adolescence; and the majority of recently infected adolescents are asymptomatic. Thus, many behaviorally infected adolescents do not become identified as HIV infected until they become symptomatic from their disease, which often does not occur until their twenties. Available CDC 2003 surveillance data⁶ from 33 HIV-reporting states indicates that three-quarters of new HIV infections

occurred among black and Hispanic youth, and that in 13–19 year olds, new cases of HIV infection among females and males were equal. Among females, heterosexual transmission was the major mode of transmission. Among males, transmission related to male-to-male sexual exposure accounted for three-quarters of all newly reported HIV (non-AIDS) infections. Rosenberg et al.⁷ have estimated that 25% of the 40,000 estimated incident adolescent/ adult HIV infections occurring each year in the United States were among adolescents and youth <22 years of age.

International trends

The major impact of HIV among children worldwide has been experienced in resource-constrained settings. As HIV is a relatively new infection, considerable infrastructure needs to be in place to diagnose and treat HIV infection, both among adolescents as well as HIV-exposed infants. Adolescents in international settings are especially vulnerable to HIV due to initiation of sexual behaviors during puberty in a background of high HIV seroprevalence. In most developing international settings, including middeveloped countries such as South Africa, the majority of adolescents do not use condoms despite broad awareness of HIV.⁸ In the 2004 antenatal seroprevalence study in South Africa, the seroprevalence among women less than age 20 years was 16.1%, increasing from 2% in 1992.⁹ As access to ARVs increases, increasing numbers of vertically infected infants will also likely reach adolescence. Currently there are few health-care programs or facilities in resource-constrained settings focusing on unique issues associated with adolescents and HIV.

Despite high antenatal HIV seroprevalence in many resource-limited settings in Africa, the introduction of mother-to-child HIV prevention programs has been slow until recently. However, with the infusion of substantive donor funding, infrastructure has improved and more is being accomplished. Perinatal HIV prevention programs are a key entry point for women and their partners into HIV prevention and identification programs. The scale is immense. For example, in South Africa this translates into HIV screening accompanied by pre- and posttest counseling for a million pregnancies per year and perinatal HIV transmission prophylaxis for 270,000 women and their infants.⁹ National prevention of mother-to-child transmission programs (PMTCT) in resource-limited settings often rely on single dose nevirapine prophylaxis because of the simplicity of the regimen coupled with moderate efficacy (12% transmission rate; 42% relative efficacy at 6 weeks¹⁰ and 18 months¹¹). Relatively more complex programs such as maternal zidovudine from 28 weeks gestation plus single dose nevirapine to mothers and their newborns have been shown to reduce transmission to 2% in a Thailand trial¹² among non-breast-feeding women and to about 5% in a West African breast-feeding setting.¹³

Trials are currently underway to assess the relative efficacy and toxicity of maternal HAART given prenatally and during 6 months of breast-feeding when compared to short course zidovudine plus single dose NVP, as well as trials assessing the efficacy of extended infant prophylaxis during breast-feeding.¹⁴ As trial results emerge and infrastructure to deliver ARV treatment improves, use of maternal HAART for perinatal HIV prevention as well as extended infant exposure to ARVs may become more widespread in resource-limited settings. Follow-up monitoring for potential late sequelae of ARV exposure as well as improvements in child survival will be important.

Early diagnosis of HIV infection among HIV-exposed infants is crucial in order to intervene against the high risk of early mortality. In a meta-analysis of nine perinatal HIV transmission prevention studies undertaken in Africa, 52% of HIV-infected children died by 2 years of age, reflecting more than sixfold higher mortality than in exposed uninfected infants.¹⁵ Infant mortality is affected by many factors, including maternal health, nutrition, and availability of medication to treat and prevent opportunistic and intercurrent infections.

Programs to reduce mother-to-child HIV transmission will not only have considerable benefit for individual children but will enable health-care workers to focus more resources on early infant HIV diagnosis, delivery of ARVs, and careful follow-up management of infected infants and children.

DIAGNOSIS AND DEFINITIONS OF PEDIATRIC HIV INFECTION

■ INFANT HIV DIAGNOSTIC TECHNOLOGIES

In the United States, capability for early detection of HIV infection among infants advanced rapidly in the 1990s with widespread use of virologic assays. Polymerase chain reaction (PCR) assays are used most commonly and are widely available for infant diagnosis. Other diagnostic technologies used less frequently include HIV culture and immune complex dissociated p24 antigen assays. The majority of HIV-infected infants in the United States are followed at tertiary care centers and can reasonably be diagnosed as infected within the first weeks to months of life given the lack of breast-feeding. In one study by Dunn et al.,¹⁶ about 40% of HIV-infected infants had positive DNA PCRs on samples within the first 48 hours of life, 93% were positive by 14 days of life, and by one month of age 96% of later confirmed infant infections were detected with a specificity of 99%.

RNA PCR is used less frequently for infant diagnosis but several studies suggest that it is as sensitive as DNA PCR for infant diagnosis and may be somewhat more sensitive than DNA PCR in the first few weeks of life.^{17,18} At some U.S. pediatric treatment centers, quantitative RNA is used as the confirmatory test after an initial positive DNA test. This approach also has the advantage of providing a baseline viral load assessment prior to initiation of ARV treatment. PCR

testing of HIV-exposed infants is usually performed with the first 48 hours of life and then repeated several times during the first several months of life in order to definitively define infant HIV status. The use of PCR kits that are more sensitive in detecting non-B subtypes should be undertaken in U.S. settings if infection with non-B subtypes is a possibility.

In resource-limited international settings, early diagnosis of HIV infection is critical due to the high mortality rate approaching 40–50% for HIV-infected infants by 18–24 months of age.^{11,15} However, there are a number of barriers to early infant diagnosis. First, PCR assays are often not widely available to confirm pediatric HIV status particularly in resource-limited settings. Under these circumstances, HIV infection is generally not definitively ascertained until serological testing in the second year of life. Second, even where PCR technology is available, it is often not possible to perform more than one HIV-specific nucleic acid test per patient because of cost and infrastructure limitations.

Given ongoing breast-feeding, the optimum timing of PCR testing has not been determined. A number of perinatal HIV studies in resource-limited settings have documented ongoing infection in breast-feeding populations with a low but continual risk of transmission of about 0.6–0.9% per month after the first 6 weeks of life with an additional absolute risk of about 8–12% for infants who are breastfed through 18–24 months.^{19,20} In the PETRA study,²¹ transmission increased from 5.7% at 6 weeks to 15.7% at 18 months in the most intensive prenatal, intrapartum, and postpartum intervention arm of the trial. Likewise, in South Africa, the Good Start Study evaluated the operational effectiveness of the South Africa National PMTCT Program in three diverse sites (in Paarl, Western Cape, East Cape, and KwaZulu Natal) and found late transmission varied substantially by site resources. In Paarl, Western Cape, 8% of HIV-exposed infants negative at 3 weeks of age became infected by 36 weeks compared to 12% in KwaZulu Natal and 19% in the East Cape.²² Currently, South Africa ARV treatment guidelines, as well as Ministry of Health guidance in a number of other African countries, recommend infant HIV testing be done on a single DNA PCR at 6 weeks of age. However, some settings such as the Western Cape of South Africa have opted for PCR testing at 4 months because of increased ease of venipuncture by clinic nurses and ability to identify additional infants who may have been infected during early breast-feeding.

There is also increasing interest in the use of rapid tests for the detection of HIV antibodies in HIV-exposed infants in resource-limited settings due to cost-effectiveness and ease of use in primary care settings.²³ Efficacy is extrapolated from adult data. The test is considered accurate in children above 18 months of age, provided it is correctly performed and that a positive test is confirmed by a rapid test from a different manufacturer and from a separate blood draw. Use of oral fluids for diagnosis could prove extremely useful and avoid the need for blood draws for infant diagnosis.

■ PEDIATRIC HIV CASE DEFINITIONS—CDC AND WHO CRITERIA

The 1994 CDC definition²⁴ of definitive pediatric HIV infection requires at least two positive HIV viral assays (generally DNA PCR) on separate specimens. Definitive exclusion of HIV infection among HIV-exposed infants is based on two or more negative virologic tests on separate specimens, one of which is performed after 1 month of age and one after 4 months, and given that the mother is not breast-feeding. Follow-up serology at 15–18 months of age is routinely performed to confirm loss of antibody in an infant with negative PCRs. A positive serology at >18 months can also be used to identify older infants if they did not receive earlier PCR testing. The current CDC Pediatric Clinical and Immune Classification system for HIV-infected children is summarized in [Table 86-1](#). Children with either a Clinical Category C diagnosis (see [Table 86-1B](#)) and/or whose CD4 percentage falls in Immune Category 3 are defined as having AIDS.

In international resource-limited settings where many HIV-infected women breast feed, diagnosis of infant infection is considerably more challenging both due to a low but ongoing risk of HIV infection throughout lactation as well as limited availability of early infant virologic diagnosis. Based on studies in Kenya²⁵ and Uganda,¹¹ the mortality for HIV-infected infants without treatment is in the range of 40–50% by age 18–24 months. With the expanding availability of ARV treatment, development and implementation of innovative strategies to support early HIV diagnosis and identify infected infants is crucial in order to provide timely ARV and prophylaxis interventions to reduce the high risk of HIV-related mortality. Testing strategies being examined for widespread implementation include collection of infant dried blood spots (DBS) from HIV-exposed infants at 6 weeks of life under a variety of field settings, which can then be transported to regional centers where real-time PCR for infant diagnosis is available at relatively low cost.²⁶ Another approach is the use of heat dissociated p24 antigen assays,²⁷ which has the advantage of being a test that can be performed at local rural sites with limited laboratory facilities. However, the test is less sensitive than PCR in the first months of life.

There will continue to be some infants born to HIV-infected women in resource-limited international settings for whom early diagnosis, based on virologic tests, is not available. In this situation, the WHO supports use of total lymphocyte count (TLC) and clinical diagnosis to help identify HIV-exposed infants who are likely to be HIV infected and would benefit from ARV interventions even without a definitive virologic diagnosis.²⁸

■ THE CURRENT WHO CASE DEFINITION²⁸ OF INFANT HIV INFECTION

Definition of HIV infection in many international settings depends on the resources available for testing. Confirmed laboratory evidence of HIV infection includes the presence of

HIV antibody when the child is >18 months and virological PCR or P24 Ag testing for those aged <18 months when these tests are available. Most important is the situation of clinically advanced disease in the absence of virological confirmation, where highly active ARV treatment is indicated.

■ WHO STAGING

One of the most important issues when initiating a new program is how to effectively deploy scarce resources. Because of late initiation of ARV treatment programs, many children already have advanced disease. The CDC pediatric HIV classification system²⁴ was devised for North America and Europe and has much predictive value. Although useful in Africa, it does not accurately describe the clinical spectrum of disease. In a study from Malawi,²⁹ the majority of HIV-infected children had died prior to having any clinical or immunologic CDC staging done. Malnutrition is inadequately dealt with in the CDC classification since in order to be classified in category C, an infant must also have either chronic diarrhea or persistent fever. Malnutrition is a major predictor for death in African children.³⁰ Only disseminated TB is considered in the CDC pediatric HIV classification although other forms of TB, especially pulmonary, occur commonly in resource-poor settings.³¹ The current WHO criteria for clinical and immunologic staging are listed in [Table 86-2](#).

WHO has proposed the following definitions of AIDS for surveillance among children under 15 years: all Clinical Stage 3 or Stage 4 disease or where CD4 is available, any clinical stage with

- CD4% <25% in infants under 12 months;
- CD4% <20% in children 12 months or over;
- CD4 absolute count <350/mm³ in children 6 years and above.

■ PEDIATRIC HIV DISEASE PROGRESSION

There are a number of factors that appear to affect the rate of pediatric HIV disease progression. These include both host immunogenetics, viral characteristics, availability and adherence to ARV regimens, completeness of viral suppression, and emergence of drug resistance. Among perinatally infected children, prior to availability of highly active ARV therapy, increased maternal illness severity based on clinical symptoms and CD4 count was noted to be associated with infant disease progression.^{32–34} Likewise, in the absence of HAART, high viral load in infants (>1,000,000 copies/mL) and CD4 percent <15 were associated with more rapid progression to AIDS and increased early mortality.³⁵

Before effective therapy, the average time till progression to AIDS was 9 years among perinatally infected children.³⁶ Since the availability of HAART, several studies have confirmed that the rate of pediatric HIV disease progression to AIDS has been slowed and survival length has increased substantively. Reports from several U.S. cohorts confirm that survival rates

Table 86-1. A. CDC 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Clinical and Immune Categories

Clinical Category N: Asymptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A.

Clinical Category A: Mildly symptomatic

Children with two or more of the conditions listed below but none of the conditions in Categories B and/or C.

- Lymphadenopathy (≥ 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Clinical Category B: Moderately symptomatic

Children who have symptomatic conditions other than those listed for Category A or C that are attributed to HIV infection. Examples of conditions in clinical Category B include but are not limited to

- Anemia (< 8 gm/dL) neutropenia (< 1000 cells/mm³), or thrombocytopenia ($< 100,000$ /mm³) persisting ≥ 30 d
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal thrush, persisting > 2 mo in children > 6 mo of age
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 mo of age
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (more than two episodes in 1 y)
- HSV bronchitis, pneumonitis, or esophagitis with onset before 1 mo of age
- Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatomes
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever lasting > 1 mo
- Toxoplasmosis, onset before 1 mo of age
- Varicella, disseminated (complicated chickenpox)

Clinical Category C: Severely symptomatic

Children who have any condition listed in the 1987 surveillance case definition for AIDS with the exception of LIP. (see Table 86-1B)

Table 86-1. B. CDC Pediatric Clinical Category C Conditions

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections with a 2-year period) of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs), Coccidioidomycosis, disseminated (at site other than or in addition to lungs, cervical, or hilar lymph nodes)

(Continued)

Table 86-1. B. (Continued)

- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting >1 mo
- Cytomegalovirus disease with onset of symptoms at age >1 mo (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 mo in the absence of a concurrent illness other than HIV infection that could explain the findings: (a) failure to attain or loss of developmental milestones or loss of intellectual ability verified by standard developmental scales or neuropsychological tests; (b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children <2 years of age; (c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance)
- Herpes simplex virus infection causing a mucocutaneous ulcer persisting for >1 mo; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child >1 mo of age
- Histoplasmosis, disseminated at a site other than or in addition to lungs or cervical or hilar lymph nodes
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, noncleaved cell (Burkitt's) or immunoblastic or large cell lymphoma or B-cell or unknown immunologic phenotype
- *Mycobacterium tuberculosis*, disseminated, or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Mycobacterium avium* complex or *M. kansasii*, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- *Pneumocystis jiroveci* (formerly carinii) pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (nontyphoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at 1 mo of age
- Wasting syndrome in the absence of a concurrent illness other than HIV that could explain the following findings: (a) persistent weight loss >10% of baseline OR (b) downward crossing of at least two of the following percentiles lines on the weight-for-age chart (e.g. 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 y of age OR (c) <5th percentile on weight for height charts on two consecutive measurements, 30 d apart PLUS either chronic diarrhea (i.e., at least two loose stools per day for ≥ 30 d OR documented fever for ≥ 30 d, intermittent or constant)

Table 86-1. C. Immune Categories Based on Age-Specific CD4 T Cell Count and Percentage^a

	Age up to 12 Mo	Age 1–5 Y	Age 6–12 Y
Immune category	Absolute CD4 (%) cells/mm	Absolute CD4 (%) cells/mm	Absolute CD4 (%) cells/mm
Category 1: No suppression	≥ 1500 ($\geq 25\%$)	≥ 1000 ($\geq 25\%$)	≥ 500 ($\geq 25\%$)
Category 2: Moderate suppression	750–1499 (15–24%)	500–999 (15–24%)	500–999 (15–24%)
Category 3: Severe suppression	<750 (<15%)	<500 (<15%)	<200 (<15%)

^aModified from CDC 1994 revised classification system for Human Immunodeficiency Virus infection in children less than 13 years of age.²⁴

for perinatally HIV-infected children born after 1996 during the time period when pediatric HAART became increasingly available in the United States were significantly better than for infected children born prior to 1997.^{33,37,38} In Europe, de

Martino et al.³⁹ reported similar trends with reduction in mortality for those born between 1996 and 1998.

Average survival of HIV-infected children in resource-limited countries has been much shorter^{11,15,25,29} than in the

Table 86-2. A Revised WHO Clinical Staging of HIV for Infants and Children (Interim Africa Region Version)

STAGE 1	Unexplained anemia (<8 gm/dL), neutropenia (<1000/mm ³) or thrombocytopenia (<50,000/mm ³) for more than 1 mo Chronic HIV-associated lung disease including bronchiectasis
Asymptomatic Persistent generalized lymphadenopathy (PGL)	
STAGE 2	STAGE 4 ^e <i>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:</i> Unexplained severe wasting or severe malnutrition ^f not adequately responding to standard therapy Pneumocystis pneumonia Recurrent severe presumed bacterial infections (e.g., empyema, pyomyositis, bone or joint infection, meningitis but excluding pneumonia) Chronic herpes simplex infection; (orolabial or cutaneous of more than 1 mo duration, visceral of any duration) Extrapulmonary tuberculosis Kaposi's sarcoma Oesophageal Candidiasis CNS toxoplasmosis (outside the neonatal period) HIV encephalopathy
Hepatosplenomegaly Recurrent or chronic upper respiratory tract infections (otitis media, otorrhea, sinusitis) Papular pruritic eruptions Seborrheic dermatitis Extensive Human papilloma virus infection Extensive Molluscum infection Herpes zoster Fungal nail infections Recurrent oral ulcerations Lineal Gingival Erythema (LGE) Angular cheilitis Parotid enlargement	
STAGE 3	<i>Conditions where confirmatory diagnostic testing is necessary:</i> CMV infection (CMV retinitis or infection of organ other than liver, spleen, or lymph nodes onset at age 1 mo or more) Cryptococcal meningitis (or other extrapulmonary disease) Any disseminated endemic mycosis (e.g., extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis) Cryptosporidiosis Isosporiasis Disseminated nontuberculous mycobacteria infection Candida of trachea, bronchi, or lungs Acquired HIV-related rectal fistula Cerebral or B-cell non-Hodgkin's lymphoma Progressive multifocal leukoencephalopathy (PML) HIV-related cardiomyopathy or HIV-related nephropathy
<i>Conditions where a presumptive diagnosis can be made using clinical signs or simple investigations:</i> Unexplained moderate malnutrition ^b not adequately responding to standard therapy Unexplained persistent diarrhoea (14 d or more) Unexplained persistent fever (intermittent or constant, for longer than 1mo) Oral candidiasis (outside neonatal period) Oral hairy leukoplakia Acute necrotizing ulcerative gingivitis/periodontitis Pulmonary tuberculosis ^c Severe recurrent presumed bacterial pneumonia Conditions where confirmatory diagnostic testing is necessary Lymphoid interstitial pneumonitis (LIP) ^d	

^aFor use in those under 15 years with confirmed laboratory evidence of HIV infection; HIV antibody where age >18 months, virological or P24 Ag testing for those age <18 months.

^bModerate malnutrition: Defined as very low weight for age - http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAH_00.1.htm or page4 http://www.who.int/nut/documents/manage_severe_malnutrition_eng.pdf

^cAs for footnote 2.TB is particularly difficult to diagnose in infants and young children

^dLymphoid Interstitial Pneumonitis (LIP) : Definitions available in accompanying notes

^eA presumptive Stage 4 diagnosis in seropositive children less than 18 months old may be made when virological confirmation of infection is not available if an HIV-seropositive infant less than 18 months is symptomatic with two or more of following; oral thrush, ± severe pneumonia, ± severe wasting/malnutrition, ± severe sepsis, severe immunosuppression should be suspected and ARV treatment is indicated

CD4 values where available may be used to guide decision making, CD4% below 25 requires ARV treatment

other factors that support diagnosis of clinical stage 4 HIV infection in an HIV-seropositive infant are recent maternal death and advanced HIV disease in mother. confirmation of the diagnosis of HIV infection should be sought as soon as is possible

^fSevere Malnutrition: Defined as very low weight or visible severe wasting or edema of both feet Ref: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/WHO_FCH_CAH_00.1.htm

(Continued)

Table 86-2 B. World Health Organization Immunological Categories for Paediatric HIV Infection^a (Continued)

Immune Status	Age up to 12 Mo	Age 13 Mo or Over	6 y or Over
Not considered to have significant immunosuppression	>35%	>25%	>500 mm ³
Evidence of mild immunosuppression	25–34%	20–24%	350%–499/mm ³
Evidence of advanced immunosuppression	20–24%	15–19%	200%–349/mm ³
Evidence of severe immunosuppression	<20%	<15%	<200/mm ³

^aCD4 values and their relation to immunological status are provided in the table below to assist clinical decision making and link with monitoring and surveillance.

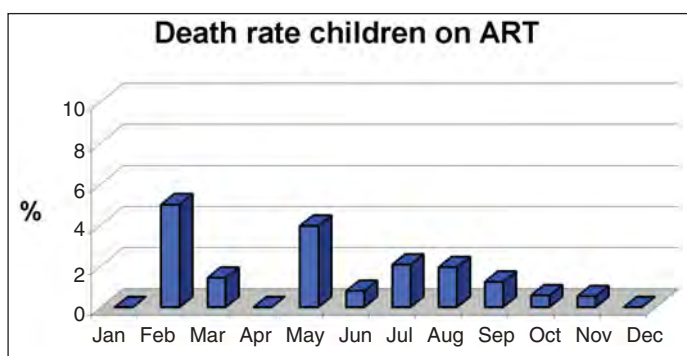


FIGURE 86-2. Death rate over first 12 months of antiretroviral roll-out at Tygerberg Children's Hospital, South Africa 2004 (data from Andre du Preez, Tygerberg Pharmaceutical Service).

United States and Europe. However, with the recent expansion of HAART availability in many international settings, it is anticipated that similar improvements in survival among HIV-infected children will be seen. Because of the scale of the pandemic, despite the high mortality in the first 2 years of life, substantial numbers of HIV-infected children survive infancy, even in the absence of ARV therapy. For example, in the recently completed CHAP trial carried out in Zambia, of 534 children, 21% of subjects were between 6 and 9 years of age and 15% over 10 years of age.⁴⁰ In a study from Cape Town, 16% of 143 children followed for more than 6 months were over 5 years of age at first visit to a family clinic for HIV.⁴¹ By this stage, the majority of children have moderate to severe morbidity due to end-organ damage such as chronic lung disease. Early experience with HAART in international settings such as Cape Town, South Africa has confirmed the survival benefit of HAART, with most mortality seen in children where treatment was initiated in the presence of advanced disease (see Fig. 86-2). Likewise, Médecins Sans Frontières (MSF) reviewed data on 1840 HIV-infected children from 13 resource-poor countries and documented a probability of survival of 91% after 24 months (www.msf.org).⁴²

TREATMENT RECOMMENDATIONS FOR CHILDREN AND ADOLESCENTS WITH HIV

■ CURRENT U.S. TREATMENT PRACTICES

Treatment of children and adolescents with HIV includes ARV therapy, prophylaxis and treatment of opportunistic and other infections, treatment of growth and neurodevelopmental problems, and psychosocial support. HAART has been largely successful in preventing many of the complications of HIV in children and adolescents. This therapy must be accompanied by the treatment of comorbid medical and psychosocial conditions.

While the principles of using HAART are similar in children and adolescents to those in adults, a few substantial differences exist. The ongoing somatic growth and nervous system development of children affect both the pharmacokinetic parameters and potential toxicities of specific ARV agents. The fact that HIV infection detected in infants is a newly acquired acute infection increases the urgency and possibly the efficacy of ARV therapy. The limitations in available or palatable formulations of ARVs for use in infants and background of socio-cultural risk factors may adversely affect adherence and thus reduce treatment efficacy in children and adolescents.

The timing of initiation of HAART in adolescents and children identified beyond the first year of life is based on the same factors as in adults. Viral load and CD4 percentage are independently correlated with a higher risk to progression to AIDS or death.³⁵ Thus, clinical disease, immune suppression, and viral load are all indications for initiating therapy. The decision to initiate therapy, as in adults, is made by the patient and provider together and should include any parent or guardian involved in the patient's care. They must take into account the likelihood of achieving the extraordinary level of adherence on which viral suppression is dependent.

Almost all infants identified as HIV-infected in the first year of life should be treated with HAART as early as possible after birth.⁴³ Newborns infected with HIV have a very high viral load in the first few months of life and have higher viral

set points in the first years of life than do HIV-infected adults.⁴⁴ Early treatment with HAART, as in acute HIV infection, may drive down the viral set point and mitigate the effects of HIV.⁴⁵ In addition, the risk of neurologic deficits in infants is increased and is not always predictable by viral or immunologic parameters, thus necessitating HAART treatment for most infected infants. The only infants for whom HAART is not automatically recommended⁴⁶ are children with no clinical symptoms and no immune deficiency based on the standard CDC classification (Table 86-1).²⁴

Initial ARV therapy for children and adolescents consists of two nucleoside analogs and either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor. The choice of specific HAART regimens is limited by the lack of pediatric indications or pediatric pharmacokinetic data for many of the medications. Pharmacokinetic parameters of several ARVs change considerably with age; thus, extrapolation of dosages from adult data is risky. Furthermore, as of 2007, only 11 of the 23 approved oral ARVs have pediatric formulations (Table 86-3) and none of the multiagent combination forms has a liquid equivalent. Initial regimens for adolescents mirror those in adults, but the recommended U.S. Working Group⁴⁶ initial regimens for HIV-infected children (Table 86-4) differ somewhat as infants and young children cannot swallow the simplified combination pills available for adults, adolescents, and older children. Over the last several years, providers have been striving to use once-daily regimens (Table 86-4) especially in adolescents to promote improved adherence. Most of these include efavirenz, which if used in women of childbearing age must be used with effective contraception because of the potential teratogenicity of efavirenz.

Many children and adolescents infected during the 1980s have undergone successive regimens without complete viral suppression, thus inducing resistance to many ARVs. Decisions about switching regimens are made using the same criteria as in adults, taking into account past ARV history, resistance testing, and the likelihood of complete viral suppression. The greatly reduced numbers of newly infected children in the United States and the hesitancy to perform clinical trials in highly ARV-experienced children make pediatric phase I trials rare in the United States. Most recently approved ARV agents have been approved without a pediatric indication. These agents must, by necessity, be used in salvage therapy for pediatric and adolescent patients by HIV specialists extrapolating adult efficacy data and using the limited pharmacokinetic and safety data that has been generated in children.⁴⁷ This dilemma underscores the need for continued clinical trials for children with HIV both in the United States and internationally.

The follow-up and monitoring of children and adolescents on ARV therapy in the United States differs little from that of adults. At many tertiary care centers, follow-up phone calls are made within a week or two of initiating or changing therapy to make sure that the patient is correctly following medication instructions and to answer questions

Table 86-3. Pediatric Indications and Formulations Approved or Available in the United States in 2005

Medication	Approval Age	Pediatric Formulation
<i>NRTIs</i>		
Zidovudine (ZDV, AZT)	All	Yes
Didanosine (ddI)	All	Yes
Zalcitabine (ddC)	13 y and up	No formulation
Stavudine (d4T)	All	Yes
Lamivudine (3TC)	All	Yes
Abacavir	3 mo and up	Yes
Tenofovir	No pediatric indication	No formulation
Emtricitabine	3 mo and up	Yes
<i>NNRTs</i>		
Nevirapine	All	Yes
Efavirenz	Dosing data for 3 y and up	No formulation
Delavirdine	No pediatric indication	No formulation
<i>Protease Inhibitors</i>		
Saquinavir	No pediatric indication	No formulation
Indinavir	No pediatric indication	No formulation
Ritonavir	All	Yes
Nelfinavir	2 y and up	Yes
Amprenavir	4 y and up	Yes
Lopinavir/r	6 mo and up	Yes
Atazanavir	No pediatric indication	No formulation
Fosamprenavir	No pediatric	No formulation
Tipranavir	No pediatric indication	No formulation
<i>Fusion Inhibitor</i>		
Pentafuside (T-20)	6 y and up	NA (not oral)

and relieve concerns related to possible medication intolerance or side effects. Viral loads are monitored within a month to assess for the expected one log initial viral load decrease. Viral load and CD4 count and percentage are then monitored every 3–4 months thereafter. Assessment for possible side effects varies depending on the regimen but always includes frequent blood counts and chemistries for the first few months to assess for hepatic, renal, or bone marrow toxicity. In general, most clinicians monitor blood counts and chemistries, including pancreatic enzymes, at

Table 86-4. Common First Regimens for HIV Infected Children in United States

2 Nucleoside Backbone		NNRTI or PI
Zidovudine (ZDV) + either Lamivudine (3TC) or Didanosine (ddl) or Emtricitabine (FTC) or ddl + either Lamivudine (3TC) or Emtricitabine (FTC)	+	Efavirenz (Nevirapine for children under 3 years old) or Preferred PI, Lopinavir/r
ONCE DAILY REGIMENS 2 Nucleoside Backbone		NNRTI or PI
Choose 2 from: (ddl or Tenofovir) + (3TC or FTC)	+	Efavirenz or Atazanavir/r

PI= protease inhibitor, NNRTI= nonnucleoside reverse transcriptase inhibitor, ZDV= zidovudine, 3TC= lamivudine, ddl= didanosine, D4T= stavudine, FTC= emtricitabine.

least every 3–4 months, and lipid profiles, yearly. Side effects of ARV medications in children are similar to those in adults though the frequency of some, such as lipodystrophy, appears to be related to age and pubertal development.⁴⁸

The improving health and longer life expectancy for HIV-infected children and adolescents have prompted concerns about both long-term adherence and possible late sequelae related to lifelong ARV therapy. Pediatricians have limited experience in the treatment of chronic hypercholesterolemia, and many of the cholesterol-lowering agents have not been approved or even tested in children. Another concern is the development of resistance should the child's adherence falters at any point such as during adolescence. Studies are currently underway to evaluate multifaceted interventions aimed at improving adherence among adolescents. Treatment decisions utilize CD4⁺ cell count and the child's clinical status, history of prior ARVs used, and resistance testing when needed. Currently available ARVs and their FDA approval status for use in HIV-infected children <13 years of age are summarized in [Table 86-3](#).

■ PEDIATRIC HIV TREATMENT STRATEGIES IN RESOURCE-LIMITED INTERNATIONAL SETTINGS

International perspectives on antiretrovirals

Although in better-resourced international settings treatment approximates that in North America and Europe, adaptations need to be made to local circumstances. Often, the variety of medications available is less than in resource-rich settings. For example, protease inhibitors are not readily

accessible in many African countries. Nevirapine is often the only option as a third component, along with two nucleosides, of antiretroviral therapy (ART). This may be complicated by the use of single dose nevirapine either alone or in combination to prevent mother-to-child HIV transmission and resulting in resistance mutations among infected infants.

Because of cost constraints, many countries rely on generics rather than “brand” drugs. Some countries, notably Brazil and Thailand have shown much vision in providing state assistance for generic drug manufacturing, thus ensuring high standards and reliability of life-saving medications at reasonable cost. India and South Africa have also made progress in manufacturing generics. However, although all classes of ARV generics are available, very few are suitable for children. Only zidovudine and lamivudine are available as suspensions. No generic protease inhibitors are available in liquid formulation. There is an urgent need for more pediatric-friendly formulations. These include fixed drug combinations that are chewable, scored for ease of cutting, and containing appropriate amounts of drug to permit flexibility. Currently, an adult formulation of stavudine, lamivudine, and nevirapine is available as a fixed drug combination for adults in many African countries. Many practitioners adapt these formulations by cutting tablets into two, three or four pieces. The effectiveness of this approach has been confirmed by Puthankit and colleagues in Thailand.⁴⁹

Another important factor is the need for refrigeration of some medications such as stavudine and didanosine suspensions, as well as most protease inhibitors. In resource-limited settings, refrigerators are often not available, even in urban centers. Many formulations, such as lopinavir/ritonavir suspension require storage at room temperature defined as <25°C. Ambient temperature may often exceed this and families need to be advised how to use simple inexpensive measures to insulate containers to keep them cool.

In addition, many of the pediatric HIV liquid medications are administered with an oral syringe. Caregivers need to be carefully trained to use syringes, including how to accurately draw up the correct dose into the syringe and how to expel excess air when drawing up the medication. Decreased visual acuity of some elderly caretakers such as grandparents requires that the exact volume amounts to be drawn up need to be clearly marked on the syringes so that dosing errors can be minimized.

The optimal time to initiate ART therapy for HIV infected children in resource limited settings is not completely resolved, but recent data from a S. African trial suggest that early antiretroviral therapy for HIV infected infants before 12 weeks of age reduces early mortality [personal communication, Prof. Mark Cotton].^{49a} The benefits of this approach are that rapid disease progression can be arrested and neurodevelopmental impairment should be prevented.⁵⁰

The WHO currently recommends initiating therapy in children with stage 3 and 4 disease or in those where CD4 counts can be measured when threshold values have been reached (Table 86-5).²⁸

Adherence is a major focus in pediatric ARV treatment programs in resource-limited settings in order to ensure that the first-line regimens are likely to succeed as long as possible. An important component is well-trained lay counselors, who assess and counsel caregivers before and during therapy. Counseling sessions to ensure ART preparedness precede therapy. Disease progression may be rapid in young infants, and clinical judgment should be used to fast-track therapy in young, highly symptomatic infants. The counselor discusses how the medication works, the importance of adherence, and introduces the caregiver to the various preparations. Most important is to designate a single caregiver to take responsibility for the medication. Disclosure of status to someone in the household is encouraged. The doctor and the counselor stress adherence at every visit. Once medication is initiated, a follow-up visit is usually arranged within a week to check adherence. Diary cards and pillboxes are useful to focus discussions. If resources permit, color-coding of medication

with the child putting a small label with the same color on the diary card is useful. Dosage must be adjusted for weight at each visit as successful therapy implies normal or even accelerated “catch-up” growth. Visits are usually monthly with triage into doctor or nurse-based visits. As therapy stabilizes, more of the visits are nurse-based.

There are a number of barriers that can affect the implementation of HIV treatment for infected children living in resource-limited settings. Although some caregivers elect to travel to tertiary centers to avoid stigmatization in communities, transport is often a major challenge and expense for caregivers who live away from available pediatric HIV treatment centers. For example, in the Western Cape Province of South Africa, pediatric ARV treatment began mainly in tertiary centers, requiring infected children and their caretakers to travel. To ease this burden, community outreach programs that can provide pediatric HIV treatment in facilities closer to the child’s home are now being introduced. Another barrier may be that community doctors and nurses are often less trained in HIV treatment of children than adults and this can result in delays in pediatric HIV treatment initiation even though the child meets WHO criteria for therapy.

Table 86-5. WHO Clinical Criteria for Initiating Antiretroviral Therapy in Resource-Limited Settings (in Infants and Children Under 15 Years)

Clinical Stage	ART	
Stage 4	Treat	
Presumptive stage 4	Treat	
Stage 3	Consider treatment for all ages. Children less than 2 y usually require ART	
	CD4 if available, and clinical conditions should be used to guide ART treatment decision	
Stage 1 and 2 where CD4 available	≤11 mo	CD4 ≤25% or ≤1 500 cells/mm ³
	12–35 mo	CD4 ≤20% or ≤750 cells/mm ³
	36–59 mo	CD4 ≤15% or ≤350 cells/mm ³
	≥5 y	CD4 ≤15% or ≤200 cells/mm ³
Stage 2 where only total lymphocyte count (TLC) available	≤11 mo	
	12–35 mo	TLC ≤4000 cells/mm ³
	36–59 mo	TLC ≤3000 cells/mm ³
	≥5 y	TLC ≤2500 cells/mm ³
		TLC ≤1500 cells/mm ³

All HIV-exposed children (until HIV infection is excluded) and HIV-infected children with signs or symptoms of HIV should be given cotrimoxazole prophylaxis. CD4% preferred in children <5 years.

Because of delays in initiating ARV programs, many children have advanced disease when starting therapy and are often on multiple drugs for other conditions, creating the possibility of increased toxicity because of overlapping side effects. For example, antituberculosis medication has overlapping hepatic and cutaneous toxicity.⁵¹ Also, the immune reconstitution inflammatory syndrome (IRIS) occurs commonly in children with advanced disease. These conditions are often best managed in a referral hospital and include Bacille Calmette-Guérin disease (BCG),⁵² worsening TB, and chorioretinitis due to cytomegalovirus (CMV).

COMPLICATIONS OF HIV AMONG CHILDREN AND ADOLESCENTS

■ COMPLICATIONS OF HIV IN CHILDREN AND ADOLESCENTS: UNITED STATES

The manifestations of HIV and its complications among infected children in the United States have changed over the course of the epidemic. In the late 1980s and early 1990s, AIDS-defining opportunistic infections and severe growth and developmental problems were commonly seen as presenting illnesses that identified a child as HIV-infected. Now, with the sharp reductions in mother-to-child transmission in the United States, early identification of HIV-infected children generally in the first few months of life and early initiation of highly effective ARV therapy with resultant preservation of immune function, most of these opportunistic infections have become rare and replaced by milder more chronic conditions.

While some clinical manifestations of HIV occur in all age groups, the incidence of others varies considerably. Behaviorally infected adolescents display manifestations similar to those seen in adults. Perinatally infected children exhibit a different spectrum of disease largely due to the unique growth and neural development occurring in children and to their immature immune systems that have yet to develop humoral immunity to common infections.

As in adults, *Pneumocystis jiroveci* (formerly *cariini*) pneumonia was a common opportunistic infection in children throughout the early part of the HIV epidemic. Other common opportunistic infections included *Mycobacterium avium* complex (MAC), herpes zoster, and invasive candidal infections. Cytomegalovirus infection was also relatively common in children, although the presentation was more varied and more often involved central nervous system (CNS), GI tract, or respiratory infection than in adults. One key difference in presentation of HIV in children compared to adults is the very high incidence of bacterial infections including sepsis, meningitis, and pneumonia in HIV-infected children.⁵³

The developing CNS of children is at particular risk for compromise from HIV. Most of the CNS involvement in children results from direct effect of HIV. This may present as

overt HIV encephalopathy with irritability, cognitive and motor deficiencies, or less intensely as global or motor developmental delay. Opportunistic infections invading the CNS such as *Cryptococcus* and toxoplasmosis are seen much less frequently in children than in adults.⁵⁴

Severe growth delay involving both height and weight was common manifestation of pediatric HIV infection in the United States in the late 1980s and early 1990s but is much less common now for children who began early on highly effective combination ARV therapy. Differences in growth rates between infected and uninfected children were seen within the first few months of life and increased in severity with time.⁵⁵ Growth delay in HIV-infected children can be directly caused by HIV but may also result from infections causing vomiting, diarrhea, or food intolerance from medication side effects or from social circumstances. HIV-infected children with growth delay experience an improvement in growth after starting treatment with HAART but deficits can persist.⁵⁶ Delayed puberty has also been reported in significant proportions of HIV-infected children.⁵⁷

Many of the more severe manifestations of HIV have become rare because of earlier identification and prompt initiation of highly effective ARV treatment of children with HIV.³⁷ *Pneumocystis jiroveci* pneumonia occurs much less frequently and almost exclusively in few children whose mothers have not been tested for HIV and thus whose identification is delayed. MAC, CMV, and cryptosporidium are now quite rare among children on HAART. Lymphoid interstitial pneumonitis (LIP), a chronic pulmonary condition possibly related to Epstein Barr Virus (EBV) infection was a common AIDS-defining condition for children early in the epidemic but now is almost never seen. However, oral and esophageal candidiasis and bacterial infections remain relatively common in chronically-infected children and adolescents whose immune function remains compromised.^{45,58} While gross HIV-related encephalopathy is now rare, developmental delays continue. Neuropsychological disease is much more common in perinatally-infected children and teens; psychiatric hospitalizations occurred at a rate more than three times that of the general population.⁵⁹ Softer neurobehavioral findings such as attention deficit/hyperactivity disorder have also been reported among HIV-infected children in some prospective perinatal studies but may be related to background environmental factors.⁶⁰

■ COMMON OPPORTUNISTIC INFECTIONS SEEN AMONG HIV-INFECTED CHILDREN IN INTERNATIONAL SETTINGS

Among the complications of pediatric HIV disease seen in resource-limited settings, chronic lung disease is common in HIV-infected children surviving infancy, often accompanied by pulmonary hypertension and cardiac failure. The extent of developmental delay is beginning to be quantified. HIV causes

many of the same opportunistic and intercurrent infections seen in developed countries prior to highly effective combination ARV therapy. Candidiasis, including oral, laryngeal, and esophageal, is a frequent opportunistic pathogen. *Pneumocystis jiroveci* pneumonia, while originally assumed to be rare in Africa, actually occurs commonly based on more recent laboratory-based findings.^{61,62} Malnutrition, bacterial pneumonia, diarrhea, and tuberculosis occur commonly, often simultaneously.^{63–65} Studies comparing bacterial infections such as pneumonia and meningitis and also viral infections in children with and without HIV show increased morbidity and mortality among HIV-infected compared to uninfected children.^{66–69} Bronchiectasis⁷⁰ and recto-vaginal or recto-vesical fistulae⁷¹ occur relatively frequently and are associated with rapid HIV disease progression.

Pulmonary tuberculosis (TB) among HIV-infected children and adults occurs commonly in resource-limited settings. In HIV-infected adults with latent TB, the annual risk of developing active TB is 5–8%, which is 12–20 times that of HIV-uninfected adults.^{72,73} Among hospitalized children in Durban, South Africa, *Mycobacterium tuberculosis* was found in 8% of children with acute pneumonia.⁷⁴ In Malawi, more than 60% of childhood TB cases are coinfecting with HIV.⁷⁵

Initial TB treatment is with isoniazid, rifampin and pyrazinamide, and sometimes with ethambutol or ethionamide is also included. For HIV-infected children who have had TB coinfection in Cape Town, South Africa, TB relapse or reinfection was documented to occur in about 16% of children on follow-up. The optimal length of TB treatment is unclear and the role and length of secondary prophylaxis following treatment for TB among HIV-infected children also needs further study.⁷⁶ BCG disease is an emerging problem. This often presents as regional right axillary adenitis and may be disseminated. It is also seen frequently as part of the IRIS. Disseminated BCG is extremely difficult to manage. Children may be coinfecting with *M. tuberculosis*. BCG is inherently resistant to pyrazinamide and may have reduced susceptibility to isoniazid as well.⁵²

MAC infection is seen increasingly, presenting in older children with severe immunological depletion. The most common presentation is intra-abdominal lymphadenopathy accompanied by pain and occasionally fever. Prophylaxis is usually not given internationally because of expense and low priority.

Cryptococcal disease is also seen in children with advanced disease in resource-limited settings. This includes meningitis with and without cutaneous and pulmonary involvement. It may be extremely refractory to treatment, occasionally relapsing, and often requiring prolonged intravenous amphotericin B beyond the recommended 2 weeks and also fluconazole at high doses (often 15 mg/kg/day). For pediatric prophylaxis against cryptococcal disease, a minimum of 6–10 mg/kg per day of fluconazole is used in Cape Town, South Africa (personal correspondence M Cotton and Helena Rabie).

A summary of CDC, national institute of health (NIH), and Infectious Disease Society of America recommendations regarding treatment for opportunistic infections among HIV-exposed and infected children is available in the 2004 CDC MMWR⁵⁸ and at <http://www.aidsinfo.nih.gov/guidelines/>. Recommendations for the prevention of opportunistic infections in children in the United States and international resource-limited settings are summarized in the USPSH/IDSA Guidelines for the Prevention of Opportunistic Infections among HIV-infected persons,⁷⁷ also available at <http://www.aidsinfo.nih.gov/guidelines/>. (see Table 86-6.)

In the United States, trimethoprim-sulfamethoxazole (cotrimoxazole) is routinely given to all HIV-exposed infants beginning at 6 weeks of age to prevent *Pneumocystis jiroveci* pneumonia and continued until an infant is determined to not be HIV infected, based on PCR testing.⁷⁷ Those infants who are infected continue on cotrimoxazole prophylaxis throughout the first year of life and then are either continued or stopped depending on their immune status.

Internationally, cotrimoxazole is likewise an important component of prophylaxis for children infected with HIV. A recent double-blind randomized study comparing active cotrimoxazole drug to placebo among HIV-infected children in Zambia demonstrated the overwhelming benefit of the active drug irrespective of immune category.⁴⁰ The authors recommended using cotrimoxazole for prophylaxis for all HIV-infected infants and children regardless of CD4 count. In a growing number of international resource-limited settings, cotrimoxazole is also being offered to all HIV-exposed infants until HIV infection can be excluded by loss of maternal antibody or by demonstrating virus. Cotrimoxazole prophylaxis is usually given at a dosage of 5 mg/kg/day of the trimethoprim component.

While TB exposure among children in the United States is relatively rare, in international settings TB represents a major problem both among HIV-exposed or -infected children and their parents. All HIV-infected or -exposed children whose parents have TB need to have tuberculosis excluded and if not infected then to receive either isoniazid prophylaxis alone for 6 months or with rifampicin for 3 months. The following pediatric TB prophylaxis guidelines are used in Cape Town, South Africa. (Personal communication HS Schaaf, Stellenbosch University)

TB prophylaxis is indicated in an HIV-infected child <5 years of age when

- a Mantoux test is >4 mm or when there is any reaction to a Tine test (after excluding disease); and/or
- the child has had contact with an infectious adult source case (after excluding disease);
- prophylaxis is individualized in older HIV-infected patients with the above-mentioned criteria.

Table 86-6. CDC Pediatric Prophylaxis Guidelines for Some Common Pediatric AIDS-Related Opportunistic Infections

Opportunistic Infection	Criteria for Primary Prophylaxis	Recommended Prophylaxis and Alternatives	Criteria for Secondary Prophylaxis (Secondary Prophylaxis)
<i>Pneumocystis jiroveci</i> pneumonia	HIV exposed infants 4–6 wks through 4 mo; Infected children 1–5 y if CD4 <500 cells/mm ³ or <15% Infected children 6–12 y if CD4 <200 cells/mm ³ or <15%	Cotrimoxazole Pentamidine, dapsone	One episode of <i>P. jiroveci</i> pneumonia. Continue lifetime prophylaxis. Insufficient safety data regarding stopping after immune reconstitution
<i>Mycobacterium tuberculosis</i>	TB-exposed infants born to HIV-infected women coinfecting with TB; or other close TB exposure	Isoniazid prophylaxis for 6–9 mo Alternative in some international settings: Isoniazid + rifampicin for 3 mo	
<i>Mycobacterium avium complex</i> disease	<1 y olds with CD4 count <750; 1–2 y with CD4 <500; 2–6 y olds with CD4 <74; and >6 y olds with CD4 <50.		Lifetime secondary prophylaxis recommended; the safety of discontinuing after immune recovery with HAART has not been well studied in children

Regimens for TB prophylaxis include

- isoniazid daily 5 days/week or 2 times/week for 6–9 months; isoniazid and rifampicin 5 days/week for 3 months, only if it is given as directly observed therapy

Since multidrug resistant TB is increasing world wide, consultation with an expert for prophylaxis and treatment is important.

INNOVATIVE MODELS OF PEDIATRIC AND FAMILY CARE

■ U.S. MODELS OF PEDIATRIC HIV CARE

In the United States, the HIV epidemic has led to significant changes in the way that care for children with chronic diseases is provided. The varied complications of HIV, both physical and psychosocial, have necessitated that pediatric HIV care be delivered in the framework of a multidisciplinary team. While other chronic diseases have employed such models, the extent to which they are used is unique to HIV care in part based on availability of substantial federal HIV-care funding.

The disenfranchised nature of populations particularly affected by HIV necessitated the inclusion of intensive social service support as part of primary care. The lack of effective

treatment early in the epidemic and the urgent need for effective medications necessitated that clinical research be a part of the general care for many children with HIV. The stigma associated with HIV demanded that psychological support and patient advocacy become part of the care. The effects of HIV on growth and neurological development similarly necessitated the inclusion of nutritionists, developmental specialists, and physical and speech therapists. The need for close-to-perfect adherence of multiple medications has led to the development of the health educator as another part of the care team.

HIV care for children has been provided in a model of care teams involving several individuals from multiple disciplines. As few new infants are becoming infected and already infected children are becoming adolescents, models of care are changing to meet the needs of the consumers. Pediatric clinics are referring patients to or becoming adolescent clinics or family care centers.

The family care model provides primary care and other services for the entire family in a convenient setting. Previously, parents (usually mothers) with HIV-infected and uninfected children had the difficulty of keeping up with appointments at three separate clinics; one for themselves, one for their infected children, and one for their

uninfected children. Even though these may have been at the same facility, often they were in different areas or at different times. The family care model attempts to focus primary care for all family members, infected and uninfected, together. Ideally, social support services, mental health services, gynecological consultation, nutritional expertise, and all other services are concurrently provided in the same location.

Another model being utilized is that of the adolescent-focused HIV care and treatment centers. As HIV-infected children age into adolescence, they often feel uncomfortable receiving care in a clinic geared toward younger children. Playrooms filled with crayons, finger paints, and books of nursery rhymes deter them from coming for care. Many centers have set up clinics and times specifically for adolescents with HIV. These are often during after-school and evening sessions, and the clinic areas are decorated by the teens themselves and have CD and DVD players creating a teen-friendly environment. Programs include informal "rap" sessions to discuss their concerns, career and school counseling, and sexual responsibility training. Such youth friendly centers are extremely effective in engaging and maintaining these youth in care.

■ INTERNATIONAL MODELS OF CARE

Most pediatric HIV ARV treatment and care programs have been based in larger better-resourced centers. However, the goal is to establish networks of district and community-based treatment clinics with links to referral centers for problem solving, where necessary. Although it is ideal for doctors to see the patients, under many circumstances, this may not be possible. Nurses or clinical officers, in small clinics, may need to manage patients. Under these circumstances, an excellent and ongoing education program, a referral network, and doctor-based outreach program are especially important.

Before treating any child, the caregiver needs to be counseled to ensure understanding and should be encouraged to disclose his or her status to someone in the household who can assist with giving medication. Such preparation may take 2–3 weeks. In young infants, the lead in time may need to be shortened because of rapid progression of disease. Once treatment has been initiated, visits can be triaged into doctor or nurse-based. Adherence monitors should regularly talk to caregivers and build up rapport.

One model of care is the establishment of a family clinic.⁴¹ In many areas, successful clinics can be established with minimal cost by reorganizing existing infrastructure. Often the same health-care worker can manage multiple family members. Clinic visits may be more convenient if more than one family member is seen on a single visit. Family clinics have created an important opportunity for family practitioners to become central in HIV management.

Comprehensive care and treatment of HIV-infected adolescents requires innovative models of care tailored to the developmental needs surrounding puberty and psychosocial issues faced by HIV-infected teenagers. Not only is adolescence a period of high risk to acquire HIV and other sexually transmitted infections, increasing numbers of perinatally infected children will reach adolescence and require care. Adolescent-friendly clinics need to be urgently established.

A major feature has been the wide range of organizations that have and are facilitating access to ART. The WHO is coordinating the "3 by 5" program seeking to facilitate and mobilize resources to treat 3 million people by the end of 2005. The program commenced in 2003 and reports major progress in access to ARV drugs in resource-limited settings.⁷⁸

FUTURE DIRECTIONS IN PEDIATRIC HIV TREATMENT AND CARE

■ INTERFACE OF PERINATAL PREVENTION AND PEDIATRIC HIV TREATMENT

In the United States, routine prenatal HIV testing using an opt out approach has helped identify many asymptomatic HIV-infected women during pregnancy who would not otherwise have been aware of their HIV status. This has resulted in a twofold opportunity: (1) to offer combination ARVs and obstetrical interventions that reduce the risk of perinatal transmission to 2% or less; and (2) to offer comprehensive HIV therapy/care to infected adolescent females and women beginning during pregnancy and to HIV-infected infants soon after birth through early virologic diagnosis. Current pediatric HIV treatment strategies in the United States and Europe have resulted in improved quality of life, decreased opportunistic infections, and prolonged survival into adolescence for children currently living with HIV.

The future in resource-rich settings currently suggests that survival gains will continue among children infected with HIV, while the pool of newly infected infants further declines. Issues that this aging pediatric cohort will need to face as they survive into adolescence and young adulthood are the psychosocial impact of dealing with a serious chronic illness, concerns over disclosure to sexual partners, use of effective strategies to ensure secondary HIV prevention, and difficult reproductive choices. Already there are a number of case reports of perinatally infected girls who have become pregnant and delivered infants.⁷⁹ Since many children and adolescents with HIV come from disadvantaged environments, a major challenge will be to support HIV-infected youth with future-directed vocational, higher education, and career opportunities. Other challenges will be ensuring availability of new drugs and simplified drug regimens that take into account the likelihood of decreased drug adherence during adolescence and the inevitable emergence of ARV resistance over a lifetime of treatment as well as dealing

with complications of long-term therapy such as diabetes and lipodystrophy.

In resource-limited international settings, the success of future pediatric treatment will be highly dependent on widespread implementation of prenatal HIV testing leading to timely identification of the majority of HIV-infected women during pregnancy, offering of perinatal interventions, and early virologic testing of HIV-exposed infants. Early infant diagnosis is crucial in these settings in order to initiate ARV treatment and prophylaxis since the majority of infected infants will die before their third birthday without treatment.^{11,15,29} Operational research addressing innovative approaches to collection of infant DBS at 6–8 weeks in rural African field conditions, solving the logistics of transportation of the DBS to regional centers for PCR testing, and getting results back to the field site in a timely manner are a high priority in order to identify infected infants early enough to intervene with effective treatment. Likewise, the availability of weight charts that provide clinicians with fixed doses for given weight ranges and scored combination tablets that can be accurately cut for pediatric doses will be needed to ensure that HIV-infected children are not left behind as ARV treatment programs roll out.

One pressing research issue is to understand whether exposure to drugs for PMTCT such as NVP with detection of transient resistance will have a negative impact on early treatment for infected infants and on subsequent maternal treatment. Another is the development of intervention strategies for minimizing nevirapine resistance, such as adding a short course of lamivudine and zidovudine, or equally effective drugs, to lower the chance of developing resistance. A further priority will be ensuring widespread ARV treatment availability for HIV-infected mothers and fathers, as HIV-exposed infants whose mothers die have a twofold to fivefold increased risk of death. Fathers are important for family stability and financial security. Innovative ways of providing ARV care need to be developed and monitoring needs to be simplified. The interrelationship between TB and HIV in infants needs to be unraveled. Ways of preventing TB, such as widespread implementation of isoniazid prophylaxis to HIV and TB exposed infants, should be explored.

In the foreseeable future, the major focus of international programs will be to facilitate the urgent access to ART for children and their families. Pragmatic and simple solutions need to be implemented to facilitate this process. Ways of implementing HAART programs and using lymphocyte counts, weight gain, and growth percentile charts for monitoring should be explored.

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DEFINITIONS

Child sexual abuse represents one facet of the far-wider spectrum of *child abuse*. Many definitions of child abuse exist in the legal and scientific literature but there is no consensus on an absolute definition. Issues that arise in the debate include the influence and attitudes of societies, cultural differences in child rearing, politics, and religious beliefs. In addition, there is a need to examine the factors involved in particular episodes, the context in which the episodes occurred, the opinion of the professionals who are describing or judging these episodes, the current knowledge of the long-term outcomes of particular behaviors to children, and the effectiveness of current interventions. Definitions are, however, very important as they provide a general framework for policy setting, statutory and legal interventions, gathering statistical information, and an understanding of current and future research.

The Federal Child Abuse Prevention and Treatment Act¹ (CAPTA) defines a child as a person who has not attained the lesser of

1. the age of 18 or
2. except in the case of sexual abuse, the age specified by the child protection law of the State in which the child resides.

Child abuse and neglect, at a minimum, is defined as any recent act or failure to act on the part of a parent or caretaker, which results in death, serious physical or emotional harm, sexual abuse or exploitation, or an act or failure to act which presents an imminent risk of serious harm.

The acts of abuse may vary in nature, frequency, intensity, or duration, and each state has statutes to help define what is considered injurious to children, and each state may vary on the required response to recognized maltreatment. Clinicians should be aware of the mandates and child protecting agencies in the state in which the child resides. To recognize sexual abuse, clinicians caring for children must recognize presentations of all forms of child maltreatment, since there is very wide overlap between sexual abuse and other forms of maltreatment.

Children who have been maltreated in any way should be considered for evaluation of sexual abuse, and vice versa.

Within the wide range of child abuse and neglect, neglect has been reported to occur most frequently and is probably the most life-threatening. Child abuse and neglect frequently occur together with other forms of interfamilial violence, including spouse battering and violence between siblings.²

Definitions of child sexual abuse vary among state statutes and medical opinions. CAPTA defines sexual abuse as

1. the employment, use, persuasion, inducement, enticement, or coercion of any child to engage in, or assist any other person to engage in, any sexually explicit conduct or simulation of such conduct for the purpose of producing a visual depiction of such conduct or
2. the rape, and in cases of caretaker or interfamilial relationships, statutory rape, molestation, prostitution, or other form of sexual exploitation of children, or incest with children.

The three primary foci of definitions of sexual abuse include age differences between child and perpetrator, the acts that are perpetrated, and the caretaking relationship between the child and the assailant. Regarding age differences, many states exclude acts between peers who have less than 5 years difference in ages, where the perpetrator is not age 13 or greater and where the victim is not age 13 or less. Regarding the acts performed, attention is often given to circumstances involving force, threat, coercion, fear, and exploitation of authority. Statutes of many states regarding criminal acts with minors include penile penetrative anal, vaginal, or oral contact; digital penetrative acts; involvement of the child in any act for sexual gratification; allowing a child to be a witness of adult sexual activity, either in person or on film; involvement of a child in the production of child pornography; use of a child for child prostitution; and general statutes such as contributing to the moral degeneration of a child, allowing a child to enter an environment that is injurious to the child's welfare, and contributing to the delinquency of a child. Regarding caretaking relationships, it is

usual to categorize a sexual assault on a child by a caretaker as “abuse” and to categorize an assault by a noncaretaker under the legal definitions of “assaults” also pertaining to adult victims. Common statutes include rape, indecent liberties, and assault on a female. In most aspects, the medical issues of abuse and of assault are similar, although the agency responses may differ widely. In this chapter, the term *abuse* is used to include both categories, unless otherwise specified.

PREVALENCE

Information on the prevalence of child sexual abuse is difficult to obtain because it is usually a hidden offense, surrounded by secrecy, criminality, and shame. It was first described by Kempe³ as a “hidden pediatric problem” and remains so to the present. The available statistics include only the cases disclosed to the child protection agencies or to law enforcement.

The 2003 annual statistics on child maltreatment from state protective services (CPS) agencies in the United States revealed an estimated 906,000 children were determined to be victims of child abuse and neglect with a victimization rate of 12.4 per 1000 children and a child fatality rate of two deaths per 100,000 children. Neglect was the commonest type of maltreatment in 61% of the child victims, physical abuse in 19%, sexual abuse in 10%, and emotional abuse in 5%. Other types of maltreatment were found in 17% (based on specific State Laws and Policies). Approximately 78,000 children were determined to be victims of sexual abuse with a victimization rate of 1.2 per 1000 children.⁴

A 1992 study by the Bureau of Justice Statistics evaluated female rape victims under age 12 years and whose perpetrators were reported under the FBI’s Uniform Crime Reporting Program in 1991 and 1992. An estimated 17,000 girls under age 12 were raped, representing 16% of all female rape victims and not including unreported rapes.⁵ Studies have suggested that each year approximately 1% of children in North America experience some form of sexual abuse resulting in sexual victimization of 12–25% of girls and 8–10% of boys by 18 years of age.⁶ Convicted rape and sexual assault offenders serving time in State prisons report that two-thirds of their victims were under the age of 18, and 58% of those (or nearly 4 in 10 imprisoned violent sex offenders) said their victims were aged 12 or younger. In 90% of the rapes of children less than 12 years of age, the child knew the offender.⁷ Studies of convicted rapists and victims indicated that 20% of victims under age 12 had been raped by their fathers and 46% by a family member.⁵

In studies by Finkelhor on adult survivors, 90% of the diagnosed cases of sexual abuse involved male perpetrators, 70–90% of whom were known to the child. Boys are reportedly abused at one-third to one-quarter the rate of girls.^{8,9} Forty percent of reported offenders who sexually assaulted children under age 6 were juveniles (under the age of 18).¹⁰

Although there are profound legal and psychosocial differences between consequences of sexual assault by a noncaretaker and sexual abuse by a caretaker, this chapter incorporates both situations into the term *sexual abuse* unless otherwise specified.

Compared with the general population, children who experience poverty, parental inadequacy, unavailability, conflict, harsh discipline, and emotional deprivation experience elevated risks of abuse.^{11–13} Substance-abusing parents, chaotic home environments, spousal abuse, other felonies on the part of household members, and high levels of stress are also commonly noted. All the above-named factors decrease the quality and quantity of supervision and protection, leaving the children more vulnerable, emotionally deprived, and at higher risk.¹⁴ Race appears not to be a risk factor.

CONSEQUENCES

The effects of sexual abuse on the behaviors of a child may vary widely, and there is no “sexual abuse syndrome” that a child develops once sexually abused. How a child internalizes a trauma and then copes with it depends on many factors. Issues that worsen the impact of sexual abuse on the emotional well-being of the child include the extent of familial denial; abuse that is longer in duration; type and frequency of abuse; closer relationships to the perpetrator; the use of violence, threats, force, or penetration; lack of maternal support; and the child’s overall functioning before the abuse began. Post-traumatic stress disorder is one of the most commonly cited aftereffects of child sexual abuse.^{15–17} Attention deficit hyperactivity disorder (ADHD) and oppositional behaviors also appear more frequently in children who have been sexually abused.¹⁸ One study of preschoolers suggested that overt sexualized behaviors (public masturbation; compulsive sexual curiosity; acting out of adult sexualized themes on toys, other children, or themselves; and exposure of genitals) comprise behaviors that are relatively specific for sexual abuse.¹⁹ However, sexual behavior is also related to a number of variables other than sexual abuse. These include family nudity, the boundaries displayed in the home, stress, exposure to sexual activity, and exposure to both pornography and sexually explicit materials.

Although there are no universal behavioral consequences of sexual abuse, there are commonly seen symptoms.^{2,20} Absence of or presence of a given symptom cannot automatically rule in nor rule out sexual abuse. Symptoms in abused males often differ from those in females.²¹ The severity of symptoms is influenced by numerous factors, including the protective response of the mother or lack thereof, use of force during the assault, duration of time during which the child experienced repetitive assaults, the relationship of the perpetrator to the child (in which assault by trusted family

Table 87-1. Common Behaviors and Symptoms of Sexually Abused Children

Perpetration of abuse on other children
Posttraumatic fear, anxiety
Concentration difficulty
Impaired sense of self
Depression
Anger, aggressiveness toward others
Social isolation
Avoidant behaviors
Sexually acting out
Promiscuity in adolescents
Cruelty to animals
Self mutilation
Indiscriminate sexual behaviors
Fire setting

members is more severe), and penetrative trauma.^{22–24} (Table 87-1) lists common behaviors and symptoms.

PERPETRATORS

Perpetrators of sexual assault or abuse of children often appear to be otherwise normally functioning citizens and may be without history of other criminal behaviors. However, higher rates of perpetrators come from populations of persons who have histories of inflicting domestic violence on any family member, have sexually assaulted other children, are alcoholic or use illicit drugs, or have criminal records of felonies. Approximately 90% of perpetrators are males. Women may be perpetrators, but only a small minority of sexual abuse allegations involve women. Caretakers appear to perpetrate more frequently than do biologic parents.²⁵

Substantial numbers of offenders are juveniles, and several studies of incarcerated adult offenders have reported accounts of perpetration against children that began while the adult was a juvenile.^{26,27} It appears that the prior experience of the adolescent as an abused or nonabused child may influence his or her behaviors as a perpetrator.²⁸

REPORTING OF SEXUAL ABUSE

Each State and U.S. Territory designate individuals, typically by professional group, who are mandated by law to report child maltreatment. Any person, however, may report incidents of abuse or neglect.²⁹

Individuals typically designated as mandatory reporters have frequent contact with children. Such individuals include

- health care workers
- school personnel
- child care providers
- social workers
- law enforcement officers
- mental health professionals

When a clinician suspects sexual abuse, reporting that suspicion is mandated. Persons making good faith reports are protected from liability. Most state statutes specify that this reporting requirement supersedes all claims of professional-client privilege. Sexual assault of a child is a crime in all 50 states and the District of Columbia. Almost all states have specific criminal penalties for failure of a “mandated reporter” to report a suspected child abuse situation. The laws regarding reporting indicate that any person or institution having cause to suspect that any child is abused, neglected, or has died as the result of maltreatment must report to the child protection agency of the county in which the child resides. The report may be made orally, by telephone, or in writing.

Laws are often vague concerning how much evidence regarding abuse must be available to a clinician in order to require that a report be made. Since abuse of children is highly prevalent in the United States, most pediatricians consider the possibility that abuse may play a role in the condition of many of their patients. Similarly, laws are often silent about the timing of a required report, and the clinician must use his or her best judgment. All clinicians who provide medical care for children should familiarize themselves with the laws and practices of their community regarding resources for evaluating children suspected of being abused. The agency that receives reports of suspected abuse or neglect is usually the county department of social services. Some communities have agencies that are very active in the protection of children, while others require a greater level of evidence before an investigation is initiated. A high level of mutual respect and education between clinicians and agencies is essential for optimal evaluation and protection of endangered children.

Although the rate of reporting has increased, only a minority of cases are actually reported. One reason for failure to report is fear of lack of adequate evidence.³⁰ Despite reporting mandates for professionals, the largest category of reports

is made primarily by victims (30%), followed by school personnel (16%), legal professionals and social service providers (each at 12%), and medical professionals (11%).³¹ In surveying physicians, 24% indicated that they had failed to report a suspected case because they felt that the child protective services were of poor quality or overreacted to reports.³⁰

MEDICAL DIAGNOSIS OF SEXUAL ABUSE

A comprehensive medical assessment of suspected victims of child sexual abuse involves careful questioning, evidence-collection procedures, specialized examination techniques, and equipment. Many physicians feel inexperienced or unprepared to conduct these evaluations and referral on to other physicians or health care professionals with expertise in this area is appropriate. Knowledge of the relevant skilled professionals, legal requirements, reporting mechanisms, procedures, and documentation are essential for all physicians.

The basic elements of the medical evaluation of a child for child sexual abuse may include

1. an intake process to coordinate the components of the evaluation;
2. gathering documentation and information about the relevant other services concerned with the child (teachers, physician);
3. interview of primary caretaker for child's medical history and review of systems;
4. investigative interview with child's caretaker(s);
5. separate investigative interview with the child;
6. physical examination of the child (general physical, genital, and anal examinations);
7. documentation of the findings;
8. laboratory tests as indicated by examination and history;
9. review of case with relevant agencies.

Investigative interviews should be conducted by social services and/or law enforcement agencies, but this does not preclude physicians asking relevant questions to obtain a detailed history and a review of systems. Medical history, past incidents of abuse or suspicious injuries, and menstrual and sexual history (for older adolescents) should be documented. The medical history should include information helpful in determining what tests should be done and when, how to interpret medical findings when present, and what medical and mental health services should be provided for the child and family. Most expert interviewers do not interview children younger than 3 years.⁶ The American Academy of Child and Adolescent Psychiatry and the American Professional Society on the Abuse of Children (APSAC) have published guidelines for interviewing sexually abused children.^{32,33} It is desirable for those conducting interviews to

avoid leading and suggestive questions as these may contaminate evidence that may be put before the courts. An interview needs to be done in a neutral manner with no suggestion that the interviewer knows what the child should feel or what has happened. The interviewer should make no personalized comments or react strongly to what the child states, since this may cause the child to withdraw.

Sexually abused children may not always disclose abuse and may present to medical settings with a variety of symptoms and signs. Physicians require a high level of suspicion and a willingness to consider abuse as a possibility. The majority of sexually abused children are abused chronically and do not come to diagnostic attention at the first assault. There are many well-studied reasons why children may not disclose sexual abuse or will disclose sexual abuse initially but subsequently will recant their statements³⁴ (Table 87-2). As many as one-quarter of the children, who have been confirmed to have been sexually abused, as evidenced by admission of the perpetrator, recant their disclosure at some time in the interviewing procedure. Most often the reason for a child to recant is pressure from the family to protect the alleged perpetrator. Disclosure is a function of the child's safety and developmental level and is a reflection of the child's environment. Disclosure is often a process rather than a one-time event and often occurs in stages rather than as an initially complete account.³⁵ A child will rarely disclose sexual abuse if he or she is living with the perpetrator. Where possible, the parent or caretaker should not be present during the interview so that influences and distraction can be kept to a minimum.

A number of aids, such as anatomic dolls,³⁶ can assist the interviewer when asking children about their abuse. These are generally only used by professionals trained in interviewing young children.

Methods of recording the professional interview include videotaping of the interview, transcription of verbatim notes, and audio recording. Methods used vary widely with each state and agency or clinic. Each of the techniques mentioned is supported by APSAC, and each technique has advantages and limitations or disadvantages. When audiotaping or videotaping is used, protocols should be coordinated with the district attorney's office in accordance with state guidelines. Because the issues of credibility and suggestibility of the child are often raised, the use of videotaping or transcription of verbatim notes provides a means of ensuring an accurate and complete record of the interview.

PHYSICAL EXAMINATION

The child should have a thorough pediatric examination performed by a health care provider with appropriate training and experience who is licensed to make medical diagnosis and recommend treatment. The physical examination should not

Table 87-2. The Child Sexual Abuse Accommodation Syndrome

1. **Secrecy.** Secrecy is both the source of fear and the promise of safety. "Everything will be OK if you don't tell." Most children never tell.
2. **Helplessness.** The adult expectation of child self-protection and immediate disclosure ignores the basic subordination and helplessness of children within authoritarian relationships. The child often has no choice but to submit quietly to the overpowering adult and to keep the secret.
3. **Entrapment and accommodation.** Often the only option for the child is to learn to accept the situation and survive. The child is given the power to destroy the family (by telling the secret) and the responsibility to keep it together (by keeping the secret).
4. **Delayed, conflicted, and unconvincing disclosure.** Many adults, including parents, teachers, doctors, social workers, and attorneys, cannot believe that a normal adult could be capable of repeated, unchallenged sexual molestation of a child. Disclosure generally is an outgrowth either of overwhelming family conflict, incidental discovery by a third party, or outreach and education by child protective agencies. Disclosure may occur months or even years after the initial abuse. It may contain details and descriptions that seem distorted or fanciful and therefore lack credibility.
5. **Retraction.** The child's retraction is often readily accepted by authorities and relatives as the truth, whereas the child's initial disclosure of abuse is considered doubtful. Unless there is consistent support for the child and immediate intervention to force responsibility on the perpetrator, the child will follow the "normal" course and retract his or her complaint.

result in additional physical or emotional trauma to the child. Provided the child agrees, it is advisable to have a supportive adult (not suspected of involvement of abuse) present during the examination. A chaperone and/or nurse support is also recommended. Careful documentation of the child's responses to questions should be made during the examination as in some cases children who have not previously disclosed may do so at this time.

The aims of the medical assessment are to assess the whole child to include

- growth, health, development, and behavior
- identification of injuries that require treatment
- identification of signs of other forms of abuse and neglect
- identification of other conditions that have not received usual medical attention
- screening for, or diagnosis of, sexually transmitted infection (STI) and prevention of infections
- evaluation of the risk of pregnancy and pregnancy prevention
- documentation of findings of potential forensic value
- forensic evidence collection
- recording and documentation of injuries and physical signs with detailed diagrams and preferably by photography

Following the general physical examination, the child receives an examination of the anal and genital areas. See (Table 87-3) for important general policies regarding these examinations. Examinations of children may require more than one appointment to gain the confidence of the

child. Gentle and careful coaching with distraction for younger children will allow most children to cooperate with an examination.

■ EXAMINATION TECHNIQUES

Various examination techniques and positions visualizing the genital and anal structures in children and adolescents have been described.^{6,37}

The examination of prepubertal girls is recommended as follows:

- The child is examined in the supine "frog-legged" position (young children can be held on a carer's lap). The knee-chest position can be used to give a better view of the posterior hymen.
- The external genitalia should be inspected; the labia majora should be gently separated to view the hymenal orifice; gentle traction at the posterior edge of the labia majora, between the thumb and index finger, allows clearer visualization of the hymen. Warm sterile water dropped via a syringe or dropper may assist in separation of the edges of the hymen.
- Buttock separation, in the left lateral position, using the palms of both hands to view the anus for 30 seconds.

The examination of a pubertal girl will require additional techniques to view the folded edges of an estrogenized hymen. A cotton tipped swab is useful to gently examine the hymenal rim. Foley catheters are becoming a popular method to spread out the estrogenized hymenal tissue. The hymenal opening should be assessed by gentle digital

Table 87-3. General Policies Regarding the Physical Examination

The genital examination of an awake prepubertal female should not include devices inserted through the hymen such as a speculum, otoscope, or ureteroscope; if the child requires an invasive examination, general anesthesia is often indicated.

A child should not be examined if he or she is unable to fully cooperate. Conscious sedation may be required for very fearful children. Physical restraint should not be used.

The child should have as much decision making as possible during the examination. He or she may be asked by whom he or she wishes to be accompanied, draping, or gowning wishes, etc. Books should be available should the child's caretaker wish to distract the child.

The accompanying caretaker should be instructed to remain at the head of the table, assisting and reassuring the child. Out of respect for the child's privacy, the caretaker should not view the child's anal or genital findings.

When sexual abuse is strongly suspected for any reason, the clinician should attempt to ensure that the child leaves the clinic to go to a safe environment. This may require urgent services from the police or department of social services.

Results of assays or clinical specimens may have legal implications. Specimens must be labeled, delivered to the laboratory, and processed in a manner that allows a chain of custody to be supported.

insertion followed by an appropriate sized speculum examination to assess for vaginal/cervical injuries and carry out sexually transmitted disease (STD) screening, once forensic sampling has been completed.

The examination of boys is recommended as follows:

- Young children can be held on a carer's lap.
- The external genitalia should be inspected; the foreskin, if present, should be gently retracted, where possible, to view the urethral meatus and frenulum; the scrotum should be gently palpated to assess for the presence, and any pathology, of both testes.
- Buttock separation, in the left lateral position, using the palms of both hands to view the anus for 30 seconds.^{38,39}

The knee–chest position is also helpful in both genders in obtaining an optimal view of the anal and perianal tissues and in assessing the child for anal dilatation.

Instruments that magnify and illuminate the genital and rectal areas such as colposcopes with photo documentation are commonly used and recommended.⁴⁰ Speculum or digital examinations should not be performed on the prepubertal child unless under anesthesia (e.g., for suspected foreign body) and digital exams of the rectum are unnecessary.⁶

During the physical examination, the child's behavior should be noted. Children who have been sexually traumatized may complete the general examination without difficulty and display various trauma symptoms when the genital or anal examination is initiated. Common trauma symptoms include a fearful inability to endure a visual examination, sexualized behaviors during the examination, and dissociative symptoms.

■ SCHEDULING OF EXAMINATIONS

Examinations should be performed without delay in the following circumstances^{38,39}:

- When the alleged sexual abuse has occurred within 72 hours.
- There is a history of acute trauma.
- There is a possibility of pregnancy resulting from the abuse in a postpubertal girl.
- The child is not considered to be in a safe or protected environment.

When more than 72 hours have passed, the child is safe, and no acute injuries are present, the examination can be carried out at the earliest convenient time for the child, the family, the physician, and the investigative team.

Forensic evidence collection is recommended when sexual abuse has occurred within 72 hours.⁶ Local policies and procedures for evidence collection should be followed. Body swabs in prepubertal children more than 24 hours after a sexual assault are unlikely to yield forensic evidence, and nearly two-thirds of the forensic evidence may be recovered from clothing and linens.⁴¹

■ INTERPRETATION OF GENITAL/ANAL FINDINGS

A clear statement by the child is the single most important factor in making a diagnosis of sexual abuse.^{6,39} A diagnosis of sexual abuse should rarely be made on physical signs alone. A substantial proportion of sexually abused children have no abnormal physical signs. The proportion varies with the types of abuse and the time elapsed since the most recent abusive

episode.³⁹ Many types of abuse leave no physical evidence and mucosal injuries often heal rapidly and completely. Absence of signs does not imply absence of abuse.^{39,42–47}

The interpretation of physical findings continues to evolve as evidence based research becomes available.⁴⁸ The physical examination may be classified as to the significance of the findings. Findings diagnostic of trauma and/or sexual contact include^{39,48}

1. abrasions or bruising to the genitalia;
2. an acute or healed laceration in the hymen that extends to or nearly to the base of the hymen;
3. bruising to the hymen;
4. a markedly decreased amount of hymenal tissue or absent hymenal tissue in the posterior aspect;
5. injury to or scarring of the posterior fourchette, fossa navicularis, or hymen;
6. perianal bruising, lacerations, or scarring;
7. pregnancy;
8. the presence of semen/sperm in specimens taken directly from a child's body;
9. the presence of a positive culture for *Neisseria gonorrhoeae* (GC), *Chlamydia trachomatis* (CT), or *Trichomonas vaginalis* (TV); or a positive serologic test for syphilis or HIV infection if perinatal or neonatal transmission has been excluded (and in the case of HIV, transmission from blood products has been excluded).

EVALUATION FOR SEXUALLY TRANSMITTED DISEASES

An integral component of the physical examination of a child for suspected sexual abuse is the evaluation of the child for STDs. The results of assessments for STDs are critical for the welfare of the child because the evaluation pertains not only to the physical health of the child and any required therapy but also may provide evidence that the child has been abused and is therefore in need of protection from further assault.

Children can acquire STDs through vertical transmission, by autoinoculation, or by sexual contact. Each of these mechanisms should be given appropriate consideration in the evaluation of a preadolescent child with an STD. Evaluation based solely on suspicion of an STD should not proceed until the diagnosis has been confirmed. Factors to be considered in assessing the likelihood of sexual abuse in a child with an STD include whether the child reports a history of sexual victimization, biologic characteristics of the STD in question, and the age of the child.⁴⁹ Two reviews^{50,51} concluded that accidental transmission (fomite, close physical contact, or autoinoculation) is an exceptionally uncommon mode of transmission of STDs to children. The identification of sexually transmissible agents in children beyond the neonatal period is suggestive of

sexual abuse. The significance of an STD as evidence of possible child sexual abuse varies by pathogen.⁵² Vertical transmission is a possibility in a child aged less than 3 years, although sexual abuse can also occur within this age group. In evaluating adolescents, it should be remembered that consensual sexual activity and sexual abuse can coexist. The social significance of each STI and the recommended action regarding reporting of sexual abuse are summarized in (Table 87-4).

THE RISK OF INFECTION

Approximately 5% of sexually abused children acquire an STD as a result of their victimization.⁴⁹ The risk of acquiring an STD is dependent on several factors including the following^{38,49}:

- The regional prevalence of STDs within the population.
- Maternal STD during pregnancy leading to vertical transmission to the infant.
- The type of sexual activity, e.g., penile, vaginal, or rectal penetration is more likely to lead to infection than other types of sexual activity.
- Injuries of the genital tract. Trauma increases the susceptibility to infection.
- The sexual maturity of the young person. A young person has an increased biological susceptibility to carcinogens and STDs due to physical and immunological immaturity of the genital tract.
- The lack of use of barrier contraception.
- The frequency of physical contact between the perpetrator(s) and the child.
- The number of assailants.
- The infectivity of various microorganisms.
- Whether the child has received intercurrent antimicrobial agent treatment.

SCREENING FOR STDs

Universal screening of postpubertal patients is recommended because the prevalence of preexisting asymptomatic infection in this group is high.⁴⁹ The decision to screen prepubertal children must be made on an individual basis. The following situations involve a high risk of STDs and constitute a strong indication for testing^{49,52}:

- The child has or has had signs or symptoms of an STD or an infection that can be transmitted sexually, even in the absence of suspicion of sexual abuse.
- A sibling, another child, or an adult in the household or child's immediate environment has an STD.
- A suspected assailant is known to have an STD or to be at high risk of STDs (e.g., has had multiple partners, a history of STDs, and a history of intravenous drug use or same sex partners).

Table 87-4. Implications of Commonly Encountered STDs for the Diagnosis and Reporting of Sexual Abuse of Infants and Prepubertal Children

STD Confirmed	Sexual Abuse	Suggested Action
Gonorrhoeae ^a	Diagnostic ^b	Report ^c
Syphilis ^a	Diagnostic	Report
HIV infections ^d	Diagnostic	Report
<i>C. trachomatis</i> infection ^a	Diagnostic ^b	Report
<i>T. vaginalis</i> infection	Highly suspicious	Report
Condyloma acuminata ^a (anogenital warts)	Suspicious	Report
Genital herpes	Suspicious	Report ^e
Bacterial vaginosis	Inconclusive	Medical Follow-up

^aIf not perinatally acquired and rare, nonsexual vertical transmission is excluded.

^bAlthough the culture technique is the "gold standard," current studies are investigating the use of nucleic acid-amplification tests as an alternative diagnostic method in children.

^cTo the agency mandated in the community to receive reports of suspected sexual abuse.

^dIf not acquired perinatally or by transfusion.

^eUnless there is a clear history of autoinoculation.

From Kellogg N and the Committee on Child Abuse and Neglect. American Academy of Pediatrics: The evaluation of sexual abuse in children. *Pediatrics* 2005; 116: 506–512.

- There were a number of assailants.
- The patient or family requests testing.
- The prevalence of STDs in the community is high.
- Evidence of genital, oral, or anal penetration or ejaculation is present.

■ SAMPLING TECHNIQUES³⁸

The genital organs of female infants, children, adolescents, and adults have important anatomical and physiological differences. These differences influence the microbiological flora of the genital tract and the sampling sites for screening.

- Sampling techniques must be specific for the sexual maturity of the young person.
- Samples should be the least invasive and the minimum necessary. Priority should be to obtain suitable specimens to identify *N. gonorrhoeae* (GC), *C. trachomatis* (CT), *T. vaginalis*, (TV) and, in the presence of genital ulcers, herpes simplex virus (HSV).

- Sterile cotton tip swabs are recommended and these can be moistened with sterile water (or the viral culture medium if performing viral cultures).
- For prepubertal girls, smaller ear, nose and throat (ENT) swabs are useful for transhymenal vaginal sampling. Avoiding contact with the hymen will reduce discomfort and increase cooperation of the young person. ENT swabs are also useful for male urethral sampling, if undertaken.
- Recommended sample sites for prepubertal females include
 - vulva
 - posterior fourchette
 - posterior vaginal wall
 - vulval or vaginal washings are also suitable. Urethral swabs cause discomfort and should be kept to a minimum
- Postpubertal females can be screened according to local protocols for female adults if tolerant of speculum examination. In some pubertal females it may be impossible to pass a speculum. Blind vaginal sampling together with

urethral and/or urine Nucleic Acid Amplification Techniques (NAAT) are advised.

- Screening of male young people will depend on their presenting history and the method of abuse (where suspected). Urethral swabs cause discomfort and their use should be kept to a minimum. Urine NAAT should be considered.

■ DIAGNOSTIC METHODS^{6,38,49,52}

Most screening tests for STDs have been developed and approved only for genital sites in the adult population. In sexually abused children the following should be considered:

- Specimens should be obtained by health care professionals with experience in the evaluation of sexually abused/assaulted children.
- The most sensitive and specific test available for the organism should be used.
- Culture tests are still considered the “gold standard” for diagnosing GC (bacterial culture) and CT (cell culture). New tests such as nucleic acid-amplification tests (NAAT) may be more sensitive but data regarding use in prepubertal children are limited.
- When an organism is isolated, the sample should be preserved for future analysis (in case of medico-legal implications).
- A positive test should be confirmed preferably by a test that involves a different process because the prevalence of STDs in children is low and the positive predictive value of these tests is lower than that of adults.
- The presence of one STD indicates the need to look for others.
- Testing before any prophylactic treatment is preferable to prophylaxis without testing.
- Specimens for laboratory analysis should be labeled carefully and standard hospital procedures for transferring specimens from site to site should be followed to preserve the “chain of evidence.”

The STD screening should focus on likely anatomic sites of infection (as determined by the patient’s history or by epidemiologic consideration).

- Specimen cultures for GC can be obtained from the pharynx and anus in boys and girls, the vulva (vagina for prepubertal girls, the cervix for pubertal girls tolerant of a speculum, and the urethra in boys (the urethral meatus is an adequate substitute for an intraurethral swab for boys with urethral discharge).
- Specimen cultures for CT can be obtained from the anus in boys and girls, the vulva (vagina for prepubertal girls, the cervix for pubertal girls tolerant of a speculum, and

the urethral meatus in boys with urethral discharge. Pharyngeal specimens in children of either sex are not recommended, as the yield is too low. NAAT may be an alternative where confirmation is available or culture systems for CT are unavailable.

- A vaginal swab for culture and wet mount should be taken for TV and bacterial vaginosis (BV).
- Viral culture swabs should be obtained from any ulcerative or vesicular lesions.
- Anogenital warts (AGWs) are clinically diagnosed without testing.
- Serum sampling for HIV, hepatitis B and C, and syphilis should be made on a case-by-case basis, taking into account the patient’s and family’s wishes, the presence of another STD, the risks from the assailant where there were multiple assailants, and the type of abuse/assault.
- Pregnancy testing and prevention should be considered in all pubertal girls.

■ SCREENING SCHEDULE FOR STDs^{38,52}

The scheduling of examinations should depend on the history of abuse (assault and incubation periods of STDs). They should be determined on an individual basis taking into account the child’s (and their parent/carer’s) psychological and social needs. A single examination may be sufficient if the child has been abused over an extended period by the same person/people or if the last episode of abuse was at least 3 months back. A general guide for examination timing is

- immediate (if practical) for oral sampling (if available), serology, and initial specimen collection
- 2 weeks after the initial abuse/assault for initial sampling or repeat sampling (if immediate sampling performed), and pregnancy testing in pubertal girls, with a follow up visit for results and counseling at a further 1–2 weeks
- 12 weeks for repeat serology and 6 months in some cases. Serum samples can be taken and stored for testing at a later date

The risk of HIV infection should be discussed, as it is a major concern of abused young people. Counseling of the young persons will need to be tailored to their age and understanding and should also involve the parent/carer. Ideally and where possible, the alleged perpetrator should be tested first.

■ PROPHYLAXIS^{38,49,52}

As the prevalence of most STDs following abuse (assault) is low and prepubertal girls appear to be at lower risk for ascending infection than adolescent or adult women, preventive therapy in prepubertal children is not recommended routinely. The potential benefit of treating a sexually abused

child should be weighed against the risk for adverse reactions and the likelihood of compliance. Each case should be dealt with individually taking into account the wishes of the child/family, the type of assault, any risk factors identified in the perpetrator, the number of perpetrators, and the local prevalence of STDs.

The following prophylactic regime can be used as a guideline:

For CT, GC, and BV, a combination of ceftriaxone 125 mg IM in a single dose plus metronidazole 2 g orally in a single dose (15 mg/kg/day orally, in 3 divided doses for 7 days in children <45 kg) plus azithromycin 1 g (20 mg/kg orally in children <45 kg) orally in a single dose (or doxycycline 100 mg orally twice per day for 7 days in children >45 kg). The efficacy of these regimes has not been currently evaluated.

Postexposure prophylaxis for HIV in children should be considered within 72 hours of the sexual abuse or assault and on an individual basis. If antiretroviral postexposure prophylaxis is being considered, a professional specializing in HIV-infected children should be consulted.

Hepatitis B vaccination prophylaxis should be considered at the initial examination if it is within 3 weeks of the sexual abuse/assault and the child has not previously been vaccinated. Follow-up doses should be administered at 1–2 and 4–6 months after the first dose.

SPECIFIC STDs

The following should be read in conjunction with the relevant chapters within this book. Treatment guidelines for each of the conditions can be found in the “Sexually Transmitted Diseases Treatment Guidelines 2002”⁵² and in the “2003 Red Book” (American Academy of Pediatrics⁴⁹). Periodic updates of both these sources should be noted by clinicians caring for children with relevant problems.

Chlamydial infection, genital warts, and GC are the most prevalent clinically evident STDs in sexually abused children. HIV infection and syphilis are rare.³⁷

■ N. GONORRHOEAE

The reported prevalence of GC in studies of sexually abused children ranges from 2.9% to 11.2%, with highest rates in adolescents.^{53,54} Infection may occur in the conjunctiva, oropharynx, urethra, vagina, endocervix, and rectum. The incubation period is 3–7 days.

The commonest symptom in prepubertal children is vaginal discharge. Asymptomatic infection, pelvic inflammatory disease, and perihepatitis can occur but are uncommon (5% had no vaginal discharge in one study of sexually abused preteenage girls⁵⁵). Rectal and pharyngeal infections are typically asymptomatic and are often unrecognized.

Currently standard culture methods are considered the “gold standard” for screening and testing.

■ CHLAMYDIA TRACHOMATIS

Chlamydial infections have been identified in 1.2–17% of sexually abused young people when specimens were routinely cultured. Coincident infection with CT has been observed in up to 27% of young people with GC. The higher rates are more common in postpubertal young people.^{54,56–58} Prolonged shedding of CT may occur after contamination of the infant in the perinatal process and may last until age 3 years⁵⁹; consequently, genital CT is a confirming STD only in children older than 3 years of age. If a positive CT culture is obtained from a child suspected of being sexually abused, the evidence for abuse is strengthened if asymptomatic maternal infection has been excluded and if urethral infection in the alleged perpetrator can be demonstrated by culture.³⁹

Chlamydial infection in children can be symptomatic including vaginitis in prepubertal girls; urethritis, cervicitis, endometritis, salpingitis, and perihepatitis in postpubertal females; epididymitis in males; and Reiter’s syndrome (arthritis, urethritis, and bilateral conjunctivitis). It can also be asymptomatic and the infection can persist for months to years. Symptomatic infection of the pharynx is rare. The incubation period of chlamydial infection is variable depending on the type of infection, but is usually 1 week.

Standard cell culture systems should be used but NAAT may be an alternative where confirmation is available or culture systems for CT are unavailable.

HUMAN PAPILLOMAVIRUS DISEASE

Genital human papilloma virus (HPV) disease may be recognized clinically as classic genital warts or, as in adults, as flat mucosal lesions in any body site (mouth, eye, anus, urethra, introitus). As in adults, an exfoliative cytologic examination of mucosal lesions may yield a diagnosis, or a biopsy may be indicated.⁶⁰ AGWs may cause soreness, irritation, or bleeding but may also be symptomless. AGWs were found in 1.8% of 1,538 young people aged between 1–12 years being evaluated for possible sexual abuse.⁵⁸

The incubation period for HPV is 1–20 months but latency periods of at least 2 years are suspected. The epidemiology of HPV transmission is complex. Children can acquire HPV infection from vertical transmission, autoinoculation, or sexual abuse/activity. It is the general consensus opinion of experts that vertical perinatal transmission is considered no longer likely as a cause of AGWs appearing after the first 2 years of life.⁶¹ Considerable evidence supports the position that AGWs in young people appearing after 2 years are usually acquired from sexual contact.⁶² Limitations in diagnosis of preverbal children have led to uncertainty regarding the means of transmission, especially in this age group.

Children with AGWs should be screened for other STDs. The parents/caretakers and siblings should be examined and screened for HPV infection.

■ TRICHOMONAS VAGINALIS

The reported prevalence of TV in studies of children evaluated for suspected sexual abuse range from 1% to 2% with higher rates in pubertal girls.^{54,63}

Perinatal infection of the vagina may occur for up to 1 year if not treated. Beyond infancy the presence of TV in a vaginal specimen is strongly suggestive of sexual abuse.⁶⁴ Vulvovaginitis is the commonest presenting symptom in prepubertal young people. In pubertal girls, infection can be asymptomatic or present with a frothy vaginal discharge, dysuria, and vulvovaginal itching. Infection in males can be asymptomatic or present with urethritis, epididymitis, or prostatitis.

The incubation period averages 1 week but ranges from 4 to 28 days.

Culture tests should be used and are more sensitive than examination of a wet mount.⁶⁴

■ BACTERIAL VAGINOSIS

The significance of finding BV in children and adolescents is unclear. Sexual transmission has not been clearly documented and it is not regarded as an STD in adults. It is of doubtful significance in the interpretation of abuse but it is commonly found following sexual assault in adults and adolescents.⁶⁵ *Gardnerella vaginalis* (*G. vaginalis*) has been cultured from various sites in the newborn but it has not been established that for how long these sites may be colonized. The majority of case reports and studies in children have been based only on the identification of *G. vaginalis*, not on Amsel's criteria (clue cells, a positive amine or "whiff" test, a white homogeneous vaginal discharge, and a vaginal fluid pH greater than 4.5). One of the four criteria cannot readily be applied to girls, as during the childhood or prepubertal period the vaginal environment is alkaline. *G. vaginalis*, has been isolated from vaginal cultures of 1–32% normal or control young people, compared to 7–34% in sexually abused or sexually active girls.⁶⁴ Hammerschlag, et al. found BV in 13% of sexually abused girls compared with none of the controls.⁶⁶ BV may cause a vaginal discharge but may also be asymptomatic. Where there are symptoms, diagnosis and therapy are frequently helpful to the patient.⁶⁶

For pubertal girls, Amsel's criteria should be used on a wet preparation of a vaginal swab. An alternative method of establishing the diagnosis is a Gram stain of vaginal secretions using Nugent's criteria. A smear containing no lactobacilli and heavy Gram-negative and/or Gram-variable rods and curved Gram-positive rods would be diagnostic for BV. This method has not been evaluated in prepubertal children.⁶⁴

■ HUMAN IMMUNODEFICIENCY VIRUS

The incidence of HIV infection acquired by children through sexual abuse/assault is unknown. One study reported that

14.6% of children with HIV infection had been assaulted sexually, and at least 4% had been infected through abusive sexual contact.⁶⁷ A second study found positive HIV tests in 0.7% of children being evaluated for sexual abuse with sexual abuse identified as the most likely source of infection in 0.5%.⁶⁸ A further study of HIV-infected children aged less than 13 years found that 0.3% had been sexually abused. Of those 0.15% had no other identified risk factors other than the sexual abuse.⁶⁹ Sexual abuse as a mode of transmission is difficult to ascertain as some cases of perinatally acquired HIV infection may not present with an AIDS defining illness until over the age of 10 years.

Where a child is found to have a positive HIV test³⁸

- maternal HIV status should be ascertained depending on the age of the young person and their lifestyle/risk factors. Sexual abuse as a cause of HIV infection should not be discarded exclusively on the grounds that the victim's mother is known to be seropositive as both sets of risk factors may occur and coincide within one family setting.⁶⁸

Where maternal testing is negative and a transfusion route is excluded, sexual abuse must be suspected and child protection procedures followed

- the subject should be referred to a pediatrician/center experienced in the care of young people with HIV and AIDS.
- the subject and their parents/carers should receive appropriate counseling and multiagency support.
- sexual contacts should be offered screening and counseling.
- a full STI screen should be performed unless already completed.

Child protection teams are seldom in a position to know with useful certainty the risk factors for HIV that a given assailant may have, whether the assailant acted alone, the HIV status of the assailant(s), or even with certainty the acts that were committed. Because of these limitations of information and concerns, each service must construct its own policies. In some states, children may be tested if medically indicated even if the parent is reluctant to permit it.

In instances in which a perpetrator is reported to the police, it is occasionally possible to obtain serologic assays from that person.

■ SYPHILIS

The prevalence of syphilis among children suspected to have been sexually abused is approximately 0–1.8%.⁶⁴ Prepubertal children with primary or secondary stages of syphilis occurring beyond the neonatal period should be presumed to be victims of sexual abuse.⁵⁰

Most adolescents with syphilis have acquired their disease through consensual sexual activity, although sexual abuse should still be considered as a possibility as studies have

demonstrated that between 10 and 32% of adolescents with syphilis had a history of sexual abuse.⁷⁰

The presentation of acquired syphilis in children is the same as adults. Children can present with primary chancres, secondary syphilis, or latent syphilis with only positive serology as evidence of infection. The incubation period of acquired primary syphilis is 3 weeks but ranges from 10 to 90 days. Nontreponemal antibody tests (Venereal Disease Research Laboratory, Rapid Plasma Reagin and Automated Reagin Test) are used for screening and treponemal tests (fluorescent treponemal antibody absorption test and *T. pallidum* particle agglutination tests) are used to establish a presumptive diagnosis.

■ HEPATITIS B AND C

We recommend that children who are being examined for HIV and/or syphilis should also be considered for testing for hepatitis B and C.

■ GENITAL HERPES

Herpetic infection is caused by HSV types 1 and 2. The incubation period for HSV occurring beyond the neonatal period ranges from 2 to 20 days. Both types of virus can cause all the clinical syndromes. HSV infection of the genitalia may present with typical multiple vesicles or may present with a more generalized erythema of varying severity. HSV 2 has been attributed to be the cause of most genital herpes, but 10–20% of genital herpes in adults can be due to HSV 1.⁶⁴ The virus type found on the genitalia of a child does not, therefore, rule out sexual abuse.

HSV 1 and HSV 2 have been recovered from the genital area in children who appear to have been sexually abused.^{71,72} The prevalence of infection following sexual abuse/assault is unknown. Children can also acquire genital infection by autoinoculation if they have a gingivostomatitis. Children presenting with genital herpes should be carefully examined for coexistent gingivostomatitis. Sexual abuse should be considered in those children with no evidence of gingivostomatitis.

Although commercially available serologic tests to distinguish HSV-1 and HSV-2 antibodies are now commercially available, their specificities vary by assay. In addition, since detection of HSV-1 antibody only does not rule out sexual abuse, their forensic value is limited. Currently, viral cell culture methods are considered the “gold standard” for screening and testing.

REPORTING CHILDREN WITH SEXUALLY TRANSMITTED DISEASES FOR SUSPECTED ABUSE

Each state mandates that persons who suspect that a child has been the victim of abuse must make a report to an authority that is constituted to receive and investigate such reports. In

many states, these laws specify that persons who are in positions of authority over children must make such reports, and clinicians are usually included as “mandated reporters.” For the clinician who has diagnosed a child with an STD, two major decisions must be made. First, he or she must decide the strength of the evidence that the child has been abused, based on the diagnosis of the STD, the details of the history, and the examination findings. Second, he or she must decide if the child should be reported to the agency constituted by that community to receive reports of suspected child abuse. Recommendations on these two issues as they pertain to the major STDs are found in Table 87-4 and represent recommendations formulated by the American Academy of Pediatrics.⁶ Acquired STDs that are considered diagnostic of sexual abuse are

- a positive confirmed culture for GC from the genital area, anus, and throat in a child outside the neonatal period;
- confirmed diagnosis of syphilis, if perinatal transmission is ruled out;
- positive culture from genital or anal tissues for CT, if the child is older than 3 years of age at the time of diagnosis, and the specimen was tested by cell culture or comparable method approved by the Centers for Disease Control;
- positive serology for HIV, if neonatal transmission and transmission from blood products have been ruled out.

The diagnosis of TV infection in a child older than 1 year of age, with organisms identified (by an experienced technician or clinician) in vaginal secretions by wet mount and by culture is considered highly suspicious of sexual abuse. The diagnosis of genital warts and genital HSV infection provides the clinician with a “suspicious” diagnosis of sexual abuse. Diagnosis of these conditions should result in a report to the investigative agency and thorough evaluation of the child for safety and for other evidence of possible abuse. The significance of BV and several other organisms, including genital *Molluscum contagiosum*, is uncertain, and their presence usually is not evidence, when seen alone, that requires a report. However, a child with BV should be evaluated for other STDs.

COORDINATION OF FINDINGS

The final diagnosis of sexual abuse may be derived from information from numerous sources. These may include the medical evaluation, school information, home evaluation, police investigation, witnesses, and acknowledgment by a perpetrator. The medical evaluation for abuse should summarize the results of the findings and the medical conclusions. The conclusions should include a statement of the level of certainty of the diagnosis and whether or not the evaluation was completed. For example, the report may state that the diagnosis of sexual abuse was confirmed, suspected, or unknown or that there was

no evidence of abuse. The basis of the conclusion should be clearly stated. The report should state whether or not a report of suspected abuse was made or had already been made. If safety measures are indicated, the report should clarify who is responsible for planning and implementing these services.

If abuse is confirmed or strongly suspected and a perpetrator identified, other siblings or children closely exposed to the perpetrator should receive an evaluation for abuse.⁷³ If no perpetrator is identified, other children sharing the same environment as the abused child should be evaluated.

Following the examination, most caretakers wish to know the results. The clinician should coordinate with any involved agencies as to whether or not a report should go to the caretakers. If a child has disclosed abuse or neglect by a family member, decisions must be made regarding the distribution of the information to the family. In addition, for most instances of suspected or confirmed sexual abuse, a mental health evaluation of the child should be scheduled. In many abusive/neglectful homes, parental compliance with treatment interventions is poor, and the child may require extensive monitoring in order to ensure safety and recovery. This is especially the case in families of sexually abused children.⁷⁴

The evaluation and management of problems resulting from sexual abuse of a child require the most skilled personnel from numerous intersecting services and agencies. These commonly include physicians, other medical examiners, social workers, police, guardians ad litem, other court personnel, and mental health evaluators and therapists. Sustained multi-agency working together with good communication between agencies is essential to safeguard and protect the welfare of abused children. Reabuse is common even when high-quality services have been provided.⁷⁵ Clinicians have a role in prompt recognition and treatment, reporting, advocacy, and surveillance of abused and/or perpetrating children.

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The Role of Primary Care Clinicians in STD, HIV, and Hepatitis Prevention and Care

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INTRODUCTION

Until the 1980s, most sexually transmitted infections (STI) services were provided in public health department STI clinics, community health centers, private physician's offices, hospital emergency departments, and health maintenance organizations (HMO).¹ By the late 1990s, about 70% of STI care was provided by private providers or to privately insured persons² and the number and hours of dedicated STI clinics had declined substantially.³ Meanwhile, enrollment in the commercial and Medicaid managed care health plans has risen dramatically, especially in the South⁴ where bacterial STI rates are highest.⁵ Another factor that prompted attention to STI care in the private sector was greater awareness of the high burden of viral STIs such as herpes and anogenital warts among Americans of all income levels and health insurance status and the introduction of new diagnostic and treatment modalities for these viral STI.⁶ The advent of high quality rapid and point-of-care human immunodeficiency virus (HIV) tests and highly effective antiretroviral therapy has resulted in a dramatic shift of HIV services from specialized HIV counseling and testing sites and dedicated HIV care clinics to primary care practices.⁷ Recent initiatives to expand hepatitis risk assessment, serologic screening, and vaccination beyond high-risk persons served by public clinics have motivated more primary care clinicians to offer this service.

Many cases of STI, HIV, and hepatitis occur in adolescents and young adults. Consequently, primary care clinicians, including obstetrician/gynecologists (Ob/Gyn), family practitioners, and pediatricians, who are often affiliated with commercial or Medicaid managed care health plans, now provide much of the STI, HIV and hepatitis services in the United States and will play a greater role in preventing, detecting, and managing these infections in the future.^{1,8,9} This chapter addresses the roles of the primary care clinicians in bacterial and viral STI, HIV, and sexually transmitted hepatitis prevention and care in primary care settings outside dedicated STI or HIV care clinics. These roles include risk assessment, physical examination, screening and diagnostic testing, treatment, risk

reduction counseling, patient education, vaccination, management of sex partners, case reporting, and collaboration in outbreak control. The chapter addresses why these are important functions, the extent to which these services are delivered in private primary care settings over the last decade, barriers to delivering these services, and interventions that have been used to improve delivery of these services.

RISK ASSESSMENT

The primary care health visit offers an important opportunity to assess risks for STIs, HIV, and viral hepatitis. Risk assessment may reveal the need for (1) risk reduction counseling or patient education to reduce risky sexual behaviors that could lead to infection, (2) screening laboratory tests, (3) vaccines to prevent STIs, HIV, and viral hepatitis, (4) condom distribution, or (5) referral for special services such as drug treatment programs. Several national organizations recommend providers assess sexual and parenteral drug use as part of the periodic health-care visit screening services ([Table 88-1](#)).¹⁰⁻²⁸ The risk assessment should be performed confidentially; for adolescents this means without parents present.^{10,13-15,21,25} [Table 88-2](#)^{13,15,17,21,25,29} lists questions about sexual activity and parenteral exposure risks for STIs, HIV, and hepatitis that providers should ask patients during a routine primary care visit. Focused sexual health risk screening and brief counseling as part of routine preventive health services to adolescent patients can be feasible and acceptable to both providers and patients.³⁰

Although preventive health-care visits offer an ideal opportunity for sexual and parenteral drug use behavior risk assessment, many adolescents and adults, especially boys and young men, do not have coverage for or do not access any preventive care services or may choose to seek services from sources other than their usual provider to protect confidentiality.³¹⁻³⁵ In an acute care or problem oriented visit, a sexual and parenteral drug use behavior risk assessment that is not related to the reason for the visit is rarely performed. Even among individuals who receive preventive health-care services, sexual and parenteral drug use behavior risk assessment is often

Table 88-1. National Recommendations by Organizations for Periodic Sexual and Parenteral Drug Use Risk Assessment and Counseling

Organization	Recommendations	Reference
American Academy of Pediatrics	<ul style="list-style-type: none"> • Integrate sexuality education and sexual risk reduction counseling into clinical practice • Obtain a comprehensive sexual history from all adolescent patients 	11–13
American College of Obstetricians and Gynecologists	<ul style="list-style-type: none"> • Ask all adolescents annually about sexual activity • Counsel adolescents about methods to prevent STIs and unintended pregnancy • Provide all pregnant women education and counseling about HIV prevention • Evaluate and counsel all women for high-risk sexual behaviors at periodic examinations 	14–17
American Academy of Family Physicians	<ul style="list-style-type: none"> • Counsel adolescents and adults regarding STI risks and how to prevent them 	18
United States Preventive Services Task Force	<ul style="list-style-type: none"> • Advise all adolescent and adult patients about risk factors for HIV and other STIs, and counsel about effective measures to reduce the risk of infection. • Offer individuals at risk for specific STIs screening for syphilis, NG, HBV, HIV, and CT • Advise injection drug users about measures to reduce their risk and refer them to appropriate treatment facilities. • Assess risk factors for HIV by obtaining a careful sexual history and inquiring about injection drug use in all patients 	19, 20
Centers for Disease Control and Prevention	<ul style="list-style-type: none"> • Educate sexually active patients regarding HIV and other STIs • Assess the patients' risk factors for infection • Offer at-risk patients advice about behavior changes to reduce the risk of infection • Offer HIV counseling with testing in areas where HIV prevalence $\geq 1\%$ • Provide all pregnant women with information about HIV and HIV testing • Routinely obtain a history that inquires about use of illegal drugs • Provide counseling and education to prevent initiation of drug-injecting practices • Provide prevention messages for persons with high-risk drug practices and for those at risk of percutaneous exposures to blood in health-care and other settings (e.g., tattooing and body piercing) 	21–24
American Medical Association	<ul style="list-style-type: none"> • Provide all adolescents health guidance regarding responsible sexual behaviors • Ask all adolescents about involvement in sexual behaviors that may result in pregnancy, STIs, and HIV • Always include a sexual history as part of their routine history and physical examination • Counsel for CT prevention • Educate patients about STIs, including HIV, and condom use 	25–28

STI: sexually transmitted infections; HIV: human immunodeficiency virus; NG: *Neisseria gonorrhoeae*; HBV: hepatitis B virus; CT: *Chlamydia trachomatis*.

overlooked due to competing priorities for other preventive services. In a nationally representative survey of noninstitutionalized individuals aged 18–64 years, among persons who reported having a routine check up in the past year, only 28% reported being asked about STIs compared to 59% being asked about smoking and 49% being asked about alcohol

use.³⁶ A nationally representative telephone survey found that 31% of women of reproductive age (18–44) have talked to their doctor about their sexual history and specific issues, such as STIs (28%) and HIV/AIDS (31%) in the past 3 years.³⁷

Nationally representative surveys of high school students have found that only 43% of female and 27% of male

Table 88-2. Questions About Sexual Activity and Parenteral Exposure Risks for STIs, HIV and Hepatitis Recommended to be Addressed During a Routine Primary Care Visit^{13,15,17,25,29}

Sexual activity:

Type of sex (oral, vaginal, and anal), age at coitarche, gender(s) of partner(s), number of current partners and number of partners in the past 6 months and in lifetime, substance use with sex

Presence of symptoms suggestive of an STI, acute HIV infection or hepatitis:

Vaginal or urethral discharge, dysuria, abdominal or scrotal pain, throat pain, oral lesions, flu-like symptoms, or jaundice

Concerns about STIs, HIV, or viral hepatitis infection

Prior STI, viral hepatitis, or HIV tests, result, or treatment

Contraception practices:

Barrier contraceptive use: condom use, frequency, and method; diaphragm, cervical cap

Hormonal contraceptive use or spermicide use

Parenteral exposure risks:

Receipt of blood products and hemodialysis

Injecting-drug use, including reusing or "sharing" syringes, needles, water, or drug preparation equipment, cleaning drug preparation equipment with bleach and water, and using sterile syringe, needles, and water from a reliable source (e.g., pharmacies)

Accidental needle stick exposure

Tattooing and body piercing history in a noncommercial site (e.g., jail or gang tattoo)

Prior vaccinations:

Hepatitis A

Hepatitis B

Other STI vaccines

STI: sexually transmitted infection; HIV: human immunodeficiency virus.

students who received a health-care visit in the past year reported having discussed STI, HIV, or pregnancy prevention at those visits³¹ and that only 31% who reported having sex without contraception discussed this behavior with their primary care provider.³⁸ In Washington State Medicaid health plans during 1998, only 15% of male and 45% of female enrollees aged 14–18 years who had received primary care services had Medicaid record evidence of a sexual history being taken.³⁹ Surveys of Colorado and California primary care providers revealed that about three-fourths reported taking sexual histories from their adolescent patients.^{40,41}

Although it is difficult to assess the proportion of at-risk patients assessed for HIV risks in primary care settings, data indicate that HIV-risks of infected persons who accessed primary care services were present but were missed until HIV infection, including AIDS, was identified. In a large commercial health plan where access to care was reasonably good, review of medical records up to 5 years before HIV diagnosis found that only a minority of patients ultimately identified as belonging to a classic HIV-risk group had such risk documented ≥ 1 year before HIV diagnosis.⁴²

In some cases, providers may initiate an STI or HIV risk assessment, but the quality of the dialogue may be insufficient to assess risk and to inform appropriate clinical actions. An analysis of videotaped patient–physician discussions about HIV risk found that in 73% of the encounters, physicians did not elicit enough information to characterize patients' HIV risk status.⁴³ In a survey of primary care physicians in Connecticut, 62% of respondents reported routinely asking all patients about a history of injection drug use, 5% did not routinely elicit injection drug use histories, and 33% reported asking about injection drug use from patients where other risk factors, such as a history of STIs, incarceration, or body tattooing, were already identified.⁴⁴

Provider-, health system-, and patient-level factors may discourage routine STI, HIV, and hepatitis behavioral risk assessment and screening in private sector settings.^{9,45} Many adolescents lack continuous health insurance, precluding care for anything but urgent problems.³⁴ The need to address competing clinical priorities during brief well-care or preventive visits is a major challenge.^{46,47} Provider-level barriers include clinician misperception that prevalence of risk behaviors in more affluent, commercially insured persons is low, or is correlated with insurance status or race, and the belief that routine sexual and drug-related risk assessment is not cost-effective.^{8,46,48} Lack of provider comfort with discussing sexual activity may also preclude sexual risk assessment. For example, surveys of adolescent and family medicine providers have shown that sexual activity is less frequently assessed than drug use.^{40,49} Family physicians cited concerns about their own and their patients' discomfort discussing sexual matters but not drug use.⁴⁹

Several interventions have attempted to promote risk assessment in primary care. They include developing policies to promote routine access to confidential care for patients, such as training providers in asking sensitive questions,⁵⁰ routinely excusing parents from adolescent encounters to allow for risk assessment;⁵¹ adopting short, standard self-administered or provider-administered risk assessment tools^{52–54} or using patient-administered, computer-based assessment tools to collect a sexual history and then providing computer-based written counseling messages tailored to that patient's risks.⁵⁵ Other methods include clinician training on risk assessment methods, using nonphysician staff to collect risk information,

such as by a confidential patient questionnaire,^{51,53,54} making risk assessment a covered service,⁵⁶ and increasing reimbursement.⁵⁷ Few of these primary care risk assessment interventions have been evaluated for their impact on risk assessment practices on a short- or long-term basis. The optimal intervention for a particular setting may vary.

PHYSICAL EXAMINATION

An anogenital examination should be performed as part of a comprehensive physical examination during a health maintenance visit or as part of a focused visit for sexual health related concerns. The genital examination should include inspection of the pubic hair for evidence of lice and vaginal or urethral discharge, and the perineum and anus for lesions such as ulcers or warts. In female patients, if vaginal, urethral, or rectal discharge is noted, a full pelvic examination, including an abdominal examination, should be performed to assess for vaginitis, cervicitis, pelvic inflammatory disease, and proctitis. For male patients, in whom urethral discharge or rectal discharge is noted, a full genital examination should be performed to assess for urethritis, epididymitis, and proctitis. For both male and female patients, physical examination of other organ systems should be included to assess for signs of STIs, HIV, and hepatitis. The oropharynx should be examined for evidence of pharyngeal *N. gonorrhoeae*, oral chancres, or herpetic lesions, especially for men who have sex with men (MSM), adolescents, or other patients who commonly engage in oral sex. Finally, the skin should be examined for dermatologic evidence of STI or hepatitis infections, such as syphilitic rash, scabies, and jaundice.²⁹

Anecdotes suggest that many providers may not provide oropharyngeal or anal examinations, thereby missing opportunities for diagnosis of infections acquired through oral or anal sexual contact. Anecdotes also suggest that common barriers to conducting a thorough examination include lack of time, lack of awareness of oral or anal sexual contact, and lack of familiarity with oral and dermatologic manifestations of STI. The mainstay interventions for promoting comprehensive physical examinations skills have been training programs in professional schools, continuing medical education, on-the-job training venues, and clinical alerts (e.g., about oral manifestations of syphilis among MSM) sent to clinicians by health departments.^{58,59} However, few of these interventions have been evaluated for their effectiveness in improving actual examination skills.^{58,59}

STI, HIV, AND HEPATITIS SCREENING OF ASYMPTOMATIC PATIENTS

STI screening of asymptomatic patients is a basic, effective tool used to identify an unrecognized condition so that treatment can be offered before symptoms or serious sequelae of

asymptomatic infection develop.¹⁹ Primary care providers play a key role in STI screening because preventive care and health maintenance are central responsibilities.

Screening and diagnostic testing can be accomplished from invasive tests, such as endocervical and urethral specimen tests for *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, blood tests for syphilis, HIV, and viral hepatitis, as well as less invasive tests, such as urine-based or vaginal swab-based *C. trachomatis* and *N. gonorrhoeae* nucleic acid amplification tests (NAAT), oral conventional HIV tests, and rapid HIV tests performed on finger-stick and oral specimens.^{60–61} Office-based, rapid screening tests for syphilis and HIV are also available but require confirmation with laboratory-based tests. Home collected tests for HIV are also available.⁶² The recent introduction of *C. trachomatis* and *N. gonorrhoeae* combination (NAAT) and DNA probes tests may be cost effective for diagnostic testing of symptomatic persons or screening populations with a high prevalence of both infections. However, when combination *N. gonorrhoeae* and *C. trachomatis* tests are used to screen for *C. trachomatis* in privately insured populations with very low *N. gonorrhoeae* prevalence, they may yield few positive *N. gonorrhoeae* cases, low *N. gonorrhoeae* test predictive value, and poor cost-effectiveness.⁶¹

Several national organizations recommend screening asymptomatic patients for STIs in specific population groups (Table 88-3).^{11,13–18,21,22,25,28,29,61,63–71} Various published STI, viral hepatitis, and HIV screening guidelines are somewhat inconsistent, a fact related to different guideline audiences and different interpretation of the clinical value and cost effectiveness of screening patients of differing age, risk behaviors, geographic location, and health-care settings. Some guidelines recommend general “STI” screening that may lead to over-screening for some pathogens, e.g., *N. gonorrhoeae* screening in commercially insured, married women with very low *N. gonorrhoeae* prevalence, and underscreening for other populations with varying prevalence rates, e.g., lack of *C. trachomatis* screening if the prevalence is misperceived to be low.^{66,72–74}

Guidelines recommend primary care providers screen for selected bacterial STIs in their patients who are adolescents or young adults (i.e., <25 years old),^{13,29,63–64} are pregnant^{14–18} (i.e., as part of prenatal care), or who engage in behaviors which may place them at risk for STI (i.e., injection drug user, prior STIs, >1 sex partner in past 6 months, exchange sex for drugs or money, MSM, or has at-risk sex partner).^{25,28,66–71} Several guidelines recommend routine prenatal screening for several pathogens and routine screening of sexually active adolescent and young adult female patients (Table 88-3). Routine screening of asymptomatic patients who lack specific risk factors for other bacterial and viral STIs and hepatitis B virus infection is not recommended due to low yield or low cost-effectiveness.^{29,67} However, screening is recommended

Table 88-3. National Recommendations for Periodic STI Screening by Organizations

Organization	CT	NG	Syphilis	HIV	HBV	Nonspecific STIs	Reference
American Academy of Pediatrics	<ol style="list-style-type: none"> 1) Test all sexually active adolescents during gynecologic examination 2) Screen 20–24 year old women if have multiple partners or do not use barrier contraception 	Screen all pregnant women at first prenatal visit and additional screening in 3rd trimester for high-risk women	Screen all women early in pregnancy and at 3rd trimester and additional screening at 28 weeks of gestation for high-risk women	Test all those requesting and encourage testing for all those with prior STI, >1 sex partner in past 6 months, IDU, sexual intercourse with partner at-risk, sex for drugs or money, homeless, MSM.	Screen all women early in pregnancy and additional screening later in pregnancy for high risk women	<ol style="list-style-type: none"> 1) Perform dipstick urine for leukocytes annually for all sexually active adolescents 2) Screen all sexually active adolescents (11–21 years) for STIs annually 	11, 13, 63–64
American College of Obstetricians and Gynecologists	<ol style="list-style-type: none"> 1) Screen all sexually active adolescent female patients annually 2) Screen all pregnant women if at-risk 	<ol style="list-style-type: none"> 1) Screen all sexually active adolescent female patients annually 2) Screen all pregnant women if at-risk 	<ol style="list-style-type: none"> 1) Screen all sexually active adolescent female patients for prenatal care, if prior STIs, multiple sex partners, exchange sex for drugs or money, illicit drug use, admitted to detention facility, or lived in endemic area 2) Screen all pregnant women 	<ol style="list-style-type: none"> 1) Screen all pregnant women 2) Periodic screening for women ≥ 19 years at risk (e.g., multiple or high-risk sex partner(s), prior STIs, attendance at STI clinic) 3) Screen all female patients if pregnant, prior STIs, multiple or high-risk sex partners, exchange sex for drugs or money, IDU, admitted to detention facility, long-term residence or birth in endemic area, blood transfusion before 1985 	Screen all pregnant women	Periodic STI screening for women ≥ 19 years at risk (e.g., multiple or high-risk sex partner(s), prior STIs, attendance at STI clinic)	14–17, 65

(Continued)

Table 88-3. (Continued)

Organization	CT	NG	Syphilis	HIV	HBV	Nonspecific STIs	Reference
American Academy of Family Physicians	<p>1) Screen all sexually active and all asymptomatic pregnant female patients age ≤ 25 years</p> <p>2) Screen female patients age >25 years and all asymptomatic pregnant female patients who are at risk (unmarried, African American race, prior STI, new or multiple sexual partners, cervical ectopy, or use barrier contraceptives inconsistently)</p>	Screen all female patients at high-risk and pregnant women at high-risk (new or multiple sexual partners in the past 12 months; other STIs, including HIV; and sexual contacts of persons with NG or CT)	Screen in pregnant women, persons who exchange sex for money or drugs, persons with other STIs, sexual contacts of persons with syphilis	<p>1) Screen pregnant women, MSM, IDU, persons who exchange sex for money or drugs and their sex partners, sex partners who were IDUs, bisexual or HIV positive, persons seeking STI treatment, persons who received a blood transfusion between 1978 and 1985, persons who request HIV test despite reporting no individual risk factors, and persons seen in high-risk or high-prevalence settings.</p> <p>2) screen infants born to high risk mothers whose HIV status is unk-nown (IDU, exchange of sex for money or drugs, seeking treatment for STIs or whose sex partner is HIV+, IDU, bisexual, or exchanged sex for money or drugs)</p>	Screen in pregnant women at their first prenatal visit		18

Table 88-3. (Continued)

Organization	CT	NG	Syphilis	HIV	HBV	Nonspecific STIs	Reference
United States Preventive Services Task Force	Screen all women aged ≤ 24 years who are sexually active or pregnant and other asymptomatic pregnant or nonpregnant women at increased risk for infection (prior CT infection or other STI, new or multiple sexual partners, inconsistent condom use, and exchanging sex for money or drugs)	<ol style="list-style-type: none"> 1) Screen women age < 25 years sexually active or pregnant and at increased risk for infection (prior NG infection or other STIs, new or multiple sexual partners, inconsistent condom use, sex work, and drug use) 2) Screen at the first prenatal visit for pregnant women who are in a high-risk group for NG infection. 	Screen all pregnant women and all persons at increased risk (MSM and engage in high-risk sexual behavior, commercial sex workers, exchange sex for drugs, and those in adult correctional facilities)	<ol style="list-style-type: none"> 1) Screen all adolescent and adult MSM after 1975; men and women having unprotected sex with multiple partners; past or present IDU; men and women who exchange sex for money or drugs or have sex partners who do; individuals whose past or present sex partners were HIV-infected, bisexual, or IDUs; persons being treated for STIs; persons with history of blood transfusion between 1978 and 1985; and persons who request an HIV test. 2) Screen all persons who are seen in high-risk or high-prevalence clinical settings, such as STI clinics, correctional facilities, homeless shelters, tuberculosis clinics, clinics serving MSM, and adolescent health clinics with a high prevalence of 	Screen in pregnant women at first prenatal visit		66–71

(Continued)

Table 88-3. (Continued)

Organization	CT	NG	Syphilis	HIV	HBV	Nonspecific STIs	Reference
Centers for Disease Control and Prevention	<ol style="list-style-type: none"> 1) Screen all sexually active women aged ≤ 25 years, whether or not they are pregnant. 2) Consider screening women >25 years if are at increased risk (i.e., having new [past 90 days] or multiple sex partners, a prior STD, or inconsistent and correct condom use) 3) Screen (urethral, rectal sites) sexually active MSM. 	<ol style="list-style-type: none"> 1) Screen pregnant or nonpregnant sexually active women at increased risk (age <25 years, prior NG infection or other STIs, new or multiple sex partners, inconsistent or use, commercial sex work, and drug use) 2) Screen (urethral, oral, rectal sites), sexually active MSM 	1) Screen all women during pregnancy	<p>STIs, and settings where HIV prevalence $\geq 1\%$ among the patient population being served</p> <ol style="list-style-type: none"> 3) Screen sexually active MSM <ol style="list-style-type: none"> 1) Universally screen all patients aged 13–64 years, at least once. 2) Include HIV as a routine prenatal screening test for all pregnant women as opt-out screening. 3) Simplify the screening process Test high-risk patients at least annually 	Screen all women during pregnancy		21, 22, 29, 61
American Medical Association	Screen, treat, and report for genital CT infections			Offer testing to at-risk adolescents (IDU, other STIs, live in high prevalence area, >1 sex partner in past 6 months, exchange sex for drugs or money, MSM, or at-risk sex partner)		Screen sexually active adolescents for STIs	25, 28

STI: sexually transmitted infection; HIV: human immunodeficiency virus; IDU: injection drug use; MSM: men who have sex with men; NG: *Neisseria gonorrhoeae*; CT: *Chlamydia trachomatis*.

for patients at high risk for hepatitis A or B virus in the context of offering hepatitis vaccine to persons with high likelihood of past infections, such as persons born in areas with high disease endemicity, MSM with large numbers of sex partners, injection drug users, and sexual contacts of persons with chronic viral hepatitis infection (Table 88-3). Hepatitis A and B serologic screening may be a cost effective option to identify noninfected patients who could benefit from hepatitis A and B vaccination.²⁹ All pregnant women, regardless of risk factors, should be tested for hepatitis B viral infection.^{16,29,67} In 2006, the CDC published revised HIV screening guidelines that recommend voluntary HIV screening for all patients aged 13–64 years, at least once, in all health-care settings and include HIV screening in the routine panel of prenatal screening tests for all pregnant women after the patient is notified that testing will be performed unless the patient declines (opt-out screening).²¹ CDC also recommends simplifying the screening process by not requiring a separate written consent or prevention counseling for HIV testing to occur.²¹ For high-risk patients, i.e., injection-drug users and their sex partners, persons who exchange sex for money or drugs, sex partners of HIV-infected persons, and MSM or heterosexual persons who themselves or whose sex partners have had more than one sex partner since their most recent HIV test, providers should test at least annually. The U.S. Preventive Services Task Force (USPSTF) HIV testing recommendations vary. USPSTF recommends that clinicians incorporate voluntary HIV screening into routine medical care for pregnant women and for individuals who engage in behaviors that may place them at risk for HIV infection, patients who request an HIV test despite reporting no individual risk factors, clinical settings serving populations at increased behavioral or clinical HIV risk (e.g., drug treatment facilities and STI clinics), and in high-prevalence settings.^{68,69} Proponents of HIV screening in primary care settings with lower HIV prevalence rates argue that the cost-effectiveness of screening is similar to that of commonly accepted interventions, and HIV infection treatment is readily available and less complex if first offered early after infection.^{75–77}

Because of a lack of nationally representative surveys or medical record reviews about screening practices, various sentinel studies best estimate screening practices. Such studies show that the extent of prenatal STI screening varies by STI and clinician specialty. In a national survey of 130 obstetrics and gynecology office-based practices, all practices reported hepatitis B prenatal screening with 95% of women tested.⁷⁸ In a 1998 national survey of primary care physicians practicing internal medicine, family practice, emergency medicine, and pediatrics reported routine screening rates of their pregnant patients between 30% and 32% for syphilis, *N. gonorrhoeae*, *C. trachomatis* and HIV.⁷⁹ However, the surveyed obstetricians and gynecologists reported much higher STI screening rates of their pregnant patients; 85% for

syphilis, 79% for *N. gonorrhoeae*, 78% for *C. trachomatis*, and 81% for HIV.⁷⁹ In a national sample of commercial health plan claims data during 1998–1999, 63% of pregnant women had claims for syphilis tests, but only 33% for HIV screening.⁸⁰ A 1998–1999 study of HIV prenatal testing in eight U.S. states found that testing rates ranged from 25% to 85%. Rates were higher in states with mandatory newborn HIV testing and in states where HIV testing was included in a standard panel of prenatal tests.⁷²

In contrast, in most primary care settings, *C. trachomatis* screening rates of sexually active female patients outside of prenatal care are low to moderate. Annual *C. trachomatis* screening of sexually active adolescent female patients was reported by over 50% of Medicaid-participating physicians (53%) and midlevel providers (54%) in seven cities,⁸¹ by 32% of primary care physicians surveyed in Pennsylvania,⁴⁸ and 54% of primary care providers surveyed in Colorado.⁴¹ In the 1998 national primary care provider survey, only a third of physicians reported routinely screening women for chlamydial infection, although obstetrician/gynecologists reported higher screening rates.⁷⁹ Since annual *C. trachomatis* screening of sexually active female health plan enrollees 15–26 years old was introduced as a health plan performance measure, average screening rates have increased slightly in commercial health plans (from 20% in 1999 to 26% in 2001) and Medicaid health plans (from 28% in 1999 to 38% in 2001).⁷⁴ Medicaid managed care plans have consistently had higher *C. trachomatis* screening rates than commercial health plans.⁸² Most studies in primary care settings demonstrate fairly high yield when screening adolescent female patients—from 3% to 9%.^{51,83–85}

Because routine, annual, *N. gonorrhoeae*, syphilis, and HIV screening are currently recommended only for selected groups, population-based screening rates are low. A national survey of internal medicine, family practice, emergency medicine, and pediatric physicians demonstrated that few primary care physicians routinely screened male (19%) and nonpregnant female (20%) patients for syphilis or for *N. gonorrhoeae*; (13% screened male and 30% screened nonpregnant female patients).⁷⁹ Although the population of persons at-risk for HIV infection is unknown, nationally representative surveys reveal that approximately 10–12% of Americans aged 18–64 years who reported being tested for HIV in the past 12 months⁸⁶ were tested outside their primary care settings, possibly to protect confidentiality. Many HIV-infected individuals are not being detected early in infection through screening in primary care and other health-care settings.^{42,73}

Provider knowledge, attitudes and practices can present barriers to widespread STI, HIV, and hepatitis screening in primary care. Misperception that STI prevalence in private sector primary care patient settings is low and the belief that routine *C. trachomatis* or HIV screening is not cost-effective have been substantial barriers to screening in the private

sector.^{8,46,48} Perception of STI as a low overall health priority may explain why *C. trachomatis* screening rates are lower for internists, pediatricians, and family physicians than for obstetrician/gynecologists.⁴⁷ Lack of awareness and confusion about new laboratory tests using noninvasive urine specimens, approved specimen types, and test performance can lead to low screening rates. For example, 80% of primary care physicians surveyed in Albany, NY were not aware of urine *C. trachomatis* NAAT availability and only 2% had ordered them in their practice.⁸⁷ Finally, many providers are unaware that in all 50 states minors may consent for their

own sexual health services and disclosure of provision of these services and screening test results to parents is not mandatory.^{88–90} Policy-level factors that discourage screening include lack of reimbursement, screening policies and routine protocols, decision support tools, noninvasive urine screening tests, performance feedback, and reminder systems. (Table 88-4).^{91,92} Also, providers may not be aware of the full range of general billing codes that can be used to document STI or HIV services without risking confidentiality violations if someone other than the patient sees an itemized medical bill or “explanation of benefits” (Table 88-4).^{46–48,74}

Table 88-4. Commonly Cited Barriers to High Quality STI Care in Private Sector Settings^{91,92}

Level	Barrier
Patient	<ul style="list-style-type: none"> • Concerns about confidentiality of medical information, medical records, or billing information that would reveal sexual activity • Discomfort with discussing sexual issues with health-care providers • Stigma of STI • Limited understanding of high prevalence and asymptomatic nature of many STI and serious and long-term consequences of untreated STI
Provider	<ul style="list-style-type: none"> • Brief patient encounters and competing clinical priorities discourage sensitive, labor intensive tasks such as sexual risk assessment, patient counseling and education, and sex partner management • Discomfort discussing sexual issues with patients and doing pelvic examinations (especially on adolescent patients) • Lack of training in sexual risk assessment and sexual risk reduction counseling and educating, and sex partner management • Difficulty keeping up with revised recommendations on STI screening and treatment • Insufficient and/or nonconfidential reimbursement methods for routine risk assessment, screening, risk reduction counseling, patient education, sex partner management, and case reporting • Lack of awareness of noninvasive STI screening tests
Health system	<ul style="list-style-type: none"> • Lack of explicit policies/protocols for STI care • Lack of decision-support tools • Lack of provider feedback and reminder systems • Cost-containment pressures that discourage STI prevention services, routine risk assessment, screening, counseling, education, and sex partner management • Limited support staff to assist with risk assessment, counseling, education, sex partner services, and case reporting • Medico-Legal/Liability concerns about potential confidentiality breaches or legal requirements to report evidence of sexual activity of minors (e.g., reporting statutory rape, sexual abuse) • Nonavailability or lack of reimbursement for noninvasive STI screening tests (e.g., urine) • Lack of centralized systems, dedicated staff, or electronic data systems that facilitate case reporting • Limited organizational commitment and “internal champions” due to stigma and perception that STI are low volume, low cost conditions • Limited demand by health-care purchasers and MCO enrollees for STI quality improvement

STI: sexually transmitted infections; MCO: managed care organization. (Reprinted from *Infectious Disease Clinics of North America*, 2005;9(2):491–511, with permission from Elsevier.)

Cost-containment pressures in health plans favor diagnostic testing of a few symptomatic patients over routine screening of large numbers of asymptomatic patients. For example, *C. trachomatis* screening is cost-effective from a societal perspective and is ranked among the top preventive services in terms of disease averted and cost-effectiveness.⁹³ However, rapid health plan enrollee turnover makes it difficult for health plans to reap benefits of prevention in the short term since many sequelae of undetected, untreated infection occur years later.⁸¹ For patients, especially adolescents, the stigma of STI and concerns about maintaining the confidentiality of sexual activity or infection status information discourages demand for and acceptance of screening.^{32,94,95} For example, in a survey of adolescent patients in two North Carolina general pediatric practices, 92% would agree to urine-based STI testing if confidentiality could be assured, but only 35% would agree to such testing if parents would find out.⁹⁵

Several interventions have been introduced to promote STI, HIV, and hepatitis screening. State laws have played a key role in improving prenatal screening rates. Syphilis testing in standard prenatal testing panels, longstanding national screening guidelines, and state regulations mandating syphilis screening have supported high screening rates for decades.⁸⁰ A study assessing state laws and regulations regarding United States prenatal syphilis serologic screening in 2001 found that 46 (90%) states and the District of Columbia had laws regarding antenatal syphilis screening and that states with a heavy burden of infectious syphilis in women were likely to require more frequent prenatal syphilis testing.⁹⁶ An eight-state HIV prenatal testing surveillance study found that states shifting from an opt-in approach (women typically are provided pre-HIV test counseling and must consent specifically to an HIV-antibody test) to either an opt-out approach (women are notified that an HIV test will be included in a standard panel of prenatal tests and that they may refuse testing) or mandatory newborn testing approach if the mother's HIV status is unknown at delivery (newborns are tested for HIV, with or without the mother's consent), increased their prenatal HIV-testing rates.⁷²

Several interventions have been introduced to promote routine *C. trachomatis* screening of sexually active adolescent and young adult female patients. Simple interventions include development, dissemination, and “championing” of print- and web-based practice or health plan-specific screening guidelines and protocols,^{51,85} and introducing noninvasive urine tests.^{51,97,98} Other methods include using nonspecific primary care billing codes for screening services to protect confidentiality,⁹⁹ routinely collecting *C. trachomatis* screening tests with every pelvic examination,^{4,85} and Web-based clinician instruction using clinical cases relevant to commercial health plans.¹⁰⁰ Laboratories can cut costs by pooling specimens from numerous patients and retesting individual specimens from positive pools.⁶¹ A multifaceted

intervention involving the use of multimedia educational materials and an intensive office-based “academic detailing” approach increased *C. trachomatis* screening rates by 17% for Medicaid and 30% for commercial enrollees.⁸⁷ More complex interventions have also increased *C. trachomatis* screening in young female health plan enrollees. Examples include inviting health plan enrollees classified as high risk through administrative data for *C. trachomatis* screening with personalized letters¹⁰¹ and a system-level practice improvement approach that provided screening performance feedback to providers, introduced routine urine-based *C. trachomatis* testing, and implemented parent “rooming in” policies that gave adolescent patients time alone with their providers.^{51,102} In contrast, no appreciable increase in *C. trachomatis* screening was observed in three different health plans that sent young adult enrollees health newsletters that included information about, and how to get access to screening.¹⁰³

Several interventions to increase HIV counseling and testing have increased screening rates in primary care settings (see Chapter 69). For example, several community-based health centers in areas with high HIV prevalence rates have implemented simplified HIV counseling and testing that takes 5–10 minutes to complete.¹⁰⁴

STI, HIV, HEPATITIS DIAGNOSTIC TESTING OF PATIENTS WITH SYMPTOMS OR SIGNS

CDC recommends *C. trachomatis* and *N. gonorrhoeae* diagnostic testing of patients who present with clinical urethritis and cervicitis (see also Chapters 55 and 59); herpes simplex virus and syphilis diagnostic testing of patients who present with genital ulcers (see Chapter 63); and hepatitis serology testing of patients with signs of clinical hepatitis, such as jaundice or signs of chronic disease, such as cirrhosis or liver cancer (see Chapter 29). CDC also recommends HIV counseling and diagnostic testing for persons with evidence of acute retroviral syndrome, opportunistic infections, and other infectious diseases with high HIV coinfection rates (i.e., syphilis and tuberculosis), and laboratory abnormalities consistent with HIV (see Chapter 69).^{21,29,105} Several organizations recommend DNA testing for high-risk types of human papillomavirus (HPV) as one option to manage women with Papanicolaou tests categorized as atypical squamous cells of undetermined significance (ASC-US).^{29,65,106–109} Under this option, female patients with positive HPV tests are advised to undergo prompt colposcopy to obtain a biopsy, whereas female patients with negative HPV tests should be followed with subsequent Pap tests. The HPV DNA test is not FDA-approved as a “stand alone” STI screening test for female patients with genital warts or for any reason in male patients (see Chapter 28).

Despite guidelines recommending STI diagnostic testing, many persons with an STI are presumptively diagnosed

without laboratory tests, especially in episodic care settings like emergency departments and urgent care centers. Analysis of National Hospital Ambulatory Medical Care Survey data examining visits by nonpregnant 15–44 year old women seen in primary care clinics between 1997 and 2000 found that STI testing occurred in only 13% of visits by women with genitourinary symptoms.¹¹⁰ For male patients with signs and symptoms of NGU, specific diagnostic criteria and treatment guidelines exist and so providers may not feel the need to perform further diagnostic testing, especially when invasive urethral specimens are the only testing option.¹¹¹

Additional challenges in STI diagnostic testing in primary care settings include managing patients who may have false positive test results. This is especially a concern when screening in low prevalence populations, e.g., positive *N. gonorrhoeae* test was performed in a patient with a suspected chlamydial infection because a combination *C. trachomatis/N. gonorrhoeae* laboratory test was used (see Chapter 55). Other challenges include interpretation of syphilis antibody titers as a recent versus latent infection because many providers may not have access to a full record of previous syphilis antibody titers, including titers obtained after treatment (see Chapter 37). There is also confusion regarding hepatitis serology results interpretation and distinguishing old versus new infections (see Chapter 29) and counseling and confirmatory testing for reactive rapid HIV tests and for indeterminate HIV western blots (see Chapter 70).

TREATMENT PRACTICES

Treatment of STIs, HIV, and viral hepatitis is critical to reduce patient symptoms, prevent serious sequelae of untreated infection, and prevent risk of transmission to sex partners and the fetus. Many treatment guidelines for STI, HIV, and viral hepatitis are issued by federal agencies, such as CDC, the Health Resources and Services Administration (HRSA) HIV/AIDS Bureau, and the National Institute of Health (NIH), professional medical organizations, such as the American Academy of Pediatrics, and various health plans.^{29,63,112,113} Treatment recommendations are also found in clinical texts, such as the Physicians' Desk Reference, the Sanford Guide, and the Johns Hopkins Hospital Guide to Medical Care of Patients with HIV Infection.^{114–116} While some treatment is straightforward, other treatment is complex. Providers may refer patients with positive screening syphilis tests to the health department for final diagnosis and management because of unique access to past serologic test and treatment information needed to interpret screening test results. Given the evolving drug resistance, *N. gonorrhoeae* treatment has become challenging.^{117,118} Given the evolving drug resistance, *N. gonorrhoeae* treatment has become challenging.^{117,118} CDC's Gonococcal Isolate Surveillance Project data demonstrate that fluoroquinolone-resistant gonorrhea

is now widespread in the United States.¹¹⁹ Therefore, fluoroquinolones are no longer recommended for the treatment of gonorrhea in the United States.¹¹⁹ Some providers treat genital warts in their practice setting; others may refer to surgical subspecialists for more invasive treatments. Because viral hepatitis treatment can be complex, primary care providers may refer hepatitis-infected patients to hepatologists. For HIV-infected patients, some primary care providers manage all care, some manage only primary care issues, some refer HIV-related care to infectious diseases or HIV care specialists, and some refer all care for HIV-infected patients.²⁹

Generally, chart review and provider reports demonstrate that uncomplicated lower genital tract chlamydial infection and gonorrhea are appropriately treated in the majority of cases. Among 1078 patients with positive tests for genital chlamydial infection in two large health plans, more than 97% of men and nonpregnant women and more than 98% of pregnant women were prescribed treatment consistent with current CDC guidelines.^{29,120} Among the primary care clinicians surveyed at these health plans, 89% reported they would use CDC-recommended treatments for laboratory-confirmed chlamydial infection in pregnant women and 62% reported they would use CDC-recommended single dose azithromycin to treat chlamydial infection diagnosed in injection drug users in whom compliance to longer regimens might be questioned.¹²¹ In a publicly funded Minnesota health plan, CDC-recommended treatment was documented for 91% of enrollees diagnosed with *C. trachomatis* and 75% diagnosed with *N. gonorrhoeae*.⁹⁹ In the seven-city Medicaid health plan study, 78% of primary care clinicians reported using single-dose azithromycin for *C. trachomatis* treatment.⁸¹ In a Massachusetts health plan, all men with symptomatic urethritis who had a positive *N. gonorrhoeae* test result, and 88% of those with a positive *C. trachomatis* test were prescribed CDC-recommended treatment at their initial visit.¹²² The rest were treated within 5 days. Treatment practices for other STIs associated with more complicated, clinically based diagnosis, polymicrobial etiology, or drug-resistant pathogens tend to be more varied than laboratory-confirmed STI associated with a single pathogen. Regarding treatment of PID, a condition that is usually diagnosed presumptively and is often polymicrobial in etiology, 52% of California physicians (78% of whom practiced in private sector settings) reported that they did not use CDC treatment guidelines.¹²³

Barriers to appropriate STI treatment include cost, compliance, drug intolerance, and other side effects. Medication costs, even generic drugs that are typically less expensive than brand names, may present a barrier to treatment for uninsured patients and those who want to pay out-of-pocket to maximize confidentiality. In some cases, single dose medications that promote adherence are more costly than multidose regimens, e.g., single dose azithromycin versus a 7-day course of doxycycline to treat uncomplicated genital chlamydial

infections. Treatment for viral STIs, such as genital herpes (e.g., chronic suppressive treatment), or genital warts (e.g., patient-applied therapy), may be difficult for patients to follow long-term. When disease recurs despite treatment, providers may encourage future adherence by educating patients about the chronic, relapsing nature of these viral diseases. Providers should be aware that medications, especially for viral STIs such as HIV may cause side effects or drug intolerance such that patients must discontinue the treatment.^{124,125}

As with any treatment challenge, providers develop creative strategies to maximize treatment success. Strategies to minimize out-of-pocket treatment expenses could include disregarding copayment fees, prescribing generic formulations, and dispensing pharmaceutical samples. Prescribing a simplified, convenient, drug regimen can maximize compliance, such as prescribing FDA-approved single dose treatment for bacterial STIs. To increase compliance, CDC recommends dispensing medication in the office, optimally at the visit where STI is diagnosed, and directly observing the patient taking the first dose.²⁹ Advising patients of possible medication side effects in advance can decrease the likelihood of unexpected unpleasant side effects and may improve compliance.

RISK-REDUCTION COUNSELING AND PATIENT EDUCATION

The phrase “risk reduction counseling” implies interactive discussion about risk reduction measures, tailored to an individual patient’s risks, a strategy recommended by CDC guidelines.²⁹ The term education implies sharing information about reducing risk of STI acquisition or transmission through clinicians or health educators, verbal instructions, print, audio and web-based materials, or referral to telephone hotlines and support groups. Risk reduction counseling to prevent chronic viral STI, HIV, and hepatitis transmission is more complex than STI counseling because of the risk of life-long sexual transmission, and, for HIV and hepatitis, parenteral transmission (Chapters 29 and 72). Tailored counseling has been shown to be an effective strategy in changing behaviors, such as increasing condom use and in reducing incidence of bacterial STI in STI clinic patients in one study.¹²⁶ This and other studies have shown that such counseling may also reduce HSV acquisition.^{127,128}

These studies and expert opinion have provided support to long-standing guidelines that patients at risk for or infected with STI, HIV, or hepatitis should be offered counseling and/or education to reduce risky sexual behaviors to prevent reinfection and transmission to current and future sex partners.^{29,129} Patients diagnosed with bacterial or viral STI, HIV, and hepatitis should be advised that abstinence, condom use, and minimizing the number of sex partners can reduce the risk of acquiring future infections or transmitting their current infection to sex partners. Some providers

directly dispense condoms at low or no cost. For patients diagnosed with acute bacterial STI, important counseling messages include the need to adhere to the prescribed treatment, especially completing the full course of antibiotics, and abstaining from sex until treatment is complete. Patients should be notified to contact recent sex partners and encourage them to seek evaluation, and patients diagnosed with an STI that is reported to the health department should be notified that health department staff may contact them to offer assistance with notifying partners.

Patients diagnosed with chronic or recurrent viral STI such as HSV, genital warts, or hepatitis B require special counseling tailored to the specific infection. For HSV, this may include counseling patients about circumstances that may promote recurrence of lesions, the benefits of suppressive therapy, the relation between symptoms and viral shedding, and long-term strategies to prevent transmission to sex partners.¹²⁸ For patients with genital warts or HPV-related cervical cytologic abnormalities, experts recommend that patients should be advised to limit the number and type of sexual partners, and that consistent condom use might afford some protection in reducing the risk of HPV transmission and associated diseases of anogenital warts and cervical neoplasia (cervical cancer precursors and invasive cancer).¹³⁰ For patients with either genital herpes or anogenital warts, patients should be advised that transmission may result from genital skin contact and does not require penetrative penile, anal, or vaginal contact. Patients with hepatitis should be counseled about both sexual and parenteral exposure risks; and if parenteral risks are identified, patients should be referred to resources to reduce risky injection behaviors and to promote use of sterile injection equipment. Special consideration must be given to pregnant patients for risk-reduction counseling and education in the prevention of transmission of HIV/STI to avoid pregnancy complications and perinatal transmission. Pregnant patients should be encouraged to avoid behaviors that put them and the fetus at risk and should be given information about how to prevent perinatally transmitted HIV, hepatitis, *C. trachomatis*, *N. gonorrhoeae*, and HSV²⁹ (see also Chapters 80, 81, and 85).

Several studies have assessed sexual risk-reduction counseling practices of private providers, but few have described if the focus was STI in general, bacterial STI, or viral STI. For example, in one nationally representative survey in 1998, 78% of physicians reported always telling their patients to avoid sex and 76% reported telling their patients to use condoms during STI-related treatment visits.¹³¹ In another nationally representative sample of clinicians that cared for patients with anogenital warts, most clinicians surveyed (>80%) reported counseling patients about the cause and prevention of warts.¹³² A survey of primary care physicians contracted to Medicaid health plans in seven U.S. cities found that 98% of physicians reported they provided prevention

counseling while taking a sexual history despite the fact that only 81% of their affiliated medical groups and 57% of their health plans explicitly recommended this practice.⁸¹

However, medical record reviews suggest that sexual risk reduction counseling is less commonly performed or documented than clinicians report in surveys. For example, studies show that HIV/STI counseling was documented in the medical records of only 30–35% of all ambulatory care visits in which HIV or bacterial STI tests were done.^{99,133} Another study showed that less than 10% of the patients had been counseled regarding risks and prevention of sexually transmitted hepatitis B virus infection, even though sexual transmission accounts for >50% of hepatitis B virus infections.¹³⁴ Most studies that have evaluated the extent and quality of HIV risk-reduction counseling have addressed HIV test settings, not private sector primary care settings (see Chapter 69). The 1995 Public Health Service guidelines that recommended that all pregnant women receive in-person pretest counseling about the risks of perinatal HIV and be offered voluntary HIV testing were later revised, making in-person counseling optional due to evidence that such counseling was not commonly delivered or was often incomplete.²²

Several barriers to sexual risk reduction counseling and patient education in primary care practices have been identified. A 1999 survey of primary care providers in staff and network health plans found that more than 30% reported that having a limited number of staff members to counsel patients or difficulties keeping up-to-date on how to manage patients at risk for STI were STI management challenges.⁹¹ Other challenges include belief that counseling is ineffective in changing behavior, patient or provider discomfort with or lack of training on counseling, competing clinical priorities during brief visits, lack of staff dedicated to counseling and education, lack of decision support tools such as counseling checklists or talking points, and the absence of guidelines, policies, protocols, reminders, feedback, and adequate reimbursement^{57,97,135} (Table 88-4). For example, a 1998 Washington State survey found that the indemnity health plans that dominated in the state were less likely to cover STI counseling services (29%) than the less common HMOs (100%).¹³⁶ Others have observed that clinicians may forego counseling enrollees of capitated health plans that do not provide added reimbursement for this service.¹⁴ In a nationally representative sample of clinicians that cared for patients with genital warts, leading barriers to counseling patients about warts (or addressing HPV with patients diagnosed with warts) included providing definitive answers about when or from whom HPV infection was acquired (86%), dealing with patients' emotional, psychosocial and relationship issues (76%), and reimbursement for time needed for patient counseling or education (73%).¹³² A significant challenge to effective implementation of counseling and educational interventions for HSV and HPV is the low level of knowledge

among clinicians, patients, and the general public about the high prevalence of these infections, the high prevalence of asymptomatic shedding, and transmission risks.^{128,130} Barriers to HIV counseling are detailed in Chapter 69.

Various interventions have attempted to increase STI and HIV counseling and patient education in primary care settings but few have been vigorously evaluated.¹³⁷ Interventions to reduce behaviors that increase HIV risk in private primary care settings have been more extensively evaluated (see Chapter 89). Simple approaches include providing clinician training in risk-reduction counseling and communication about sexual issues.¹¹⁸ A group-model health plan saw sustained improvements in sexual health knowledge and counseling among providers after training was offered, staff roles were clarified, tools and materials were provided, and reminder and feedback systems were implemented.¹³⁸ Increases in counseling rates for adolescents by pediatric primary care providers have also been found after targeted training and the integration of screening and charting tools in two HMO outpatient pediatric practices.⁵³ Successful adolescent STI prevention counseling strategies have included interactive educational opportunities for patients to assess their own risks, developing personalized, realistic plans for self protection, and addressing barriers to change.¹³⁹ Since interactive counseling may require more time than a standard office visit, health educators and educational resource supports may be needed for effective counseling in the primary care setting. Patient educational supports include pamphlets, videos, hotlines, websites, or referrals to group counseling or community support groups.¹⁴⁰ One potentially time-saving tool is a patient-administered, computer-assisted program that tailors counseling messages to patient's risk factors,⁵⁵ or an interactive, computer-based program to educate patients about STIs.¹⁴¹ Because inadequate reimbursement may preclude counseling, some Medicaid agencies include counseling and patient education as a covered service in health plan service contracts to encourage delivery of these services.⁵⁶ Information on the extent of counseling and patient education for HIV and hepatitis, barriers to delivering these services and interventions to improve service delivery are detailed in Chapter 89. There is little specific data available on successful interventions to improve delivery of HIV and hepatitis counseling and education for adolescents, adults, and pregnant women in private sector primary care. However, interventions that streamline and improve delivery of counseling and education services for other STI in general may be applicable to these specific infections as well.

VACCINATION AGAINST HEPATITIS B AND OTHER STI

Vaccinations are considered one of the most important clinical and public health interventions. Primary care providers have critical roles in offering vaccines to their patients to prevent serious acute infections in individual patients and to prevent

disease transmission in the community. In the United States, vaccines against hepatitis B and hepatitis A are licensed by the FDA and are recommended for use in selected patients by several national organizations^{142,143} (Table 88-5). In addition, several vaccines against bacterial and viral STI are in various stages of development, but not yet approved for clinical use.

■ HEPATITIS B VACCINE

Vaccination against hepatitis B is important to prevent acute liver inflammation and insufficiency and chronic liver disease, cirrhosis, and hepatocellular carcinoma.¹⁴⁴ Since licensure of

the vaccine in 1982 and implementation of recommended guidelines by several national organizations, the number of new cases of hepatitis B has declined dramatically (see Chapter 29).¹⁴⁵ Current recommendations include vaccination of all children and adolescents through age 18 years¹⁴⁶ and of adults at high risk for hepatitis B infection, such as persons with multiple sexual partners, intravenous drug users, MSM, patients receiving hemodialysis, and health-care workers. For sexually active adolescents and adults, providers should assess risk for acquiring hepatitis B infection and offer hepatitis B vaccine if the patient is considered high-risk. Serologic testing to determine if the patient is already immune before vaccination is

Table 88-5. Recommendations for Hepatitis Vaccinations for Adults and Children

Organization	Recommendation	Reference
Advisory Committee on Immunization Practices (ACIP)	Hepatitis A	142
Centers for Disease Control and Prevention (CDC)	Infants/children-routine vaccination recommended for children aged ≥ 1 year	
American Academy of Pediatrics (AAP)		
American College of Obstetricians and Gynecologist (ACOG)		
American Academy of Family Physicians (AAFP)		
American Medical Association (AMA)	Adolescents/Adults: Recommended vaccination is for the following: All susceptible persons traveling to or working in countries that have high or intermediate HAV endemicity should be vaccinated or receive IG before departure. Men who have sex with men Illegal-drug users Persons who have occupational risk for infection Persons who have clotting-factor disorders Susceptible persons who have chronic liver disease	
	Hepatitis B	143
	Infants/children-vaccination is recommended for all infants, regardless of the HBsAg status of the mother. Hepatitis B vaccine should be incorporated into vaccination schedules for children.	
	Adolescents: Vaccination recommended for all unvaccinated adolescents aged <19 years. All children aged 11–12 years should have a review of their	

(Continued)

Table 88-5. (Continued)

Organization	Recommendation	Reference
US Preventive Services Task Force (USPSTF)	<p>immunization records and should complete the vaccine series if they were not previously vaccinated or were incompletely vaccinated</p> <p>Adults: Vaccinate persons at high risk of HBV infection including:</p> <ul style="list-style-type: none"> Persons with occupational risk Susceptible persons who have chronic liver disease HIV positive persons Clients and staff of institutions for the developmentally disabled. Hemodialysis patients Recipients of certain blood products, i.e., clotting factors Household contacts and sex partners of HBV carriers. Adoptees from countries where HBV infection is endemic International travelers if spending more than 6 months in areas with high endemicity Injecting drug users. Sexually active homosexual and bisexual men Sexually active heterosexual men and women Inmates of long-term correctional facilities <p>Hepatitis A vaccine is recommended for persons at high risk for hepatitis A virus (HAV) infection.</p> <p>Hepatitis B vaccine is recommended for all young adults not previously immunized and for all persons at high risk for infection.</p>	19

only recommended within populations with high prevalence (>20%) of past infection. The hepatitis B vaccine is highly effective; in adolescents and healthy adults aged <40 years, approximately 30–50% develop a protective antibody response (anti-HBs >10 mIU/mL) after the first vaccine dose, 70% after the second, and >90% after the third dose. Consequently, even if providers are concerned that the patients will not complete the series of the three vaccinations, the first dose should be offered to provide partial protection.²⁹ Providers who care for HIV-infected persons should also be aware that vaccination may be complicated by blunted antibody response to past hepatitis infection, an issue that also complicates interpretation of hepatitis serologic tests that determine eligibility for vaccine.¹⁴⁷

Despite vaccination recommendations, gaps in vaccination coverage exist among children and adults served by private

sector providers. In 2000, approximately 30% of self-identified high-risk men and women reported having received a single dose of hepatitis B vaccine despite having previous visits to a clinic within the past year.¹⁴⁸ In 2002, despite children 19–35 months having vaccination coverage of 90%, adolescents 13–15 years only had coverage of 67%.¹⁴⁶ Barriers to hepatitis B vaccination include the cost of the vaccine and the lack of reimbursement to providers, reluctance to start the vaccine series if it may not be completed, and lack of provider awareness of the high prevalence of patient behaviors that may expose patients to hepatitis B.¹⁴⁶

Several interventions have increased the vaccination rates of children, adolescents, and adults by primary care providers. Introduction of mandatory hepatitis B vaccination for adolescents entering middle school in several states in the late 1990s has been followed by large increases in vaccination

rates.¹⁴⁹ The Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American Academy of Pediatrics (AAP), and the American Medical Association (AMA) recommend a well-child office visit at 11–12 years to evaluate the vaccination status for varicella, MMR, and hepatitis B; this visit provides an opportunity for catch-up vaccination.^{150,151} Other methods to increase vaccination coverage include educating patients and parents about vaccine benefits and safety, and implementing practice systems that support adherence to vaccination guidelines such as standing orders and reminder recall systems to avoid missed vaccination opportunities, developing immunization registries to deal with fragmented care and to track multidose vaccinations, and giving fair reimbursement of vaccines to providers.¹⁵² For high risk adults, integration of hepatitis B vaccination into programs that provide services to persons with risk factors for HBV infection (e.g., STD clinics, HIV counseling and testing sites) have increased vaccination rates in high risk adults.¹⁴⁶ Special measures to protect confidential information about sexual behavior and drug use in billing and medical records may also be needed to encourage vaccine acceptance by adults, adolescents, and children and their parents. Streamlining consent procedures for adolescents may promote vaccination in states that require parental consent for adolescent vaccination, e.g., classifying hepatitis B vaccination under “comprehensive STD services” that may not require parental consent. (See http://www.guttmacher.org/statecenter/spibs/spib_OMCL.pdf for further information on state-specific regulations on adolescent consent for such services.)

■ HEPATITIS A VACCINE

Vaccination against hepatitis A can prevent acute hepatitis A disease and its rare sequelae of liver failure. Hepatitis A is acquired primarily through fecal-oral transmission by person-to-person contact, or ingestion of contaminated food or water. With the recent decline in incidence of hepatitis A among children, adults (especially men ages 30–49 years) are now more likely than children to acquire this disease, in contrast to past decades. Recently, outbreaks related to sexual and parenteral transmission have occurred among MSM and injecting drug users. The proportion of hepatitis A cases among MSM has increased from 1.5% in 1992 to 8.4% in 2002,¹⁵³ but a slight decrease in cases among MSM has also occurred most recently in 2004.¹⁵⁴

Hepatitis A vaccine was first licensed in 1995 and is highly protective. In adults and children, adequate antibody levels develop in 94–100% of recipients 1 month after the first dose and all recipients develop protective levels after the second dose.¹⁴² Vaccine introduction has been associated with substantial declines in disease, especially among children residing

in states where vaccination is universally recommended.¹⁵⁵ In 1999, the Advisory Committee on Immunization Practices and several national organizations recommend hepatitis A vaccine for certain individuals, including children and adults living in populations with high rates of disease (e.g., American Indian/Alaska Native [AI/AN], Asian/Pacific Islander, and selected Hispanic and religious communities), travelers to countries with high or intermediate disease endemicity, MSM, injecting-drug users, and persons with chronic liver disease to avoid additional liver damage due to hepatitis A.¹⁴² Routine vaccination is strongly recommended for children residing in 11 states with high disease prevalence (Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, Utah, and Washington) and is recommended as an option for children in six states with moderate prevalence (Arkansas, Colorado, Missouri, Montana, Texas, and Wyoming).¹⁴² In 2006, recommendations for hepatitis A vaccine were expanded to include routine vaccination of all children aged ≥ 1 year.¹⁴⁵ Some organizations recommend that primary care providers of children offer vaccine to children at well-care visits¹⁵⁶ and should assess adult risk factors for hepatitis A acquisition (e.g., multiple sexual partners, and travel to endemic areas) and risk factors for hepatitis A transmission (e.g., commercial food handlers) at primary care visits.¹⁴² Several organizations also recommend that HIV-infected persons be routinely assessed for hepatitis A vaccine eligibility and offered vaccine, if eligible.¹⁵⁷

Barriers to providing hepatitis A vaccine in private sector settings are similar to those related to hepatitis B vaccine, and relate to provider awareness of vaccine recommendations, identification of individuals at risk, and costs and reimbursement of the vaccine. Interventions to increase coverage of hepatitis A vaccine and to reduce disease transmission have included promoting the guidelines of national organizations that recommend routine vaccination of children, who are often a source of infection for adults. Introduction of combination vaccines against both hepatitis A and B have also been shown to be cost-effective in increasing vaccination coverage of high-risk persons.¹⁵⁸

■ PROPHYLACTIC VACCINES AGAINST GENITAL HUMAN PAPILLOMAVIRUS (HPV) INFECTION

Genital HPV infection is the most commonly sexually acquired infection, with an estimated 40 million people in the United States infected (see Chapter 28). Although most genital HPV infections are transient, asymptomatic, and clear without medical interventions, some cases of persistent infection may lead to anogenital warts, intraepithelial neoplasia and cancer of the cervix, penis, vulva, vagina, anus, and oral cavity, and infantile respiratory papillomatosis.^{159,160} A quadrivalent vaccine against the two most common types of HPV associated

with cervical cancers (16 and 18) and the two most common types associated with anogenital warts (6 and 11) has been approved by the FDA; an application for licensure for a bivalent vaccine against HPV types 16 and 18 is under FDA review. In 2007, the ACIP recommended the quadrivalent HPV vaccine for females aged 9–26 years.¹⁶¹ If HPV vaccine is approved by the FDA, primary care providers may consider its use in patients before the onset of sexual activity.

■ PROPHYLACTIC VACCINES FOR OTHER STIS

Clinical trials have evaluated vaccines for *N. gonorrhoeae*, *C. trachomatis*, herpes simplex virus type 2, cytomegalovirus (CMV) and HIV.¹⁶² Based on usual research, development, and approval timelines, these vaccines for these STI are not likely to be approved for clinical use within the next 5 years.

MANAGEMENT OF EXPOSED SEX PARTNERS

Prompt evaluation and treatment of sex and needle-sharing partners of patients infected with STI, HIV, and hepatitis is also recommended to prevent reinfection of the index patient and further transmission in the community.²⁹ Although managing sex partners has inherent value at the level of an individual patient or sexual partnership, there is little evidence that clinician recommendations to infected patients to notify sex partners, and partner notification by health department staff are effective in reducing STI or HIV incidence at the population-level. Providers should encourage their patients to notify sex partners of potential STI risk and urge them to seek evaluation, testing, and treatment.²⁹ Ideally, cases of notifiable bacterial STI and HIV infection that are reported to public health departments should prompt disease investigation specialists to contact a patient and offer assistance in notifying their partners and referring them for evaluation. However, staff shortages in most public health agencies often limit partner notification services to the small number of patients with HIV and syphilis, two potentially fatal diseases, the latter of which has a limited period of infectiousness most amenable to partner interventions. Syphilis cases may be prioritized over chlamydial and gonorrhea cases because prompt partner management is required to prevent infection during the short period of primary and secondary infectiousness¹⁶³ (see also Chapter 54).

In the 1998 national primary care physician survey, 80% of providers reported always asking STI-infected patients to notify their partners, but less than half of physicians indicated they always reported patients' names to health departments to initiate partner services, and less than 5% reported always contacting partners themselves.^{131,164} A minority of private providers surveyed in Seattle reported addressing sex partner management.¹⁶⁵ Among physicians affiliated with Medicaid

health plans in seven cities, 62% reported testing and treating sex partners even if they were not enrolled in the index patient's health plan, despite the fact that only 61% of their medical groups and 10% of their health plans explicitly recommended this.⁸¹ A minority of patients with STI reported to health departments are provided partner management services by health department staff, even in high-morbidity areas of the U.S.^{81,163} The extent of partner notification and referral for patients infected with HIV and Hepatitis is addressed elsewhere (see Chapters 53, 54, and 72).

Primary care clinicians cite several challenges to addressing sex partners of patients diagnosed with STI and HIV. Few clinicians or health plans collect contact information or notify sex partners because of the lack of clear policies about out-of-plan partners, medicolegal liability concerns, cost containment pressures, lack of reimbursement, and time or staffing constraints.^{9,166} Other barriers include lack of providers' and patients' comfort discussing partners, and patients' and providers' concern about maintaining confidentiality or adverse consequences to relationships when partners are notified. Primary care providers also face challenges addressing partner services for MSM with numerous anonymous sex partners who may be impossible for patients or health department staff to contact.¹⁶⁷

These challenges have prompted alternative approaches to partner management, such as expedited partner therapy, in some private sector settings. In a few states, laws or regulations allow clinicians to prescribe treatment for their patients' sex partners, even if the partners are not their patients, or to permit their patients to deliver treatment to partners.¹⁶⁸ Some health plans allowing clinicians to write antibiotic prescriptions for sex partners of patients diagnosed with chlamydial infection or gonorrhea not enrolled in the health plan have introduced methods for third party reimbursement for uninsured partners.^{4,9,97,169} A recent trial showed that notifying patients with chlamydial infection and gonorrhea that they could refer their partners to get treatment at commercial pharmacies without visiting a physician was acceptable and increased partner treatment.¹⁷⁰ Some health plans provide brief "after visit summaries" for patients diagnosed with or tested for STI that list actions to take with sex partners and have explored using telephone advice nurses to explain sex partner management services to patients with positive STI tests.¹⁷¹ Notification and referral practices for partners of HIV-infected and hepatitis-infected patients are detailed elsewhere (see Chapters 53, 54, and 72).

CASE REPORTING AND COLLABORATION IN STI OUTBREAK CONTROL

Public health departments use compilations of case reports of STI, HIV, and hepatitis reported by clinicians or affiliated laboratories to plan, implement, and evaluate prevention and

control efforts, to prompt partner notification services, and to detect outbreaks.¹⁷² Name-based reporting of *N. gonorrhoeae*, *C. trachomatis*, and syphilis cases by laboratories and/or providers is mandatory in every state.⁵ HIV, Hepatitis A, B, and C cases are also reportable by name or other unique identifier in every state.¹⁷³ Some states accept only reports of laboratory-confirmed cases, while others accept reports of clinically diagnosed cases with or without lab confirmation. Providers should be aware of reporting requirements in their local jurisdiction, and whether the reporting responsibility falls to them, their staff, their health plan, or the laboratories, and whether cases without laboratory confirmation are reportable. They should also notify patients that if a case is reported, the patient may be contacted by the health department to offer them assistance notifying sex partners.¹⁷¹ Anecdotes suggest that patients may decline STI or HIV testing (or decline testing under their real name) if they do not want their name reported to health authorities, but the extent of this practice is uncertain. There has also been particular concern that high-risk individuals will defer testing due to name-based reporting requirements. Name-based HIV reporting policies have been shown to result in delays in testing in injection drug users, but have not been shown to be associated with avoidance of HIV testing because of worry about reporting.^{174,175}

STI reporting appears to be more complete and timely from public STI clinics than from private-sector providers.³¹ Most physicians surveyed in various private-sector settings and Medicaid health plans are aware that laboratories report STI cases to health authorities.^{47,79,176} Nevertheless, studies suggest that 9–28% of laboratory-confirmed cases of *C. trachomatis* and *N. gonorrhoeae* from such plans are not reported.^{177–179} In an evaluation of reporting in commercial health plans in three states, most cases were reported 1–3 weeks after specimen collection, and reporting was faster when laboratories electronically reported cases to health departments.¹⁷⁷

Factors that may preclude STI case reporting include (1) lack of provider awareness about reporting obligations, (2) confidentiality concerns with billing, medical records, and health department staff, (3) lack of reimbursement for reporting functions, (4) lack of centralized systems to facilitate reporting, and (5) a limited public health perspective of private sector providers who may not appreciate how case reports are used to detect outbreaks, initiate sex partner services, and track disease trends in the community.^{177,179}

Several interventions have been designed to increase completeness and timeliness of STI case reporting for primary care settings. These include having dedicated staff members, such as infection control specialists assigned to reporting functions, use of secure methods to electronically transfer positive laboratory test reports directly to health departments, attaching case report cards to positive laboratory

results received by clinicians, and regular communication between health plans, clinicians, and health departments about types of cases that might activate sex partner notification by health departments.¹⁷⁷ Some California health plans have developed systems to automatically track and report STI cases to speed reporting and measure enrollee STI burden.⁴ Policy-level interventions that may improve reporting include reimbursing clinicians for time spent on reporting and disseminating memoranda of understanding that detail reporting roles of providers, laboratories, and health department staff. Some states have formal contracts that require out-of-state laboratories to report cases to the state where the patient resides, an important issue as large regional laboratories now serve health plans in several states.^{4,180}

Over the past decade, several STI outbreaks have occurred among the persons cared for outside public STI clinics, underscoring the growing role of primary care providers in outbreak detection and control.⁵⁹ In some instances, primary care providers may note an increase in STI cases in their practice; such suspicions should be reported to the local health department for confidential follow-up. In addition, health departments may alert primary care providers of local outbreaks of STI, HIV, and hepatitis through newsletters, press releases, letters, email alerts, or phone calls.⁵⁹ These alerts may recommend increased screening of asymptomatic patients, routine examination for STI signs, or educating patients about STI symptoms or STI prevention.

CONCLUSION

Private sector primary care providers provide critical functions in STI, HIV, and hepatitis prevention and care in the United States and will become more important as more patients at risk for these infections are cared for in private sector settings. Primary care providers will continue to promote and test new tools, such as computer-based assessment and counseling methods that require less provider time, hepatitis and STI vaccines, rapid and/or noninvasive HIV and STI tests, and expedited sex partner management strategies. Evidence suggests that in many primary care settings, the extent and quality of diagnosis and treatment of symptomatic infections is better than the extent and quality of STI prevention services such as risk assessment, screening, counseling and patient education, management of sex and needle-sharing contacts, and hepatitis B vaccination. These gaps point to areas that merit attention for quality improvement efforts in primary care settings. Fortunately, there are many examples of policy-, health system-, provider-, and patient-level interventions that have improved delivery of STI, HIV, and hepatitis services in primary care settings. Health plans, quality improvement

experts in health systems, medical directors of practices, and individual clinicians interested in improving STI, HIV and hepatitis services should consider how these intervention approaches can be tailored to their practice setting, patient population, and clinical priorities.

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PART 14

Prevention and Control of STI and HIV Infection

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Multilevel Approaches to STD Epidemiology and Prevention

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The essence of any public health program is prevention, which is strictly defined as “action intended to obviate or provide against an anticipated danger or mischief” (Oxford English Dictionary, 2005). Broadly speaking, the anticipated danger or mischief in this case is transmission of, acquisition of, or complications associated with sexually transmitted diseases (STDs) or HIV infection. Preventing such events requires a complete understanding of the complexity of influences on risk behaviors, which span across and interact with each other on the individual, group, and population levels.

Hippocrates, arguably among the earliest to conceptualize causes and prevention of illness, emphasized risk factors for disease that have largely population level impacts such as season of the year, local weather conditions, and community behaviors. Today, however, many would argue that more attention is paid to the individual and less to the population. Partly in response to this focus on the individual, Geoffrey Rose introduced the importance of differences between “sick individuals” and “sick populations” and the need for different prevention strategies for the control of individual and population level health problems.¹ This perspective has been reinforced even more recently with the growing interest in social epidemiology and its emphasis on examining the social and economic determinants of health² alongside the traditionally evaluated individual-level risk factors. In this chapter, we hope to reinforce this notion and focus on STDs and HIV as multilevel problems.

The foundation of an effective prevention intervention at any level is the epidemiologic data that guide its development. Thus, etiologic research must be appropriately designed or it will fail to identify the points in the causal pathway that will yield the greatest reductions in disease. With this in mind, we discuss separately etiologic research and related methodological considerations before discussing preventive intervention research.

Table 89-1 presents examples of how the individual, the group, and the population can be considered in epidemiologic and prevention intervention research. For epidemiologic research, risk factors can be measured on an individual,

group, or population level, and likewise, the disease of interest may be measured in individuals, groups, or across populations. Similarly, in prevention intervention research, the target or beneficiary of the intervention may be an individual, group, or a population and the mechanism, vehicle, or agent of change may also be considered on an individual, group, or population level. For example, peer-led interventions that use individuals to implement change and that target groups of commercial sex workers benefit not only the individual prostitutes but also their clients and the wives and other sex partners of their clients so that ultimately the general population benefits. Indeed, the benefit to the population may exceed the benefit to the individual sex workers. For example, in areas characterized by high occurrence of HIV infection, such as Thailand or Kenya, many individual female sex workers eventually become infected, because of repeated high-risk exposures, despite continuously striving toward consistent condom use, even though incident infection is reduced in the population.^{3,4}

ETIOLOGIC RESEARCH AND METHODOLOGICAL CONSIDERATIONS

Preventive interventions target those risk factors identified in etiologic research that influence the probability of acquiring infection for individuals, the possibility of transmission within the population and, given acquisition of infection, the likelihood that complications will result. Table 89-2 provides examples of two possible risk factors for HIV infection, hormonal contraception and infection with herpes simplex virus (HSV), as well as the kinds of research needed at individual and population levels to support development of interventions addressing these risk factors for STDs and HIV. For risk factor research, the difference between individual and population levels may sometimes be one of measurement, because all individual variables may be assessed by summarizing the results across several individuals; for example, an individual's age versus the average age of a population, or an individual's infection status versus the prevalence of infection in a

Table 89-1. Examples of Individual, Group, and Population-Level Approaches in STD/HIV Preventive Interventions

Level of Intervention	Risk Factor	Target of Intervention	Beneficiary of Intervention	Mechanism of Change	Measure of Disease Change
Individual	Unprotected intercourse with partner(s)	Women attending family planning clinics	Individual woman and her partner(s)	Counsel women to use condoms	Individual infection
Group	Unprotected intercourse with clients	Female sex workers	Clients of sex workers subsequent female partners of these clients	Peer leader mediated condom promotion with female sex worker (FSW)	Prevalence or incidence of infection in group or sub-population
Population	Social status of women	School-aged female children	Women; whole population	Education of school-aged female children	Prevalence or incidence of infection in population

Table 89-2. Individual and Population Perspectives on Objectives of Research on Potential Risk Factors for HIV Infections, with Two Examples

	Individual Perspective	Population Perspective
Objective of research	Assess individual risk factors associated with susceptibility or progression to disease	Consider risk factors measured across groups or populations associated with transmission
Contraception	Study OCP use and other forms of contraception, as risk factors for an individual acquiring HIV	Study oral contraceptive pill (OCP) use and other forms of contraception as risk factors for mucosal shedding and transmission of HIV
Herpes simplex virus infection	Determine association of HSV-infection with increased risk of an individual acquiring HIV	Assess the effect of suppressive acyclovir therapy in persons with HSV infection on population-level HIV incidence

population. Alternatively, factors that affect morbidity in the population may not be reducible to the individual level (e.g., herd immunity subsequent to vaccination).

At the smallest group or partnership level, factors such as the type of partnership, the gender power dynamics in the partnership, and the contextual pressures on the partnership may be important.^{5,6} Just as individuals are embedded in sexual partnerships, partnerships are embedded in sexual networks. The structure of the sexual links among individuals who make up the network determines the potential paths

through which sexually transmitted pathogens may travel. While sexual networks are difficult to identify, interventions that make use of the structure inherent in social networks are beginning to be tested.⁷

Factors that only apply at the population level include degree of urbanization, political factors such as the amount of governmental funds spent on public health or war, or social factors such as cultural norms. On a population level, higher levels of social inequality in populations have been correlated with higher syphilis rates.⁸ Furthermore, poverty,

the ratio of men to women, and racial segregation influence sexual behavior, which in turn influences risk of STDs.⁹

The very nature of infectious diseases has methodological implications as well. For chronic, noncommunicable diseases, the relative risk, risk difference, and attributable risk, together with the distribution of a particular risk factor in the population measure the overall importance of the factors as a cause of the disease. These measures are unconditional, meaning that they are defined as events per person-time, and do not depend on the occurrence of other events. However, communicable diseases in general, and STDs in particular, are transmitted by intimate person-to-person contact, and thus the risk of acquiring an infection depends on the overall prevalence of infection in the population and contacts between infected and susceptible individuals. This essential feature of communicable disease transmission is known as the dependent happenings relation¹⁰ and is illustrated by the fact that a single infected individual with many exposures can cause infection of many others. Because of this, traditional measures of effect such as attributable risk, that are static in nature, may be less straightforward for STDs than for chronic, noncommunicable diseases.^{11–13} More complex mathematical models are required to predict the proportion of communicable disease that could be prevented by the elimination of a risk factor.

One additional complication with communicable diseases is that risk factors measured on an individual level can contribute either to increased individual susceptibility or increased infectiousness. For example, infection with an STD may increase both the infectiousness of an HIV-infected individual and the susceptibility of an HIV-uninfected person and thus, such individual level factors may amplify the spread of infection in the population. Therefore, it may be inappropriate to use purely individual level models when assessing risk factors for STD/HIV infection.^{13,14} Yet another level of complexity is added when sexual contact patterns and networks are considered. The pattern of sexual mixing, which can only be measured at the population level, may be the most important determinant of disease spread and is increasingly being studied through simulation modeling.^{13,15}

Most risk and health-promoting behaviors are not distributed randomly in populations. Such behaviors tend to cluster with one another and are correlated with the positions of individuals in the social structures they inhabit. The structure and dynamics of the social hierarchy and of sexual networks also interact with contextual factors. Demographic, epidemiological, social, and political contexts directly influence the structure and dynamics of social hierarchy and sexual networks and, in turn, are influenced by them. Political conflict, economic and social disruption, and migration predictably lead to the breakdown of existing structures and the formation of new ones.¹⁶

PREVENTION RESEARCH

The concepts of primary and secondary prevention, although developed by preventive medicine specialists in the context of noncommunicable disease, apply equally to infectious diseases, although with some adaptation. The term “primary prevention” generally refers to prevention of the first occurrence of disease, and “secondary prevention” refers to prevention of complications or reoccurrence of disease among those who are already affected. Interventions for STDs including HIV differ somewhat from those developed for chronic disease because of the dependent happenings relation; infection is regulated by contact between susceptible and infected individuals. Thus, while detection and treatment of existing infections constitute secondary prevention of complications of infection in the individual patient, early detection and treatment of infected individuals can also prevent further transmission to others and thus provide primary prevention of infections at the population level. In fact, for STDs, this strategy may provide the greatest primary prevention impact at the population level as demonstrated by the efficacy of expedited partner therapy for STDs^{17,18} and periodic presumptive therapy for sex workers.^{19,20} The reductions in viral load subsequent to initiating HAART would, theoretically, be another example of a primary prevention treatment intervention to reduce the transmission probability, yet the impact of this on HIV incidence at the population level has not yet been empirically demonstrated. However, trials examining this are currently underway.

Finally, because of the social stigma attached to diseases transmitted via sexual contact, prevention of STDs also has powerful political, social, and related economic consequences. In communicable diseases, individuals “at risk” for acquiring disease (the uninfected) are often perceived by society as differing markedly from those likely to transmit it (i.e., the former may be perceived as potential victims, the latter as threats or vectors). This same social stigma likely impacts the effectiveness of preventive interventions. Embarrassment over stigmatizing conditions can lead to nondisclosure of disease status, unwillingness to negotiate condom use, or reluctance to seek testing and treatment. Previously, many countries selectively avoided developing prevention efforts specifically designed to prevent transmission by individuals with chronic viral STDs out of fear that targeting prevention efforts to infected individuals would carry the risk of stigmatization and discrimination. However, this has begun to change with the advent of more affordable therapies both for HIV and HSV infection.

The distinction between acquisition and transmission is not trivial. Interventions focused on infected individuals and designed to limit transmission benefit the population. Alternatively, interventions focused on susceptible individuals limit acquisition and more directly benefit the individual.

Thus, emphasis on preventing acquisition of infection among all susceptible individuals in the community versus emphasis on preventing transmission of infection from a relatively small number of infected individuals produces different distributions of costs and benefits across the population.²¹ In the United States, by the time the HIV/AIDS epidemic was recognized, a large proportion of men having sex with men and IV drug users had become infected, and prevention emphasized changing the behaviors of all susceptible members of high risk groups and even on changing behaviors of the general population. In contrast, in Sweden, where only a small proportion of individuals in these highest risk groups had become infected by the time the HIV/AIDS epidemic was recognized, a much greater emphasis was placed on identifying and changing the behaviors of the few who had become infected. This emphasis on secondary prevention among HIV-positive individuals, or “prevention for positives” to reduce transmission in the population has come late to the United States, and only recently have trials of such preventive interventions been undertaken. Most notably the WILLOW program demonstrated that HIV-positive women receiving care at health departments or HIV/AIDS clinics who attended group sessions emphasizing sexual risk reduction, gender pride, and enhanced social networks experienced an 81% decrease in incidence of bacterial STDs when compared to controls.²² This reduced incidence of bacterial STDs demonstrates empirically the effects of safer sex practices, which should translate to less HIV transmission to susceptible new partners.

When the emphasis is on prevention of acquisition for all susceptibles (a universal prevention strategy), the whole population incurs the financial costs of interventions and the intangible costs of undergoing preventive behavior change and they collectively receive the benefits of avoiding acquisition of infection. With emphasis on prevention of transmission by a relatively small proportion of the population, a more targeted approach would be justified. The general population still receives the benefit of avoiding acquisition and associated future health costs and may again incur the financial costs of implementing the intervention. However, these financial costs may be less, and fewer people incur the major burden of behavior change.

In this age of limited resources, cost effectiveness analyses are becoming increasingly important. Using a simulation model to estimate the costs per disability adjusted life year (DALY) averted in 2000 international dollars (\$Int) for two of the regions with the highest HIV/AIDS burdens (sub-Saharan Africa and South East Asia), one group has concluded that mass media, education, and treatment of STDs were the most cost-effective interventions, at costs of <\$Int150 per DALY averted. Voluntary counseling and testing, in contrast, was over twice as expensive (<\$Int350 per DALY averted). Prevention of mother-to-child transmission

was extremely cost-effective in sub-Saharan Africa (<\$Int50 per DALY averted) but much less so in South East Asia (~\$Int850 per DALY averted). School-based education strategies were slightly less cost-effective (\$Int430–790 per DALY averted) than first-line antiretroviral therapy (~\$Int550 per DALY averted).²³

PREVENTIVE INTERVENTIONS

Like prevention research, preventive interventions are designed and conducted on several different levels and may be conceptualized in terms of the level of intervention (individual, group, or community); the implicit or explicit primary outcomes (decreased acquisition, transmission, or complications of STDs/HIV); and the intervention modality (behavior change, vaccination, topical microbicide use, treatment [prophylactic, curative, or suppressive], surgical intervention). **Figure 89-1** presents a framework, showing points of intervention to prevent acquisition of STDs/HIV by an uninfected individual and those to prevent STD/HIV transmission from and/or complications in infected individuals or sexual dyads.²⁴

Clearly a given behavioral, biomedical, or structural intervention may influence multiple outcomes. For example, a successful HPV or HIV vaccine might reduce the risk of acquisition of subsequent transmission or the risk of complications.

In contrast to individual or group-level interventions, community level trials evaluate more complex pathway linkages and indirect and total intervention effects.²⁵ For example, in community randomized trials of early treatment of STDs,^{26–28} a fall in prevalence or incidence of STDs in the general population presumably reflects both decreased duration of infection and resulting decreased STD transmission, whereas the resulting decline in HIV incidence at the

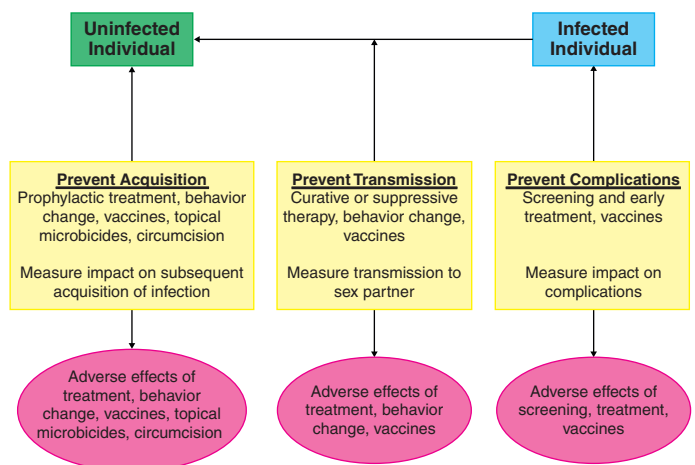


FIGURE 89-1. Framework for outcomes analysis at the individual or sexual dyad level: examples of types of preventive intervention trials, with outcomes potentially measuring sexual acquisition, or transmission, or complications of STDs/HIV.

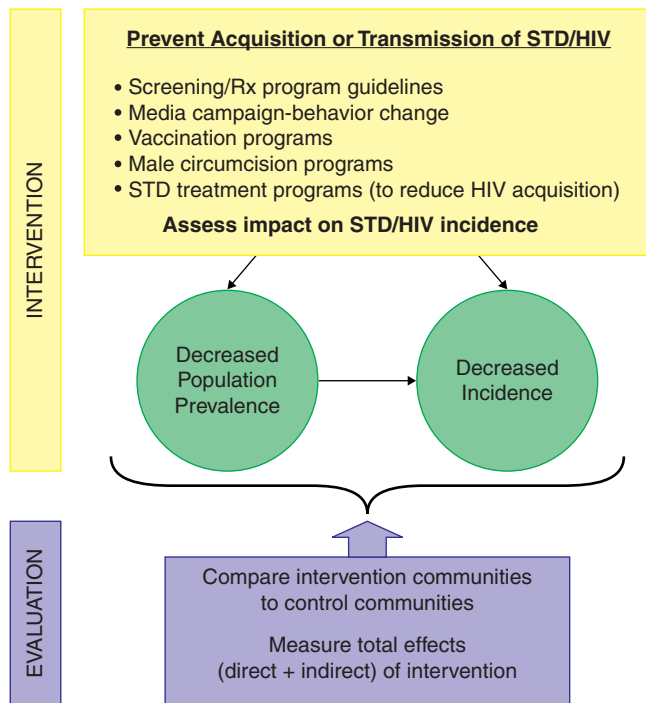


FIGURE 89-2. Framework for outcomes analysis at the population level: examples of causal pathway linkages in community intervention trials to prevent sexual transmission or acquisition of STDs and HIV.

population level could reflect the potential impact of reduced STD morbidity on transmission or acquisition of HIV, or both. Thus, a separate analytic framework applies to community level interventions (Fig. 89-2).²⁴

This separation of levels is not always straightforward or distinct. For example, use of screening tests in asymptomatic women in family planning clinics to identify those needing treatment for infection primarily benefits the individual woman but may also contribute to decreasing transmission to future partners. Such screening also defines the prevalence of infection within that group, thereby guiding decisions to implement largescale population-level prevention interventions, such as mass condom promotion. Thus, these various approaches should be viewed as complementary and overlapping, both in implementation and impact. Nevertheless, it is conceptually important to clarify the meanings of the terms “individual,” “group,” and “population” level interventions.

Table 89-3 provides individual and population perspectives on the objective of STD/HIV preventive interventions, as well as examples of specific behavioral and biomedical interventions, and prevention research. Note that the distinction between biomedical and behavioral prevention research, although commonly made, is misleading because biomedical interventions require supportive behavioral intervention components. In addition, biomedical outcomes are needed in the more definitive behavioral intervention research; and multiple component (biomedical plus behavioral) interventions are of growing interest in prevention research (as in the

Masaka, Uganda study that combined behavioral and STD treatment interventions for HIV prevention).²⁷ The principles here are similar to those that apply to research on etiology of disease. From an individual perspective, interventions may prevent initial acquisition of infection and prevent subsequent development of associated sequelae, whereas the most important principle from the population perspective is to prevent transmission. Depending on whether the focus is on the beneficiary or the target, some of the interventions listed here could be classified either as population- or individual-level interventions. Further, risk factors defined on a population level can influence interventions directed toward individual risks. For example, accepted social norms defined on a population level can constrain and shape behavioral interventions targeted toward individuals.²⁹

Although we advocate a multilevel approach to STD/HIV prevention that goes beyond the medical model of providing detection and treatment to individual patients, limited resources may constrain choice. Furthermore, choice of the level on which to target an intervention might also depend on the phase of an epidemic. In general, at the early phases of an epidemic in settings where small core groups of high-risk individuals are the first to acquire disease and account for most transmissions, core group interventions may be most feasible and cost-effective. In later phases of a mature epidemic, when prevalence is more widespread, interventions directed toward core groups may remain highly cost-effective but no longer sufficient to rapidly contain the epidemic.³⁰

The next section describes particular interventions in detail and reviews interventions that occur among progressively larger units of analysis: individuals, couples, groups, communities, populations, and the networks that link individuals and groups. Examples of the strengths and weaknesses of approaches at each level are discussed, as are relevant methodological issues.

INDIVIDUAL INTERVENTIONS

Examples of individual approaches to prevention include programs that seek to alter the modifiable individual-level factors. Individual-level risk factors include factors related to host susceptibility in susceptibles or increased infectiousness in the infecteds and include biological factors such as cervical ectopy, vaginal flora, immunological competence, and viral load; behavioral risks including sexual practices; number, temporal spacing, and choice of partners; and preventive behaviors such as use of condoms, vaccines, and microbicides. The mechanism of change involves vaccination, counseling and testing, partner notification and treatment, or case finding (either clinic-based or active outreach screening programs) and subsequent treatment.

Table 89-3. Individual and Population-Level Perspectives on Objectives of STD/HIV Preventive Interventions, with Examples of Preventive Intervention and of Biomedical and Behavioral Prevention Research

	Individual Perspective	Population Perspective
A. Objectives of preventive interventions	Prevent acquisition Relieve symptoms and prevent progression to complications or death	Prevent transmission Intervene in those most likely to transmit, to achieve maximum effect with minimum expense
B. Examples of intervention		
Partner notification, treatment	Treat exposed partner	Treat source partner
Screening	Screen individuals and treat those found to be infected Screening based upon risk factors for having infection, or developing a complication; for example, screen all younger females regardless of number of partners	Establish subpopulation specific prevalences and mass treat subgroups depending on prevalence Screening based upon risk factors for spreading infection, for example, screen males with many partners
Condom promotion	Detect, treat infectious and late syphilis Promote use of condoms by male with spouse	Detect, treat infectious syphilis Promote use of condoms by men during sex with sex workers
Improve access to STD/HIV services	Provide STD services in managed care organizations for employed, insured individuals Provide treatment for early chlamydial or gonococcal infection in women to prevent tubal factor infertility	Provide free access to STD services for uninsured inner city crack cocaine users Provide treatment for early chlamydial or gonococcal infection in men to prevent tubal infertility in women
Counseling /education risk reduction	Counsel or educate uninfecteds on decreasing acquisition	Counsel or educate infecteds on decreasing transmission
C. Biomedical prevention research		
Male circumcision	Evaluate effect of male circumcision on acquisition of HIV among circumcised males	Evaluate effect of male circumcision on acquisition of HIV among female partners of circumcised and uncircumcised males
Vaccine programs	Evaluate therapeutic vaccine to reduce progression of HIV	Evaluate preventive HIV vaccine to reduce acquisition or mucosal shedding and thus prevent subsequent transmission
STD treatment to prevent HIV infection	Randomized trial of selective routine treatment of STD in sex workers to lower their risk of acquiring HIV	Community randomization trial of syndromic management of STD (Mwanza trial) or of mass treatment of STD (Rakai trial) to lower community-wide incidence of HIV infection

Table 89-3. (Continued)

	Individual Perspective	Population Perspective
HIV antiretroviral treatment	Evaluate impact of antiretroviral therapy on progression of immunodeficiency	Evaluate impact of antiretroviral therapy on mucosal shedding or transmission to partners
Microbicides	Evaluate existing spermicides and new microbicides on prevention of acquisition of HIV and other STDs	Evaluate impact of spermicide and microbicide use on preventing transmission of STD/HIV
Needle exchange/ drug treatment	Evaluate impact of needle exchange program on incidence of HIV in exchange participants	Evaluate impact of needle exchange program on incidence of HIV in the general population of injecting drug use (IDU) who do not use the exchange
	Randomized trial of impact of increased access of uninfected IDU to drug treatment programs on individual risk of acquisition of HIV, HBV, HCV, or HTLV-II	Community randomization trial of the impact of improved access of infected IDU to drug treatment programs on incidence of HIV, HBV, HCV, and HTLV-II among communities cohorts of IDU
Behavioral research	Evaluate individual behaviors associated with risk of acquiring infection	Evaluate individual behaviors associated with transmission of infection
	Randomized trial of impact of individual, small group, or work site information, education, or counseling on rate of acquisition of STD/HIV	Evaluate characteristics of risky sexual networks Community randomization trial of impact of population-wide information education and communication for STD/HIV prevention on incidence of STD/HIV

Using the individual as a target for an intervention allows for tailoring the intervention to the needs of particular individuals. Because of the communicable nature of STDs, an additional benefit to this kind of program may be that prevention or treatment of infection in one individual may break a chain of transmission, preventing further spread. Individual risk profiles may be developed and appropriate interventions can then be selected. Prochaska's stages of change model is an example of this kind of approach where individuals are "staged" according to their readiness to adopt a prevention strategy and then the intervention is tailored to this stage.³¹ Another theory that has received increasing attention is motivational interviewing and the related information-motivation-behavioral skills model. Implementation of this model in a clinician-delivered intervention with HIV-positive patients resulted in significant reductions in unprotected sex, thus reducing transmission.³² One weakness of this kind of individual behavioral approach is that the time and labor involved

in individual assessment can make the intervention costly. In addition, it may be difficult to identify those individuals at risk who would benefit most from the intervention.

Male circumcision is an individual-level intervention with population-level implications. The potential efficacy of this intervention was suggested by early ecologic studies showing that HIV prevalence was lower in countries where the majority of the male population practiced circumcision^{33,34} and subsequent observational studies supporting this hypothesis.^{35,36} In the three randomized controlled trials of male circumcision, the risk of acquiring HIV was reduced by 50–60% among men who had been circumcised, compared to those whose circumcision was deferred.^{37–39} While this individual-level intervention works presumably by reducing the circumcised man's susceptibility to HIV, it should also reduce overall transmission of HIV on the population level, provided behavioral disinhibition does not result in offsetting increases in risk behavior.

■ COUPLE-BASED INTERVENTIONS

Because STDs, by definition, are transmitted between individuals, it may be more appropriate to use couples rather than individuals as the smallest unit of analysis for epidemiologic study. This enables simultaneous examination of factors related to infectiousness and susceptibility, including those individual factors delineated above. The mechanisms of change in couple-based interventions may parallel those identified for individual interventions, such as case finding, counseling, and testing.

Interventions directed toward couples discordant on either their infection status or their risk status provide excellent examples of prevention strategies at this level. In one study, Kamenga et al. followed 149 HIV serodiscordant couples in Zaire.⁴⁰ At entry into the study, fewer than 5% of the couples consistently used condoms compared to 77% of couples 18 months later. They detected a seroconversion rate of three new infections per 100 person years of follow-up. In a similar study in Rwanda, Allen et al. counseled and followed 60 serodiscordant couples.⁴¹ Condom use was reported by 3% of couples at baseline and by 57% at 12 months follow-up. They reported an HIV seroconversion rate of 4 per 100 man years of follow-up and 9 per 100 woman years of follow-up. Among participating women, the seroconversion rate was >50% lower than the estimated rate in women whose partners did not undergo HIV counseling and testing. Finally, Padian et al. followed 175 discordant couples in California.⁴² Among these couples, 32% reported consistent condom use at entry into the study and 75% reported consistent condom use as many as 9 years later. In this study, which had no control group, no new seroconversions were observed during greater than 3000 couple months of follow-up. Although these studies have focused on behavior change and condom promotion among HIV-discordant couples, discordance on other STDs may merit other approaches. For example, discordant couples have been the subject of studies assessing the effect of HSV treatment and vaccination on reducing transmission.^{43,44}

The strengths of the “couples” approach are apparent. Because transmission events are associated with sexual activity between infected and susceptible individuals, targeting interventions toward couples is obviously appropriate. A weakness of this approach is that these interventions are only appropriate for couples who are in relationships that remain stable. In the case of studies or interventions targeting discordant couples, length-biased sampling may be an issue. Many believe that most transmission in a partnership occurs early on and that couples who both remain together and remain discordant are somehow different from couples who do not. Thus, long-standing discordant partnerships are probably not fully representative of all couples. This limitation can be overcome by enrolling people in a study or intervention at partnership formation, but this approach has only rarely

been used.⁴⁵ Additionally, interventions delivered to couples may be less effective for individual members of the couple following the break-up, and selection of couples likely to remain together throughout the research trial may require very restrictive eligibility criteria, increasing recruitment costs and reducing generalizability. Furthermore, delivering a behavior change intervention to both members of a couple is not always associated with any increased effect.^{46,47} Finally, including serostatus as part of eligibility adds complexity because not all individuals know or want to know their serostatus and because these parameters, such as the status of the partnership itself, change over time. The importance of couples-based prevention research and interventions is highlighted by the two ongoing trials of HSV-suppressive therapy currently being conducted among HSV-discordant couples. If efficacious, this intervention may have a greater impact on the population level transmission dynamics than its effect at the level of the sexual dyad.

■ “CORE” GROUP INTERVENTIONS

Groups may be thought of as clusters of individuals and couples. One such group considered central to STD epidemiology is the “core group,” first described by Heathcote and Yorke.⁴⁸ Although the definitions of core groups vary somewhat, they are generally characterized by individuals connected to each other through social and sexual networks, who display risk behaviors and high infection rates and who sustain transmission of an STD pathogen within the population. The theory is that population rates of STDs are driven by spread among groups of individuals that are characterized by high rates of exposure to an STD (often related to frequent concurrent exposure), longer duration of infection (often related to poor access to acceptable health care), and highly efficient transmission of infection per exposure (often related to undiagnosed or untreated coinfection with other STDs, young age, risky practices, lack of male circumcision, etc.). These groups act as foci for STD spread so that a pathogen newly introduced into the community soon becomes concentrated in these groups. By virtue of mixing (or “bridging”) with individuals outside of the group, they may also be responsible for seeding infection among individuals who are not identified as being part of the core group.⁴⁹ Examples of core groups include men and women involved in commercial sex, migrant workers, truckers, STD clinic attendees who have repeat infections, individuals who have many sexual partners over a defined period of time, or persons living in a defined geographic area characterized by high STD/HIV incidence.⁵⁰

One intervention strategy for core groups employs peers as the agents of change, since peer leaders such as opinion leaders, role models, or peer educators may best influence the behavior of the entire group.^{51,52} Their objective is to change social norms. Another strategy involves population-based

actions such as changes in laws or health codes as they apply to such groups. These approaches, characterized by removal of barriers to implementation of prevention interventions or creation of barriers that prevent risky behavior, have been called “enabling” approaches because they enable the desired behavior change to occur.⁵³

One example of interventions targeted at core groups is the many condom distribution programs aimed at female sex workers. In both Kenya and Zimbabwe, such programs increased rates of condom use and decreased rates of STDs among women as well as in the larger community.⁵² The major part of these interventions was delivered by peer educators and counselors who distributed condoms and provided information about safe sex along existing social networks linking at-risk women. In Kenya, 1 year after initiation of this program, sex during menstruation and the number of clients during the prior week decreased, the charge per client increased, and the frequency of condom use with all clients increased from 4.6% to 36.5%. Similar results were reported in Zimbabwe where condom use increased from 18% to 66% within 2 years of the program.

In the condom promotion program among sex workers implemented in Thailand, individuals educated other individuals, but governmental sanctions were added to insure behavior change and STD treatment was expanded through the opening of 508 district STD clinics.⁵⁴ Here, the government required condom use at brothels and free condoms were distributed. This was supplemented by mass advertising, interviews of brothel workers to insure that condoms were used, and identification of particular customers when a worker was diagnosed with an STD. Over 2 years, reported condom use in brothels increased from 14% to 94%, and five major STDs (syphilis, gonorrhea, nongonococcal urethritis, lymphogranuloma venereum, and chancroid) decreased in men by 79% over 5 years. Nevertheless, although rates of these STDs were reduced, HIV incidence among young men initially remained high. Eventually, in military conscripts who were also targeted by HIV prevention programs, HIV rates also fell.^{3,4}

Another example of a core group intervention is the provision of periodic presumptive therapy to commercial sex workers, with the goal of preventing acquisition of STDs and HIV by them and subsequent transmission to their clients. One study in Kenya, and another in Zimbabwe, have demonstrated efficacy in reducing STDs other than HIV but no reduction in HIV acquisition was observed in one,¹⁹ and rapid reinfection rates were observed in the other, suggesting that frequent dosing would be required to ensure ongoing success.²⁰

The benefits of targeting interventions at core groups extend beyond the core to the larger community in which such groups reside.^{55,56} In addition, targeting many individuals within the core group simultaneously provides a greater opportunity for concomitant changes in social norms than if

such programs are targeted at individuals. Such interventions could also be cost-effective because they do not require assessment of infection status or behavioral risks among individuals. Weaknesses of this kind of program include the potential for stigmatization where core group identification results in labeling. Likewise, because core group membership is ill-defined and individuals may move in and out of such groups, it may be difficult to successfully identify members. Furthermore, the phase of the epidemic must be considered. Mathematical models have shown that core group interventions are most effective during concentrated epidemics with a low reproductive potential. However, in epidemics with a high reproductive potential, although core group interventions are still necessary, they are not sufficient and interventions in the general population are also required.⁵⁷

■ COMMUNITY-BASED INTERVENTIONS

Groups of individuals who live or work together or who have similar life styles represent another kind of group characterized by more heterogeneous behavioral risks than in the core groups just described. Examples of these kinds of communities include minority, urban teens of low socioeconomic status, gay men of diverse risk status, or geographic or work-site clusters. Here, the strategy for intervention can resemble that described for core groups but often involves intervention on multiple levels.

One example of a community intervention was that conducted among gay men by Kelly et al.⁵⁸ The intervention began with selection of peer opinion leaders who then engaged other men who have sex with men (MSM) in bars in conversations about the benefits of safe sex, resulting in so-called “diffusion” of the intervention into the community. The intervention, conducted in a staggered, serial fashion in three cities, resulted in a 15–24% decrease in unprotected anal intercourse, a 14–29% decrease in insertive anal intercourse, and a 26–28% decrease in unprotected receptive anal intercourse. In a follow-up randomized community trial where pairs of small cities in Wisconsin, New York, West Virginia, and Washington were randomized to a similar intervention, men in intervention cities reported a significant decrease in the number of episodes of unprotected anal intercourse and increased uptake of condoms at gay bars, while no change was observed in the control cities.⁵⁹

The Mwanza study of improved syndromic management of STD in rural communities in Tanzania represents another example of a successful community-based intervention.²⁶ Six intervention villages were paired with six control villages. The intervention included training of clinic staff in syndromic diagnosis and treatment of STDs, provision of necessary antimicrobial drugs, and dose supervision. After a 2-year period, HIV seroconversion rates were 42% lower in the intervention communities compared to the control communities.

Despite these two successful community level interventions, more recent examples have demonstrated mixed success. In a community level intervention in Masaka, Uganda that used mixed intervention modalities (syndromic management of STDs and/or information, education, counseling [IEC]), only the IEC intervention arm experienced a reduction in HSV-2 seroconversion, while participants in the combined intervention only experienced declines in incidence of syphilis and gonorrhea. No decrease in HIV incidence was observed.²⁸ In the Mema Kwa Vijana study in Mwanza, Tanzania, although knowledge increased and sexual-risk behaviors decreased subsequent to a 4-component intervention consisting of in-school sexual and reproductive health education, enhanced reproductive health services for youth, condom distribution, and community activities, there were no significant reductions in HIV or HSV-2 seroincidence, STDs, or pregnancy outcomes in communities receiving the intervention.⁶⁰ Similarly, another multicomponent intervention in Manicaland, Zimbabwe (community based peer education, free condom distribution, income generating projects, clinic-based STD treatment and counseling services) did not reduce population level HIV-1 incidence or STD symptoms, despite reducing HIV-1 incidence in the immediate male target group.⁶¹

The strengths of these community-level interventions are similar to those that result from targeting core groups of sex workers. It is easier to change social norms when multiple individuals are targeted at once. However, transmission dynamics at the community level are complex and more work remains to be done to design multicomponent community-level interventions that are consistently successful.

■ POPULATION-BASED INTERVENTIONS

As with group or community-level interventions, changing social norms may also be a goal of interventions targeting entire societies. Programs that operate at this level may include structural mechanisms to restrict risky behaviors and encourage healthy ones. Mechanisms of change employed may include use of mass media for health education, modifications in the environment, institution of laws or regulations, taxation of alcoholic beverages, service delivery (clinical guidelines for HIV or chlamydia screening), or large-scale vaccination programs. Examples have included legalizing needle exchanges, outlawing bath houses or closing brothels, providing routine selective screening and treatment for STDs, mandating 100% condom use in brothels, and providing training and economic opportunities for women. The Thai condom promotion distribution programs described earlier used a structural mechanism of change, but targeted a core group rather than the whole population even though the whole population might benefit from the intervention.⁵⁴

In the HIV-control program in Cuba, government regulations resulted in a ban on all imported blood and blood

derivatives; enforced widespread screening of travelers, blood donors, pregnant women with STDs, prisoners, and individuals identified in certain neighborhoods where infection rates were prevalent; imposed quarantine of infected individuals; and recommended abortions among HIV-infected pregnant women.⁶² Although this program has not been objectively evaluated by an external group, infection rates remain low, and unlike many of its Caribbean neighbors, Cuba does not seem to have a major HIV epidemic. On the other hand, it has been argued that segregation of high-risk individuals away from the rest of the population could accelerate the spread of infection within the high-risk group so that occasional contact with others outside the group through so-called “bridge populations” could continue to spread infection.⁴

Although vaccination can be considered an individual level intervention because it is given to unique individuals and confers individual-level protection, widespread vaccination also confers substantial protection on a population level in the form of herd immunity. Perhaps one of the most exciting recent advances in STD prevention has been the successful development of a highly efficacious vaccine against HPV.^{63–65} These vaccines protect not only against acquisition of HPV but also against progression to precancerous lesions.⁶⁶ The vaccines are just now being implemented and hold tremendous promise not only for preventing individual infections but also for reducing transmission overall on a population level.

One strength of population-level programs is that the cost of strategies employing use of mass media may be lower than the cost of individual and group outreach. In addition, the potential for social stigma could be avoided if universal prevention strategies are employed, even though some individuals may be more affected by the strategy than others. For example, outlawing bathhouses applies to everyone, although frequent patrons may be more likely to feel the effects of this change. Although Rose and others have argued that prevention must be universal so that shifts in the distribution of risk can be made for the entire population, many individuals not at risk are targeted.¹ Such programs may curtail individual rights and privileges to benefit the health of the population.

■ NETWORK ANALYSES

Prevention approaches that seek to identify social and sexual networks to characterize patterns of mixing between individuals combine considerations of individual, group, and population approaches. Both the overall rate and the extent of spread of STDs/HIV depend on the structure of sexual networks.⁶⁷ Frequent rates of concurrent sexual interactions among people lead to rapid rates of STD/HIV spread. Greater numbers of sexual linkages among subgroups can lead to extensive dissemination of infection between subgroups and throughout the population. Conversely, if a population is

divided into isolated subpopulations with low rates of sexual interaction within each, STDs entering the population tend to be confined primarily to one subpopulation and to spread slowly in that subpopulation.⁶⁸

The sexual networks that fuel the spread of STDs do not tend to overlap greatly with the social networks that channel the spread of prevention information and preventive behaviors. Sexual networks that spread STD are most frequently located in subpopulations at the lowest levels (tails) of the education, income, power, and prestige distributions, whereas networks responsive to prevention efforts are generally located within subpopulations at the highest levels of these distributions. In addition, although sex partners are usually chosen from among those with whom social linkages already exist, particular types of sexual linkage, for example, commercial or casual sex, take place between individuals less likely to be socially linked to each other.⁶⁹ Nevertheless, in a unique approach using social networks to disseminate prevention and risk reduction messages in Bulgaria, social networks of Roma men randomized to the intervention (counseling by a trained network leader) had significantly lower prevalence of unprotected intercourse at follow-up when compared to control networks.⁷⁰

Just as the structure of sexual networks and sexual-mixing patterns determine routes of transmission of STDs, the structure of social networks and social-mixing patterns determine routes of the diffusion of attitudes, beliefs, life styles, and behavior patterns through a society.^{71,72} Social networks tend to be more open than sexual networks and are marked by higher rates of interchange within population subgroups, greater numbers of social contacts, and greater numbers of linkages across population subgroups. Thus, attitudes, beliefs, and behavior patterns, including preventive patterns, would spread more rapidly and extensively throughout the population. Moreover, the responsiveness of individuals to prevention information and interventions varies across population subgroups. For example, population subgroups marked by higher levels of education would be more accessible to prevention programs and more responsive to prevention messages. Similarly, population subgroups with lower prevalences of risk behaviors may respond more effectively to prevention efforts owing to their higher levels of education and their health-seeking orientation.⁷² In summary, prevention efforts first reach and affect subpopulations that are least likely to contain sexual networks that spread STD. Furthermore, the nature of social networks within subpopulations having high STD rates may hinder diffusion of prevention information and interventions into the sexual networks within these subpopulations.

Although health education and health promotion interventions utilize the social network concept, partner notification, mentioned previously under couple-based interventions (where infected individuals name sexual partners and these

partners are then identified, tested, treated, and counseled), is a public health intervention based on the sexual network notion. Attempts have been made to identify more extensive sexual networks that trace partners of partners and so on. The technique known as “cluster contact tracing,” in which serologic screening for syphilis was extended to social contacts of persons with infectious syphilis, was an interesting experiment in extending disease control efforts from sexual networks to social networks. However, behavioral and other prevention interventions that target this more complex type of network have been given little attention. Probably the closest approximation is those interventions based on social diffusion where few individuals who are integrally bound into the community initiate and model social change, described in community-based interventions.⁵¹ Such diffusion models are theoretically capable of changing social norms throughout the community while identifying and targeting sexual networks. This is clearly an area that merits additional research.

CONCLUSION

The acknowledgment of differences within the population with respect to infection status, risk behaviors, incurring of intangible and financial costs, as well as receipt of benefits, has led to the formulation of a series of questions related to the political economy of STD epidemiology and prevention and related issues of policy. Who is at risk? Should prevention strategies be targeted or universal? Who should pay for the intervention? In this chapter, we have highlighted only a few examples of successful interventions applied using targets and levels of intervention at various units of analysis. Our goal was to illustrate individual, group, and population perspectives on STD/HIV prevention. Glib references to “individual level” or “population-level” interventions, without distinguishing between the target of the intervention, the beneficiary of the intervention, and the mechanism and agent or vehicle of the intervention, has often led to confusion and poorly conceived design and evaluation of STD/HIV interventions. We do not advocate any one approach over another but suggest that STD/HIV is a multi-level problem. In the same way that risk factors can be defined on multiple levels, interventions must be designed and evaluated appropriately for multiple levels.

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STD/HIV Prevention Programs in Developed Countries

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INTRODUCTION AND DEFINITIONS

STD prevention programs emerged in developed countries in the early twentieth century. Initial efforts were largely focused on “social hygiene,” emphasizing the dangers of prostitution and relying on education and structural approaches to discourage it.^{1,2} Subsequent strategies, particularly focused on syphilis, emphasized screening, treatment, partner referral, and public education, which were the mainstay of the first national STD program in the United States beginning in 1938.^{2,3} The discovery of penicillin and its increased use in the 1940s reinforced an increasingly biomedical approach to STD prevention, which expanded to include screening and treatment for gonorrhea in the 1960–1970s and chlamydia in the 1990s. The advent of HIV/AIDS in the 1980s dramatically altered the balance between secondary prevention (efforts to diagnose and treat infection to prevent complications and ongoing transmission) and primary prevention (behavioral approaches to prevent initial acquisition of infection). The high mortality associated with AIDS, its prominent political profile, and the varying routes of HIV transmission (parenteral as well as sexual) have often led to a separation of STD and HIV prevention program. However, particularly with the advent of highly active antiretroviral therapy (HAART), STD and HIV prevention approaches are becoming more similar, and there is an increasing recognition that coordination of HIV and STD prevention activities can provide important synergies.^{4,5}

Historically, STD prevention programs have focused on curable bacterial infections, although there is a growing programmatic interest in the non-HIV viral STDs of genital herpes simplex virus (HSV), genital human papillomavirus (HPV), and hepatitis B virus (HBV) infection, given the large population burden and increasing possibility of specific prevention activities (e.g., diagnostic tests, suppressive therapy, and vaccines).^{6–8} HIV prevention programs have also evolved over time, moving from an initial emphasis on preventing acquisition of infection among the uninfected (e.g., blood screening, reduction of risky sexual and needle use behavior,

and condom promotion) to a greater focus on prevention of transmission from those already infected (e.g., enhanced case finding, treatment of HIV-infected pregnant women, risk reduction activities, and STD screening promoted as part of HIV care).⁹

This chapter begins with an overview of key concepts that influence the design of STD/HIV prevention programs and then reviews essential program components in the areas of surveillance, prevention interventions, and program support. While there is generally consensus about the broad domains of activity needed for effective STD/HIV prevention programs, the conceptualization of what constitutes essential program components has varied slightly.^{5,10,11} This chapter considers essential components of STD/HIV prevention programs in three key domains: surveillance, four essential interventions (clinical, laboratory, partner management, and individual and community behavioral intervention services), and four program support components (program leadership and management, professional training, monitoring and evaluation, and research). Although there are variations in the specifics of STD/HIV programs by country, the background concepts are applicable to all developed countries. Specific examples in this chapter will be drawn largely from the United States and the United Kingdom, with illustrative examples from other developed nations.

OVERVIEW OF KEY CONCEPTS FOR STD/HIV PREVENTION PROGRAMS

■ INDIVIDUAL VERSUS POPULATION GOALS

STD/HIV prevention programs focus on two levels of prevention outcome: that of the individual and that of the larger population. Individuals benefit from activities that prevent acquisition of infection, alleviate symptoms, and reduce complications, but for the general population, the primary goal of prevention is to reduce ongoing transmission and thus overall population prevalence and health impact.^{11,12} Since most activities that prevent acquisition of infection or

lead to detection and treatment of curable infections also prevent subsequent transmission, they provide population as well as individual impact. The relative value of individual versus population benefit will vary by the subpopulation. Specifically, prevention programs targeted at subpopulations more likely to be involved in ongoing transmission, such as “core groups” (discussed below), can be more important for population benefit than those targeted at the general population.¹³

■ DETERMINANTS OF STD/HIV TRANSMISSION AND THEIR IMPACT

Over the past 20 years, a key concept in understanding STD/HIV epidemiology and possible strategies for prevention at the population level is a transmission dynamics model described by May and Anderson.¹⁴ This model defines the average number of new infections that an infected individual generates, or the reproductive rate in a population (R_0), as a function of three parameters—the average probability of transmission per sexual contact between susceptible and infected individuals (B), the average number of sexual partnerships formed per unit time between susceptible and infected persons (c), and the duration of infectiousness (D)—with $R_0 = BcD$. When R_0 exceeds one in a population, infection spreads and population incidence and prevalence increase. Likewise, if R_0 is maintained below 1, incidence and prevalence decrease. Thus, an increase in any of the three parameters will increase R_0 and population incidence and prevalence, while a decrease in any will reduce both parameters.^{15,16}

STD/HIV prevention interventions achieve population impact by reducing one or more of these three transmission determinants, and examples of the impact of different interventions on each are outlined in Table 90-1. Reducing the duration of infectiousness by enhancing detection and treatment of infected persons has been the mainstay of programs for the prevention and control of bacterial STDs. These measures include approaches to enhance access to and utilization of health care, to improve case finding, and to increase likelihood and timeliness of treatment following clinical contact.

The prevention interventions that reduce transmission efficiency (B) and the number of partnerships exposing susceptible to infected partners (c) are important for control of all STDs, but are critical for HIV and other viral STDs for which curative therapy is not available. The primary approaches to reducing transmission efficiency have been behavioral—health promotion efforts to increase the use of condoms and to reduce practices with relatively high STD/HIV transmission risk such as anal sex and needle sharing. In addition, a number of biomedical approaches to reduce transmission efficiency have been or are under evaluation. For example, many STDs serve as cofactors for HIV transmission by an increasing susceptibility and/or

infectiousness.¹⁷ There is substantial evidence that control of bacterial STDs can reduce HIV transmission at the population level when STD prevalence is high and HIV prevalence is relatively low,^{5,18,19} and suppression of genital HSV-2 infection with antiviral therapy may also reduce HIV transmission.²⁰ Finally, immunization with effective vaccines can dramatically reduce susceptibility.

Approaches to reduce the rate of exposure of susceptible to infected partners can potentially impact the broadest array of infections. However, they can be difficult to implement effectively. Programs encouraging delayed onset of sexual activity have been widely promoted in the United States during the last 10 years. Although as yet incompletely evaluated, there are indications that promoting abstinence in adolescents without providing education about other prevention strategies such as condom use and STD testing may not reduce STD rates.^{21–24} The benefit of reducing sex partner number is supported by observations about the association of most STDs with number of recent and lifetime partners, the impact of concurrent sex partners on amplifying the transmission at the population level,²⁵ and observations from several countries with successful reductions in HIV prevalence.²⁶ Promoting the concept of avoiding partners who may be infected with an STD is likewise a plausible approach, although one that may not be practical in settings of unequal power, such as those experienced by many women. Finally, for HIV infection, reduction in exposure of susceptible to infected partners may be enhanced through intentional selection of partners of the same HIV serostatus (i.e., serosorting).²⁷

■ CORE GROUPS AND SEXUAL NETWORKS

A related key concept in STD/HIV epidemiology and control is that of the “core group,” who are persons in a small subset of the population with multiple partners who maintain endemic foci of STDs.^{28–30} Core groups have been defined as those with a high enough rate of sex partner change to maintain $R_0 > 1$. Their characteristics will vary by specific STD based on the efficiency of transmission and duration of infection of the STD in question. When B and D are relatively low, c must be relatively high to maintain disease transmission, resulting in a smaller core group. The latter circumstance occurs when effective STD/HIV prevention programs are in place, although this smaller core group may become increasingly hard to reach as it shrinks.³¹ Because of the importance of the core group in sustaining transmission, targeting prevention efforts at them is theoretically more cost-effective than broader programs.³² However, defining strategies that can practically access core groups is difficult, and for many persons, inclusion in a core group is dynamic, changing over time.²⁸

Because of the communicable nature of STDs, including HIV infection, the concept of “population” is important not

Table 90-1. Impact of STD/HIV Prevention Program Activities on Determinants of Transmission^a

Determinant of Transmission	Examples of STD/HIV Prevention Interventions
Efficiency of transmission between infected and susceptible person (<i>B</i>)	<p>Immunization</p> <p>Use of physical or chemical barriers with partners at risk of infection (e.g., male or female condoms, possibly topical microbicides)</p> <p>Reduction of risky sexual practices (e.g., anal sex) or needle-sharing</p> <p>Reduction of cofactors that may enhance susceptibility or infectiousness (e.g., treatment of bacterial STI and possibly suppression of HSV-2 shedding to reduce HIV acquisition or transmission)</p> <p>Suppressive therapy of chronic viral infections to reduce viral burden (e.g., for HIV, HSV-2)</p> <p>Postexposure prophylaxis after known or likely exposure to STI/HIV (e.g., antimicrobials, antivirals, immunization, immune serum globulin; possibly preexposure antiretroviral prophylaxis)</p> <p>Reduction of sexual exposure during times of likely increased infectivity (e.g., outbreaks of genital herpes, acute and advanced HIV infection)</p> <p>Male circumcision to reduce susceptibility (e.g., HIV, HSV-2)</p>
Average rate at which new sexual partners are acquired (<i>c</i>)	<p>Promotion of abstinence and delay of sexual debut among young people as part of a comprehensive prevention strategy.</p> <p>Promotion of monogamy and reduced rates of partner change</p> <p>Promotion of messages about potentially safer partners (e.g., those with fewer prior partners, those known to have been recently tested) or avoidance of partners in higher risk settings (e.g., bathhouses, brothels)</p> <p>Promotion of selection of partners known to be concordant for chronic viral infections (e.g., HIV)</p>
Duration of infectivity (<i>D</i>)	<p>Detection of infection through screening, diagnosis, and partner evaluation</p> <p>Accessible, high-quality health services for testing and treatment</p> <p>Evaluation and treatment of exposed partners</p> <p>Health promotion activities to enhance regular care-seeking for screening and early diagnosis/treatment of symptomatic persons</p> <p>Development and availability of simple, effective, inexpensive treatments for cure or suppression of infection</p> <p>Strategies to increase likelihood of treatment following clinical or public health contact (e.g., syndromic management, rapid point of care tests, systems to rapidly communicate test results and locate infected but untreated persons, possibly mass treatment of selected populations)</p> <p>Laboratory monitoring of antimicrobial resistance</p>

^aModified from St. Louis M, Holmes H. Conceptual Framework for STD/HIV Prevention and Control. In: Holmes K, Mardh PA, Sparling P, et al., eds. *Sexually Transmitted Diseases*, 3rd edn. New York: McGraw-Hill, 1999, pp. 1239–1253.

only as a level at which to measure public health impact, but also because it contains structures and networks that influence likelihood of transmission.^{13,33,34} Sexual networks are groups of individuals directly or indirectly sexually connected to each other. The location of an individual in such a network can be as or more important than personal sexual behavior because it affects the prevalence of infection in those to whom the person is directly sexually connected.

PHASE-SPECIFIC TOPOLOGY OF STI EPIDEMICS

The phase-specific topology construct provides a useful theoretical framework for understanding the evolution of STD epidemics over time,³⁵ especially when applied to localized outbreaks of bacterial STDs. The construct describes STD/HIV epidemics as evolving through four main phases characterized by changes in the subpopulations in which STDs/HIV are concentrated (Fig. 90-1), starting with a growth phase followed by hyperendemic, decline, and endemic phases. This progression is affected by sexual behavior, as manifested in the patterns of sexual partnerships and networks, as well as effectiveness of prevention services and related health-seeking behaviors. The construct also includes two types of sexual networks (spread and mainte-

nance) that are important in facilitating population spread of STD/HIV. The spread networks or core groups are generally dense and characterized by high rates of partner change and concurrency (e.g., commercial sex workers [CSW], some MSM core groups). They enhance STD/HIV transmission both within networks as well as between networks due to bridge populations (e.g., bisexual men) or bridging behaviors (e.g., new sex partner acquisition while on holiday). The maintenance networks comprise individuals or partnerships characterized by lower prevalence of risk behaviors and lower interconnectedness. However, given their greater prevalence in the population, the maintenance networks are a key determinant of continued endemic disease propagation.

MULTILEVEL DETERMINANTS AND SOCIAL CONTEXT

Variance in the evolution of STD/HIV epidemics in different populations has increasingly highlighted the complex impact of societal determinants on disease transmission.^{36,37} For example, the prevalence of an individual risk behavior (such as unprotected sex) may generate and, in turn, be influenced by social norms (a group-level factor) regarding its acceptability, which also reflects demographic and social trends and the delivery and effectiveness of prevention

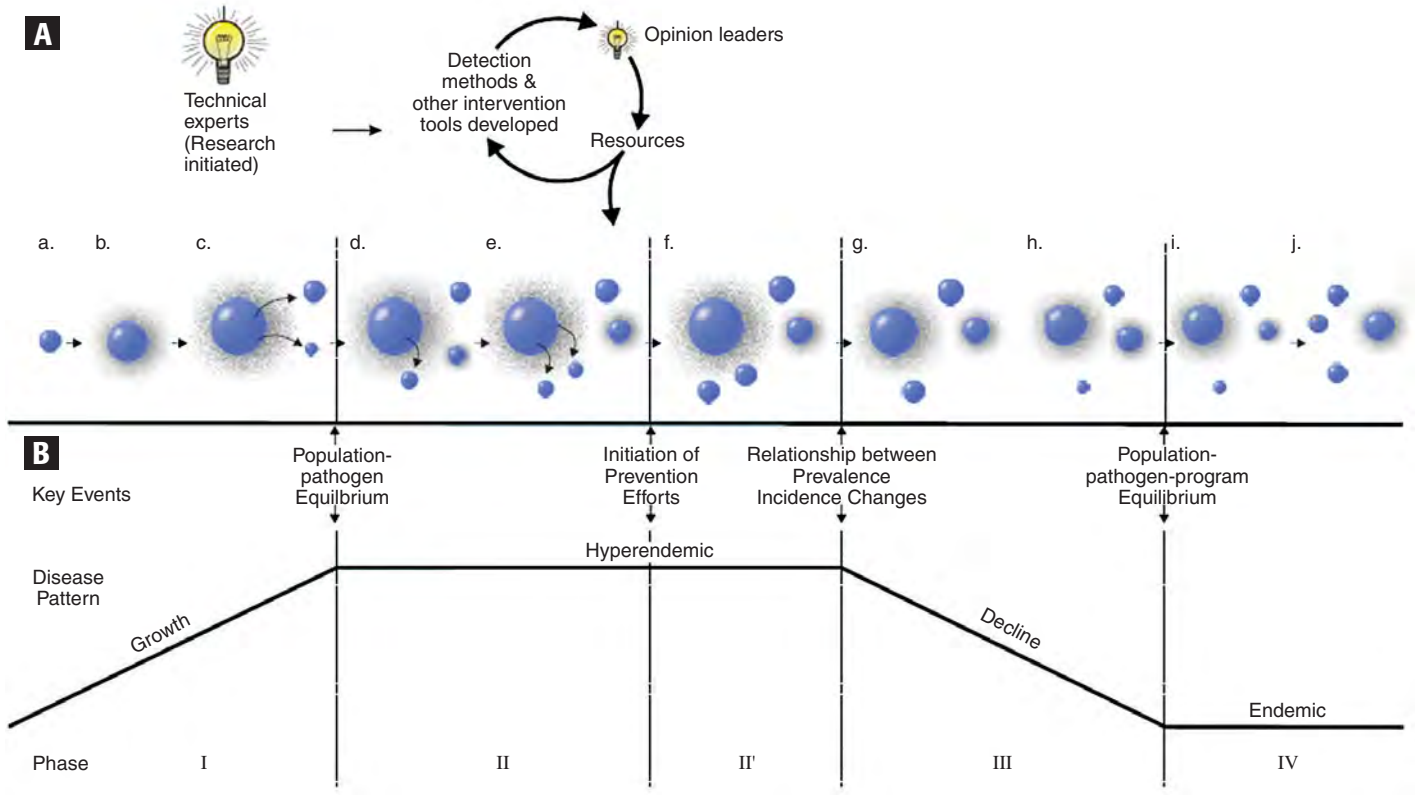


FIGURE 90-1. Dynamic trajectory of phases of STD epidemics, indicating complementary changes over time from perspective of sexual networks and disease patterns. **A.** Trajectory from perspective of subpopulations in which spread and maintenance sexual networks are located, emphasizing importance of different types of sexual networks and of public health interventions. “Dense spheres” indicate subpopulations with spread networks, “mottled halos” represent larger subpopulations containing maintenance networks, and “arrows” represent bridge populations. **B.** Trajectory from perspective of disease patterns, reflecting population-pathogen relationship.

interventions. This complex ecology of disease transmission, in turn, influences prevention by demanding that comprehensive HIV/STD interventions take into account the occurrence and interactions of factors operating at numerous levels within a given society.^{33,38} At the *individual level*, many factors affect STD/HIV transmission, including age, presence of other STIs, circumcision status, nutrition, immunogenetic factors, type of exposure, and, most critically, having sex with an infected partner. At the *partnership level*, factors affecting transmission include type of partnership and societal contexts (e.g., social norms and expectations, gender roles). At the *sexual network level*, demographic, epidemiological, social, and political contexts directly influence the network structure and dynamics and, in turn, are influenced by them.^{12,39,40} Political conflict and economic and social disruption may all result in the breakdown and formation of novel sexual and social networks.¹²

■ SELECTING PREVENTION PRIORITIES

Given the large number of STDs and the growing range of prevention options, programs must determine which infections to target and which activities to prioritize. The criteria for selecting priorities include the following: (1) relative importance of specific STDs in terms of population burden and cost; (2) potential effectiveness and cost-effectiveness of interventions in preventing transmission and complications; (3) intervention feasibility and acceptance by providers and target populations; (4) potential for alignment with other prevention programs.^{11,16} While some interventions can be effective against a variety of STDs, most are infection-specific, based on biomedical tools such as diagnostic tests, treatments, and vaccines. Prevention interventions must be acceptable to both providers and target populations if they are to achieve broad coverage and be sustainable.^{16,41} For providers, feasibility can be impeded by clinician discomfort with an intervention, cumbersome logistics or limited resources. For patients, acceptability is affected by quality and cost of services⁴² and by misunderstanding of risk or perception of stigma in seeking STD services.⁵

As an example of the situation in many developed nations, [Table 90-2](#) outlines recent estimates of the burden of infection, the phase of the epidemic, and key prevention strategies in the United States. Prevention activities have primarily focused on curable bacterial STDs, HIV, and HBV. The target of the longest-standing prevention programs, syphilis, has been at historically low levels for 10 years and efforts are now focused on elimination. Gonorrhea is also at historically low levels, albeit at an intermediate level of endemicity with wide population variability by race and ethnicity, and prevention efforts are increasingly focused on reducing these disparities.⁴³ In contrast, after a relatively shorter period of national prevention effort, chlamydia remains hyperendemic and broadly distributed in the population. Twenty-five years into

the AIDS epidemic, HIV incidence has fallen from peak levels, but now plateaued, prompting new efforts at intensive case finding and prevention case management among those HIV-infected.⁹ HBV has been dramatically reduced as a result of widespread vaccination in children, although rates of infection remain high among at-risk adults for whom there are no systematic immunization programs.⁶ Prevention efforts for HPV have largely focused on preventing complications, with impressive reductions in cervical cancer after 50 years of Pap smear screening programs.⁸ The advent of an effective HPV vaccine provides an opportunity to prevent other manifestations of infection, such as genital warts and abnormal Pap smears, as well as further reduce cervical cancer.^{44,45}

Finally, although prevention strategies are typically assessed as individual interventions,⁴⁶ they are usually implemented programmatically as part of a package. As prevention options grow, it is vital to understand how most effectively to implement and evaluate such packages, especially when they operate at multiple levels.³³ Sometimes this involves program trade-offs. For example, resource-constrained programs in the United States responding to outbreaks of syphilis in MSM are attempting to balance the relative value of provider education, health communication to affected communities, outreach testing, and partner services activities.^{47,48} Similarly, U.S. HIV prevention programs are balancing prevention approaches (e.g., increased testing and condom promotion) in high-risk populations such as MSM and African Americans, with those focused on persons known to be HIV-infected (e.g., partner services, serostatus disclosure, and STD testing).⁹

■ INTEGRATION OF PREVENTION SERVICES

As noted above, one of the criteria for prioritizing various STD/HIV prevention activities is the degree of alignment with other public health programs. Such alignment can enhance program synergies by improving cost-effectiveness and feasibility of implementation and can range from selected attempts to integrate services at the patient level (e.g., STD screening in family planning clinics and contraceptive care offered in STD clinics) to full consolidation of public health programs.⁴ Probably the most important focus of recent integration efforts is that between STD and HIV prevention programs, which have been largely separate for the past 20 years in the United States. There is increasing attention to potential programmatic synergies in a variety of areas including surveillance, clinical services (e.g., routine HIV testing in STD clinics and STD testing in HIV care settings), partner management, education and health promotion, and community partnerships.⁴ An equally important partnership is that between STD prevention and reproductive health,⁵ which led to the initiation of a national chlamydia prevention program in the United States in the early 1990s, with an emphasis on screening in both family

Table 90-2. Health and Economic Impact of STDs in the United States

STD	Reported 2005 Incidence	Estimated (2000 Incidence/Prevalence) ^a	Estimated Annual Direct Cost (2000 \$ in Millions) ^b	Major Sequelae in the United States	Phase/Focality	Key Prevention Strategy ^c
Bacterial and Protozoal						
Chancroid	17 ^d	NA ^e	N/A	HIV transmission	Low endemic/High	Typical presentation, curative therapy
Syphilis	32,499 ^d	50,000–70,000/NA	\$16.5	Congenital infection and still-birth, neurosyphilis, HIV transmission	Low endemic/High	Serologic Testing for screening and diagnosis; curative therapy
Gonorrhea	339,593 ^d	718,000/NA	\$128	Infertility and ectopic pregnancy, congenital infection, HIV transmission	Intermediate endemic/Medium	Testing for screening and diagnosis; curative therapy
Chlamydia	976,445 ^d	2.8 million/ 1.9 million	\$464	Infertility and ectopic pregnancy, congenital infection and low birth weight, HIV transmission	Hyperendemic/ Low	Testing for screening and diagnosis; curative therapy
Trichomoniasis NNN ^f		7.4 million/NA	\$133	Low birth weight/prematurity, HIV transmission	Hyperendemic/ Low	Testing for diagnosis, curative therapy
Viral						
HIV	35,537 ^g	40,000/560,000	\$5,994	Opportunistic infections and malignancies	Low endemic/High	Testing for screening and diagnosis; risk reduction counseling; suppressive antiviral therapy
HBV	5,494 ^h	81,000/417,000	\$31.5	Chronic hepatitis, cirrhosis, liver cancer	Decline	Immunization
HSV-2	NNN	1.6 million/ 45 million	\$732	Congenital infection, HIV transmission	Hyperendemic/ Low	Testing for diagnosis; suppressive antiviral therapy
HPV	NNN	6.2 m/≥20 million	\$3,891	Anogenital cancer	Hyperendemic/ Low	Clinical diagnosis and local therapy for genital warts; cervical cancer prevention by Pap and HPV testing, immunization;

^aRef. 204.^bRef. 205.^cAdjunctive strategies include partner management services and risk reduction counseling for selected conditions.^d2005 STD Surveillance Report.⁴³^eNA, not available.^fNNN, not nationally notifiable.^gTotal from 38 states with confidential names-based HIV reporting in 2005.²⁰²^hDivision of Viral Hepatitis, CDC.²⁰³

planning and STD clinics.⁴⁹ In addition, with the growing possibility of vaccines for a variety of STDs, there is increasing recognition of the importance of linking STD and immunization programs, especially as the latter involve adolescents and adults. Correctional health care, including both jails and prisons, is another important setting for STD/HIV prevention activities, with particular focuses on screening for chlamydia⁵⁰ and syphilis,⁵¹ and HBV immunization.⁶

Integrating prevention services into existing programs with different health goals can present challenges. Although integrated prevention services enhance convenience and thus coverage for clients, they can require additional resources to implement.⁵⁶ Other problems may include the potential for diffusion of expertise or overshadowing of programs dealing with less visible priorities (e.g., chlamydia or syphilis prevention) by those focusing on more visible ones (e.g., HIV prevention and care).⁵² In spite of these issues, coordination and integration of programmatic activities remains a high priority for STD/HIV prevention.

ESSENTIAL PROGRAM COMPONENTS

Given the issues raised by the concepts outlined above, we next consider the key attributes of each of the essential components of effective STD/HIV prevention programs.

■ SURVEILLANCE

Accurate surveillance is the cornerstone of effective public health and is critical for optimal performance of other program components. Public health surveillance is defined as the systematic and ongoing collection, analysis, interpretation, and dissemination of health-outcome-specific information for the purpose of planning, implementing, and evaluating public health practice.^{53,54} Such data allow public health staff to develop prevention strategies, prioritize resources, and determine health impact of programs. They also allow the recognition of outbreaks of new or reemerging health problems and thus are essential for effective outbreak responses. The legal authority for surveillance activities is based on laws and regulations of the relevant jurisdiction. In the United States, such authority resides at the level of the individual states, although other organizations, such as the CDC, play important roles in developing surveillance approaches and case definitions and in interpreting and disseminating data. Because of the stigmatizing nature of STD/HIV,⁵³ the confidentiality relevant to all personal health records is especially critical for surveillance of these diseases and is generally required by statute.

In the United States, a variety of surveillance approaches are used to monitor STDs and HIV/AIDS. These include case reporting (disease registries), prevalence monitoring, sentinel surveillance, and population-based surveys. In addition,

behavioral and health services surveillance can provide useful supplemental information.^{53,55} Each surveillance approach has strengths and limitations which must be considered when interpreting data, and because they are complementary, multiple approaches are often used to better “triangulate” a problem.⁵⁵

Case reporting provides a measure of new cases of disease per unit of time. It is the core surveillance activity for most diseases and can help assess the overall burden of disease, monitor trends over time, and detect the emergence of outbreaks. In the United States, STDs reportable in all states include gonorrhea, chlamydia, chancroid, syphilis, hepatitis B, and AIDS. Other STDs such as genital and neonatal herpes, genital warts, and pelvic inflammatory disease (PID) are reportable in a few states.⁵⁵ While reporting of AIDS cases has been a national priority for many years, reporting of HIV infection has been more controversial, and has only recently become routine in all states, limiting national trend data. Case reporting generally relies on voluntary reporting by both providers and laboratories; the latter is of growing importance because of the capacity to rapidly and accurately transfer computerized data. Completeness of reporting affects the value of surveillance data, and it is impacted by both underdetection and underreporting. Underdetection results from both empiric treatment of STD syndromes or sexual partners without diagnostic testing, as well as the asymptomatic nature of many STDs, which never come to clinical attention. For example, the dramatic rise in the rate of reported chlamydia infection in the United States and the threefold higher rate of infection in women than men is largely due to increased screening of asymptomatic persons, especially women.⁴³ For those infections with confirmed diagnoses, estimates of the completeness of reporting range from 64% to 95% for gonorrhea, 55–98% for chlamydia, and 79% for syphilis.^{55–58} Completeness of reporting of AIDS is even higher and is considered to be among the most complete of any notifiable disease.⁵⁹

Prevalence monitoring is used to assess STD/HIV prevalence among defined populations undergoing routine screening. These efforts complement case report data and can provide assessments of disease burden when changes in testing behavior cause spurious increases in reported disease. For example, CDC prevalence monitoring activities for chlamydia among women attending family planning and STD clinics have confirmed that, in contrast to reported cases, prevalence has changed relatively little over the past decade.⁴³ Monitoring of HIV seroprevalence has also been used in routinely screened persons in the United States, such as those entering the Job Corps or military.^{60,61}

Sentinel surveillance refers to the collection of data from small “sentinel” populations, thought to be representative of the larger population, often for outcomes not typically monitored or reported. Sentinel surveillance has been useful in monitoring antimicrobial resistance and in assessing HPV

prevalence in clinic-based populations.⁶² Because the chronic nature of HIV infection makes assessment of new infection difficult, sentinel surveillance using “detuned” serologic tests is playing an increasing role in helping define HIV incidence in high-risk populations.^{63,64}

Finally, *population-based surveys* extend sentinel surveys by conducting surveillance among samples thought to be representative of the general population. A series of assessments of STD/HIV prevalence have been carried out in the United States as part of the National Health and Nutrition Examination Survey, including studies of HSV-2, HPV, chlamydia and gonorrhea, and syphilis.^{62,65–67} While these surveys provide limited behavioral data, they have been essential in determining both disease burden and trends at the population level. Several such surveys have recently documented similar rates of chlamydia in the United States and Europe, with little variation by gender.^{62,68,69}

In Western Europe, surveillance for acute bacterial STDs relies primarily on case reporting from clinicians and/or laboratories. Case reporting is mandatory for gonorrhea and syphilis for all providers in most European Union countries, and for GUM clinics in the U.K. In contrast, for chlamydia, clinician reporting is required only in Sweden, Ireland, and the U.K. (from GUM clinics only), with other countries relying upon laboratory or sentinel case reporting.⁷⁰ Congenital syphilis is reportable in all countries except France and the Netherlands. Reporting of viral STDs (genital herpes and warts) is required in relatively few EU countries at present, similar to the U.S. Prevalence can be monitored in Denmark, Norway, and Sweden (and in Greece for gonorrhea) where reporting of denominator data is routine.⁷⁰

In addition to assessment of morbidity, supplemental behavioral and health services surveillance can provide valuable programmatic insights. *Behavioral surveillance* data can be useful in monitoring prevention program impact and detecting behavioral trends that may affect transmission patterns. In the United States, national surveys collecting data relevant for STD/HIV prevention include the youth risk behavior survey (YRBS), which assesses health-risk behaviors in high-school students, and the national survey of family growth (NSFG), which includes women and men 15–44 years of age in the U.S. household population. A national sexual attitude and lifestyle survey carried out in 1990 and 2000 in the U.K. also provided general population data and showed increases in sexual risk behaviors, including the proportion of MSM.⁷¹ *Health services surveillance* can use administrative data from clinical encounter, laboratory, and pharmacy records to assess provider compliance with prevention guidelines and the population coverage of prevention interventions. Excellent systems are in place in the United States to monitor childhood immunization coverage.⁷² In addition, coverage of annual chlamydia screening in sexually active women younger than 25 years of age has been tracked

through the health plan employer data and information set (HEDIS) measure since 1999.⁷³

■ HIV/STD PREVENTION INTERVENTIONS

The actual impact of STD/HIV prevention programs in providing individual and population health benefit results from application of the four intervention components: clinical services, the closely allied component of laboratory services, partner management services, and health promotion and education services.

Clinical services

Clinical services for STD/HIV prevention include a broad array of diagnostic, treatment, and prevention services. Considered by transmission determinants (Table 90-1), virtually all activities designed to reduce the duration of infectivity are delivered through clinical services, as are the biomedical interventions designed to reduce the efficiency of transmission and the individual counseling interventions focused on both transmission efficiency and exposure of susceptible to infectious partners. Although these services are typically offered in settings such as STD, HIV, family planning, and primary care clinics, screening can be conducted in a variety of nonclinical, outreach settings.

Traditionally, the mainstay of clinical service provision for STDs has been through dedicated specialty settings such as STD clinics in the United States and GUM clinics in the U.K. In other western European countries, dedicated STD clinics also play an important role.⁷⁴ Patients seeking care in STD and GUM clinics generally have lower incomes and greater risk behaviors than the general population.^{75,76} These clinics are often staffed by health-care providers with greater clinical expertise and access to supportive diagnostic and treatment services than other providers and are often publicly funded, offering care that is both confidential and low cost. Both attributes are considered critical in reducing barriers to timely access to care in persons with possible STDs.^{77–79,42} The availability of adequate resources to ensure sufficient clinical capacity is a longstanding issue in STD clinics. A 1995 survey indicated that only 61% could see a new patient on the day of initial request,⁸⁰ and the recent increase in STDs in the U.K. and Europe has created a similar backlog.^{81,82}

In the United States, Program Operation Guidelines published by the CDC in 2001 offer recommendations about core clinical services for STD clinics. They outline clinical management, laboratory support, partner services, and reporting functions expected of such clinics (Table 90-3), as well as a broad array of recommendations regarding clinic accessibility, clinic environment, registration processes, and quality assurance procedures.⁸³ More detailed STD management recommendations for providers are provided in CDC’s regularly updated STD treatment guidelines (see Appendix B).⁸⁴

Table 90-3. Recommended Core STD Clinic Services, CDC Program Operations Guidelines

Range of clinical services	–urine pregnancy test
Accurate diagnosis, treatment of bacterial STD	Mechanism for providing non point-of-care testing
Clinic availability of treatment for other locally prevalent STD	–Gonorrhea: culture or nonculture definitive testing
Provision of condoms and risk reduction counseling	–Chlamydia: nonculture definitive testing
Specific protocols for follow-up/referral of other services if offered (e.g., Pap testing, pregnancy testing)	–Syphilis: quantitative nontreponemal and confirmatory treponemal testing
Specific protocols for referral for related services (e.g., family planning, prenatal care, drug counseling/treatment)	–HIV antibody testing
Collaboration with immunization programs to provide immunization services for HBV	Partner services
HIV prevention: Confidential testing, risk reduction counseling, partner services, referral to care	Protocols specifying conditions and patients to receive partner services
Laboratory support for clinical services	On-site or on-call staff for partner services
On-site certified laboratory	Procedures to assure regular communication, consistent prevention messages, confidential exchange of information between clinical and partner services staff
On-site point-of-care laboratory services	Reporting
–light microscopy for gram stain for detection of white blood cells, intracellular gram negative diplococci	Staff familiarity with applicable STD/HIV reporting and confidentiality statutes
–saline wet mount examination for <i>T. vaginalis</i> , clue cells	Procedures for prompt submission of reports of notifiable diseases
–KOH wet mount for identification of yeast and amine odor (whiff test)	If medical or laboratory records computerized, linkage to electronic morbidity reporting
–nontreponemal antibody rapid test	Clinic protocols for reporting, and referral of suspected sexual assault, child sexual abuse, and domestic assault
–darkfield microscopy for <i>T. pallidum</i>	

Similar guidelines have been developed for Europe (European STD Guidelines 2001).

Although STD and GUM clinics are recognized as a critical safety net for clinical services, such services are increasingly provided in other public and private clinic settings in both the United States and Western Europe.^{43,74,75} For example, in the United States, sites other than STD clinics now report the majority of cases of primary and secondary syphilis (67%), gonorrhea (65%), and chlamydia (76%).⁴³ Much of this care is provided through screening programs in other public clinic settings where STD services can be integrated with other prevention programs. In the United States, the national chlamydia control program has effectively focused on both family planning and STD clinics,⁸⁵ while screening in correctional facilities has played an important role in syphilis elimination activities.⁴⁸ In the U.K., the national chlamydia screening program is centered primarily on non-STD

focused health-care facilities.⁸⁶ However, primary care and other private sector clinicians also play a large role in both the United States and Europe.^{43,74}

Clinical services for HIV prevention include those focused both on persons not known to be infected as well as persons diagnosed with HIV infection. In the United States, publicly-funded HIV counseling and testing sites (CTS) have provided the most visible HIV prevention clinical services infrastructure, although as for STD, most testing occurs in other settings.⁸⁷ Despite a high volume of testing nationally in the United States, the substantial proportion of HIV-infected persons who are diagnosed at an advanced stage of infection or who remain undiagnosed altogether⁸⁸ has increased support for HIV screening. Routine screening of all sexually active persons in health-care settings is considered to be cost-effective^{89,90} and recommendations to enhance screening in a variety of clinical settings have recently been emphasized.^{9,91}

The growing number of persons living with HIV as a result of improved treatment has led to increased focus on preventing transmission from those who are HIV-infected.^{9,92} While HAART reduces blood and genital viral load and, thus probably the efficiency of transmission, treatment is not recommended for all HIV-infected persons⁹³ and even those with undetectable plasma viral loads may still be infectious.⁹² Thus, HIV care providers are advised to consider a variety of other prevention activities for persons in care, including assessment and behavioral interventions for ongoing risk behavior, screening and treatment of STDs, referral for services such as substance abuse treatment, and facilitation of partner management services.^{92,94}

Laboratory services

Laboratory services are a core component of both accurate surveillance and clinical services. Diagnostic tests are critical for early and accurate disease detection and can be used for diagnosis of symptomatic persons, screening of high-risk persons or general populations, and assessment of sexual partners of persons with STDs.¹⁰ Ideally, tests for diagnosis of STD/HIV should be accurate, inexpensive, simple, and rapid. For curable STDs, sensitivity has traditionally been considered a higher priority than specificity, since the risk of failing to diagnose an infection with transmission potential was considered to be greater than the risk of a false positive diagnosis resulting in a short course of unneeded treatment.¹⁰ However, the growing importance of chronic infections, such as HIV and HSV-2, as well as the desire to avoid the distress and stigma of a false-positive diagnosis, underscore the need for high specificity.

Rapid “point-of-care” diagnosis at the time of initial evaluation enhances the ability of early treatment to resolve symptoms and reduce ongoing transmission and also supports prevention counseling and partner management. STD clinics have traditionally emphasized stat labs with both microscopy for rapid detection of gonorrhea and urethritis by gram stain, trichomoniasis by wet mount, and syphilis by darkfield examination, as well as rapid nontreponemal serologic tests⁸³ (Table 90-3). In settings with poor return for follow-up, rapid tests result in a larger proportion of infected persons treated than more sensitive but slower conventional tests.⁹⁵ Rapid HIV antibody tests have recently become available and are increasingly used both to encourage testing and to reduce the problem of patients failing to return for results.⁹⁶ These tests are also simple enough to use in outreach settings where they may be performed by nonlaboratorians, and they can enhance testing of hard-to-reach persons.⁹² Rapid syphilis tests may have a similar value, although are not currently licensed in the United States.^{48,97}

Most laboratory tests for STD/HIV prevention are not point-of-care tests and are performed in conventional laboratory

settings. In the United States, public health laboratories have traditionally played an important role in such testing, although as for clinical care, laboratory testing is increasingly provided by the private sector. Recent surveys in the United States of manufacturers of STD diagnostics and public laboratories^{98,99} indicate that of approximately 26 million chlamydia tests sold in the United States, only 19% were sold to the public laboratories, in contrast to 41% and 23% in 1994 and 2000, respectively. The surveys also documented the growing proportion of testing using the more sensitive NAATs format (57% for chlamydia and 49% for gonorrhea). Appropriate use and selection of laboratory tests remains an ongoing challenge. For example, the most recent survey indicated that many labs still offer non-type-specific HSV serologic tests, which are less reliable than tests that can differentiate HSV-1 and -2.⁹⁹

In addition to screening and clinical management, laboratory testing is essential for monitoring trends in antimicrobial resistance. Such surveillance has been essential in monitoring trends in gonococcal resistance since the 1970s, documenting the emergence of resistance to penicillins, tetracyclines, and more recently fluoroquinolones.⁴³ National surveillance systems exist in many developed countries, such as the gonococcal isolate susceptibility project (GISP)⁴³ in the United States and the European Surveillance of STI (ESSTI) programs in Western Europe.¹⁰⁰ More recently, the recognition of emerging resistance to all classes of antiretrovirals has led to recommendations for susceptibility testing among those failing treatment and consideration of testing at initiation of therapy as well.⁹³

Partner management services

Partner management services, also known as contact tracing or partner notification, is a well-established disease control measure that has long been important for STD control and is now playing a growing role in HIV prevention. Its primary focus is informing sex or drug-injection partners of persons diagnosed with STD/HIV of their exposure and facilitating their testing and treatment.^{101–103} There are two basic approaches to partner management: provider referral and patient-referral.^{101, 103} Provider referral involves an interview of the index patient by a clinician or public health worker to elicit partner names, exposure, and identifying information, followed by confidential notification of partners about their exposure, with referral for examination and treatment. Patient (or self)-referral relies upon the index patient to notify partners, often assisted by written materials from a provider or public health worker. Contract- or conditional-referral is a hybrid approach in which providers notify partners if patient-referral has not been completed within a specified timeframe. For patients with multiple partners, these approaches can be combined. For all approaches, the voluntary participation of the index patient and strict adherence to confidentiality are essential.

The impact of partner management is most commonly measured as the number of new cases of STD diagnosed and treated per index patient interviewed. A recent review of the effectiveness of partner management reported a similar yield for syphilis, gonorrhea, and chlamydia, with approximately 0.22–0.25 infected partners treated for every index case interviewed.¹⁰² Not surprisingly, patient referral has a lower yield than provider referral.^{102,104} Assessing the impact of partner services on disease transmission and population prevalence has been challenging, although several studies have reported temporal associations of declining gonorrhea incidence with intensified partner management efforts,^{105–107} and modeling studies suggest that for chlamydia, partner treatment can enhance the benefit of screening in reducing prevalence.¹⁰⁸

In the United States, partner management has been an essential element of syphilis control since the 1940s and has also been recommended and used for the other curable STDs. The STD program in each jurisdiction prioritizes the STDs for which partner management will be provided, with providers encouraged to advise patient referral for other STDs.¹⁰¹ Questions have been raised in recent years about the population coverage provided by partner management services. A recent national survey of U.S. STD programs indicated that provider referral by public health staff was conducted for 89% of syphilis cases, but only for 17% of gonorrhea cases and for 12% of chlamydia cases.¹⁰⁹ This situation has promoted interest in alternative approaches. One such promising strategy is expedited partner therapy, in which partners are provided treatment without an examination, often via oral medications delivered by the index patient. This strategy can be effective in preventing re-infection with gonorrhea and chlamydia,^{84, 110–112} and its greater cost-effectiveness¹¹³ could increase population coverage and reduce disease prevalence.¹¹⁴

Partner management for HIV infection^{84,107,110} has been more controversial because of concerns over confidentiality, heightened by fear of HIV-associated stigma.^{102,103,115} Thus, although long-recommended as an important component of HIV prevention,¹¹⁶ U.S. surveys indicate that provider referral is offered to only 32–52% of newly diagnosed patients.^{109,117} The increased focus on prevention for HIV-infected persons has led to a renewed emphasis on partner management for HIV infection.⁹ Recent reviews have documented both high yield of provider referral, with 80% of named partners notifiable and 21% of those tested found to be HIV-positive,¹¹⁸ as well as high client acceptance (59–82%).¹¹⁵

In Europe, although partner management has been a component of STD control in some countries since the early 1900s, there is a considerable variability at present.¹¹⁹ Partner notification is compulsory for notifiable STDs in a few countries such as Norway and Sweden. In others, partner management is voluntary, with variable practices and degrees of emphasis in national guidelines. As in the United States, the primary focus is on the bacterial STDs, although services are

offered for genital HSV and HPV in some countries. Most countries use patient-referral but provider referral is used in some settings in Norway, Sweden, Finland, Ireland, and the U.K. Expedited partner therapy is used in many countries, although only in a small proportion of cases.

Individual and community behavioral intervention services

Individual-focused interventions. Individual-focused behavioral interventions aim to change behavior at the individual level by providing knowledge or attempting to alter beliefs, attitudes, norms, motivation, or skills.^{120,121} Examples of individual-focused interventions include: outreach and counseling programs for substance-abusing populations; client-centered risk reduction counseling and skills-building programs for women, adolescents, and MSM; and condom distribution programs for CSW and other high risk individuals.^{122–125} Individual-focused interventions are most efficiently delivered in settings where high-risk individuals can be easily accessed.¹²⁰ For example, in Project Respect, risk reduction counseling of STD clinic patients resulted in fewer new STDs at 6 and 12 months of follow-up compared with controls.^{126,127} Interventions targeting adolescents must address the issue that youth often feel relatively invulnerable and thus may choose not to remain sexually abstinent or to use condoms if they do become sexually active.^{120,128} Nevertheless, several individual-focused interventions have reported significant impact on adolescent sexual risk behaviors.^{125,129,130}

Community-focused interventions. The goal of community-focused interventions is to modify social norms, influence social networking opportunities, and reduce barriers to healthy sexual and healthcare-seeking behaviors.^{120,131} They address the behavioral risks of individuals in the context of their personal networks and social environments.¹²⁰ These interventions include capacity building of community organizations, community mobilization, peer outreach, mass media campaigns, and community-based health promotion.^{132–134} An example of a community-focused intervention that was successful in changing social norms among MSM was the Mpowerment Project, which utilized outreach, small groups, and a media campaign,¹³⁵ and which resulted in a reduction in anal intercourse. Another community-focused intervention, the AIDS Community Demonstration Projects, targeted hard-to-reach populations in community settings and resulted in an increased condom use and intention to use bleach kits.^{136,137}

Health communication and health marketing. Health communication and health marketing have become increasingly important for both individual and community behavioral change. Health communication involves design and delivery of messages and strategies based on consumer research to promote the health of individuals and communities.^{132,138}

Its goal is to help shape perceptions regarding health issues, and it is particularly useful when combined with other prevention approaches.¹²⁰ Health marketing is an emerging field that integrates traditional marketing approaches with public health research, theory and practice, and provides a framework for designing health interventions.¹³⁹ It involves creating and delivering health information and interventions by using customer-centered and science-based strategies to promote healthy behaviors. At the *individual level*, effective health communication can help raise awareness of health risks and solutions, provide motivation and skills to reduce these risks, help individuals find support, and affect or reinforce attitudes.¹²⁰ At the *community level*, health communication influence can help the public agenda, advocate for policies and programs, improve delivery of public health and health-care services, and encourage healthy social norms.

■ PROGRAM SUPPORT

Program leadership and management

Effective leadership and management are essential to direct, energize, and integrate all of the other program intervention and support components. Leadership and management are closely related, but focus on different levels of activity. While leadership focuses on broad directions, characterized as “doing the right things,” management deals with an array of operational issues (planning, budgeting, staffing, etc.) involved with “doing things right.”¹⁴⁰ The key aspects of effective leadership and management include partnerships and collaboration, priority setting and planning, and policy development and implementation.

Partnership and collaboration are leadership activities of growing importance. Governmental public health agencies have historically played the primary role in assessing need and assuring delivery of services.¹⁴¹ However, a sole reliance on government to assure public health is increasingly inadequate for several reasons, including limited resources, recognition of the broad array of sectors that can impact health, and increased understanding of the importance of collaborations among individuals, communities, and institutions to improve health.¹⁴² A more robust approach to public health involves a collaborative response by other sectors of society including the health-care delivery system, academia, communities, businesses, and the media.¹²⁶ Participation by community-based organizations in the delivery of prevention services has been a key aspect of HIV prevention in many countries since the mid-1980s, and is also now playing an important role in syphilis elimination efforts in the United States.⁴⁸ Another essential partnership has been with professional organizations and the health-care delivery sector in support of the U.S. national chlamydia screening program.^{143,144,145} Health

system support will be similarly critical in attempts to expand HIV screening and prevention in HIV-infected persons.

An equally important leadership focus for STD/HIV prevention is priority setting and planning. For example, national planning of HIV prevention has been supplemented over the last decade by a community planning process, involving collaboration between public health and community organizations to tailor plans based on local considerations.¹⁴⁶ In addition, re-assessment of HIV prevention activities following the publication of an IOM report on HIV prevention in 2001¹⁴⁷ led to greater prioritization of screening and prevention in HIV-infected persons.⁹ Likewise, the shift in syphilis epidemiology in the United States, with resurgence in MSM, has put greater priority on awareness campaigns aimed at the MSM community and at providers serving them⁴⁷ and also led to a renewed emphasis on local tailoring of prevention strategies.⁴⁸

Finally, policy development creates an overall architecture for public health programs, and successful policy implementation is the primary driver of long-term public health benefit.¹⁴¹ It is a critical leadership responsibility at all levels of public health practice. Important examples of national STD/HIV prevention policy efforts in the United States include the Congressionally authorized national Infertility Prevention Program,⁸⁵ the National Syphilis Elimination Plan,⁴⁸ and the recent Advancing HIV Prevention initiative, focusing on screening and prevention in care.⁹ A notably comprehensive national policy effort was the National Strategy for Sexual Health and HIV released by the U.K. Department of Health (DOH) in 2001,¹⁴⁸ which broadly frames an approach intended to reduce STD, HIV, and unintended pregnancy. An increasingly critical component of policy development is an effective communication of prevention needs and opportunities to public and private decision-makers. In the United States, key aspects of such effort include activities by groups such as the National Coalition of STD Directors and the American Social Health Association, as well as proactive efforts to communicate policy issues through mass media.¹⁴⁷

Professional training

High quality workforce training is vital for implementation of each of the other essential STD/HIV program components. For public health in general, as the spectrum of responsibilities has grown from a largely biomedical approach to one encompassing new areas of expertise such as behavioral science, communications, and informatics, the range of educational and training needs has similarly broadened.¹⁴² The same is clearly true for STD/HIV prevention training. Given the growing role of nonspecialty clinics in providing STD clinical services, STD management training of primary care providers is a particularly high priority.¹²⁶

In the United States, a core element of such training is provided by government-sponsored training networks, the most

important of which are the AIDS Education and Training Centers (AETCs)¹⁴⁹ and the National Network of STD Prevention Training Centers (NNPTCs).¹⁵⁰ These efforts are supplemented by reproductive health training offered by the Regional Training Centers.¹⁵¹ The AETCs provide training for primary care physicians, reaching over 125,000 participants per year.¹⁵⁰ The NNPTCs offer not only clinical training, but also training in behavioral intervention, partner services, and program management, accessing over 25,000 students per year.¹⁵⁰ The growth of the Internet as a training medium has enhanced possibilities for low cost and easily accessible training. The Internet may be particularly useful in providing “just in time” training and rapid access to guidelines for clinicians who infrequently manage STD/HIV.^{152,152,153} Finally, similar to the need to better integrate STD and HIV prevention program activities, there is a need to coordinate training efforts, both to enhance efficiency and to support the practice of integrated prevention approaches.

In the U.K., the DOH works with the Health Development Agency to develop and disseminate information and evidence for professionals’ need, including good examples of best practices. The DOH also supports continuing professional development, and has included sexual health information in its practice Development Toolkit available for all health visitors and school nurses.¹⁵⁴ Additional training is provided by professional organizations such as the British Association of Sexual Health and HIV and the Society for Sexual Health Advisors.

Monitoring and evaluation

Monitoring and evaluation (M&E) is a key support component for optimal and accountable performance of all other program activities.¹⁵⁵ Its overall purpose is to measure and assess performance in order to more effectively manage program outputs and outcomes. Monitoring describes a continuing function that provides management and main stakeholders of a prevention program with ongoing indications of progress in the achievement of outputs. Evaluation, in contrast, intermittently assesses progress towards and the achievement of outcomes. The objectives of results-oriented M&E of STD/HIV prevention programs are many, but key among them are to enhance organizational learning, ensure informed decisionmaking, and support accountability and organizational redirection.^{155, 156}

At the national level in the United States, STD performance measures have been developed by CDC as part of its commitment to standardized, measurable outcomes of program performance activities.¹⁵⁷ These measures are in alignment with CDC and U.S. Government goals such as those outlined in Healthy People 2010.¹⁵⁸ To ensure quality programs and measure progress, project areas track a set of measures related to specific program components such as timeliness and completeness of case reporting and adequacy of clinical services. Another example of STD M&E activities is the inclusion since

1999 of chlamydia screening as a health plan employer data and information set (HEDIS) measure.⁷³ HEDIS is a set of standardized measures that provides a “report card” on the performance of managed care organizations. HIV prevention program monitoring is conducted by the project evaluation and monitoring system (PEMS),¹⁵⁹ a system jointly developed by CDC and its partners. It consists of a comprehensive set of standardized variables and integrates multiple data sets into one system. Although the uses of automated performance measuring systems are less developed within Europe, mechanisms are in place to ensure accountability of funds and use of data to improve programs. For example, in the U.K., recent development of systems to monitor waiting times in GUM clinics¹⁶⁰ provides an assessment of local clinic capacity and performance in response to the local health needs.

Research

The final support component is research, the impetus for ever-improving, science-based policy and practice. Virtually all of the major STD/HIV prevention programs and policy advances of the last 10 years have resulted from focused research efforts. Basic research refers to investigation in fundamental areas such as molecular biology, microbiology, immunology, psychology, statistics, economics, etc. In contrast, clinical research focuses on research on human participants. Another approach, operations research, aims to develop a scientific model of a system to predict and compare the outcomes of alternative decisions, strategies, or controls.¹⁶¹ More recent interest has focused on the role of translational research, defined as the bidirectional transfer of knowledge between the basic work and the whole patient or population.¹⁶² Such efforts can provide better understanding of the mechanisms of disease and maintenance of health as well as lead to new methods of diagnosis, treatment, and prevention.

Research priorities in STD/HIV prevention have been defined for many western industrialized countries. In the U.K., nationally funded priorities are established by the Medical Research Council Sexual Health and HIV Research Strategy Committee.¹⁶³ In the United States, a framework for prevention research priorities has been developed by the CDC in its research guide: *Advancing the Nation’s Health: A Guide for Public Health Research Needs, 2006–2015*.¹⁶⁴ It documents priority research areas for the next decade for CDC and its partners, including issues related to sexual and reproductive health. The CDC prevention research portfolio is complemented by the much larger investments in research by the National Institutes of Health.

FUTURE DIRECTIONS

The overall challenge for STD/HIV prevention efforts in developed countries is ensuring that comprehensive prevention services are provided through a well-coordinated system

that is seamless at the client level and utilizes a broad array of community resources. The essential components of STD and HIV public sector programs are in place in most developed countries; however, these components must be strengthened and better linked with other prevention programs to maximize public health impact. This section highlights some of the emerging prevention approaches that are likely to impact the nature and form of STD/HIV prevention services over the next decade.

Program collaboration and service integration

Program collaboration and service integration describes a mechanism of organizing and coordinating activities and services so that they are designed, implemented and evaluated to maximize public health impact.^{165,166} Examples of collaboration between STD and HIV programs are found across many U.S. and European contexts, although the level of collaboration varies tremendously.¹⁶⁷ There are a number of barriers to better collaboration between categorically funded programs, including lack of local flexibility to shift funds across budget lines, lack of guidance for program integration, and difficulties in merging surveillance and evaluation data.^{3,5,168} Program collaboration and service integration has the potential in many settings to enhance prevention effectiveness and efficiency.

Mathematical modeling

Mathematical models can serve many purposes including delineating basic processes underlying disease transmission, defining the most important determinants of an observed pattern, designing and evaluating interventions, and examining the impact of population-level factors on intervention efficacy.¹⁶⁹ Models have been used extensively to explore the processes determining observed patterns of infection in STD epidemiology, the effect of sexual mixing, the intersection between epidemics, and the impact of prevention programs on population levels of infection.^{170–172} Of particular importance, models may help to demonstrate how prevention campaigns can benefit targeted populations.^{173,174}

Cost-effectiveness analyses

Cost-effectiveness analysis (CEA) is a technique for selecting among competing priorities in the context of finite resources by comparing the relative value of various strategies.^{175,176} In its most common form, CEA compares a new strategy with current or established practice. For example, Cohen et al.,¹⁷⁷ estimated the relative cost-effectiveness for 26 HIV prevention interventions and found that the two most important factors were population HIV prevalence and cost per person reached. Consequently, in low-prevalence populations, the most cost-effective interventions were population-level interventions (e.g., mass media and condom distribution), whereas in high-prevalence populations, individually focused

behavioral interventions were also relatively cost effective. In the future, wider use of CEA will be essential to prioritize the best mix of interventions.

Structural interventions

Structural interventions refer to public health interventions that promote health by altering the structural context within which health is produced.^{178,179} For example, structural interventions may be used to influence the social, political, or economic environments in which people live to effect positive health outcomes.²⁶⁴ Micro-credit and other programs aimed at improving women's economic status may impact STD/HIV prevention by reducing economic dependency on male partners.^{180,181,182} As a component of a multilevel approach to STD/HIV prevention with an especially broad reach, structural interventions are likely to be of increasing importance.^{183,184}

Network analysis

Social network analysis provides an essential tool for analyzing social structures, including sexual networks. Work in this area is growing¹⁸⁵ as new studies emphasize the importance of understanding the structure of sexual networks in STD/HIV transmission.¹⁸⁶ Patterns of sexual mixing, concurrency of partnerships, and the existence of sexual bridges help create the socioeconomic, racial, and ethnic disparities seen with STDs/HIV.¹⁷² Practical programmatic use of the concept of networks is still evolving; however, there are promising examples from syphilis control^{187,188} and HIV prevention.¹⁸⁹

The internet

The past decade has seen a dramatic expansion in population access to the Internet, as well as the diversity of sexual activities that may be pursued through this media. Both trends are likely to continue for the foreseeable future. Elevated levels of high-risk sexual behavior among people who meet sexual partners through the Internet are well-documented.^{190–192} Although substantial progress has been made using web-based technologies to enhance health communication, partner notification, disclosure of HIV status, and STD/HIV screening, future prevention efforts must increase the focus on the practical uses of this emerging field^{193,194} (see Chapter 108).

Biomedical interventions for STD/HIV prevention

In addition to ongoing research on HIV vaccines, there is an enthusiasm regarding novel biomedical approaches for STD/HIV prevention,^{195,196} including vaginal microbicides,¹⁹⁷ cervical barrier methods, pre/postexposure prophylaxis,¹⁹⁸ suppression of HSV-2,²⁰ and male circumcision.^{199,200} Combinations of methods must be studied, as no single intervention is likely to be 100% effective. The development, implementation, scale-up, and M&E of these interventions

will require commitment from many sectors, including industry, foundations, research networks, and communities.

CONCLUSIONS

As the STD/HIV prevention programs in developed countries move into the twenty-first century, they face a variety of opportunities and challenges. There has been great progress in the control of curable bacterial infections such as syphilis and gonorrhea, on which prevention programs have been focused for the longest period. Although chlamydia remains hyperendemic, improving diagnostic tools make effective screening programs more feasible than ever, while enhanced partner management offers great potential for preventing ongoing transmission. Immunization programs have been highly effective in reducing the incidence and impact of HBV, and new HPV vaccines offer similar hope. Newer approaches to HIV prevention, such as rapid testing and prevention services for HIV-infected persons, and male circumcision promise to complement the improvements in care over the past decade, and, relevant to all STD and HIV, the growth of evidence-based behavioral interventions offer tremendous opportunities. However, the high population burden posed by STD/HIV, despite concerted prevention efforts, point to obvious challenges, as well. These include gaps in our biomedical approaches (e.g., viral infections for which curative therapy is not available, rising antimicrobial resistance for infections such as gonorrhea and HIV, and absence of vaccines for most STDs), and challenges in behavioral approaches, such as the difficulty of sustaining behavioral change. Challenges also include the varied social and environmental determinants that affect behavior and access to prevention services and are likely to become more complex as broad phenomena such as population increase, growing economic disparity, and global warming continue to unfold and impact sexual networks and social and health structures. Finally, in societies in which so many resources are focused on curative medicine, “marketing” prevention to enhance societal commitment to full population coverage of prevention programs will be critical to achieve the full benefits of STD/HIV prevention.

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Although the need to integrate clinical and preventive services for HIV and other sexually transmitted diseases (STDs) is intuitive, in practice, health-care systems globally have often fragmented these services. In most developed nations, STD clinics have long played a central role in public health efforts to identify new cases of HIV^{1–3} and have served as sentinel surveillance sites to monitor trends in HIV incidence and sexual risk behavior.^{4–10} However, how to best counsel and test persons for HIV has been controversial, and little attention has been paid to the role of STD clinics in the ongoing care of persons with HIV infection. Although HIV prevalence is frequently high among STD clinic patients in developing nations, these clinics have not, to date, been regarded as a central component of most national HIV prevention plans. In both high- and low-income nations, HIV clinics have not consistently provided quality STI services, despite evidence that these infections are common in this setting and important biologic markers of risky behaviors.

Widespread acceptance of the idea that STDs other than HIV enhance HIV transmission,¹¹ and a new emphasis on directing prevention efforts toward persons already aware of their HIV infection^{12,13} have prompted wider consideration of how to integrate STD and HIV services, and how to incorporate prevention into the care of persons with HIV wherever they are seen. In this chapter, we discuss the role of STD clinics in HIV diagnosis, medical care and prevention, and the integration of STD services into the ongoing activities of HIV clinics in both developed and developing nations, emphasizing the many areas in need of further study. The integration of preventive services other than STD care into HIV medical care is covered elsewhere in this text (Chapter 72).

INTEGRATION OF STD AND HIV SERVICES IN HIGH-INCOME NATIONS

■ INTEGRATING HIV CARE INTO STD CLINICS

STD clinics play an important role as centers for HIV testing and counseling in most developed nations. The prevalence of HIV among tested STD clinic attendees in the United States

and Europe is typically 1–2% overall^{14–16} but varies considerably by HIV risk. In a study of 52,260 STD clinic patients tested in 14 U.S. cities in 1997, 9.1% of men who have sex with men (MSM), 5.1% of injection drug users (IDUs), and 1.4% of non-IDU heterosexuals tested HIV positive.¹⁶ HIV prevalence in European STD clinics is variable but somewhat higher overall. Among 128,602 STD clinic patients tested in 17 European nations between 1990 and 1996, 16.5% of MSM (range 2–53%), 28% of IDUs (range 0–80%), and 0.6% of non-IDU heterosexuals (range 0.01–3.9%) tested HIV positive¹⁷; HIV prevalence in this study declined over time.

Data on the proportion of all HIV tests and all new cases of HIV diagnosed through STD clinics are fragmentary and, at times, conflicting. A study evaluating the HIV testing experience of a probability sample of Americans found that 24% of tests were performed in public testing sites but that only 0.1% was performed in STD clinics.¹⁸ This is somewhat at odds with CDC data that almost a quarter of all publicly financed testing occurs in STD clinics.¹⁴ Regardless of the percentage of all tests that are performed in such clinics, it is clear that STD clinics diagnose large numbers of cases. In 1998, the last year for which national U.S. statistics are available, 25% of all cases of HIV diagnosed through publicly financed testing were diagnosed in STD clinics.¹⁴ Estimating the percentage of all new cases in the population identified in STD clinics is more difficult. In King County, Washington in the United States, an estimated 35% of all HIV cases are diagnosed through publicly financed testing, and 20% of all newly reported cases are diagnosed in a single STD clinic (unpublished data). In the U.K., the majority of all HIV diagnoses are thought to occur in genitourinary medicine (GUM) clinics.¹⁹ Between 1986 and 1994, 14% of all HIV cases diagnosed in Sweden originally tested HIV positive in an STD clinic.²⁰ Between 1995 and 2005, 14% of HIV cases diagnosed in British Columbia, Canada were diagnosed in STD clinics (personal communication, Paul Kim and Daphne Spencer).

Two main obstacles have impeded the optimal use of STD clinics as sites for HIV diagnosis: the low percentage of persons tested and large number of tested persons who do not receive

their HIV test results. A 1997 anonymous unlinked serosurvey of over 52,000 patients seen at U.S. STD clinics found that clinics tested a median of 58% of patients, and HIV seroprevalence was higher among persons not tested for HIV, even after excluding persons previously known to be HIV infected as documented in their medical records.¹⁶ (Some persons previously diagnosed with HIV may not have informed evaluating clinicians of their HIV diagnosis.) Similarly, in the U.K., 55% of GUM clinic patients without a prior diagnosis of HIV were tested for HIV in 2003; almost half of HIV infected persons were not tested, and persons who sought evaluation for an acute STD were less likely to be HIV tested.²¹ The problem of poor uptake of testing is compounded by the relatively high proportion of persons who test but do not learn their test results. In 1998, only 55% of all HIV-infected persons tested in U.S. STD clinics received their results.¹⁴ Factors significantly associated with a higher risk of not returning for test results include younger age, African American race, seeking evaluation for symptoms of STD, and male gender.^{22,23}

Recognition of these problems has prompted U.S. and U.K. public health authorities to advocate making HIV testing more routine. How to do this is uncertain. Explicit informed consent has been identified as a barrier to HIV testing acceptance,²⁴ and recent attention has focused on adopting more of an “opt out” approach to HIV testing in which patients would be told that testing was routine and no written consent would be required. Rapid HIV tests may also lead to more effective HIV testing. Patients prefer rapid HIV tests²⁵ that provide preliminary positive results in 20 minutes, and these tests clearly increase the proportion of all tested persons who receive their results.^{26,27} A growing body of literature suggests that rapid tests may also increase testing acceptance. One study evaluating rapid tests found that 80% of STD clinic patients agreed to take such a test when offered, a number that is higher than traditional levels of testing acceptance, and a randomized trial that compared rapid tests to standard HIV testing found that rapid tests resulted in more eligible clients accepting testing and receiving HIV test results in gay men’s bathhouses (16% vs. 9%, $p < .0001$) and in a needle exchange (7% vs. 3%, $p < .0001$).²⁸ Recently, investigators at the Denver STD clinic evaluated a new system of opt out testing coupled with routine use of rapid tests for all HIV testing. Compared to a historical control period during which written consent and standard serological testing were performed, the percentage of persons accepting HIV testing increased from 81% to 97% with no change in the percentage of persons testing HIV positive; while the number of new HIV diagnoses in MSM was relatively stable during the standard testing and rapid testing time periods (30 vs. 33 new cases), the number of new diagnoses in non-MSM increased substantially (9 vs. 17).²⁹

There are also some potential downsides to rapid tests. The tests are somewhat more costly than standard HIV tests and probably add time to clinic visits, further increasing the cost of testing. In Denver, an effort was made to limit the

amount of time added to visits by rapid testing procedures by having nonclinical staff initiate HIV testing on all patients before they were seen by clinicians. By eliminating the need for follow-up clinic visits or telephone calls to receive results, rapid tests may be cost saving in some settings, though insofar as most STD clinic patients have other laboratory tests performed that require follow-up to receive results, rapid tests probably save little in terms of follow-up in most STD clinics. There are also some downsides to rapid tests. Recent evidence suggests that at least some rapid tests may be less sensitive than 3rd generation enzyme immunoassays,³⁰ and weakly positive tests are sometimes false positives.³¹ Rapid test may also involve some loss in counseling efficacy, at least in selected populations. Project Respect II, a randomized trial that compared rapid and standard HIV testing in 3297 STD clinic patients, found no significant difference in sexual risk behavior or in STD incidence between patients tested using rapid and standard tests at 6 and 12 month follow-up. However, among MSM, the group at highest risk for HIV infection, STD rates were higher in the rapid test group (21.8% vs. 11.8%, RR 1.86 95% CI 0.92–3.76). This finding was not statistically significant, was observed in a subgroup analysis of only 172 men, and merits future study. However, it raises concerns that among MSM, two-session client-centered counseling may be more effective than single session testing and counseling. More broadly, it also raises the issue of what counseling should be performed with HIV testing in STD clinics.

Project Respect I, a randomized trial that enrolled 5758 HIV-negative heterosexual STD clinic patients, compared HIV testing with pre- and posttest counseling involving either a didactic message or brief client-centered counseling. Persons in the client centered counseling arm experienced a lower incidence of STD over 6 months follow-up than those in the didactic counseling arm (7.3% vs. 10.4%, $p = .005$).³² This study substantially defined CDC’s HIV testing and counseling guidelines in the 1990s.³³ However, STD clinics were inconsistent in adopting the approach supported by the Project Respect findings, possibly because of the high cost such an approach might involve if applied to all patients.³⁴ Recent U.S. initiatives have de-emphasized counseling, placing greater weight on the benefits of simply ensuring that infected persons know their status.^{12,13} To date, the intensity of HIV counseling in the United States has not varied based on patient risk, though a more flexible approach based on patient risk seems rationale and merits consideration.

Thus, while STD clinics are clearly important sites providing HIV testing, there are unanswered questions regarding how to best HIV test STD clinic patients. These include (1) how can clinics increase the proportion of all patients tested, (2) who should be tested using rapid tests, (3) how can we most efficiently counsel persons being tested for HIV, and (4) how can clinics selectively intensify counseling among those at greatest risk?

■ CARE OF PERSONS WITH PREVIOUSLY DIAGNOSED HIV IN STD CLINICS

Beginning in the early 1990s, studies began to draw attention to the occurrence of incident STD in HIV-infected persons who were already aware of their HIV serostatus. Initial reports in both the United States and Europe focused primarily on patients seen in STD clinics^{35–39} and called for greater attention to the problem of ongoing risk among persons with HIV infection (Table 91-1). Several of these reports examined trends in the occurrence of STD among persons with HIV infection and documented a decline in STD incidence that paralleled the general decline in STD rates seen among MSM in the late 1980s and early 1990s.^{41,42,54,63,64} However, since that time, studies from both the United States and Europe have reported rising rates of STDs among MSM, as well as increases in high-risk sexual behavior.^{5,6,64–72} Prompted by the increased recognition that STDs can enhance HIV transmission and a community-level randomized trial showing that treating STDs can decrease HIV incidence,^{11,73} in the 1990s CDC began to emphasize the control of STD as a means to prevent HIV transmission.⁷⁴ In 2001, CDC initiated a new HIV prevention program that explicitly emphasized the importance of individuals knowing their HIV serostatus and developing and instituting HIV prevention interventions among persons who are HIV-infected.¹²

■ SERVICES FOR HIV-INFECTED PERSONS IN STD CLINICS

Although STD clinics frequently treat persons with previously identified HIV infection, to date, little has been done to modify STD services and prevention counseling for such patients. The impact of STD clinics on HIV positives is uncertain, though public health program data from King County Washington provide some insight into at least one STD clinic's reach into the high-risk HIV-positive population. Clinicians in the Seattle-King County STD clinic evaluated 329 different MSM with previously diagnosed HIV in 2004. Forty-three percent of these men reported having unprotected anal intercourse with partners of unknown or discordant HIV status.⁷⁵ There are an estimated 40,000 MSM in King County, of whom 15%, or 6000, are HIV-infected. A 2003 random digit dial study of MSM in King County found that 15% of HIV-infected MSM had engaged in unprotected anal intercourse with a partner of unknown or discordant HIV status in the preceding year, or approximately 900 HIV-infected men.⁷⁶ Thus, in a single year, the STD clinic sees approximately 15% of MSM who are aware of their HIV status and potentially transmitting the virus to others. HIV-infected MSM seen in STD clinics have been successfully recruited into small research studies⁷⁷ but, to date, have not been actively enrolled into prevention programs. Developing interventions for this population is a high priority, as well as

a relatively neglected area of research and public health practice. However, to the extent that King County estimates are accurate and generalizable, they also demonstrate that most high-risk MSM do not attend STD clinics.

■ STD SERVICES IN HIV CLINICS

Clearly, greater emphasis should be placed on incorporating STD care and prevention into the care of persons with HIV infection. Table 91-1 summarizes studies assessing the incidence and prevalence of STDs among HIV-infected persons. These studies suggest several conclusions that affect how STD services might be provided in HIV clinics. First, the incidence of STDs among some populations of persons with HIV is relatively high. This conclusion is supported by studies employing passive surveillance among HIV-infected STD clinic patients,^{35–37,41,42} data from a multicenter surveillance analysis of persons receiving HIV care,⁴⁷ and studies in which women were serially tested for STDs.^{49–53,56} Prospective studies of STD incidence with scheduled STD testing have not been performed in men. Second, in women, trichomoniasis is overwhelmingly the most common curable STD. Indeed, the incidence of bacterial STDs among women has been quite variable. Third, asymptomatic urethral infections in men are relatively uncommon and are usually present in <2% of men, including MSM. Fourth, the prevalence of asymptomatic cervical infections in women is highly variable, ranging from <2% to ~10%. Fifth, asymptomatic bacterial infections in the rectums of MSM are relatively common and are present in ~5% of men.

Table 91-2 presents a summary of the CDC, Infectious Disease Society of America, and U.S. Health Resources and Services Administration STD screening recommendations for persons with HIV infection.⁷⁸ UK guidelines also recommend annual screening for STDs among persons with HIV but are less explicit.²¹ Additional recommendations related to STD prevention in HIV-infected persons are discussed in Chapter 71.

Although recommendations to screen HIV-infected persons for other STDs are now well established, the proportion of HIV-infected patients who actually receive recommended STD testing is not known, and how to institute existing recommendations is uncertain. Urine-based testing for genitourinary infections using nucleic acid amplification tests (NAATs) is relatively simply performed, whereas screening for rectal infections in MSM is more difficult. At present, chlamydial culture, the only FDA approved test to identify *Chlamydia trachomatis* in rectal specimens, is not widely available. Some investigators and public health programs have used NAATs on rectal specimens^{61,79,80} but the operating characteristics of these tests on such specimens are not well established, and the tests are not FDA approved for use on rectal specimens, creating a substantial barrier to widespread compliance with existing recommendations.

Table 91-1. Studies Evaluating the Prevalence and Incidence of Bacterial STDs in Persons with HIV

Author (Year)	Population	Type of Follow-Up ^a	Study Years	Disease Incidence	Comment
<i>Incidence studies</i>					
Lee (1990) ³⁵	139 Kansas City STD clinic patients (92% men)	Passive	1988–89	13 (9%) developed gonorrhea and 6 (5%) nongonococcal urethritis	Incidence not calculated Subjects knowledge of HIV positivity uncertain
Zenilman (1992) ³⁶	615 Baltimore STD clinic patients (77% men)	Passive	1988–89	60 (9.7%) returned with gonorrhea, syphilis, or trichomonas	Incidence higher in men than women
Otten (1993) ³⁷	897 Miami STD clinic patients (72% men)	Passive	1987–89	Gonorrhea incidence 11/100 py	Excludes persons not seen in STD clinic prior to HIV diagnosis
Fennema (1995) ⁴⁰	59 Amsterdam female commercial sex workers	Active	1985–92	Gonorrhea—27/100 py trichomonas 66/100 py Early syphilis 5/100 py Chlamydia 12/100 py	
Osewe (1996) ⁴¹	5615 persons diagnosed with HIV in a Miami STD clinic	Passive	1988–92	16% of persons diagnosed in 1988 and 2.4% of those diagnosed in 1992 returned within 1 y with a new STD or as contacts to an STD	
Golden (1996) ⁴²	1157 Baltimore STD clinic patients (75% men)	Passive	1988–1989 and 1991–93	77 (7%) were diagnosed with gonorrhea or syphilis during follow-up. Incidence STD 8.6/100 py 1988–89 and 2.3/100 py 1991–93	
Belongia (1997) ⁴³	2315 persons in Minnesota, USA	Passive	1983–94	30 (1.3%) of persons were reported with a new STD (gonorrhea, chlamydia, or syphilis) in a median of 3	Cases ascertained through matching of STD and HIV case registries Gonorrhea incidence 10 times the state's age adjusted incidence
Sorvillo (1998) ⁴⁴	212 women in an HIV clinic in Los Angeles, USA	Passive	1992–95	37 (17%) of women were diagnosed with trichomonas incidence 14/100 py	
Munoz-Perez (1998) ⁴⁵	1161 Spanish IDUs receiving HIV care	Active follow-up for symptoms but no routine testing	1993–96	STD diagnoses during follow-up: Syphilis (3.7%), gonorrhea (1.8%), trichomonas (0.3%)	Median or mean length of follow-up not reported
George (1998) ⁴⁶	132 STD clinic patients	Passive	1994–95	1 (1%) was seen with gonorrhea, chlamydia, or syphilis during 1 year follow-up	

Table 91-1. (Continued)

Author (Year)	Population	Type of Follow-Up ^a	Study Years	Disease Incidence	Comment
Do (2001) ⁴⁷	9 areas of the USA	Passive	1991–98	Gonorrhea incidence per 100 py MSM—8.5 Men—8.1 Women—15.3	Chart review based surveillance Clinic policies related to testing not indicated
<i>Studies measuring both prevalence and incidence</i>					
Olaitan (1997) ⁴⁸	185 women followed in a London HIV clinic	Active STD testing every 6 mo	1990–96	3 (2%) women had a bacterial STD or trichomonas at initial testing. No incident STDs were detected	
Capps (1998) ⁴⁹	323 women enrolled in a trial of fluconazole prophylaxis	Active	1992–94	Prevalence of any STD at enrollment 13% (11% trichomonas) 25% of women developed at least one STD during a median follow-up of 2.1 y -15% developed trichomonas	STD includes trichomonas, gonorrhea, chlamydia, syphilis, and pelvic inflammatory disease Incident STD significantly associated with prevalent STD at enrollment, African American race, and IDU sex partner
Wilson (1998) ⁵⁰	232 women receiving HIV care in Brooklyn, NY	Active		23% of women had an STD at enrollment. 14% developed a new STD during a mean follow-up of 15 months	STD includes trichomonas, gonorrhea, chlamydia 31/37 (84%) of incident STDs were trichomonas
Bersoff-Matcha (1998) ⁵¹	143 women receiving HIV care in St. Louis, USA	Active testing every 6 mo per clinic policy	1995–97	STD prevalence at enrollment: trichomonas (11%), gonorrhea (3%), chlamydia (3%), syphilis (6%) STD incidence: trichomonas (18%), gonorrhea (7%), chlamydia (3%), syphilis (6%)	Proportion of women actually tested per policy not reported
Bentham (2000) ⁵²	487 women with HIV in 12 European nations	Variable	1993–98	Prevalence at enrollment: gonorrhea (2%), chlamydia (3%), trichomonas (12%) Incidence per 100 py gonorrhea (1%), chlamydia (6%), trichomonas (3%)	Incident STD significantly associated with history of commercial sex and less condom use

(Continued)

Table 91-1. (Continued)

Author (Year)	Population	Type of Follow-Up ^a	Study Years	Disease Incidence	Comment
Magnus (2003) ⁵³	1665 women in an HIV clinic in New Orleans, Louisiana USA	Active STD screening recommended in clinic every 6 mo	1990–2000	Prevalence gonorrhea (4.9), chlamydia (5.3), trichomonas (13.1) Cumulative incidence over mean follow-up 5.5 y gonorrhea (9.5), chlamydia (14.9), trichomonas (30.2) Trichomonas incidence per 100 py: Initial episode trichomonas 8.9 Subsequent trichomonas 16.4	STI in this population also evaluated in other publications ^{54,55} Trichomonas positivity associated with younger age, African American race, drug use, and presence of other STDs Proportion of infections that were asymptomatic identified through screening not defined
Monteiro (2004) ⁵⁶	225 women in an HIV clinic in Birmingham, Alabama, USA	Active Cross-sectional at enrollment with every 6 mo testing	1996–2001	Prevalence gonorrhea (0), chlamydia (1.3%), trichomonas (5.3%) Incidence: 36 (16%) of women any STD— 5.8/100 py	
<i>Prevalence studies</i>					
Erbelding (2000) ⁵⁷	691 patients (52% men, 46% of whom were MSM) in an HIV clinic in Baltimore, Maryland USA	Cross-sectional prevalence urethral/cervical infection	1997–98	Men—gonorrhea (1.5%), chlamydia (2.8%) Women—gonorrhea (1.7%), chlamydia (2.1%)	7.5% of patients had gonorrhea or chlamydia on screening or reported having one of these infections in the preceding year
Klausner (2001) ⁵⁸	447 patients in an HIV clinic in San Francisco, California	Cross-sectional prevalence urethral/cervical infection		No new cases of syphilis detected in men or women Men—2/372 (0.6%) prevalence chlamydial infection with no cases of gonorrhea Women—0/75 women infected	
Whittington (2002) ⁵⁹ (personal communication)	170 MSM tested for STD in an HIV clinic or as part of a cohort study	Cross-sectional prevalence of urethral, pharyngeal, or rectal infection	1999–2000	Gonorrhea or chlamydia 8.8% Rectal gonorrhea or chlamydia 5.9% Syphilis 2.4%	
Farley (2003) ⁶⁰	2610 persons in an HIV clinic (53% men)	Urine tested for gonorrhea and CT Protocol was to test patients every 6 mo	1998–2001	Men—gonorrhea (1.4%), chlamydia (1.2%) Women—gonorrhea (2.1%), chlamydia (3.3%)	STI prevalence higher in younger patients

Table 91-1. (Continued)

Author (Year)	Population	Type of Follow-Up ^a	Study Years	Disease Incidence	Comment
Phipps (2005) ⁶¹	814 patients (76% men) in an HIV clinic in San Francisco	Cross-sectional prevalence of urethral, pharyngeal, or rectal infection		Men Urethral/cervical gonorrhea (0) chlamydia (1.2%) Pharyngeal gonorrhea (3.8%) chlamydia (1.6%) Rectal gonorrhea (5.5%) chlamydia (2.9%)	BD Prob-Tec used to detect rectal and pharyngeal gonorrhea and chlamydia. Test has not been validated for these specimen types
Rug (2005) ⁶²	107 MSM in an HIV clinic in London	Cross-sectional prevalence	2003	Chlamydia 1.9%	

^aActive follow-up defined as microbiologic testing at routine intervals.

Table 91-2. CDC, IDSA, HRSA Guidelines for Integrating Prevention into the Care of HIV-Infected Patients

Risk Screening	<p>STD symptoms—All visits</p> <p>Sexual history— perform at initial visit and at least annually thereafter</p> <ul style="list-style-type: none"> • Any sex— vaginal, anal, oral • Number of sex partners • Partners' HIV status (infected, uninfected, unknown) • Types of sex— vaginal, anal, oral • Condom use • Barriers to abstinence or condom use • Desire to become pregnant <p>Injection drug use</p> <ul style="list-style-type: none"> • Any injection drug use • Sharing of needles or other injection equipment • Number of persons with whom patient has shared needles or other injection equipment • HIV status of persons with whom patient shared needles or other injection equipment • Use of new or sterilized injection equipment • Barriers to ceasing illicit drug use or adopting safer injection practices 	<p>Initial Screening Men</p> <ul style="list-style-type: none"> • All: RPR • If patient reports receptive anal sex: rectal cultures for gonorrhea and chlamydial infection^a • If patient reports receptive oral sex: pharyngeal culture for gonorrhea • Consider screening for urethral gonorrhea or chlamydial infection based on local epidemiology <p>Screening should be repeated at least annually</p> <p>More frequent testing indicated in persons with any of the following risks:</p> <ol style="list-style-type: none"> 1. Multiple or anonymous partners 2. History of STD 3. Identification of behaviors associated with transmission of HIV and other STD 4. Sex or needle sharing partners with any of the above 3 risks 5. Developmental changes in life that may lead to behavioral change with increased risky behaviors (e.g., dissolution of a relationship) 6. High prevalence of STDs in the area or in the patient population
STD screening	<p>Initial Screening Women</p> <ul style="list-style-type: none"> • All women: Trichomonas, RPR, • Chlamydia—age ≤ 25 or “increased risk,” consider in patients based on local epidemiology • Gonorrhea—consider based on local epidemiology 	

^aSome clinicians use nucleic acid amplification tests. Requires local laboratory validation.

Existing recommendations on STD screening in persons with HIV do not explicitly recommend testing for herpes simplex virus II (HSV-2). However, detection and treatment of HSV-2 may be particularly important in HIV-infected persons, both because of the high prevalence of coinfection and because of the multiple mechanisms by which HSV-2 facilitates HIV transmission. In most populations, 50% or more of persons with HIV infection are also infected with HSV-2.^{81–84} HIV can be detected in herpetic lesions,⁸⁵ and the presence of recent genital ulcers has been associated with HIV transmission.⁸⁶ In addition to creating portals of exit (and entry) for HIV, HSV-2 appears to augment HIV replication, resulting in increases in plasma viral load by as much as 0.5 log copies/mL,^{87,88} suggesting that HSV-2 may increase the transmissibility of HIV infections as well as progression of HIV disease. Chronic suppressive therapy with acyclovir or valacyclovir has been shown to decrease HSV-2 shedding and the occurrence of clinic outbreaks of HSV-2 in persons with HIV⁸⁹ and to decrease HSV-2 transmission in HIV-uninfected heterosexuals.⁹⁰ These findings suggest that routine screening for HSV-2 and chronic suppressive therapy for HSV-2 infected persons may be an effective means to decrease HIV transmission. Ongoing trials are testing this hypothesis. At present, routine serological screening and treatment is not promoted. However, some experts recommend that HSV type-specific serologies be offered to HIV-infected patients at their initial visit and that chronic suppressive therapy be considered for persons with HIV and HSV-2 coinfections⁹¹ (see Appendix B) particularly in the context of frequent recurrences.

INTEGRATION OF HIV AND STD SERVICES IN RESOURCE CONSTRAINED COUNTRIES

Many of the barriers that limit STD and HIV integration in developed nations also affect developing nations. Health-care systems are fragmented and HIV testing has not been adequately routinized; persons with HIV experience high rates of other STDs that are inadequately addressed, and little has been done to integrate prevention into the ongoing medical care of persons with HIV or those at greatest risk for HIV.

The disease burden of STDs in developing countries is discussed in Chapter 101. Many publicly funded STD services in developing countries are chaotic, overloaded, and poorly supported.⁹² The adverse, frequently delayed consequences of STDs are underappreciated and, in most countries, the formal response from government sectors for prevention and care has been inadequate. However, efforts to recognize the epidemiological synergies between other STDs and HIV infection^{11,93} and to create shared prevention strategies to reduce sexual risk behaviors and introduce proven interventions are occurring.^{94,95}

The specific role of STDs and STD treatment interventions in HIV transmission across HIV epidemic settings remains controversial.⁹⁶ In 2000, UNAIDS and WHO published the document *Consultation on STD Interventions for Preventing HIV: What Is the Evidence* as an outcome of a review of strategies for HIV prevention.⁹⁷ The consultation concluded that substantial scientific evidence supported the observation that controlling STDs reduces HIV incidence at the population level and recommended that STD management be an essential component of AIDS control programs. Subsequent reviews have explored the specific, significant roles of genital herpes and chancroid in augmenting HIV transmission.^{98,99} However, the most recent UNAIDS HIV prevention monograph (2005) *Intensifying HIV Prevention* no longer identifies STD management as a specific intervention.¹⁰⁰ In July 2006, UNAIDS/WHO again convened an expert panel to examine these issues, particularly in the context of generalized epidemics such as those that now exist in much of sub-Saharan Africa. The report emphasized that the contribution of STDs to HIV transmission is likely to remain significant across epidemic phases, but that the relative contribution of specific STDs usually changes because the curable, bacterial STDs that are more common in concentrated epidemics are often replaced by currently incurable, viral STDs such as HSV-2 as HIV epidemics become generalized.¹⁰¹ The recommendations also highlighted the importance of STD services as an entry point for early identification of HIV-infected and at-risk individuals and the risks of resurgence of STDs if STD services are cut back in settings in which they have successfully controlled these diseases.

■ INTEGRATING HIV CARE INTO STD CLINICS

STD services and resources in resource-limited societies can be broadly categorized as (a) syndromic management and care programs; (b) screening programs; (c) prevention programs; and (d) laboratory support services. Model programs are described in the literature.^{94,102} Unfortunately, in 2006, few have been brought to scale and in most countries, there is little integration with HIV services. Currently, individuals with symptomatic STDs receive care from shopkeepers, pharmacies, the private health sector, and occasionally from public clinics.^{79,103–112} The proportion of persons with STDs who receive care through public STD clinics is variable but in most low-income countries it is probably very low.^{106–108} For example, a survey conducted in Accra, Ghana in the 1990s found that in 1 year governmental clinics treated 2000 cases of STD, while the city's pharmacies treated an estimated 90,000 cases.¹⁰⁴ The high cost of medical care prompts many patients to seek care outside of the formal health sector, and patients frequently seek care in the formal health-care sector only after treatment with medications obtained through other means are unsuccessful.^{110,112–114} In many regions of the

world, the public sector is perceived negatively by at-risk populations for a wide variety of reasons including inferior, often stigmatizing services, inadequate drug supplies, and fear about lack of confidentiality.¹⁰³ As a result, few individuals choose these services unless no alternative exists. However, this perception is not consistently accurate. In Kenya, investigators used simulated patients to test the quality of care in several settings and determined STD case management adhered to preset criteria more often in the public setting compared to other venues.¹⁰² Moreover, numerous studies have documented poor adherence with national STD guidelines among private sector clinicians, as well as pharmacy workers.^{105,107,111} With the rapid implementation of HIV care programs, a multibillion dollar investment is occurring (2004–2008) throughout much of the resource-constrained world in both public and nongovernmental sectors to enable HIV-infected individuals to access care and other services within their communities. This includes investments in capital projects, human resources, drugs, and prevention strategies. Opportunities to achieve prevention and care synergies with STD services are obvious if these are complementary to HIV prevention and care.

An STD service delivery center, whether in a caregiver's office, a nursing station, or a public health clinic should provide (a) trained personnel with knowledge about STD care and prevention; (b) counseling services, including provision of condoms with clear, client-centered interaction about their use; (c) essential drugs, particularly antiinfectives; and (d) some laboratory services. In addition, the capability to perform a complete physical exam to search for STD clinical signs remote from the genitalia and a facility to perform pelvic exams with visualization of the cervix should be a part of all STD services. Unfortunately, most STD care sites do not currently fulfill several, if not most, of these "minimal" requirements, and integrating HIV care into an inadequately resourced and managed clinic may only make services more ineffective.

Table 91-3 summarizes the prevalence of HIV among persons accessing care in various developing country settings for a variety of reasons, but largely due to perceived STD symptoms or serological surveys.^{115–121} The opportunity to counsel, screen for HIV, facilitate entry into HIV/AIDS care programs, and mitigate the societal consequences of HIV are obvious. A huge, often undiagnosed, burden of HIV infection exists in the population of patients seeking care for other STDs in most of the resource constrained world. STD patients should be routinely offered screening for HIV infection with the option to decline. This does not occur in most STD clinics due to policies restricting testing, limited counseling services, lack of laboratory resources, and the reticence of caregivers to create a conducive environment where most clients would choose to be tested for HIV.¹⁰³ Limited investigation supports the thesis that a significant majority of individuals offered HIV counseling and testing would accept an

HIV test.¹²⁵ In some STD clinics in Africa, 50% or more of the patients are HIV-infected. Without testing, they remain unaware of their status and present for HIV care with advanced disease, often just prior to death. Screening, counseling, and support for HIV-infected individuals in STD clinic settings would be cost-effective in reducing expensive, often fatal AIDS-related infections, reduce the probability of transmission of HIV (and perhaps tuberculosis) to regular and casual contacts, and possibly identify individuals during their acute HIV infection, when multiple partners may be common and transmission is particularly frequent.¹²⁶ Rapid test technologies could ensure that individuals learn of their HIV test results during the screening clinic visit, make it more "user" friendly, and reduce the requirement for clients to return for follow-up²⁷—often a barrier in rural areas in developing countries. Moreover, some individuals in STD clinic settings are aware of their HIV status but have acquired an STD. Counseling in this setting can reinforce the HIV prevention message.

STD clinics can also be useful as sentinel sites for tracking HIV prevalence in high-risk populations, or in identifying "hot spots" for HIV transmission where intensified prevention activities could be provided. Commonly transmitted STI pathogens such as *Neisseria gonorrhoeae*, *C. trachomatis*, *Trichomonas vaginalis*, and *Treponema pallidum* can predict where communities and/or individuals are at increased risk of HIV transmission and prevention programs can be scaled up and made more effective at these sites.

While integrating HIV testing into STD clinics is an important goal, because these clinics typically see so few patients, they are likely to play a limited role in voluntary counseling and testing (VCT) programs in most developing nations unless their number and capacity is greatly expanded. Other sources of reproductive health services in most developing countries have traditionally not offered HIV counseling or care services. However, family planning clinics could become efficient vehicles for integrated services for the diagnosis, care, and prevention of STDs, including HIV infection. "One stop" demonstration models are needed for delivery of integrated reproductive health services that attract men to share in the responsibilities of family planning, promote sexual health, facilitate STD screening, and encourage HIV VCT.¹²⁷ In addition, innovative efforts to integrate VCT, perhaps using self-testing kits, into care within the informal health-care system, such as pharmacies, merit consideration.

Both HIV and other STDs are embedded within a social milieu that fosters the spread of infection. As a result, ideally, prevention efforts would address factors such as gender equity and violence against women, sexual coercion and abuse, poverty and illiteracy, legal rights, and cultural practices. The efficacy of public health campaigns to address these problems is uncertain, and, even if successful, change in many of these areas is likely to require one or more generations. However, some interventions specifically designed to reduce HIV and

Table 91-3. Incidence and/or Prevalence of HIV in STD Settings or of Other STDs Among HIV-Infected Populations in Resource-Constrained Countries

Author (Year)	Population/Site	Study Years	Disease Prevalence/Incidence	Comments
Mehendale (1996) ¹²²	Two STD clinics in Pune, India 5321 attendees	1993–1995	HIV prevalence in women 32.3%, in men 19.3% Overall HIV incidence 10.2% annually	90% of men were contacts of sex workers
Wilkinson (1998) ¹²³	360 STD patients at Hlabisa Hospital in rural South Africa	1997	42.5% HIV prevalence	Rural clinics
Fonck (2000) ¹²⁴	520 female STD clinic attendees	1998	HIV prevalence 29% <i>N. gonorrhoeae</i> 6% <i>C. trachomatis</i> 4% syphilis 4%	Most women were at low risk for STDs; only 11% had multiple partners
Eis-Hubinger (2002) ¹¹⁶	161 in STD clinic in Douala, Cameroon	1998	17.4% HIV-positive	HSV-2 higher in HIV-positive patients (85.2% vs. 64.1%)
Connolly (2002) ¹¹⁷	77 female sex workers, all HIV-positive	1996–1999	Incidence: <i>N. gonorrhoeae</i> 66/100 py <i>C. trachomatis</i> 30/100 py <i>T. vaginalis</i> 150/100 py	
Msuya (2003) ¹¹⁸	382 females, 3 PHC's in Moshi, Tanzania	1999	HIV prevalence 11.1%	HSV-2 highest in HIV-positive 61.4% vs. 36.1%
Joesoef (2003) ¹¹⁹	STD clinics: 15,889 patients in several cities in Kenya	1990–2001	HIV 16% 1990; 41.8% 1997	
Kaul (2004) ¹²⁰	466 HIV-negative female sex workers in a Nairobi slum	1998–2002	HIV incidence 3.6/100 py	HSV-2 (prevalence 72.7%) predicted HIV-1 incident infections (RR 6.3)
McClelland (2005) ¹²¹	1215 female sex workers in Mombassa, Kenya	1993–2003	HIV infection increased incidence by a hazard ratio (HR) for <i>N. gonorrhoeae</i> 1.6, for genital ulcer disease 2.8, and for vulvovaginal candidiasis 1.5	
Reynolds (2006) ¹¹⁵	2732 HIV seronegative at 4 clinics in Pune, India	1993–2000	HIV incidence 5.8/100 py Syphilis 5.4/100 py	Adjusted hazard ratio for HIV infection with "incident" syphilis was 4.44

other STDs have been spectacularly effective at the country level. Success has occurred with condom promotion for risky sex in the Thai military, behavioral modification including delay in sexual debut and fewer lifetime partners in Uganda and Zimbabwe, and risk reduction among sex workers in Kenya.^{128–132} These prevention activities have markedly reduced several STDs in populations where they have been measured. Synergies among these interventions occur, and together, they may reduce the incidence of STDs, including HIV, within regions and even countries, if applied consistently. In particular, HIV prevention programs should assist sex workers in reducing their incidence of all STDs; obtaining skills and counseling to leave sex work when possible; and, if sex work continues, reducing transmission risks to their partners. Such programs have been shown to reduce the prevalence and incidence of all STDs including HIV.^{130,131}

■ INTEGRATING STI SERVICES IN HIV PREVENTION AND CARE SETTINGS

As in high-income nations, the need to integrate STD services into the care of persons with HIV is justified both by the increased risk of STDs among persons with HIV and the role the STDs may play in enhancing HIV transmission.^{121,133,134} While relatively few data are available on the incidence of other STDs in persons with HIV infection in low-income nations, a study conducted in Pune, India found that persons with HIV experienced a much higher incidence of syphilis than HIV-uninfected persons, with an adjusted hazard ratio of 4.44.¹¹⁵ Studies conducted among men in Malawi have shown that both genital ulcer disease, primarily chancroid and herpes, and urethritis are associated with elevated levels of HIV in semen, suggesting an increased probability of HIV transmission.¹³⁵ Preventing, diagnosing, and treating STDs are of particular importance in the setting of HIV care. However, screening programs for STDs do not generally occur in HIV care settings in most resource-poor areas. The consequences were highlighted in a recent study from Haiti, where the failure to screen HIV-infected pregnant mothers for syphilis led to infants dying of congenital syphilis despite adherence to a complex intervention to prevent HIV transmission.¹³⁶ Prenatal syphilis screening must be employed alongside HIV screening.¹³⁷ Of particular note, oncogenic HPV types are more persistent and invasive in HIV-infected patients, and cervical screening cytology programs should ideally be routine to prevent invasive cervical cancer.¹³⁸ Failure to assess sexual risks, screen for and treat STDs, initiate partner notification where necessary, and counsel patients should, perhaps, be viewed as a form of negligence in the HIV clinic setting in both resource-limited countries and industrialized nations.

Monitoring the occurrence of STDs among persons receiving care for HIV may also be useful for program evaluation and

surveillance purposes. Common STDs detected during clinical care or through screening can be viewed as biologic surrogates for potential HIV transmission and, though imperfect, can be used to validate behavioral outcomes measured to assess interventions designed to reduce HIV transmission. With behavioral surveys, the veracity of the results is dependent on subjective responses. In particular, with the concern about disinhibition in patients treated with antiretroviral drugs, objective parameters become critical for program evaluation.¹³⁹

Syndromic therapy for symptomatic STDs has been promoted as the “practice standard” by WHO for two decades and adopted in most countries. Essential drug programs include the specific antimicrobial agents needed and public programs have often provided them. Most symptomatic STDs in HIV-infected populations present with similar or more flagrant symptoms and signs compared with those seen in HIV-negative patients, though standard syndromic management is generally effective even in immunocompromised patients. As a result, caregivers can usually treat STDs without reference to their HIV serostatus. Herpes simplex virus 2 (HSV-2) is an exception. The severity, prevalence, and recurrence likelihood together have made this pathogen the major STD challenge in HIV clinics. Acyclovir is not on most countries’ essential drug list in 2007, and substantial, often prolonged, distress due to extensive ulceration experienced by a large proportion of HIV-infected patients. The growing evidence that HSV-2 is a major risk factor for HIV transmission, perhaps increasing both infectiousness and susceptibility,⁹⁹ coupled with the clinical importance of the infection and evidence suggesting HSV may increase viral load mandates that national STD programs respond rapidly and integrate HSV-2 management into HIV clinics. No studies conducted in the developing world have looked at the health-seeking behaviors of HIV-infected individuals with STD syndromes, and additional research is required to determine what health education and promotion practices would increase the uptake of STD services, if such services were offered at HIV care clinics.

POLICY AND PROGRAM INTEGRATION

Regardless of whether they are implemented by governments, schools, NGOs, or workplace sites, HIV and STD prevention policies and activities should be linked throughout the health care and education systems in both wealthy and resource constrained societies. Evaluation activities should further the goals of program integration. Sexual and reproductive health, due to their inherent importance to all societies, are issues that have an audience in every setting. The desire to prevent HIV that is now evident globally can be further enhanced with individual and societal consensus that STDs are serious and “worth avoiding.” Important health issues such as infertility, ectopic pregnancy, the risks of STD

transmission to infants, and the consequences of “sexual ill health” should be combined with the better known adverse consequences of HIV infection. Health promotion activities can be carried out jointly and, when appropriate, combined with family planning, prenatal, postpartum, school, workplace, and other programs to create a continuum of consistent messages that impact on the individual. Increased awareness of these illnesses should allow effective communications to be presented through a variety of media and health promotion outlets. Moreover, cultural practices such as vaginal douching, the absence of male circumcision, early female sexual debut, concurrent partnerships, and sex work increase the incidence not only of HIV infection but also other STDs.¹³⁹ Prevention synergies can occur if policies are aligned with effective promotion of sexual and reproductive health. Sustained effective advocacy led by the multinational agencies is essential for this to occur. Organizational changes may be necessary to ensure that STD programming is integrated bidirectionally with HIV prevention and care. Model programs, disease burden studies, and observational and controlled intervention trials are needed, but societies must proceed with program implementation without waiting for additional scientific evidence of effectiveness. Current scientific evidence must be translated into action plans that will dramatically reduce the burden of all STDs, including HIV.

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STD-Related Health-Care Seeking and Health Service Delivery

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INTRODUCTION

Timely treatment of sexually transmitted diseases (STDs) and HIV infection plays a central role in the prevention of sequelae of STD/HIV and in limiting their spread. Treatment constitutes primary prevention of that STD for other members of the population and secondary prevention of complications for infected individuals. To the extent that the encounter between infected individuals and the health-care system delivers effective primary prevention messages, STD/HIV treatment may also constitute primary prevention of repeat infections with the same organism, or future infections with other sexually transmitted organisms, for the infected individual him/herself.

Three large categories of social and behavioral factors contribute to the timely treatment of STD/HIV. These are health-care seeking behaviors of members of the population, behaviors of STD/HIV health-care providers, and the organization of STD/HIV-related health service delivery. Each of these three components can be conceptualized at both the individual and the population levels, and is influenced by and, in turn, influences factors at both levels.

This chapter summarizes conceptual frameworks applicable to STD/HIV-related health-care seeking, the provision of STD/HIV services, and the behaviors of health-care providers. It proposes an STD/HIV-specific conceptual framework based on integration and adaptation of the general conceptual models, through the consideration of selected additional factors that are specific to STDs or HIV infection. These factors include characteristics of the STDs and the populations affected by them; phase of the particular STD/HIV epidemic; the detection strategies and technologies employed; the therapeutic regimens and sex partner management approaches utilized; characteristics of providers who see STD/HIV patients (e.g., their skill levels); and the health system (e.g., availability, accessibility and acceptability of services, the availability of patient management guidelines, and the extent to which compliance with such guidelines is assured).

Research findings relevant to STD/HIV-related health-care seeking, behaviors of STD/HIV care providers, and organization of STD/HIV services are summarized in separate sections. The conclusion discusses implications of current conceptual frameworks and empirical findings for future directions in STD/HIV research and prevention efforts.

The underlying integrating focus is provided by the health outcome of interest, which is defined as the timely and appropriate treatment of individuals infected with sexually transmitted pathogens to achieve cure of bacterial and parasitic STDs, and suppression of incurable viral STDs, including HIV. Cure of bacterial or parasitic STDs stops symptoms and infectiousness, and prevents complications. Suppression of incurable viral STDs, in general, decreases severity of symptoms and viral shedding (thereby decreasing infectiousness), and may slow disease progression. Both cure of bacterial STDs and suppression of incurable viral STDs decrease duration of infectiousness, which slows the rate of transmission in the population. To the extent that infection with some STDs increases infectiousness of and susceptibility for other STDs, a decrease in the duration of infectiousness with one STD will also decrease the transmissibility (and therefore the rate of spread) of other STDs and sequelae such as PID. Recent data suggest that PID has in fact diminished in conjunction with decreases in chlamydial and gonococcal infections among women.

A final theme in this chapter is interaction among concepts and variables. With respect to STDs/HIV, if suppression is incomplete, as is the case for HAART, treatment interacts with both infectiousness and duration, decreasing the former but potentially *increasing* the latter. Current modeling research suggests duration or infectiousness may predominate, depending on the nature and epidemiology of the disease.

Interaction of variables in the epidemiologic equation is reflected in the potential for interaction among the various levels of health-care seeking and service delivery with one another. During a single episode of disease, the levels function in a given order, with an individual's recognition or suspicion of infection followed by some probability of health-care seeking,

then some probability of service provision, and so forth. But the type of service provision experienced on one occasion may affect the likelihood of health-care seeking on the next.

CONCEPTUAL FRAMEWORK

Several theoretical approaches have dealt with the issues of health service utilization and health-care seeking, in general, at both the population and individual levels of analysis. These are helpful in understanding STD/HIV-related health-care seeking and provision.

■ POPULATION LEVEL, GENERAL CONCEPTUAL MODELS

At the population level, two general conceptual models that deal with implications of health policy decisions in health service utilization are relevant. McKinlay's Major Approaches to Characterizing Predictors of Health Services Utilization is an inductively constructed model based on integration of research findings.¹ The Behavioral Model of Health Services Utilization is a systems model originally formulated by Ronald Andersen in 1968 and further developed by Aday, Andersen, and other colleagues between 1974 and 1987.^{2,3}

According to McKinlay, the six approaches to health service utilization are the demographic; social structural; social psychological; economic; organizational; and systems approaches.¹ The demographic approach focuses on age, sex, marital status, family size, and residence as predictors; the social structural approach emphasizes social class, ethnicity, education, and occupation; the social psychological approach considers health beliefs, values, attitudes, norms, and culture; the economic approach covers family income, insurance coverage, price of services, and provider–population ratios; the organizational approach looks at the organization of physicians practices, referral patterns, and regular source of care. The systems approach adopted by McKinlay includes all or most of the predictors mentioned in the context of a set of relationships. Interactions among the levels are evident in research employing this model; for example, the interaction of physician and patient attributes in diagnosis of depression.⁴

The Behavioral Model of Health Services Utilization^{2,3} assumes that health policy decisions, whether they deal with issues of financing or organization, will have an effect on utilization of health services, consumer satisfaction, and the characteristics of both the population at risk and the health delivery systems, which, in turn, affect each other.⁵ The characteristics of the population, including demographic, social structural, and belief variables, are predisposing factors that describe the propensity of individuals to use services. The means individuals have available to them to use services, such as income and insurance are enabling factors. Finally, health status, or need for health services is a key determinant of utilization in this

model. These factors may be alterable by health policy (mutable), or by biological or social givens, not open to alteration by health policy (immutable).

This model has been applied to evaluate whether services are equitably distributed.⁶ To the extent that differences in utilization are explained by need variables and demographic correlates of need such as age or sex, differential distribution of services is considered equitable. If other factors such as income or insurance coverage are the most important predictors of who-gets-care, then the system is considered to be inequitable.

Applications of this model have shown that, of the population characteristics, age is curvilinearly related to health service utilization, with the young and the old having higher utilization than those in the middle.⁶ Utilization is also higher among women than men and among those in poor health than in good health. Some inequities exist: utilization is higher among whites than nonwhites (although the gap is narrow to nonexistent for reproductive health care among adolescents by race⁷); among whites and nonwhites than Hispanics; among those living in metropolitan and urban areas than those living outside metropolitan areas and in rural areas.

Education and income are related to health service utilization in more complex ways. People with higher education tend to utilize preventive services more than those with less education, whereas people with less education have higher rates of hospitalization. Prior to Medicare and Medicaid, persons with greater income tended to utilize health services to a greater extent; however, following the enactment of Medicare and Medicaid, lower income persons have started using certain health services at higher rates than persons with high incomes.

Focusing on the characteristics of the health-care delivery system, regular source of medical care consistently emerges as a strong, consistent predictor of health service utilization, particularly the utilization of preventive services. Moreover, the directionality of this association has been explored and availability of regular source of medical care appears to have a direct and causally prior impact on health services utilization.⁶

■ INDIVIDUAL-LEVEL, GENERAL CONCEPTUAL MODELS

At the individual level, there are at least four conceptual models of patient decision making regarding health-care seeking. One of these is Suchman's sociological five-stage decision-making model that focuses on an illness episode and describes the stages of decision making as experience of symptoms; assumption of the sick role; establishment of contact with medical care; assumption of the dependent patient role; and recovery and rehabilitation.⁸ According to Suchman's model, persons with traditional, parochial affiliations, and a popular orientation to medical care would tend to delay assuming the sick role and seeking medical care, and would not comply with therapeutic recommendations.^{8–10}

Kosa and Robertson's psychological stage model of patient decision making describes four stages, including assessment of disturbance; anxiety arousal; application of the person's own medical knowledge to address the problem; and an attempt to alleviate anxiety either through rational therapeutic activities or through gratifying activities that facilitate denial.¹¹ Later, Folkman and Lazarus described problem-focused and emotion-focused stress responses as general coping mechanisms applied to health behaviors.¹²

A third conceptual model of patient decision making was developed by David Mechanic.¹³ According to this model, the social and psychological factors that affect perception of need to seek care are symptom recognizability; perceived seriousness of symptoms; the extent to which symptoms disrupt regular activity; the frequency, persistence, and recurrence of symptoms; the tolerance level of persons evaluating the symptoms; the information, knowledge, and cultural assumptions of the evaluator; basic needs that lead to denial; needs that compete with illness responses; competing interpretations for symptoms; and finally the availability of care and financial and psychological costs of taking action, including issues of stigma, social distance, and humiliation.¹³

The fourth conceptual model that has focused on patient decision making regarding health-care seeking is Marshall Becker's health belief model.¹⁴ This model focused on the individual's subjective state of readiness based on perceptions of susceptibility and severity of consequences of illness; the individual's evaluation of the costs and benefits of seeking care; and a cue to action that may be "internal" (e.g., symptoms) or "external" (e.g., coverage of the issue in the mass media). These models are all visible in a summarizing principle posited by Fisher and Fisher; that health-related behavior is a function of both information and motivation.¹⁵

Such conceptual work focusing on individual level factors that affect health-care seeking behaviors has also viewed health-care seeking along continuous dimensions. These recent approaches focus on delays in seeking care. Such conceptualization represents a departure from earlier models, discussed above, which have constructed health-care seeking as a dichotomous variable measuring a decision either to seek or not seek health care. Recent conceptual work has also concentrated on integrating independently conceived approaches. Predicting health behavior at the individual level relies on three cardinal elements: intentions (reflecting motivations), suitable skills, and lack of environmental constraints.¹⁶ Subsidiary considerations include beliefs about prevailing social norms, net positive outcomes, and one's own abilities.

The logical application of analyzing dimensions rather than categories is to focus on delays in seeking care rather than seeking versus not seeking. One recent model proposes that appraisal of whether an unusual bodily condition is, indeed, a symptom typically accounts for the major portion of the delay

in seeking care.¹⁷ Expectations lengthen this period of appraisal in various ways, including the attribution of the cause of the condition to factors in the environmental context; an unrealistic optimism regarding the risk of contracting disease (optimistic bias); denial that a threat exists; and biased monitoring of bodily changes.¹⁸⁻²⁰ In addition, "lay theories of disease" also contribute to delays in seeking care.²¹

One recent STD-specific conceptualization, recognizing that the process of problem identification differs from the process of resolving barriers to seeking care, used the timing of the decision to seek care to distinguish two intervals: an "appraisal interval" defined as the time between recognition of a problem and the decision to seek clinical care, and a "procrastination interval" defined by the interval between the decision to seek care and actual care.²² As would be expected, factors that influence the appraisal interval are different from the factors that influence the procrastination interval. That these factors differ illustrates the interactive nature of individual level and system-level approaches. For example, increased skills building at the individual level can be mirrored by system-level interventions that make it easier for to seek health (e.g., increased health-care seeking by HIV-positive patients exposed to active case management versus passive referrals²³). Health-care seeking and health-care provision are thus two interacting concepts affecting the same health outcomes.

At the health-systems level, how care is organized and financed has a great impact on both health-care seeking behaviors and health-care providers' behaviors. The most immediate operational indicators for the individual patient of how care is organized and financed are whether one has a regular source of care and insurance coverage, and the particular type of care and coverage. Currently, in the United States, these factors remain in flux as they relate to STD care. Persons falling within the age ranges with greatest prevalence of many STD (e.g., 19 to 24-year-olds) are among those least likely to have consistent insurance.^{24,25}

■ PERSON-TIME OF INFECTIOUSNESS (PTI): A BEHAVIORAL MODEL IN A SYSTEM CONTEXT

The conceptual model being proposed here has several important characteristics. First, the outcome being focused on is a health outcome rather than a behavioral outcome. Second, the health outcome of interest here is jointly determined by factors at the individual, population (or societal), and health-system levels, and the interactions among these factors. Third, this health outcome itself is influenced by the behaviors of infected individuals and providers, and properties of the health system.

As mentioned earlier, the health outcome of interest is the timely and appropriate treatment of individuals infected with sexually transmitted pathogens to achieve the cure of bacterial

and parasitic STDs and suppression of incurable viral STDs. This particular health outcome translates into the product of duration of infectiousness (D) and efficiency of transmission (β), two of the three determinants of the reproductive rate in infectious disease transmission dynamics.^{26,27} Even if suppression is not total, such that β does not fall to zero and D may actually increase, the health outcome should be such that the product of β and D over a given period of time lowers the reproductive number relative to the product for an untreated STD. In cases with effective antimicrobial therapies, β does fall rapidly to zero, making duration of infectiousness the key parameter to consider in elucidating STD-related health-care seeking and health service delivery.

The timely and appropriate treatment of STDs is a function of four basic detection and treatment components (11 subcomponents) and one additional prevention component. These components may be viewed both in terms of the proportion of the infected population that never successfully complete the component (percent of individuals experiencing delay) *and* the time spent in each component by those who are able to move to the next one (duration of infectiousness) (Fig. 92-1). Although in the final analysis, both types of concepts are reducible to the single measurement of “infectious person days” or “person days of infectiousness” (referred to as person time of infectiousness [PTI]), conceptually differentiating between proportions of the population who never complete a component,

and the time it takes to complete the component for those who do, facilitates the identification of individual, population, and system level factors and the behaviors of infected individuals and providers that influence the components and the outcome of interest. The four components of the model follow.

Component I: lost to detection and resolution of infectiousness

This component refers to the proportion of infected individuals (both symptomatic and asymptomatic) who never receive treatment. It translates into PTI terms as the time elapsed from infection to resolution of infectiousness (if applicable) as determined purely by biological dynamics between the pathogen and the host. It includes symptomatic individuals who never seek health care, symptomatic or asymptomatic infected individuals who are not detected through testing, and symptomatic or asymptomatic individuals who are not brought to treatment through partner notification. Individuals may not be brought to treatment because they are never detected or because they are lost to follow up during components III or IV.

Component II: health-care seeking delays

This component focuses on time elapsed from infection to initial contact with the health-care provider who makes the

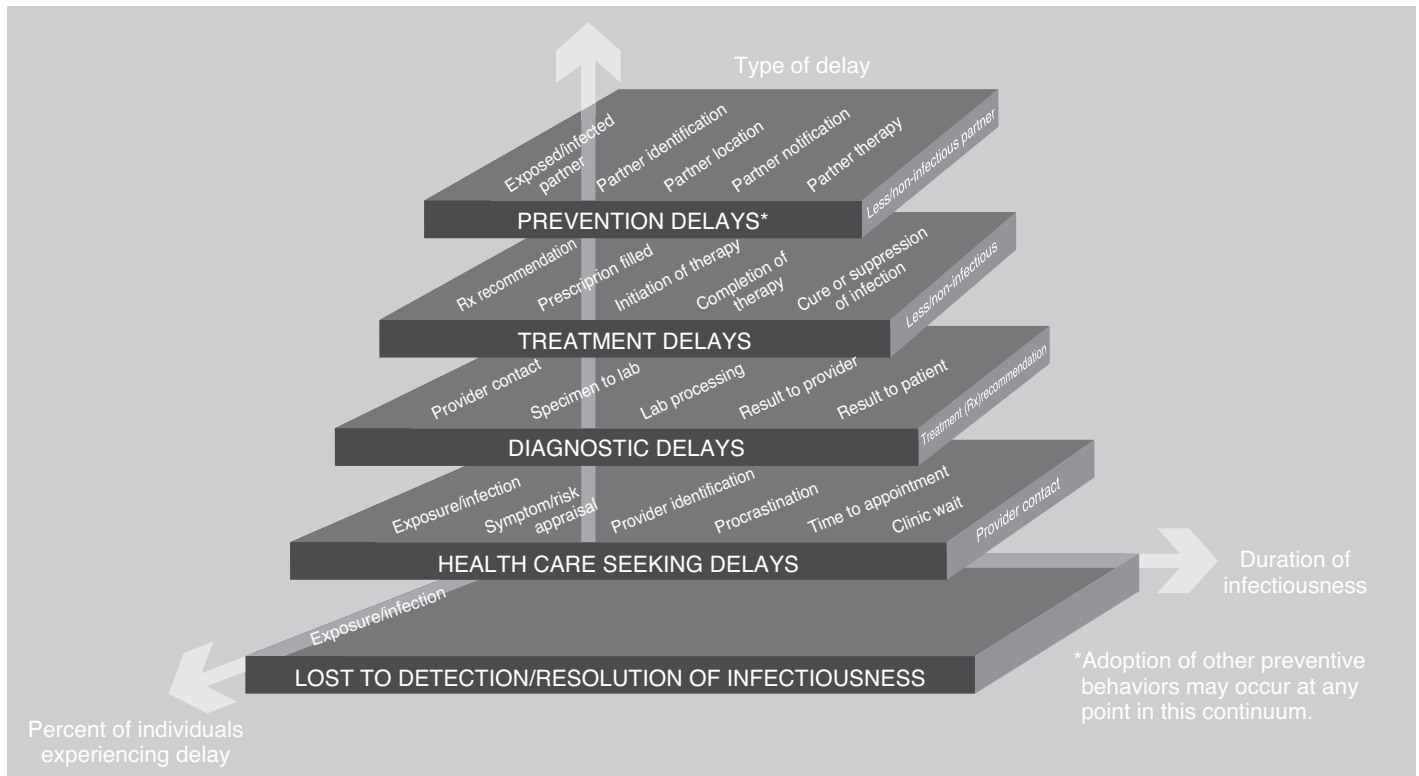


FIGURE 92-1. The person–time of infectious model.

diagnosis and recommends therapy. It is composed of five subcomponents: (1) Time elapsed in symptom or risk appraisal, during which the individual attempts to interpret symptoms, often by gathering additional information regarding the symptoms and their significance. Individuals may wait and see if the symptoms resolve on their own or they may attempt to treat themselves during this period. Asymptomatic individuals who suspect exposure may gather information regarding their potential risk of infection and wait to see if symptoms occur. (2) Time elapsed from decision that symptoms (or risk of exposure) require attention from a health-care provider to decision regarding where to seek care, often involving information gathering regarding types of providers and accessible service sites. (3) Time elapsed from decision to seek care from a specific provider or clinic to making the call or the visit to make the appointment, referred to as the procrastination period. (4) Time elapsed from making the appointment until the time of the appointment, which may range from minutes to days or weeks depending, often, on the health-care provider and system. (5) Time elapsed from arriving at the health-care facility to initial contact with the provider, which generally would not be longer than a few hours.

Component III: diagnostic delays

Time elapsed from initial contact with the health-care provider to communication of a diagnosis to the patient constitutes this component. It is conceptually composed of two subcomponents: time elapsed from initial contact with provider to diagnosis; and time elapsed from diagnosis to the provider's presentation of that diagnosis to the patient. In some circumstances, these subcomponents entail time elapsed to establishment of a laboratory diagnosis, followed by time elapsed from test result to the infected individual's return to the health facility to receive the test result. The first subcomponent includes the time it takes to send the specimen to the laboratory, the laboratory processing of the specimen, and the communication of the test result to the provider.

In other circumstances, providers may rely on clinical diagnosis based on signs and symptoms, reducing time elapsed for each subcomponent substantially. Availability of rapid tests on site can have the same effect. On the other hand presumptive treatment and clinical diagnosis may lead to coinfections being missed or misdiagnosed. Although a laboratory test will only reveal those infections for which tests are run, a negative test provides diagnostic information not available to providers relying on clinical diagnosis alone.

Component IV: treatment delays

This component consists of time elapsed from therapy recommendation to cure of bacterial and parasitic infections

and suppression of viral infections. It is composed of four subcomponents: (1) Time elapsed from the infected individual receiving the therapy recommendation to filling the prescription. (2) Time elapsed from the individual filling the prescription to actually starting the medication. (3) Time elapsed from initiation of therapy to completion of therapy. (4) Time elapsed from completion of therapy to actual cure or suppression. In some cases cure or suppression may occur prior to completion of therapy; however, data on the frequency of this occurrence are scarce. Some light is shed through study of incomplete adherence to multidose therapy regimens. One study observed therapeutic effects, even for partial completion of doxycycline regimens for chlamydial infection.²⁸ As such results may not generalize to other therapies and STD, multidose regimens nevertheless pose problems in that individuals may not complete the recommended course. On the other hand, single dose, directly observed therapy may also pose problems in that individuals may assume they are cured instantaneously and may resume sexual activity while still infectious.

Component V: prevention delays

An additional, post-PTI component in the model, referred to as *prevention delays*, includes time elapsed to the treatment of partners and adoption of preventive behaviors to prevent reinfection and infection with other sexually transmitted pathogens.

FACTORS THAT INFLUENCE PERSON-TIME OF INFECTIOUSNESS

A certain proportion of individuals infected with sexually transmitted pathogens are never identified as cases and are never treated (component I, Fig. 92-1). Properties of the pathogen and host, health seeking behaviors of the infected individuals, behaviors of providers, health system, and societal parameters all contribute to this component (Table 92-1). Some STDs tend to be more frequently asymptomatic compared to others. For example, only one out of ten individuals who had serologic evidence of infection with herpes simplex virus Type 2 reported ever having had genital herpes.²⁹ The odds of whether or not a particular infection is symptomatic also vary by gender. Many STDs tend to be more frequently asymptomatic among women than men. Persons with asymptomatic infections do not have a reason for seeking STD-specific health care, and some evidence suggests that asymptomatic persons and those with short symptom duration are less likely than others to seek care.³⁰ However, symptomatic persons are not always more likely than others to seek treatment, even when they suspect they are infected,^{22,31} especially if they lack appropriate skills and believe the net outcome of care-seeking will be negative.¹⁶

Table 92-1. Factors Influencing PTI: Lost to Detection

Properties of the pathogen and host	Proportions symptomatic; proportions with signs
Individual behavior parameters	Gender, risk recognition, symptom recognition, symptom description, extent of routine contact with health care
Provider behavior parameters	Risk assessment practices, screening practices, counseling practices, PN practices, compliance with programmatic and diagnostic guidelines
Health system parameters	Existence and quality of guidelines on risk assessment, screening, counseling, PN and diagnosis; existence and quality of STD health-education/health promotion programs; extent of reinforcement for provider compliance with existing guidelines; extent and quality of provider training, cost of care
Societal parameters	Level of education, level of overall health, available diagnostic technologies, availability, acceptability, accessibility of health care, cultural factors affecting sexuality, health, and disease, phase of epidemic and stage of program

The STD prevention program may successfully identify asymptomatic persons as being infected if effective screening initiatives are in place. Whether or not wide-scale screening is conducted depends on the stage of the particular prevention program and the phase of the particular epidemic.³² In addition, if the prevention program has effective health education initiatives for the general population in place and values the quality of the relationship between provider and patient, individuals who have been exposed to infection may recognize their risk and seek screening.

Another element of a prevention program that identifies infected persons (whether they are symptomatic or not) is partner notification. Provider behaviors also contribute to component I. Providers who do effective risk assessment help identify infected individuals even if the person is not seeking STD care. Thus, those STDs that tend to be asymptomatic; those providers who do not conduct effective STD risk assessment; and those prevention programs that do not include effective screening, partner notification, and health education for the general population all contribute to higher proportions of infected individuals who never get treated.

At a more global or societal level, the availability, accessibility, and acceptability of health care may contribute to the proportion of infected individuals who are never identified as cases and treated. Acceptability of available STD/HIV services may be a major issue for members of particular subpopulations. The interactions among levels of the PTI are visible here: for example, quality of physician–patient relationship (component II) affects medication adherence among Latino patients.³³ High levels of overall poor health may be associated with persons not seeking care even for severely symptomatic STDs. For example, observations in South Africa indicate that this may be the case for some parts of the population (Ronald Ballard, personal communication). The quality of existing clinical and laboratory STD diagnoses is another system level factor that may contribute to the proportion of infected individuals who may never be detected and treated, even if they are seen in a clinic setting. For example, in Morocco, some women with vaginal infections are not diagnosed as such.^{34,35} Lack of insurance (presumptively a marker for inability to pay) is a third contributor. Parents of children in the United States (up to age 17) with no or inconsistent insurance coverage were over 12 times more likely than those with continuous coverage to delay health-care seeking.³⁶ Uninsured 19–24-year-old men and women were three to four times more likely to delay or avoid seeking medical care and three to four times more likely to not fill a prescription. In Australia, lack of (private) insurance was correlated with leaving a clinic without seeking care.³⁷ Thus, among infected individuals who do seek care or get screened, a certain proportion may not be identified as cases. All infected individuals, whether asymptomatic or symptomatic, who are never identified as STD cases are considered to contribute to component I in the model proposed here. That is, component I refers to all infected individuals who are never identified as cases.

For those who are ultimately identified, there may be a variable period of delay before they are identified as infected. Such delays increase the probability of complications following infection and may contribute to further transmission of infection in the population. Properties of the pathogen and host, in combination with the symptom recognition and description behaviors of infected individuals and risk-assessment behaviors of providers contribute to health-care seeking delays (Table 92-2).

Some STDs are easier to detect than others, and some providers are better at detecting disease than others. For the latter, there appear to remain substantial knowledge gaps among primary care providers responsible for reproductive health care.³⁸ Even more troubling is that knowledge appears associated with putatively irrelevant factors such as physician age and gender (controlling for factors such as specialty). Ease and rapidity of detection may be affected by the diagnostic approach employed, including clinical versus laboratory diagnosis, choice of diagnostic test, and laboratory in

Table 92-2. Factors Influencing PTI: Health-Care Seeking Delays

Symptom/Risk Appraisal	Exposure/Infection		Contact with Provider	
	Identification of Provider	Procrastination	Time to Appointment	Clinic Wait
Properties of the pathogen and host	Proportions with symptoms			
Individual behavior parameters	Gender; ^a risk recognition, symptom recognition, symptom description, extent of routine contact with health care, awareness of availability, and properties of STD specific health services			
Provider behavior parameters	Clinical and referral practices, partner notification practices			
Health system parameters	Availability, accessibility, acceptability <i>and</i> visibility of services, clinic overload, hours of operation, waiting time to clinic appointment, waiting time in the clinic (after clinic arrival)			
Societal parameters	Organization of STD health services; organization of funding for STD health services; cultural factors influencing STD, STD services, and sexuality stigma			

^aThis demographic parameter is included here because it is so strongly associated with symptom status and health-care behaviors.

Table 92-3. Factors Influencing PTI: Diagnostic Delays

Specimen to Laboratory	Provider Contact	Treatment Recommendation	
	Lab Processing	Result to Provider	Result to Patient
Properties of the pathogen and host	Proportions with symptoms; proportions with signs: the extent to which signs and symptoms are differentiating		
Individual behavior parameters	Risk recognition and reporting; symptom recognition and reporting		
Provider behavior parameters	Risk assessment practices; clinical diagnostic practices; laboratory diagnostic choices; specimen collection practices		
Health system parameters	Availability of and choice for diagnostic technologies; availability and quality of diagnostic guidelines and protocols; quality and timeliness of laboratory procedures; extent and quality of training for clinicians and laboratory personnel; sanctions association with compliance with clinical and laboratory guidelines		
Societal parameters	Phase of epidemic; stage of program; technological, societal and economic development stage		

which the testing is performed. Some laboratory tests take longer than others. The prevention program and the health-care system affect these parameters both directly and indirectly through availability of screening guidelines, systems for timely reporting of laboratory results, and specific training for health-care providers and laboratory workers. Thus, factors that affect detection delays include properties of the infection that influence severity and duration of symptoms; symptom recognition and reporting behaviors of infected individuals; risk assessment, clinical diagnosis, and specimen collection behaviors of providers; and their test and laboratory

choices (Table 92-3). At the health-system level, diagnostic delays are affected by the availability of diagnostic technologies, availability and quality of screening guidelines, quality and timeliness of laboratory processing and reporting procedures, and the extent and quality of required training for clinicians and laboratory personnel. For example, rapid tests for HIV require training not just in their use and diagnostic parameters, but in counseling changes and possibly in identifying those for whom a test that does not require a blood draw and that gives results during the clinic visit would be most appropriate.

Table 92-4. Factors Influencing PTI: Treatment Delays

Treatment Recommendation		Less/Noninfectious	
Prescription Filled	Initiation of Therapy	Completion of Therapy	Cure of Suppression of Infection
Characteristics of the pathogen and host	Proportions symptomatic, severity of symptoms, responsiveness to medication, existence of resistant strains		
Individual behavior parameters	Adherence with dosage and recommendations; patient nonadherence may be owing to misunderstanding, forgetting, or intention (person may decide the dosage is too much or they are cured and do not need to continue medication)		
Provider behavior parameters	Therapy choices of providers, including number, dosage, timing of medications, and side effects provider compliance with treatment guidelines, consideration of patients' adherence to recommended therapy in therapy choices, communication behaviors in explaining the need for compliance.		
Health system parameters	Availability, accessibility, affordability of medications; availability, quality, extent of dissemination of treatment guidelines; availability of effective surveillance or resistant strains, emerging and reemerging infections; phase of the epidemic and stage of the program.		
Societal parameters	Overall level of education, level of development, level of health, relative importance of health		

At a more global societal level, the levels of economic and technological development and the phases of the program and the STD epidemic influence the choices of diagnostic protocols, the levels of training, the availability of appropriate guidelines, and the extent to which provider compliance with guidelines is assured.

Many factors contribute to treatment delays once a therapy recommendation has been made by the provider (Table 92-4). Properties of the infecting pathogen affect responsiveness or resistance to therapy. Therapy compliance (or adherence) behaviors of the infected individual determine whether the patient takes all of the prescribed medication at the prescribed times. Patients' nonadherence may be due to misunderstanding or forgetting, or may be intentional—the patient may experience a side effect, or decide the drug dosage is too much, or that he or she is already cured. Therapy delays are also influenced by the providers' compliance with treatment guidelines and choice of therapy, including the timing and duration of therapy, the number of medications to be taken, and consideration of whether the patient can adhere to the recommended therapy regimen. The providers' communication behaviors, including counseling the patient on the importance of taking the full course of medication at the recommended times, and assessing the patient's ability and willingness to comply with the recommendations, are also important. Finally, health-system properties including the availability, accessibility, and affordability of medications; quality and dissemination of treatment guidelines; and existence of an effective surveillance system that detects emergence of resistant strains in a timely manner are important in this context. In the United States, provider and

health-system adherence to CDC-recommended treatment guidelines is high,^{39,40} but the relative costs of single dose versus multidose regimens may still reduce patient adherence.

Factors that influence prevention delays or adoption of preventive behaviors also include those at individual, provider, and health-system levels (Table 92-5). At the individual level, motivation to reduce risk; current behaviors; current social environment; extent of control over social environment; ability and willingness to help with the identification, location, and notification of partners or to offer medication to partners all influence prevention delays. Providers' counseling behaviors, including counseling patients on adoption of preventive behaviors and on partner management issues are important in this context, especially to counter behavioral disinhibition. While HIV-infected patients overall appear to reduce their risk behaviors subsequent to discovering their status,⁴¹ some persons do not. Similarly, a Ugandan study of persons receiving ART revealed overall reductions in risk behavior, but not within marriage.⁴² Other Ugandan men exposed to a condom promotion campaign used more condoms, but also increased their numbers of partners.⁴³ Health-system characteristics, including the availability of continuous and effective health education and health promotion initiatives, maintenance and reinforcement of good relationships that encourage trust between health agencies and the populations they serve, availability of a variety of partner management procedures, effective triaging of patients to the partner notification and management procedures most appropriate to their needs, and well-trained staff to assist with partner notification and management,

Table 92-5. Factors Influencing PTI-Prevention Delays

Exposed/Infected Partner		Less/Noninfectious Partner		
Partner Identification	Partner Location	Partner Notification	Partner Therapy	Adoption of Preventive Behaviors
Individual behavior parameters	Level of motivation, current behaviors, social environment, control over social environment; ability and willingness to help with the identification, location and notification of partners or to offer medication to partners; willingness to engage in safer sex behaviors and future health promotion strategies (e.g., condom use, periodic testing).			
Provider behavior parameters	Counseling patients on adoption of preventive behaviors; counseling patients on partner management issues, partner notification practices, partner management behaviors; provision of risk reduction education or counseling to partners (via individual or dyadic intervention); distribution of condoms.			
Health system parameters	Availability of a variety of partner management procedures; effective triaging of patients to the partner management procedures most appropriate to their situation; availability of continuous and effective health education/health promotion; existence of good relationships that encourage trust between health agencies and population; stage of epidemic, stage of program.			
Societal parameters	Overall level of education, level of development, level of health; relative importance of prevention; the extent to which social networks are conducive to diffusion of interventions.			

when appropriate, may be the factors with the greatest impact on prevention delays. For example, King County's public health service permits patients infected with chlamydial or gonococcal infections to take prescriptions or medications to partners if they do not fall into empirically derived high-risk categories such as having many partners, or not expecting to see a given partner again.⁴⁴

The model described in the preceding is influenced by at least two conceptual approaches formulated earlier, namely, the force-of-infectivity concept and the application of Piot's public health model on tuberculosis to STDs, by Fransen.^{45,46} However, this particular conceptualization is new. Thus, the existing literature in this area does not lend itself to an organization exclusively by the components of our conceptual model. On the other hand, each component of the model is influenced by factors related to patients, providers, and the health system. In the following, we review the available data on STD/HIV care-seeking behaviors, provision of health services, provider behaviors, and health-care system characteristics.

STD CARE SEEKING BEHAVIORS

■ WHERE CARE IS SOUGHT

Available data on STD-specific care seeking behaviors are limited. However, interest in empirical investigations in this area has increased drastically within the past decade. Recent data from the United States indicate that the majority of people seek care for bacterial STDs at private physicians' offices (53%) or non-STD public facilities (35%), and only a

minority (12%) report seeking care at dedicated STD clinics.⁴⁷ The proportions seeking care for viral STDs are even more skewed (80, 15, and 5%, respectively). The proportion of adolescents and women seeking care at STD clinics are still lower.⁴⁷ A 1999–2000 national probability sample of U.S. physicians showed that physicians in private settings diagnosed STD widely,⁴⁸ with physicians in emergency departments diagnosing more STD per physician than even obstetricians and gynecologists.⁴⁹

Similar patterns are observed in health-care seeking for pelvic inflammatory disease (PID). Women with acute PID often seek care in emergency departments (EDs). According to data from the National Hospital Ambulatory Medical Care Survey (NHAMCS), an average of 258, 235 cases (4.2 per 1000 women between 15 and 44 years) of PID were treated in ERs.⁵⁰ High proportions of ER visits for PID occur among adolescents.

A somewhat different picture is gleaned from a focus on STD clinic attendees in a study that sought to characterize the demographic characteristics, STD morbidity, insurance status, reasons for attending the STD clinic, and preferences for where clients would seek STD services under universal access to STD care.⁵¹ Responses of 2490 clients attending five STD clinics for new problem visits indicated that walk-in services, confidentiality, and low cost were the major reasons why clients sought care at STD clinics. Even if they had unlimited choice, two-thirds of clients surveyed would still prefer to be seen at STD clinics in the future.

One study sought to determine how often STD clinic patients use other health-care sources and whether choice of other sources of care differed by gender and STD diagnosis.⁵²

Among STD clinic patients who reported treatment for an STD within the past year, 14% of men and 35% of women treated for STDs reported receiving care only in non-STD clinic settings. Women were significantly more likely to have received care in non-STD clinic settings, including doctor's offices (19.9 vs. 6.1%); emergency rooms (10.0 vs. 4.9%), family planning clinics (4.7 vs. 0.5%), and other sites (3.7 vs. 0.7%).

Results of a nationally representative general population survey conducted in the United Kingdom indicate that health-care seeking behaviors of people living in England are, in general, similar to those of people living in the United States.⁵³ Of the respondents, 8.3 % of men and 5.6% of women had attended an STD clinic in their lifetime, and, 3.4% of men and 2.6% of women had done so within the last 5 years. Behaviors, but not the attitudes, of STD clinic attendees differed markedly from those of nonattendees. As in the United States, clinics appear to attract primarily those with high-risk lifestyles but only a minority of those reporting risk markers for STD transmission attend STD clinics.⁵³

■ DELAYS IN CARE SEEKING

At the individual level, the first delay in receiving treatment for STDs relates to the time elapsed between the perception of STD-related symptoms by the patient and health-care utilization. A common response to illness is to “wait and see” if symptoms subside, persist, or worsen.⁸ For example, symptoms of gonococcal and chlamydial cervicitis are often mild, inconspicuous, or completely absent, and syphilitic chancres are not only painless, but resolve spontaneously, which presumably contributes to delayed health-care seeking. Many women interpret their STD symptoms as part of normal variation in their menstrual cycle.⁵⁴ Uncertainty regarding genital symptoms ultimately leads to health-care seeking, but only 45% of women motivated to seek care do so immediately.⁵⁴ In another study, about 25% of individuals with STD-related symptoms waited longer than 4 weeks before seeking care.⁵⁵ Delay in seeking care was particularly long among women living with one “permanent” partner, perhaps reflecting their perception of low STD risk associated with their own monogamous sexual behavior.⁵⁵ These data also suggested that the stigma concerning STDs may act as a barrier to prompt care seeking. Moreover, neither higher perception of vulnerability resulting from having sex with more than one partner without using a condom, nor being a recurrent attendee at STD clinics with STD-related symptoms resulted in less delay in seeking health care.⁵⁵ In fact, previous delayed health-care seeking may be a predictor of delayed health-care seeking in the present and future.⁵⁶ Perceptions about quality of care received may affect health-care seeking: a multicity study of 1201 health facility attendees and 806 persons from the surrounding communities showed that perceptions of quality of care were more closely related to seeking care for gonorrhea than were stigma or inconvenience

(even though the latter two factors were more negatively rated by respondents).⁵⁷

Apparently, prior to health seeking, compared to adolescent men, adolescent women spend a longer period of time on symptom appraisal, whereas time spent seeking social support, seeking information, and self-treating are common to both men and women.²² The average total care seeking interval (the interval from presumed infection to seeking care) was 9.6 days for symptomatic women, 5.8 days for asymptomatic women, 6.3 days for symptomatic men, and 7.3 days for asymptomatic men. Low income and perception of stigma related to STD were associated with longer delays in health-care seeking for adolescent women.²²

These findings highlight the importance of differentiating between symptomatic and asymptomatic infection with respect to delays in detection. In the case of symptomatic infection, the most important social and behavioral factors contributing to delays in detection are factors related to the client. In the case of asymptomatic infections, factors related to the behaviors of health-care providers and those related to the health system may play a more important role. Asymptomatic women may recognize that they are at risk following a risky sexual encounter, and seek screening. Alternatively, health-care providers may recognize risky behavioral patterns through history taking, or respond to demographic characteristics associated with risk for infection and screen asymptomatic women for a particular STD. Cases of disease may be missed and treatment delays may result through existing deficits in sexual history-taking,^{58,59} including comfort doing so.⁶⁰ Finally, the health system may provide guidelines that result in routine screening of asymptomatic women on the basis of individual or population level markers that may not be recognized by either the client or provider such as current U.S. recommendations to screen women ≤ 25 years annually for chlamydial infection.⁶¹ But these recommendations are not always followed and overall screening of women for STDs is inconsistent.⁶²

On the other hand, the difference between symptomatic and asymptomatic infections should not be overemphasized. In some populations, response to STD symptoms may be minimal and may, in fact, be associated with considerable delays in seeking health care. In one investigation of a chancroid outbreak in Mississippi, an assessment of health-care seeking behavior of male patients with ulcers showed long delays in seeking treatment and a substantial amount of unprotected sex with untreated ulcers during this delay.⁶³ The median time from onset of symptoms to clinic visit was significantly longer for syphilis (14 days) and chancroid patients (10 days) than for HSV patients (4 days); for 65% of all male ulcer patients there was at least a 1-week delay in receiving care.

Similarly, in one multisite study of delay in care seeking, of 1621 patients with genitourinary symptoms, over one-third (35% of men and 37% of women) presented to STD clinics

only after 1 week or more of symptoms.⁶⁴ Men with genital warts (73%), with nongonococcal urethritis (23.1%) or symptomatic men who were recent contacts to sex partners with STDs were significantly more likely to delay clinic attendance more than 1 week than men with gonorrhea (6.5%, $p < 0.001$ for each). Overall, 43.8% of women receiving specific clinical diagnoses other than genital warts delayed clinic attendance for more than 1 week. When asked why they delayed clinic attendance respondents were most likely to respond that they hoped their symptoms would “go away” (48.5% of men and 49.4% of women who waited 1 week or more before seeking care).

An additional issue related to health-care seeking among adolescents involves confidentiality. In a recent survey, a majority (58–69%) of adolescents indicated that they had health concerns they wished to keep confidential and that they would not seek health services because of these concerns.⁶⁵ An experimental manipulation of confidentiality guarantees (unconditional, conditional, none) found adolescents without an unconditional guarantee would be less likely to seek future health care and to disclose sensitive information during a visit.⁶⁶ Moreover, some jurisdictions have stringent requirements for reporting sexual behaviors. For example, providers in Texas are required to report identities of persons under 17 who are sexually active.⁶⁷

Perhaps related to issues of confidentiality, seeking to cure symptoms through self-treatment is one specific reason why people delay health-care seeking after onset of symptoms. In one study, women were almost two times more likely to self-treat than men, and the average incremental delay in health-care seeking associated with self-treatment was 2 days.⁶⁸ In another study conducted in Kenya, self-treatment was the most important factor contributing to delayed care seeking.⁶⁹

■ ADHERENCE TO THERAPY RECOMMENDATIONS

Poor adherence to therapy recommendations on the part of infected individuals is another factor that contributes to delays in cure and some proportions of infected persons not being cured. The literature suggests that among women with PID who seek care, suboptimal adherence to multidose regimens may exceed 65%.⁷⁰ Among women with asymptomatic gonococcal or chlamydial infections, on multidose regimens, noncompliance rates may be even higher. As noted earlier, some persons may be cured even with partial adherence to multidose regimens.²⁸

PROVISION OF STD SERVICES

■ SOURCES OF CARE

As is the case in the health-care seeking area, data on STD-related health-care provision are scant. Often, available data

are not specific to particular population subgroups or particular STD diagnoses. Nevertheless, in order to minimize time elapsed between infection and treatment for cure of curable bacterial or parasitic STDs and suppression of incurable viral STDs, it is important that information on where to seek care for STD-related symptoms (or suspicion of exposure to STDs) is available to the population; STD services are accessible and acceptable to the target population; communication between providers and patients is effective; and, where necessary, outreach services are available for hard-to-reach populations.

According to the first survey of a nationally representative sample of public health department STD programs ever conducted, in 1994, U.S. public sector STD services are limited in distribution, clinic hours, and outreach capacities and address a limited range of STDs. An estimated 1437 local health departments half of all local health departments in the country, provided STD diagnosis and treatment to clients, through 2 million visits, at 2587 clinic locations.⁷¹ Of those clients who received these services, 16% were under 18 years of age, 19% were 18 to 19, and 30% were 20 to 24; 6 out of 10 clients were women; 45% had incomes below the official poverty level, and 38% were between 100% and 250% of the poverty level; 55% were non-Hispanic whites, 35% were African Americans, and 9% were Hispanic. On average, 43% of these clients did not have any STDs. Among those who had a STD, 40% had chlamydia, 22% had gonorrhea, 5% had early syphilis, and 32% had some other STD. Almost all agencies offer testing and treatment for gonorrhea and syphilis, but only 82% offer testing for chlamydia.

Only 14% of local health departments that offer STD services do so in clinic sessions solely devoted to STDs. These health departments are much more likely to be in large metropolitan areas, and to have large client caseloads; they provide 37% of all STD visits annually, and most of their clients are men. Most local health departments that offer STD services integrate STD and other health services, such as family planning in the same clinic session (37%), or offer both integrated sessions and sessions devoted to STDs (49%). Providers that integrate STD services and other health care in the same clinic sessions tend to serve nonmetropolitan areas, serve smaller number of STD clients, and have women as the majority of their clients.⁷¹

The findings from the survey also indicate that 40% of the half of the local health departments that do provide STD services cannot see a new patient on the same day that he seeks care and 15% report that new clients have to wait 3 days or longer before being diagnosed and treated. Only 23% of STD clinics are open evenings, and only 5% are open on weekends. These data are consistent with those from a 1993 study of STD clinics in 24 metropolitan areas demonstrating that up to 46% of patients cannot be seen on the same day that they present for care.⁷² In terms of prevention delays (component V), two surveys found

health departments interview the vast majority of patients (89%) with syphilis for information pursuant to partner notification, but as few as 32% of HIV patients and less than 20% of patients with gonorrhea or chlamydial infection.^{73,74}

In aggregate, these data are remarkable in that they document the overburdening of public health department STD clinics serving clients living in metropolitan areas. An average of 3 days' delay in diagnosis and treatment would significantly add to the duration of infectiousness, and in the ecologic setting of metropolitan areas may greatly accelerate the spread of STDs.

Public health departments provide only one portion of all STD services. Preliminary results from a pilot study conducted in four states in the United States indicate that STD clinics report the greatest numbers of new STD cases diagnosed within the past 2 weeks: 46% report five or more new STD cases; followed by family planning clinics, 36%; colleges, 16%; hospitals, 15%; and abortion clinics, 12% (Abt. associates, personal communication). Of the specialties surveyed, those in emergency medicine and general practice reported the greatest numbers of new STD cases, similar to results found in a national probability sample of physicians in private (88%) and public (12%) settings.^{48,49}

STD vaccines have the potential to reduce the overall morbidity of associated diseases and to reduce their burden upon all practice settings where STD are diagnosed (see Chapter 99). In 2006, a safe, highly efficacious human papillomavirus (HPV) vaccine, developed by Merck, was licensed for use in 9–26-year-old women. Both this quadrivalent (HPV 6/11/16/18) vaccine, and a bivalent (HPV 16/18) vaccine developed by GlaxoSmithKline, prevent precancerous cervical and vaginal lesions, and for the Merck vaccine, genital warts persistent infection.^{75–77,78} For HSV-2, a 2002 trial estimated 73–74% efficacy for women who were seronegative for HSV-1 as well as HSV-2, but no efficacy for men or for women who were seropositive for HSV-1.⁷⁹ Efforts to produce a vaccine continue, as they do for HIV.

Most young women (for whom the HPV vaccines would be most useful), health-care providers, and parents are generally well-disposed toward STD vaccines, including for HPV.^{80–82} The effect of any efficacious vaccine eliminates delays attributable to care-seeking, diagnosis, testing or treatment, but only for those STDs for which a vaccine exists. Behavioral research is needed to inform how to ensure vaccination does not result in reduced health-care seeking or provision for other STDs (or for disease related to nonvaccine types of HPV and Pap smear screening for cervical cancer). However, with attention to such negative unintended consequences, the potential savings to health-care systems from virtually eliminating the need to test for vaccine-preventable diseases may be considerable and present opportunities to focus resources on other STDs.

Vaccine uptake is certainly not guaranteed by its mere presence. Vaccination against HBV has been available since 1982, when a national strategy targeting high-risk adults was implemented in the United States. The approach achieved poor coverage and was subsequently revised to the current universal immunization strategy. Primary HBV vaccination now occurs in infancy, and HBV incidence data between 1990 and 2002 (a decline of 90 among children and adolescents, 67% over all ages) reflect increasing success with this route.⁸³ However, vaccination of adults at risk for this sexually transmissible disease continues to be far less successful in spite of recommendations to vaccinate all previously unvaccinated adults.⁸⁴ Recent surveys in STD clinics indicate prevalent vaccination rates of roughly 10–20%.^{85,86} Although subsequent agreement to be vaccinated across studies runs to around 50–70%,^{87–89} adherence to the six-month, three-dose schedule results in many under-vaccinated at-risk adults.⁹⁰ Individual-level motivations to protect health and prosaic concerns such as time to protect health are related to refusal rates: some have suggested prevaccination counseling.^{85,88,89}

■ STD HEALTH-CARE PROVIDER BEHAVIORS

Health-care provider behaviors constitute a major contributing factor in determining the proportions of STD-infected individuals who never get detected or who are not treated even if detected. Provider behaviors also contribute to the delay between infection and cure. Provider behaviors that are important in this context include conducting STD risk assessment, arriving at a clinical or laboratory diagnosis, providing a therapy recommendation, providing counseling for preventive behaviors, and providing partner referral counseling and management. Available data on provider behaviors are limited; however, in recent years a few studies of provider behaviors have been conducted both in the United States and in the developing countries.

A recent national survey of U.S. health-care providers indicated that most providers do not actively assess patients' risk for STDs, but rely on patients to mention STD symptoms or concerns,⁹¹ although they do report taking appropriate clinical actions (but minimal partner management) when they suspect STDs.⁹² STD risk assessments are rarely a routine part of care by physicians or other office-based health-care staff. Only 16% of physicians and only 27% of other health-care professionals assess STD risk in all new adult patients. Fifty-five percent of physicians and 43% of other health-care providers stated that they conduct a risk assessment only when prompted by patients' symptoms or complaints. As considerable proportions of common STDs are asymptomatic,⁹³ and patients typically prefer physicians to bring up the topic of sexual behavior,⁹⁴ reliance on patients to disclose symptoms can easily lead to missed diagnoses or delayed

treatment. Only 65% of physicians and 63% of other providers collect information on a patient's prior history of STDs. A 1992 national survey of primary care physicians found that although the majority of these providers routinely asked about cigarette, alcohol, and contraceptive use, the percentage of physicians who would "usually" or "always" assess STD risk by asking about condom use, number and type of sex partners, or sexual orientation ranged from 27% to 31% with new adult patients and 27–52% with new adolescent patients.⁹⁵

Other provider behaviors related to STD detection are perhaps more difficult to study and data on these behaviors are not available. However, at a population level, whether providers use clinical diagnostic approaches, based on signs and symptoms, or laboratory diagnostic approaches may have a great effect on the proportion of infected individuals who are appropriately diagnosed, and on the length of time that elapses between the infected individual's initial contact with the provider and the identification of a cause of infection and, ultimately, effective treatment. Indeed, there are trade-offs between the more timely detection and treatment of a larger number of patients using clinical diagnosis and the more accurate detection of a smaller number of patients whose treatment may be delayed. Symptoms and signs for some STDs may not be reliable for diagnostic purposes. Many STDs are asymptomatic, particularly in women; moreover most populations do not receive adequate STD-related health education to provide them with symptom recognition skills. As mentioned earlier, in a nationally representative serologic survey, only one out of ten individuals with serologic evidence of HSV-2 reported having genital herpes.²⁹ Signs for STDs may also be misleading, particularly in women and particularly for nonulcerative STDs. However, even clinical diagnosis of genital ulcers may be problematic if providers fail to recognize that multiple etiologies are common in their population and do not tailor treatment regimens accordingly. For example, in a recent chancroid outbreak in Mississippi, cases of ulcers that were not clinically diagnosed as being caused by chancroid were found to be caused by *Hemophilis ducreyi* on testing with the polymerase chain reaction (PCR) technique.⁶³ In South Carolina, a 1993–1994 trial of STD diagnosis using clinical signs and symptoms with only Clinical Laboratory Improvement Act (CLIA) waived laboratory test (vaginal pH and endocervical swab test) instead of "moderately complex" CLIA tests (RPR, dark fields, Gram stains, and wet mounts) resulted in substantial increases in misdiagnosis, particularly for genital ulcers and discharge syndromes in women (Greene and Lindman, personal communication). Moreover, signs may vary across populations, depending on the phase of the particular epidemic and whether infections being diagnosed are predominantly incident infections or longstanding prevalent infections.^{32,35}

The choice of a laboratory test may be associated with other issues. The type of specimen that is required for a given test will determine not only patient acceptance of testing, but also ease of specimen collection, storage, and transport by the provider. Ease of specimen collection has increased with the advent of urine-based screening and rapid tests for some STD, including gonorrhea, chlamydial infection and HIV. But reliance on a particular method of specimen collection can inhibit collection of specimens for which, for example, blood draws are still required (e.g., syphilis). Time elapsed between specimen collection and receipt of the test result is another consideration in choosing between alternative diagnostic tests. Delay in receipt of test results contributes to longer durations of infectiousness in infected individuals and, in addition, may result in lower proportions of infected individuals being treated since some persons do not return to get their results and therapy recommendations. In one study that compared a rapid office-based test with standard cell culture for screening of women for chlamydial infections, the median interval between testing and therapy for women with positive screening cultures was 14 days. Nearly 25% of the women with positive screening cultures did not return for therapy.⁹⁶

Another study evaluated treatment outcomes of patients with positive cultures who had not received presumptive treatment at their initial visit, using retrospective chart reviews of computerized medical records. The findings indicated that overall, 20% of patients with positive screening cultures for gonorrhea and chlamydia failed to return to the clinic for treatment within 30 days of screening. Of those who did return, 30% did so only after at least 2 weeks had elapsed.⁹⁷

Although recommendations for detection and treatment are important factors influencing provider behaviors in these areas, some providers do not adhere to such recommendations. A recent study compared PID screening, diagnosis, treatment, and reporting practices among primary care physicians with the CDC guidelines for PID.⁹⁸ Fifty-five percent of primary care physicians surveyed had treated at least one case of PID during the preceding 12 months. Of these, 52% were unsure of, or did not follow, the CDC guidelines for PID, and only 44% reported that they consistently followed the CDC guidelines. Among the physicians who reported treating PID during the past year, only 3% answered all of the PID management questions in accordance with the CDC guidelines. Major deviations from the guidelines occurred in the areas of diagnosis (11%), overtreatment (11%) and undertreatment (12%).⁹⁸ A more recent study conducted in an emergency department did not address treatment deficits, but noted only 10% of PID as judged by CDC standards was reported within 6 months of diagnosis.⁹⁹

Based on findings from the national survey of providers, counseling behaviors of health-care providers could also be improved. Only 35% of physicians and 38% of other

providers routinely discuss safer sex or condom use with their herpes patients. Only 31% of physicians and 29% of other providers discuss telling sex partners about STDs,⁹¹ and less than half of adolescent males (26%) and females (43%) report discussing sexual health with a provider at their last visit.¹⁰⁰ Clinics with written protocols tend to fare better in regard to asking patients about their sexual practices than those without.¹⁰¹ Patient and provider expectations of the clinical encounter may vary significantly. Patients expect to be examined in a timely fashion, and excessive waiting times or early clinic closures tend to frustrate and distance patients from the health service delivery system. Lack of privacy and confidentiality in the clinical encounter create further problems. In one study, in St. Louis, Missouri, 55% of women and 44% of men were dissatisfied with the amount of time they had to wait to be seen; and 26% of women and 34% of men stated that their privacy was not preserved in interactions with the clinical staff.¹⁰²

■ STD HEALTH-CARE SYSTEM CHARACTERISTICS

Several properties of the health system have important effects on the time elapsed between infection and cure of bacterial or parasitic STD or suppression of viral STD. These include education and training of providers, availability and distribution of diagnostic tests, availability and distribution of medications, and program and practice guidelines, organization and funding of basic services necessary for effective STD prevention including laboratory diagnostic services, screening services, and partner management services.

Education and training of health-care providers in STD and HIV/AIDS is often inadequate, although curricula for sexual health care exist.^{103,104} In 1991, 102 medical schools of 126 queried in the United States and Puerto Rico reported the extent of clinical training for medical students in the areas of sexually transmitted diseases (STD) and HIV/AIDS. The median number of hours of clinical training in STD, ranged from 1 to 5 hours (internal medicine and obstetrics and gynecology were the highest). The median number of hours of clinical training in HIV ranged from 1 to 4.5 hours (internal medicine). The departments most likely to have STD training as an explicit objective were obstetrics and gynecology (87%) and internal medicine (73%), whereas the least likely were dermatology (26%), urology (26%), and psychiatry (21%). Clinical training in HIV/AIDS was most likely to be an explicit objective in internal medicine (86%) and obstetrics and gynecology (68%), and was least likely in dermatology (23%) and urology (15%). A clinic specifically devoted to STD existed at 42% of institutions, and one devoted to AIDS existed at 73%, but an exclusive elective for medical students in STD or HIV/AIDS existed at only 37% of the institutions. In the 10 years prior to 1991, the amount of

clinical training in STD had decreased at 6% of the institutions, remained the same at 17%, and increased at 77%.¹⁰⁵ Particularly in the areas of STD diagnosis, treatment, and prevention, new technologies and knowledge accumulate rapidly. Thus, there is an additional need for continuing education of health-care providers. However, national data on the numbers and proportions of health-care providers who receive continuing education in the STD area are not available. Moreover, a formal assessment of provider education, training, and continuing education needs has not been conducted. Posteducation training that involves physicians carries promise: in one trial, physicians in a managed care organization who participated in ongoing sessions devoted to improving screening conducted more screening and uncovered more disease than other physicians.¹⁰⁶ But these results are minimally applicable to physicians in solo practice or small-group multispecialty settings.

Since many STDs are asymptomatic or have nonspecific symptoms, laboratory diagnosis is required for their detection. Underuse of laboratory testing, owing to lack of availability of reagents or other resources, may limit appropriate detection, reporting, and treatment of STDs. No national data are available to assess the facilities that offer testing for various STDs or estimate training and support needs for the future.¹⁰⁷ A 1996 study analyzed responses to a survey inquiring about the range of tests offered, changes in testing, and reasons for changes.¹⁰⁷ Results indicated that, in recent years, the number of facilities testing for *Chlamydia trachomatis* has increased with increased funding and availability of nonculture tests; the number of facilities testing for chancroid and gonorrhea has decreased; and that the implementation of the Clinical Laboratory Improvement Act (CLIA) may be associated with a decrease in the number of facilities performing tests for STDs. Most of the 405 responding facilities collected specimens for nontreponemal tests for syphilis (86.9%). Since each facility's information was last updated, the number reporting testing for *C. trachomatis* rose from 39.5% to 71.1%, but testing for gonorrhea and chancroid decreased from 90.1% to 81%, and from 44.9% to 7.9%, respectively. Of the 364 responses to a question on changes in tests performed in the last 2 years, 249 (68.4%) reported no change, 81 (22.3%) reported an increase, and 37 (10.2%) reported a decrease. The most frequently added tests were nonculture tests for *C. trachomatis* (34 of 81 [42%]), and the most frequent reason for adding tests was targeted funding (25 of 81 [30.9%]). The most frequently discontinued tests were cultures and Gram stains for gonorrhea (15 of 37 [40.5%]) and other in-house tests (9 of 37 [24.3%]). Most facilities that discontinued testing cited CLIA as the reason. By 2004, 94.7% of 114 labs surveyed reporting conducting over 3.5 million tests for *C. trachomatis*, of which 64.4% were through nucleic acid amplification tests (NAATs).¹⁰⁸

Gonorrhea testing had rebounded compared with the 1996 results, with the same proportion of responding labs reporting testing for *N. gonorrhoeae* as for *C. trachomatis* (94.7%).¹⁰⁸ Sixty-one percent of tests for *N. gonorrhoeae* in 2004 were NAATs. Of the 114 responding labs, 93.9% reported testing for syphilis, although the proportion using a treponemal test was lower, 75.4% (i.e., some labs presumably had to send RPR-positive samples for confirmation as syphilis elsewhere). The proportion of labs running tests for other STD was much lower: 47.4% tested for HSV; under 5% tested for HPV or trichomoniasis.¹⁰⁸

More promising, however, is the rise in attention to home-based testing using urine-based tests, which may decrease delays in care-seeking and possibly prevention (if tests can be sent to partners of infected persons). Home testing appears popular with adolescent females relative to clinic visits,¹⁰⁹ although the presence of asymptomatic disease suggests routine health-care seeking should not be compromised.

The advent of new tests for HPV and HSV presents both opportunity and challenges for laboratories. A newly approved DNA test is suitable for detecting high-risk HPV types (although it does not detect *which* high-risk type exists); the specimens are cervical cells as for a Pap test.¹¹⁰ The DNA test reduces diagnostic delays in that high-risk HPV can be identified from a single test collected during a Pap test. For HSV-1 and HSV-2 testing, “real time” PCR tests have reliably detected HSV among asymptomatic individuals¹¹¹ and can even be used for estimating susceptibility of a given infection to treatment (which could reduce treatment delays).¹¹² The challenge for laboratories lies in the training and equipment needed for a new test.

An additional aspect of laboratory diagnosis that affects the timely and appropriate treatment of STDs relates to the timeliness of laboratory testing and reporting of positive test results. Many health-system level factors may contribute to timeliness of laboratory services, including inadequate resources, overburdening of particular facilities owing to absolute overload or uneven distribution of demand for laboratory services, and characteristics of diagnostic technology. In a study of completeness and timeliness of laboratory surveillance for syphilis, timeliness was found to be a much more serious problem than completeness, especially for laboratories outside public clinics.¹¹³

Availability of up-to-date program and practice guidelines for the prevention, detection, and treatment of all STDs is an important health-system parameter with great potential impact on timely and appropriate STD management. However, such availability does not assure provider compliance with guidelines. In fact, recent data indicate that compliance levels may be quite low, even in the United States, where higher levels of compliance with practice guidelines would be expected in light of malpractice legislation.⁹⁸

Organization and funding of STD services may be the most important health-system parameter influencing timely treatment of STDs. In the United States, the evolution toward managed care has accelerated dialogue between public health and private medicine regarding the mutual responsibilities of these sectors. In general, the public health sector is more narrowly defining its responsibilities to encompass population level health services, including health planning, disease surveillance, and primary prevention activities (such as health promotion and education, partner notification, vaccines, and regulatory strategies). It will rely on the private medical sector to accept more of the responsibility for providing individual level detection and treatment services.

For STDs, the private sector can play an important and expanded role in disease prevention. However, those without insurance for private care include many of the economically and socially marginalized persons most likely to acquire and transmit STDs. Furthermore, with the advent of Medicaid managed care, some of the distinctions between private and public sector are beginning to blur. Because early detection and curative treatment represent primary prevention for communicable diseases, the public health sector must ensure that accessible, acceptable services for STD prevention are available to both the uninsured and insured alike.¹¹⁴

STD health-system characteristics in the United States are probably not as favorable to minimizing time elapsed from infection to cure or suppression of STDs as those in other developed countries. The limited data available from developing countries indicate that health-system characteristics in many of these countries also greatly compromise the timely and appropriate treatment of STDs.

One initiative undertaken by AIDSCAP, called targeted intervention research (TIR), has brought to light many aspects of STD health-system characteristics as well as health seeking and provider behaviors in several developing countries, including Malawi, Senegal, Ethiopia, Zambia, and the Philippines.¹¹⁵ Findings point to the importance of lack of knowledge regarding STDs, lay theories regarding STD etiology, perceptions of stigma, seeking of health care through inappropriate sources such as pharmacies and traditional healers, inadequate knowledge and training regarding STD diagnosis and treatment among health-care providers, lack of resources for appropriate diagnostic technologies, and inadequate communication between patients and providers as the main factors impeding appropriate and timely diagnosis and treatment of STDs in many developing countries.¹¹⁴ A survey of STD case management conducted in Malawi in 1994 found that the prevention indicator rate for correct assessment and treatment of STD patients was 11% (81% for history taking, 46% in physical examination, and 13% in current antibiotic treatment according to national guidelines).¹¹⁵ In the same study, the prevention indicator

rate for overall patient counseling was 29% (65% for partner notification and 40% for condom advice). Only 16% of patients with genital ulcers were treated effectively for chancroid and 56% were treated effectively for syphilis. Female STD patients were treated less comprehensively than male STD patients, and only 20% of STD patients were offered condoms.¹¹⁵ These findings reflect the net effects of inadequacies in the prevention and control of STDs resulting from a multiplicity of problems in the interface of health seeking behaviors, provider behaviors, and health system-characteristics related to STDs.

IMPLICATIONS FOR FUTURE RESEARCH AND PREVENTION EFFORTS

The AIDS epidemic has resulted in far-reaching advances in our understanding of and ability to change risky sexual behavior. In contrast, empiric work on the prevalence and determinants of timely and effective STD-related health care, and on the development and evaluation of interventions to achieve it remains extremely limited. Future research in this critical area must bridge factors operating at the client, provider, and health-system levels in considering each of the components and subcomponents contributing to “person-time of infectiousness.” Research to define and address factors shaping component I (lost to detection) is likely to be particularly important because of the large numbers of infected individuals that fall into this category, especially in subpopulations and communities with the highest STD rates. New STD and HIV detection technologies, including urine and saliva tests, will facilitate the kinds of population-based studies that are needed to answer questions about component I. Research on factors shaping components III and IV (diagnostic delays and treatment delays) is even more limited than that on health-care seeking. Such research is critical to conduct since provider behaviors and health-system variables may prove more responsive to interventions than behaviors of the general population. Advances in STD and HIV detection technologies, prevention technologies (especially vaccines), and the organization of health services in the United States also suggest that, in many communities, STD/HIV-related health-care behaviors may be uniquely vulnerable to intervention or in transition already. This makes the need for both descriptive and intervention research in this area particularly urgent and relevant to prevention of all STDs, including HIV infection.

The PTI conceptual framework and the data summarized in this chapter also have profound implications for STD prevention efforts. They highlight the need for interventions that promote early and effective STD-related health-care behaviors to go beyond the traditional focus on partner notification, and, in some settings, clinic-based counseling. STD prevention programs must build on local assessment of the PTI

components and subcomponents not only to target improvements in clinical prevention services to those provider and health-system factors responsible for the greatest delays, but also to incorporate into health promotion efforts tailored messages that will reduce loss to detection, health-care seeking delays, and noncompliance with management recommendations in high-risk subpopulations. Partner notification approaches should also be reexamined in light of the concepts discussed here. Finally, available data clearly indicate that the majority of STD care is not sought through public sector categorical clinics. To optimize STD-related health care, STD services must also be offered as part of routine primary health care by both public and private sector providers. This means that, in the future, efforts directed at provider behaviors, such as guideline development, training, and evaluation, must extend to providers in these settings, and stronger linkages must be forged across these health-system components.

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Condoms and Other Barrier Methods for Prevention of STD/HIV Infection and Pregnancy

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INTRODUCTION

When used consistently and correctly, male latex condoms can reduce the risk of pregnancy and many sexually transmitted infections (STIs), including HIV. Strong evidence, based on biologic plausibility, laboratory studies, and mounting data from clinical studies supports the public health recommendation that condom use reduces the risk of STI for sexually active persons. The general consensus is male condoms must play a central role in any STI/HIV prevention program.¹

In this chapter we provide an overview of the effectiveness of male latex condoms for prevention both of STI/HIV and pregnancy and describe trends in condom use. The majority of the chapter is dedicated to the latex male condom because this method represents the most commonly used barrier method worldwide. We also provide brief overviews of the effectiveness of other physical barriers, including natural membrane and synthetic male condoms, female condoms, diaphragms, cervical caps, and barriers for oral sex.

MALE CONDOM

Male condoms protect the wearer and his partner from infection by covering the penile glans and shaft, which are the major portals of entry and exit for STI pathogens. To be effective, condoms must be placed on the penis prior to any genital contact and used throughout intercourse, must remain intact, and must be used consistently. About 97% of male condoms available in the United States are manufactured from latex.² Other male condoms available are made of either the intestinal caecum of lambs (“natural membrane” condoms) or synthetic materials.

Condoms are regulated as medical devices by the U.S. Food and Drug Administration (FDA), and manufacturing standards have become more stringent in recent years.³ Every condom is tested electronically for holes and weak spots before it is packaged. Samples of condoms also undergo a series of additional laboratory tests for leakage, strength, dimensional requirements, and package integrity.⁴ A recent Consumer

Reports Survey showed that all condoms tested met industry standards, and that test performance was not related to condom price, thickness, or country of manufacture.⁵

■ LATEX CONDOMS, EFFECTIVENESS

Laboratory studies indicate that latex condoms provide an effective physical barrier against passage of even the smallest sexually transmitted pathogen (hepatitis B).^{2,6–12} When placed on the penis before any genital contact and used throughout intercourse, the condom prevents direct contact with: (1) semen; (2) genital lesions and subclinical viral shedding on the glans and shaft of the penis; and (3) penile, vaginal, or anal discharges. Condoms reduce the risk of STIs that are transmitted primarily to or from the penile urethra such as HIV, gonorrhea, chlamydia, trichomoniasis, and hepatitis B. Condoms should also reduce the risk of STIs that are transmitted primarily through skin or mucosal surfaces when these areas are covered by the condom, such as genital herpes, syphilis, chancroid, and human papillomavirus (HPV) infection. The protection provided by condoms may be less when these STIs involve areas not covered by the condom.

The levels of protection from condoms are likely to vary for different STI because STIs vary in their routes of transmission, infectivity, and prevalence. Clinical studies have shown inconsistent protective effects for most STIs, with the exception of HIV.² Much of this inconsistency in condom use effectiveness estimates can be attributed to limitations in study design. Specifically, limitations in measurement of self-reported condom use and exposure to infected partners complicate the interpretation of condom effectiveness estimates.^{2,3,13–32}

HIV

Clinical studies have shown latex condoms to be highly effective against sexually acquired HIV infection,^{17,32–34} the most consistently fatal STI. Thus, male latex condoms should be promoted to sexually active clients at risk for STI for this reason alone.³⁵ Studies of discordant couples (where one partner is infected with HIV and the other is not) consistently

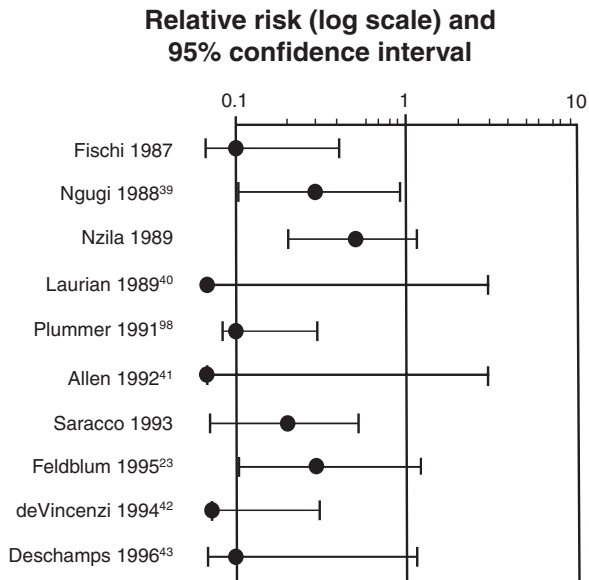


FIGURE 93-1. Risk of HIV infection among heterosexual couples using condoms (selected cohort) studies.

demonstrate that condoms provide effective protection against HIV (Fig. 93-1).^{36–44}

Investigators have summarized estimates of the effectiveness of condoms for HIV prevention into a single measure in meta-analyses.^{17,33,45,46} Because these meta-analyses are also impacted by biologic and epidemiologic factors (e.g., stage of HIV infection, coinfection with other STIs, validity of self-report) that may vary across studies, these summary estimates of effectiveness should not be considered precise. The two most recent meta-analyses^{17,33} place the estimated effectiveness of consistent condom use between approximately 80% and 95%. The most recent meta-analysis¹⁷ of discordant couples also illustrates that transmission of HIV infection among consistent condom users is infrequent. Across the 13 cohort studies reviewed, there were only 11 seroconversions among 587 consistent users, and many individual studies showed no seroconversions.

Other STIs

The overall quality of clinical studies to assess the effectiveness of condoms against acquisition of STIs other than HIV is considerably weaker. Systematic reviews have been conducted for clinical studies for several STIs, including gonorrhea, chlamydia, genital herpes, and HPV.^{13,31,32,47,48} A recent systematic literature review of 45 published studies of condom use and gonorrhea and chlamydia concluded that condoms reduce risk in both men and women (Figs. 93-2 and 93-3).¹³ Many studies did not measure critical factors such as exposure to infected partners, consistent and correct condom use, or incident infection. Therefore, the observed protective effects are likely to be underestimates of the true protective effect.

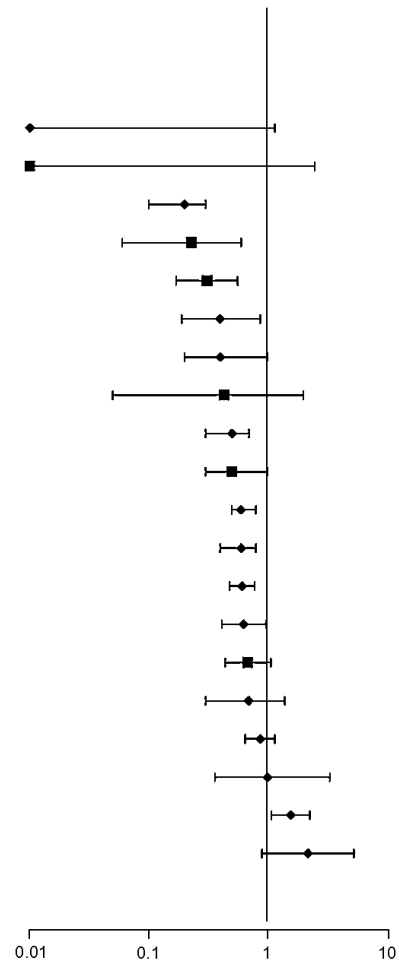


FIGURE 93-2. Studies assessing the association between condom use and risk of gonorrhea (1966–2004). Measure of effect and 95% CI (Females = ♦, Males = ■). (Adapted from Warner L, Stone KM, Macaluso M, Buehler JW, Austin HD. Condom use and risk of gonorrhea and Chlamydia: A systematic review of design and measurement factors assessed in epidemiologic studies. *Sex Transm Dis* 2006; 33: 36–51.)

Adequately controlling for confounding from differences between condom users and nonusers (such as exposure to infected partners) appears to be among the most critical limitations of studies. Two recent studies of gonorrhea and chlamydia restricted to sexually transmitted disease (STD) clinic patients with known exposure to infected partners, for example, reported protective effects for condom use which were two-to-three times stronger than those reported for patients with unknown exposure in the same studies.^{18,49} Moreover, other recent analyses^{14–16} have clearly documented that condom effectiveness is underestimated in studies because of limitations in study design.

For HPV, a systematic literature review in 2004 concluded that the effectiveness of condoms to prevent HPV infection in women and men is unknown due to difficulties distinguishing new from preexisting infections and the failure of most studies to analyze consistent and correct condom use.⁴⁸ Since then, a well-designed prospective study has

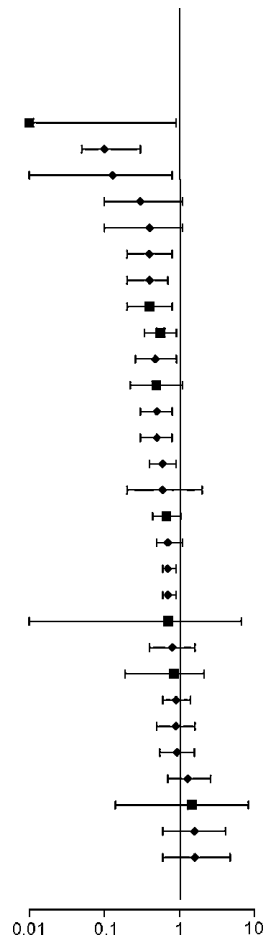


FIGURE 93-3. Studies assessing the association between condom use and risk of chlamydia (1966–2004). Measure of effect and 95% CI (Females = \blacklozenge , Males = \blacksquare). (Adapted from Warner L, Stone KM, Macaluso M, Buehler JW, Austin HD. Condom use and risk of gonorrhea and Chlamydia: A systematic review of design and measurement factors assessed in epidemiologic studies. *Sex Transm Dis* 2006; 33: 36–51.)

demonstrated that consistent and correct use of condoms can reduce incident cervical HPV infection in young women.⁵⁰ In addition, literature reviews have concluded that condom use can reduce the risk of HPV-associated diseases including genital warts in men^{2,31,48} and women,⁴⁸ cervical intraepithelial neoplasia (CIN), and cervical cancer.^{2,31,48} Two recent randomized trials showed condom use was associated with higher rates of regression of HPV-associated penile lesions in men,⁵¹ CIN in women,⁵² and higher clearance rates of HPV infection in women.⁵²

Systematic literature reviews have concluded that condom use reduces risk of genital herpes simplex virus (HSV) transmission in women^{32,47} and men.³² The single study of discordant couples found that condom use was associated with a significant reduction in risk of acquiring HSV-2 for women but not men.⁵³ Two recent prospective studies showed that condom use reduced risk of HSV-2 acquisition for both men and women.^{54,55}

The body of literature examining condom effectiveness for preventing the remaining STIs is sparse by comparison.

Despite limitations that would tend to underestimate the protective effect, several studies have demonstrated that condom use reduces the risk of PID^{56–58} and trichomoniasis^{59–61} in women^{62,63} and syphilis in men and women.^{59,62,64–66} One study showed condoms reduced risk of Hepatitis B in women.⁶⁷ No studies have specifically addressed condom use and risk of chancroid.

Pregnancy

Three studies meeting modern standards for design, conduct, and analysis⁶⁸ provide compelling evidence on the effectiveness of male latex condoms to prevent pregnancy.^{69–71} The most recent review of these three trials estimated that during the first 12 months of consistent use of the male latex condom, 2% of women will conceive; the corresponding annual pregnancy rate for typical use (including inconsistent and/or incorrect use) is estimated to be 15%.⁶⁸ By contrast, the typical annual pregnancy rate for women not using contraception is 85%.

FACTORS REDUCING CONDOM EFFECTIVENESS

Condom effectiveness depends heavily on the skill level and experience of the user.³ Studies have documented relatively high levels of problems when condoms are used, many of which can be minimized with appropriate counseling and practice.^{16,19,72–74}

Common problems with condoms that may place users at risk for STIs and pregnancy include the following:

1. *Failure to use condoms with every act of intercourse.* Nonuse of condoms, rather than poor condom quality or other condom-related problems, is the most common problem.⁷⁵ The highest single priority for any STI/HIV program should be to address factors that lead to nonuse of condoms.
2. *Failure to use condoms throughout intercourse.* Recent studies have documented that some men put on condoms after starting intercourse or remove condoms before ejaculation.^{16,19,23,76} These behaviors, which represent product misuse, could expose users and their partners to risk of pregnancy or STI. Men and women should be encouraged to use condoms every time from start to finish.
3. *Condom breakage and slippage.* Although users often fear the condom will break or fall off during use,^{77,78} these events are rare with proper use and tend to be concentrated among a small proportion of users.⁷⁹ The majority of studies show that, during vaginal sex, condoms break approximately 2% of the time during intercourse or withdrawal; a similar proportion slip off completely.^{3,69,80–84} However, rates of breakage and slippage vary widely across some studies (0–22% for breakage;^{73,80} 0–9% for slippage).^{80,85} For studies that have recorded

higher breakage and slippage rates, it is unknown how much of this variability is attributable to incorrect use and how much is due to misreporting of these events.

Reviews of studies evaluating breakage and slippage during anal intercourse indicate the rates may be slightly higher than during vaginal intercourse.^{86,87}

4. *Improper lubricant use with latex condoms.* Unlike water-based lubricants (e.g., K-Y Jelly), oil-based lubricants (e.g., petroleum jelly, baby oil, and hand lotions) reduce latex condom integrity⁸⁸ and may facilitate breakage. Some individuals use oil-based products as condom lubricants, mistaking them for water-based lubricants because they readily wash off with water. Because vaginal medications (e.g., for yeast infections) often contain oil-based ingredients that can damage latex condoms, clients who will be using these medications should be advised to remain abstinent, use synthetic condoms, or use other protective measures until the medication is fully completed and the infection is cured.

■ N-9 LUBRICATED CONDOMS

Condoms lubricated with a small amount of the spermicide nonoxynol-9 (N-9) have been available in the United States since 1983. However, their use is not recommended because spermicidal condoms are no more effective than other lubricated condoms despite their higher cost and shorter shelf life.⁸⁹ Also, concerns have been raised about N-9 products in general, because high frequency use of vaginal N-9 products may cause genital ulceration and irritation and therefore facilitate transmission of STIs including HIV (see Chapter 94 on Topical Microbicides and Other Chemical Barriers for Prevention of STD/HIV Infection and Pregnancy). Since the amounts of N-9 contained in a spermicidal condom are much lower than those found in vaginal products, they are probably less likely to cause adverse effects; however, spermicidal condom use was associated with increased risk of urinary tract infections in young women in one study.⁹⁰

■ NATURAL MEMBRANE CONDOMS

Natural membrane condoms (“natural skin,” or “lambskin”) are made from the intestinal caecum of lambs. No contraceptive or STI prevention effectiveness data are available. Unlike latex condoms, natural membrane condoms contain small pores in the surface that may permit the passage of viruses, including hepatitis B virus, herpes simplex virus, and HIV and thus may not offer the same level of protection as latex condoms.^{9,91} Therefore, they should not be recommended for STI/HIV prevention.

■ SYNTHETIC MALE CONDOMS

Male condoms manufactured from polyurethane or other synthetic materials offer several advantages over natural rubber

latex condoms. Synthetic condoms are generally odorless, colorless, nonallergenic, have a longer shelf life, and are compatible with both oil-based and water-based lubricants.^{3,92} Three synthetic condoms have been cleared by the U.S. FDA and are currently available in the United States (Avanti, Trojan Supra, and eZ·on). For pregnancy prevention, synthetic male condoms have similar rates to their latex counterparts. However, the effectiveness of synthetic condoms in preventing STI/HIV has not been studied and FDA labeling restricts their recommended use to latex sensitive condom users.

■ CONDOM PROMOTION

Despite evidence that condom use can effectively reduce the risk of unintended pregnancy and many (STI), including HIV infection, the promotion of condoms remains controversial in many countries, including the United States. According to two recent reviews,^{93,94} behavioral interventions featuring condom promotion have been associated with increases in reported condom use^{95–101} and, to a lesser extent, decreases in STI incidence.^{94–96,102}

The type of condom offered has little influence on measured level of protection. A four-country intervention focused on condom attributes found that providing a choice of condoms led to increased acceptability but had no impact on self-reported use or incident infections.¹⁰³

Latex condoms are among the most inexpensive and cost-effective contraceptives, given the additional protection provided against STI.³ Condom distribution has also been shown to be cost-effective for STI prevention in high-risk populations.^{104,105} Though widespread support exists for targeted interventions to encourage condom use,¹ concerns have been raised about the potential negative consequences of condom promotion.¹⁰⁶ Increased promotion¹⁰⁷ or availability¹⁰⁸ of condoms may not necessarily translate into increased levels of use. Also, some interventions promoting condoms may result in a “disinhibition” effect¹⁰⁶ that facilitates the onset or frequency of high-risk sexual activity, as suggested by some studies.^{109,110} However, the most recent meta-analysis of 174 sexual risk reduction intervention studies concluded that condom-related interventions do not “inadvertently undermine sexual risk reduction efforts by increasing the frequency of sexual behavior.”¹¹¹

Levels of condom use have increased in recent years; however, current levels of use remain low based on results of national surveys of adolescents^{112,113} and adults.^{114–117} The low levels are insufficient to have a major public health impact on preventing pregnancy and STI. Not surprising, consistency of condom use is higher in casual than primary partnerships because of the perceived higher risk of infection. However, even among couples discordant for HIV or genital HSV, where a risk for infection is known, fewer than

half of couples regularly use condoms.^{17,53} New strategies that emphasize condom use for contraception in addition to disease prevention (dual protection),¹¹⁸ as well as new condom technologies that can address personal (e.g., device, psychological, and logistical) barriers to use, may help increase overall levels of use.

■ ROLE OF CONDOMS IN COMPREHENSIVE HIV/STD PREVENTION STRATEGIES

Like any prevention tool (e.g., seat belts, airbags, smoking cessation programs, virginity pledges), condoms are not 100% effective. What then is the appropriate role of an imperfect prevention method, like condoms, among strategies to reduce HIV spread? Those using various approaches to preventing STI/HIV, as well as other health conditions, recognize that incremental, partially effective steps work best to produce collectively effective (but not perfect) prevention programs.¹¹⁹ Controlling the spread of STIs will require different, mutually reinforcing techniques.

Although these combined prevention strategies can dramatically affect HIV spread,¹²⁰ they need to be carefully designed and implemented. Accurate messages about condoms must build on (and not substitute for) a wide range of HIV/STI risk avoidance and risk reduction approaches.¹²¹ These approaches include delayed initiation of sexual intercourse, mutual faithfulness, and selection of low-risk partners.¹²² Together with condoms, these reinforcing epidemiologic truisms have been labeled both now and in the past as an “ABC strategy:” abstinence, be faithful to one partner, or—if “A” or “B” cannot be achieved—use condoms.¹ This ABC approach defines an appropriate role for condoms as an essential part of a larger armamentarium for HIV prevention.

■ CONDOM INSTRUCTIONS

Instructions for condom use are often overcomplicated and may have no scientific basis.^{3,123} During a WHO experts meeting (Geneva, June 22–24, 2005) to develop a Global handbook for family planning providers, consensus was reached on five key condom instructions. These five messages, with minor modifications, are as follows:

1. Use a new condom for each act of intercourse if any risk of pregnancy or STI exists.
2. Before any genital contact, place the condom on the tip of the erect penis with the rolled side out.
3. Unroll the condom all the way to the base of the erect penis.
4. Immediately after ejaculation, hold the rim of the condom and withdraw the penis while it is still erect.
5. Throw away the used condom safely.

Additional, more detailed condom instructions are available elsewhere.^{3,124}

FEMALE BARRIER METHODS

Though modern vaginal barriers such as caps and diaphragms have been used for pregnancy prevention since the early nineteenth century,¹²⁵ recent effort has focused on developing effective female barrier methods that women may use as an alternative to male condoms for prevention of HIV/STI.

■ FEMALE CONDOMS

The female condom provides a physical barrier that lines the vagina and shields the introitus. The first female condom, originally called Reality, was approved by the FDA in 1993 for over-the-counter sale in the United States. This device is a soft, loose-fitting polyurethane sheath with two flexible polyurethane rings. One ring lies inside, at the closed end of the sheath, and serves as an insertion mechanism and internal anchor. The other ring forms the external, open edge of the device and remains outside the vagina after insertion. This female condom is now called FC1, has been introduced in over 90 countries and is still the only such device cleared by the FDA in the United States.¹²⁶ Variations to its basic design have been developed and distributed outside the United States.

■ FEMALE CONDOM, EFFECTIVENESS

Limited laboratory data suggest that the female condom provides an impermeable barrier to HIV and cytomegalovirus¹²⁷ and to much smaller viruses.¹²⁸

A study comparing male and female condoms found that the female condom had significantly lower breakage rates (0.1% vs. 3.1%) but significantly higher slippage rates (5.6% vs. 1.1%).⁸² A recent randomized crossover study using prostate specific antigen (PSA) as a marker for semen exposure found significantly more PSA after female condom use compared to male condom use.¹²⁹ Self-reported problems were significantly higher with the use of female condoms as well.

No clinical studies have evaluated the female condom's ability to prevent HIV transmission. One small clinical study detected no trichomoniasis reinfection in a group using female condoms consistently but was underpowered to detect differences between consistent female condoms users and two control groups.¹³⁰ In two of three randomized trials of behavioral interventions promoting the female condom, groups assigned female condoms had lower STI rates than groups assigned male condoms although the differences were not statistically significant.^{131,132} In the third trial the STI rates in the group with access to only male condoms was the same as in the group with access to both male and female condoms.¹³³ A nonrandomized study provides evidence that adding female condoms to a male condom distribution program targeting sex workers may significantly increase both the proportion of protected acts and significantly reduce STI prevalence.¹³⁴

Because these devices cost substantially more than male condoms, the cost-effectiveness of providing female condoms in public sector programs remains under study.^{126,135} One approach to reducing the cost of female condoms is reusing the device. Different protocols for disinfecting female condoms have been evaluated for their effectiveness.^{136–138}

For pregnancy prevention, the most rigorous data are from the US-based study submitted to the FDA of 221 couples using the Reality female condom for pregnancy prevention.¹³⁹ In this study, the risk of pregnancy during the first twelve months of consistent use of the female condom was 5% (21% during typical use), a figure higher than that associated with consistent use of male condom. Additional published studies in the UK and Japan had somewhat lower rates.^{140,141} In conclusion, head-to-head comparisons of male and female condoms using both pregnancy and STI outcomes are still lacking.

■ CERVICAL BARRIERS

Diaphragms and caps usually combine two contraceptive mechanisms: a physical barrier to shield the cervix and a chemical to kill sperm. Moreover, these devices help to hold spermicide in place against the cervix. In recent years, the choice of cervical barrier methods has expanded from the traditional latex diaphragms and cervical caps to a new generation made of silicone.¹⁴² The N-9 sponge has both physical and chemical properties (see Chapter 94).

■ CERVICAL BARRIERS, EFFECTIVENESS

The cervix is the primary target for gonorrhea, chlamydia, and possibly for HIV because it contains a high number of specific chemokine receptors known to be HIV coreceptors.^{143,144} No published studies have evaluated cervical barriers for HIV prevention, although several are underway. Although no cohort or intervention studies have evaluated cervical barriers for other STIs, a review of the case-control and cross-sectional studies evaluating cervical barriers suggest that diaphragms may reduce the risk of some STI.¹⁴⁴ We have to await results from current prospective trials before drawing more definitive conclusions about cervical barriers' protective effect against STI/HIV.

On the other hand, the contraceptive effectiveness of cervical barriers is well established. Cervical barriers are among the least effective contraceptive methods, with the pregnancy rate for the first year of consistent use ranging between 6% and 26% (pregnancy rates for typical use range between 16–32%).⁶⁸

■ BARRIERS FOR ORAL SEX

Condoms are recommended for use during fellatio.^{3,89} Latex sheets to be used for cunnilingus/anilingus have also been

cleared by the FDA for sale over the counter. Household plastic wrap (including the microwaveable variety) is another option for cunnilingus/anilingus, although it has not been manufactured, intended, or cleared by the FDA for this use. No effectiveness data are available.

CONCLUSION

Male latex condoms, if used consistently and correctly, reduce the risk of transmission of HIV (the most serious STI), many other STIs, and unintended pregnancy. The public health endorsement of male latex condoms is based on the barrier properties of condoms, biologic plausibility, and evidence of risk reduction from clinical studies.

For other barrier methods, the evidence for STI/HIV protection, while weaker, is strongest for the female condom based on biologic plausibility and limited laboratory and clinical studies. For the remaining barrier methods, we need to wait for results from well-designed, on-going clinical studies before deciding whether and how these devices should be incorporated into prevention strategies.

For all barrier methods shown to be effective in clinical studies, achieving consistent and correct use remains the largest problem impacting their “real world” effectiveness. To optimize use of male condoms in sexually active populations with a high prevalence of HIV/STIs, public health messages must reinforce and unequivocally communicate the scientific evidence on condom effectiveness.

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Topical Microbicides and Other Chemical Barriers for the Prevention of STD/HIV Infection

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HISTORY

Less than 2 years after the earliest reports of what came to be known as AIDS, a case series published in 1983 indicated that the syndrome was beginning to surface among women.¹ Their only identifiable risk was a male sexual partner with AIDS. Less than a decade later, the incidence of HIV infections worldwide among women exceeded that among men, with a large fraction of infections attributable to their sole lifetime male partner.² To address the need for women to protect themselves from HIV infection, research on “germicides for HIV and other microbes” emerged as a high priority on the HIV prevention agenda.²

That same summer in 1992, results appeared from the first controlled clinical trial of a commercial spermicide-impregnated sponge for preventing vaginal transmission of HIV.³ Although the active ingredient, nonoxynol-9 (N-9) effectively destroyed HIV *in vitro*, in this trial, N-9 was associated with a nonsignificant increase in risk for HIV acquisition compared with a non-N-9 product. It was also found to produce elevated rates of vulvitis and genital ulcers.³ Investigators hypothesized that the dose of N-9 (1000 mg) and frequent exposure to its surfactant activity may have disrupted healthy epithelial tissue to cause the genital lesions and inflammation found among the Kenyan sex workers. Women’s health advocates remained hopeful about prospects for N-9, but some scientists urged caution while further data on lower doses and different formulations were being collected.⁴

For the next decade, the unrelenting global spread of HIV continued, with an increasingly disproportionate impact on women, especially young women and adolescent girls.⁵ Among women surveyed in southern Africa, 40% were HIV-positive even though 66% reported having only a single lifetime sexual partner and 79% had abstained from sex until at least 17 years of age.⁶ For a large fraction of women in many developing countries, the greatest source of risk was their husband.⁷ Even with increased access to female condoms,⁸ less than 5% of married women of childbearing age worldwide used condoms regularly.⁹ Men’s extreme resistance

to condoms, women’s reluctance to risk reprisals by suggesting them, and cultural and familial norms that make childbearing a critical determinant of women’s status together rendered condoms ineffectual against the risk of HIV exposure by nonmonogamous husbands.^{10–13}

During that same decade, a series of other commercially available N-9 formulations entered clinical trials for efficacy against HIV and other STDs.^{14–17} The fact that these products were already approved by U.S. regulatory authorities for use as contraceptives meant that alternative forms of N-9 products could be evaluated in trials rapidly. Additional trials were also motivated by the hope that lowering the dose of N-9 and delivering it in a different formulation such as a film or gel would retain microbicidal potency while avoiding toxicity to healthy tissue. Phase I and II “safety” trials of these N-9 formulations provided evidence to substantiate their safety but Phase III results for HIV prevention showed no evidence of protection. Additional evidence of toxicity to vaginal epithelium was found among high frequency users, even at low doses and despite variations in the delivery system. These findings prompted the abandonment of N-9 as a potential microbicide for HIV prevention¹⁸ and heightened caution about toxic effects of other candidate surfactants.¹⁹

While the N-9 trials were being conducted, a new class of microbicides, polyanions, was being developed. These products entered efficacy trials in 2004–2005 among women living in sub-Saharan Africa. Newer classes of products, based on HIV antiretroviral therapy were developed and evaluated in preclinical and clinical safety studies. The importance of targeting multiple mechanisms as a principle of HIV antiretroviral therapy that increases efficacy and delays onset of resistance has begun to influence microbicide product concepts. However, all microbicide products evaluated for efficacy in the first wave of trials and most products in advanced preclinical testing represent single agents, some of which may have dual modes of anti-HIV activity.

In addition to vaginal microbicide use, increased attention has been directed at product safety with rectal administration.^{20,21} Acceptability of surrogate products for a rectal microbicide is

being investigated.²² In addition to an unmet need for additional methods for reducing risk of unprotected sex between men, an important incentive for such research came from studies showing that anal intercourse was part of the sexual repertoire among a substantial number of sexually active heterosexuals worldwide.^{23,24} Moreover, rectal exposure appears to transmit HIV more efficiently than vaginal intercourse.

Finally, protection against unintended pregnancy is an issue. A product with dual efficacy as both a contraceptive and microbicide would increase its appeal for women who do not wish to become pregnant. However, in many developing countries, a woman's economic survival and social well-being, as well as the durability of her marriage, may depend on her capacity to bear children. Thus, for those women desiring pregnancy, a noncontraceptive method to avoid HIV infection is essential. Using condoms is not an option in this context.

MICROBICIDES: CONCEPTS AND CHARACTERISTICS

Topical microbicides are designed to kill or inactivate HIV and/or other STDs to interrupt mucosal (vaginal and/or rectal) transmission at or near the site of exposure. Various criteria describe a successful microbicide, beginning with safety and efficacy, the sine qua non of a successful product (Table 94-1). Other considerations range from those that influence feasibility, such as heat stability (which is critical in developing countries where refrigerated storage is impractical) through those that may influence speed of dissemination, such as expeditious approval of over-the-counter availability.

HIV TRANSMISSION AND INACTIVATION

Opportunities to prevent HIV infection have emerged with the elucidation of specific cellular and molecular processes involved in the establishment of infection. The critical threshold for protection is successful blocking of the integration of the viral genome into host cell DNA.^{25,26} Integration is problematic because resting cells that contain the HIV genome are indistinguishable from uninfected cells, putting HIV out of reach of therapeutic drugs. Eventually, these resting cells are likely to be reactivated, whereupon they begin to translate HIV genes into infectious viral particles capable of disseminating infection to previously uninfected host cells.

More than a decade of research has elucidated specific molecular structures and mechanisms involved in the process through which cell-free or cell-associated HIV from an infected, transmitting partner establishes infection in lymphocytes and other susceptible cells. Each such step that can be interrupted offers a hypothetical point of attack for microbicides designed to prevent the establishment of latent infection (Figure 94-1).

Initially, HIV either crosses a breach in otherwise intact vaginal or cervical epithelial tissue to reach susceptible host

lymphocytes beneath or encounters macrophages, lymphocytes, or Langerhans cells, a specialized type of dendritic cell, in the vaginal lumen or the cervix. Among macrophages and lymphocytes, establishment of infection may occur directly after HIV has attached to the membrane of those target cells.

In contrast, Langerhans cells may be exploited as a kind of "Trojan horse" by HIV: normally present within the vaginal mucosa with processes that extend into the vaginal lumen, they adsorb and deliver infectious agents to reservoirs of T cells in regional lymph nodes²⁶ that are activated to respond to the pathogen that has been adsorbed by the Langerhans cell. When a Langerhans cell that has adsorbed HIV migrates to a regional lymph node, it may recruit additional susceptible cells to the site of infection.

Once attachment occurs, binding, fusion, and entry of HIV continue via an interaction between gp120 molecules on the outer envelope of HIV with CD4 receptors on the surface of host target cells.²⁷ An additional molecular interaction must occur to effect HIV entry, in which binding sites on the HIV envelope interact with a coreceptor molecule on susceptible target cells,²⁸ called a "chemokine receptor" because its conventional immunologic role is to respond to the presence of specific chemokines, a family of molecules that normally regulate immune cell activity.

HIV subtypes are characterized by their coreceptor binding specificity. Most sexually transmitted subtypes preferentially bind to CCR5.²⁸ Consequently, CCR5-blockers are of great interest as potential microbicides. CXCR4 may mediate sexually transmitted HIV infections²⁹ and has been isolated in early specimens from sexually exposed individuals who lack a pair of functional genes required for expression of CCR5, but it is otherwise much less likely to be implicated in sexual transmission. CXCR4 subtypes emerge among about half of patients with advanced HIV disease—they cause more rapid lymphocyte depletion than CCR5-tropic subtypes.²⁸ Dendritic cells also express a third coreceptor, DC-SIGN.

Interactions between HIV envelope binding sites and target cell receptors and coreceptors initiate a conformational change that exposes gp41,³⁰ another molecular constituent of the HIV envelope that participates in the fusion of viral envelope with the target cell membrane. The specific interactions between HIV binding sites and target cell receptors present opportunities for blocking HIV attachment, fusion, and entry into susceptible cells. The first drug approved for treatment that uses this strategy, enfuvirtide or Fuzeon^{TM,31} is a fusion inhibitor that blocks a region of gp41 that is involved in the fusion of viral envelope with host cell membrane.³⁰ Other agents that block interactions between gp120 binding sites and either CD4 or the coreceptors CCR5 and CXCR4 are areas of active research for therapeutic drug development.

Once HIV gains entry into a susceptible host cell, its genetic sequences, encoded in a single-stranded RNA molecule, provide a template for the synthesis of a two-stranded DNA

Table 94-1. Fundamental Microbicide Characteristics

Essential	
efficacious	randomized controlled clinical trial(s) demonstrate at least 30% effectiveness, with sufficient power to assure that the lower bound of the confidence interval for the effectiveness point estimate exceeds zero
nontoxic	absence of product-related epithelial lesions detectable with the naked eye or under colposcopic examination absence of subclinical inflammatory responses that recruit susceptible target cells to the vaginal mucosa absence of interference with natural defenses against infection, e.g., low pH, presence of peroxide-producing <i>Lactobacillus</i> absence of symptoms or sensations that may discourage use, e.g., itching, burning
acceptable	women's willingness to use product is foremost; men's responses, if any, likely to influence product use. acceptability pertains to completeness of coverage for all sex acts not protected by barrier and to adherence with guidelines for product administration (e.g., timing, dose)
Critical	
heat stable	storage and distribution have no cold chain requirement, which would be unfeasible for many resource-poor countries
readily commercialized	no intellectual property issues threaten technology transfer, licensing, etc. methods used for pilot amounts of product for large-scale clinical trials can be scaled up readily for large-scale manufacturing
Desirable	
active against other STDs	reduces direct mortality and morbidity, including potential threat to fertility; may reduce susceptibility to HIV infection associated with STD-associated genital lesions or inflammatory responses
noncontraceptive and contraceptive	noncontraceptive product addresses a need for protective method compatible with social/cultural/family incentives or pressures to bear children; dual efficacy against HIV and for pregnancy prevention may facilitate product use among women who seek to prevent pregnancy
minimal adherence barriers	noncoitally dependent expected to improve adherence and facilitate protection against HIV for unplanned sex acts, both elective and coerced
low cost/dose	use by women in resource-poor settings will depend on cost; if access depends on securing price subsidies, availability may be delayed or unevenly distributed
discreet	women can use the product without requiring male acceptance or approval in those situations where male cooperation may be problematic

transcript of the proviral genome. The process of reverse transcription of viral RNA uniquely characterizes the lifecycle of retroviruses. Two strategies for blocking the unique retroviral requirement for reverse transcription have been a focus for development of therapeutic drugs. One technique substitutes a rogue molecule, instead of the normal subunit, into the developing linear sequence of the DNA transcript. This substitute subunit is unable to form a chemical bond with the next subunit, thereby terminating the DNA transcript before

it has been completed. This approach was the first component of the HIV lifecycle targeted for therapeutic drug development, which has generated an array of nucleoside reverse transcriptase inhibitors (NRTIs) as therapeutic drugs, as well as one nucleotide compound with similar activity.

Instead of interfering with the DNA transcript, a second strategy for interfering with reverse transcription employs a molecule that has been engineered to bind preferentially to an active site on reverse transcriptase, blocking the enzyme from

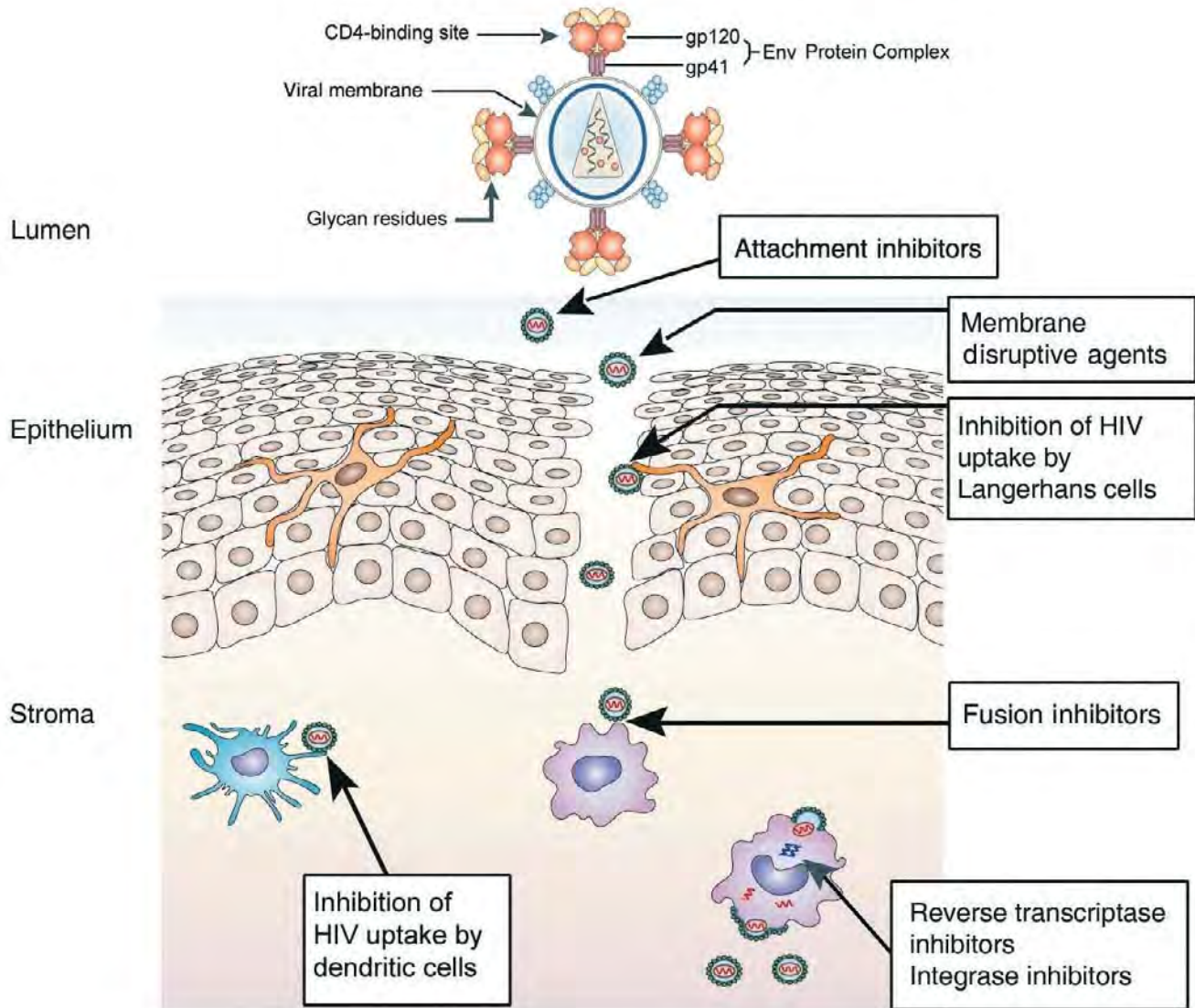


FIGURE 94-1. Potential approaches to prevention of HIV infection by topical microbicides. The lower portion of the figure illustrates potential mechanisms by which a topical microbicide could block HIV-1 infection of sub-epithelial target cells in the vaginal lumen. In the upper portion of the figure, an enlarged schematic of an HIV-1 particle identifies specific molecular structures associated with HIV-1 binding, fusion, or entry into target cells. (Adapted from Shattock RA, Moore JP. Inhibiting HIV-1 Sexual transmission. *Nat Rev Microbiol* 2003; 1: 25–34.)

assembling a DNA transcript of proviral RNA. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) include some of the most potent therapeutic drugs, and development of new agents in this class that have minimal cross-resistance with licensed NNRTIs is a vigorous area of therapeutic antiretroviral research.

Before a completed DNA transcript can be integrated into host cell DNA, another enzyme, integrase, must effect a series of molecular modifications associated with “strand transfer” in which proviral and host cell DNA are prepared by a specific cutting reaction followed by joining together of the processed ends of the two dual-stranded DNA molecules.³² Integrase inhibition is one of the newest components of the HIV lifecycle to be targeted for therapeutic drug development.

Among strategies to interrupt the postentry HIV lifecycle, reverse transcription and integration are of particular relevance

for microbicides designed to disable HIV before proviral DNA sequences are integrated into the genome of host cells. In contrast with the blockade of HIV before proviral DNA is integrated into the host cell genome, protease inhibitors, another class of antiretroviral drugs that have proven highly effective for treatment of chronic infection, interfere with the HIV lifecycle after infection has been established, when the proviral genome has already begun to direct synthesis of new viral particles.

MICROBICIDE MECHANISMS AND CANDIDATES

Microbicides are most often categorized by their mode of action: (1) nonspecific antimicrobial agents,³³ (2) nonspecific and specific attachment/fusion/entry inhibitors,³⁴

Table 94-2. Selected Microbicides in Development

Class	Compound	HIV Research & Development Status	Sexually-Transmitted Infections ^a						Preclinical Contraceptive Activity
			CT	HD	NG	TP	HPV	HSV	
Membrane Disruptive Agents									
	Sodium lauryl sulfate ^b	Phase I/II					V	V	V
	Sodium dodecyl sulfate (SDS)	Preclinical							
Acidifying Agents									
	Carbopol (Buffergel)	Phase IIb	V A		V		V A	V A	
	Acid buffering gel (Acidform)	Phase I	V A					V A	V A
Attachment/Fusion/Entry Inhibitors									
Polyanions	Carageenan (polystyrene-4-sulfonate) (Carraguard)	Phase III	V		V A		V A	V A	
	Naphthalene sulfonate polymer (PRO 2000/5)	Phase IIb, III	V		V A		V A	V A	V
Dendrimers	Vivagel (SPL7013)	Phase I					V A	V A	
CCR5 Blockers	L-860,167	Preclinical							
	PSC-RANTES, RANTES analogs	Preclinical							
gp120 Inhibitors	BMS-599793	Preclinical							
Reverse Transcriptase Inhibitors									
Non-nucleoside Reverse Transcriptase Inhibitors	MIV-150 ^c	Phase I							
	TMC120 (dapivirine)	Phase I							
	UC781 ^d	Phase I							
	S-DABO	Preclinical							
Nucleotide Reverse Transcriptase Inhibitor	PMPA (Tenofovir)	Phase II/IIb							
Uncharacterized Mechanism	Praneem (polyherbal tablet)	Phase II							

^aCT, *Chlamydia trachomatis*; HD, *Haemophilus ducreyi*; NG, *Neisseria gonorrhoea*; TP, *Treponema pallidum*; HPV, human papilloma virus; HSV, herpes simplex virus; A, animal model; V, in vitro.

^bFormulated in a thermoreversible gel as “invisible condom” designed to supplement surfactant activity with a physical barrier.

^cFormulated in Carraguard gel as PC-815.

^dFormulated in cellulose acetate phthalate.

(3) intracellular replication inhibitors,³⁵ and (4) unspecified mechanism (see Table 94-2).

■ NONSPECIFIC ANTIMICROBIAL AGENTS

Although absence of evidence of HIV protection led to the cessation of N-9 and C31G development as active microbicides, other surfactants remain under consideration. For example, there is still some research being conducted on sodium lauryl

sulfate and sodium dodecyl sulfate. A critical question for surfactant molecules is whether effective performance against HIV can be achieved without clinically significant toxicities.

Another means of nonspecifically inhibiting HIV seeks to enhance natural vaginal antimicrobial defenses. Two products in clinical development—Acidform and Buffergel—help maintain low vaginal pH even in the presence of semen (which elevates pH). An additional natural vaginal defense mechanism is associated with the normal colonization by *Lactobacillus*

species that secrete hydrogen peroxide, a disinfectant. The hydrogen peroxide produced by some species of *Lactobacillus* can combine with halide (Na⁺) and myeloperoxidase to create reactive oxygen species, which have potent antimicrobial properties. Suppositories have been developed which contain a large dose of *Lactobacillus* in a preserved state. It is hoped that these exogenous *Lactobacillus* might help restore an optimal vaginal microbiota. In addition to hydrogen peroxide, these bacteria also help maintain low pH by producing lactic acid.

■ ATTACHMENT/FUSION/ENTRY (A/F/E) INHIBITORS

Nonspecific attachment inhibitors

A group of negatively charged polymers, or polyanions, electrostatically binds to the positively charged HIV envelope, physically blocking attachment of virus to target cells in the vagina. Three of these molecules entered large-scale efficacy trials in 2004–2005. PRO2000/5 may have contraceptive activity; Carraguard is expected to be noncontraceptive. Two phase 3 trials of cellulose sulfate gel, a third polyanion attachment inhibitor, were not completed after an external study monitoring group review found that preliminary data from one trial had exceeded protocol-determined thresholds for stopping.³⁶ No evidence for effectiveness could be reached. Dendrimers, such as VivaGel, are highly branched macromolecules that also prevent HIV from attaching to the target cells in *in vitro* studies.³⁷ VivaGel safety studies were initiated in 2005–2007.

Cellulose acetate phthalate (CAP) another polyanion, is water insoluble at low pH and formulated as micronized beads in an acid-buffering system (Aquateric). Seminal plasma seems to lower the effective dosage of Carraguard, cellulose sulfate, and PRO2000/5 *in vitro*, but acid buffering preserves anti-HIV activity of Aquateric and Buffergel.³⁸

Specific A/F/E inhibitors

Specific molecular structures and interactions are associated with attachment and fusion of HIV with the membrane of target cells. For example, cyanovirin-N and BMS-599793 both bind to gp120 to prevent its interaction with the CD4 docking site on host target cells. Drugs in preclinical development that block CCR5 include analogs of RANTES, a naturally occurring chemokine that binds to the CCR5 receptor and CMPD-167. Suppression of CCR5-tropic virus may permit CXCR4 subtypes to predominate, resulting in accelerated disease progression, a concern that might be addressed by including compounds that block CXCR4 in a combination product.¹⁹

Another hypothetical risk of blocking coreceptors stems from their role in the regulation of normal immune responses. Effects of long-term blockade of the CCR5 receptor on T cell functionality have yet to be determined. While approximately 1% of Caucasians do not express the CCR5 receptor and yet maintain a normal inflammatory response,²⁹

their responses may not pertain to immunoregulatory interactions among individuals who do express CCR5.¹⁹

The dendritic cell coreceptor DC-SIGN³⁹ is inhibited by compounds such as mannan, but the majority of dendritic cells also express CCR5 and CXCR4 coreceptors, as well as the CD4 surface marker. Compounds like mannan would function most effectively in a microbicide with complementary activity, e.g., molecules that blocked CD4 or the alternate coreceptors CXCR4 or CCR5.¹⁹

Therapeutic efficacy of Fuzeon in chronic HIV infection demonstrates the potential utility of blocking that component of the viral lifecycle, but the large size and complex 3-dimensional structure of the Fuzeon protein requires a costly manufacturing process, even with economies that derive from large-scale production. Smaller, less costly molecules are being developed that would be more feasible as candidate microbicides.^{40,41}

■ INTRACELLULAR REPLICATION INHIBITORS

Two classes of antiretroviral drug that target postentry mechanisms seem well-adapted to the requirements for a microbicide administered at a mucosal site of potential HIV exposure: reverse transcriptase and integrase inhibitors.

Reverse transcriptase inhibitors

Most NRTIs approved for treating established HIV infection are nucleosides, which require three phosphorylation reactions,⁴² a process influenced by cellular factors such as cell type, stage in the cell division cycle, and activation and infection status of the cell in which they occur.⁴² In particular, initial phosphorylation by nucleoside kinases is believed to be rate-limiting.⁴³ One NRTI, tenofovir, is a nucleotide, which does not require the initial, rate-limiting step and which undergoes only two phosphorylation reactions,⁴³ making it more suitable for microbicide development. Clinical studies are in progress with tenofovir formulated as a microbicide gel,⁴⁴ including one efficacy study.

Among molecules that have been designed to block a binding site on reverse transcriptase, a subgroup of NNRTIs bind irreversibly to reverse transcriptase, are highly potent, and have long half-lives. In addition to inhibiting the replication of HIV within the host cell, NNRTIs may also inhibit infection by cell-free virus⁴⁵ that may enable a microbicide based on such a compound to inactivate HIV in the vaginal lumen. However, the mechanism of this cell-free inhibition has yet to be determined and its relevance *in vivo* is unknown.⁴⁶ NNRTIs currently in development as microbicides include dapivirine (TMC120), MIV 150, UC 781, and S-DABO.^{37,47,48}

Integrase inhibition

The integration of the proviral DNA into host cell DNA involves multiple steps that are catalyzed by the HIV-1

enzyme integrase. Integrase inhibitors are a new class of antiretroviral compounds that prevent this process from occurring, which in turn prevents translation of the HIV genome into enzymes and proteins that would generate new HIV particles. Although designed to block incorporation of the viral genome into host cell DNA, integration occurs after transcription of viral RNA, which is relatively late in the HIV lifecycle. In theory, infection may be established if only one viable copy of the viral genome evades an integrase inhibitor. Therefore, an active agent from this drug class may be effective only if used in combination with drugs that supplement this strategy with other modes of action.

■ COMBINATION PRODUCTS

If HIV escapes from one blocking or inhibitory mechanism, a product that exploits an additional vulnerability of HIV would be expected to increase overall efficacy. For example, one of the NNRTIs, MIV-150, has been formulated in Carraguard for clinical evaluation.⁴⁸ Further advantages observed during *in vitro* and animal model studies of combination product concepts stem from synergistic effects of some combinations, as observed, for example, *in vitro* for UC-781 formulated in CAP.⁴⁹ Such synergy may permit reduced drug concentrations of the active agents without loss of potency that may reduce the risk of local or systemic toxicities and, possibly, per dose manufacturing cost. On the other hand, preclinical and clinical studies should take into consideration that multiple active ingredients may display unexpected toxicities.¹⁹ Combination products also address two hypothetical concerns about microbicides using antiretroviral drugs that may develop cross-resistance with drugs in use for HIV therapy. The first is the potential for transmission of drug-resistant strains that may overcome a microbicide based on an antiretroviral drug.⁴⁶ As with HIV therapy, combinations of active agents may pose a higher barrier against infection by cross-resistant HIV subtypes in circulation. However, because resistance reflects reduced susceptibility of HIV rather than total invulnerability,⁵⁰ microbicide resistance will also depend on drug concentration in the vaginal lumen or target tissues.

The second concern about resistance pertains to microbicide use among HIV-positive women who are unaware of their HIV status. If concentrations of an adsorbed antiretroviral were high enough to select for resistance, fewer treatment options may remain available to infected women.⁴⁶ Combination products may reduce the likelihood of selecting for cross-resistance to therapeutic drugs, especially in mucosal tissue where active drug is delivered. To reduce the potential for systemic toxicity, microbicides based on antiretroviral drugs are formulated to deliver effective concentrations of active ingredients locally while minimizing systemic concentration, which may also reduce the possibility of

selecting for resistance. To gain a better understanding of the relevance of these concerns, resistance studies are planned in conjunction with the development of microbicides based on antiretrovirals. It will also be critical to follow women who acquire HIV infection during evaluation of ART-based microbicides, to assess the impact of microbicide exposure on emergence of resistant virus populations and the long-term impact on response to treatment.

Just as antiretroviral therapy achieves potency and durability by combining drugs that together erect a higher genetic barrier against drug resistance,^{51,52} microbicide concepts that anticipate and preempt potential resistance may avoid potential disadvantages associated with sustained use. For example, investigators studying agents that block coreceptor utilization by CCR5-tropic HIV subtypes have suggested including activity against CXCR4 coreceptor binding in order to avoid selecting for the more pathogenic CXCR4 subtype.¹⁹ Combination microbicides may also retain potency longer than single-agent products in the context of rapid mutation or recombination of circulating viral strains. Future microbicide development will include technologies designed to accommodate combinations of active components.⁵³

FORMULATION IN MICROBICIDE DEVELOPMENT

One of the important recent advances in microbicide development efforts has been the increased emphasis on formulation science. Composition and physicochemical properties of a formulation can influence a product's efficacy, including its delivery of an active ingredient to target tissue, timing of its release from a vehicle or other delivery system, physical dispersion on mucosal surfaces, systemic absorption, and toxicity. Formulation influences both cost and acceptability to the user. Delivery systems that allow for coital independence and techniques for modifying the sensory properties of a candidate microbicide are especially pertinent to microbicide development. Specialized techniques for measuring delivery of active molecules by topically applied vehicles and for examining intravaginal distribution and retention of vehicle prototypes and candidate products contribute to product optimization.

Formulation expertise also supported development of a placebo that meets stringent requirements for an inert gel against which the performance of a variety of candidate topical products can be compared. To maintain study blinding, an ideal placebo gel would be identical to the gel vehicle in the active arm. However, an identical placebo is not feasible for microbicide vehicles that have bioadhesive, lubricating, and pH buffering properties, all of which might contribute to the protective effect of the active gel.

These considerations suggested the utility of a "universal placebo" for multiple trials, which might be distinguishable

from the investigational microbicide, but still could be masked so that participants and research staff would not know which study gel is placebo and which is the investigational product. Key considerations were absence of clinically significant microbicidal activity, lack of detectable toxicity, and sensory properties sufficiently similar to those of candidate products to minimize differences in frequency of product use, which could otherwise confound the analysis of efficacy or toxicity outcomes. Based on these premises, a universal placebo gel was developed for the control arm of many current efficacy trials of polyanion gels.⁵⁴ Ongoing studies, which will evaluate the impact of this placebo gel versus no gel, will provide a critical assessment of whether the placebo gel has any impact on HIV acquisition.

Although topically applied products initially captured attention because they could be applied just before sex and seem more compatible with sexual pleasure than latex or urethane barrier devices, coitally dependent products pose obstacles that may impair the consistency with which they are used.⁵⁵ Since adherence problems can reduce the effectiveness of microbicide candidates, coitally independent products that eliminate the need to administer the product just before sex are in development. If the flexibility of daily or less frequent application helps assure fuller coverage of all sexual contacts, especially those which are unanticipated or coerced, overall effectiveness should be improved over coitally-dependent approaches.

Taking this concept one step further, vaginal rings are being studied as a means of delivering a drug or combinations of drugs for periods of 1 month or more.⁵⁶ The feasibility of a vaginal ring to deliver the NNRTI, dapivirine, has recently been demonstrated in both animal studies and pilot clinical trials.⁵⁷

Sustained release formulations may be able to control delivery⁵⁸ so as to minimize the likelihood of systemic absorption. However, even with good control over systemic absorption, local toxicity or irritation to the vaginal or cervical mucosa remains a concern for all topically applied products. Severe local toxicity could breach the mucosal epithelium, allowing HIV to enter the systemic circulation and reach susceptible target cells.⁵⁹ Cell types recruited to the vagina or cervix by more subtle inflammatory responses are also target cells for HIV,⁶⁰ suggesting the possibility that subclinical markers of inflammation may predict an elevated risk of HIV infection. As discussed in the context of preclinical and clinical testing, establishment of sensitive, reliable markers of unacceptable toxicities is an extremely high microbicide research and development priority.

Formulation science may help minimize perturbations of vaginal ecology that would compromise this natural barrier to infection, for example, by minimizing interference with hydrogen peroxide producing *Lactobacillus* species. *Lactobacillus* is also under consideration as a potential drug delivery system that might be another way to achieve coital

independence. The concept involves vaginal insertion of *Lactobacillus* modified by genetic engineering to express a gene for an anti-HIV protein or nucleic acid fragment with specific anti-HIV activity. In effect, this is a kind of combination microbicide in which the drug delivery system, modified *Lactobacillus*, delivers an active molecule with specific activity against HIV while offering the nonspecific protective benefits associated with colonization by peroxidase-secreting bacteria.

Regional variations in cultural preferences and sexual practices suggest that no single product-type will be universally acceptable. Microbicide developers are investigating diverse formulations including lotions, films, intravaginal devices, and solid dosage forms such as foaming pills, as well as novel polymers and biologically triggered drug release systems.^{53,61}

MICROBICIDES AND PREVENTION OF OTHER STDs AND PREGNANCY

Initial microbicide interest focused on the active ingredient in commercial spermicides, N-9, and examined its effects on the full range of sexually transmitted infections. In vitro assays and animal studies indicated that N-9 was effective against herpes simplex virus (HSV), *Neisseria gonorrhoeae*, *Treponema pallidum*, and *Trichomonas vaginalis*.²⁵ Moreover, the widespread commercial availability of N-9 contraceptives permitted epidemiologic studies of both its safety and its efficacy against STDs but findings were inconsistent.⁶²

Beginning in 1990, well-conducted randomized controlled trials compared different N-9 formulations—sponge, film, and various gels—and dosages^{3,15–18,63} for their efficacy against HIV and other STDs. Taken together, these studies demonstrated little (if any) protection against gonorrhea and chlamydia. Accordingly, N-9 products are not recommended for STD protection.

Newer candidates in large-scale HIV efficacy trials demonstrate activity against other STDs when tested in vitro or through vaginal challenge studies among animals. Several also display some level of contraceptive efficacy (Table 94-2). Dual activity in protecting against HIV and other STDs could enhance a candidate's future because of the potential synergy between direct activity against HIV and control of STDs that otherwise might increase HIV susceptibility. Statistical models of dual activity against HIV, as well as other STD that potentiate HIV acquisition, predict an amplified impact on HIV transmission.⁶⁴

Large-scale efficacy studies of topical microbicides generally include frequent screening for sexually transmitted pathogens such as *N. gonorrhoeae*, *Chlamydia trachomatis*, HSV-2, syphilis, and *T. vaginalis*. It is likely that these studies will provide some evidence about whether microbicides have substantial impact on the acquisition of other STD organisms.

RECTAL MICROBICIDE DEVELOPMENT AND EVALUATION

Epidemiologic data suggest that HIV is more transmissible rectally than vaginally, which is consistent with biological differences between rectal and vaginal mucosa. Columnar epithelium in the rectum poses a less robust barrier to pathogens like HIV than stratified squamous epithelium in the vagina. Even in the absence of infection, the gastrointestinal tract is enriched in susceptible target cells for HIV in comparison with vaginal mucosa.²⁰ In addition, men who engage in anal sex have indicated a high level of interest in topical products for rectal use to reduce HIV⁶⁵ risk when condoms are not used or as a backup against condom failure.

Anal sex, the predominant mode of HIV transmission in the United States and many other industrialized countries, is also a part of the sexual repertoire of heterosexuals in both developing²³ and developed²⁴ countries. Heterosexuals who engage in anal sex typically report that they are less likely to use condoms for that practice than when they have vaginal intercourse.

Evaluation of the safety of candidate microbicides when administered rectally has become one component of vaginal microbicide research and development. Until recently, most of this activity has involved preclinical systems, but clinical safety trials are increasingly included in product development programs. Rectal safety of candidates currently in large-scale efficacy trials has been assessed by nonclinical studies using tissue explants and mouse or macaque animal models. Markers of toxicity employed in those studies include sloughing of rectal epithelium, cytotoxicity measured in cell viability assays, and rectal challenge studies with HSV-2 as a marker of disruption of rectal epithelium. Phase I studies have been conducted or are planned for the NNRTI candidates UC-781 and TMC-120,⁴⁴ as well as VivaGel.

Participants in large-scale trials of vaginal microbicides are advised not to apply products rectally and are asked to refrain from anal intercourse. Caution about rectal administration of candidate products recognizes that preclinical and clinical safety markers still have uncertain predictive value. Avoidance of anal sex helps assure that infections during efficacy trials provide the most accurate measure of protection against vaginal HIV transmission, the indication for which current products are being tested. A higher rate of infections from anal sex would be indistinguishable from vaginally transmitted infections, leading to a deceptively low estimate of protection against vaginal transmission.

Early efforts to develop rectal microbicides recapitulated the beginnings of vaginal microbicide research and development, starting with a Phase I trial of the N-9 spermicide applied rectally.⁶⁶ Absence of rectal toxicity in that study may have depended on the time at which observations were made, 12 hours on average after administration. Subsequently, rectal

lavage studies demonstrated that within 15 minutes of exposure to N-9, large patches of epithelial tissue slough off rectal walls.⁶⁷ Observations such as this quickly ended consideration of N-9 as a potential active ingredient in a product designed for rectal protection. Further studies demonstrated the potential risk of N-9 as an ingredient in various brands of sexual lubricant.⁶⁸

Research has progressed on the biology of rectal HIV transmission in a compartment anatomically, physiologically, and immunologically unlike the vagina and cervix.²⁰ Efforts to identify sensitive, predictive, clinical, and laboratory markers of rectal toxicity of candidate products continue.²⁰ Studies have also been undertaken to evaluate completeness of coverage of rectal mucosa by various vehicles that might be used to formulate a rectal product. Acceptability research has progressed from surveys of prospective users' opinions of hypothetical products to studies of acceptability and tolerability of different volumes and types of vehicles and delivery systems potentially useful for rectal products.²² Critical new research is also being conducted on the applicators to be used for rectal microbicides.

PRECLINICAL TESTING PROCEDURES AND UNCERTAINTIES

Guidelines for specific *in vitro* and animal safety and efficacy data have been largely standardized (Table 94-3). Most refer to *in vitro*, *ex vivo*, and animal model studies of safety and efficacy before any humans are enrolled in clinical trials. Others parallel the transition from the earliest, small-scale safety studies to larger trials that involve greater risks, e.g., reproductive toxicology in animals in conjunction with approval to expose pregnant women to an investigational product. Additional studies that require the longest time to complete, e.g., carcinogenicity testing, may be required only when clinical trials have been completed and the product's sponsor seeks regulatory approval of an application for licensure or registration.

■ IMPROVING SENSITIVITY AND PREDICTIVE VALUE

Ability to predict the two key outcomes that preclinical tests are designed to evaluate, safety and efficacy, remains elusive in microbicide research and development. The large trials of N-9 have highlighted the inadequacy of standard *in vitro* and animal models designed to predict toxicity and show plausibility of efficacy. Even Phase I and II clinical trials failed to signal toxicity risks.

Such disconnects are not unique to the field of microbicides, as illustrated by other pharmaceuticals that revealed unanticipated safety problems late in development or postmarketing. Nevertheless, additional efforts at assay development and standardization are a high priority both for assuring minimal toxicity and for screening multiple candidates to select the most promising for advanced clinical evaluation.

Table 94-3. Preclinical Microbicide Assessments^a**Pre-phase I^b**

- **In vitro**
 - efficacy:
 - multiple HIV subtypes including lab-adapted and primary isolates; CCR5 and CXCR4-tropic; variants representative of circulating strains of HIV
 - activity against STD, especially Chlamydia, gonorrhea
 - safety
 - cytotoxicity (cellular viability): vaginal, cervical, rectal, penile, oral mucosa
 - antiretroviral drug resistance, cross-resistance
 - condom integrity
 - carcinogenicity
 - genotoxicity: bacterial genome alterations + mouse lymphoma thymidine kinase or mammalian cell cytogenicity
 - product characterization
 - mechanism of action
 - chemistry and manufacturing controls (CMC): purity, stability, strength
- **ex vivo tissue explant system**
 - efficacy^c
 - safety
 - cellular viability, integrity of epithelial cell-cell junctions
 - cytokine and chemokine response to microbicide exposure
- **in vivo^d**
 - local toxicity: exposure: 2 animal species (one nonrodent, usually daily exposure in 10-day rabbit vaginal irritation model)
 - macroscopic: epithelial lesions detectable by naked eye and colposcopy-assisted
 - microscopic: histological assessment of inflammation (local recruitment of HIV target cells)
 - immunologic: changes in proinflammatory cytokines (interference with, or up- or down-regulation of, HIV binding to cell surface receptors)
 - pK (absorption, disposition, metabolism, and excretion),
 - systemic toxicity^e
 - reproductive toxicology
 - teratogenicity (2 mammalian species, usually rat and rabbit)
 - hypersensitivity
 - maintenance of low vaginal pH
 - effect on normal vaginal flora (especially hydrogen peroxide-producing lactobacilli)
 - efficacy in animal challenge studies

Prephase II

- **in vivo**
 - chronic toxicity: 6 months rodent, 1 year nonrodent
 - completion of reproductive toxicology, teratogenicity studies

Prephase IIb/III – Pre-NDA

- **in vivo**
 - carcinogenicity: rats, mice (2-year exposure data prior to NDA submission unless otherwise agreed upon)

^aSources: Points to Consider in the Nonclinical Pharmacology/Toxicology Development of Topical Drugs Intended to Prevent the Transmission of Sexually Transmitted Diseases (STD) and/or for the Development of Drugs Intended to Act as Vaginal Contraceptives. (July 6, 2005), Bethesda, MD: Division of Reproductive and Urologic Drug Products, Office of Drug Evaluation II, Division of Antiinfective Drug Products and Division of Antiviral Drug Products Office of Drug Evaluation IV, Center for Drug Evaluation and Research, Food and Drug Administration; Hillier, S. Keeping the Promise: The Urgent Need to Define Safety and Effectiveness of Microbicides. Microbicide Safety Consensus Meeting March 1–3, 2006 Bethesda, Maryland USA; Wu TC. Considerations for Topical Microbicide Phase 2 and 3 Trial Designs: A Regulatory Perspective, Division of Antiviral Drug Products, FDA. Bethesda: Antiviral Drugs Advisory Committee, Wednesday, August 20, 2003; Lard-Whiteford SL, Matecka D, O'Rear JJ. Recommendations for the nonclinical development of topical microbicides for prevention of HIV transmission: an update. *J Acquir Immune Defic Syndr* 2004;36(1): 541–552.

^bWhen feasible assess in vitro and in vivo safety and efficacy in the presence of seminal plasma.

^cNot required for regulatory purposes but possible correlate of protective efficacy in human trials and potentially useful in clarifying anti-HIV mode of action.

^dUse formulated product equivalent to the material that will enter clinical trials.

^eIf human absorption exceeds level in animal model, FDA recommends 3-month oral exposure for in vivo evaluation of systemic toxicity.

The importance of candidate selection is crucial given limited research capacity available to support multiple large-scale registrational trials. Clinical trials are the most costly component of pharmaceutical research and development, with the cost of pivotal efficacy trials to support licensure for a single product estimated at up to \$100 million.^{69–71}

■ INNOVATION IN PRECLINICAL ASSESSMENT

Increased knowledge of both immunoregulation and the molecular and cellular processes associated with sexual transmission of HIV have helped to refine *in vitro*, *ex vivo*, and animal model systems for nonclinical testing. Institutionally, a program has been initiated to facilitate collaboration among microbicide research laboratories to devise improved preclinical safety assays, standardize protocols for critical preclinical methods such as tissue explants, and support quality assurance of assay performance among laboratories volunteering to utilize the program.⁷²

Tissue explant systems

The increased use of animal and human tissue explants is among the most important innovations in preclinical methods. Human cervical tissue explants from patients who have undergone hysterectomies have been employed to predict both safety and efficacy in subsequent clinical trials. A particular advantage of such a system is that it includes migratory Langerhans cells, which permit studies of the ability of potential products to block dendritic cell transport of HIV to subepithelial target cells. Rectal tissue explants, using specimens from surgical resection or endoscopic biopsy, are being used to develop analogous methods to predict rectal safety and efficacy,²⁰ and pilot studies of foreskin explants for evaluation of penile toxicity are also underway.

Inflammatory markers

Intensive studies of the cellular and molecular intricacies of HIV infection after exposure to the virus have generated an appreciation for the complexity of immunologic signaling systems, which may influence both susceptibility and resistance to infection. Cytokines involved in immunologic signaling regulate the intensity and duration of inflammatory responses. Elevated levels of proinflammatory cytokines in vaginal mucosa may recruit target cells susceptible to HIV infection and may also upregulate the density of target cell receptors to which HIV binds. Molecules that resemble naturally occurring cytokines or bind to cytokine receptors also might downregulate some protective immune responses. In addition, some novel peptides or proteins developed for use as fusion or entry inhibitors may be sufficiently immunogenic to elicit antibodies that neutralize their beneficial microbicidal activity.¹⁹

Clarifying the specific assays that are most useful for predicting toxicities and establishing appropriate thresholds for such markers would be a valuable contribution. They are apt to be more sensitive than visual inspection or histological assessment and they can be more reliably standardized among diverse laboratories. These methods may also provide less invasive approaches for use in clinical trials. Such assays should, ideally, permit more frequent sampling than is feasible for vaginal exams, given considerations of cost, logistics, space, availability of specialized staff, and participant burden.

Animal models of efficacy

Recent progress has occurred in animal models for preclinical testing of microbicides efficacy. New HIV challenge stocks have been developed to investigate the protective utility of NNRTI-based microbicide candidates. One NNRTI-sensitive viral construct that can infect rhesus macaques has recently been developed but results from its use in experimental studies of an NNRTI-based microbicide candidate are not yet available. Another NNRTI-sensitive construct is currently in development.

A new testing algorithm with repeated animal exposures to virus may more accurately model sexual transmission in humans. Another rationale for this low dose, multiple-challenge model was the potential to quantify relative efficacy of different products. Previously, animal challenge studies were designed with high dose challenge stocks standardized to assure that infection would occur with only one exposure to the test virus. Reliable infection after a single exposure of control animals was intended to avoid ambiguity in interpreting absence of infection in microbicide-treated animals.

However, a consequence of this strategy is the requirement for a large number of costly and scarce macaques for comparative tests capable of discriminating quantitatively between candidate products. The typical animal protection study might compare from three to six control animals with an equivalent number of animals that received a candidate microbicide. Statistically, protection of four out of six animals could not be differentiated from protection of six out of six with sufficient certainty to assert a product-related difference in protective efficacy.

Use of a low dose multiple-challenge strategy was designed to introduce a source of variability associated with protective efficacy that might allow quantitative comparisons of the performance of different candidates, which would be measured by continuing the experiment until all control animal(s) and experimental animal(s) given the experimental product became infected. Level of protection would be correlated with the number of exposures required to establish infection.

Comparison of the two model systems with the same microbicide candidate and the same challenge stock has shown that the two models require the same cumulative

animal infectious dose of virus even though the delivery of that dose is spread across multiple exposures in the multiple-challenge system.¹⁹ Ongoing examination of the performance of these models and the question of equivalence would be useful to achieve consensus on methods to compare candidates.⁷¹

Antiretroviral drug resistance

Microbicide candidates based on antiretroviral compounds elicit concerns about both durability of microbicide efficacy and impact on treatment options for individuals and communities using such a microbicide. Preclinical techniques for assessing the potential of a microbicide to elicit resistance can help evaluate various scenarios, including exposure of uninfected microbicide users to cross-resistant subtypes, or use of a microbicide by a woman who is unaware that she is HIV-infected. One concern is decreased efficacy of therapeutic drugs locally available for infected individuals. A second concern is infection with microbicide resistant subtypes that begin to circulate in a community and gradually undermine the efficacy of a microbicide as selective pressure causes the resistant variants to predominate.¹⁹ To date, these concerns are quite speculative. Different modeling approaches have provided inconsistent conclusions. Moreover, if an antiretroviral microbicide is eventually found to be effective, the relative value of prevention versus treatment must be weighed.

■ DOSE DETERMINATION

Preclinical tests are also used to help establish a target dosage and frequency of drug administration. Ideally, laboratory assays could be performed on human volunteers to achieve precision in dose determination. For drugs used to treat HIV, assays that measure the concentration of HIV particles in peripheral blood provide a sensitive marker of response to treatment and a useful predictor of clinical benefit based on studies correlating viral load with reductions in HIV-related morbidity and mortality. For microbicides, no such validated surrogate marker exists.

Dose levels for Phase III microbicide studies are selected primarily based on in vitro antiviral activity assessments, animal model studies of product safety and efficacy in response to different doses of a candidate, pharmacokinetic data in women, and on the physicochemical characteristics of the product such as its intravaginal coverage, distribution, and retention, as well as the drug release properties of the formulation. Further specification of a dosage for large-scale trials comes from Phase I/II clinical trials that are typically designed to escalate dosage through several levels and to double the frequency of exposure (if applicable) from once to twice daily until a threshold is reached based on clinically significant indicators of toxicity or tolerability concerns that

impair a product's acceptability. However, the only definitive measure of whether a microbicide administered at the selected dosage (and frequency, if applicable) will work remains the large-scale efficacy trial.

CLINICAL EVALUATION OF MICROBICIDE PERFORMANCE

A series of unique characteristics of microbicide research has prompted innovative modifications to clinical trial methods, some of them controversial. Other aspects of microbicides pose unresolved dilemmas that have implications for clinical trial designs now and in the future.

Microbicide trials depart from the conventional sequence of Phase I through Phase III (Table 94-4). Phase I trials typically evaluate safety with healthy volunteers, unaffected by the condition being addressed, and determine pharmacokinetic parameters such as bioavailability and half-life. Phase II trials evaluate safety in individuals affected by the condition and demonstrate that the product has the anticipated effect on a surrogate marker that predicts clinical benefit from the investigational product. Phase III trials are specifically designed to support licensure by providing a precise estimate of efficacy in a randomized, placebo-controlled study.

Microbicide clinical trials represent a more fluid continuum of these goals. For example, expanded safety data in higher risk populations may begin with the last cohorts enrolled in Phase I trials. Likewise, the clinically intensive safety goals of Phase I and II trials may be integrated into the study protocol for the first several hundred women enrolled in large efficacy trials, in effect transforming such trials into Phase II/III or Phase II/IIb trials. This strategy enables cohorts that otherwise would have been enrolled in a separate Phase II expanded safety trial to contribute to the sample enrolled in large-scale efficacy trials.

■ SPECIAL CONSIDERATIONS FOR MICROBICIDE CLINICAL TRIALS

Although the issues discussed below are not necessarily unique to microbicide trials, each has had a notable impact on how the field approaches clinical trial design.

Absence of surrogate markers of safety and efficacy

Phase II clinical trials typically provide the first preliminary indication of likely safety and efficacy in the population to be studied in Phase III trials. Without validated surrogates for microbicide safety and efficacy, the latter can be determined only through large-scale efficacy trials.⁷³ Moreover, the same measure used to determine efficacy, HIV seroconversion, is the most important measure of safety. Experience with N-9

Table 94-4. Clinical Trial Phases

Trial Phase	Objectives	Endpoints	Duration	Population: Cohorts, Sample Sizes, Overall Design
I	safety pharmacokinetics tolerability	cervicovaginal mucosal findings (unaided visual and colposcopic examination) subjective signs and symptoms integrity of vagina I milieu (pH, microbiology for normal Lactobacilli) local, systemic absorption willingness of participants to comply with study-specified use-frequency, dose, and method of application/administration/insertion	2 wk product exposure; total trial=6 mo	$N=10-50$ [10 per exposure cohort] low risk [mutually monogamous, no recent STD history, with option of initial sexually-abstinent cohort] May include control comparison group or may use participants at baseline as their own controls
II	expanded safety acceptability	cervicovaginal mucosal findings (unaided visual and colposcopic examination) subjective signs and symptoms survey, qualitative: product attributes, interest in future product	2-6 mo, usually with ≥ 1 mo of exposure per participant	$N=50-250$ women at increasing risk, e.g., recent (past 3 mo) STD
IIb/III	effectiveness against HIV and other STD if supported by preclinical data expanded safety adherence to product use acceptability	HIV seroincidence STD incidence cervicovaginal mucosal findings subjective signs and symptoms vaginal sex with: microbicide, condom, microbicide + condom, neither quantitative and qualitative self-reports on product	6 mo to 3 y, usually with 1 yr maximum duration of participant enrollment and use of product	randomized, controlled trial [usually blinded design with control by placebo, possibly unblinded with no gel as control] $N=1000-10,000$ women at high risk, characteristic of those for whom product would be recommended if licensed
I/II	supplementary prephase IIb/III/ licensure safety/ tolerability trials: • penile tolerance • rectal safety	visual lesions (rectal + penile); rectal anoscopy/ flexible sigmoidoscopy subjective signs and symptoms mucosal [penile/rectal] findings (e.g., urethral screen by leucocyte esterase urinary dipstick, rectal swab for cytokine markers, biopsy for histopathology)	3-6 mo each, usually with 1-2 wk of product exposure	$N = 20-50$ each; cohorts ($N \geq 10$) of HIV- and HIV + circumcised and uncircumcised cohorts for penile study

will hopefully allow laboratory scientists to identify surrogates for microbicide safety.

Relatively low event rate for the primary efficacy outcome

For many pharmaceuticals used to treat diseased populations, clinical testing is expedited by high event rates that permit definitive efficacy trials to enroll relatively small samples, often less than 1000 participants, for relatively brief enrollment periods, e.g., 6-12 months. However, prevention trials

are an order of magnitude more challenging than treatment trials. HIV incidence, even among the highest risk cohorts identified for microbicide trials, is typically 5% per year or less, which translates into sample sizes in thousands and follow-up periods of 12-24 months in trials, intended to measure microbicide efficacy.

If HIV incidence in the study population falls below the rate used in trial design calculations, adjustments must be made to accrue sufficient endpoints to measure efficacy reliably. If the departure from an initial estimate is great

enough, it may not be feasible to complete the trial. For example, a Phase III trial of a surfactant product, Savvy, was terminated because the incidence rate, initially estimated at 3.7%, was 2% about 2 years in the study⁷⁴ at clinical trial sites in two different countries in West Africa. Prospective cohort studies that emulate trial conditions are a time-consuming and costly prerequisite for determining efficacy trial design parameters such as HIV seroincidence. Other less costly approaches available for estimating event rates once the trial is underway are being evaluated.

Pivotal importance of behavioral factors, especially adherence and acceptability

Microbicides only work if they are used. Consistency of product use is so important a modifier of efficacy outcomes that all phases of clinical research include assessments of product use and factors that increase or decrease its acceptability.

Ethical standards for the conduct of microbicide trials require that participants are provided with, and counseled to use, condoms.⁷⁵ This has led to relatively high levels of self-reported condom use, and various studies are using biologic measures to validate these self-reports. A confounding factor is that self-reported microbicide use tends to correlate with condom use. This will attenuate the trial's ability to demonstrate microbicide efficacy.

Low rates of product use may also provide a misleading underestimate of a product's efficacy. For the coitally dependent gels currently in efficacy trials, participants report utilization rates ranging from 40% to 80%.⁷⁶ Social desirability influence on such self-reports may generate overestimates of adherence to product use. Therefore, consideration must be given to ways of improving levels, and measures, of adherence in studies.

Selection of suitable control(s)

The universal placebo used in most of the efficacy trials now underway shows no protective efficacy in vitro and in animal models. However, its effect on HIV incidence in humans is unknown. Moreover, although it shows no evidence of toxicity preclinically and, thus far, in clinical use, hypothetical concerns persist about its long-term safety in the clinical trial context.⁷⁷ One current trial has included both placebo and no-gel control ("condom only") arms to address these concerns. The no-gel control is also intended to assess the hypothetical risk that use of microbicides could decrease condom use, resulting in a net increase in HIV infection rates.⁷⁸

Critics of this design have suggested that the safety concern could be addressed separately and more efficiently than by requiring two control arms. The use of a no-gel control to assess microbicide-related reductions in condom use seems irrelevant to the situation in resource-poor countries where condom use rates remain low even when promoted. Methodologically, differences in condom use

between comparison arms may be neither interpretable nor generalizable.^{75,79,80} Since a third arm requires a 50% increase in the size of the study, with consequential increases in time, cost, and strain on the limited capacity of clinical trial sites,⁷⁹ hopefully, the data from the current dual control arm trial will obviate a need for no-gel control arms in future efficacy trials.

■ TRIAL DESIGN DILEMMAS

Cost, constraints on capacity, and a sense of urgency about identifying effective products and delivering them to high-risk populations generate questions about how to design future efficacy trials. Underlying many of these dilemmas is a tension between establishing proof of concept as efficiently as possible versus designing more complex and costly trials that may expedite access to a product, if it is found to be safe and effective.

Efficacy trial precision

Two designs have been used in microbicide efficacy trials: (1) the conventional, definitive Phase III trial establishes targets for sample size and duration of follow-up that can yield a precise estimate of the efficacy of the investigational product; (2) a "screening trial" or "Phase IIb" design has been used as an alternate strategy to obtain a less robust estimate of product efficacy more quickly and with a smaller number of participants. The Phase IIb trial is considered a particularly appropriate design when considerable uncertainty exists about the efficacy of an intervention because it can eliminate ineffective approaches from further consideration. However, unless an intervention is highly effective, an intermediate outcome means that a definitive trial would subsequently need to be conducted to satisfy most regulatory authorities.

Such an intermediate outcome poses a policy dilemma for those who feel that the result is not persuasive enough to proceed with implementing a new and urgently needed means of preventing a potentially lethal infection. It also raises ethical problems because the evidence for efficacy it provides may make it difficult to gain agreement about a subsequent placebo-controlled trial to meet regulatory requirements. Even if a second trial were determined to be ethically acceptable to a host country and community, information provided during informed consent might make it difficult to enroll participants or else difficult to maintain trial integrity (e.g., participants might share some of their supplies of the investigational product so that they all gain access to some samples that are protective).

Enrolling adolescents in efficacy trials

Adolescent girls and young women are important target populations for microbicides. They are among the most severely affected groups and the most vulnerable to pressure not to use condoms. However, enrolling adolescents in efficacy trials triggers special requirements, often including

parental consent for their participation, and can put adolescents at a “social” risk. Moreover, their vulnerability may lead policy officials to discourage sponsors from trying to include adolescents. It will be critical to perform at least some safety studies among adolescents to provide “bridging” data to support labeling of microbicides approved for the prevention of HIV in young women.

Pregnancy during the conduct of clinical trials of reproductive aged women

Women enrolled in Phase III efficacy trials are required to use at least one form of contraception during the study.⁷⁵ However, despite this prerequisite, high pregnancy rates of up to 70% have been observed in some of the current efficacy trials,^{81,82} while other effectiveness studies have had pregnancy rates in the 15% rate range. Some microbicide protocols require women who become pregnant to discontinue product use and leave the study, while other protocols allow for the continued follow-up of women who become pregnant on the trial. High pregnancy rates complicate data interpretation and result in a study that is underpowered to demonstrate whether a microbicide is effective. Improved access to contraception at the clinical trial sites is one characteristic of clinical trial protocols that have had fewer incident pregnancies. The possibility of maintaining pregnant women on product throughout pregnancy has been proposed, provided the preclinical program has been completed, including the full package of reproductive toxicity studies and carcinogenicity studies.⁸¹ However, completing all of these studies prior to the initiation of efficacy studies would mean substantial delays prior to the initiation of these trials.

Even if favorable efficacy outcomes precede completion of reproductive toxicology and carcinogenicity studies, it may be important to complete these studies before licensure. Licensing a new microbicide that women are told to stop using during pregnancy poses daunting logistical problems related to assuring ongoing, appropriately frequent pregnancy testing among users. Even if such a product were subsequently qualified for use during pregnancy, the initial restriction during product rollout may adversely influence future attitudes about its safety and/or cause confusion among prospective users long after pregnancy-related concerns have been resolved by additional data.

Measuring non-HIV STD endpoints in efficacy trials

In addition to causing serious morbidity themselves, non-HIV STDs may also facilitate HIV transmission. Thus, trials designed to measure efficacy against HIV should include other STDs as endpoints. If the microbicide also has activity against other STDs, approval for STD indications and adoption of a microbicide for that purpose in areas where HIV has not begun to spread may forestall a future HIV epidemic. Expanding the

market for a microbicide by also disseminating it for STD prevention may increase overall acceptance. However, designing efficacy trials to include definitive endpoints for STDs is almost certain to increase complexity and cost of such trials.

Optimal duration of enrollment and follow-up

Retention in clinical trials, especially those with follow-up periods beyond 1 year, is particularly challenging to HIV prevention trials.⁸² Unlike treatment trials that integrate follow-up care for a medical condition with research procedures, prevention trials enroll populations that are at risk for a condition but not under treatment. Often, the populations at greatest risk and, therefore, most appropriate for evaluation of a new prevention intervention are the most difficult to reach, both for enrollment and especially for retention. Unstable housing and occupational migration may exacerbate the challenges of sustained contact, as well as the ability to complete scheduled follow-up visits. Nonetheless, some of the large-scale efficacy trials of topical microbicides have demonstrated participant retention of 90% or greater after 18 months of follow-up, suggesting that conducting high quality trials among women at high risk of HIV is feasible.

Relatively brief follow-up periods have many potential benefits. These include higher retention, the ability to evaluate intensive interventions such as directly observed product administration (a strategy that should increase adherence in trials of a coitally independent microbicide requiring daily administration), and increased validity of behavioral assessments. However, the longer the period of trial participation, the better the trial will be to identify toxicity or tolerability problems that emerge after relatively longer exposure periods. Such trials will also be more informative about time-dependent reduction in participants’ willingness to use the product.

Prevention interventions for trial participants

Populations at greatest risk of HIV infection must have access to the most effective prevention interventions available, if they are to bear the risks of microbicide testing. Currently, this amounts to HIV testing with risk reduction counseling, free supplies of male and female condoms, and periodic diagnosis of and treatment for non-HIV STDs. Ethical considerations pose a dilemma regarding when to offer newly-established HIV prevention interventions to participants in microbicide efficacy trials. New and potential prevention interventions include male circumcision, use of cervical barriers, HSV-2 suppressive drugs to reduce HIV susceptibility and/or infectiousness, use of oral antiretroviral drugs for preexposure prophylaxis, and preventive HIV vaccines. Failure to expedite access by microbicide trial participants and their sexual partners to such new methods, as soon as their effectiveness and safety are established, may be criticized as unethical.

However, each host country for microbicide trials will differ in its pattern and rate of adoption of new HIV prevention

interventions such as male circumcision. In settings where such new methods have not yet been made readily available, expediting access for prospective trial participants (or their partners in the case of male circumcision) may, itself, be unethical if it is perceived as a coercive inducement to join a microbicide trial. The challenge will be striking a balance between an ethical obligation to assure that participants in microbicide trials are offered the best available standard of prevention and an ethical obligation to avoid undue incentives that compromise an individual's decision making during the informed consent process.⁷⁵

PLANNING FOR SUCCESS

Ongoing progress in HIV prevention research has two important implications for microbicide research and development. First, success in demonstrating efficacy of a new method to prevent HIV will affect continuing efforts to optimize existing methods and to evaluate other approaches. Second, proof of microbicide efficacy will shift the focus to implementation: whether and how to mainstream an experimental prototype into an accessible product in the most resource-poor regions of the globe.

■ RAISING THE BAR FOR EFFICACY TRIALS

Although every advance in preventing HIV is unarguably a welcome outcome, each incremental reduction in HIV incidence increases the difficulty of designing efficient, affordable, feasible efficacy trials of experimental interventions. Establishing partial efficacy of an investigational microbicide—even at levels of protection of 30–50%, which has been considered sufficient to justify licensure in some settings—sets a new basis for comparison for a next generation of investigational microbicides that shows promise of greater efficacy. Once regulatory approval has been secured, comparison of an investigational microbicide with the equivalent of a “no gel” or a placebo would violate ethical principles of research on human subjects. Trials designed to measure superiority would require considerably larger sample sizes than current efficacy trials. Moreover, the dilemmas associated with identifying a suitable control condition only become more complicated if a proven effective product uses a different delivery system (e.g., coitally dependent gel) than the newer investigational product (e.g., once-daily gel). In this case, the evaluation of efficacy may offer little information about biological efficacy if confounded by the impact of coital dependence or independence on adherence.

■ FROM CANDIDATE TO COMMODITY

Adoption and adherent use of a self-administered protective product requires active and sustained efforts to encourage consistent and correct use, especially for coitally dependent

products. Ongoing surveillance for any adverse effects or indicators of declining effectiveness will be important.

If the first approved product is available only by prescription, the gateway role of a health-care provider may challenge the capacity of an already fragile health infrastructure. Optimal availability and broad dissemination would require additional studies to support over-the-counter distribution and regulatory submissions to obtain such approval.

The fastest possible access depends upon availability of suitable manufacturing capacity and effective distribution and dissemination strategies. Advance arrangements to address financial barriers would expedite access by the poorest populations in need of products that otherwise might be financially out of reach.

As daunting as these and derivative challenges will be, success in demonstrating that a microbicide works to prevent HIV infection will represent a profound breakthrough in HIV prevention science and a boon to humanity.

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Behavioral Interventions for Prevention of STDs and HIV Infection at the Community Level

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Community outreach and education programs have a long history of use in many public health primary prevention, early disease detection, and health care interventions. Within the primary prevention arena, community-level approaches have been widely used, with varying degrees of effectiveness, to address issues such as cigarette smoking cessation, cancer and cardiovascular risk reduction, and alcohol and other drug abuse prevention. Community-level early disease detection methods have been used to encourage care-seeking behaviors related to screening and early diagnosis of breast cancer, hypertension, prostate cancer, and other diseases where early intervention is critical. Community outreach methods have also been widely used in both developing and developed countries to promote other health care-related behaviors such as pre- and postnatal care, child immunizations, and HIV testing among persons at risk for AIDS. These interventions have in common their focus on using community-level interventions to encourage behavior change on the part of population members, particularly those at risk for negative health outcomes. Similar community outreach and prevention methods, targeted toward sexual behavior change, are pertinent to efforts to prevent and control sexually transmitted diseases (STDs).

People contract STDs and HIV in the community, not inside STD clinics, physicians' offices, or other clinical and health care settings. Communities, therefore, are appropriate venues for STD prevention interventions. Although secondary prevention efforts often need to take place within settings that treat people who have already contracted STDs, including HIV, primary prevention efforts to reduce the incidence of STDs or HIV infection may have their greatest potential effect when they are undertaken in communities, not just in clinics. To the extent that it is possible to reduce levels of sexual risk behavior in population segments presently vulnerable to STDs and HIV, it should also be possible to reduce the number of new disease cases arising in those communities.

In this chapter, we will consider how community-level and community outreach interventions can be used in the primary prevention of STDs or HIV infection. We will organize

this discussion around four major issues: (1) psychosocial characteristics of community or population members associated with high levels of sexual risk behaviors that, therefore, are characteristics that can serve to define the nature and targets for community interventions; (2) the goals of community intervention; (3) models and examples of successful community-level STD prevention interventions undertaken to date; and (4) important new directions for work in the field of community-level STD/HIV prevention interventions.

PSYCHOSOCIAL CHARACTERISTICS RELATED TO SEXUAL RISK BEHAVIOR IN STD-VULNERABLE POPULATIONS

Community-level STD/HIV prevention interventions and, indeed, behavior change interventions of any kind, are effective only when they are focused on changing psychological and social characteristics that presently "drive" risk-taking behavior. Understanding the determinants of high-risk sexual behavior within populations vulnerable to STDs or HIV infection provides information needed to tailor interventions to change those relevant determinants. Fortunately, behavioral and social science research, guided by several theoretical frameworks concerning behavior and its change, has identified a set of psychosocial factors that predict levels of sexual risk behavior in a variety of STD/HIV-vulnerable populations, including ethnic minority heterosexual adolescents, sexually active college students, heterosexual men and women, and gay and bisexual men.¹⁻⁵ The fact that a relatively consistent set of sexual risk-taking behavioral determinants has been identified across multiple and diverse community populations attests to the salience of these psychosocial factors.

There are at least six key elements and objectives of community-level sexual risk behavior change interventions (Table 95-1). Normative perceptions concerning whether peers and sexual partners use condoms and practice safer sex are highly predictive of an individual's own level of risk behavior. To the extent that peers or members of one's social reference group, as well as one's own sexual partners, are

Table 95-1. Key Elements and Objectives of Community-Level Sexual Risk Behavior Change Interventions

Element	Community Change Objective
Sexual behavior normative perceptions	Creation of social reference group norms, especially among peers and sexual partners, that encourage and support behavior changes to reduce or avoid STD/HIV risk
Behavior change intentions	Strengthening population members' intentions and personal commitment to reduce or avoid sexual risk behavior
Attitudes toward condoms	Creating positive attitudes toward condoms including perceived benefits, positive outcome expectancies, and connotation of condom use with positive attributes (concern, caring, pride, and sponsibility)
Perceived risk reduction self-efficacy	Instilling confidence that individuals can successfully enact personal risk reduction or risk avoidance behavior change strategies
Risk reduction behavioral skills	Providing opportunities to observe, model, and rehearse behavioral skills needed to reduce risk including technical skills (such as condom use) and sexual assertiveness, negotiation, and communication skills
Readiness for change	Tailoring messages that encourage movement along a continuum from behavior change contemplation to preparation to action to maintenance of action in reducing risk

believed to subscribe to the norm that condom use is accepted and expected, individuals are more likely to use condoms themselves.^{6–10} Strength of behavior change intentions, a robust predictor of behavior change enactment in many health-related areas, also predicts condom use.^{2,8,10–12} Positive attitudes toward condoms, including perceived benefits of condom use and positive outcome expectancies, are associated with greater likelihood of engaging in STD preventive behavior.^{13,14} Individuals high in perceived self-efficacy for enacting risk reduction behavior change—those who are confident in their ability to take risk reduction steps in relevant personal situations—are more likely to exhibit behavior change than persons low in self-efficacy.^{15,16} Well-developed sexual communication skills, including assertiveness skills for refusing high-risk sexual coercions and sexual negotiation skills for initiating discussion with potential partners about condom use, have been associated with lower levels of sexual risk behavior.^{13,17} Finally, and recognizing that different members of a population are at different stages of contemplating, attempting, making, and maintaining change, an individual's present stage or readiness for change has proven to be a useful heuristic for understanding the type of intervention that may best meet the needs of given populations and population members.^{3,18–20}

These are not the only determinants shown in the literature to predict STD/HIV high-risk behavior or success in behavior change efforts. A number of situational factors, including substance use, relationship status and familiarity of sexual partners, positive HIV serostatus knowledge, and presence of competing life stressors, also influence levels of sexual risk behavior in some populations.^{21–24} Although AIDS risk knowledge does not frequently appear as a strong determinant of sexual risk behavior, probably because basic factual knowledge about AIDS is now quite high in most populations, there are likely to be more widespread misconceptions about STDs other than HIV, and it is possible that these misconceptions contribute to STD risk-taking behavior. For example, women's use of oral contraceptives protects against pregnancy, but oral contraceptive use not only increases risk of cervical chlamydial infection but also predicts nonuse of barrier methods that protect against STDs.²⁵ Perhaps this is owing, in part, to misconceptions about the protective effects of birth control pills.

The body of research identifying determinants of sexual risk behavior in populations is critical to the development of community-level and outreach-based STD/HIV prevention interventions because it identifies domains in which those intervention efforts should focus their attention. Based on

research conducted to date and summarized here, important targets for community-level STD/HIV prevention programs include changing population normative perceptions about the social desirability of risk reduction steps; strengthening behavior change intentions, attitudes, and perceived efficacy of change; and increasing population member skills (and motivation to use those skills) to resist coercions to engage in unwanted or unsafe sex and to negotiate safer sex practices.

DEFINING A COMMUNITY FOR INTERVENTION AND IDENTIFYING THE GOALS OF INTERVENTION

It is possible to conduct mass (and usually mass media) sexual behavior change encouragement programs directed toward the entire population of a city, state, or county. “America Responds to AIDS” is an example of a broadly focused media campaign directed, especially in its earlier years, toward the American population as a whole. Evaluations of such untailed educational campaigns indicate that they can increase public awareness of a problem, can increase public knowledge and correct misconceptions, and may influence general attitudes but rarely have been shown to reduce actual sexual risk behavior, especially among hard-to-reach and high-risk population segments.^{26,27} This may be owing to what is usually the very general and nontailored nature of mass media campaign messages directed toward the public as a whole, messages likely to be intentionally non-explicit in a potentially controversial area such as sexual behavior. The preponderance of both theory and research literature indicates that community-level risk reduction behavior change interventions, whether undertaken using mass media or other community and outreach intervention approaches, are most successful when they are directed toward a particular and identifiable segment or subpopulation of a community; when the community intervention is carefully tailored to the culture, attitudes, beliefs, and change readiness that characterize that population segment; when the intervention is sustained and uses multiple channels of delivery; and when the intervention is based on psychological, motivational, and social principles, rather than factual information provision alone.^{28–30}

The ultimate public health goal of STD/HIV prevention interventions is to reduce the incidence and prevalence of STDs. However, community-level STD/HIV prevention behavioral intervention trials rarely have been designed to examine change in disease rates in a population as a primary intervention outcome endpoint. Instead, most community interventions tested to date have sought to change population risk behavior characteristics or, even less proximal to the disease change outcome, to change population psychological or motivational characteristics related to risk behavior. Examples of behavior change outcomes relevant to STD/HIV prevention

are reducing rates of multiple-partner sexual contacts, reducing sexual network “mixing” between members of presently low-STD/HIV prevalence population segments and members of high-STD/HIV prevalence population segments (such as commercial sex workers), or increasing rates of condom use in sexual encounters that might otherwise confer STD/HIV risk. Less proximal endpoints in community-level interventions are promoting changes in population member risk behavior knowledge, attitudes, or change intentions. Although much less convincing as a sole endpoint than outcomes that demonstrate change in population risk behavior levels or STD/HIV rates, it is possible to make the case that attitudinally “moving” a presently condom-resistant population toward greater acceptance of condom use, for example, is an intervention goal not without merit.

Community-level and outreach-based interventions may also have behavior change goals other than sexual risk behavior change. Examples of such goals might be encouraging greater HIV or STD testing within the population or encouraging population members to access more intensive and personalized risk behavior change assistance resources in their community. The key point here is that community and outreach-based STD/HIV prevention refers to a modality for delivering prevention services to population members in the community; the behavioral objectives of these programs may vary, and the elements to be incorporated in a given program need to be defined by what kind of change—sexual risk behavior change, attitude or motivation change, or other kinds of prevention help-seeking—the intervention is meant to bring about.

Finally, community-level interventions may be critical for promoting not just the initiation of risk reduction behavior change but also its successful maintenance in STD/HIV-vulnerable populations. Traditional one-on-one and clinic-based counseling—even when intensive, culturally-tailored, and guided by sound behavior change principles—is based on the presumption that persons will be able to carry forth successfully their risk reduction efforts in the real world when they “leave” counseling and that they will be able to do this for long periods. However, the real world does not always, and perhaps does not often, reinforce persons’ risk avoidance efforts. Resisting coercion to have sex or insisting on condom use are actions that may elicit negative reactions from sexual partners or potential partners, and risk reduction behavior changes are not yet accepted norms within many of the populations segments at greatest risk for STDs, including HIV infection. It is possible to view STD/HIV prevention as the task of attempting to change an individual’s attitudes, motivations, and skills and then hoping that the individual will be able to sustain change when confronting unsupportive real-life relationships and risk pressures. Alternatively, it is possible to take a broader social learning perspective in which behavior change maintenance is viewed not only as a function

of an individual's efforts but also of peer group social norms that may either help to reinforce change efforts or contribute to relapse over time.¹ Community and outreach-based interventions that change norms and behavioral expectations within at-risk populations to support risk avoidance efforts can play an important role in creating social environments that promote behavior change maintenance.³¹

EXAMPLES OF COMMUNITY AND OUTREACH-BASED INTERVENTIONS TO REDUCE SEXUAL RISK BEHAVIOR

A number of investigations and program descriptions of community-level risk behavior change interventions have appeared in the literature and have advanced our knowledge concerning how to produce population-level risk reduction. Most of these interventions have been cast primarily as AIDS/HIV prevention efforts. Because many of the same behavior changes that afford protection from HIV also reduce risk for other STDs, we will consider HIV and STD sexual risk reduction interventions together. Three types of community-level intervention have most commonly been reported in the literature. These are (1) approaches that use community opinion leaders to redefine sexual norms and safer sex expectations within the peer groups; (2) outreach-based risk reduction workshops offered in community settings; and (3) multifaceted community mobilization and activation risk reduction programs.

OPINION LEADER COMMUNITY NORM CHANGE INTERVENTIONS

Peers and, in particular, those members of one's own social reference group who are considered popular, influential, and likable are potentially important models of behavior. From a social learning experience, well-liked peers can serve to influence the behavior standards of those who observe their actions.¹ From the perspective of diffusion of innovation theory, popular individuals within a community social network often function as opinion leaders who can set new trends that are observed by others, that are then copied by "early adopters," and that gradually diffuse throughout the social network until the new trends become accepted and normative.³² From either theoretical framework, the implication for behavior change promotion is that cadres of well-liked, popular opinion leaders or peer models can, through endorsement and modeling processes, influence the social norm perceptions and behavior of the larger population segment or social network in which they are influential.

In a set of community-level trials, Kelly and colleagues evaluated whether interventions based on diffusion of

innovation principles can produce population-wide reductions in the level of HIV high-risk sexual behavior among gay men who lived in small cities and patronized gay bars in those cities.³³⁻³⁵ The project focused on gay men in small cities because prior research had revealed that many small-city gay men, unlike their counterparts in major AIDS epicenters, continue to engage frequently in high-risk sexual behavior and do not perceive safer sex as a socially accepted peer norm.³⁶ To establish baseline levels of population risk behavior, all men entering all gay bars in each study city were administered anonymous surveys eliciting information on their sexual behavior practices in the past 2 months and on their perceptions concerning the safer sex norms held by friends. Although there was some variability across city populations, about one-third of men reported engaging in unprotected anal intercourse in the past 2 months, usually not with an exclusive partner of known HIV serostatus.

When the intervention was ready to be initiated sequentially in a city, bartenders were trained to observe the crowd of people in a city's clubs and to identify those persons who were most popular, most sought out for conversations by others, and most frequently seen to interact with others. About 15% of the total number of persons in the bars were identified as popular opinion leaders by multiple, independent bartender observers. These key opinion leaders were then contacted and invited to attend a series of four group sessions that taught them how to communicate effective risk reduction behavior change endorsement messages to their friends and acquaintances, provided guidance and problem solving in how to initiate norm change conversations with others, and systematically engaged each opinion leader to seek out opportunities to have peer conversations following each group session. Some opinion leaders self-monitored up to 100 risk reduction endorsement conversations with friends over a 6-week period. The opinion leaders also wore distinctive buttons that visually demonstrated their personal involvement and support of risk reduction efforts.

To determine the effectiveness of the intervention in changing population-wide sexual risk behavior in initial studies,^{33,34} all men patronizing bars in each intervention city were surveyed 3 months following the intervention. In each city population, reductions of between 15% and 29% from baseline levels were found in the proportion of population members who reported engaging in any unprotected anal intercourse in the past 2 months. In a subsequent expansion of the trial to eight additional cities, half of which received the same opinion leader intervention and half of which served as comparison cities, a reduction of about 30% in the prevalence and frequency of self-reported high-risk sexual behavior was found at a 1-year follow-up.³⁵ Taken together, these findings indicate that interventions that

actively engage a sufficient number of key opinion leaders to endorse and recommend behaviors change to their peers can produce reductions in population sexual risk behavior levels.

OUTREACH-BASED RISK REDUCTION WORKSHOPS OFFERED IN COMMUNITY SETTINGS

A number of randomized clinical outcome trials have demonstrated the efficacy of intensive small-group intervention programs based on cognitive-behavioral change principles for producing reductions in HIV risk behavior among gay and bisexual men, at-risk inner-city women, and disadvantaged adolescent males and females.^{17,37-43} Although tailored in content to the different risk circumstance confronting each population, these interventions delivered in workshops or in multiple-session programs have all combined such elements as risk education, sexual assertiveness and negotiation skills training, teaching condom use and risk behavior self-management skills, enhancing positive attitudes and motivations toward behavior change, and reinforcing efforts to change risk behavior.⁴⁴ All of these intervention trials produced effect sizes indicative of moderate to large reductions in self-reported sexual risk behavior, usually reflected by reductions in rates of unprotected sex and increases in condom use. Behavior change self-reports have often been corroborated by change in other indices of risk reduction such as condom redemption or purchase, improvement in objectively assessed sexual assertiveness skills, and other validation measures.

For the most part, research evaluations of these small-group and workshop interventions have taken place in clinic or institutional settings. However, a number of projects have utilized outreach methods to “market” and recruit participants in AIDS-vulnerable communities to attend the workshops or small-group programs, and, in this sense, the interventions can be viewed as prevention resources available for at-risk community members who are identified through community outreach.^{37,40}

Another form of workshop intervention widely used by community-based organizations in the United States and abroad is the “Stop AIDS” program.⁴⁵⁻⁴⁷ Originating in the gay community but extended more recently to other HIV-vulnerable populations, Stop AIDS consists of workshop programs usually led by trained volunteer facilitators that involve discussion about risk behavior, promotion of positive attitudes toward behavior change, and skills training exercises in areas related to the successful implementation of changes. The 3–4-hour workshops are often conducted in community members’ homes and frequently include members of entire social networks and friendship circles who participate together in the same session. Because

Stop AIDS originated as a grassroots community-based HIV prevention program to deal with a health emergency, it was implemented directly without planning for scientifically controlled or randomized evaluation methods. Nonetheless, outcome evaluations have shown that participants exhibit change in sexual risk behavior knowledge, attitudes, change intentions, and behavior following attendance at Stop AIDS groups.^{46,47}

MULTIFACETED COMMUNITY MOBILIZATION AND ACTIVATION INTERVENTIONS

Several community-level interventions focused on shifting population risk behavior utilizing multiple components have recently been described in the literature. Those interventions differ from those described earlier because they rely on a combination of different programs and levels of effort in order to mobilize or activate population behavior change.

Because young gay men continue to contract HIV and other STDs at high rates and have been less influenced by AIDS prevention efforts than their older counterparts, young men who have sex with men constitute a population of importance in HIV/STD prevention efforts.⁴⁸ Kegeles and colleagues evaluated a community intervention in a small California city that combined risk reduction workshops with ongoing community social events that included risk reduction endorsement messages disseminated by opinion leaders identified in the populations of young gay men.⁴⁹ The intervention also included distribution of safer sex education materials, t-shirts, and logos among young men in the cities’ bars, clubs, and other socializing areas. Cross-sectional population member and cohort follow-up surveys revealed reductions in rates of self-reported risk behavior of about 20% from preintervention levels to follow-up in each city.

Sikkema and colleagues have undertaken a community mobilization intervention focused on women who live in 18 housing developments within inner-city census tracts with high rates of STDs.⁵⁰ In nine housing developments that received the HIV prevention intervention, women identified by their neighbors as key opinion leaders were invited to attend workshop programs offered in the developments; the workshops focused on women’s health concerns, HIV and STD, risk education, risk reduction skills building, and strategies for “networking” HIV prevention messages to other women in the development. The opinion leader women also recruited successive “waves” of their neighbors to attend the same program, and the key group of women initially identified as opinion leaders formed “Women’s Health Councils” in each development to plan ongoing social events organized around AIDS prevention and awareness themes. The program was evaluated by conducting anonymous risk behavior surveys of all women in the nine intervention and nine control condition housing developments before and again

3 months and 9 months after intervention. Findings of the study indicate that condom use among women in the intervention housing developments increased from about 24% of intercourse occasions at baseline to approximately 43% of intercourse occasions at follow-up, with the effects most pronounced among those women who both attended risk reduction workshops and were also exposed to the community-level AIDS awareness events. No significant change was found over time in rates of unprotected sex or condom use among women in the control condition housing developments.

Finally, in a large multisite demonstration project, investigators at the Centers for Disease Control and Prevention (CDC) have evaluated the impact of community-level and population-focused HIV prevention interventions for a variety of AIDS-vulnerable, but hard-to-reach populations, including men who have sex with men, youth in high-risk situations, female partners of IDUs, and female commercial sex workers.^{23,51} The interventions tested in these AIDS community demonstration projects include community educational outreach by lay prevention educators, the use of culturally tailored “role model” portrayals used in “small media” campaigns to illustrate how peers have changed risk behavior, and intervention elements intended to increase population member readiness or stage of change for enacting risk reduction steps. Evaluated with street intercept interviews conducted with targeted population members before and following intervention, outcome findings of the project indicate evidence of attitude, change readiness, and risk behavior change in a number of the population. Among community members who reported exposure to the intervention elements, consistent condom use with nonprimary partners significantly improved relative to rates of risk behavior found in comparison neighborhoods. Greater behavior change readiness was also observed in the intervention area populations.⁵²

Most of the community-level intervention trials described in this chapter were undertaken in the United States. STD/HIV disease burden is far greater in resource-poor and developing countries. Some culturally tailored community approaches have shown efficacy in international contexts. For example, Roma (Gypsies) are the largest and one of the most disadvantaged ethnic minority populations in Eastern Europe, vulnerable to STDs and other social health problems.^{53,54} Living in impoverished insular communities and distrustful of outsiders, Roma rely on members of their personal social networks for trusted advice. A recent randomized trial recruited intact high-risk social networks or friendship groups of Bulgarian Roma men, assessed all participants’ reported sexual risk behaviors, tested participants for STDs treating all positive cases, provided risk reduction counseling, and randomized networks to experimental or comparison conditions.⁵⁵ The influence leader of each experimental condition network was identified and attended a group intervention that provided

ongoing training and guidance for counseling other members of the same network in STD/HIV risk reduction. Follow-up behavioral and STD testing assessments undertaken over the subsequent 12 months revealed declines in the prevalence of unprotected intercourse, especially with casual partners. By 12-month follow-up, 14% of men in the control group had contracted gonorrhea relative to only 8% of members of experimental condition networks. The trial is one of the few community-level interventions conducted in a resource-poor country to demonstrate impact on both behavioral and disease outcomes.⁵⁵ A similar social network intervention undertaken with gay or bisexual men in Russia also showed similarly promising outcomes.⁵⁶

GAPS IN OUR KNOWLEDGE ABOUT COMMUNITY-LEVEL INTERVENTIONS

Outcomes from these trials of community-level interventions for sexual risk reduction have shown considerable promise. However, the effects even of successful interventions are not necessarily permanent. There were sharp declines in risk behavior and in the incidence of HIV and other STDs among gay or bisexual men during the decade following the appearance of AIDS and the development of wide-scale community prevention programs.^{57–59} However, now there are more frequent reports of STD outbreaks, especially syphilis, and a resurgence of high-risk behavior in some segments of the gay community. This finding underscores the importance of sustaining community-level interventions, ensuring that new generations of young people who become sexually active are also exposed to prevention interventions and targeting community approaches to reach highest-risk social and sexual networks within the community. It is well known that STDs cluster within high-risk networks.^{60,61} Behavioral interventions targeted directly toward vulnerable community social networks constitute a level of precision that is promising and worthy of greater attention.⁵⁶

Although the programs described in this chapter have demonstrated the effectiveness of community outreach interventions in promoting sexual behavior change in some populations at risk for HIV infection, there remain important unanswered questions about how best to apply these approaches to other STD-vulnerable groups. Most community-level sexual behavior change interventions have been developed from the perspective of HIV prevention, and the populations targeted by intervention often have been gay men. With the exception of the Sikkema et al. community-level intervention and several reports describing risk reduction small group programs undertaken in community settings with at-risk women, there have still been very few applications of community outreach sexual behavior change interventions tailored expressly for women, even though women are, in many respects, the population most affected

by non-HIV STDs.^{17,39,40,50} In addition, community-level behavioral interventions have had AIDS as their primary focus, a disease widely-known, widely-feared, and likely to motivate strong mobilization responses. Non-HIV STDs are less understood and less feared by most people, and different approaches may be needed to motivate population-level protective efforts related to STDs other than HIV.

Related to this, most conceptualizations of factors related to sexual risk behavior change appear to be based on the premise that sexual behavior decisions are volitional and determined primarily by an individual's own wishes, attitudes, intentions, skills, and normative perceptions. However, these models do not adequately take into account the behavior change barriers; social, economic, and cultural factors; and relationship pressures faced by women who are in coercive and power-imbalanced relationships with high-risk men resistant to condom use. Until further advances are made in female-controlled STD and HIV prevention methods, special obstacles will continue to be faced by women in dependent relationships with high-risk men. Because men's attitudes substantially influence whether or not condoms will be used during sex, community-level outreach interventions focused on changing the attitudes, norm perceptions, and behavior practices of high-risk heterosexual men are essential. To date, little intervention attention has been directed to this critical population.

Finally, STD/HIV prevention community-level interventions to date have primarily targeted reductions in sexual risk behaviors. A protective vaccine against human papillomavirus (HPV) is now available, and recent studies have shown that male circumcision considerably reduces the probability of HIV transmission in developing country populations with high HIV disease prevalence.⁶²⁻⁶⁵ Whereas HPV vaccination and male circumcision are medical procedures, the process of getting persons to accept, seek, and obtain these procedures is behavioral. The success of such medical prevention advances will require that individuals perceive acceptance of them as desirable, beneficial, and culturally and socially normative. Further, the protective benefits of procedures such as male circumcision could be lost or diminished if persons then felt overly protected, reduced their condom use, or increased their sexual risk behavior. Community-level behavioral interventions that promote population acceptance and seeking out of new medical protective approaches, while also avoiding risk behavior increase compensation, can play an important role in translating medical prevention advances into public health benefits.

CONCLUSIONS

Community- and outreach-based interventions to encourage reduction in sexual risk activities hold considerable promise for the primary prevention of STDs. Such approaches to intervention have the potential for bringing culturally-tailored

prevention services to hard-to-reach population members and for changing the risk awareness, social norm perceptions, attitudes and change readiness, and sexual risk behavior of populations presently vulnerable to STDs and HIV infection. A specific and unique benefit of community interventions for STD/HIV prevention is their potential for creating social norm changes in populations that encourage the maintenance of sexual risk behavior changes. The field of community-level interventions to prevent STDs including HIV infection is still relatively new, and many issues concerning how best to tailor, implement, and evaluate the effectiveness of these programs still require attention and study. Nonetheless, community and outreach programs are important components of comprehensive approaches to STD and HIV primary prevention.

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Marketing, Communication, and Advocacy for Large-Scale STD/HIV Prevention and Control

William A. Smith and Robert Hornik

This chapter focuses on large-scale behavior change efforts using marketing, communication, and/or advocacy to influence the behavior of individuals at risk of disease. It defers discussion of face-to-face (individual and small group) approaches that have been characteristic of counseling and testing, for example, in favor of a better understanding of mass approaches that mediate direct contact with the target audience through radio, television, billboards, diffusion of new products and services, and/or policy change. In practice, both face-to-face and large-scale approaches often work together (e.g., a mass media program can be used to increase the number of individuals volunteering for counseling and testing). In this chapter, however, we focus on the unique problems and opportunities for behavior change on a large or mass scale.

Large-scale approaches offer significant public health advantages in scale of effect. Large-scale programs are often characterized in three ways: product/service, message, or policy approaches. The basic assumptions underlying this chapter are as follows:

1. The objective quality of products, services, and behaviors promoted by persuasive messages about them, and the reduction of barriers to using them, are important determinants of successful behavior change.
2. People's perceptions of the products/services, messages, and policies vary among individuals and groups and are the means by which people judge the objective characteristics of a product, service, or behavior.
3. Marketing, communication, and advocacy are three approaches, individually or in combination, to successfully promote products/services, messages, and policies to large-scale audiences. They integrate the objective and perceived values of new behaviors to foster effective behavior change. See [Fig. 96-1](#).

PRODUCT/SERVICE APPROACHES

Product/service approaches make it easier for a large number of people to make healthy choices by increasing the access

and attractiveness of products/services that make prevention and control more viable (longer operating hours, services closer to home, ensured confidentiality, etc.).

MESSAGE APPROACHES

Message approaches (campaigns, entertainment media, and news reporting) help ensure that people are both aware of and believe in the choices opened to them. These approaches provide basic information and increase the perception that the target behavior is widely acceptable and even popular. Successful message approaches ensure that information is clear, accurate, and persuasive. They use targeted channels of communication to reach an intended audience frequently, appropriately, and with high credibility to the audience.

POLICY APPROACHES

Policy approaches use law, regulation, and enforcement actions to provide disincentives for unhealthy behavior (criminalize sex with minors, criminalize prostitution, close bathhouses, tax pornography, etc.), or provide positive incentives for healthy behavior (lower insurance premiums, tax breaks, antidiscriminatory legislation).

The successful practice of large-scale behavior change is the story of how these three approaches are combined in different ways to meet the needs of specific audiences and conditions. Although different in many important ways, all three program strategies share a common belief that interventions should be designed based on the perceived desires, the real-world barriers, and the objective health needs of the at-risk population. They share a basic logical process model ([Fig. 96-2](#)) in which behavior is influenced by people's perceptions, as well as objective reality of the intervention changes.

This logical process model illustrates the steps between problem identification and problem solution. For example: a health problem (rapid rise in HIV/AIDS cases) is detected through surveillance. A behavioral cause—untreated sexually

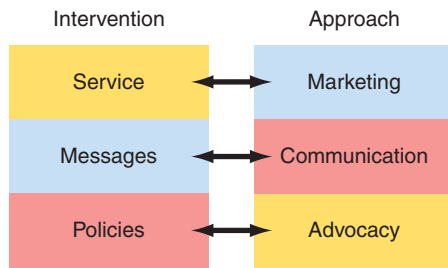


FIGURE 96-1. Associating intervention strategies and approaches to behavior change.

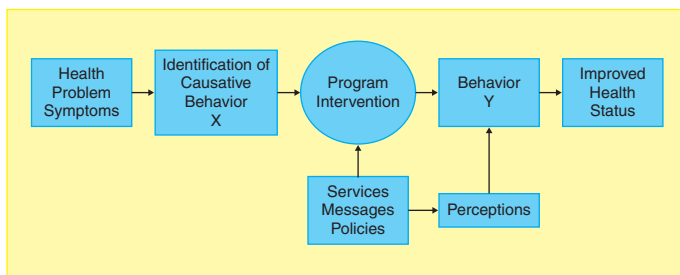


FIGURE 96-2. Logical process model.

transmitted infections (STIs) of that health problem is identified. A program intervention (counseling, testing, and treatment services) is expanded to address the behavioral problem. How people perceive that intervention influences whether people use the new services as much as the objective quality of the service itself.

Objective quality and personal perception are indispensable partners of effective behavior change in this logical process model. Several key perceptions have been identified as targets of opportunity to foster positive change, including (1) perceived benefits (*If I go to be tested and treated for STI, will I get something that I want or that is better for me than not knowing*); (2) self-efficacy (*I know I should get tested, but I just can't face telling my family if I have the disease—It's just something I can't do*); and (3) social norms (*I'd get tested if I knew my friends expected me to get tested or were getting tested, but I am not going to be the first one to do it*).

PRODUCTS, SERVICES, OR “BEHAVIORS”

A discussion of several recent success stories of HIV prevention illustrates how products, services, and behaviors differ from each other and yet play complementary roles in the success of a large-scale program. Take, for example, two of Uganda's ABC (abstinence, being faithful, condom use) behaviors that have received a great deal of attention: sexual abstinence and being faithful. Both of these behaviors are lifestyle decisions influenced primarily by internal perceptions of what is best, what is possible, and what is popular.

The prevalence of HIV in Uganda peaked in 1991 at 15% in the overall population and 30% among pregnant women

in urban areas. By the end of 2003, HIV prevalence had dropped to 4.1% nationally.¹ These declines were accompanied by declines in the number of young men reporting to have ever had sex and increases in the age at which young women reported having had their first sexual encounter. Levels of self-reported monogamy increased and condom use rose among unmarried sexually active men and women. Some analysts have pointed out that other African countries saw similar increases in condom use with little or no decline in HIV prevalence but did not experience similar increases in monogamy or abstinence as reported in Uganda. David Wilson of the University of Zimbabwe concludes, “...condoms may not be the primary intervention for reducing HIV prevalence in generalized high-prevalence epidemics spread largely by heterosexual transmission. They remain essential, however, in interventions targeted to high-risk groups.”²

Abstaining from sex and sticking to one partner are not behaviors that can be packaged, distributed, put on a shelf, priced in a currency, and sold. Neither are they services that can be identified and used. They are life decisions, sometimes called “lifestyle” decisions which, even though they are not products or services, are susceptible to marketing, communication, and advocacy approaches. Like product and service behaviors, lifestyle behaviors have benefits and barriers as interpreted or perceived by a specific target audience.

To market a lifestyle behavior it is necessary to address these benefits and barriers—tip the balance between perceived costs and benefits so that the perceived benefits outweigh the costs for specific high-risk audiences. Mass media is helpful in shaping the perceptions of a nation as to what acceptable behavior ought to be. Uganda did not just have a policy of ABC, it promoted that policy through multiple communication channels. The President of Uganda became a major spokesperson. Entertainment media, news media, and mass media campaigns, all targeted these lifestyle behaviors over a long period in culturally persuasive ways at the same time that condoms were being made widely available and marketed. The effect was to create a new social norm around sexuality. A young man no longer had to have multiple sexual partners to be a “man” in Uganda. A young woman no longer had to say yes to an older man's sexual advances. At the same time that new perceived benefits were being added to the behaviors, the negative consequences of alternative behaviors (multiple partners) were being made more “costly” by using the fear of AIDS to make the dangers of multiple partners seem real.

Thailand's 100% condom use program, which targeted sex workers and used policing strategies to enforce tough new laws, also received world attention as an alternative approach to Uganda's ABC strategy. Between 1989 and 1993 results of a comprehensive sexually transmitted disease (STD) monitoring program in Thailand showed that condom use in commercial sex workers in Thailand increased from 14% to 94% and in

men the occurrence of the five most common STDs dropped by 79%. New cases of STDs in women declined by 54%.³

From a large-scale behavioral perspective it is important to point out two aspects of this success not immediately apparent in this data. First, the Thai program was much more than simply 100% condom use among female sex workers (FSWs).⁴ Indeed, a massive multi-intervention national program was initiated by Thailand's new Prime Minister soon after his inauguration in 1991, including the establishment of 508 STD clinics significantly expanding access to treatment. There was a massive education campaign directed by one of the world's foremost and most successful social showmen, Mechai Viravaidya, with anti-AIDS messages broadcast every hour on the 488 state-owned radio stations. A number of repressive policies that required the reporting of the names and addresses of AIDS patients were repealed.⁵

The second aspect of the Thai experience is that it builds on Thai history and culture. Thailand is a predominantly Buddhist culture which is supportive of men and women sharing decision-making power. Thailand also had one of the world's largest and most successful long-term programs of family planning, fostered by the same Mechai Viravaidya mentioned above. The family planning program was visible for years in Thailand,

where condoms were a focal point of activities. In sum, condoms were not an innovation in Thai society.⁶

From a large-scale communication perspective the most important lessons to draw from both the Ugandan and Thai experiences are that comprehensive, multifaceted national programs, supported by top political leaders, well-financed and culturally competent within each society can make an important contribution to the large-scale behavior change required by complex social problems like STD and HIV epidemics. The stories of programs in Brazil, San Francisco, and Switzerland, three other vastly different cultural contexts, demonstrate similar lessons.

There is one more lesson that may be drawn from the analysis of the Thai experience. Figure 96-3 provides information about behavior change, health status, and intervention inputs over time. The figure includes the period prior to the major evaluation of the STD program cited above but also looks backward to the earlier, pre-AIDS period. There was a sharp decline in STDs associated with the launch of the program in 1989, but the figure also makes clear that STDs were already beginning to decline in Thailand, well before full implementation of any mass campaign or 100% condom use program. What explains that downward trend? It is not clear.

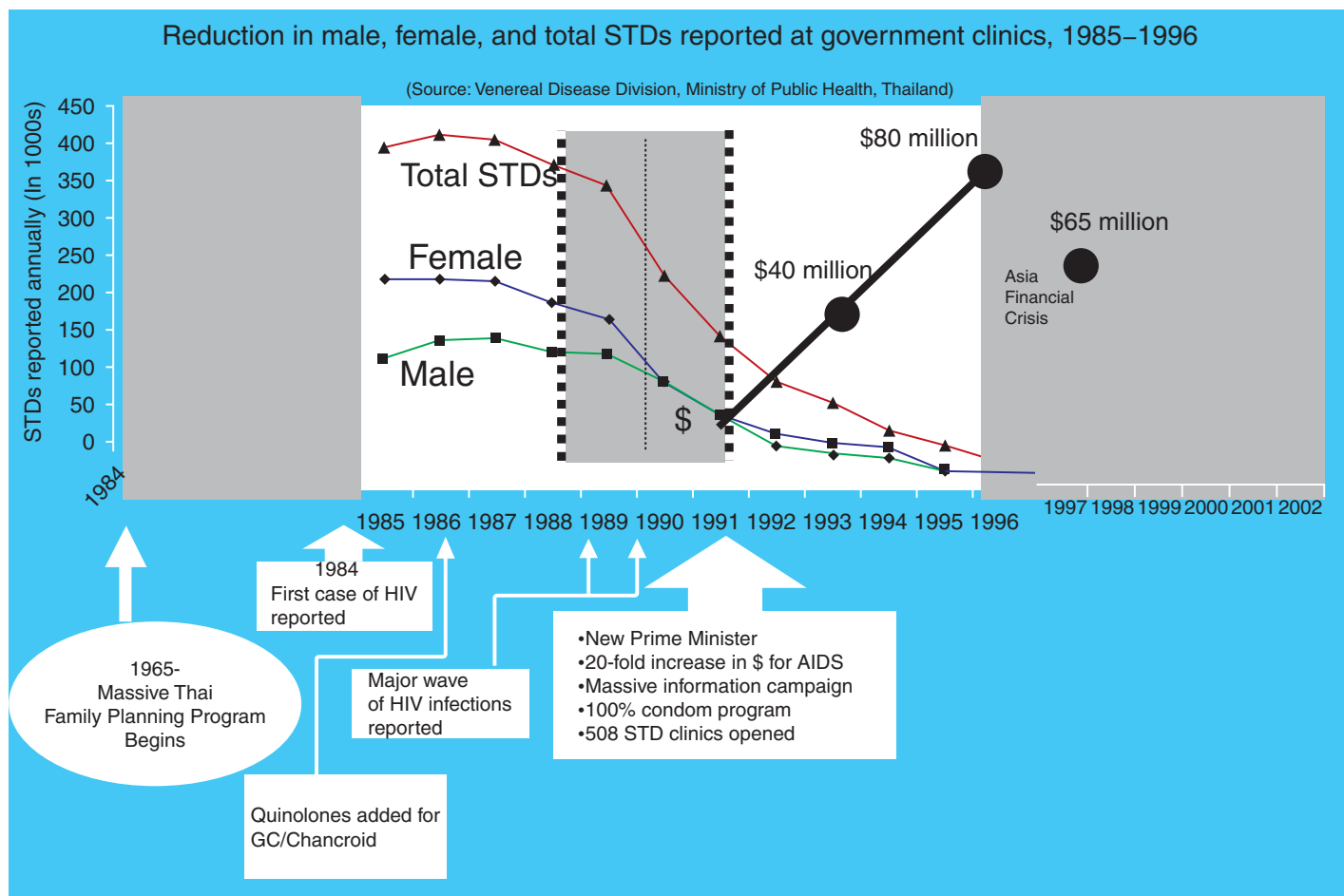


FIGURE 96-3. History of Thai STD program, 1985–2002.

Perhaps the advent in news stories of the first cases of HIV reported in 1984. This coupled with the prior history of a condom-friendly country began to break the back of STD growth in the country. The targeted campaign on syphilis that began in the late 1980s and the introduction of quinolones for treatment of gonorrhea and chancroid in 1986 certainly were additional explanatory factors. There may well be others we do not yet understand that explain the dramatic decline in STIs that began as early as 1987. It is doubtful that the decline post-1989 can be seen as independent of previous interventions. The most positive view is that the post-1989 activities accelerated a trend already in place, which might have otherwise leveled off.

IMPLEMENTATION STRATEGIES

Social Marketing. Social marketing can be defined as a program-planning process that promotes the voluntary behavior of target audiences by offering benefits they want, reducing barriers they are concerned about, and using persuasion to motivate their participation in program activity leading toward improved personal and social welfare.⁷ Social marketing uses in-depth information about both consumers and the health system to (1) define products, services, and behaviors that are most acceptable to users; (2) organize delivery systems or places that ensure easy access and facilitate adoption of products and behaviors; (3) establish a price in terms of barriers (dollars, time, social status, or convenience) that users are willing to accept; and (4) create and diffuse messages about those products and behaviors that motivate and persuade.⁸

Health Communication. Health communication can be defined as a process for the development and diffusion of messages to specific audiences in order to influence their knowledge, attitudes, belief, and behavior in favor of a healthy behavioral choice.⁹ Health communication has a long history in international public health and has many varied meanings. For the purpose of this discussion, health communication is considered largely a “message” approach to behavior change. While it recognizes that messages alone are insufficient to influence complex behavior change, health communication generally does not assume responsibility for the organization and management of new products/services or policy approaches. Health communication shares many characteristics with social marketing. For example, an emphasis on consumer research and a commitment to consumer-centered program development are common to both approaches.

Social Advocacy. Social advocacy, sometimes referred to as media advocacy, is defined as a process for influencing public policy and institutional structures leading to improved health behavior and health outcomes.¹⁰ To address the increasing need for new policy and regulatory controls, social advocacy

programs emerged as an approach to behavior change. Much of the legislative support to limit smoking and drunk-driving, and indeed support for HIV/AIDS prevention, has come from the determined, strategic, and creative work of social advocates. Advocates are often frustrated by social marketing and communications approaches, which they argue “blame the victim.” Advocates place primary emphasis on public policy and institutional change to make it unnecessary or easier for individuals to change their behavior. Important examples of successful advocacy efforts include the 20-year fight for controls on the U.S. tobacco industry and the U.S. effort to reduce drunk-driving accidents and fatalities.¹¹

The growing complexity of social problems has fostered a growing specialization within the social marketing, health communications, and social advocacy communities. However, many of the specific program tools, such as awareness campaigns, public advertising, public relations, demonstrations, audience segmentation, consumer research, and policy research are used by marketers, communicators, and advocates alike. More important, the central organizing approach shared by all three strategies remains (1) an in-depth understanding of their consumer (e.g., high-risk individual, influential family and friends, community, general public, or policymaker); (2) based on strategic consumer research; and (3) driven by a desire to satisfy what that consumer wants in order to make the right decision—whether that decision is to use a condom, talk supportively to a friend, or pass a law closing bathhouses. All three action strategies are fundamentally consumer-centered and focused on large-scale social and human behavior change.

Today there is a growing belief that comprehensive programs that strategically combine marketing, communication, and advocacy strategies do better than piecemeal and opportunistic efforts.¹² Lessons from three large-scale programs of health behavior change illustrate the importance of sustained integration of these three implementation strategies over time.

THE TOBACCO WARS

The history of smoking prevention in the United States represents a test case for the use of marketing, communication, and advocacy over a long period to confront a major public health threat. Very early, tobacco became one of the colonial America’s first cash crops and a force in the introduction and spread of slavery. The first American cigarette factory opened in 1864. Camels were introduced in 1913, the year often credited as the birth of the cigarette. Dr. Ernst Wynder’s first study identified a definitive biological link between smoking and cancer in 1954. The first public health statement about the dangers of smoking was published in 1957, and in 1966, the first warning labels appeared on cigarette packs.¹³

Over the next 20 years, from 1966 to 1986, there was a gradual increase in public education on the dangers of smoking in the face of strong pro-tobacco marketing by the

tobacco industry. In 1990, the era of public education ended and environmental smoke becomes the focus. Smoking was banned on all interstate buses and domestic airlines. For the next decade, the focus was on environmental controls until 1998, when Attorney Generals from 46 States, the District of Columbia, and 5 U.S. territories negotiated a \$200 billion tobacco settlement agreement. In 1999, 46 years after the first biological link between smoking and cancer was discovered, the Phillip Morris Company admitted that smoking was addictive, that it caused cancer, and said there was no safe cigarette.¹⁴

The public health impact of this history is reflected in a trend in smoking prevalence in America that peaked around 1966 at 42.6 smokers per 100 and then fell to a prevalence rate in 2002 of 22.5 per 100. The largest single drop occurred between 1966 and 1970 when prevalence dropped from 42.6 to 37.4 per 100, a period when there was heavy antismoking advertising on television.

What makes the cigarette wars unique is the existence of a well-organized, counter-public health and well-financed force of industry professionals dedicated to defeat public health goals. On the one hand, they were a fierce foe and on the other hand, they gave public health advocates a clear target to demonize and blame for American smoking behavior.

Within this broad history of tobacco there are hundreds of studies throughout the world that have tested specific tactics, programs, tools, and approaches. It is important to note that many of these failed in the short-run to produce any public health effect. But the persistence and the continual creativity of the antismoking professionals in medicine, politics, community education and mobilization in meeting new threats from the tobacco industry are landmarks in the history of large-scale behavior change and public health. Perhaps one of the most important lessons of the tobacco wars is that “science” itself may not change behavior in the context of competing interests with substantial economic and political influence. Deliberate and persistent efforts to change institutional and individual behavior were required.

THE “VD” WARS

In *No Magic Bullet*, Allan Brandt documents the history of venereal disease (VD) in the United States since 1880.¹⁵ In this compelling story, equally as complex as the history of smoking prevention in the United States, many of the same tools and tactics are used to both prevent disease and promote the treatment of “VD” or STDs. Mass media campaigns, legislation to control behavior, the marketing of products like condoms and services such as testing and treatment, all take center stage in the drama. The U. S. military plays a key role in both stories—in the tobacco wars they were part of an industry promotion strategy to introduce and addict young men and women to tobacco, while in the battle against VD

the military was a frontline force to educate men about the dangers and prevention of “unholy” diseases.

The STDs wars were not against a highly organized and powerful industry but rather against a highly rewarding human behavior that is often morally scorned, driven underground and stigmatized. While tobacco was a celebrated American institution, STDs were a dangerous betrayal of America’s ability to defend itself against German aggression—a threat to America’s fighting capacity. Brandt marks a dramatic change in the history of STDs with the discovery of penicillin. Here was a proposed “magic bullet” that would allow men to engage in risk behavior and yet be “cured” of its health consequences. However, Brandt points out that it was society’s continuing stigmatization of STDs that, despite the magic bullet of penicillin, drove people and the disease underground and made eradication all but impossible.

SIDS

The story of large-scale behavior change in the case of sudden infant death syndrome (SIDS) is another unique case. Here, a relatively simple behavior, placing sleeping infants on their backs rather than on their stomachs, was a message which resonated with millions of mothers, and within a matter of months mothers of newborns had made significant behavior change.¹⁶ There was no organized opposition, no economic interests, and no stigma associated with the behavior. The problem was addressing long-held beliefs transmitted from mother to daughter about child-rearing. This behavior did not prove as resistant to change as tobacco use or the adoption of safe sexual practices.

The point here is that the characteristics of a particular behavior change may be as influential in determining the duration and effectiveness of a large-scale program of behavior change as the choice of strategic direction and the quality of execution. Within the field of STD alone, the differences among behaviors, such as condom use, testing and counseling, and needle exchange are significant and require different combinations of marketing, communication, and advocacy interventions.

As illustrated earlier in this chapter, the experience of Uganda’s ABC program, along with other successful HIV/AIDS programs in San Francisco, Zambia, Thailand, and Brazil, again demonstrates the important difference that the choice of behavior (100% condom use for sex workers, versus ABC for a large generalized populations) continues to make in the effectiveness of any large-scale program of behavior change.

THE EVIDENCE FOR EFFECT

There is ample evidence for the effectiveness of large-scale social marketing, health communication, and advocacy

programs.¹⁷ However, before considering these data, it should be understood that the evidence does not, and, more important, most often could not, satisfy a requirement for randomized controlled trials as the basis for inference about effects. One way that effective programs work is to reach their target audiences directly in face-to-face encounters, such as counseling. However, a complementary path of effect, one often deliberately incorporated into the best population-oriented programs, is to stimulate the activities of other channels that reach audiences, including the general mass and news media. The level and characteristics of these activities are beyond the control of the marketer or advocate. A program can direct its public service announcements (PSAs), but the occurrence of unplanned or unintended news events (such as an announcement by Magic Johnson that he is HIV-positive) is uncontrolled. An unplanned, breaking news event can stimulate attention to AIDS through a national or local talk show or a network news broadcast. Despite the benefit to social programs of unplanned events, measurement of their effects cannot be easily distinguished from the effects of the planned events. In this context, it serves no purpose to separate the effects of a deliberate social marketing PSA from those resulting from operations of the rest of the news media. This is true, in particular, because deliberate stimulation of the news media has, in fact, become a major strategy that many population-oriented interventions now use regularly. Thus, the way that the media cover health issues is often linked to efforts by advocates or public health authorities. Random assignment to condition is unhelpful and often meaningless in the context of a long-term program exploiting serendipitous events and engaging with what is often a national media machine. Definition of effects and causality, however, is hampered by our inability to isolate the size or importance of the inputs.

CDC's America Responds to AIDS (ARTA) campaign depended, in part, on PSAs. Evidence for the reach of that campaign includes estimates of the value of media time made available (\$67 million between 1987 and 1991) and the number of times the average adult between 18 and 54 had the opportunity to view an ARTA PSA during the period (56 times per month).¹⁸ However, it is likely that other elements of CDC's efforts to stimulate attention to HIV/AIDS, including a flood of press releases and video and audio format materials for use by local television and radio stations, were also responsible for a great deal of exposure. Similarly, the announcements by Rock Hudson, Magic Johnson, and Arthur Ashe of their personal HIV status—events not planned by CDC—had significant impact on public attention given to AIDS. Efforts by other agencies, including community organizations, state health departments, and national nonprofit organizations, along with expanded commercial marketing of condoms, operated simultaneously and with similar purposes.

We know that there have been substantial changes in knowledge, attitudes, and behavior among Americans during this period, with resulting health benefits. For example, reported condom use during the last intercourse has increased from 25% to over 50% among young people since the onset of the epidemic, and reported gonorrhea rates have declined from 324/100,000 in 1987 to 247/100,000 by 1991, 150/100,000 in 1995, and 113.5/100,000 in 2004.¹⁹ Similarly, in other countries with major public communication and social marketing programs, the evidence for a shift toward safer behavior is even stronger.

Although these programs have operated inseparably from the broader mass media environment, there are a few cases where the possibility of attributing effects to a more limited social marketing or health communication effort is plausible. Harvey provides evidence about 1991 condom sales in 24 condom social marketing programs in less developed countries, where condoms had relatively little usage before the introduction of these programs and where sales data refer to specific brands of condoms not previously in the marketplace.²⁰ Usage of these products was close to 0 at baseline. The sales vary a great deal across sites, but among those 12 programs where the cost of 100 condoms per year was less than 1% of GNP per capita, sales were between 0.2 and 1.0 condoms per capita. One condom per capita represents sales equivalent to 5% of the population using condoms for contraception but a much larger percentage use them on an irregular basis.²¹ So, if a large proportion of condom use already achieved was focused on men who were having sex outside of marriage, a great deal of protection from HIV transmission could be achieved. This was the pattern in some contexts.^{22,23}

Another type of evidence that allows direct attribution to specific social marketing efforts has to do with promotion of AIDS hotlines. There is evidence, for example, that the use of such hotlines is directly affected by increased promotion. In 1988, the number of calls monthly to the Surgeon General's AIDS hotline tripled (from 70,000 to 210,000) during the period when the Surgeon General's pamphlet, including the hotline phone number, was mailed out.

There are also important data on large-scale effects of social marketing, health communication, and advocacy programs from work done in other health areas. The National High Blood Pressure Education Program (NHBPEP) was a prototype for such efforts. Begun in 1972, it included institutional consensus building, education of health professionals, some public education through community organizations, and major efforts in mass media education. These media efforts included distribution of PSAs for broadcast on radio and television and stimulation of coverage of hypertension by various media outlets. The effects associated with this program were very great. Between 1960 and 1972, before the initiation of the NHBPEP, the age-adjusted stroke mortality rate was declining at 1.6% per year for all U.S. whites and from

1972 to 1984, the rate declined at 5.9% per year.²⁴ There is some controversy about the attribution of all of this decline to improvements in hypertension control associated with the NHBPEP. Nonetheless, the sheer volume of the effect precisely timed to the introduction of the NHBPEP is impressive. The National Cholesterol Education Program appears to have been associated with sharp declines in cholesterol consumption in an analogous fashion, as much because it changed the public agenda concerning cholesterol because of its direct educational programs.

Interventions often need to stimulate demand for services provided by the health system. The 1989–1990 Communication for Child Survival campaign in the Philippines used heavy television and radio advertising along with improvements in the system to encourage early immunization. The number of children with timely, complete coverage increased from 32% to 56% in 1 year. Much of the effect of this program was to reduce delay in coming for vaccination, with a smaller effect in reaching children who otherwise would have remained unvaccinated.²⁵

Thus, in other areas of health, as well as STD-specific work, there is a good ecological evidence for an association between the large outreach operations of social marketing, health communication, and advocacy programs and effects on behavior and even health outcomes. However, while these examples focus on successful programs, we don't want to suggest that all such programs are successful—many programs are unsuccessful. For example, the U.S. government has spent more than \$1 billion to address drug use (particularly marijuana use) among youth in its National Youth Anti-Drug Media Campaign. The carefully executed evaluation shows no evidence for a positive effect of the campaign, and there is some suggestion that the Campaign might have boomeranged, encouraging rather than discouraging marijuana use.

Programs are unsuccessful for a variety of reasons: they have chosen a behavior not susceptible to these sorts of behavior change efforts; the strategy itself was poorly chosen or not maintained for a long enough time; the strategy was poorly implemented. Nonetheless, well-designed, large-scale behavior change programs that integrate social marketing, health communications, and advocacy approaches may have substantial impact under some conditions.

AN APPROACH TO STD CONTROL AND PREVENTION

The first problem that any program of HIV/STD behavior change must face is understanding why some people are engaging in the recommended behavior and some people are not. For example, Fishbein et al. wanted to understand the determinants of condom use in two Caribbean islands prior to the development of a comprehensive intervention.²⁶ There

were many possibilities for the intervention: the program might address the availability of condoms, the perception that AIDS was not a personal risk to the at-risk population, or the perception that there was a widely shared social norm not favoring condom use in risky sexual contact.

The results of a preprogram audience survey were clear: condom access was not a problem for this population, and the perception of the risk of AIDS was shown to be unrelated to whether or not an individual used condoms frequently.

In contrast, three types of reports of normative pressure to use condoms (talking with friends about condom use, reporting that friends used condoms, and reporting that sexual partners had ever requested the respondent to use a condom) were each substantially related to frequency of condom use. The authors recommended that the program focus on increasing the perception of normative pressure to use condoms and not waste resources on personal risk messages, or new condom distribution systems.

This approach to analysis is totally situation specific. Its relevance relates entirely to particular audiences at particular times for particular behaviors. For example, if STD clinics are inaccessible and ordinary clinics are ineffective at diagnosing or treating STDs, public education to increase treatment-seeking alone may be counterproductive. An intervention, in this case, might better target providers whose skills are problematic or legislators who must allocate funds for expanded STD facilities. In another situation, if knowledge about the negative outcomes of a particular disease is low (e.g., infertility associated with untreated chlamydia), yet those who know about the risks are much more likely to obtain treatment, an information campaign to increase knowledge of the risks of untreated STDs makes sense.

The principle is clear. Before the program is designed, the nature and complexity of the behavioral problem must be well understood. This information guides the definition of audience(s) to be reached (legislators, medical providers, individuals engaging in high-risk behaviors) and the social networks that surround those individuals and suggests strategies to best influence their behavior.

Any strategy must also be well executed to be effective. Many programs fail, despite good messages and good definition of target audiences, because they do not achieve the exposure they need in order to affect the thinking and behavior of those audiences. Chang et al. interviewed STD clinic clients in 1988 and found that they were quite knowledgeable about AIDS.²⁷ However, only 30% said they acquired information from the clinics. Similarly, poorly implemented provider training, poorly supplied condom distributors, or poorly positioned advocacy approaches produce poor results.

A particularly striking example of this issue of gaining audience exposure to messages comes from the National

Cancer Institute–sponsored Community Intervention Trial for Smoking Cessation (COMMIT)²⁸. This was a major smoking education intervention that tried to affect the smoking cessation rates among heavy smokers. Twenty-two cities were randomly assigned to receive the intervention or be in a control condition. At completion, there was very little difference between intervention and control cities in smoking cessation rates (both were around 18%). This apparent failure of outcome belied a more fundamental failure: there was little difference between the intervention and control communities in the level of reported exposure to messages on the five major channels used. The intervention communities did not do any *better* than the control communities because they did not do any *more* than the control communities.

DOING IT RIGHT. DOING IT ENOUGH

In Connecticut, a survey of members of the target audience for community AIDS outreach programs noted that more than 30% had heard of the program, but only 6% of those who described themselves at medium or high risk of AIDS had actually made use of the services of those agencies.²⁹ The problem in some communities has been assuring contact with the audience on a continuing basis. This has led some experts to argue that these socially marginalized groups might be reached through mass media-based programs, both to encourage safer sexual and needle-use behavior and to encourage involvement with available outreach programs.³⁰

Evidence exists that some of these populations are commonly exposed to the mass media and do not conform to the stereotypes of street people isolated from common channels of communication. Jason et al. report that among a sample of Baltimore Intravenous Drug Users (IDUs), the median television viewing was 4 hours a day in a home setting.³¹ Ross et al. found that among Australian IDUs, general media habits looked much like those of the general population.³²

Although exposure to AIDS information through the mass media is apparently as common for these groups as for others, there is only tenuous evidence about the effect of organized mass media-based programs on the behavior of these groups. The examples that follow show evidence of effects of general campaigns and general messages on groups frequently targeted in narrowly focused campaigns. We do not discuss the large number of campaigns that address narrowly focused groups alone. Van den Hoek et al. reported on the changes in sexual behavior among a cohort of IDUs in Amsterdam before (1988–1989) and after (1989–1990) a large national AIDS prevention campaign.³³ They found some increases in regular condom use for casual sex and a reduction in the number of female IDUs working as FSWs. Similarly, de Fine Olivarius et al. found substantial declines in gonorrhea (but not other STDs) at an “inner city STD clinic” in Copenhagen, Denmark, comparing women studied before

(1984) and after (1988) a general campaign for safer sex.³⁴ Neaigus et al. found evidence in New York that behavior changes among IDUs enrolled in an outreach program were partly attributable to the outreach intervention and partly attributable to external trends, including, presumably, the general education efforts then prevalent.³⁵ Similarly, Swiss researchers found in a 1989–1990 study that “drug users and ex-drug users used condoms more often than the rest of the population,” with the implication that the several years of campaigning prior to that study had produced that effect.

There are several conclusions that may be drawn from this and other evidence about social marketing, health communication, and advocacy for STDs. Crucial to program success is the need for planners to understand their audience well: what the audience is doing now and how it perceives the new proposed behavior; what the major determinants of current behavior are; promising routes to influencing those behaviors; and what channels of outreach are likely to reach and influence them. Appropriate research approaches for investigating these issues will reflect the resources available and the scale of the program. Informal interviewing may be all a small individual clinic can justify before launching a program for its clientele. Major surveys, multiple focus groups, continuous monitoring of exposure to messages, and effects on knowledge and behavior can easily be justified, however, by national programs with a long-term agenda.

No less central is a clear plan for assuring adequate exposure to messages to affect behavior. There is, unfortunately, little systematic evidence about dose-response to exposure, i.e., how much exposure is required to produce how much behavior change. It is clear that programs that achieve high levels of exposure have shown substantial effects. Programs with little or no exposure have little or no effects. The dose-response curve surely is a reflection of the presence of countervailing influences, the quality of the messages to which an individual is exposed, and the complexity of the behavior change being addressed. Cigarette smoking has yielded only slowly to growing exposure from multiple sources. This slow yield is in the context of an addictive behavior and an extensive promotion of cigarettes. In the area of STD-relevant behavior, it appears that condom use in casual sex has proved susceptible to comprehensive broad-based programs, but behavior favoring abstinence has been slow to change.

It is sometimes suggested that the major work of public awareness in HIV prevention is done and that future shifts in behavior will all reflect work done locally and directed specifically to high-risk individuals and their communities. Thus, the role for large-scale social marketing programs is over. An alternative view is that this shift will have a major cost. If national social marketing efforts end, the support they provide for maintaining and increasing the patterns of safer behavior that have been adopted in the general population will be lost. The COMMIT study suggests not that the target

intervention was weak but that the control intervention was strong. The strength of that control intervention was largely due to a broad national effort. A national effort provides continued attention in the national media. A critical goal is that STD/HIV prevention continues to be supported as an area of political and popular attention and budgetary priority. If the national focus is softened, the funds and political will that underpin local programs also may be lost.

FUTURE APPLICATIONS TO STD/HIV CONTROL AND PREVENTION

STD/HIV control and prevention programs are already using social marketing, communication, and advocacy extensively. Social marketing of condoms, for example, is now a widespread enterprise with significant documented success (as in Portland, the Caribbean, India, and Switzerland, among others).³⁶ Communication approaches, including the management of the news media, have greatly increased the world's understanding of HIV/AIDS. Polls consistently indicate high levels of AIDS knowledge. Advocacy was successful in the United States in protecting funding for HIV prevention during a period of political skepticism about prevention. Other STDs might well benefit from a strategic review of program goals using a broad marketing, communication, and advocacy framework and in addition, the application of specific intervention techniques, such as (1) integrating targeted audience research; (2) developing lifestyle profiles for high-risk populations; (3) long-range planning and integrating services, messages, and policies targeted to a narrow, high-priority problem; (4) maintaining program intensity levels that could incorporate all tactics into existing and new programs; and (5) increasing attention to policy change and advocacy approaches.

Finally, there is the question of message fatigue and behavioral recidivism. Even in areas where HIV/AIDS prevention messages have been widely diffused and behavioral change documented, such as San Francisco, there is evidence that new populations of young gay men are not practicing safe sex. From a communication perspective, this is a well-documented characteristic of human behavior and certainly to be expected. Even with simple behaviors, such as using a seat belt, studies have documented that without regular reminders and new tactics to maintain behavior, behavioral compliance degrades sharply. With addictive behaviors, like smoking and drug use, recidivism has also been widely documented. Similarly, relapse to riskier sexual behaviors or behavioral disinhibition has been observed, particularly with the advent of new interventions such as antiretroviral therapy that may alter risk perceptions. It will be a challenge to refresh public attention, develop new tactics, messages, and services to address the needs of new populations who were not convinced by the original arguments or not exposed to these campaigns.

A NEW RESEARCH PARADIGM

Social marketing, communication, and advocacy research continue to be dominated by a "vaccine" paradigm that attempts to establish the "efficacy" of various communication interventions so that those interventions can be discarded, improved, or replicated in other communities. Studies continue to compare different interventions (peer education vs. mass media approaches) as though these were competing "behavioral vaccines" or they attempt to establish the efficacy of a particular intervention in a real-world setting (community trials of smoking cessation interventions) as though those interventions would be widely applicable to diverse audiences in different cultural and political setting. This vaccine approach to behavioral intervention research has led to disappointing results. Behavioral interventions are not like biological vaccines. The variability of hosts (social groups vs. human anatomy) over time is much greater in social institutions than biological entities. The replicability of intervention effectiveness is much less robust in social communities than in biological laboratories. New forms of research are needed that respect the characteristics of effective behavioral interventions, such as: (1) the importance of multiple interacting forces; (2) the need for responsive changes in interventions to meet unpredictable changes in the social and political environment; and (3) the importance of both intensity and long-term durability of interventions to produce measurable effect. Behavioral intervention research might better turn to marketing research models or the practice of clinical medicine, where a set of best practices are applied by highly trained and experienced practitioners and adapted by them to meet the needs of different patients or clients. Research, in this case, is formative as well as evaluative. It helps shape programs as well as document their apparent success or failure.

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Innovations in Public Health Surveillance for HIV/AIDS and Other STDs: Guideposts for Prevention and Care

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Public health surveillance is the ongoing and systematic collection, analysis, and interpretation of outcome-specific data for use in the planning, implementation, and evaluation of public health practice.¹ Surveillance data are collected in order to describe the needs for prevention, treatment, and care programs; to characterize populations at greatest risk of infection and in greatest need of services; and to describe the impact of prevention and treatment programs. Dissemination of data from surveillance systems is a critical aspect of public health surveillance,² and surveillance data are used by health departments, local planning bodies, managers of treatment and prevention programs in communities, and politicians at all levels of government for decision making and resource prioritization (Fig. 97-1).

There are many kinds of surveillance systems that collect data to characterize the HIV/AIDS epidemic and the epidemics of other STDs. These systems include *case surveillance systems* (or disease registries) and *supplemental surveillance systems*. Case surveillance systems are primarily concerned with the enumeration of unique cases of reportable diseases and the description of the characteristics of those cases. Typically, HIV/AIDS and other STD case surveillance systems collect information about demographic and geographic characteristics of cases, as well as limited information about risk behaviors that may represent

routes of acquisition. Case surveillance systems also collect information to identify the cases, so that summary data are available on unique (unduplicated) persons diagnosed with disease. Case surveillance relies primarily on the collection of existing information for medical records or laboratory reports.

Supplemental surveillance systems differ from case surveillance systems in several important ways. First, supplemental surveillance systems may not endeavor to collect information on all diagnosed cases of disease but may, instead, collect data from a subset of those with disease. Second, supplemental surveillance systems may collect more in-depth information than case surveillance systems. Third, supplemental surveillance systems may collect data beyond what exists in medical records—for example, data collected from interviews with patients or data from supplemental laboratory tests on biologic specimens from patients. Finally, supplemental systems that estimate the prevalence of disease may collect more information about the populations in which disease is identified.

The legal authority for surveillance resides in state laws and public health regulations that authorize states to collect data for the purposes of disease control.³ In the case of case reporting for HIV/AIDS, most states have specific laws or regulations requiring disease reporting. In the case of case reporting of other STDs, legal mandates for case reporting may be embodied in more general statutory language about reportable diseases. For supplemental surveillance systems, the extent to which legal authority to collect data is conferred by statute or regulation varies by state.

Although the legal authority for surveillance resides in states, and state health department staff collect case surveillance data, other institutions play important roles in the supporting and coordinating surveillance activities. In order to assure the collection of surveillance data in a consistent and comparable way across states, the United States Public Health Service and states work together to establish surveillance case definitions that comprise the national

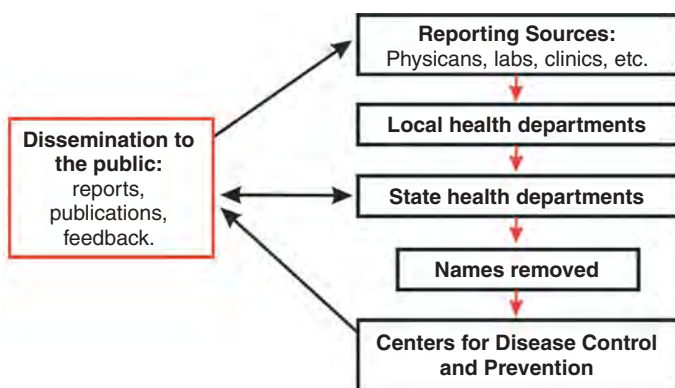


FIGURE 97-1. HIV/STD surveillance system flow of information.

standards for surveillance systems. The Council of State and Territorial Epidemiologists and the Association of State and Territorial Health Officers serve critical roles in providing consultation and recommendations for which diseases should be nationally notifiable, and for changes to surveillance case definitions for those diseases.³ This consultative process also seeks a broad range of input from professional, community, and policy-oriented organizations. The Centers for Disease Control and Prevention (CDC) publishes case definitions for reportable diseases, makes recommendations to states on best methods for implementing surveillance programs, and provides financial support and technical assistance to state health departments to conduct surveillance activities.

The data collected by state and local health departments are reported to CDC on a voluntary basis, with the caveat that all information that could identify a particular person is removed from the data before transmission to CDC.⁴ Surveillance data shared with the federal government are

protected from release by a federal Assurance of Confidentiality; surveillance data retained in states, where names and other identifying information are held, are protected by state laws. In most states, release of confidential surveillance information is punishable by criminal penalties.⁵

HIV/AIDS SURVEILLANCE

■ CASE DEFINITION—UNITED STATES

The case definition for AIDS has changed six times since the original case definition was established in 1982; the major revisions of the case definition are summarized in [Table 97-1](#). The evolution of the case definition has followed increased understanding about the natural history, pathogenesis, and treatment of HIV infection. For example, the morbidity associated with infection with HIV was first recognized in 1981, when clusters of relatively young, homosexual men who did not have predisposing

Table 97-1. Major Revisions of the Case Definition for Surveillance of HIV and AIDS in the United States

Year (Reference)	Main Features and Changes
	<i>Adults and adolescents ≥13 yr of age</i>
1981 ⁶	Informal case definition in response to reports of Kaposi's sarcoma (KS) and <i>P. carinii</i> pneumonia (PCP) in young, homosexual men.
1982 ⁷	No known cause for diminished cell-mediated immunity with the onset of serious opportunistic infections (OIs) including but not limited to PCP, KS.
1985 ¹⁴³	Positive serologic or virologic test for the human T-cell lymphotropic virus type III/lymphadenopathy associated virus (HTLV-III/LAV) with expanded list of OIs. Persons with positive HTLV-III results and no opportunistic infections were included.
1986 ¹⁴⁴	Classification system for severity of immunosuppression among persons with HTLV-III infection based on CD4 count and OIs.
1987 ¹⁴⁵	Expansion of the list AIDS indicator OIs to include human immunodeficiency virus (HIV) encephalopathy and wasting syndrome as well as acceptability of presumptive OI diagnoses in the presence of HIV infection.
1993 ⁶²	AIDS definition expanded to include immunologic criteria (CD4 cell count <200 cells/ μ L) and additional OIs including cervical cancer, recurrent bacterial pneumonia, and pulmonary tuberculosis.
1999 ¹⁶	Guidelines for integrating HIV and AIDS case surveillance including an updated HIV case definition that included newer virologic detection tests (e.g., HIV nucleic acid, p-24 antigen, and viral culture).
2005 ⁹	AIDS case definition limited to persons with documented laboratory evidence of HIV infection regardless of the OIs identified or other immunologic markers.
	<i>Children <13 yr of age</i>
1985 ¹⁴³	Updated case definition included specific conditions for children.
1987 ¹⁴⁴	Classification system for severity of immunosuppression for children.
1994 ¹⁴⁶	Updated case definition included improved testing technology and information about progression of HIV among children.
1999	Updated case definition to include virologic detection tests to identify perinatally exposed infants as <i>not infected with HIV</i> .

Adapted from Nakashima AK, Fleming PL. HIV/AIDS surveillance in the United States, 1981–2001. *J Acquir Immune Defic Syndr* 2003; 32(Suppl 1): S68–S85.

immunosuppressive diseases developed *Pneumocystis carinii* pneumonia (PCP; now known as *Pneumocystis jirovecii*) and/or Kaposi's sarcoma (KS).⁶ Four years later, all state and territorial health departments in the United States had instituted surveillance for the clinical conditions (such as PCP and KS) associated with immune dysfunction that became known as the acquired immunodeficiency syndrome (AIDS) using a standardized case definition.⁷ In 1993, the case definition was expanded to include CD4 lymphocytopenia, with CD4 counts less than 200 cells/ μL , as an AIDS-defining condition. This expansion was based on the recognition that severe immunosuppression at this level required medical intervention for prevention of opportunistic infections, and, therefore, this morbidity should be documented for resource planning purposes. Notably, many other industrialized countries did not adopt this aspect of the 1993 case definition.⁸

Most recently, the case definition was modified in 2005 to require that all AIDS case reports contain documentation of a laboratory diagnosis of HIV infection.⁹ Before this most recent change, AIDS was reportable even when diagnostic tests for HIV were negative. This was because surveillance of the HIV epidemic began before the identification of the etiologic agent of AIDS and because of the incremental nature of changes in the AIDS case definition. The current case definition for HIV and AIDS is shown in [Table 97-2](#) but will continue to evolve, in order to accommodate the ongoing advances in diagnostic and therapeutic technologies.

■ CASE SURVEILLANCE: METHODS, ISSUES, MAJOR FINDINGS—UNITED STATES

Methods of case surveillance

Surveillance for AIDS and HIV employs a combination of passive and active case ascertainment methods. In passive methods, local and state health departments receive reports from multiple sources, including physicians and other health-care providers, hospitals, clinics, and laboratories. In active surveillance methods, health department staff supplement information from passive reports through follow-up by reviewing medical records and, on occasion, interviewing patients and providers. Active case surveillance also includes health-department-initiated review of administrative, clinical, and laboratory records in facilities that care for large numbers of persons with HIV infection. Formal evaluations have consistently found that AIDS case reporting is one of the most complete and accurate population-based registration systems for diseases or health conditions in the United States.¹⁰

AIDS case reporting was historically the standard method for surveillance of the HIV epidemic and was used until the mid-1990s, as a distant proxy for trends in HIV transmission.

All U.S. states have collected data on AIDS cases using consistent methods since 1985.¹¹ AIDS data were used to model trends in the incidence of HIV infection,¹² underpinned by the fact that there was a relatively consistent 8–10-year interval from time of HIV infection to onset of AIDS. The assumption of the constancy of the time lag from HIV infection to onset of AIDS produced two serious limitations to the use of AIDS case reports to describe HIV incidence. First, analysis of contemporary data reflected trends in transmission a decade earlier. This limited the usefulness of the data for planning prevention activities. Second, the duration of the lag time was increased by effective therapies, as they became available.

The introduction of effective antiretroviral therapy in 1996 resulted in welcome delays in disease progression¹³ but changed the meaning of a new AIDS diagnosis. Whereas before 1996 a new AIDS diagnosis represented a new HIV infection a decade earlier, after 1996 a new AIDS diagnosis became more indicative of failures in treatment, poor access to health services, and delays in diagnostic testing. Therefore, AIDS surveillance data alone no longer provide adequate information about trends in the transmission of HIV.

In order to describe more recent trends in the epidemic in the setting of effective therapy, reporting of cases of asymptomatic HIV infection is required. Several states implemented mandatory reporting of HIV infection shortly after the licensure of the first diagnostic test in 1985. However, not all states implemented HIV case reporting systems, because of concerns in some communities about the stigma and discrimination associated with HIV infection, and concern that HIV reporting registries would be used for political retribution, criminal prosecution, or discrimination in employment, housing, and insurance. Some also speculated that mandatory reporting of HIV diagnoses would deter high-risk persons from seeking diagnostic testing.¹⁴ Over the past two decades, significant advances in legal protections against discrimination have been made,⁵ and studies have demonstrated little correlation between disease reporting policies and the extent of HIV testing among high-risk persons.^{10,11,15}

In 1999, CDC recommended that all states implement reporting of HIV infections as part of an integrated HIV/AIDS surveillance system.¹⁶ By 2004, every state and the District of Columbia mandated reporting for persons diagnosed with HIV, even if AIDS has not developed—but with inconsistent methods. The method recommended by CDC—the use of patient name as the identifier in the surveillance system¹⁶—was not implemented in all areas. Some states implemented HIV reporting systems based on codes derived from patient characteristics such as birthdate, race, and partial identifiers such as the last four digits of the social security number, rather than names.¹⁰ Systematic, population-based evaluations of coded identifiers have not established that systems using non-name methods can maintain data equivalent

Table 97-2. Current Integrated HIV and AIDS Case Definition among Persons \geq 13 Years

Condition	Criteria
HIV infection	<p>I. Laboratory criteria:</p> <p>Positive result on a screening test for HIV antibody (e.g., repeatedly reactive enzyme immunoassay) followed by a positive result on a confirmatory (sensitive and more specific) test for HIV antibody (e.g., a reactive Western blot or immunofluorescence antibody test)</p> <p style="text-align: center;">Or</p> <p>Positive result of a detectable quantity on any of the following HIV virologic (nonantibody) tests:</p> <ol style="list-style-type: none"> HIV nucleic acid (DNA or RNA) detection (e.g., DNA polymerase chain reaction [PCR] or plasma HIV-1 RNA) HIV p24 antigen test, including neutralization assay HIV isolation (viral culture) <p style="text-align: center;">Or</p> <p>II. Physician diagnosis:</p> <p>Diagnosis of HIV infection, based on the laboratory criteria above, that is documented in a medical record by a physician.</p>
AIDS	<p>I. Documentation of an HIV infection</p> <p>And one of the following:</p> <p>II. Depressed CD4⁺ T Lymphocytes defined as either of the following:</p> <ol style="list-style-type: none"> CD4⁺ T-lymphocytes count of less than 200 cells/μL CD4⁺ T-lymphocyte percentage of total lymphocytes of less than 14% <p style="text-align: center;">Or</p> <p>III. Diagnosis of any of the following AIDS indicator conditions:</p> <ul style="list-style-type: none"> Candidiasis of bronchi, trachea, or lungs Candidiasis, esophageal^a Cervical cancer, invasive Coccidioidomycosis, disseminated or extrapulmonary Cryptococcosis, extrapulmonary Cryptosporidiosis, chronic intestinal (greater than 1 month's duration) Cytomegalovirus disease (other than liver, spleen, or nodes) Cytomegalovirus retinitis (with loss of vision)^a Encephalopathy, HIV related Herpes simplex: chronic ulcer(s) (greater than 1 month's duration) or bronchitis, pneumonitis, or esophagitis Histoplasmosis, disseminated or extrapulmonary Isosporiasis, chronic intestinal (greater than 1 month's duration) Kaposi's sarcoma^a Lymphoma, Burkitt's (or equivalent term) Lymphoma, immunoblastic (or equivalent term) Lymphoma, primary, of brain <i>Mycobacterium avium</i> complex or <i>M. kansasii</i>, disseminated or extrapulmonary^a <i>Mycobacterium tuberculosis</i>, any site (pulmonary^a or extrapulmonary^a) <i>Mycobacterium</i>, other species or unidentified species, disseminated or extrapulmonary^a <i>P. carinii</i> pneumonia^a Pneumonia, recurrent^a

Table 97-2. (Continued)

Condition	Criteria
	Progressive multifocal leukoencephalopathy
	<i>Salmonella</i> septicemia, recurrent
	Toxoplasmosis of brain ^a
	Wasting syndrome due to HIV

^aCondition may be diagnosed presumptively. Guidance on diagnosis of these diseases in the context of all nationally notifiable diseases is available at http://www.cdc.gov/epo/dphsi/casedef/case_definitions.htm.

in accuracy and completeness, when compared to reporting systems that include names.^{10,17} Because identification and elimination of duplicate reports across jurisdictions cannot occur without a standardized means of identifying unique cases, CDC has only accepted surveillance data from areas that include names with the reports at the local level.

One important coordination function of CDC in the national HIV surveillance system is to provide a framework for deduplication of case reports from different states. This is accomplished using the recorded date of birth, sex, and soundex (an algorithm-generated code computed locally from the last name that is not unique for each name). CDC routinely produces a list of HIV cases for each state, for which the values from these three variables match with those from records in other reporting jurisdictions. Surveillance personnel across jurisdictions then communicate to identify situations where multiple reports have occurred on a single case.

Trends

HIV and AIDS case surveillance data remain the most comprehensive source of information about the epidemic in the United States and elucidate several fundamental trends.

Through December 2005, an estimated 984,155 persons had been diagnosed with AIDS in the United States and 550,394 of them had died.¹⁸ Throughout the latter part of the 1980s and into the mid-1990s there was a rapid increase in the annual number of AIDS cases and deaths among persons with AIDS (Fig. 97-2). After 1995, the incidence of AIDS and deaths among persons with AIDS substantially decreased until 1998. Subsequently, AIDS has been diagnosed annually in approximately 40,000 persons, and 15,000–18,000 persons with AIDS have died each year through 2005.

The decreases in new AIDS diagnoses and deaths after 1995 are attributed to introduction of effective antiretroviral therapies in 1996, with concomitant slowing of the progression of HIV to AIDS and prevention of deaths among the infected.¹⁹ The improvements in survival resulted in a continued increase in prevalence, with over 433,000 persons living with AIDS by the end of 2005.

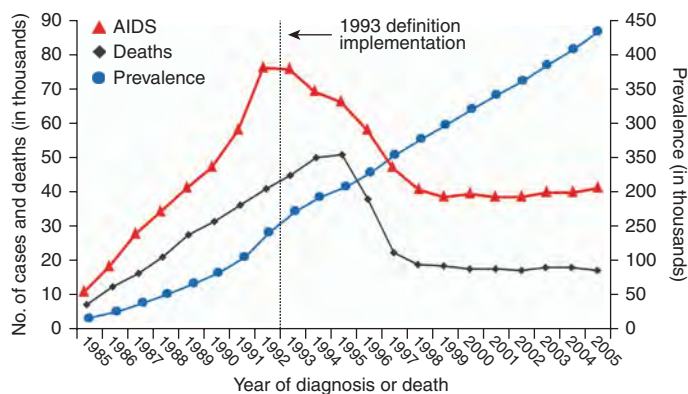


FIGURE 97-2. Estimated AIDS cases and deaths, and persons living with AIDS, 1985–2005, United States.



FIGURE 97-3. Estimated numbers of perinatally acquired AIDS cases, by year of diagnosis, in the United States (including U.S. territories), 1985–2005. Data are adjusted for reporting delays and cases in persons reported without an identified risk factor.

One of the most effective interventions to prevent HIV transmission has been the use of antiretrovirals in pregnant, HIV-infected women during pregnancy and after delivery in their infants.²⁰ AIDS surveillance data have demonstrated the enormous effectiveness of these regimens since they were put into widespread use in 1994 (Fig. 97-3).²¹ The number of

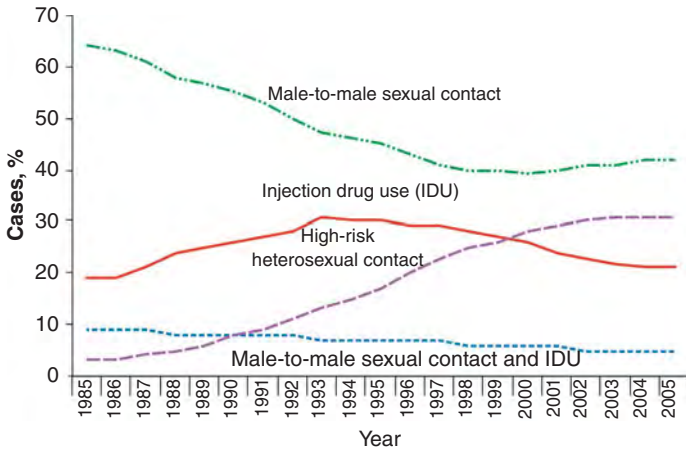


FIGURE 97-4. Proportion of AIDS cases among adults and adolescents, by transmission category and year of diagnosis, 1985–2005, United States.

AIDS cases attributed to perinatal transmission peaked in 1992 at 952 and, subsequently, decreased to only 67 during 2005.¹⁸

Case surveillance data reflect changes in the relative importance of different modes of transmission; these changes suggest that priorities for prevention activities need constant reevaluation. Most AIDS cases in the United States are attributed to male–male sexual contact (Fig. 97-4). However, there has been a steady transition to cases that are attributed to heterosexual transmission, with decreases in the relative burden from injection drug use. Most of the heterosexually attributed cases occur in women.¹⁸

Trends in newly diagnosed HIV infections, with or without AIDS, provide a window into an earlier stage of the disease process and may more closely approximate the true incidence of transmission of HIV.²² Information from 2001 through 2005 in 32 states that had long-standing HIV reporting demonstrate that the rates of HIV diagnoses have been relatively stable among women and men of all racial and ethnic groups (Fig. 97-5).²³ However, there were enormous

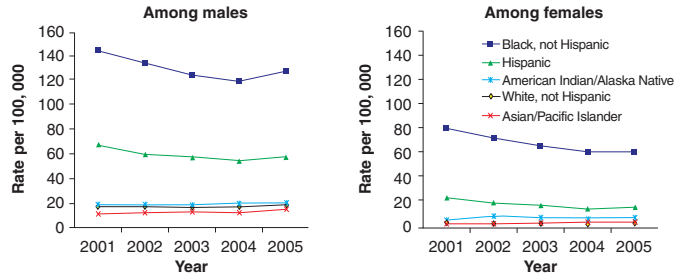


FIGURE 97-5. Annual age-adjusted rate of diagnosis of HIV/AIDS by sex and race/ethnicity—32 states, 2001–2005. HIV/AIDS designates HIV infection regardless of the presence of AIDS. The rates were directly adjusted using the 2000 U.S. population as the standard. States included in the analysis were Alabama, Alaska, Arizona, Arkansas, Colorado, Florida, Idaho, Indiana, Iowa, Kansas, Louisiana, Michigan, Mississippi, Missouri, Nebraska, Nevada, New Jersey, New Mexico, North Carolina, North Dakota, Ohio, Oklahoma, South Carolina, South Dakota, Tennessee, Texas, Utah, Virginia, West Virginia, Wisconsin, and Wyoming.

racial/ethnic disparities in the rates of disease for both men and women, with rates among non-Hispanic black males and females being seven and 19 times higher, respectively, than those for white males and females.²³

There are also large differences in the prevalence of persons living with HIV and AIDS by region of the country (Fig. 97-6). In general, rates among adults and adolescents tend to be lower in the northern Midwestern states such as North Dakota (diagnosed prevalence rates of HIV and AIDS in 2005 were 13.8 and 12.6 living cases per 100,000 persons, respectively), where relatively fewer racial/ethnic minorities reside. High rates are seen in the South, where the highest AIDS prevalence rates in 2003 were in Florida (298.8 per 100,000 persons), California (201.3 per 100,000 persons), and New York (461.3 per 100,000), where such populations are more prevalent and where there are substantial communities of men who have sex with men (MSM).^{11,24,25} Although geographically specific information is important for making decisions about targeting resources to address the health-care needs of persons



FIGURE 97-6. Estimated rates for adults and adolescents living with HIV infection (not AIDS) or with AIDS (per 100,000 population), 2005—United States.

diagnosed with HIV, this information is not considered optimal for tracking the true incidence of HIV infection, because changes in patterns of testing may affect trends in HIV diagnoses.¹⁰

■ SUPPLEMENTAL SURVEILLANCE SYSTEMS FOR HIV/AIDS—UNITED STATES

Behavioral Surveillance

Behavioral surveillance data complement the data available from HIV case surveillance, provide a context in which to interpret case surveillance data, and provide additional information to evaluate the impact of HIV prevention programs. Behavioral surveillance is an ongoing, systematic way of measuring behaviors that are related to sentinel events in life of a person who becomes infected with HIV.²⁶ For example, behavioral surveillance systems measure behaviors related to HIV acquisition (risk behaviors and condom use behaviors), diagnosis of HIV infection (HIV testing behaviors and barriers to HIV testing), and progression of HIV disease (care seeking, access to care, and adherence to prescribed therapy). Behavioral surveillance data are needed from the general population, from at-risk populations such as MSM and IDUs, and from persons living with HIV infection (Table 97-3).

In the United States, behavioral surveillance among persons at risk of HIV infection is realized in the National HIV Behavioral Surveillance System (NHBS). NHBS has been conducted in 25 cities by state and local health departments, in collaboration with CDC, since 2003.²⁷ The 25 cities represent those cities with the highest AIDS prevalence in the United States as of 2003 and represent approximately 70% of the United States' burden of AIDS. NHBS collects data in waves, with a 3-year project cycle in which data are collected 1 year among MSM, 1 year among IDUs, and 1 year among high-risk heterosexuals (HRH). The recruitment methods used in the surveillance system vary; MSM are recruited using a time-space sampling approach,^{28,29} and IDU

are recruited using respondent-driven sampling.^{30,31} Methods for recruitment of HRH are under development, for implementation in 2007. The system collects data from persons at high risk for HIV infection, who are asked to consent to an anonymous interview. The interview includes questions about risk behaviors for HIV acquisition, HIV testing history and knowledge of serostatus, and use of local HIV prevention services.

Behavioral surveillance data are important to many aspects of public health prevention programs and surveillance. For diseases such as HIV, with a long latent period between infection and clinical manifestations, behavioral surveillance provides endpoints that are more proximate to HIV infection and that allow evaluation of progress toward primary prevention goals.³² For example, a campaign to reduce infections among IDUs may be judged a success if, 5 years after its implementation, rates of new diagnoses of HIV infection among IDUs decrease. However, the ability to measure the rate of needle sharing in the months following the implementation of the campaign provides a more proximate, if intermediate, outcome for evaluation. Also, behavioral surveillance data on HIV testing provide a context in which to interpret case surveillance data: since cases are only reported to the surveillance system after they are diagnosed, surveillance case reports can be influenced by changes in patterns of HIV testing.³³ In the past, these types of data have been provided by nonsurveillance approaches, such as episodic HIV testing surveys,^{34–36} and by evaluation of programmatic data from publicly funded counseling and testing programs;³⁷ in the future NHBS will be the primary ongoing source of such surveillance data.²⁷

Resistance surveillance

Surveillance for resistance to antiretroviral drugs is a critical supplemental surveillance activity that provides data for the formulation of treatment recommendations and provides an evidence base for empiric choice of therapy for HIV

Table 97-3. Sentinel Events, Behaviors, and Populations for HIV Behavioral Surveillance

Sentinel Event	Sentinel Behaviors	Sentinel Populations
Exposure	Risk behaviors Acquisition Transmission	At risk, general, and infected Infected
Diagnosis of HIV infection	Testing behaviors	At risk, general, infected
Morbidity (AIDS)	Care seeking; adherence	Infected
Death	Care seeking; adherence	Infected

Behaviors related to sentinel events are targets for behavioral surveillance data collection.

infection.³⁸ Resistance to antiretroviral drugs is a concern in the management of HIV infection, because, in treated patients, the emergence of resistant quasispecies is almost inevitable unless pharmacologic therapy is successful in totally suppressing replication, and the patient is flawlessly adherent to therapy.³⁹ The high levels of resistance observed in treated individuals have raised concerns about trends in the transmission of resistant strains.⁴⁰ A high rate of such transmission could compromise the success of standardized, initial regimens; increase the cost and complexity of providing care to newly diagnosed patients;³⁸ and compromise the efficacy of available medications to prevent transmission through postexposure prophylaxis⁴¹ or perinatal exposure.

There is a need for surveillance for resistance to antiretroviral drugs in the United States, because surveys in convenience samples of patients have serious biases, which limit the generalizability of their findings. Most investigations that have attempted to assess trends over time have involved relatively small numbers of patients from highly selected clinical settings, where there is limited variability in the modes of transmission.^{42–44} One of the largest assessments of the drug resistance mutations in newly diagnosed, treatment-naïve patients was conducted in 10 U.S. cities during the period 1997–2001 and involved testing of 1082 patients.⁴⁵ The overall prevalence of resistance to antiretroviral agents was 8.3% but varied substantially by the presumed route of transmission for the infected person. MSM had the highest prevalence at 12%, 8.2% of IDUs had resistant strains, and heterosexual transmission was associated with a 5.1% prevalence.

Transmission of drug-resistant virus appears to be occurring with sufficient frequency to warrant surveillance as a regular public health activity. Therefore, many public health programs have begun to obtain resistance information as part of the surveillance for transmission incidence.⁴⁶ These systems involve acquisition of an aliquot of the diagnostic phlebotomy specimen used to execute the confirmatory Western Blot and forwarding to a public health laboratory. In this laboratory, the specific virus from this specimen is isolated, amplified, and sequenced to identify mutations associated with resistance to antiretroviral medications. Most of these programs are in the initial stages of development and will take several years to produce sufficient data to guide public health prevention and treatment practices.⁴⁶

Seroprevalence surveys

Seroprevalence surveys that are ongoing and systematic may serve as a supplemental surveillance system. Unlinked anonymous serosurveys, in which remaindered blood specimens collected for other purposes are tested anonymously, have a key advantage in that in certain populations they provide estimates of seroprevalence that are not biased by the decision of individuals to seek testing. They are most often applied in settings of

special interest to HIV prevention programs, such as in STD clinics, drug treatment centers, adolescent clinics, and obstetrical delivery services.

In the United States, unlinked seroprevalence surveys, supported by the federal government and coordinated by CDC, were conducted from the late 1980s until 1997.^{47–50} The surveys of childbearing women were discontinued in 1995, and all other federally funded surveys ended 2 years later.⁵¹ Results from the U.S. surveys suggested that the prevalence of HIV infection during the early 1990s remained stable, with the aggregate rate across all survey areas for childbearing women remaining between 0.1% and 0.2%, for the period 1989–1994. By 1995, when these surveys were discontinued, the highest prevalence was observed in New York (0.46%), and some states had no detected infections in pregnant women. Higher prevalence rates were measured among patients attending 29 STD clinics in 16 cities during 1997, where the median value among all participating clinics was 3.9%, with a range of 0.5–11.4%. Prevalence was highest among MSM (19.3%).⁵¹

Systematic and ongoing collection of HIV seroprevalence data also occurs among applicants for Job Corps and for military service and among blood donors.⁵¹ However, the usefulness of this information for epidemiologic purposes is limited. Persons with behavioral risk factors for HIV are explicitly discouraged from donating blood, or entering the military, and eligibility for the Job Corps program varies among areas. The interpretation of trends in prevalence data has been further complicated by the introduction of effective therapies, which inevitably results in increases in the number of persons infected, regardless of the underlying transmission rates.

The only national data on HIV testing of a probability sample of the U.S. population is from the National Health and Nutrition Examination Survey (NHANES).⁵² During 1999–2002, this survey found a prevalence of 0.43% (95% confidence interval, 0.25–0.72%) among persons 18–49 years of age. This was an increase from the prevalence of 0.33% (95% confidence interval, 0.22–0.52%) found when this survey was conducted during the early 1990s.⁵² However, this difference was not statistically significant, due to the imprecision associated with the relatively small numbers of infected persons identified in both waves.

Incidence surveillance

Surveillance for incident HIV infections, as opposed to surveillance for newly diagnosed cases of HIV infection, is critical for targeting prevention programs and evaluating their impact. One method for estimating HIV incidence is to identify relatively recently infected persons among those who are being tested. The most widely used approach is known as the serologic testing algorithm for recent HIV seroconversion (STARHS).⁵³ The approach relies on the understanding that

in the first 6–12 months after HIV infection, the host antibody response to HIV changes, both quantitatively and qualitatively. A variety of assays has been developed, which measure these labile aspects of antibodies to HIV infection. The results of these assays allow identification of persons with immune response profiles indicative of recent infections (i.e., within 6 months).⁵⁴

These serologic methods for identifying recently infected persons were initially implemented on specimens collected in a variety of clinical settings, where large numbers of persons were tested during the 1990s and were conducted on anonymized specimens. These investigations generally indicated that incidence rates were highest in MSM and were stable throughout the decade.^{55–57} However, because most of these incidence studies were not population based and because the studies were susceptible to selection biases that resulted from changing patterns in the populations seeking care and testing at the participating facilities, the findings of these studies were not generalizable.⁵⁸ In order to establish a national system of incidence surveillance, CDC has supported efforts in the areas with the highest HIV morbidity to apply STARHS to the serum specimens from persons identified as new diagnoses through population-based HIV surveillance.⁵⁹

Clinical outcomes surveillance

Clinical outcomes surveillance is concerned with documenting outcomes of HIV infection, which are not consistently captured as part of case surveillance. For example, AIDS case surveillance systems document the diagnosis of an AIDS-defining opportunistic illness (AIDS-OI) when it is the first indication of AIDS; however, subsequent AIDS-OI diagnoses are not routinely ascertained. Clinical outcomes surveillance systems may also provide data useful in evaluating quality of care for HIV infection, by documenting adherence to care and treatment guidelines.⁶⁰ Thus, clinical outcomes surveillance provides important insight to secondary prevention practices and outcomes.

In the late 1980s, CDC, in collaboration with 10 state and local health departments, developed a supplemental surveillance system to help define the spectrum of HIV disease in the United States.⁶¹ This project, the Adult/Adolescent Spectrum of HIV Disease Project (ASD), collected detailed information from the medical records of persons receiving care for HIV infection in clinic and hospital settings from 1991 to 2004. This system was designed as a longitudinal medical records abstraction project, and observed over 60,000 persons in care for HIV infection over this period. The data were used to inform the revision of the AIDS case definition in 1993,⁶² as well as to inform the development of guidelines for clinical care of HIV. After the expansion of the AIDS case definition in 1993, the case surveillance system had very limited capacity to

measure the incidence of opportunistic illnesses, since most AIDS cases were diagnosed based solely on immunologic criteria, with limited capacity to document subsequent opportunistic illness diagnoses. ASD served as a primary mechanism to measure opportunistic illness incidence (an important indicator of the success of secondary prevention) in the United States (Fig. 97-7).^{63,64}

The primary limitations of ASD were the lack of representativeness of the data and the fact that only 10 U.S. states were supported to collect these data. To address these limitations, CDC and 20 state health departments have recently undertaken the development of a new system for clinical outcomes surveillance.^{65,66} This new system, the Medical Monitoring Project, is a surveillance system that will use probability sampling methods to obtain a nationally representative sample of persons in care for HIV infection, in the United States. Each year, 6000–8000 HIV-infected persons will be selected using multistage cluster sampling;⁶⁷ for each person selected, medical records will be abstracted, and consent to interview will be sought. Data from medical records will focus on treatments for HIV, laboratory values, and HIV-related diagnoses. Interviews will represent behavioral surveillance for persons living with HIV infection and will collect data on risk behaviors for HIV transmission, as well as behaviors (such as care seeking and adherence to antiretroviral therapies) that have impact on the prevention of morbidity and mortality (e.g., secondary prevention). Data from the first national sample will be available in 2008.

The key advantage of the MMP system is that it will produce surveillance data that are representative of the underlying population, without requiring collection of data on all patients. The underlying methodology has been demonstrated in the Health Care and Services Utilization Study (HCSUS),^{68–70} which was a one-time study of persons receiving care for HIV infection.

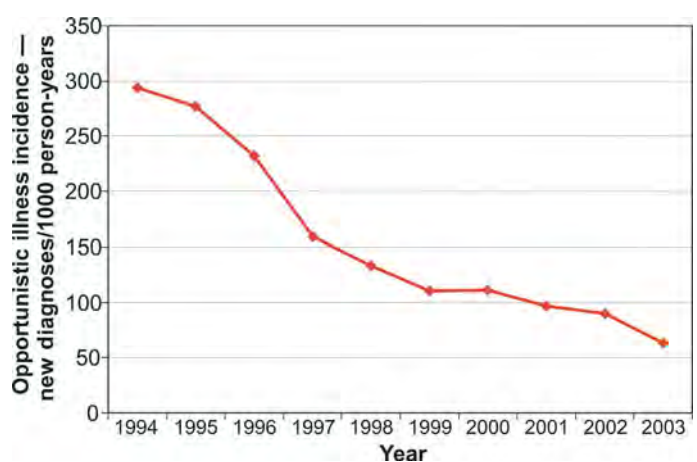


FIGURE 97-7. Opportunistic illness diagnoses per 1000 person years among persons living with HIV infection, 1994–2003, 10 U.S. cities.

HIV/AIDS SURVEILLANCE—INTERNATIONAL SETTINGS

Developed countries

The World Health Organization (WHO) recommends that AIDS case surveillance be conducted in all countries.⁷¹ AIDS case surveillance has been ongoing in most developed countries, including those of Western Europe, Canada, Australia, and Japan, since the mid-1980s. However, the availability of effective therapy for persons with HIV infection in these countries has resulted in substantial decreases in the number of AIDS cases and HIV-related deaths.⁷² To better monitor the underlying trends in HIV transmission, case surveillance of persons diagnosed with HIV infection, regardless of the level of immunosuppression, has been implemented in many developed countries.^{72–74} These HIV reporting systems are of variable quality and have been in place for variable lengths of time. Many use coded patient identifiers similar to those used by some jurisdictions in the United States. The inability to reliably deduplicate HIV infection case reports in countries where code-based systems are used leads to increased uncertainty in interpretation of data, especially in comparisons involving small differences in trends within and among these countries. Despite these challenges, these systems are based on standardized case definitions are supervised by experienced public health scientists, and the data collected represent the most comprehensive, population-based information available regarding the status of the HIV epidemic in these countries. The major epidemiologic characteristics of HIV in selected developed regions of the world are discussed below.

Western Europe. Trends in AIDS cases in Western Europe have been consistent with those observed in the United States, but with generally lower rates of disease in most countries (Fig. 97-8).⁷³ For example, in 2002, the AIDS incidence rate in Western Europe was 2.4 cases per 100,000 persons, whereas in the United States it was 14.7.^{24,73} However, there is

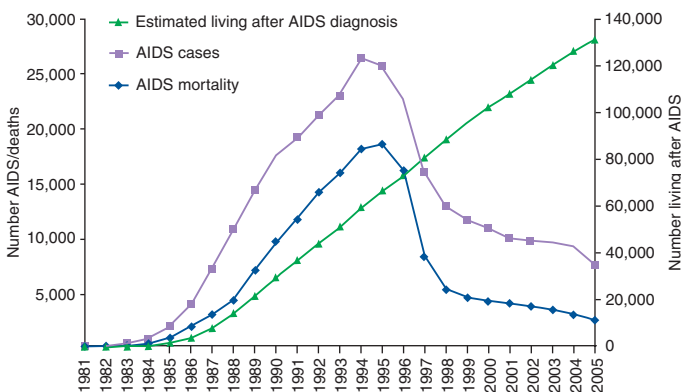


FIGURE 97-8. Number of AIDS cases, AIDS deaths among AIDS cases, and persons living with AIDS by year, 1986–2002, western Europe. Countries included are Denmark, Germany, France, Italy, Portugal, Spain, UK, and Netherlands.

substantial variation in rates among European nations, with Spain and Portugal experiencing relatively high rates.

The highest rates of HIV and AIDS diagnoses in Western Europe continue to be observed among MSM in urban centers. In recent years, European countries have experienced increases in syphilis and gonorrhea cases among MSM, which suggest important changes in behaviors associated with HIV transmission.^{73,75,76} Increases in reported HIV cases among MSM in the UK and Germany have paralleled increases in other sexually transmitted infections.^{76,77} However, it is unclear whether these trends in HIV are the result of increases in testing or greater rates of transmission.⁷² Injection drug use continues to play a major role in the epidemic in Italy, Spain, and Portugal, where, in recent periods, up to half of the cases have been attributed to this mode of transmission.

One of the most striking recent trends in European countries that have ongoing surveillance of newly diagnosed HIV infections is the number of cases attributed to heterosexual contact. During the latter part of the 1990s and early 2000s, cases attributed to heterosexual contact increased over 100%.⁷⁸ This trend is particularly notable in the UK, where many of the heterosexually acquired cases were identified in immigrants from sub-Saharan Africa (Fig. 97-9).

Canada. The HIV epidemic in Canada has been relatively stable during the late 1990s, with the number of AIDS cases and new HIV diagnoses remaining constant during the period 1996–2002. However, changes in the distribution of the major risk factors occurred. During this period, MSM became the predominantly affected group, with an increase in the percentage of cases among MSM increasing from 30% to 40%. The estimated percentage of new HIV cases diagnosed among IDUs decreased from 47% to 30%, while the proportion of new diagnoses attributed to heterosexual transmission increased from 17% to 24%.⁷⁹

Developing countries

HIV/AIDS surveillance in resource-limited settings focused initially on case surveillance, using a clinical case definition that did not require HIV serologic testing, due to the its gen-

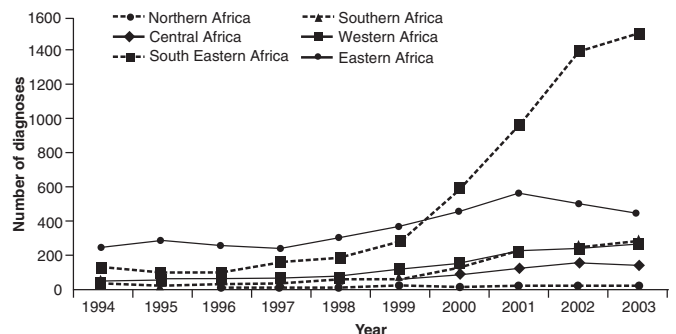


FIGURE 97-9. Probable region of infection for reported heterosexual HIV infections that were probably acquired in Africa (diagnosed in UK), 1994–2003. Only cases with identified probable country of infection are included.

eral lack of availability. The clinical case definition developed during a conference in Bangui, Central African Republic, in 1986, defined AIDS as the presence of two major conditions (e.g., wasting and chronic diarrhea) and one minor condition (e.g., varicella zoster), or single diagnoses of disseminated KS or cryptococcal meningitis.⁸⁰ In Latin America, based on the increasing availability of serologic testing, the Pan American Health Organization at a 1989 conference in Caracas proposed a definition based on a laboratory diagnosis of HIV infection and a system of points assigned to various AIDS-related conditions, which was subsequently revised in 1992.⁸¹ Focusing primarily on the African context, WHO published a revised definition in 1994, which proposed the continued use of the Bangui definition when serologic testing was not available but expanded the definition to include a positive HIV test and any one of a set of clinical conditions.⁸²

Although case surveillance was important for identifying the presence of infection in a country, it was inadequate for assessing the extent of the epidemic. The primary focus of HIV surveillance in resource-limited settings became HIV seroprevalence surveys in selected populations that could be easily accessed. These populations included women in antenatal care, blood donors, military recruits, and, in some countries, persons at high risk, such as IDUs and sex workers.⁸³ Such serosurveys began to define the extent to which HIV infection was prevalent in most countries of the

world and to describe the large variation in disease burden and epidemiology from country to country.

However, by the late 1990s, it was recognized that existing surveillance was not systematically addressing the data needs for a comprehensive response to the epidemic or adequately reflecting differences among countries.⁸⁴ Surveillance strategies had not been adapted to the characteristics of the epidemic in each country. Tracking of risk behaviors was limited. Insufficient use was being made of data from other sources that could usefully complement HIV prevalence surveys, most notably data on other STDs.

Based on a workshop held by WHO and UNAIDS in Berlin in 1997, a set of new recommendations was developed, focusing on “second-generation surveillance.”⁸⁵ A key principle of second-generation surveillance is that it is important to consider the epidemic state within a country, defined as low level, concentrated, or generalized (Table 97-4), a concept adapted from a similar typology described in a report of the World Bank.⁸⁶ In generalized epidemics, monitoring of HIV prevalence, STDs, and behavioral risks in the general population through serologic screening of pregnant women or national demographic and health surveys are a priority, whereas, in concentrated and low-level epidemics, the primary focus should be on monitoring HIV seroprevalence, other STDs, and risk behaviors among sentinel populations at high risk of acquiring or transmitting HIV. Second-generation surveillance

Table 97-4. Classification of HIV/AIDS Epidemics

Low grade

Principle: Although HIV infection may have existed for many years, it has never spread to significant levels in any subpopulation. Recorded infection is largely confined to individuals with higher risk behavior: e.g., sex workers, drug injectors, and men having sex with other men. This epidemic state suggests that networks of risk are rather diffuse (with low levels of partner exchange or sharing of drug injecting equipment), or that the virus is only very recently introduced.

Numerical proxy: HIV prevalence has not exceeded 5% in any defined subpopulation.

Concentrated

Principle: HIV has spread rapidly in a defined subpopulation but is not well established in the general population. This epidemic state suggests active networks of risk within the subpopulation. The future course of the epidemic is determined by the frequency and nature of links between highly infected subpopulations and the general population.

Numerical proxy: HIV prevalence over 5% in at least one defined subpopulation. HIV prevalence below 1% in pregnant women.

Generalized

Principle: In generalized epidemics, HIV is firmly established in the general population. Although subpopulations at high risk may continue to contribute disproportionately to the spread of HIV, sexual networking in the general population is sufficient to sustain an epidemic independent of subpopulations at higher risk of infection.

Numerical proxy: HIV prevalence over 1% in pregnant women.

guidelines also recommended that biological data (e.g., data on HIV infection and other STDs) be compared with behavioral data collected through surveys and that better overall use be made of complementary data sources, including STD surveillance data, HIV/AIDS case reporting, data on HIV infection among persons with TB, and death registration, to provide a more comprehensive picture of the epidemic.

A further concept of second-generation surveillance is to work toward obtaining information on the evolution of the epidemic within a country, by obtaining measures of incidence. An indirect indicator of trends in incidence has been examination of trends in HIV seroprevalence among adolescents and young adults (i.e., 15–24-year-olds), because such trends are more likely to reflect recent infection than trends among older age groups; for many surveys, this has required substantially increasing sample sizes among this age group. Following the development of serologic assays for recent HIV infection (STARHS assays) in the United States, the use of STARHS or related methods is increasing for estimating incidence in developing country settings. Studies have recently validated certain STARHS assays with non-B subtypes that are common in developing countries; certain methodologic issues in the interpretation of these data, based on sampling biases and statistical considerations, are still being addressed.⁸⁷

With the rapidly increasing availability of antiretroviral therapy, even in settings with minimal infrastructure, new issues in surveillance are emerging, which relate to monitoring aspects of HIV/AIDS care.⁸⁸ Chief among these is the surveillance of resistance to antiretroviral drugs, focusing on therapy-naïve persons. The many questions about the long-term effects and impact of using antiretroviral therapies on such a large scale will likely compel the development of supplemental surveillance systems or studies that can provide for monitoring of risk behaviors, STDs, tuberculosis and other opportunistic infections, adverse events, and mortality among persons on antiretroviral therapies.

Estimates of HIV seroprevalence derived from a variety of data sources are reported annually by the WHO and UNAIDS.⁸⁹ In 2006, HIV prevalence among adults aged 15–49 years was estimated to be 5.9% in sub-Saharan Africa, 1.2% in the Caribbean, 0.9% in Eastern Europe and Central Asia, 0.6% in South and Southeast Asia, and 0.5% in Latin America, with lower estimates of prevalence in other geographical regions. Within each of these regions, prevalence varies substantially; for example, in several sub-Saharan countries, HIV prevalence among adults exceeds 25%.

STD SURVEILLANCE

■ CASE DEFINITIONS—UNITED STATES

Case definitions for most sexually transmitted diseases were revised in 1996.⁹⁰ Current case definitions are presented in [Table 97-5](#).

■ CASE SURVEILLANCE: METHODS, ISSUES, MAJOR FINDINGS—UNITED STATES

Methods of case surveillance

Only a few sexually transmitted diseases are reportable in all states and notifiable to the CDC: syphilis (including congenital syphilis), gonorrhea, chancroid, and chlamydia. Other STDs are reportable in certain states but not nationally. Both providers and laboratories are required to report positive results of tests for STDs to local health departments. Surveillance systems are mostly passive, relying on voluntary reporting from providers and laboratories. For syphilis and occasionally for other STDs, case reporting is linked directly to public health intervention, in the form of field investigations to ensure treatment of STDs and testing of sexual partners of the index case.

In the case of syphilis, providers and laboratories are required to report reactive serologic test results, even if a diagnosis of syphilis has not been made. However, health departments often develop guidelines (based on the titer, age of patient, and local epidemiology) to determine which syphilis case reports should result in field investigation. This is required because a reactive serological test for syphilis may not necessarily indicate active, untreated infection. On the basis of such guidelines, some local health departments may choose not to evaluate or contact individuals determined to be at low risk of having or transmitting active disease.^{91,92}

In 2002, case reports of chlamydia, gonorrhea, and syphilis accounted for more than 1.3 million cases, which was >80% of all infectious disease notifications to CDC.⁹³ Still, these case reports are considered to be a substantial underestimate of the true burden of disease. For example, the incidence of chlamydial infections in the United States was estimated to be about 2.8 million new infections per year in 2000, compared with reported cases of about 700,000.⁹⁴

Trends

Chlamydia. *Chlamydia trachomatis* infections are the most commonly reported notifiable disease in the United States. They are the most prevalent of all bacterial STDs and, since 1994, have comprised the largest proportion of all STDs reported to CDC. In women, chlamydial infections, which are usually asymptomatic, may result in pelvic inflammatory disease (PID), which is a major cause of infertility, ectopic pregnancy, and chronic pelvic pain. As with other inflammatory STDs, chlamydial infection may facilitate the transmission of HIV infection.

Although highly prevalent, trends in chlamydial infections are hard to describe with confidence for several reasons. First, screening recommendations and practices for chlamydia have changed greatly over the past 10 years. For example, a new Health Plan Employer Data and Information Set (HEDIS)

Table 97-5. STD Case Definitions for Public Health Surveillance⁹⁰**Notifiable STDs:****Chancroid** (revised 9/96) clinical description

A sexually transmitted disease characterized by painful genital ulceration and inflammatory inguinal adenopathy. The disease is caused by infection with *Haemophilus ducreyi*.

Laboratory criteria for diagnosis:

- Isolation of *H. ducreyi* from a clinical specimen

Case classification probable: a clinically compatible case with both (1) no evidence of *Treponema pallidum* infection by darkfield microscopic examination of ulcer exudate or by a serologic test for syphilis performed greater than or equal to 7 d after onset of ulcers and (2) either a clinical presentation of the ulcer(s) not typical of disease caused by herpes simplex virus (HSV) or a culture negative for HSV.

Confirmed: a clinically compatible case that is laboratory confirmed.

Chlamydia, genital infections (revised 9/96) clinical description

Infection with *C. trachomatis* may result in urethritis, epididymitis, cervicitis, acute salpingitis, or other syndromes when sexually transmitted; however, the infection is often asymptomatic in women. Perinatal infections may result in inclusion conjunctivitis and pneumonia in newborns. Other syndromes caused by *C. trachomatis* include lymphogranuloma venereum (see Lymphogranuloma venereum) and trachoma.

Laboratory criteria for diagnosis:

- Isolation of *C. trachomatis* by culture, or
- Demonstration of *C. trachomatis* in a clinical specimen by detection of antigen or nucleic acid

Case classification

Confirmed: a case that is laboratory confirmed.

Gonorrhea (revised 9/96) clinical description

A sexually transmitted infection commonly manifested by urethritis, cervicitis, or salpingitis. Infection may be asymptomatic.

Laboratory criteria for diagnosis:

- Isolation of typical gram-negative, oxidase-positive diplococci (presumptive *N. gonorrhoeae*) from a clinical specimen, or
- Demonstration of *N. gonorrhoeae* in a clinical specimen by detection of antigen or nucleic acid, or
- Observation of gram-negative intracellular diplococci in a urethral smear obtained from a male

Case classification probable: (1) demonstration of gram-negative intracellular diplococci in an endocervical smear obtained from a female or (2) a written morbidity report of gonorrhea submitted by a physician.

Confirmed: a case that is laboratory confirmed.

Syphilis (all definitions revised 9/96)

Syphilis is a complex sexually transmitted disease that has a highly variable clinical course. Classification by a clinician with expertise in syphilis may take precedence over the following case definitions developed for surveillance purposes.

Syphilis, primary clinical description

A stage of infection with *T. pallidum* characterized by one or more chancres (ulcers); chancres might differ considerably in clinical appearance.

Laboratory criteria for diagnosis:

- Demonstration of *T. pallidum* in clinical specimens by darkfield microscopy, direct fluorescent antibody (DFA-TP), or equivalent methods

Case classification probable: a clinically compatible case with one or more ulcers (chancres) consistent with primary syphilis and a reactive serologic test (nontreponemal: Venereal Disease Research Laboratory¹⁴⁷ or rapid plasma reagin {RPR}; treponemal: fluorescent treponemal antibody absorbed {FTA-ABS} or microhemagglutination assay for antibody to *T. pallidum* {MHA-TP}).

Confirmed: a clinically compatible case that is laboratory confirmed.

Syphilis, secondary clinical description

(Continued)

Table 97-5. (Continued)

A stage of infection caused by *T. pallidum* and characterized by localized or diffuse mucocutaneous lesions, often with generalized lymphadenopathy. The primary chancre may still be present.

Laboratory criteria for diagnosis:

- Demonstration of *T. pallidum* in clinical specimens by darkfield microscopy, DFA-TP, or equivalent methods

Case classification probable: a clinically compatible case with a nontreponemal (VDRL or RPR) titer greater than or equal to 4.

Confirmed: a clinically compatible case that is laboratory confirmed.

Syphilis, latent clinical description

A stage of infection caused by *T. pallidum* in which organisms persist in the body of the infected person without causing symptoms or signs. Latent syphilis is subdivided into early, late, and unknown categories based on the duration of infection.

Case classification probable: no clinical signs or symptoms of syphilis and the presence of one of the following:

- No past diagnosis of syphilis, a reactive nontreponemal test (i.e., VDRL or RPR), and a reactive treponemal test (i.e., FTA-ABS or MHA-TP)
- A past history of syphilis therapy and a current nontreponemal test titer demonstrating fourfold or greater increase from the last nontreponemal test titer

Syphilis, early latent clinical description

A subcategory of latent syphilis. When initial infection has occurred within the previous 12 months, latent syphilis is classified as early latent.

Case classification probable: latent syphilis (see Syphilis, latent) in a person who has evidence of having acquired the infection within the previous 12 months based on one or more of the following criteria:

- Documented seroconversion or fourfold or greater increase in titer of a nontreponemal test during the previous 12 months
- A history of symptoms consistent with primary or secondary syphilis during the previous 12 months
- A history of sexual exposure to a partner who had confirmed or probable primary or secondary syphilis or probable early latent syphilis (documented independently as duration less than 1 year)
- Reactive nontreponemal and treponemal tests from a person whose only possible exposure occurred within the preceding 12 months

Syphilis, late latent clinical description

A subcategory of latent syphilis. When initial infection has occurred greater than 1 year previously, latent syphilis is classified as late latent.

Case classification probable: latent syphilis (see Syphilis, latent) in a patient who has no evidence of having acquired the disease within the preceding 12 months (see Syphilis, early latent) and whose age and titer do not meet the criteria specified for latent syphilis of unknown duration.

Syphilis, latent, of unknown duration clinical description

A subcategory of latent syphilis. When the date of initial infection cannot be established as having occurred within the previous year and the patient's age and titer meet criteria described below, latent syphilis is classified as latent syphilis of unknown duration.

Case classification probable: latent syphilis (see Syphilis, latent) that does not meet the criteria for early latent syphilis, and the patient is aged 13–35 y and has a nontreponemal titer greater than or equal to 32.

Neurosyphilis clinical description

Evidence of central nervous system infection with *T. pallidum*

Laboratory criteria for diagnosis:

- A reactive serologic test for syphilis and reactive VDRL in cerebrospinal fluid (CSF)

Case classification probable: syphilis of any stage, a negative VDRL in CSF, and both the following:

- Elevated CSF protein or leukocyte count in the absence of other known causes of these abnormalities
- Clinical symptoms or signs consistent with neurosyphilis without other known causes for these clinical abnormalities

Table 97-5. (Continued)

Confirmed: syphilis of any stage that meets the laboratory criteria for neurosyphilis.

Syphilis, late, with clinical manifestations other than neurosyphilis (late benign syphilis and cardiovascular syphilis) clinical description

Clinical manifestations of late syphilis other than neurosyphilis may include inflammatory lesions of the cardiovascular system, skin, and bone. Rarely, other structures (e.g., the upper and lower respiratory tracts, mouth, eye, abdominal organs, reproductive organs, lymph nodes, and skeletal muscle) may be involved. Late syphilis usually becomes clinically manifest only after a period of 15–30 y of untreated infection.

Laboratory criteria for diagnosis:

- Demonstration of *T. pallidum* in late lesions by fluorescent antibody or special stains (although organisms are rarely visualized in late lesions)

Case classification probable: characteristic abnormalities or lesions of the cardiovascular system, skin, bone, or other structures with a reactive treponemal test, in the absence of other known causes of these abnormalities, and without CSF abnormalities and clinical symptoms or signs consistent with neurosyphilis.

Confirmed: a clinically compatible case that is laboratory confirmed.

Comment: Analysis of CSF for evidence of neurosyphilis is necessary in the evaluation of late syphilis with clinical manifestations.

Syphilitic stillbirth clinical description

A fetal death that occurs after a 20-week gestation or in which the fetus weighs greater than 500 g and the mother had untreated or inadequately treated syphilis at delivery.

Comment: For reporting purposes, syphilitic stillbirths should be reported as cases of congenital syphilis.

Syphilis, congenital (revised 9/96) clinical description

A condition caused by infection in utero with *T. pallidum*. A wide spectrum of severity exists, and only severe cases are clinically apparent at birth. An infant or child (aged less than 2 y) may have signs such as hepatosplenomegaly, rash, condyloma lata, snuffles, jaundice (nonviral hepatitis), pseudoparalysis, anemia, or edema (nephrotic syndrome and/or malnutrition). An older child may have stigmata (e.g., interstitial keratitis, nerve deafness, anterior bowing of shins, frontal bossing, mulberry molars, Hutchinson teeth, saddle nose, rhagades, or Clutton joints).

Laboratory criteria for diagnosis:

- Demonstration of *T. pallidum* by darkfield microscopy, fluorescent antibody, or other specific stains in specimens from lesions, placenta, umbilical cord, or autopsy material

Case classification probable: a condition affecting an infant whose mother had untreated or inadequately treated syphilis at delivery, regardless of signs in the infant, or an infant or child who has a reactive treponemal test for syphilis and any one of the following:

- Any evidence of congenital syphilis on physical examination
- Any evidence of congenital syphilis on radiographs of long bones
- A reactive CSF VDRL
- An elevated CSF cell count or protein (without other cause)
- A reactive fluorescent treponemal antibody absorbed–19S-IgM antibody test or IgM enzyme-linked immunosorbent assay

Confirmed: a case that is laboratory confirmed.

Comment: Congenital and acquired syphilis may be difficult to distinguish when a child is seropositive after infancy. Signs of congenital syphilis may not be obvious, and stigmata may not yet have developed. Abnormal values for CSF VDRL, cell count, and protein, as well as IgM antibodies, may be found in either congenital or acquired syphilis. Findings on radiographs of long bones may help because radiographic changes in the metaphysis and epiphysis are considered classic signs of congenitally acquired syphilis. The decision may ultimately be based on maternal history and clinical judgment. In a young child, the possibility of sexual abuse should be considered as a cause of acquired rather than congenital syphilis, depending on the clinical picture. For reporting purposes, congenital syphilis includes cases of congenitally acquired syphilis among infants and children as well as syphilitic stillbirths.

(Continued)

Table 97-5. (Continued)**Non-notifiable STDs:****Genital herpes** (herpes simplex virus) (revised 9/96) clinical description

A condition characterized by visible, painful genital or anal lesions.

Laboratory criteria for diagnosis:

- Isolation of herpes simplex virus from cervix, urethra, or anogenital lesion, or
- Demonstration of virus by antigen detection technique in clinical specimens from cervix, urethra, or anogenital lesion, or
- Demonstration of multinucleated giant cells on a Tzanck smear of scrapings from an anogenital lesion

Case classification probable: a clinically compatible case (in which primary and secondary syphilis have been excluded by appropriate serologic tests and darkfield microscopy, when available) with either a diagnosis of genital herpes based on clinical presentation (without laboratory confirmation) or a history of one or more previous episodes of similar genital lesions.

Confirmed: a clinically compatible case that is laboratory confirmed.

Comment: Genital herpes should be reported only once per patient. The first diagnosis for a patient with no previous diagnosis should be reported.

Genital warts (revised 9/96) clinical description

An infection characterized by the presence of visible, exophytic (raised) growths on the internal or external genitalia, perineum, or perianal region

Laboratory criteria for diagnosis:

- Histopathologic changes characteristic of human papillomavirus infection in specimens obtained by biopsy or exfoliative cytology, or
- Demonstration of virus by antigen or nucleic acid detection in a lesion biopsy

Case classification probable: a clinically compatible case without histopathologic diagnosis and without microscopic or serologic evidence that the growth is the result of secondary syphilis.

Confirmed: a clinically compatible case that is laboratory confirmed.

Comment: Genital warts should be reported only once per patient. The first diagnosis for a patient with no previous diagnosis should be reported.

Granuloma Inguinale clinical description

A slowly progressive ulcerative disease of the skin and lymphatics of the genital and perianal area caused by infection with *Calymmatobacterium granulomatis*. A clinically compatible case would have one or more painless or minimally painful granulomatous lesions in the anogenital area.

Laboratory criteria for diagnosis:

- Demonstration of intracytoplasmic Donovan bodies in Wright or Giemsa-stained smears or biopsies of granulation tissue

Case classification confirmed: a clinically compatible case that is laboratory confirmed.

Lymphogranuloma venereum clinical description

Infection with L1, L2, or L3 serovars of *C. trachomatis* may result in a disease characterized by genital lesions, suppurative regional lymphadenopathy, or hemorrhagic proctitis. The infection is usually sexually transmitted.

Laboratory criteria for diagnosis:

- Isolation of *C. trachomatis*, serotype L1, L2, or L3 from clinical specimen, or
- Demonstration by immunofluorescence of inclusion bodies in leukocytes of an inguinal lymph node (bubo) aspirate, or
- Positive microimmunofluorescent serologic test for a lymphogranuloma venereum strain of *C. trachomatis*

Case classification probable: a clinically compatible case with one or more tender fluctuant inguinal lymph nodes or characteristic proctogenital lesions with supportive laboratory findings of a single *C. trachomatis* complement fixation titer of greater than 64.

Confirmed: a clinically compatible case that is laboratory confirmed.

Mucopurulent cervicitis (revised 9/96) clinical description

Cervical inflammation that is not the result of infection with *N. gonorrhoeae* or *Trichomonas vaginalis*. Cervical inflammation is defined by the presence of one of the following criteria:

Table 97-5. (Continued)

- Mucopurulent secretion (from the endocervix) that is yellow or green when viewed on a white, cotton-tipped swab (positive swab test)
- Induced endocervical bleeding (bleeding when the first swab is placed in the endocervix)

Laboratory criteria for diagnosis:

- No evidence of *N. gonorrhoeae* by culture, Gram stain, or antigen or nucleic acid detection, and no evidence of *T. vaginalis* on wet mount

Case classification confirmed: a clinically compatible case in a female who does not have either gonorrhea or trichomoniasis.

Comment: Mucopurulent cervicitis (MPC) is a clinical diagnosis of exclusion. The syndrome may result from infection with any of several agents (see *Chlamydia trachomatis*, Genital Infections). If gonorrhea, trichomoniasis, and chlamydia are excluded, a clinically compatible illness should be classified as MPC. An illness in a female that meets the case definition of MPC and *C. trachomatis* infection should be classified as chlamydia.

Nongonococcal urethritis (revised 9/96) clinical description

Urethral inflammation that is not the result of infection with *N. gonorrhoeae*. Urethral inflammation may be diagnosed by the presence of one of the following criteria:

- A visible abnormal urethral discharge, or
- A positive leukocyte esterase test from a male aged less than 60 y who does not have a history of kidney disease or bladder infection, prostate enlargement, urogenital anatomic anomaly, or recent urinary tract instrumentation, or
- Microscopic evidence of urethritis (greater than or equal to five white blood cells per high-power field) on a Gram stain of a urethral smear

Laboratory criteria for diagnosis:

- No evidence of *N. gonorrhoeae* infection by culture, Gram stain, or antigen or nucleic acid detection

Case classification confirmed: a clinically compatible case in a male in whom gonorrhea is not found, by culture, Gram stain, or antigen or nucleic acid detection.

Comment: Nongonococcal urethritis (NGU) is a clinical diagnosis of exclusion. The syndrome may result from infection with any of several agents (see *Chlamydia trachomatis*, Genital Infection). If gonorrhea and chlamydia are excluded, a clinically compatible illness should be classified as NGU. An illness in a male that meets the case definition of NGU and *C. trachomatis* infection should be classified as chlamydia.

Pelvic inflammatory disease (revised 9/96) clinical case definition

A clinical syndrome resulting from the ascending spread of microorganisms from the vagina and endocervix to the endometrium, fallopian tubes, and/or contiguous structures.

In a female who has lower abdominal pain and who has not been diagnosed as having an established cause other than pelvic inflammatory disease (PID) (e.g., ectopic pregnancy, acute appendicitis, and functional pain), all the following clinical criteria must be present:

- Lower abdominal tenderness, and
- Tenderness with motion of the cervix, and
- Adnexal tenderness

In addition to the preceding criteria, at least one of the following findings must also be present:

- Meets the surveillance case definition of *C. trachomatis* infection or gonorrhea
- Temperature greater than 100.4°F (greater than 38.0°C)
- Leukocytosis greater than 10,000 white blood cells/mm³
- Purulent material in the peritoneal cavity obtained by culdocentesis or laparoscopy
- Pelvic abscess or inflammatory complex detected by bimanual examination or by sonography
- Patient is a sexual contact of a person known to have gonorrhea, chlamydia, or NGU

Case classification confirmed: a case that meets the clinical case definition.

Comment: For reporting purposes, a clinician's report of PID should be counted as a case.

measure for chlamydia was recently implemented, to document screening of sexually active women 15–25 years of age who receive medical care through managed care organizations. This HEDIS measure is expected to result in increased chlamydia diagnosis and reporting, because health plans will report data on proportion of women screened as a measure of quality of care. Second, diagnostic tests have increased in sensitivity in the past decade, with the increasing availability and use of nucleic acid amplification tests.⁹⁵ Third, until 2000, not all states had regulations requiring the reporting of chlamydia infections. Finally, evolving screening recommendations have resulted in differential screening of women, as compared to men. This latter trend is changing with the increasing availability of urine testing, a less invasive method of testing men and women.

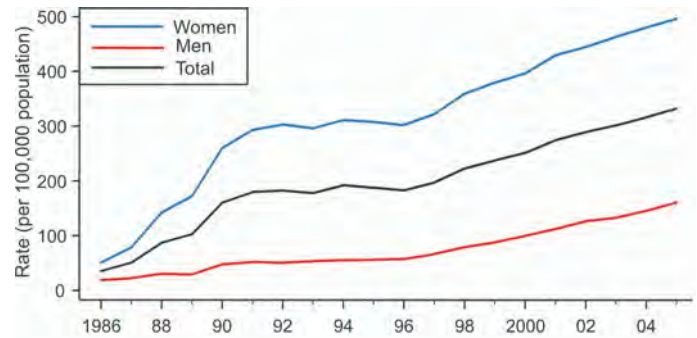
In 2005, 976,445 chlamydia infections were reported to CDC. This case count corresponds to a rate of 332.5 cases per 100,000 population. The rate varied considerably by sex: The rate of chlamydia among women (496.5 per 100,000 population) was over three times the rate among men (161.1 per 100,000 population); this is likely because of the larger number of women screened for this infection. The chlamydia rate in men increased by 43%, compared with a 16% increase in women from 2001 to 2005 (Fig. 97-10); this likely represents increased testing among men in this period.

Because of the expansion of chlamydia screening activities, the number of reported new diagnoses of chlamydia is not useful for examining trends in disease burden in the general population. To better monitor trends in disease burden, an alternate measure, prevalence of chlamydia among persons screened in defined populations, may be used (Fig. 97-11). This is not influenced by the expansion of screening programs. In 2005, the median state-specific chlamydia test positivity among 15–24-year-old women who were screened during visits to selected family planning clinics in all states and outlying areas was 6.3% (range 3.0–20.3%).

Gonorrhea. Gonorrhea is the second most commonly reported notifiable disease in the United States. Infections due to *Neisseria gonorrhoeae*, like those resulting from *C. trachomatis*, are a major cause of PID. In addition, epidemiologic and biologic studies provide strong evidence that gonococcal infections facilitate the transmission of HIV infection.^{96,97}

From 1975 through 1997, the national gonorrhea rate declined 74%, following implementation of the national gonorrhea control program in the mid-1970s (Fig. 97-12). Rates have subsequently plateaued, although a small increase was observed in 2005. Before 1996, rates among men were higher than rates among women. Since then, rates among men and women have remained similar. Diagnostic testing for gonorrhea is changing, with the increasing use of less invasive and more sensitive nucleic acid amplification tests and decreasing use of culture methods.⁹⁸

In 2005, 339,593 cases of gonorrhea were reported in the United States. The rate of gonorrhea in the United States was



Note: As of January 2000, all 50 states and the District of Columbia had regulations requiring the reporting of chlamydia cases.

FIGURE 97-10. Annual rates of reported *Chlamydia* infections per 100,000 population, by sex, 1984–2005, United States.

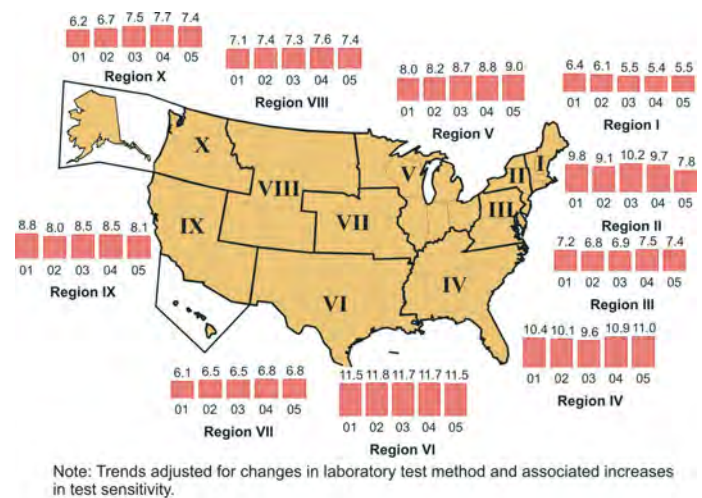


FIGURE 97-11. *Chlamydia* positivity among 15–24-year-old women tested in family planning clinics, by HHS regions, 1988–2005. Trends are adjusted for changes in laboratory test method and associated increases in test sensitivity.

116 cases per 100,000 population in 2005, the lowest rate since reporting began in 1975. Substantial disparity in gonorrhea rates in 2005 was observed by race/ethnicity: The rate among African Americans was 18 times greater than the rate for whites. The highest rates by age were seen among adolescents and young adults, aged 20–24 years, particularly African Americans. In 2005, the gonorrhea rates among 15–19-year-old African American women (2814 per 100,000 population), 20–24-year-old African American women (2543 per 100,000), and 20–24-year-old African American men (2362 per 100,000) were the highest race/age-specific rates observed.

Syphilis and congenital syphilis. The rate of primary and secondary (P&S) syphilis reported in the United States decreased during the 1990s; in 2000, the rate was the lowest since reporting began in 1941 (Fig. 97-13). The low rate of infectious syphilis and the concentration of the majority of

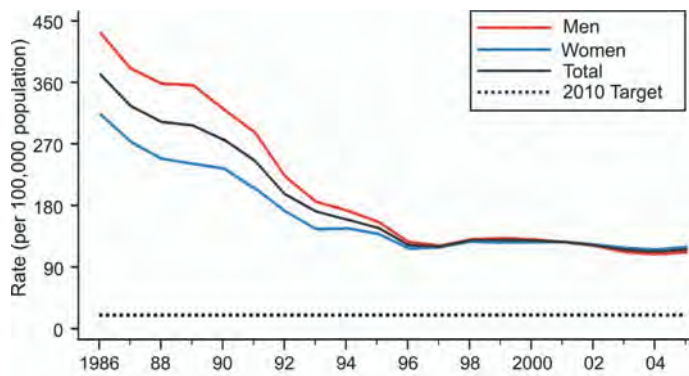


FIGURE 97-12. Rates of reported gonorrhea cases per 100,000 population, by sex, 1981–2005, United States.

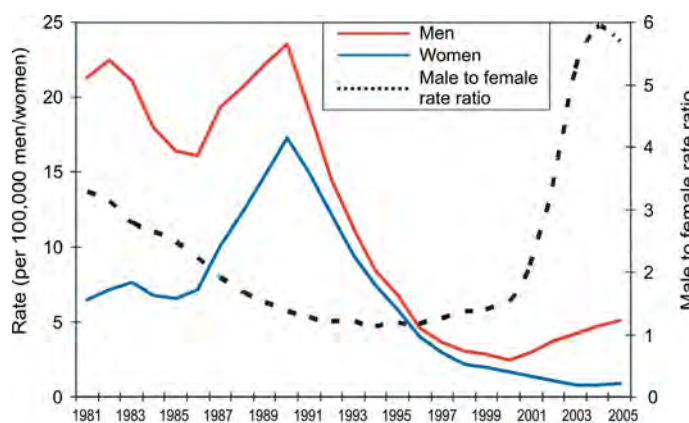


FIGURE 97-13. Rates of reported P&S syphilis cases and male to female case ratio, 1981–2005, United States.

syphilis cases in a small number of geographic areas in the United States led to the development of the CDC’s National Plan to Eliminate Syphilis,⁹⁹ which was announced by the Surgeon General in October 1999 and updated in 2006.¹⁰⁰ Although the rate of P&S syphilis in the United States declined by 89.7% during 1990–2000, the rate of P&S syphilis remained unchanged between 2000 and 2001 and increased from 2001 to 2005. The number of P&S syphilis cases reported to CDC increased 43% from 6103 cases in 2001 to 8724 in 2005. The rate of P&S syphilis in the United States in 2005 (3.0 cases per 100,000 population) was 43% higher than the rate in 2001 (2.1 cases per 100,000 population).

Trends in syphilis rates vary considerably between men and women. For example, overall increases in rates during 2000–2005 were observed predominantly among men. Outbreaks of syphilis among MSM have been reported since 2000, characterized by high rates of HIV coinfection and high-risk sexual behaviors.^{101–106} The rate of P&S syphilis increased 70% among men (from 3.0 cases to 5.1 cases per 100,000 men) between 2001 and 2005. During this time, the overall rate declined 36% among women (from 1.4 to

0.9 cases per 100,000 women), although there was a slight increase in 2005.

Information on the risk behaviors of persons infected with syphilis have not been collected nationally, and, thus, the numbers of persons with reported syphilis who are MSM are not known. In the absence of data on male–male sexual behaviors, the male-to-female case ratio has been used as a proxy for transmission among MSM. The male-to-female rate ratio for P&S syphilis increased from 2.1 in 2001 to 5.7 in 2005, suggesting increases nationally among MSM during this period (Fig. 97-13).

Between 1990 and 2005, the overall rate of congenital syphilis decreased 91% in the United States.¹⁰⁷ The continuing decline in the rate of congenital syphilis likely reflects the substantial reduction in the rate of P&S syphilis among women that has occurred during the last decade.

■ SUPPLEMENTAL SURVEILLANCE SYSTEMS FOR STDs—UNITED STATES

Representative national surveys

Special surveillance-related studies include population-based sample surveys such as the NHANES. This nationally representative probability sample survey of the noninstitutionalized U.S. population has examined the prevalence of antibodies to HPV-16,¹⁰⁸ antibodies to herpes simplex virus types 1 and 2,¹⁰⁹ and chlamydia and gonorrhea.¹¹⁰ Other surveys include the National Hospital Discharge Survey (NHDS), which is a continuous survey of a probability sample of records of patients discharged from acute care hospitals in the United States. The National Ambulatory Medical Survey (NAMCS), a survey of private physicians’ office practices, and the National Hospital Ambulatory Medical Survey (NHAMCS), an emergency room discharge survey and hospital outpatient clinic survey, are both performed through abstraction of information from medical records. The National Disease and Therapeutic Index (NDTI) is a probability sample survey of private physicians’ practices, which provides estimates of the number of initial visits to private physicians’ offices for many conditions, including STDs. While subject to many limitations, NDTI has for many years been the only source of national data on office visits for genital herpes, genital warts, and trichomoniasis.¹⁰⁷

Prevalence monitoring

Prevalence monitoring is the assessment of STD prevalence among persons in defined populations who are routinely screened. In this context, prevalence refers to the number of persons with positive test results divided by the number of persons screened the first time in a defined time interval (for example, the number of women who are screened for chlamydial infection at a family planning clinic in a year, excluding

repeat test results). Because in practice there are relatively few repeat test results, positivity (the number of positive tests/number of adequate test results) is often used as a surrogate for prevalence. Positivity data are often more easily obtained than are data on prevalence, because of the difficulty in identifying and excluding repeat tests from these calculations. In most clinic settings, chlamydia positivity differs little from prevalence.⁹⁵

In the United States, the systems best developed for monitoring STD prevalence have been established by the regional infertility prevention projects, which are in each of the 10 Public Health Service regions.¹¹¹ These federally funded projects, which have the primary purpose of providing support for chlamydia screening of women seeking family planning services, have made it possible to monitor chlamydia positivity among approximately 2.8 million women annually who are screened for chlamydial infection in selected family planning clinics, prenatal clinics, STD clinics, and juvenile detention centers. Some regional infertility prevention projects also provide support for gonorrhea screening. These systems have made it possible to compare state-specific prevalence across the United States, for women screened for chlamydial infection in family planning clinics and for chlamydia and gonorrhea in some other settings. Other sources of STD prevalence monitoring data include results of STD screening of persons entering jails and juvenile detention facilities, of MSM seen attending STD clinics and other primary-care settings, and screening of adolescent and young adult women and men entering the National Job Training Program (Table 97-6).¹⁰⁷

Gonococcal resistance surveillance

The treatment and control of gonorrhea has been complicated by the ability of *N. gonorrhoeae* to develop resistance to antimicrobial agents. Surveillance for antimicrobial resistance is critical for establishing a rational basis for the empiric

selection of gonococcal therapies. In the United States, antimicrobial resistance in *N. gonorrhoeae* is monitored through the Gonococcal Isolate Surveillance Project (GISP). GISP is an ongoing system for sentinel surveillance of resistance through the analysis of isolates from STD clinics in approximately 28 cities. The first 25 isolates from male patients with gonococcal urethritis in each of these cities are analyzed for the minimum inhibitory concentration of antimicrobials using a standardized agar dilution method. Detailed data from each city participating in GISP is available in CDC's annual report on this project.¹¹²

Resistance to ciprofloxacin (a fluoroquinolone) was first identified in GISP in 1991.¹¹² From 1991 through 1998, fewer than nine ciprofloxacin-resistant isolates were identified each year, and these isolates were identified in only a few GISP clinics. In 2000, 19 (0.4%) ciprofloxacin-resistant GISP isolates were identified in seven GISP clinics. In 2005, 581 (9.4%) ciprofloxacin-resistant GISP isolates were identified in 25 of 27 clinics (Fig. 97-14).

The proportion of fluoroquinolone-resistant *N. gonorrhoeae* (QRNG) isolates from MSM increased from 1.6% in 2001 to 29% in 2005. During the same time period, the proportion of QRNG isolates from heterosexuals increased from 0.6% in 2001 to 3.8% in 2005. As of June 2006, cephalosporin resistance had not been identified in GISP and the proportion of GISP isolates demonstrating decreased susceptibility to ceftriaxone or cefixime has remained very low.

■ STD SURVEILLANCE—INTERNATIONAL SETTINGS

Although the burden of curable STDs globally is estimated to exceed 300 million new cases annually, systems for public health surveillance of STDs vary in coverage and quality in developed countries outside of the United States¹¹³ and are particularly weak in resource-constrained countries.¹¹⁴ Key factors limiting the availability of STD surveillance data in developing countries

Table 97-6. Gonorrhea Prevalence in Different Populations and Clinical Settings, 2005^{107,110}

Women		Men	
Population (age)	Prevalence	Population (age)	Prevalence
Juvenile corrections	4.7%	MSM attending STD clinics	11%
Adult corrections	2.8%	Adult corrections	2.3%
Job training program (16–24)	2.4%	Job training program (16–24)	2.2%
Prenatal care clinics (15–24)	0.9%	Juvenile corrections	1.0%
Family planning clinics (15–24)	1.0%	NHANES, 1999–2002 (14–39)	0.16%
NHANES, 1999–2002 (14–39)	0.33%		

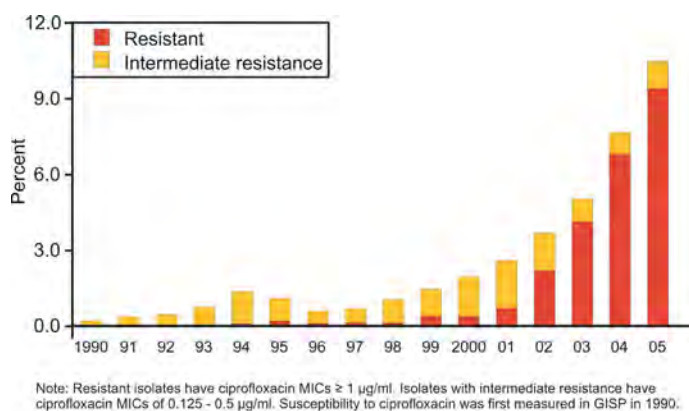


FIGURE 97-14. Percentage of *N. gonorrhoeae* isolates from men in sexually transmitted disease clinics (Gonococcal Isolate Surveillance Program, or GISP) with intermediate resistance or resistance to ciprofloxacin, 1990–2005, United States.

are lack of services for effective diagnosis and treatment of STDs, lack of availability of sensitive diagnostic tests that are sufficiently inexpensive to make them broadly available, and lack of information systems that provide for reliable reporting.

Given these constraints, WHO/UNAIDS have developed strategies for strengthening STD surveillance in resource-poor settings.¹¹⁴ Key components include (1) case reporting of a limited set of STD syndromes and of congenital syphilis cases; (2) prevalence assessment and monitoring, focusing on populations that are routinely screened, vulnerable populations at high risk of STDs, and integration of STD testing into national demographic and health surveys where feasible; and (3) monitoring of antimicrobial resistance in *N. gonorrhoeae*.

STD syndromic surveillance

STD syndromes currently recommended by WHO/UNAIDS for reporting in developing country settings are urethral discharge in men and genital ulcers in men and women. Other syndromes are considered too nonspecific to provide an accurate reflection of STD incidence.¹¹⁵ Most cases of vaginal discharge are caused by bacterial vaginosis and vulvovaginal candidiasis, which are not considered STDs. Although the differential diagnosis of lower abdominal pain in women includes PID due to sexually transmitted pathogens, in the absence of diagnostic tests, the findings are too nonspecific to be reliably reported through public health surveillance in resource-poor settings.

Any reporting of STD syndromes will reflect the quality and coverage of primary health-care services; therefore, trends in syndromic reporting must be interpreted in the context of changes in the health-care system. Expansion of services may result in larger numbers of case reports; declines may be anticipated only after the system stabilizes, the control program becomes more effective, and true morbidity declines.

Reporting of congenital syphilis cases varies greatly by country and is complicated by the complexity of case

definitions and lack of definitive diagnostic tests in many settings. However, strengthening congenital syphilis surveillance will be essential for strengthening control programs, and for working toward elimination of this disease.¹¹⁶ Key measures to be taken include ensuring broader coverage of syphilis serologic screening of women during prenatal care, assuring the quality of diagnostic testing, and applying a sensitive epidemiologic case definition for presumptive congenital syphilis that includes infants born to women with untreated syphilis. The increasing availability of rapid syphilis diagnostic tests that are easily performed on whole blood should facilitate surveillance and control of congenital syphilis in many parts of the developing world.

As is the case for STD surveillance in the United States, prevalence assessment is an essential component of STD surveillance in resource-constrained settings, and perhaps even more essential in those settings because of the lack of availability of STD diagnostic testing as a routine component of care. However, in many developing countries, diagnostic testing is not readily available, and data on prevalence cannot be assembled from routine STD screening data in various populations. Therefore, focused prevalence assessments must be performed periodically, using sensitive diagnostic tests, during defined time intervals or on defined survey samples, to obtain reliable data.

STD surveillance programs in developing countries should make use of existing sources of data on STD prevalence, although they should be careful to interpret them in the context of that program. Some countries have substantial data on prevalence of reactive syphilis serologic test results among women screened in antenatal care, as an essential component of their national program for prevention and control of congenital syphilis,¹¹⁷ and among female sex workers who are routinely screened and treated syphilis, as a component of their HIV prevention program.¹¹⁸ Data on prevalence of other STDs, including gonorrhea and chlamydial infection, have usually been much more limited.¹¹⁴

One model for obtaining reliable data on a larger scale has been integration of STD diagnostic testing into population-based surveys in developing country settings,^{119,120} similar to inclusion of gonorrhea and chlamydial screening that is done in the United States as part of NHANES.¹²¹ A second option has been to integrate STD diagnostic testing into behavioral surveillance surveys of specific populations,^{119,122} resulting in data on comparative prevalence among persons at various levels of risk. Such data can be of great help in designing a national STD and HIV prevention strategy.

Monitoring of antimicrobial resistance in *N. gonorrhoeae*

With the broad availability of antimicrobial drugs, continued monitoring of resistance in *N. gonorrhoeae* is an essential component of STD surveillance in all countries.¹²³

These surveillance data are of critical importance for developing national guidelines for STD treatment, considering antimicrobial resistance profiles and local availability of drugs. WHO provides support for this activity through the Gonococcal Antimicrobial Surveillance Program (GASP), with a set of WHO collaborating centers that support various aspects of this activity.¹²⁴ Globally, resistance to penicillin has been demonstrated to be too high to include this drug in national STD treatment guidelines. Fluoroquinolone resistance has been high in Asia and in countries of some other regions of the world. Emergence of resistance to third-generation cephalosporins has been reported only rarely, although the cost of these drugs limits their use in some settings.

USES OF SURVEILLANCE DATA

■ HIV/AIDS

In the United States, there are three primary uses of surveillance data: (1) epidemic monitoring to estimate incidence and prevalence of HIV-related morbidity and mortality in the population, to estimate incidence of HIV infection, and to identify trends in HIV transmission and populations at risk; (2) prevention planning to target prevention interventions and evaluate their effectiveness and to facilitate access to health, social, and prevention services; and (3) allocation

of HIV program funds for prevention, care, and treatment services, including funds provided to state and city governments as part of the Ryan White Care Act.

The use of HIV/AIDS data maintained by governmental agencies for purposes other than epidemiologic monitoring, including activities such as case management for referral to treatment, or the counseling and referral for testing and treatment of persons identified as sexual or needle-sharing contacts to infected persons, has been the subject of substantial controversy.¹²⁵ A set of principles that was derived through a consultative process between academics, governmental officials, public health professionals, and representatives of affected communities are provided in [Table 97-7](#). These tenets, designed to guide public health officials in the legitimate use of data collected about persons with HIV, have been published.¹²⁶

In the international setting, HIV seroprevalence data on pregnant women have commonly been used to make estimates of overall adult population prevalence, and increasingly data on HIV seroprevalence from national demographic and health surveys are being used for this purpose.¹²⁷ Prevalence data are used to estimate the overall burden of HIV infection using several different methods and also to make projections of future trends¹²⁸; certain of these models factor in interventions for prevention and treatment, which may have substantial impact on the future directions of the epidemic within a country.

Table 97-7. Guidelines for the Use of Personally Identifying Public Health Data Regarding Persons with HIV/AIDS

1. Identifiable public health data can only be used for legitimate public health purposes. A legitimate public health purpose enhances or has significant potential to enhance the capacity to reduce morbidity and mortality or direct resources to prevention, treatment, or other public health interventions at the individual or population levels without creating undue burdens.
2. Research serving public health ends represents a legitimate and appropriate use of personally identifiable data related to HIV/AIDS.
3. Personally identifiable data may be shared within public health agencies or among other governmental public health agencies at the federal, tribal, state, territorial, and local levels for legitimate public health purposes.
4. Public health data should not be shared with those charged with law enforcement, immigration control, management of the public welfare system, or other nonpublic health functions, except in circumstances involving the threat of imminent danger of grave physical harm to individuals or populations.
5. Public health agencies should disseminate nonidentifiable summary data to stakeholders.
6. Population-level data should be released in a way that minimizes the imposition of new burdens on those who are vulnerable, for example, because of disease, social class, or ethnicity.
7. Ongoing public consultation should be undertaken as a means of minimizing any burdens that may be created as a consequence of the release of population-level data.

Adapted from Gostin LO, Bayer R, Fairchild A, Gable L, Sweeney P. *Ethical Principles and Guidelines for the Use of Public Health Data with a Focus on HIV/AIDS*. Atlanta, GA: CDC Consultation, November 4, 2004.

■ OTHER STDs

The uses of STD surveillance data reflect the varying strengths and limitations of the many different surveillance data sources for case reporting, prevalence monitoring, and surveillance for antimicrobial resistance. Even though substantial underreporting has been documented for certain STDs, the overall consistency of reporting systems for case detection and reporting of some conditions has made case reporting data useful for monitoring increases and decreases in incidence. In the United States, national trends in case reports of P&S syphilis and of gonorrhea have been considered reflective of actual trends in the incidence of these diseases and are used as the basis for establishing national disease control objectives.¹²⁹

STD surveillance data are commonly used to identify disease outbreaks.^{101,102,130} Local and state health departments have the authority to investigate outbreaks of reportable and nonreportable conditions of public health importance, including STDs.¹³¹ These investigations can be performed to better determine the extent of disease and to identify risk factors for transmission so that focused control measures can be implemented.¹¹⁶ Using traditional partner notification techniques, detailed investigations can also be used to describe social and sexual networks that provide the context for disease transmission.¹³²

STD case report data can effectively be used to identify persons at risk of disease, who should be the focus of control programs. For example, the age–gender groups with the highest rates of gonorrhea are women aged 15–19 years and men aged 20–24 years.¹⁰⁷ Detailed mapping of case reports can be performed to assist in identifying specific neighborhoods where transmission is occurring.¹³³

Data obtained from the case-reporting process are used by health departments to assure that patients have been properly treated and to facilitate or assist in the process of confidentially notifying their sex partners that they also can be confidentially evaluated and treated. In all localities, these functions are performed for patients with early syphilis and, in some localities, for patients with gonococcal and chlamydial infections.

Prevalence data from populations that are routinely screened can be used to develop and modify local criteria for screening; such data have been used extensively for developing screening criteria for chlamydial infections in the United States.¹³⁴ *Chlamydia* prevalence data have also been used to assess screening coverage, both directly, through data gathered on numbers of persons and characteristics of the populations screened, and indirectly, by considering case rates, prevalence, and estimates of the population eligible for screening.¹³⁵ States that have low rates of case reports despite high reported prevalence are most likely places where screening coverage is low.

Surveillance data on antimicrobial resistance in *N. gonorrhoeae* play an important role in developing recommendations for treatment of gonococcal infection. Such data were essential, for example, in the recommendation for abandoning penicillin as the drug of choice for treatment of gonorrhea in the United States in 1989, in favor of ceftriaxone, despite the higher cost of this drug.¹³⁶ Surveillance data on antimicrobial resistance have become increasingly important for treatment recommendations, as nonculture tests for *N. gonorrhoeae* infections come into widespread use, reducing capacity for culture and susceptibility testing at many clinical and public health laboratories. Highly resistant isolates identified through GISP trigger special investigations to determine the source.

Although most U.S. isolates with high levels of resistance to fluoroquinolones were initially linked to Asia,¹³⁷ cases of endemic transmission have occurred on the U.S. mainland and in Hawaii.^{138,139} GISP has also provided early indications of the emergence of decreased susceptibility of *N. gonorrhoeae* to azithromycin.⁹¹ Sentinel systems such as GISP also provide more detailed information on the characteristics of patients than can national surveillance data through case reports. For example, as early as 1996, GISP documented increases in the proportions of gonorrhea patients in STD clinics who were MSM,¹⁴⁰ heralding increasing HIV risk behavior and large outbreaks of STDs in this population.¹⁴¹

■ SURVEILLANCE AND THE CLINICIAN

The clinician plays critical roles in public health surveillance, as both a critical source of information through reporting cases and a beneficiary of the aggregate data produced by surveillance systems. Reporting of cases of HIV, AIDS, and reportable STDs is a legal requirement of health-care providers in the United States. Recent legal protections to the privacy of health information, conferred by the Health Insurance Portability and Privacy Act (HIPPA), are not at odds with the legal duty to report such diagnoses. Guidelines for application of the protections conferred by HIPPA specifically recognize the imperative of case reporting for surveillance purposes, and a public health “carveout” specifies that case reporting for the purposes of public health surveillance and disease control is a permissible release of protected health information.¹⁴² State health departments are empowered to take action against licensed health-care providers who do not report cases as required, to include actions against professional licensure.

Although providers bear responsibility for case reporting, they are also beneficiaries of surveillance programs in many ways. Data from surveillance programs are used to formulate treatment guidelines and empiric recommendations for therapy. Data on disease burden are used locally and nationally to demonstrate met and unmet

needs for care resources, and to advocate for such resources. Clinicians may also routinely receive surveillance reports from the health department, describing the local HIV and STD epidemics. These data are guideposts for care, serving as an evidence base for decisions about which groups in the local community are at greatest risk of certain infections and, therefore, in which groups consideration for screening or clinical suspicion of infections should be enhanced.

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Monitoring and Evaluation of Prevention and Control Programs for HIV/AIDS and Other STD

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Sound monitoring and evaluation are a core component of prevention and treatment programs for HIV/AIDS and STD. This chapter defines monitoring, evaluation and its purposes and presents a simple input-output-outcome-impact framework used in monitoring and evaluation (M&E) system design. It reviews issues related to indicator development and target setting in both international and national contexts. Measurement issues related to different components of this combined framework, such as exposure to or coverage of the intervention and behavioral and biological outcomes, are presented to guide the design of programs and interpretation of findings. The M&E framework is linked to epidemiological knowledge about the transmission of HIV and sexually transmitted disease (STD) to better guide the evaluation of programs, including the implications for study design.

DEFINING MONITORING AND EVALUATION

There are multiple definitions of monitoring and evaluation. In general, all definitions flow from a common basic M&E framework that is used to organize the data required to monitor program implementation and presents a hierarchical order for collecting and analyzing results (Fig. 98-1).¹⁻³ For a program to achieve its goals, inputs such as money and staff time are used to implement a process, a set of activities such as training and distribution of drugs, which should result in planned outputs such as service delivery points (e.g., for HIV testing and counseling, condom distribution, or treatment). If these outputs are well-designed and widely utilized by the populations for which they were intended, the program is likely to have immediate effects, such as number of people HIV tested and counseled. Outputs may lead to outcomes (intermediate effects, such as risk behavior change) that in turn may lead to impact (long-term effects such as a reduction in HIV or STD transmission). The left side of the input-output framework is based on program elements, the right side moves into population health issues.

Monitoring is defined as the routine tracking and reporting of priority information about a program and its intended outputs and outcomes.¹ This primarily includes monitoring of program inputs and outputs through record keeping and regular reporting systems, which is sometimes referred to as process evaluation. Data collection and results should be linked to ongoing management decisions, such as those related to supplies and logistics. However, monitoring may also include the routine tracking of short-term, immediate program outcomes, such as the number of people using a specific service, and long-term impact, such as STD or HIV incidence. Monitoring is a basic component of all programs to assess if resources are spent according to plan and whether the program is resulting in the expected outputs. Limiting the number of indicators is essential, as often too much information is collected and reported but not used for management or evaluation.

HIV or STD Surveillance can be considered as a form of monitoring, often targeted toward specific populations but it is mostly not directly linked to specific programs (see Chapter 97). Surveillance can be defined as the ongoing or periodic tracking of infection, disease, or risk behavior using the same data collection system over time. In case of HIV, surveillance systems typically track impact in terms of HIV and sometimes STD prevalence and outcomes in terms of sexual risk behavior.

Evaluation is defined as a rigorous, science-based collection of information about program activities, characteristics, and outcomes that determine the merit or worth of a specific program. Evaluation is also performed to understand enabling factors that may have an influence on the effectiveness of a program. Evaluation is an episodic assessment of the change in the specified results that can be attributed to the program. Evaluation studies are used to improve programs and inform decisions about future resource allocations.¹⁻³ This may include economic evaluation, including cost-effectiveness analysis.

Monitoring and evaluation systems often have to address partly competing demands. These include program improvement, management-related decision making, and accountability. The latter has become increasingly dominant,

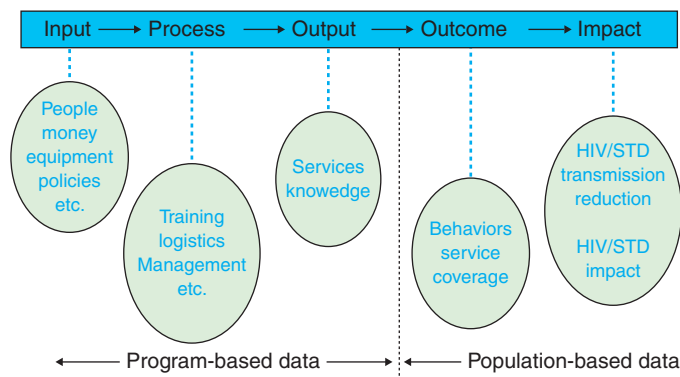


FIGURE 98-1. A framework for monitoring and evaluation.

with international donors and global health initiatives such as the Global Fund to Fight AIDS, TB, and Malaria, linking disbursements of resources to demonstrable results (performance-based funding).

Monitoring and evaluation are intertwined and many publications refer to *comprehensive* monitoring and evaluation systems.¹⁻⁴ Such a system is essential to make optimal use of limited resources and integrate lessons learned with the response required for scaling up HIV/AIDS or STD programs to achieve national level impact. At the national level, a good M&E system includes an established monitoring and evaluation unit as part of the National AIDS /STD program, clear program goals and objectives, a well defined set of indicators to track progress, a plan for data collection, and analysis and dissemination of results at all relevant levels (subnational, national, and global).¹ Given the diversity of factors influencing the spread of HIV and consequently a multifaceted response, program activities and related monitoring and evaluation systems must go beyond the reach of the Health Sector (e.g., education and labor).

During program planning stages data are collected to conduct a situation analysis. This is also referred to as *formative evaluation*, which explores the need for interventions, provides the information necessary to define realistic goals and objectives for the program interventions, and helps program planners make decisions about selection of effective, feasible intervention strategies. Formative evaluations use a mix of quantitative and qualitative research methods that can rapidly provide relevant information to program planners. Because of the nonstandardized manner in which formative evaluations are conducted, they generally do not provide good baselines for future impact evaluation.

Operations research is a special type of evaluation that investigates the operational issues in scaling-up programs and interventions. It typically addresses questions of how best to implement programs designed and evaluated in small-scale projects or under certain conditions and places. It is also used to identify bottlenecks in the implementation as programs go to scale. The main goal of operations research is

to provide program managers and policy makers with the required information to develop, improve, or scale-up programs. It can be considered a practical systematic process for identifying and solving program-related problems.

INDICATORS AND TARGETS

A wide array of indicators has been proposed for monitoring HIV/AIDS and STD related program components and results.^{1, 5, 6} Many international guidelines and lists of indicators aim to assist programs in developing a core set of indicators that are comparable between countries and programs. These indicators are used to monitor program context (such as the development of appropriate policies or guidelines) and effort, knowledge, attitudes and risk behavior, the availability and quality of health and other services, and HIV/AIDS and STD prevalence. Several indicators have gained major prominence because they are part of the monitoring toward the United National General Assembly Special Session (UNGASS) Declaration of Commitment on HIV/AIDS or the Millennium Development Goals (MDGs).

At the highest level, the United Nations General Assembly has agreed on two concrete targets and impact indicators that are related to the MDG to “halt and begin to reverse the spread of HIV by 2015”: the reduction of HIV in young people and the reduction of infants with HIV (Table 98-1). The monitoring for the framework UNGASS Declaration of Commitment on HIV includes a core set of indicators measuring commitment and action at global and national level (resources, policy, and advocacy) and a series of indicators to track program efforts in prevention, treatment, care, and impact mitigation.⁷

Indicator selection should be guided by what one would like to know to manage or monitor a program. A number of guiding principles facilitate the selection of an appropriate set of indicators for M&E of AIDS and STD programs. First, the input-output-outcome-impact framework for monitoring and evaluation needs to be used when selecting indicators to make sure the different levels are covered as appropriate and the hierarchy of indicators is clear. Second, specific qualities of the indicators need to be considered such as the link with program goals, the indicator’s ability to measure change, the cost and feasibility of data collection and analysis, and comparability both with past indicators and between countries and populations. Ideally, indicators should be valid (measure the condition or event they purport to measure), reliable (produce the same result when used more than once under the same circumstances), specific (measure only the condition they purport to measure), sensitive (reflect changes in the state or event under observation), and feasible. Finally, the value of an indicator is greatly enhanced if a clear target can be set. A target that resonates with programs, supported by accurate baseline information and feasible monitoring strategies, can enhance the value of an indicator.

Table 98-1. Global Impact Targets for HIV Prevention of the United Nations

	By 2005	By 2010	By 2015
Millennium Development Goals UNGASS on HIV/AIDS			Halt and begin to reverse the spread of HIV
	25% reduction in HIV among young people <i>in the most affected countries</i>	25% reduction in HIV among young people <i>globally</i>	
	20% reduction of the proportion of infants infected with HIV	50% reduction of the proportion of infants infected with HIV	
Intervention coverage	90% of youth have information, education, services, and life-skills that enable them to reduce their vulnerability to HIV infection ^a	95% of youth have information, education service, and life-skills that enable them to reduce their vulnerability to HIV infection*	
Input	Annual spending on combating the epidemic in low- and middle-income countries to reach between U.S. \$7 billion and \$10 billion	80% of pregnant women in ANC receive VCT, ART, and breast-milk substitutes	

^aMeasured through comprehensive knowledge of HIV prevention.

Goals can be defined as general or broad objectives of initiatives or programs. Unlike specific objectives and targets, goals are not necessarily constrained by time or existing resources, nor are they necessarily attainable but are rather an ultimate desired state toward which actions and resources are directed. Examples include the “Health for All,” the “Education for All,” or the Global Polio Eradication initiative. Goals are often accompanied by specific targets and indicators, which are used as proxy measures to track progress against the ultimate goal. For example, the 8 Millennium development goals, which include three sets of health goals, also define quantitative targets within each goal with a clear process on how to monitor and evaluate progress.

Targets express a commitment to achieve specified outcomes in a defined period and should enable monitoring of progress toward the achievement of broader goals and objectives. Targets are instruments that can facilitate the achievement of a policy and can assist in defining priorities. They may be inspirational to facilitate achieving greater political commitment and resources but they should also be considered realistic and build on information about current rates of scale-up of services. Finally, they must be measurable so that reports on progress can be produced using intermediate targets or milestones. Targets are also critical in measuring performance of programs. While programs may achieve and

demonstrate progress (increasing coverage over time), it is only progress against agreed targets that ensures accountability and enables systems of performance based funding.⁸

International goals and targets are often an important influence on the response to HIV/AIDS at country levels. A detailed review of national strategic plans for HIV/AIDS 2005–2010 conducted by UNAIDS in 19 countries in sub-Saharan Africa and Asia showed that the majority of countries explicitly acknowledge and use the targets of the UNGASS Declaration of Commitment. As a consequence of the declaration, a number of countries added specific coverage targets, others adapted the targets taking into account their planning, implementation capacities, and the availability of financial resources.

However, there is an important concern related to the development of indicators in recent years: the proliferation of indicators without concomitant investment in data collection and analysis.⁹ International organizations have led the development of large and growing numbers of indicators to monitor international goals, enhance accountability, and improve country programs. M&E of HIV/AIDS programs started off with 10 priority prevention indicators in 1994 which grew to 57 indicators for national programs in 2000.¹ Since then, at least six separate publications each with dozens of indicators have been published to guide monitoring and evaluation in

specific components of HIV/AIDS programs, such as prevention for young people, care and support, or tuberculosis/HIV interventions. A major purpose of these large numbers of indicators is to help program implementers and policy makers specify what the intended achievements are. Data availability and quality are often a major constraint. And even if data are available, interpreting levels, trends, and differentials of statistics for such large numbers of indicators are beyond the capability of most programs.

There is a fundamental imbalance between investments in indicator development and measurement strategy. Most international initiatives and programs do not have an explicit data collection and analysis investment strategy and are limited to defining data sources for individual indicators. This tends to lead to quick fixes in data collection, poor data quality, and a systematic lack of investment into a comprehensive health information system that can provide regular quality data over time.²

■ MEASUREMENT ISSUES

The ability to produce reliable and valid statistics for an indicator determines the utility of the indicator. If no means of accurate measurement or estimation are available, the primary goal of the indicator to track trends for management, resource allocation, or evaluation purposes is not met. There are three major questions that need to be answered for each indicator as follows:

- Is there a good measurement instrument such as a biological test, well-established interview questions etc.?
- Is there a good vehicle for implementation of the measurement instrument, such as a population-based sample survey or surveillance system?
- Are there valid methods to adjust for known and unknown biases to obtain estimates using established models and imputation procedures?

Table 98-2 summarizes the main instruments, data collection methods, and estimation methods for measurement of indicators related to exposure to interventions or coverage (program output), behavioral outcomes, and biological outcomes (impact).

BIOLOGICAL OUTCOMES: HIV TRANSMISSION

■ INSTRUMENTS

The ability to say whether well-implemented HIV/AIDS and STD programs are making a difference in terms of health improvement depends on how well health outcomes can be measured. Compared with many other diseases such as tuberculosis or malaria, HIV/AIDS has the advantage of the availability of a simple low-cost biological test to ascertain the level of HIV transmission at the population level. An HIV

antibody test measures prevalence of HIV infection. HIV antigen tests are available, though more difficult, more costly to apply, and less sensitive and specific than antibody tests. Standardized testing protocols have been developed for HIV testing, both for surveillance and diagnostic purposes.¹⁰ HIV prevalence is not an adequate measure to track short-term changes in HIV transmission. Tests establishing a recent HIV infection (HIV incidence) using a single blood sample are still under development but appear to work well for an increasing number of HIV subtypes.^{11,12} For instance, trends in HIV-1 seroincidence among different sentinel surveillance groups were assessed using a newly developed IgG capture BED-enzyme immunoassay (BED-CEIA) in Cambodia¹³ and Atlanta, Georgia.¹⁴ However, other studies have found that the BED-based method grossly overestimates the true incidence rate.^{15,16} Further validation studies are needed before widescale application is justified.

■ DATA COLLECTION

The main vehicles used to obtain population-based information on HIV incidence and prevalence trends in countries are HIV surveillance systems (see Chapter 97). The recommended selection of surveillance populations depends on the type of epidemic. In generalized epidemics, defined as epidemics with at least 1% infection rates in the adult population,^{17,18} surveillance systems have focused on pregnant women attending a selected number of (sentinel) antenatal clinics. HIV prevalence trends among such women have been available for many countries since the late eighties and form the basis for long-term trend analysis. For instance, in 2004, long-term trends could be ascertained for 75 predominantly urban antenatal clinics in sub-Saharan Africa.¹⁹ In concentrated epidemics, where HIV has not spread into the general population but prevalence is at least 5% in at least one risk population such as sex workers, injecting drug users, or men who have sex with men, the primary focus of the surveillance system is on tracking trends in selected at-risk populations, supplemented by antenatal clinic-based surveillance.¹⁷ In low level epidemics, where prevalence is below 5% in all risk populations, a focus on risk population only should be maintained.

Trends in the HIV incidence rate are preferable to pick up recent changes in HIV transmission and therefore the preferred monitoring and evaluation indicator. HIV incidence rate monitoring has not been used on a large scale in most countries but is a major outcome used in longitudinal research studies where multiple blood samples are collected from the same person. For M&E purposes, however, the lack of a well-established test that can be used on a single blood sample and the large sample sizes required to detect changes in HIV incidence rates have hitherto been obstacles to widespread use.

Table 98-2. Measurement Issues for Output, Outcome, and Impact Indicators: Availability of Measurement Instruments, Data Collection Strategies, and Estimation Methods

	Instrument	Data Collection	Estimation
Impact: HIV transmission	HIV antibody test Test for new infection from single sample HIV antigen test	Surveillance among high- and low-risk populations General or risk population sample surveys	Standardized software to obtain population-based estimates from sentinel or risk population surveillance data; uncertainty ranges
Impact: STD transmission	Diagnostic test for current infection Diagnostic test for past exposure Clinical diagnosis	Surveillance among high- and low-risk populations, including STD clinic attendees General or risk population sample surveys	None
Impact: Survival and functioning among HIV-infected persons	Age and sex patterns and trends in mortality; verbal autopsy; individual survival data among those on treatment; AIDS case reporting CD4 cell count HIV viral load Questions on functioning and quality of life	Vital registration systems with cause of death Population based surveys and longitudinal studies Survival on treatment studies based on clinic data and follow-up if defaulting	Model life tables to detect impact HIV/AIDS on age and sex patterns of mortality No models for cause of death patterns with HIV/AIDS Cohort analyses
Outcome: sexual behavioral trends	Interview questions—(self-reported risk behavior)	General or risk population sample surveys	None, in-depth interviews held to assess bias but no methods to adjust
Output: coverage preventive interventions and treatment	Service delivery record keeping; Interview questions	Accurate and complete reporting by service delivery points General or risk population sample surveys Surveys used for STD treatment utilization; not useful for ARV therapy	Coverage computed by using denominator estimate None

HIV prevalence rate among young people (15–24 years) has been selected as the key proxy indicator to monitor trends in HIV incidence rate in the absence of direct data on the new infection rate. This is because the time of exposure to HIV in young people is limited and therefore closer to incidence than in older age groups with a much longer duration of sexual activity. In addition, recent HIV infection in young people is not so strongly associated with increased mortality as infections acquired in the more distant past.²⁰ The fertility-decreasing effects of HIV will also be less important at those young ages, and this is especially relevant in the context of antenatal clinic-based surveillance in low contraceptive use countries.^{21,22}

Ideally, population-based samples of young people 15–24 years provide estimates of the HIV prevalence rates among young men and women, but almost no country had conducted multiple surveys by 2007. Therefore, the major source of trend information in countries with high fertility and generalized epidemics, however, are pregnant women attending antenatal clinics. Most pregnant women under 20 years will have started sexual activity recently, and as such, prevalence in this age group should be a sensitive measure of HIV incidence. Despite the higher sensitivity of younger age groups in reflecting recent HIV infections, the 15–24-year-old age category may be more appropriate to obtain a robust

estimate of prevalence trends. HIV prevalence among sexually active people is determined by the length of exposure to sexual activity and the risk of HIV transmission, which is related to the HIV prevalence in the general population and to the level of sexual mixing between high-risk groups and the general population and between age groups. The composition of the group of pregnant women aged 15–19 years is strongly affected by changes in age at sexual debut, and prevalence in this group may not adequately reflect trends in prevalence in adolescents in the population at large.²³ In general, the later the age at sexual debut, the more atypical are young pregnant women and, therefore, the greater the degree of overestimation in ante-natal (ANC) estimates in the youngest age groups. In addition, where contraceptive use is low, HIV prevalence from ANC surveillance in the youngest age groups overestimates prevalence in the general population due to selection bias for sexual activity. In high contraceptive use populations, where young women take more effective measures to prevent both pregnancy and HIV infection, HIV prevalence in pregnant women of young age will overrepresent women with higher risks for HIV-infection and this overrepresentation would persist in older age groups.²⁴ Furthermore, sufficiently large sample sizes required to obtain robust age-specific prevalence estimates are not often available for these younger age groups. [Figure 98-2](#) presents an example of trends in HIV prevalence observed among young pregnant women attending sentinel antenatal clinics in selected African countries.

Few sentinel systems in developing countries provide any data on HIV prevalence in men but such data are sometimes provided by surveillance among STD clinic attendees. HIV prevalence measured among STD patients overestimates prevalence in the general population because such patients obviously represent a high-risk group. Trends of HIV prevalence in this population may be biased due to changes in treatment seeking for STD or changes in epidemiology of STD. The magnitude of such bias is likely to differ in men and women. Patterns of

health-seeking behavior and differentials in characteristics related to HIV transmission between sentinel STD clinic users and those opting for other alternatives (e.g., private clinics, pharmacies, self-treatment) may influence the estimated indicators. Among young people, especially young women, a further limitation related to the use of data from STD clinics is due to lack of access to or use of STD services by adolescents, which may also introduce bias into estimates of HIV prevalence.

Population-based household surveys with HIV testing can provide a more representative picture of the levels and trends in HIV prevalence in the general population than surveillance systems. Since 2001, a large number of countries have conducted such surveys, which are only useful for populations with generalized epidemics, as high-risk populations are generally seriously underrepresented in surveys. Such surveys are particularly useful because they can provide information on men and nonpregnant women and on the socioeconomic determinants of HIV infection. They can also provide a detailed geographic snapshot of the spread of HIV within a country provided sample sizes are adequate. The main challenges are nonresponse rate, especially among men in urban areas, which may be due to refusal or absence during the survey. In eight national, population-based surveys supported by the Demographic and Health Surveys (DHS) during 2001–2004, nonresponse rates varied from less than 10% in women in Cameroon and Burkina Faso to nearly 30% in urban men in Kenya. However, an evaluation of the effect of the response bias on estimates of HIV prevalence showed that the impact was relatively limited.²⁵ Only by maintaining very high quality standards for study design, data collection and laboratory testing, can surveys produce reliable results. Considerations of costs and nonresponse may lead to a data collection strategy whereby population surveys are used every 5 years or so to calibrate the annual results of HIV sentinel surveillance among antenatal clinic attendees.

ESTIMATION METHODS

Generating valid and reliable estimates for HIV prevalence and incidence rates is also important to M&E efforts. UNAIDS, WHO and partners have developed standard methods of estimation including a software package that can be used by countries or at the subnational level. For generalized epidemics, Epidemic Projection Package (EPP) uses antenatal clinic-based HIV prevalence data to draw an epidemic curve using a four parameter epidemiological model.²⁶ For concentrated and low-level epidemics EPP is replaced by a workbook approach, which uses data on the size of the risk populations, the HIV prevalence among risk populations, and the contact rate between the risk and general populations to obtain an estimate of the level of the epidemic.²⁷ The results of either the EPP analysis or workbook approach are fed into a second software package, Spectrum, to obtain a series of

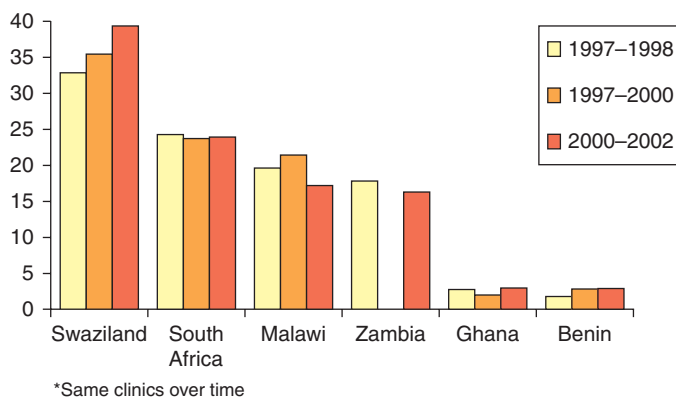


FIGURE 98-2. Median HIV prevalence (%) among women 15–24 years old attending antenatal clinics,* selected African sites, 1997–2002.

epidemiological and demographic statistics.²⁸ Uncertainty in the estimates of HIV/AIDS prevalence, incidence, and mortality are also presented by UNAIDS and WHO.²⁹ These plausibility bounds not only take into account the uncertainty associated with sampling error but also use expert opinion on other aspects of uncertainty such as the phase of the epidemic and the quality and coverage of the sentinel surveillance system that provides the underlying data.

In the context of M&E it is useful to keep in mind that the use of modeling to fill data gaps needs to be done with caution. In general, health statistics can be divided into three types: crude, corrected, and predicted.³⁰ Crude statistics are simply reported data without any adjustment or correction and are generally of little use to M&E. Corrected health statistics are measurements of indicators where analytical methods and techniques are used to correct for known biases such as nonrepresentativeness or misclassification bias. Corrected statistics also include measurements where the primary data collected are on an indirect consequence of the phenomenon under study. An example is estimating HIV prevalence among the adult population from data on antenatal clinics and assumptions about the association between levels and trends among antenatal clinic attendees and the general adult population. Predicted statistics are based on projections in time or from one population to another. For forward-looking decision making, when corrected statistics are not available, predicted statistics can play an important role. For monitoring progress toward agreed upon targets and evaluating what works and what does not, however, predicted statistics should not be used.

BIOLOGICAL OUTCOMES: STD TRANSMISSION

■ INSTRUMENTS

Diagnostic tests for many STDs are available but only some are useful for monitoring and evaluation. A combination of serological tests for syphilis can distinguish between recent, active, and past or cured infection. A positive Rapid Plasma Reagin (RPR) or VDRL test, confirmed by a positive nontreponemal test, indicates recent infection. The Treponema Pallidum Hemagglutination (TPHA) or similar test is positive if there is a history of syphilis (or other treponemal infection). A positive TPHA with negative RPR suggests past but cured infection. Serologic tests are available for herpes simplex virus-type 2 (HSV-2) as are multiple polymerase chain reaction (PCR) assays for genital ulcers, including syphilis, HSV-2, and chancroid. Urine tests using PCR or ligase chain reaction (LCR) are used to detect genital infection with *Neisseria gonorrhoeae* and *Chlamydia trachomatis*. Cervical specimens can also be tested using PCR assays for *C. trachomatis*, *N. gonorrhoeae*; human papilloma virus (HPV) and *Trichomonas vaginalis*. Some population-based surveys have used these tests but costs, laboratory, and

logistical demands have hampered widescale application.³¹ *T. vaginalis* infection in women can also be detected from a vaginal swab using a wet mount examination or a simplified culture method, the In-Pouch TV culture system. The latter has been used in some population surveys.³²

In addition, clinical diagnosis of STD and self-reported diagnosis of STD through survey questions are used to measure the incidence or prevalence of STDs. The clinical diagnosis can be made with or without supporting laboratory testing, which may include microscopic examinations and cultures. The syndromic approach bases the clinical diagnosis on a systematic set of questions and physical examination findings³³ to identify genital ulcer syndromes and genital discharge syndromes. Individual interviews in household surveys have used questions on specific diseases (e.g., “Did you ever have syphilis in the last year?”) or syndromic questions (e.g., “Did you have a genital ulcer in the last year?”). Neither approach has been particularly successful.

The use of clinical data to monitor trends in STDs, particularly discharge syndromes in women, has a further limitation, asymptomatic infection. Studies have shown that among women seeking reproductive health services, more than half of those with gonorrhea and at least 70% of those with chlamydial infection exhibited neither symptoms nor signs of infection.^{34,35} Population-based studies of men also documented that significant proportions of those with gonorrhea or chlamydia reported no symptoms.³⁶

■ DATA COLLECTION

In most countries, routine STD case reporting by health facilities is required by national law or regulations (such as a law on communicable diseases). However, in the majority of countries, especially in those with limited resources, STD reporting is of poor quality. Underreporting and misclassification are common problems and the clinic population is not representative of the general population due to self-medication and private sector attendance. Private providers are often particularly delinquent in reporting STD diagnoses. The denominator is frequently unknown, and extrapolation from the clinic reports to estimates of the magnitude of the STD problem or trends over time at country or regional levels is difficult. Very few countries have established an STD sentinel surveillance system in which special efforts are made to obtain accurate trends from a selected set of STD service delivery points.

Alternative sources of STD surveillance data are populations that seek health care or visit potential sentinel sites for reasons unrelated to STDs or other specific diseases. As for HIV surveillance, one important group that is accessible and representative of the general population is women attending antenatal clinics. In most countries, testing of antenatal clinic attendees is limited to RPR for active syphilis detection and treatment. Such data, however, have provided information on

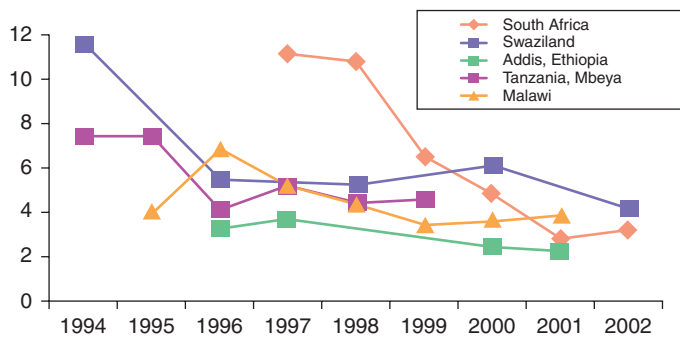


FIGURE 98-3. Syphilis seroprevalence (%) among women attending antenatal clinics at selected African sites.

trends in active syphilis (Fig. 98-3). Other possible sentinel populations include blood donors or military recruits.

In addition to disease surveillance from data collected during routine health-care delivery, special surveys can also be conducted to assess the scope and the specific types of STD burden in communities. Such studies are conducted during defined time periods and may be repeated if appropriate. Surveys of random samples of the population that include STD testing are increasingly feasible with the availability of urine-based tests and self-administered swabs.

Surveys can also be performed to measure prevalence and incidence in high-risk populations such as sex workers or truck drivers. These populations are usually not seen in general health-care facilities and STD surveillance in these groups usually requires development of specific outreach activities or special services. In addition, special clinics for risk populations may provide data for monitoring and evaluation.

In areas where etiologic diagnosis of STDs is difficult due to limited resources, only special studies can determine the common pathogens causing the syndromes and their antimicrobial sensitivity.

ESTIMATION METHODS

While there has been some investment in modeling the spread of specific STDs^{37,38,39} and the role of STDs in HIV transmission,^{40,41} there is very little available to countries to estimate levels and trends of STDs in the general and specific populations from the incomplete data collected for monitoring and evaluation purposes.

BIOLOGICAL OUTCOMES: SURVIVAL AND TREATMENT RESPONSES

INSTRUMENTS

In the context of M&E of HIV/AIDS programs, measurement of mortality has two aspects. The first is to measure the impact of antiretroviral or other treatment on survival among those who are or have been on treatment. This

requires a good system of clinical records and a follow-up system outside of health services in case the death does not occur in the health facility or if the patient drops out of the treatment cohort before dying.

The second aspect relates to measurement of trends in mortality due to HIV/AIDS in the general population, irrespective of whether treatment was provided. The measurement instruments are those that are used for population mortality measurement in general. These are based on active reporting systems (vital registration system) or questions about deaths in the household or among relatives (household survey or census). The gold standard for determining the cause of death is autopsy. If the cause of death is not available through medical certification (using clinical information, with or without autopsy), as is the case in most developing countries, an interview with the relatives of the deceased is used to ascertain a probable cause of death (verbal autopsy). Among adults, validation of verbal autopsy studies have shown moderately high sensitivity and specificity of the algorithms for the diagnoses of AIDS and TB.⁴²⁻⁴⁴

The diagnosis of AIDS is based on the AIDS clinical case definition. Several definitions have been used based on a mix of clinical and laboratory criteria.⁴⁵ To obtain reliable trend data, consistency in the use of definitions and classification criteria is essential. CD4 T-lymphocyte cell counts are a good indicator of progression of infection to disease and may be used for monitoring purposes at the population level.

In addition, various measures of quality of life can be used. The simplest is a question on working status of the person on treatment. More elaborate measures include indices based on a set of questions related to the quality of life, e.g., standardized activities of daily living (ADL), self-reported health status in a series of domains such as mobility, cognition, and mental health. At the population level summary measures that combine mortality (years of life lost) with disability (loss of health years of life due to disability or nonfatal conditions) could be used to estimate the burden of disease due to HIV/AIDS (e.g., disability-adjusted life years (DALYs)).⁴⁶

DATA COLLECTION

Monitoring the scaling-up of HIV therapy including antiretroviral treatment (ART) requires clinical records (with a home follow-up component, if needed, to maximize follow-up rates) that are able to provide individual level data for survival analysis. Because ART programs are still young and developing, many resource-constrained countries lack such data except for those collected in special studies.

Population mortality data are only available from countries with vital registration systems with high levels of coverage that are usually accompanied with high levels of medical certification of the cause of death. In countries without such a system, sample vital registration systems (e.g., India) or

demographic surveillance systems in local populations (e.g., Tanzania) may provide cause of death data, mainly through verbal autopsy. Special studies have also been conducted and may be institutionalized in the context of M&E. An example is mortuary investigation that allows HIV testing of corpses.⁴⁷

Morbidity surveillance relies primarily on AIDS case reporting but severe underreporting limits the usefulness of these data in many developing countries. ART programs may improve this situation, especially if clinical and surveillance definitions are fully aligned.

■ ESTIMATION METHODS

The HIV/AIDS mortality levels and trends can be estimated from models that are based on HIV prevalence estimates through the use of standardized software.²⁶ The estimates of the incidence of AIDS cases are obtained from the same application. Survival rates of people who initiated treatment are generally computed using standard life table approaches (such as Kaplan-Meier survival analysis) to allow for left and right censoring.

BEHAVIORAL OUTCOMES

■ INSTRUMENTS

Sexual behavior data are an essential complement to biological evidence of changes in HIV or STD prevalence or incidence. Data on sexual behavior are generally self-reported and subject to multiple reporting biases. The validity and reliability of behavioral self-reports may not be high, as is also true for other sensitive topics such as substance abuse.⁴⁸ Individual interviews provide limited information on factors affecting the efficiency of transmission, particularly if the interviews between sexual partners are not linked and if the HIV status of the respondents is unknown. Self-reported condom use data are relatively easy to obtain in sexual behavior surveys, but, even if reporting is reasonably accurate, the ultimate impact of condom use on transmission efficiency is difficult to gauge without information on whether condoms are used during acts where sexual contact is between infected and susceptible persons.

Long questionnaires requesting specific details on most recent partnerships seem to lead to the reporting or registration of less sexual-risk behavior compared to much shorter instruments. For example, the four-city study that used the UNAIDS model questionnaire resulted in less disclosure of nonregular partners than the basic Demographic and Health Surveys (DHS) module on sexual behavior.⁴⁹ On the other hand, a detailed study in a community cohort study in Tanzania found good consistence between short and in-depth questionnaires on the last five partners within the last year.⁵⁰

■ DATA COLLECTION

Structured face-to-face interviews are the dominant mode of data collection. Comparison of results from household surveys in low- and middle-income countries have indicated that reporting of sexual-risk behavior appears to be highly sensitive to survey designs.⁴⁸ Therefore, tracking of trends must be done by high quality surveys in which the methods of survey design and data collection are highly standardized and repeatable over time.

The ability of surveys to document trends can be illustrated with two examples from the USA and Zambia. Data from six surveys in the United States since the 1970s allow an assessment of trends in sexual behavior among adolescents.⁵¹ Comparing measures over time was complicated because of differences in mode of administration of the questions, sample populations, definitions used, and survey implementation. The general picture, however, is consistent and shows some modest changes in sexual activity and an increase in condom use during the eighties and nineties.

In Zambia, which has a generalized AIDS epidemic, five national household surveys with questions on sexual behavior were conducted between 1996 and 2003.⁵² These included two major types of survey design, two general Demographic and Health Surveys, and three Sexual Behavior Surveys, with similar kinds of questions on sexual behavior. Different survey methods produced significantly different estimates of sexual behavior, although some consistency in trends emerged. There is also evidence of changing reporting bias over time with respondents less likely to report a young age at sex in later surveys.

Several methods can be used as an alternative to try to elicit higher quality information on sensitive topics such as non-marital sex.⁴⁸ These include qualitative methods to reduce the barriers to disclosure by gaining the trust of the respondents through unstructured, often repeated, interviews. Alternatively, it may be helpful to reduce or eliminate the interaction between data gatherer and respondent by using self-administered questionnaires, computer assisted interviews, and audio-computer-assisted interviews. In general, alternatives for face-to-face interviews yield higher and more plausible estimates of nonmarital sex but results are generally less favorable in low- and middle-income countries with lower levels of education and great linguistic variability.

The use of multiple methods of data collection, such as applying alternative methods to a subsample in a survey, may provide information to adjust for under- or misreporting in survey-based estimates. Moreover, biological validation, such as the detection of male semen in vaginal swabs, or the presence of an STD pathogen in genital secretions may provide additional information for validation purposes. Reporting biases are likely to be even greater among young people, especially young girls where sanctions against premarital sexual

behavior may be more severe. For instance, in a study of secondary school pupils in Zimbabwe only 13% of those infected with HIV and/or an STD admitted to having had sex.⁵³ In general, however, more work is required in this area to better understand the complex societal and individual factors creating biases in self-reported behaviors.

Estimation methods

No widely accepted estimation methods to correct for biases or fill data gaps are currently available.

OUTPUTS: INTERVENTION COVERAGE

■ INSTRUMENTS

Coverage can be defined as the proportion of people who receive a specific service among those who need it. It is a combination of service provision and health-seeking behavior by those who need the service. Coverage of the target population by intervention programs can be measured in different ways. The first is based on the number of people using the services from provider records. Such records provide counts of the number of events of interest, which is the numerator of the coverage estimate. Accurate data on the denominator may be harder to obtain depending on the type of coverage estimate. For instance, the need is best defined if it is recommended for a well-defined population group, e.g., an HPV vaccination program aiming to provide 3 doses to all women up to age 26 years. For treatment coverage it is often much harder to estimate the true need, e.g., the proportion of men with chlamydia infection who receive appropriate treatment.

The second method uses interview questions in household or risk population surveys. The respondents are asked questions about exposure to specific interventions. The reliability and validity of the results are affected by two factors. First, it is determined by the extent to which the intervention can be defined unambiguously and clearly in a brief question, the presence of factors that affect reporting by the respondent (e.g., stigma, cultural norms, intervention programs), and the quality of the interview and survey in general. Second, it also depends on how accurately need can be measured. For instance, estimates of coverage of condom use at last higher risk sex depend on how well the respondent reports on higher risk sex. Estimates of STD treatment coverage depend on the ability and willingness of the respondent to report a recent STD episode.

Ideally, data are collected on all steps from identification of the need to successful or effective treatment. For instance, for an STD infection this requires information on the prevalence of infection among the target population, the proportions who are symptomatic, recognize symptoms, seek care, receive care, quality of diagnostic and treatment care, and the efficacy of treatment. For prevention of mother-to-child HIV

transmission, information is needed about antenatal care attendance, exposure to counseling, HIV testing, feedback of results, treatment provision and use among HIV-infected women, and the efficacy of treatment.

■ DATA COLLECTION

Data on exposure to interventions and coverage are primarily collected through household or risk population surveys. Such data may include condom use at last sex with a high-risk partner, utilization of voluntary counseling and testing services, HPV vaccination, or exposure to specific radio programs.

Service records are also used, but detailed monitoring of completeness of reporting and evaluation of reporting patterns and frequencies over time are necessary.

■ ESTIMATION METHODS

The denominator is often estimated if service records are used but otherwise no standard methods are available to estimate coverage or exposure to interventions. The estimation of some denominators is relatively straightforward. For instance, the denominator of a coverage estimate for an HPV immunization program can be drawn from census data on the number of 9- to 26-year-old females in the population. Similarly, the denominator of a coverage estimate for prevention of mother-to-child transmission of HIV programs can be obtained directly from data on HIV prevalence among pregnant women and number of pregnant women or deliveries in a population, or indirectly from census projections of the population by age and sex. Others are more difficult, e.g., the denominator of a voluntary HIV testing and counseling indicator, as the number of persons and the number of times the same person needs to be tested are subject to discussion.

EVALUATION

Evaluation aims to assess whether and how programs are successful in bringing about the anticipated improvements in health in order to strengthen their effectiveness. This requires careful measurement of the exposure to interventions, non-intervention factors affecting the outcomes, and accurate measurement of behavioral and biological outcomes before any effects can be attributed to interventions. Furthermore, a specification is required of the pathways through which programs can affect behavioral and biological outcomes, which includes nonprogram factors, such as sociocultural and economic determinants, a hierarchical structure of determinants, and a specification of interactions between different levels of the framework. Evaluation or evaluation research, as it is sometimes referred to, should be distinguished from research conducted to prove the efficacy or effectiveness of a

specific intervention. For instance, randomized community trials have been conducted to examine the effectiveness of male circumcision as a way to reduce HIV incidence among men.^{54–56} The research results are leading to the incorporation of male circumcision into prevention programs. Evaluation studies are needed to assess the impact of such programs on HIV incidence.

■ FRAMEWORKS

A conceptual framework for the evaluation of programs or specific interventions presents a schematic simplification of the possible links and pathways between intervention and the outcome of interest. This section describes different elements of and approaches to the development of an evaluation framework.

■ EVALUATION AS AN INTEGRAL PART OF MONITORING SYSTEMS

Comprehensive program evaluation may focus on national or subnational levels. A major focus is on involvement of the program staff at all stages and program improvement is a primary goal. A utilization-focused evaluation approach is generally developed at the start of a program with strong involvement of program staff.^{57,58} Such an approach also includes an evaluation of actual use and learning of what factors enhanced or inhibited use. External accountability is only a secondary objective.

First, a basic program logic model is developed to describe characteristics of program implementation and to specify expected outcome and impact of the program. Program staff, with or without external involvement, should conduct process or implementation evaluations before conducting outcome evaluations and outcome evaluations before conducting impact evaluations.⁵⁸ Figure 98-4 shows an example of an evaluation framework used for HIV prevention programs in the USA. The process evaluation activities on the left of the framework provide information on where resources are spent, the quality of prevention programs, the implementation status, and the ability to reach the people for whom they are intended. The next set of evaluation activities involves outcome evaluations that tell whether the programs are making a difference in changing behavior. Impact evaluation activities provide information on whether overall prevention efforts are carried out on a large enough scale and with sufficient intensity and duration to make a difference in HIV transmission in a given population. Finally, policy and economic evaluations are conducted to provide information on the political and social effects and the relative costs and effectiveness of prevention.

The California HIV Prevention Indicators Synthesis Project is a good example of a comprehensive effort to

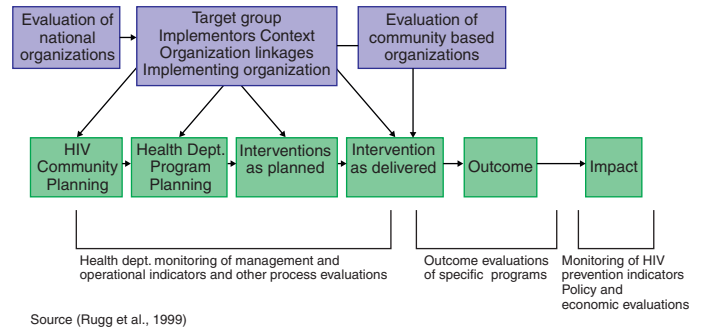


FIGURE 98-4. Evaluation framework for HIV prevention programs, USA. (From Rugg D, Buehler J, Renaud M, et al. Evaluating HIV prevention: a framework for national, state and local levels. *Am J Eval* 1999; 20: 35–56.)

monitor HIV prevention efforts and outcomes, with strong stakeholder participation.⁵⁹ The indicators are divided into six groups: policies, characteristics of prevention interventions, characteristics of populations, utilization of interventions, risk taking and protective behaviors, and disease impact. The grouping is along the lines of the conventional monitoring and evaluation framework (input–output–outcome–impact) with the addition of the epidemiological context (characteristics of population), including size and HIV prevalence of different risk populations. For many indicators, annual data are available and for others there is a need for special surveys. For every variable there is a need to carefully interpret the data and take into account known and unknown biases.

■ POPULATION AND INDIVIDUAL VARIABLES

The importance of both macro- and microlevel factors necessitates the use of more complex models and analyses to study the causes of infectious and chronic diseases. The comparative study of HIV and STD epidemiology across populations and evaluation of similar preventive programs and interventions in different settings have highlighted the importance of contextual factors in HIV and STD epidemiology and preventions.⁶⁰ Such factors not only affect the prevalence and incidence of HIV and STDs but also the effectiveness of interventions.

In STD and HIV research the importance of population-level factors in shaping the epidemics and risks among individuals further corroborates the need for comprehensive models that include population-level and individual-level factors that contribute to disease outcomes. Multilevel analysis has emerged as a powerful statistical tool that allows the inclusion of population and individual-level variables in the same model. It is important, however, to realize that in addition to multilevel statistical analyses, the more general issues of investigating the determinants of outcomes at multiple levels are necessary.⁶¹

Population impact

The population impact of an intervention can be estimated from three factors⁶²: efficacy of the proposed intervention, proportional contribution of the outcome of interest, and effective coverage of the intervention. These factors need to be taken into account when developing an evaluation framework. All three components face measurement challenges.

The efficacy of an intervention is generally derived from research studies. A randomized controlled trial (RCT) is the preferred method of establishing that an intervention is efficacious, but the body of RCT evidence for HIV and STD prevention is small at best. An extensive review of RCTs of individual-level, population-level, and multilevel interventions for preventing STDs, including HIV, identified 83 trials of which 41 met the inclusion criteria.⁶³ Interventions to prevent STDs can be classified according to level of intervention (individual, group, or community), modality of intervention (behavior change, treatment, vaccine, structural change, screening, microbicide, and surgical change), and outcome measured (acquisition in the uninfected individuals, transmission to susceptible individuals by infected individuals, and complications). Only one intervention showed efficacy against sexual transmission of HIV but 22 showed effectiveness against other STDs. In 2007, the results of three research studies in sub-Saharan Africa on the effect of male circumcision on HIV incidence in men could be added to that list.^{54–56}

To estimate the fraction of the total transmission or poor health that can be addressed by the intervention is difficult and can be highly variable between populations. Grassly et al.⁶⁴ show how the ultimate impact of an intervention in reducing sexual behavior risks is strongly affected by the socioeconomic setting and public health capacity. The epidemiological context determines whether such risk reduction translates into a measurable impact on the rate of HIV incidence. Four measures of the epidemiological context are the phase of the epidemic (characterized by HIV prevalence or incidence to prevalence ratios⁴¹), cofactor STD prevalence, mixing of target population with other at-risk populations, and sexual behavior of populations not targeted by the intervention. The epidemiological context is dynamic: three of their four measures can be changed by interventions, the fourth (HIV prevalence) affects the probability of exposure and will change as a result of changing incidence and mortality.

The interpretation of the discrepant results of three community-randomized trials of the impact of STI treatment on the prevention of HIV infection in Mwanza, Tanzania, and Rakai and Masaka, Uganda provides an illustration.^{40, 41} A synthesis of the evidence indicates that epidemiological differences between the populations were the most important explanation for the low trial impact in the Ugandan studies compared to the large impact in Tanzania. Simulation modeling of HIV and STI transmission showed that the considerably

lower prevalence of curable STI due to lower risk sexual behavior and the mature HIV epidemics, with most HIV transmission occurring outside core groups with high STI rates, in the two Ugandan studies were the key factors in the differential impact.

Finally, coverage of interventions or programs has several dimensions, including need for treatment, quality of care and treatment, and user adherence. Effective coverage has been defined as the probability that individuals will receive health gain from an intervention if they need it.⁶⁵ This definition requires distinguishing between perceived and true need, which may be affected by socioeconomic, cultural, and personal factors (including treatment expectations). Biological factors such as type of STD may also play a role. Effective coverage also captures quality of the intervention and adherence to treatment.

■ AN EPI–DEMOGRAPHIC FRAMEWORK

The proximate determinants model presents a conceptual framework for the study of the distribution and determinants of HIV infection in populations by combining demographic and epidemiological approaches that have been used extensively in fertility and child survival research⁶⁶ (Fig. 98-5). The framework links the social system, which includes the programs and interventions, to the biological system, including the health outcomes, through a set of variables called proximate determinants, which can be influenced by changes in contextual variables or interventions. These proximate determinants affect health outcomes through a set of biological mechanisms which are the components that determine the reproductive rate of infection, defined as the average number of secondary cases that arise from any new case of infection.⁶⁷ Models of transmission suggest that this reproductive number is determined by the product of three biological factors: the rate of contact between susceptible and infectious persons, the efficiency of

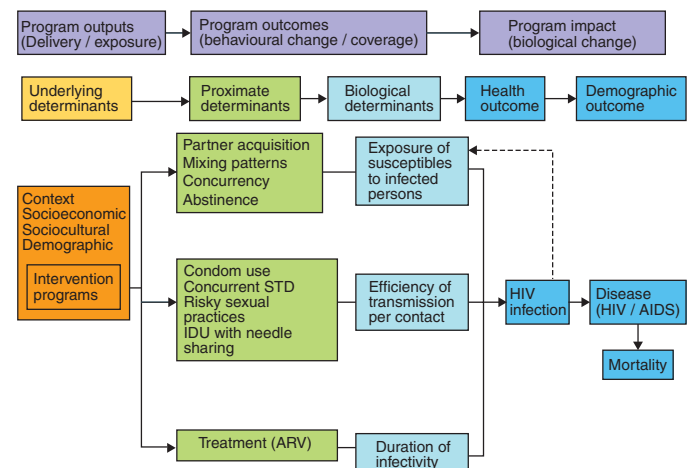


FIGURE 98-5. Proximate determinants framework showing the links between interventions programs and biological outcomes in HIV.

transmission during exposure between susceptible and infectious partners, and the duration of infectiousness.

The underlying social, economic, and environmental determinants must operate through proximate determinants to affect the biological outcome. The distinction between underlying and proximate determinants is important for the conceptualization of pathways through which underlying determinants, including interventions, may affect infection.

Even though the conceptual framework is primarily designed for the study of the distribution and determinants of disease, it can be used for intervention research since programs will have to influence one or more proximate determinants to affect HIV and STD transmission. The framework makes the pathways more transparent by which the components of a prevention program can be effective by targeting proximate determinants and underscores the limited utility of program outcomes such as increased knowledge of transmission if there is not an accompanying change in any of the proximate determinants. For example, an AIDS prevention program (an underlying determinant) may aim to increase knowledge of the modes of HIV transmission (another underlying determinant), delay sexual initiation (a proximate determinant of exposure to HIV), and increase condom use and early detection and treatment of STDs (two proximate determinants of the efficiency of transmission).

The proximate determinants schema described in [Fig. 98-5](#) is deliberately simple and is meant to outline a process moving conceptually from underlying determinants on the left to mortality on the right. The schema does not attempt to show the complex interactions that may occur between the underlying, proximate, and biologic determinants, nor include feedback mechanisms that link outcomes on the right with determinants on the left. However, one critical feedback mechanism, HIV prevalence, is included in the schema due to its importance in estimating the probability of exposure of susceptible to infected persons.

STUDY DESIGNS

There are a number of criteria that need to be taken into account when choosing a study design for evaluation purposes.⁶⁸ The single most important criterion in assessing a method is the validity of its estimates of program impact. Other criteria include required assumptions for the method, ability to isolate program effects, costs, data requirements, and ethical considerations.

Three types of scientific inferences can be distinguished for making health policy decisions.⁶⁹ Probability statements are based strictly on RCT results. While RCTs are the gold standard for clinical decision-making purposes, they are often not sufficient by themselves for public health evaluations. Causal chains in public health are complex and require further analyses for adequacy and plausibility.⁷⁰ Plausibility

statements are derived from evaluations that aim to make causal statements using observation designs with a comparison group. Adequacy statements result from demonstrations that trends in process indicators, impact indicators or both show substantial progress, suggesting that the intervention is having an important effect.

Interventions are usually multiple, their pathways to impact are complex and subject to effect modification; the intervention outcome association varies according to the presence of external factors. This may be behavioral or biological effect modification that affects the external validity of the evidence from the trials. Therefore, an intervention that works well in a given setting may be ineffective elsewhere. Evidence-based public health must rely on a variety of types of evidence.

The main challenges for evaluation of the effectiveness of programs are to carefully document trends in health outcomes and to assess whether such changes can be attributed to the programs. To be able to attribute changes to programs, evaluations need to reduce the noise introduced by nonprogram related factors as much as possible.

RANDOMIZED EXPERIMENTS

Randomized experiments are a key instrument for research on the efficacy of interventions. Evaluation research generally does not use this type of study design, as it requires major investments and is often directed toward a single intervention. Evaluation, however, may make use of methods that aim to come close to the gold standard for measuring what has happened as a result of an intervention and provides the strongest evidence of effectiveness or impact. In a randomized experiment, study subjects or groups are assigned to “treatment” and control or comparison groups randomly. Given a sufficiently large sample size, randomization enhances the chances of isolating the effects of a program or intervention by distributing confounding factors other than the exposure to the intervention equally across groups. The intention-to-treat analysis is an adaptation that allows the inclusion of all randomized individuals in the groups to which they were randomly assigned, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. Such analyses, therefore, provide an assessment that takes into account issues such as noncompliance.

STD and HIV prevention programs are suited to be evaluated using community randomized control trials. The unit of randomization in such trials is the community. This design can be used to estimate the indirect or total effects of an intervention, i.e., the effects on the treatment or vaccine but might have been indirectly protected because the intervention reduced STD or HIV prevalence in the community. An application of such a trial in Mwanza, Tanzania to assess the effect of STD case management on HIV incidence used

six pairs of intervention comparison communities in three geographic strata (roadside, rural, and island communities).⁷¹

Despite being the gold standard, randomized experiments have been used less than is desirable on scientific grounds in public health, including the field of HIV and STD.⁶⁸ First, trials are costly and time-consuming. The need to measure HIV or STD incidence rates implies the need for large sample size. Changes in the HIV or STD incidence rates can only be expected after the program efforts have matured in a community setting and the measurement of medium and long-term health impact takes time. Second, political and ethical issues are often raised because of concerns about withholding a (potentially) desirable program from some parts of the population and may lead to opposition to the trial. Third, the generalizability of the findings of a trial, conducted in one or two localized areas may be challenged. Finally, randomized experiments are subject to several potentially serious threats to validity including contamination of the comparison group if exposed to the intervention, confounding external influences, and variations in treatment (the intervention or program). Randomized experiments, however, tend to be less vulnerable to such biases than all other evaluation designs.

■ QUASI-EXPERIMENTAL STUDIES

The term “quasi-experiment” refers to a group of experimental research designs in which study subjects or groups are not randomly assigned. Therefore, these studies are easier to conduct than experimental designs but are more vulnerable to threats to validity. The most commonly used quasi-experimental designs, referred to as “constructed control designs,” involve the comparison of intervention and control groups that have not been randomly selected.⁷² In other designs, referred to as “reflexive control designs,” treatment group subjects or groups serve as their own controls and time series methods are used to measure net program impact. In a time series design, the effects of treatment or program interventions are inferred by comparing measures taken at many points in time before and after treatment or intervention. In a matched design, the response of the experimental group is compared to that of a “control” group before and after the intervention.

■ OTHER METHODS

A third approach consists of nonexperimental or observational study designs that have no experimental or control groups, per se. The treatments or interventions vary between populations and areas as a result of decision-making processes that are not controlled by the evaluation. Also, the criteria used to target programs or allocate resources may not be known to the evaluation researchers.

Observational studies may include cohort studies with concurrent controls, cohort studies with historical controls, and case-control studies. Cross-sectional surveys with no control groups may be repeated surveys in target populations and pre-post intervention surveys. The repeat studies may have a panel design in which data are collected from the same communities or facilities at least twice at different points in time.

In some cases, a placement bias may further complicate evaluation. The interventions and programs are focused on populations and areas where the problems are thought to be greatest or most amenable to program success. This effect, also referred to as endogeneity, has implications for the analysis, which must use multiequation random effects or fixed effects panel models.

Multilevel regression analytical methods are a useful tool that allows simultaneous investigation of how population-level (or group-level) and individual-level factors contribute to health outcomes.⁶¹ These methods are of particular importance for STD and HIV, where population-level factors play an important role in shaping the epidemics and risk of disease among individuals. However, they have implications for study design. Cross-sectional surveys need to be complemented by group or community-level data.

An example of a broad-based evaluation of a national program, using a wide variety of data sources is the Thailand HIV/AIDS success story which is listed among 17 major achievements in public health programs in the developing world.⁷³ It is one of the few well-documented national program success stories.⁷⁴ The national “100% condom program,” required all sex workers in brothels to use condoms with clients. Health officials provided boxes of condoms free of charge and local police held meetings with brothel owners and sex workers. Improved STD treatment, including the opening of 508 district STD clinics and STD contact tracing into brothels was also part of the program. Multiple data sources provided the basis for the evaluation. Surveys with sex workers and young men conducted by the epidemiology division of the Ministry of Public Health were the core source of data on trends for key indicators. The use of condoms in brothels increased from 14% in 1989 to 90% by mid-1992. There were also declines in the self-reported rate of new partner acquisition. HIV prevalence in sentinel surveillance populations and the clinic-based incidence of STDs fell dramatically. Prospective cohort studies in several parts of the country confirmed the suspected decline in HIV incidence.

Multicountry studies are another way to enhance the power of evaluation studies. For instance, by using a similar design in several countries and interpreting the results from several countries in an integrated manner, the evaluation of the Integrated Management of Childhood Illnesses was able to draw convincing conclusions about the effectiveness of the program.⁶⁹

CONCLUSIONS

Sound monitoring and evaluation have become a priority component of HIV/AIDS/STD prevention and control programs to improve programs, management-related decision making, and accountability. Particularly in low- and middle-income countries, international initiatives such as the UN Declaration of Commitment; the Global Fund to Fight AIDS, Tuberculosis, and Malaria; and the U.S. President's Emergency Plan for AIDS Relief are accompanied by lists of indicators and increased reporting frequency and quality demands.

Strengthening M&E and health information systems would be an important step in building program management capacity in many countries. Too often, M&E plans are not included at the set up and planning stage of programs and rather seen as an add-on to measure results (rather than being seen as a tool for learning and iterative improvements in management). Resource allocations at national level, and from external sources, are generally far below the recommended 5–10% of program cost. Focus on M&E from the planning phases should lead to increased investments in the generation and use of relevant program and health information. At the same time, this will help programs to show greater accountability both to the people they serve and to the donors that support them, often resulting in program achievements in excess of expectations.

Despite these encouraging results, many countries still do not have the capacity and systems in place to appropriately monitor, evaluate, and manage HIV and STD programs. Many countries have basic systems in place to track prevalence of HIV infection but such systems are far more limited for STDs. Systems to measure outcomes and impact are generally poor.

This weak capacity must be seen against the dramatic increase of resources to substantially scale-up programs in prevention, treatment, and care of HIV and STDs over the last decade. Without concerted efforts to strengthen M&E capacity, these new resources may not be spent in the most efficient ways, in the best case, or may be used for activities that may do more harm than good, in the worst case. The potential for development of resistance to antiretroviral drugs during large-scale treatment programs that are not appropriately monitored may be an example. Not only would treatments lose their power in the individuals living with HIV/AIDS under treatment but also the resistant strains might be transmitted to others, posing a serious, new challenge to health systems and societies.

Systematic learning through specific evaluations, and operational research, is even less developed than systems to monitor programs and defined health indicators. Most of the limited research done in developing countries that carry the vast majority of the global burden of HIV and other STDs is designed and implemented by research institutions in the high-income countries, and there is no consistent mechanism

to collect and compile the many lessons learned, good or bad, from programs that have received substantially increased support in recent years.

New and positive developments include the increasing experience and much greater focus on biomarkers as part of population-based surveys. In an increasing number of countries, population-based surveys such as the Demographic and Health Surveys now include testing for HIV antibodies, greatly enhancing the understanding of level, distribution, and trends in HIV infection and its determining factors.

While much remains to be done, an analysis of other health fields shows that HIV may well serve as a forerunner for health and program measurement in other areas. The growing appreciation of the importance of M&E in the development of high quality HIV and STD prevention and control programs will greatly enhance progress in the field.

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Michael L. Rekart and Robert C. Brunham

INTRODUCTION

In human history, no infectious disease has been eliminated (incidence $\leq 0.5/100,000$) without an effective vaccine. Vaccines against sexually transmitted diseases (STDs) have incredible potential to save lives, reduce morbidity, decrease global STD expenditures, reduce HIV spread, prevent AIDS, and contribute to improved reproductive health. STD vaccines will also circumvent many of the very significant challenges to nonvaccine STD prevention and control strategies.

■ VACCINES AND SOCIETY

Society supports modern vaccines, but the vast number of illnesses avoided and lives saved are not widely recognized (Fig. 99-1).¹ As recently as 1967, when the smallpox eradication campaign entered its final intensified phase, there were an estimated 10–15 million cases of smallpox in 31 countries.² Since smallpox eradication in 1977, 15–20 million lives have been saved. By 1989, over 1.4 million deaths from measles, diphtheria, and pertussis had been averted by vaccination. By the turn of the century, vaccination campaigns against diphtheria, pertussis, and polio had achieved success rates as measured by cohort coverage of 92%, 99%, and 92%, respectively.² In 2002, the lives of 1.3 million children were saved by vaccines.¹

Haemophilus influenzae type B (Hib) conjugate vaccine could avert 3 million cases of serious Hib disease and 400,000–700,000 deaths annually. The pneumococcal vaccine could save 1 million lives per year. Currently available typhoid vaccines with 50–70% efficacy have the potential to avert 16 million cases of typhoid fever and 600,000 deaths annually.² These authors agree that “vaccines are the cornerstone of contemporary medicine and the best approach to reduce morbidity and mortality due to infectious disease.”³

With the global incidence of curable STDs at 300–350 million and the prevalence of viral STDs over 1 billion,^{4,5} the potential for STD vaccines, even imperfect ones, to reduce morbidity and mortality is vast. Syphilis, gonorrhea, chlamydia,

and pelvic inflammatory disease (PID) together rank second behind obstetrical causes among women 15–44 years of age in developing countries as a cause of disability-adjusted life years (DALYs) and HIV ranks fourth.^{4,6} Among men, HIV is the leading cause of healthy life lost in this same age group. Tuberculosis, the most common AIDS-associated opportunistic infection in the world, ranks second in men and third in women as the cause of DALYs.⁶

Together with their long-term health consequences, including cancers, reproductive problems, neurological consequences, and chronic liver disease, the direct and indirect effects of STDs including HIV comprise a huge global burden on health. Even in rich countries, the impact of STDs is significant despite effective diagnostic, treatment and prevention interventions. Over 12 million Americans are infected with STDs annually, including 3 million teenagers, and five STDs were among the top 10 most frequently reported diseases in the United States in 1995 accounting for up to 87% of all communicable disease cases reported.⁴ STDs, including HIV/AIDS, cost the health-care system in the United States around \$12 billion annually.⁷

The promise of STD vaccines is more than a dream. In British Columbia, Canada, where the hepatitis B (HBV) vaccination program advanced from grade 6 immunization in 1992 to universal infant immunization in 2001 followed by immunization of high risk groups, hepatitis B incidence declined 81% from 7.4 per 100,000 in 1992 to 1.4 per 100,000 in 2003.⁸ Acute hepatitis B was eliminated among adolescents (Fig. 99-2).

Vaccines are highly cost-effective. The traditional childhood vaccines (measles, polio, diphtheria, pertussis, and BCG) are cheap to manufacture, inexpensive to deliver, safe and highly successful.² Childhood vaccination with these antigens can lay claim to a cost-to-effectiveness ratio of \$15–25 per quality-adjusted life year (QALY). Most other routine health-care interventions and prevention programs are more costly to deliver, usually hundreds or thousands of dollars per QALY.² The estimated cost per QALY for Hib vaccine is \$21–480 and for HBV vaccine \$8–219.²

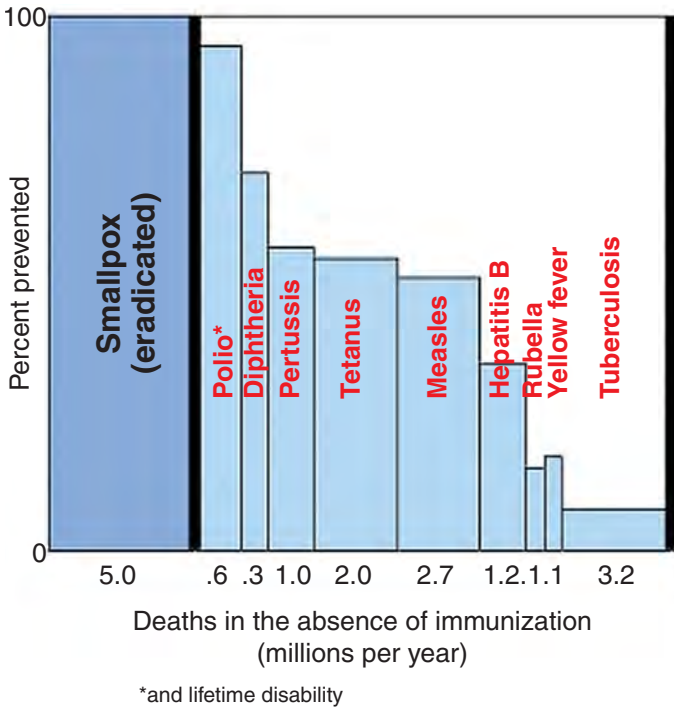


FIGURE 99-1. Deaths (global) from vaccine-preventable diseases in the absence of immunization (millions per year). * and lifetime disability (Reprinted from Diamond B. A real shot. *Nat Med* 2003; 11(Suppl 4): S3–S4. With permission from the Nature Publishing Group).

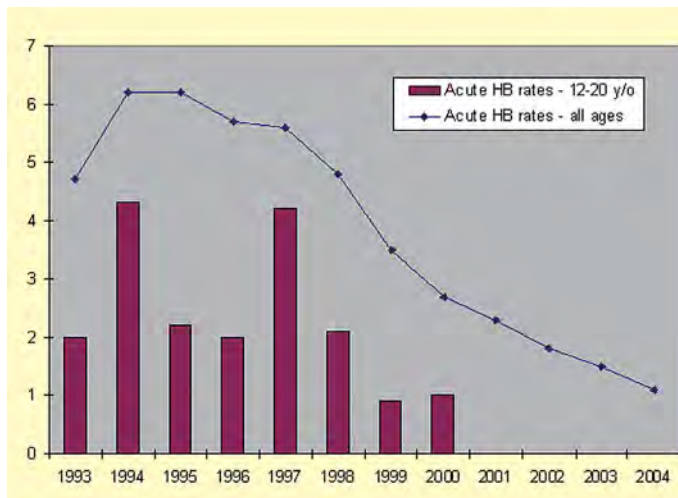


FIGURE 99-2. Acute hepatitis B (HB) rates (per 100,000) for the Province of British Columbia (blue line) and for the 12–20 year age group (red bars) after the introduction of HBV vaccination (Adapted from Patrick DM, Bigham M, Ng H, et al. Elimination of acute hepatitis B among adolescents after one decade of an immunization program targeting Grade 6 students. *Pediatr Infect Dis J* 2003; 22(10): 874–877).

Effective STD vaccines could change the face of HIV and AIDS. In a systematic review, Rottingen and colleagues found that ulcerative STDs increased male susceptibility to HIV fourfold and female susceptibility threefold.⁹ Nonulcerative STDs increased male susceptibility to HIV threefold and female susceptibility twofold. STDs significantly increase HIV

infectiousness as well;¹⁰ and HSV-2 and *T. pallidum* can directly increase HIV levels. Herpes simplex virus (HSV) infections, especially HSV-2, account for over 60% of genital ulcer disease worldwide. Its high worldwide prevalence, lack of a cure, frequency of reactivation, and ability to amplify HIV replication make HSV-2 infection the most important STD in the global HIV epidemic.¹¹ In Rakai, HIV risk in monogamous, serodiscordant couples was 70% higher in the presence of HSV-2 infection.¹² Wald found the population attributable risk (PAR) of HSV-2 for HIV acquisition to be 19% in populations with 22% HSV-2 prevalence and 47% in populations with 80% HSV-2 prevalence.¹³

STD vaccines will improve reproductive health, especially for women, children, and marginalized populations. PID and cervical cancer are examples. In the United States, over 1 million women experience acute PID annually with 100,000 becoming infertile as a result.¹⁴ In sub-Saharan Africa, up to 40% of reproductive age women are infertile probably due to previous PID.¹⁵ Cervical cancer, a malignancy associated with sexually transmitted human papillomavirus (HPV), was the second most common cancer (493,000 cases) and the most common cause of cancer deaths (274,000) among women in developing countries in 2002.¹⁶

VACCINES AND STD CONTROL

In addition to direct benefits, STD vaccines will circumvent the challenges to nonvaccine control strategies including behavioral change, societal impediments, biological obstacles, and translating intervention-trial efficacy into real-world effectiveness.

Several of the major determinants of sexual and health seeking behavior (substance use, knowledge, and personal skills) are not improving. Drug use is increasing in North America and globally; alcohol is almost universally legal and widely prevalent; and initiatives to combat drug and alcohol dependence have largely failed.¹⁷ The proportion of 15–24-year-old females with adequate knowledge about HIV and AIDS is 30% for Latin America and the Caribbean, 23% for South Asia and Southeast Asia, 18% for sub-Saharan Africa, and 5% for Eastern Europe and Central Asia.¹⁸ In 13–20-year-old students in Egypt, over 90% knew nothing about gonorrhea and syphilis.¹⁹ In U.S. surveys, only one-third of adults have any basic awareness of non-HIV STDs.⁴ Condom use in sex acts with noncohabiting partners ranges from 13% in Southeast Asia to 19% in sub-Saharan Africa.¹⁸ In Haiti, Gabon, and Malawi, the percentages of 15–19-year-olds reporting an STD who sought care were 68%, 51%, and 42% respectively.¹⁸ In the United States, less than 60% of persons symptomatic with an STD ever seek care.⁴

As a consequence, the global epidemic of HIV remains out of control with rising incidence rates in all geographic areas, both genders and all age groups.¹⁸ In 2003, an estimated

4.8 million people were infected with HIV, the most for any year on record, and the proportion of sexually transmitted HIV/AIDS is increasing, mostly in women.^{5,18} The global estimate of curable STDs changed little from 1995 (333 million) to 1999 (340 million).⁵

Sociocultural impediments to STD control include stigma and discrimination, sexuality taboos leading to lack of open discussion and unbalanced media messages, inadequate STD prevention and care services, low priority among decision makers, large social disruption, and widespread poor determinants of health.⁴ According to UNAIDS, prevention services reach only 30% of men who have sex with men (MSM) in the Americas, 6% of MSM in sub-Saharan Africa, 32% of 2.5 million sex workers in sub-Saharan Africa, and 16% of 2.2 million sex workers in Southeast Asia.¹⁸ In the Western Pacific, only 13% of primary school students have access to AIDS education.¹⁸

STDs are difficult to diagnose because of lack of symptoms, nonspecific symptoms, problems collecting specimens, and performing laboratory tests in the high-risk, and the lag time to complications. Most herpes infections are spread by asymptomatic and unaware index patients. Because STD complications occur months or years after the initial, often unrecognized, infection, STDs are often not associated in the public mind with serious illness. Treatment, a critical component in control, is restricted to bacterial and protozoan STDs. There are no cures for HPV, HBV, HSV, or HIV. Effective suppressive therapies for HIV and HSV are available but these are not accessible for patients in most of the world. For decades, effective prevention, treatment, and control strategies have been available for the “curable” STDs (gonorrhea, syphilis, chlamydia, and trichomonas), but this has not reduced their overall global incidence because of poor access and antibiotic resistance. STD vaccine delivery programs would be easier to implement, evaluate, and maintain, narrowing the dichotomy between intervention-trial efficacy and real-world effectiveness.^{20,21}

Widespread and culturally ingrained cofactors exist that enhance STD transmission and are difficult to address including douching, the use of intravaginal substances, “dry sex,” and the lack of male circumcision.²² The latter has been linked to HIV infection (combined odds ratio 1.43, 1.32–1.54), urethral discharge, venereal warts, and chancroid.²³

Because chlamydia protective immunity develops gradually over several months of infection, early treatment may block natural immunity and enhance the risk of reinfection.^{24,25} The highest risk core transmitters reenter sexual networks sooner, get reinfected more easily and spread their infection throughout these networks more readily. This may explain increasing chlamydia rates in localities where chlamydia control has received priority attention. In British Columbia, the relative risk of chlamydia reinfection increased by nearly 5% per year over the course of an enhanced

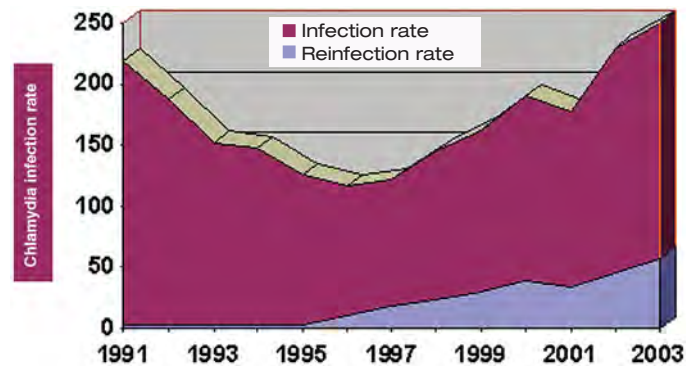


FIGURE 99-3. Annual rates of new case reports of total *C. trachomatis* genital infections (red and blue) and *C. trachomatis* genital reinfections (blue) for the Province of British Columbia (Adapted from Brunham RC, Pourbohloul B, Mak S, et al. The unexpected impact of a *Chlamydia trachomatis* infection control program on susceptibility to reinfection. *J Infect Dis* 2005; 192: 1836–1844.)

chlamydia control program from 1988 to 2004 (Fig. 99-3).²⁵ The relative risk was greater for younger individuals and women. Antibiotics have been shown to blunt the development of immunity to *C. muridarum* in mouse challenge models.²⁶ Mathematical modeling supports this hypothesis and suggests that the most efficient way to control or eradicate chlamydia in the absence of changing sexual networks is vaccination.²⁵

A similar immunity phenomenon has been reported for trachoma, an ocular *C. trachomatis* infection. Reinfection rates increased significantly in patients treated with azithromycin but not those treated with surgery.²⁷ Natural immunity may also be an important factor in syphilis epidemic cycling and reinfection rates after treatment.^{28,29}

■ VACCINE BASICS

The word *vaccine* is derived from the Latin *vacca*, cow. Vaccines were named from Edward Jenner’s use of cowpox virus inoculation against smallpox in 1796. A vaccine is a preparation of live, attenuated, or killed microorganisms or antigenic proteins derived from them, administered for the prevention, amelioration, or treatment of an infectious disease. Currently licensed vaccine formulations include live attenuated (measles), whole inactivated (hepatitis A), protein subunit (hepatitis B), polysaccharide (pneumococcal), and polysaccharide conjugate vaccines (*Haemophilus influenzae* type B). DNA vaccine candidates are capable of inducing broad cellular immune responses whereas most licensed vaccines induce primarily a humoral antibody response. For tuberculosis, herpes, and HIV, cellular immunity plays a major role.

Live vectored vaccines are preparations of living, attenuated organisms (e.g., *vaccinia*) with pathogen genes inserted. Protective immune responses, especially cytotoxic T-lymphocytes, are generated against the pathogen and the vector. Vaccines often contain immune adjuvants, such as alum salts,

to improve the host antibody response. Virulence factors, such as adhesions and capsules, are preferred vaccine targets.

Human immunity is comprised of an innate and an adaptive component. Innate immunity defends against microorganisms via nonspecific immune responses to all antigens delaying the progression of infection so the adaptive immune system can respond more specifically and effectively. Adaptive immunity can be humoral or cellular. Humoral responses clear free virus particles from body fluids and prevent viral reinfection while cellular responses are directed at virus-infected cells and generating immune memory.³⁰ Humoral immunity is mediated by antibodies produced by B lymphocytes. Antibodies coat the invading microbe or cause conformational changes leading to pathogen inactivation, e.g., binding to cellular receptors preventing host cell entry. Cellular immunity, commonly called cell-mediated immunity (CMI), is mediated by T lymphocytes—CD4⁺ helper cells, CD8⁺ cytotoxic cells, and CD4⁺CD25⁺ regulatory cells. The CMI response involves both cytokine secretion and activation of immune cells—macrophages, natural killer (NK) cells, and antigen-specific cytotoxic T lymphocytes (CTLs).

Protective immunity relies on both humoral and cellular immune factors. Antigen recognition stimulates the activation and clonal expansion of antigen-specific B lymphocytes, which may ultimately protect against a secondary challenge as “memory B cells”. Antibody-mediated protection may involve preexisting antibody, such as secretory IgA (sIgA) at the mucosal surface (sterilizing immunity) and/or a robust secondary immune response by serum IgG. After the expansion phase of CMI, 90% of activated cells die by activation-induced apoptosis. The remaining cells enter a memory phase, which can be maintained for long periods. These “memory T cells” are either resting or effector cells. Resting cells are found in the major lymphoid organs whereas effector cells reside in peripheral tissues. Effectors respond rapidly with cytokines and direct cytolytic activity.

The goal of vaccination is to provide at least the same degree and duration of protection as natural infection without the accompanying clinical illness. A good vaccine produces a humoral, cellular, and innate immune response protective against both clinical disease and reinfection for a lifetime with minimal immediate side reactions and no delayed effects. Administration would be simple, safe, and acceptable. The cost and benefits would outweigh the cost and risk of natural disease and the adverse consequences of vaccination.³¹

EVIDENCE FOR NATURAL IMMUNITY TO STDs

The immune system of the human genital tract is linked with the body’s common mucosal and systemic immune systems. It also has unique elements. Attachment to host cells is a necessary first step in the development of infection and an immune response (see Chapter 13). Attachment (adhesion)

can result in colonization, local inflammation, or invasion of the host. STDs may preferentially attach to specific cells, for instance, *N. gonorrhoeae* and *C. trachomatis* attach to columnar epithelium whereas HPV and *T. vaginalis* attach to squamous epithelium. The first lines of defense against attachment involve physical barriers (skin and mucous), the vaginal pH, and the symbiotic natural flora that discourages colonization by pathogens.

Mucous provides an obvious physical barrier to microorganisms but it also serves as a supportive substrate for opsonization by immunoglobulins and cytokine-enhanced phagocytosis. Rich in carbohydrate, the mucous may also directly interfere with adherence by binding to pathogens.³² The stratified squamous epithelium of the vagina, ectocervix, penis, and glans represent a second barrier to infection. However, the epithelium of the cervical canal beginning at the transformation zone, the male urethra, the rectum, and the usually sterile upper female genital tract are composed of columnar epithelium, which is a single-cell-layer thick and allows antigens to be taken up more readily. STD pathogens have developed mechanisms to circumvent these defenses with varying efficiency. For example, *T. pallidum* results in new infection after 30% of sexual contacts whereas HIV transmission per sexual contact is usually less than 1%.

Innate immune responses occur quickly (within minutes), mediated by receptors that recognize stable, evolutionarily conserved signatures shared by large groups of pathogens. Innate immunity comprises: (1) ever-present antimicrobial factors, (2) early-induced cytokine secretion, (3) phagocytosis by neutrophils and macrophages, (4) lysis of infected cells by NK cells, and (5) antigen presentation to naïve T cells.³³

Ever-present, constitutive, nonspecific antimicrobial factors include lactoferrin, natural antibody, complement, defensins, adhesions, and lysozymes (“the body’s own antibiotic”).^{34,35} Lactoferrin, for instance, competes with pathogens for iron and has direct bactericidal activity. The male genital tract also contains zinc, polyamines, and prostaglandins.^{32,36}

Cytokines are nonantibody proteins released by cells on contact with antigens that act as intercellular signalers/mediators in the immune response. Cytokines classes include (1) proinflammatory cytokines (e.g., interferon (IFN), interleukin (IL), tumor necrosis factor (TNF), granulocyte macrophage colony stimulating factor (GM-CSF), (2) chemokines (C-X-C family and C-C family), and (3) downregulatory cytokines [e.g., transforming growth factor (TGF)].

Pattern recognition receptors (PRRs), including toll-like receptors (TLRs), recognize stable, evolutionarily conserved signatures from pathogens [pathogen-associated molecular patterns (PAMPs)]. TLRs are expressed by antigen-presenting cells (APCs) in the genital tract—macrophages, dendritic cells, and neutrophils—and at lower levels, fibroblasts, endothelial, and epithelial cells. Recognition of PAMPs leads to cell activation, cytokine secretion, and attraction of inflammatory cells.³⁷

After antigen is endocytosed, APCs migrate to regional lymph nodes where specific B and T cells activation takes place. Activated T cells then enter the circulation and “home” to tissues committed to antigen-specific responses.³² This links the innate and adaptive immune systems.

In contrast to innate responses, the adaptive immune system involves a “learned response” that requires clonal expansion of T and B lymphocytes. This response is slower but more specific and long-lived. The adaptive system includes humoral and cell-mediated immune responses, both under hormonal control in females.

The humoral immune response to microbial invasion centers on the production of antigen-specific antibody (immunoglobulin) by plasma cells (derived from activated B cells), which bind microbial antigen and activate complement. Antigen–antibody complexes are then inactivated via agglutination and precipitation, blockage of pathogen receptor sites and phagocytosis. Antibody also activates complement to which pathogens succumb through a variety of mechanisms including opsonization. Immunoglobulin classes include IgA, IgD, IgE, IgG, and IgM. SIgA and IgM are produced locally by penile urethral and endocervical cells, especially the transformation zone;^{35,38,39} however, most IgG in the genital tract is produced by B cells in lymphoid tissues in the rectum, small intestine, regional lymph nodes, and perhaps the nasal cavity.⁴⁰ These are called inductive sites. IgG predominates in most genital secretions, including semen and vaginal fluid, but IgA levels may be higher in cervical and urethral secretions and the preejaculate.⁴⁰ Nasal, vaginal, and perhaps transcutaneous administration of vaccine but not systemic, oral, or rectal immunization stimulate a mucosal immune response, especially sIgA, in the female genital tract.^{32,39,40}

Antigen-specific antibodies are present in genital tract secretions after infection; however, their role in protection against infection is unclear. SIgA specific for pathogens such as *C. trachomatis*, *N. gonorrhoeae*, and *E. coli* has been found in semen and cervical secretions.³² PID, tubal infertility, and ectopic pregnancy are associated with high titers of antibody to pathogens such as *C. trachomatis*.

Less is known about CMI than about humoral responses in the genital tract. Mediated by activation of CD4⁺ helper and CD8⁺ cytotoxic T lymphocytes, CMI responses include (1) direct lysis of infected cells, (2) activation of macrophages and NK cells, (3) stimulation of cytokines, and (4) antibody-dependent cell-mediated cytotoxicity (ADCC). T helper cells direct the immune response by stimulating the secretion of cytokines in two distinct pathways (Fig. 99-4).⁴¹ The Th1 pathway is mediated by IL-12 and acts to enhance a predominantly CMI response to intracellular microbes through the synthesis of cytokines, especially IFN- γ and IL-12. IFN- γ activates the bacteriocidal activities of macrophages, NK cells and CTLs while inducing B-cells to produce opsonizing antibody.

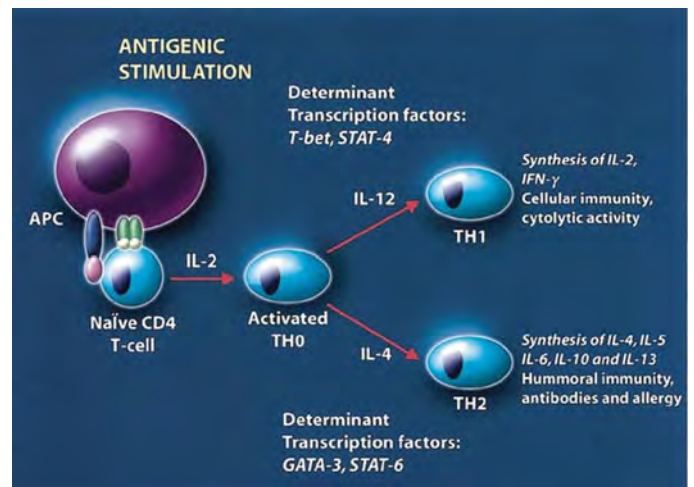


FIGURE 99-4. CD4⁺ T-helper cell differentiation into Th1 or Th2 type depending on antigenic and cytokine stimuli. (Reprinted from Chinen J, Shearer WT. Basic and clinical immunology. *J Allergy Clin Immunol* 2003; 111(3): S814. With permission from the American Academy of Allergy, Asthma and Immunology.)

The Th2 pathway is mediated by IL-4 and acts to enhance a predominantly humoral immune response to extracellular pathogens through the synthesis of cytokines, especially IL-4 and IL-10, and the activation of B cells to produce neutralizing antibody. Specific transcription factors are required for each pathway: T-bet and signal transducer and activator of transcription (STAT) 4 for Th1 and STAT-6 and GATA-3 for Th2 cells.⁴¹

The extravasation of immune cells such as lymphocytes from the circulation into genital secretions is a CMI phenomenon called cell trafficking, which is controlled by adhesion molecules, e.g., intracellular cell adhesion molecules (ICAMs). After infection, genital tract epithelial cells produce cytokines that induce the expression of vascular cell and mucosal vascular addressin cell adhesion molecules (VCAMs and MadCAMs). DC-SIGN (dendritic cell-specific ICAM-3 grabbing nonintegrin) is a high-affinity ICAM-3 receptor expressed by dendritic cells.

In pregnancy, the maternal genital tract immune system must develop tolerance for a foetus with foreign antigens. Initially, the maternal–foetal interface is devoid of lymphocytes but later there is an influx of T lymphocytes with the placenta acting as an immunological barrier between the mother and the semiallogeneic foetus.³⁹ During pregnancy, a global depression occurs in T cell responsiveness to microbial antigens including STDs.⁴²

Protective immunity for STDs requires durable humoral and CMI, including strong IgA responses, mediated by memory B and T cells. Systemic, rectal, and oral immunization are ineffective at inducing genital tract IgA antibodies. However, nasal and vaginal immunization have resulted in strong IgG and IgA antibody responses in the female genital tract and the serum.⁴³ These were strongest during the follicular phase of the

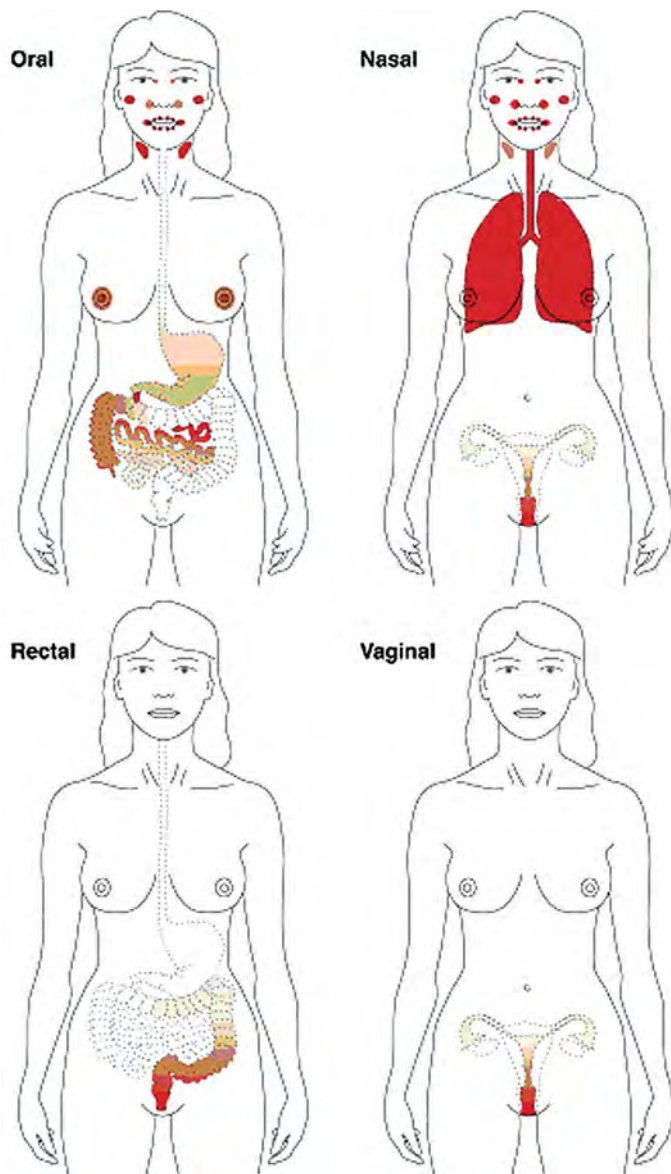


FIGURE 99-5. Routes of vaccine administration: Expression of mucosal IgA immune responses after different routes of vaccination. Shading indicates strength of response. (Reprinted from Holmgren J, Czerkinsky C. Mucosal immunity and vaccines. *Nat Med* 2005; 11(4 Suppl): S45–S53. With permission from the Nature Publishing Group.)

menstrual cycle.⁴³ Collectively, these observations may affect STD immunization strategies (Fig. 99-5).

No STD stimulates complete protective immunity to natural infection, as occurs for several other vaccine-preventable diseases such as measles and pertussis. Distinctive immune evasion strategies are exploited by different STD pathogens. These strategies contribute to the long duration of infection and the extended time required for a protective immune response following infection.

■ HEPATITIS B VIRUS (HBV)

HBV preferentially infects hepatocytes but is not, itself, cytopathic. Innate, humoral, and cellular immunity all play

critical roles in the host response. A vigorous immune response is delayed for about 2 months, probably due to the limited quantity of HBV antigen. At 4–7 weeks, a burst of HBV replication triggers the innate immune system, followed by the adaptive cellular response at 7–10 weeks and the adaptive humoral response at 10–12 weeks.⁴⁴ While the innate immune response predominates early, the coordinated and efficient activation of the adaptive humoral and cellular immune responses is ultimately responsible for control of HBV infection. A deficient adaptive immune response is associated with chronic HBV infection.^{45–47}

The innate immune response within the liver relies on several cell lines including hepatocytes, NK cells, NK-T cells (NKT), and Kupffer cells, a macrophage unique to the liver.⁴⁵ Initially, infected hepatocytes produce IFN- α and IFN- β which interfere with HBV replication and activate macrophages which in turn secrete cytokines and chemokines. NK cells that are recruited lyse HBV-infected cells, downregulate HBV replication by producing IFN- γ and TNF- α , and produce chemokines that modify the polymorphonuclear (PMN) response.⁴⁴ In addition, liver-resident NKT cells mediate direct cytotoxicity, produce IL-4 and IFN- γ , and influence the priming of antigen-specific cells. Kupffer and dendritic cells link the innate and adaptive immune responses by acting as APCs.⁴⁴

The cell-mediated immune response to HBV is characterized by vigorous multispecific, polyclonal antiviral CD4⁺ and CD8⁺ T cell responses to epitopes on all HBV proteins with a Th1 pattern of cytokine production.⁴⁶ T helper cells recognize viral peptides on APCs leading to activation and differentiation of B cells, and induction and maintenance of HBV-specific CD8⁺ T cells. CD4⁺ and CD8⁺ T cells secrete IFN- γ and TNF- α and directly lyse HBV-infected cells. CTLs can “cure” hepatocytes of HBV particles, intermediates, and templates without killing them via an IFN- γ and TNF- α mediated process.⁴⁴

The adaptive humoral immune response is characterized by the sequential production of antibodies against hepatitis B core antigen (anti-HBc), hepatitis e antigen (anti-HBe) and hepatitis surface antigen (anti-HBs). Anti-HBc is the first marker of HBV infection; anti-HBe is an early sign of recovery; and anti-HBs is neutralizing and associated with protective immunity after both natural infection and vaccination.⁴⁷

The clearance of most HBV virions during the incubation phase of acute, self-limited hepatitis is followed by antigen-independent amplification of the HBV-specific T cell infiltrate in the liver. This process is mediated by chemokines and cytokines, especially IFN- γ , and likely accounts for disease pathogenesis, necroinflammatory liver disease and the clinical manifestations of acute hepatitis.^{44–47}

After resolution of acute hepatitis, there is a substantial reduction in the absolute number of HBV-specific T cells but immune status is maintained for decades because of a very

high level of T cell responsiveness to HBV challenge.⁴⁴ Small amounts of transcriptionally active HBV probably persist in immunoprivileged sites maintaining cell-mediated and antibody-mediated immunity that, in turn, prevents HBV spread and reinfection. This nonsterilizing immunity is called concomitant immunity.

Chronic HBV infection in neonates probably results from a deficient early immune response during acute infection. However, chronic HBV in immunocompetent adults is associated with a narrowly focused and weak HBV-specific T cell response. Three explanations have been proposed: (1) insufficiently activated CD8⁺ T cells due to partial HBV downregulation, (2) HBV replication outpacing the host response, and (3) viral escape through mutations in T cell recognition sites.^{44,46} Although the T cell response in chronic hepatitis is too weak to eliminate HBV, it is likely strong enough to destroy small numbers of infected hepatocytes leading to the progressive necroinflammatory liver disease associated with chronic infection.⁴⁴

The continuous stimulation of the antigen-specific immune response during chronic HBV infection increases the risk of progressive liver disease manifest as fibrosis, cirrhosis, and/or hepatocellular carcinoma.⁴⁵ HBe-Ag negative chronic hepatitis is characterized by a balance between HBV-specific T cells and lower levels of replicating virus resulting in less liver damage. A few patients exhibit complete recovery later with a loss of HBsAg, the major marker for active replication and infectiousness. This delayed recovery is associated with reactivation of the immune response possibly during clearance of HBeAg.⁴⁴

Finally, it appears that high HBV viral load impairs the action of HBV-specific T cells during hepatitis and that these T cells recover when viral load decreases. In this context, the inhibition of HBV replication by antiviral drugs can restore the cellular immune response. This effect is greater for pegylated IFN than for nucleoside/nucleotide analogues.

■ HUMAN PAPILLOMAVIRUS (HPV)

Over 90% of incident HPV infections resolve spontaneously, presumably due to an effective immune response.⁴⁸ Other markers of an effective immune response include the rarity of reinfection with the same serotype, the lack of recurrence after ablative therapy for preinvasive lesions, the age-dependent natural history of HPV infection, the increased risk of infection in immunosuppressed patients, and the active immune response during lesion resolution.^{49,50}

HPV replicates in an immunological privileged site, the keratinocyte. HPV evades the innate immune response by delaying nuclear condensation (and premature death) in the infected, differentiating keratinocyte forming the koilocyte, an abnormal, pyknotic vacuolated epithelial cell characteristic of HPV infection.³⁰ The virus-laden koilocyte then dies of

“natural causes” and desquamates, far from immune surveillance, without releasing proinflammatory cytokines to alert the immune system.³⁰ Additionally, high-risk HPV subtypes downregulate IFN- α -inducible gene expression, an antiviral defense mechanism; and HR(high risk)-HPV oncoproteins E6 and E7 directly block the interferon signaling system and deregulate key cell cycle check points.³⁰ This local immune nonresponsiveness and low levels of viral proteins compromise the antigen processing and presentation functions of the dendritic cells in the squamous epithelium [Langerhans cells [LCs]].^{30,50} The HPV antigen-specific effector cell response is thus weak or absent. With host defenses irrevocably compromised, unimpeded E6 and E7 oncoprotein expression can result in progression to high-grade intraepithelial lesions and invasive carcinoma.³⁰

In most incident HPV infections, however, an effective innate immune response involving immune cells (phagocytes, LCs, and NKs) and cytokines (IFN- α , IFN- β , IL-4, and GM-CSF) allies with a strong, local CMI response leading to regression of lesions and serum neutralizing IgG antibody formation against the HPV major capsid protein L1.^{30,51–53} Type-specific antibody seroconversion occurs within 18 months in 60% of HPV-16, 54% of HPV-18, and 69% of HPV-6 incident infections.⁵⁴ In natural infection, anti-L1 antibodies are stable for at least 10 years and memory B cells specific for HPV-16 and 18 have been shown.⁵⁵ Cross-reactivity at nondominant neutralizing epitopes has been demonstrated between types 6 and 11, types 31 and 33, types 16 and 31, and types 18 and 45.³⁰ Seronegativity can occur with transient infections and with persistent infections. Peak antibody levels are low; however, seropositive animals are protected against reinfection and this protection is serum-transferable.^{30,56,57} About 50% of women with cervical cancer show antibodies to E6 and E7.³⁰

The key immune response involved in the clearance of HPV infection is CMI with Th1-type immunity controlling the outcome of HPV infection. Regressing HPV lesions are correlated with local mononuclear cell infiltration and Th1 cytokines. Systemic, HPV-specific, T cell responses, such as cytotoxic T cells and DTH measured by skin testing, have also been detected in patients with regressing lesions. Immature dendritic cells present in the genital squamous epithelium (LCs) act as APCs promoting the production of HPV-specific CD8⁺ and CD4⁺ cells that release cytokines (including IFN) and directly lyse infected cells. Regression is also associated with significant induction of adhesion molecules (ICAM1 and VCAM1), which direct lymphocyte trafficking.⁵⁹ Nonregressing genital wart lesions, on the other hand, lack immune cells.

A role for CD4⁺CD25⁺ T regulator cells (T regs) in the natural immune response to HPV infection may be emerging. Normally, T regs suppress the immune system to prevent self-reactivity (i.e., autoimmune disease) via cell-to-cell contact and by secreting the immunosuppressive cytokines IL-10 and

transforming growth factor (TGF) β . Accordingly, T reg activity is normally downregulated during immune responses to infecting microorganisms to facilitate their elimination. Some pathogens may have evolved immune evasion mechanisms that stimulate T reg activity to immunosuppress the host and improve their own chances of survival.⁵⁹ HPV has been implicated in this phenomenon along with retroviruses, Leishmania, and malaria.⁶⁰

A shift from Th1 to Th2 cytokine production may correlate with more extensive HPV infection and carcinogenesis.^{61,62} Immunosuppression is associated with HPV persistence and resistance to treatment. Genetic defects affecting humoral immunity have little effect on HPV infection whereas persons with CMI deficiencies have higher HPV prevalence.³⁰ Despite the evidence of a central role for CMI, the highly successful results of recent HPV vaccine studies defines a key role for the humoral response in preventing both progression and incident HPV infections.^{63–65}

■ HERPES SIMPLEX VIRUS (HSV)

Human herpes viruses have developed an array of mechanisms to evade the host immune response. These include targeting of antigen presentation, resistance to complement (mediated by glycoprotein C), inhibition of antibody binding (mediated by glycoproteins gE and gI) and blocking of CTL activity through inhibition of caspase activation.⁶⁶ Latency-reactivated viral production evades the immune response by replicating in an immune-privileged site and by downregulation of the Th1 antiviral response.

During early, primary infection, host resistance relies on innate immunity—IFN, macrophages, and NK cells. Within a few days, the adaptive immune system responds with neutralizing antibody and CMI, including CD4⁺ and CD8⁺ T cells and antiviral cytokine release.^{66–68} In recurrent HSV, the immune response is activated more rapidly resulting in shorter duration of lesions and viral shedding. CMI appears to play the central role.⁶⁸ Accordingly, mucocutaneous herpes is more severe with impaired CMI than with deficiencies in humoral immunity.⁶⁸

The immunohistology of recurrent HSV lesions reveals an initial infiltration with macrophages and CD4⁺ lymphocytes followed by an influx of CD8⁺ lymphocytes.⁶⁷ The late introduction of CD8⁺ cells is probably a function of the ability of HSV to downregulate MHC class I expression on the surface of infected epidermal cells. CD4⁺ cells appear earlier than CD8⁺ cells since they are able to recognize infected epidermal cells expressing MHC class II. By secreting IFN- γ , CD4⁺ cells partly restore MHC class I expression allowing recognition by CD8⁺ lymphocytes which mop up the remaining infected cells.⁶⁷ Herpetic lesions demonstrate a Th1-pattern of cytokine production resulting in the secretion of IL-12, TNF- α , IFN- α , and IFN- γ . These cytokines attract monocytes and

T lymphocytes, enhance CD4⁺ lymphocyte secretion to a T-helper pattern, activate CD8⁺ cytotoxic lymphocytes, and directly eliminate virus-infected cells.

IFN- γ plays a particularly key role by upregulating MHC classes I and II, activating macrophages, purging infected cells of viral proteins, and preventing HSV spread in concert with IFN- α .⁶⁷ T cell production of IFN- γ and T cell-stimulated NK activity correlate with fewer recurrences. This is called relevant immunity. Persons with frequent recurrences show lower levels of HSV-specific IFN- γ , higher levels of downregulatory Th2-type cytokines and higher titers of serum HSV antibody.^{66,68} Asymptomatic HSV shedding probably results from resumed transcription of latent HSV DNA under the control of stress-induced cellular proteins with intact antiviral Th1 immunity whereas symptomatic recurrences may reflect unimpeded viral replication through downregulation of the Th1 response.⁶⁶

Humoral immune mechanisms also have an important role in controlling infection. HSV surface glycoproteins are the targets for neutralizing IgG antibodies and antibody-dependent cell-mediated cytotoxicity (ADCC). Secretory IgA likely plays a minor role.⁶⁹ HSV monoclonal antibodies protect against neurologic disease and prevent latency in animal models.⁷⁰ The quantity of neutralizing and ADCC cytotoxic antibodies correlates inversely with disseminated disease in newborns but correlates directly with high frequency and severity of recurrent disease in adults. This paradox may reflect a more severe primary infection and repeated antigenic stimuli during recurrences.⁷¹

The HSV immune response is not optimal but several lines of evidence indicate that an effective vaccine against herpes type-2 is possible: (1) transplacentally acquired HSV-2-specific maternal antibodies are associated with reduced perinatal HSV-2;⁷² (2) new infection with the same HSV-2 subtype is rare;^{72,73} (3) prior HSV-1 infection ameliorates subsequent HSV-2 disease;^{72,74} (4) humoral and cellular immune responses have prevented HSV in animal models;^{72,75} and (5) humans develop postimmunization neutralizing antibodies to HSV-2 similar to natural infection.⁷²

■ NEISSERIA GONORRHOEA

Potent virulence mechanisms characterize the pathogenesis of *N. gonorrhoeae* including a weak antibody response, pronounced antigenic variation, resistance to complement-mediated bacteriolysis, production of an effective IgA protease, deployment of antibody blocking strategies, and minimal protective immunity.⁷⁶ Absence of an adequate nonprimate animal model has impeded research into the immune response. Furthermore, gonococci grown in vitro may bear little similarity to organisms causing in vivo infections.⁷⁶ Barriers to the development of a gonococcal vaccine are formidable.

Little is known about the innate immune response or the effect on gonococci of local microflora, pH, and mucous. However, gonococci can effectively use lactoferrin-bound iron. The intense inflammatory response reflects the failure of innate defenses. Leukocyte homing and phagocytosis occur but whether opsonins are required and whether organisms can survive ingestion is controversial.⁷⁷

The adaptive humoral immune response to a single infection with *N. gonorrhoeae* does not result in solid immunity to reinfection with all strains. The outer membrane of the gonococcus contains several proteins, which stimulate serum antibody production. Pili, Protein I (PI or Por), and Protein II (Opa) are the predominant antigens in the local humoral immune response.⁷⁸ Naturally occurring serum bactericidal antibodies to gonococci have been demonstrated prior to infection and strain-specific antibodies have been shown in immune sera. Both are mostly IgG.⁷⁸ Antigonococcal IgG, IgA, and IgM have been detected at the genital mucosal surface. IgA levels were often higher than those in serum at the time of infection but rapidly decreased.⁷⁸ The predominant immunoglobulin in genital secretions in gonorrhea appears to be IgG in females and IgA in males.⁷⁸ Gonococci from patients with disseminated infection are resistant to the killing action of most normal and convalescent human sera. This is called serum resistance.

CMI responses during gonococcal infection have been clearly identified. Peripheral blood lymphocytes are capable of ADCC and possess natural killing activity against *N. gonorrhoeae*.⁷⁹ Fallopian tube lymphocytes produce antigonococcal cytokines (including TNF) which may cause ensuing fallopian tube damage.⁷⁹ Antigen-specific T cell responses directed against Por have been demonstrated in humans.⁸⁰ The cytokine profile of Por-specific T cells suggests a predominantly Th2 response with the production of IL-4. Antigenic presentation and resultant T cell stimulation may occur locally, systemically, or both.⁸⁰ Delayed-type hypersensitivity (DTH) has also been documented.⁸¹ In vitro gonococcal binding to CD4⁺ cells arrests activation and proliferation, perhaps interfering with T cell memory.⁸² Overall, there has been no consistent correlation between the development of gonococcal-specific CMI and protection.

■ CHLAMYDIA TRACHOMATIS

The development of a vaccine for *C. trachomatis* may be easier than for *N. gonorrhoeae*. Chlamydia is not nearly as antigenically variant as the gonococcus and epidemiological evidence for immunity has been documented. Chlamydiae are obligate intracellular pathogens suggesting that CMI may be important to host resistance. However, infections are transmitted between hosts by an extracellular form, termed the elementary body, and, at this stage, antibody may be important to protection.

Epidemiologically, the strongest evidence for chlamydia immunity is that the risk of infection is inversely related to age. Teenagers and young adults are much more likely to be infected than older adults. Adaptive immunity and age-related changes in sexual behavior probably interact to explain this. Among female sex workers, years of prostitution are the proximate behavioral risk factor for chlamydia infection and infection is rare after 10 years of sex work. HIV appears to increase sex worker risk of infection suggesting that immunity is operative.

Acquired immunity is also supported by quantitative shedding of chlamydia, with younger individuals shedding larger numbers of organisms. In trachoma, a horizontally transmitted ocular *C. trachomatis* infection, increasing age correlates with lower loads of organism and shorter durations of infection. These observations suggest that age-related changes in immunity relate to rapid clearance of reinfection rather than sterilizing immunity to rechallenge.

C. trachomatis immunity is still under study. The innate immune response involves phagocytes, dendritic cells, NK cells, lymphocytes, and cytokines. With respect to humoral immunity, one early observation was that the prevalence of cervical sIgA to *C. trachomatis* was inversely related to the load of organisms shed. Since *C. trachomatis* is susceptible to neutralization in tissue culture with antibody to surface proteins such as major outer membrane protein (MOMP), sIgA *in vivo* may inhibit attachment to susceptible epithelial cells. Local antibodies may also play a role in opsonization since PMNs and macrophages are commonly found at infection sites. Lastly, certain isotypes of antibody, such as IgA, are important in targeting antigen to dendritic cells and enhancing CMI.

CMI is likely key to clearance of infection given the intracellular residence of chlamydiae. CD4⁺ and CD8⁺ T cell responses have been documented and at least eight different chlamydial proteins contain T cell epitopes. Th1 CD4⁺ cells secreting IFN- γ correlate with resistance to reinfection and reduced risk of PID. The role for CD8⁺ cells is less clear. Nonprotective Th2 or T regulatory cells secreting IL-10 are present, especially in the fallopian tubes of women with tubal infertility. They appear to increase the risk of reinfection. The durability for *C. trachomatis* immunity is uncertain. One study of STD clinic patients with prior chlamydia infection noted resistance to reinfection for only 6 months.

C. trachomatis has several immune evasion mechanisms and can cause persistent infection. Molano et al.²⁴ demonstrated that 50% of infected women clear infection by 1 year and 90% by 3 years. This suggests that an immune response resulting in clearance takes many months and that not all hosts mount a protective immune response. Persistence in vitro has been attributed to low concentrations of IFN- γ driving the organism into an altered biochemical form capable of long-term intracellular survival. Genital strains of

C. trachomatis genomically respond to IFN- γ in a stereotypic fashion, including the synthesis of tryptophan synthase, a key enzyme in evading the actions of IFN- γ . In the presence of IFN- γ , these strains can convert indole into an essential nutrient tryptophan, via tryptophan synthase. Indole is not synthesized by human cells and is derived only from certain components of the host microbial flora. These observations may explain the association of *C. trachomatis* mucopurulent cervicitis with bacterial vaginosis (a condition with raised vaginal indole concentrations) and to the polymicrobial nature of PID.

C. trachomatis can also evade the protective effects of antibody to surface protein. The MOMP is the dominant target of antibodies but is strain variant resulting in different immunotypes of the organism. Antibody to one immunotype may not protect against others. Furthermore, the surface of chlamydia also appears to have phase-variant proteins termed polymorphic membrane proteins (PMPs) to which protective antibodies are also directed. However, the phase variation of a PMP may allow for antigenic variation and immune escape.

Immune responses to *C. trachomatis* also appear to be involved in the pathogenesis of disease and tissue damage. Individuals persistently infected or frequently reinfected often develop reproductive sequelae. The antigen-specific patterns in protective versus pathological immune responses are different. High titers of antibody to *C. trachomatis* heat shock protein 60 (hsp 60) are found more frequently among women with PID, tubal infertility, and ectopic pregnancy than among pregnant seropositive women or those with uncomplicated cervicitis.

In aggregate, a vaccine for *C. trachomatis* appears feasible because evidence for immunity is demonstrable. A vaccine will need to be molecularly defined in order to exclude immunopathological hypersensitivity reactions to specific chlamydial antigens. Antigens for a potential vaccine will likely include the MOMP and perhaps PMPs.

■ *TREPONEMA PALLIDUM*

The causative agent of syphilis, *T. pallidum* subspecies *pallidum*, is an obligate human parasite with a worldwide distribution. Since the organism cannot be cultivated in vitro, our knowledge of the immune response is based on animal studies with limited human data. Studies at Sing Sing Prison using human intradermal challenge demonstrated resistance in individuals with untreated latent syphilis whereas those with treated latent syphilis were fully susceptible.⁸³ This form of concomitant immunity is operative with HBV, as previously discussed, and with Leishmania, where it is due to IL-10 secreting T regs inhibiting CD4 IFN- γ -mediated clearance at lesional sites. However, circulating Th1 CD4⁺ cells protect the host from challenge at new cutaneous sites. This mechanism

may be operative during latent syphilis. Magnusson also noted resistance to intradermal challenge in late syphilis irrespective of treatment.⁸³ This appears to be a different (perhaps vaccine-inducible) immune mechanism.

Syphilis is transmitted by local contact leading to penetration of intact mucous membranes and/or through microabrasions bypassing the chemical and mucous barrier and the normal, resident flora.⁷⁷ *T. pallidum* attaches to eukaryotic cells via attachment ligands followed by cell invasion and local replication. The organism then penetrates tissues by traversing the junction between endothelial cells, enters the bloodstream and disseminates throughout the body via blood and lymphatics.⁸⁴ Virulent *T. pallidum* stimulates the expression of the adhesion molecules ICAM-1, VCAM-1, and e-selectin.⁸⁴

Early syphilitic lesions (days 1–3) show heavy mononuclear cell infiltration and cytokines IL-1 and IL-2 from monocytes and lymphocytes respectively.⁷⁷ Immature dendritic cells in the skin (LCs) act as APCs taking up spirochetes and migrating to the regional lymph nodes to activate T cells.⁸⁴ As the LCs mature, they produce proinflammatory cytokines that further activate endothelial cells and attract inflammatory cells. These cytokines include IL-1 β , IL-6, IL-8, IL-12, and TNF- α . Activated T cells react strongly to several treponemal lipoproteins in the cytoplasm and the flagella, including TpN47, a key cytoplasmic protein that is not surface localized.⁸⁴ TpN47 also induces expression of the T cell chemoattractant cytokines MIP-1 α and MIP-1 β .⁸⁴

On days 4–9, antigen-specific T cells are recruited to the site of infection where a predominantly Th1 cellular response leads to secretion of IFN- γ , IL-2, IL-12, and IL-10. These T cells also activate macrophages, enhance antibody production by B cells and exhibit direct cytotoxicity. In primary syphilis, CD4⁺ cells outnumber CD8⁺ cells but that balance is reversed in secondary syphilis lesions.⁷⁷ A similar phenomenon is seen in recurrent HSV lesions, as discussed above.

Around day 10, activated macrophages together with opsonizing antibody (IgG and IgM), complement (especially c3b), and IFN- γ begin cleaning the lesion of most organisms. Between days 13 and 17, organisms decline sharply. A DTH-like mechanism appears to be operative.⁸⁴ The immune response that heals syphilitic chancres thus results from a combined Th1/Th2 effect.^{85,86} As the organisms are phagocytosed and ingested by macrophages, the prostaglandin PGE₂ is produced which then downregulates the local immune response. A small number of organisms are able to resist ingestion by macrophages and persist.

The acquired humoral immune response begins with IgM quickly followed by IgG directed at seven major treponema specific antigens and nontreponemal lipid antigens. The former response is measured by the FTA-Abs and MHA-Tp tests while the RPR and VDRL tests measure the nonspecific

response. IgG with complement neutralize and immobilize treponemes, enhance phagocytosis through opsonization, and block cellular attachment. IgG persists throughout late latent syphilis in humans.⁸⁴ Treatment leads to the loss of antigen-specific antibody at a rate and to a degree dependent on the duration of the infection. Thus, both cellular and humoral responses are necessary for treponemal clearance.

A characteristic of syphilis is the ability to cause a persistent, lifelong infection in one-third of the patients despite the elimination of millions of spirochetes. Possible immune evasion mechanisms include (1) an antigenically inert cell surface due to few outer membrane proteins and/or a coat of host serum proteins (“slime layer”), (2) intracellular location or location in an immunoprivileged site, (3) a subpopulation of organisms that are resistant to phagocytosis, (4) suppression of the immune system, possibly by premature downregulation through the PGE₂ mechanism, (5) slow metabolism never reaching “critical antigen mass”, (6) the ability to use iron bound to transferrin and lactoferrin (iron sequestration), and (7) the ability to use iron alternatives such as zinc and manganese.^{84,87} A continuing T cell response probably acts to keep latent organisms in check, unless immunosuppression intervenes and the infection reactivates.

LICENSED STD VACCINES AND VACCINES IN DEVELOPMENT

Successful vaccination often requires not only the specific microbial antigens to elicit the protective immune response but also an adjuvant to enhance the magnitude of the immune response and to polarize it in the desired direction. Adjuvants are especially important for subunit and recombinant vaccines. The route of administration can also be critical.

ADJUVANTS

Adjuvants are components added to vaccine formulations to enhance the immunogenicity of vaccine antigens. They can be immune potentiators or delivery systems. Immune potentiators stimulate the innate response directly or through pattern recognition receptors (PRRs). Delivery systems present concentrated vaccine antigens to APCs and bring together antigens and immune potentiators. Choosing the optimal adjuvant can have beneficial results: (1) an accelerated, more robust and sustained immune response, (2) stimulation of highly active, neutralizing antibodies, (3) elicitation of a cytotoxic T lymphocyte response, (4) improving the immune capacity of persons with weakened immunity, (5) increasing the response rate in low-responder groups, and (6) reducing the amount of antigen required.³⁷ Until recently, adjuvant research and development has focused on enhancing the antibody response; however, the importance of vaccines against HIV, HSV, HCV, and tuberculosis has shifted the

focus to adjuvants capable of eliciting a cellular immune response especially Th1 and CTL responses.³⁷ Only alum salts acting as delivery systems but not as immune potentiators, have been approved for human usage in prophylactic vaccines.

ROUTE OF ADMINISTRATION

Because STDs originate at mucosal surfaces, it is logical to hypothesize that a mucosal route of vaccine administration may produce a more rapid and protective immune response than systemic immunization via intramuscular or intradermal administration. This hypothesis is supported by the success of oral vaccines against gastrointestinal infections such as *Helicobacter pylori* and rotavirus, and inhaled vaccine administration against respiratory infections such as *Mycoplasma pneumoniae* and influenza virus.⁸⁸ This corollary may hold for HIV, *C. trachomatis*, *N. gonorrhoeae*, and HSV but has yet to be conclusively demonstrated. At the genitourinary mucosal surface, the humoral immune response involves locally produced IgM and IgG, serum-derived IgG, and, importantly, sIgA. The local CMI response is characterized by cytotoxic T lymphocytes and IFN- γ producing CD4⁺ T cells.⁸⁸ Both responses are affected by the menstrual cycle. Nasal and local vaginal vaccine administration have produced the best IgA immune response at the genital-vaginal mucosal surface (Fig 99-5).

LICENSED STD VACCINES

Currently, two vaccines are licensed by the FDA for prevention of STDs, vaccines for HBV and HPV infections (Table 99-1).

Hepatitis B virus

A hepatitis B virus (HBV) vaccine has been available for over 20 years. The initial 1982 preparation was purified surface antigen or HBV envelope proteins from the plasma of infected individuals. This was replaced in 1986 by a genetically engineered vaccine manufactured in a yeast recombinant (*S. cerevisiae*) expressing the gene for the surface antigen. This yeast-derived vaccine is immunogenic, safe and cost-effective in preventing HBV infection in neonates, children, and adults.⁸⁹ An additional HBV vaccine is derived from mammalian cells using an identical process.⁹⁰ HBV vaccination is also protective against hepatitis D (delta), which requires simultaneous or prior HBV infection to replicate. Combined hepatitis B and hepatitis A vaccine preparations have proven highly effective and HBV vaccines have been combined with other vaccines, notably a tetravalent preparation with HAV, diphtheria, tetanus, and pertussis.

Seroprotection after vaccination is defined as anti-HBs status ≥ 10 mIU/mL. This is achieved in over 95% of young vaccinees. HBV vaccines are well tolerated with minimal side

Table 99-1. STD Vaccines: Characteristics of the Natural Host Immune Response, Vaccine Status, and Vaccine Key Issues

STD	Target cells	Nature of Infection/ Disease	Host Immune Response			Antigenic Diversity	Protective Immunity	Vaccines: Status and Key Issues
			<i>Innate</i>	<i>Humoral</i>	<i>CMI</i>			
HBV	Hepatocyte	Acute	Phagocytes hepatocytes, NK, NKT, Kupffers	Anti-HBc	Th1 response CD4/CD8 (CTL) IFN- γ , TNF- α , IL-12 DTH	Rare	Concomitant	Status—licensed <u>Key issues</u> Duration of protection, vaccine escape mutants Birth dose & follow-up doses in poor countries Cost including administrative infrastructure Vaccine mistrust, 3 dose IM regimen
		Chronic	APC/DCs, IFN- α , β , γ TNF- α , IL-4 lysozymes	Anti-Hbe Anti-HBs				
HPV	Keratinocyte	Latent	Phagocytes APC/DCs, NK cells IFN- α , β ; GM-CSF IL-4	IgG, IgA, anti-L1 anti-E6/E7, IL-4	Th1 response CD4/CD8 (CTL) INF- γ , IL-12, TNF- α DTH	Low	Type-specific	Status—licensed <u>Key issues</u> Duration of protection, cross-protection Cost, distribution, 3 dose IM regimen, who to vaccinate Coverage of cancer types, changes to Pap programs Increased sexual activity, parental approval of STD vaccine
HSV	Squamous epithelium	Acute	Phagocytes, NK, NKT LC cells, natural IgM T-bet, IFN- α , β , γ	IgG complement	Th1 response CD4/CD8 (CTL) IFN- α , β , γ ; IL-2 TNF- α , ADCC	None	Type-specific	Status—phase I, II <u>Key issues</u> Vast array of immune evasion techniques Immune mediators and immunogenic proteins unknown HSV rapidly enters immune protected sites Lack of credible animal model
	Sensory ganglia	Latent	TNF- α , IL-1, 8, 12, 15, 18; Complement					
Ng	Columnar epithelium	Acute	Phagocytes, NK cells APCs, IL-1	Th2 response	CD8 (CTL), IL-2 IL-12, TNF- α , DTH ADCC	High	No	Status—early preclinical <u>Key issues</u> Antigenic diversity between strains and within strains

Table 99-1. (Continued)

STD	Target cells	Nature of Infection/ Disease	Innate	Host Immune Response <i>Humoral</i>	<i>CMI</i>	Antigenic Diversity	Protective Immunity	Vaccines: Status and Key Issues
				IgG, IgA, IgM "natural" serum antibodies, IL-4 IL-10, complement				Low antigen levels avoid immune system stimulation Lack of credible animal model Anti-Rmp blocking antibodies, Masking by LOS sialylation
Ct	Columnar epithelium	Acute Subacute	Phagocytes, NK cells IFN- γ , APC/DCs TNF- α , IL-1, 8 lysozymes	IgM, IgG, anti-hsp60 anti-MOMP IL-10, sIgA	Th1 response CD4/CD8 (CTL) IFN- γ , TNF- α IL-12	Low	Gradual	Status—early preclinical <u>Key issues</u> Molecularly defined vaccine Heterotypic infections cause immunopathology Need for immune-potent adjuvant Strategies to target dendritic cells
Tp	Squamous/ columnar epithelium CNS, CV, MS	Acute Latent	Phagocytes lymphocytes APC/LCs, IL-1 β , IL-2 M1P α , Mip β , PGE ₂	IgG, IgM anti-TROMPS complement C3b	Th1 response CD4/CD8 (CTL) IL-6, 8, 10, 12, IFN- γ TNF α , DC-SIGN DTH	Low	Concomitant	Status—early preclinical <u>Key issues</u> <i>T. pallidum</i> cannot be cultivated Immune protected sites Antigenically inert surface No critical antigenic mass Immune down-regulation by PGE ₂ mechanism Subpopulation resistant to phagocytosis Iron sequestration Chancre clearing by combined Th1/Th2 response

Bold indicates primary immune response

Data in this table was extracted from peer-reviewed publications (see text for references and explanation of abbreviations). Ng, *Neisseria gonorrhoeae*; Ct, *Chlamydia trachomatis*; Tp, *Treponema pallidum*.

effects. Factors associated with nonresponse include age more than 40 years, male gender, obesity, tobacco smoking, HIV infection, immunocompromising chronic diseases, hemodialysis, subcutaneous or buttock injection, vaccine freezing, and an accelerated schedule.⁹¹ Symptomatic hepatitis B infection is extremely rare after successful immunization even though anti-HBs levels may become nondetectable in up to 50% of individuals within 5–10 years. Immunization also prevents perinatal infection in infants born to HBsAg-positive mothers. The usual immunization course is three doses including a final booster at least 4–6 months after the initial two-dose primary series. Neither anti-HBs testing nor late booster doses are routinely recommended after vaccination.

Long-term follow-up (9–15 years) of HBV vaccinees in Alaska, Quebec, Taiwan, and Italy have shown that (1) HBV vaccine provides excellent protective immunity for at least a decade, (2) breakthrough infections are asymptomatic, rare ($\leq 1.26/1000$ persons-years), and mostly affect persons who did not demonstrate seroprotection at the time of primary vaccination, (3) anti-HBs antibody levels fall faster and further for infants and small children, (4) some vaccinees do not demonstrate an anamnestic response to a single booster (again associated with younger age) but all of those studied who received a second booster did respond, and (5) pre- and postbooster anti-HBs levels correlate.^{92–98} A routine adolescent wellcare visit might present an opportunity to deliver a “precautionary” HBV booster along with HPV, DPT, and meningococcal vaccines.⁹⁹ However, few are advocating across-the-board HBV boosters at this time.

In spite of early evidence to support high-risk, targeted HBV vaccination, this immunization strategy failed.¹⁰⁰ This has important implications for other STD vaccines. Routine childhood and infant vaccination is now the goal of the WHO, CDC, and most official bodies. To date, 151 of 193 WHO member countries have adopted universal childhood HBV vaccination policies; 76 have a policy for administering the first dose soon after birth; and six have policies for vaccinating adolescents.¹⁰¹ Seventy-two percent of the high prevalence member states have adopted universal infant immunization and 53% of those recommend a birth dose. Infant and childhood vaccination programs on every continent have been successful including The Gambia, China, Indonesia, Senegal, Canada, Thailand, Alaska, and Taiwan.^{8,101–108} WHO’s goal is HBV vaccination in all countries by 2007 and 90% coverage by 2010. Dramatic successes in the prevention of HBV infections and hepatocellular carcinoma have been reported.¹⁰⁸ STD patients were initially recommended for HBV vaccination but this quickly expanded to all persons attending STD clinics.¹⁰⁸ In the United States, the Healthy People 2010 goal for HBV vaccination of STD clients is 90%. Success in STD clinics and correctional facilities has been well documented.^{106,108}

Several important challenges remain in the global effort to eliminate new HBV infections through vaccination. Chief

among these are the cost (including the administrative infrastructure), the administration of a dose at birth and follow-up doses, the mistrust of vaccines, the potential impact of virus mutants and inadequacies in the existing vaccination program infrastructure that are amplified by a three-dose regimen.^{101,109} The monovalent HBV vaccine price is only \$0.30 USD but this is still costlier than other routine infant immunizations. The world’s poorest countries require financial support to deliver this vaccine. The highly effective birth dose can be challenging since most births occur at home without immediate access to health-care. Administration by trained traditional birth attendants has been successful in Indonesia.¹⁰¹ Finally, HBV immunization programs in Africa have been shown not to negatively impact existing vaccination programs;¹⁰¹ in fact, they may provide a boost to existing WHO Expanded Programme on Immunization (EPI) efforts.¹¹⁰ Vaccine freezing and wastage can be a problem, however. One potential challenge is HBV vaccine escape mutants. While antibodies induced by HBV vaccination are neutralizing across all subtypes, point mutations in the HBV genome have been found which bind vaccine-induced antibodies. The mutant HBV is not neutralized. These mutants are being investigated.¹¹¹

If everyone were immunized against HBV today, 350 million chronically infected carriers would still need treatment. The success of postexposure immunization has raised the possibility of a therapeutic HBV vaccine. Additionally, HBsAg clearance has been observed in individuals who received bone marrow transplants from HBV-immune donors.⁴⁴ This correlated with detection of CD4⁺ T cell reactivity against HbC in the blood. These and other data suggest that therapeutic vaccination should include HBcAg.⁴⁵ The Hepacore Project is attempting to develop a therapeutic vaccine based on chimeric HbC VLPs.¹¹²

To induce a CD8⁺ T cell response, studies have focused on DNA immunization and HBV polymerase, a highly immunogenic CD8⁺ target essential for early virus replication.⁴⁴ Since inhibition of HBV replication can be separated from the mechanisms of liver injury, a therapeutic vaccine could stimulate tissue-sparing cytokine production and/or antibodies to prevent the antigen-nonspecific amplification of the intrahepatic infiltrate and thereby inhibit liver damage.⁴⁴ Some have suggested strategies to optimize the immune response to enable a therapeutic vaccine to be successful; for instance, inhibition of viral replication by antiviral drugs.⁴⁵ Lamivudine treatment has been associated with improved HBV-specific helper and cytotoxic T cell function in chronically HBV-infected individuals.^{45,113}

Human papillomavirus

Human papillomavirus (HPV) type 16 was first identified as a significant factor in the pathogenesis of preinvasive and

invasive cervical cancer in 1983. Over 200 types have now been described; 40 can infect the genital tract and more than 20 types have been associated with cervical cancer.¹¹⁴ Seventy percent of cases of cervical cancer are associated with types 16 and 18; and 90% of genital warts are associated with types 6 and 11. In 1991, papillomavirus-like particles were created in the laboratory allowing accelerated vaccine research. These virus-like particles (VLPs) are empty viral capsids, which copy the structure of the natural virion but are devoid of DNA. They are noninfectious but generate a potent immune response.

In 2002, the remarkable efficacy of a preventive HPV-16 vaccine was demonstrated in a phase II randomized, multicenter, double-blind study involving 2391 young women 15–26-year-old.^{114–116} Using VLPs of the L1 protein in the viral capsid, the vaccine was protective against preinvasive disease (efficacy = 100%), persistent HPV-16 infection (efficacy = 100%) and transient HPV infection (efficacy = 91%). Efficacy against persistent infection remained 100% even including participants who had violated the study protocol. The three-dose regimen had few side effects and generated an antibody response in 99.7%. At month 7, the mean antibody level was 58.7 times as high as women with natural infection.¹¹⁵ Immunogenicity bridging studies have demonstrated anti-HPV titers two-to-threefold higher in boys and girls 9–15 years of age compared to females over 15. The antibody levels generated in girls are constant over the 9 to 11 year age range but fall off significantly when the vaccine is given at 12–13 years of age.^{117–118}

Highly consistent results were subsequently obtained from a bivalent (HPV-16/18) vaccine in a phase IIb trial¹¹⁹ and a quadrivalent (HPV-6/11/16/18) vaccine in one phase II and two phase III trials.^{65,120} Participants were from North America and South America, Europe, and the Asia-Pacific. The bivalent vaccine (Cervarix®, GlaxoSmithKline Biologicals) is manufactured in an baculovirus/insect cell expression system whereas the quadrivalent vaccine (Gardasil®, Merck and Co., Inc.) uses a yeast system (*Saccharomyces cerevisiae*).^{114,116} Cervarix® includes an adjuvant composed of 500 µg of aluminum hydroxide with 50 µg of 3-deacylated monophosphoryl lipid A (AS04).^{114,116} Gardasil® includes an adjuvant of 225 µg of aluminum hydroxyphosphate sulfate.⁶⁵ The vaccines should be stored at +2°C to +8°C and not allowed to freeze.

In mid-2007, the updated results of four randomized, double-blind, placebo-controlled trials in individuals over 15 years of age involving the quadrivalent vaccine were reported.^{121–124} In susceptible women, vaccine efficacy was 99–100% for the following endpoints related to vaccine-containing HPV types: condyloma (venereal warts), cervical intraepithelial neoplasia (CIN2-3), adenocarcinoma *in situ* (AIS), cervical cancer, vulval intraepithelial neoplasia (VIN2-3), vaginal intraepithelial neoplasia (VaIN2-3), vulval cancer and vaginal cancer. The intention-to-treat analyses of all randomized women (including those who were naive or infected with

vaccine-containing HPV types at day 1) demonstrated vaccine efficacies of 44% for HPV-16/18-related CIN2-3, AIS and cervical cancer; 18% for any cervical endpoint; 71% for HPV-16/18-related VIN2-3, ValN2-3, vulval and vaginal cancers; 49% for any vulval or vaginal endpoint; 73% for HPV-6/11/16/18-related condyloma; and 51% for any condyloma. An update of the original phase II Cervarix® trial after 4.5 years showed continued vaccine efficacy against HPV-16/18 incident infection (96.9%), 6 and 12 month persistent infection (94.3% and 100% respectively) and CIN (100%).¹²⁵ An interim analysis of a large, international phase III bivalent vaccine trial (n=18,644) showed near 100% vaccine efficacy against HPV-16/18-related CIN2+ in susceptible subjects.¹²⁶ This study also demonstrated significant cross-protection against 6-month persistent infections with HPV-45 (59.9%), HPV-31 (36.1%), HPV-52 (31.6%) and against 12-month persistent infections with 12 combined oncogenic HPV types excluding HPV-16 and HPV-18 (27.1%). Gardasil® generates cross-reactive and cross-protective antibody concentrations against HPV-31 and HPV-45, as well.¹¹⁷ Gardasil® has shown partial cross-protection against persistent infection (combined efficacy 27%) and against CIN2/3 and AIS (combined efficacy 39%) caused by 10 non-vaccine oncogenic HPV types (HPV31/33/35/39/45/51/52/56/58/59).^{126a}

The sharp fall-off in efficacy in the intention-to-treat analyses for Gardasil® probably relates to previous exposure to vaccine-containing types, as well as the role of oncogenic HPV types not present in the vaccines. Type-replacement has not been ruled out.¹²⁷ These data and others underscore the critical value in vaccinating girls before the onset of sexual activity, i.e., 9–12 years of age.

In already-infected quadrivalent trial participants who received vaccine, there was no significant protection against CIN2-3 disease related to vaccine-containing serotypes, but there was a trend towards a reduction in the combined incidence of CIN1-3 and adenocarcinoma *in situ* in those with recent-onset infection with vaccine-containing HPV types, i.e. HPV DNA in cervicovaginal specimens but non-detectable circulating antibodies to that HPV type on Day 1.^{117,128}

A cohort of Gardasil® recipients (n = 241) followed for 60 months after dose 1 exhibited high, sustained vaccine efficacy with no evidence of waning immunity.^{114,116} Antibody titers peaked 30 days after dose 3, declined until month 18, and then plateaued for the 5 years of follow-up. This plateau was well above naturally acquired HPV-11 and HPV-16 antibody levels but similar to natural infection with types 6 and 18.^{114,116} Similar results have been documented for a Cervarix® cohort followed for 4.5 years.⁶⁵ The administration of a challenge dose of Gardasil® at 60 months produced a classic anamnestic response:¹²⁹ Additionally, enhanced humoral and memory B cellular immunity was generated when the bivalent vaccine was adjuvanted with MPL/ASO4 (as is the case with Cervarix® compared to aluminum salt only).¹³⁰

Both vaccines were safe and well-tolerated. No adverse effects were seen in the pregnant vaccine recipients or their breastfed infants.^{65,114} Gardasil® can be given with HBV vaccines and there is no need to restart the vaccination series if it is interrupted.^{114,116} Since both vaccine preparations are non-infectious, administration to immunocompromised patients is not contraindicated. The antibody response to Gardasil® in already-infected recipients is faster, stronger, and longer lasting.⁶⁵ Neither vaccine is recommended in pregnancy, for males, or for females older than 26 or younger than 9 years. HPV vaccine studies in each of these groups are underway and no additional risks are anticipated.⁶⁵ Changes in Pap screening recommendations are inevitable once HPV immunization programs are implemented; for instance, HPV-negative women probably require less frequent Pap smears. However, vaccine recipients may already be infected (and at risk of cancer) and HPV types associated with 30% of cervical cancer cases are not included in current vaccine formulations.

By the end of 2006, Gardasil® was licensed in 49 countries, including FDA approval on June 9, 2006. Cervarix® was licensed in Australia in May 2007. Everyone agrees that these vaccines will be most effective for young girls before initiation of sexual activity although sexually active girls and women even with previous Pap abnormalities, may benefit since they may not be infected with all four vaccine types. The expense of the recommended three-dose schedule (\$360USD) has already stimulated proposals for two-dose trials (personal communication—S. Dobson, G. Ogilvie).

Issues remain. The duration of protection remains unknown although follow-up data indicates at least a decade of protection, as discussed previously. By vaccinating only girls before they become sexually active, one might expect an 85% reduction in cervical cancer, a 44–70% reduction in abnormal Pap smears attributable to HPV, and a 95% reduction in cervical cancer deaths.⁵¹ Mathematical modeling, however, suggests advantages to vaccinating both men and women.¹³¹ It is unknown whether nonvaccine high-risk HPV types will fill the void counteracting vaccine benefits.¹³¹ This is called type replacement.

Different models have estimated the cost per QALY to be in the range of \$3000 to \$24,300 USD for HPV vaccines administered to females at 12 years of age.¹¹⁴ One analysis predicted that the most cost-effective HPV strategy was vaccination followed by biennial Pap screening beginning at age 24 years; however, vaccination followed by annual screening beginning at 18 years of age showed the greatest overall reduction in cancer incidence and mortality.¹³² A different model predicted a 61.8% reduction in cohort cervical cancer with a cost-effectiveness ratio of \$14,583 per QALY when 12-year-old girls were vaccinated with HPV 16/18.¹³³ In this model, vaccinating males was not cost-effective. Models that evaluated the catch-up vaccination for 12–24-year-old females predicted more rapid declines in both cervical cancer incidence and precursor lesions.¹¹⁴

Oncogenic HPV can cause several other cancers including penile, oropharyngeal, laryngeal, oral and anal neoplasms. This argues for vaccinating boys, men, and women outside 9–26 years of age. Plus, women can acquire HPV at any age. Merck is sponsoring a clinical trial of Gardasil® in 4000 men, including 500 self-identified gay men. Lastly, vaccine formulations including HPV 6 and 11 will prevent most genital warts.

In studies of adolescents and adult women, vaccines against HPV and herpes were acceptable with vaccine efficacy, health profession endorsement, and cost as significant determining factors.^{134–136} Nurse practitioners and physicians specializing in Obstetrics and Gynecology are willing to administer these vaccines;^{137,138} and studies on parental attitudes have shown a willingness to accept STD vaccination of adolescent children.^{134,137} Many jurisdictions in Canada, the United States, and elsewhere are planning to roll-out HPV vaccination programs in 2007 or 2008.

A 2003 WHO consultation recommended histologically classified cervical intraepithelial neoplasias (CIN) of moderate or high-grade and cancer as the efficacy measure for population-based studies with special reference to developing countries.¹³⁹

Amid the euphoria, some have called for second generation HPV vaccines to address problems with the current VLP products.¹⁴⁰ VLP vaccines are expensive to produce and difficult to distribute because of the need for a cold chain, the three intramuscular injections and the hard-to-access primary target group (preadolescent girls), especially in developing countries.¹⁴⁰ Also, type-specific protection is risky in places that lack Pap testing to rule out infection with other oncogenic types. An HPV DNA vaccine would be simpler to produce; an HPV viral vector vaccine might be compatible with mucosal delivery; and an HPV L2 vaccine would likely be broadly cross-neutralizing.¹⁴⁰ A combined prophylactic and therapeutic HPV vaccine using L1/L2 and E6/E7 chimeric VLPs is feasible.

Progress toward a therapeutic HPV vaccine has not been as dramatic although three therapeutic vaccine candidates are in phase II trials. Most research has focused on the early viral proteins (E1, E6, and E7) that are required for viral DNA replication, maintenance, and papilloma formation. E6 and E7 are consistently expressed in tumour cells. Therapeutic vaccination of animals has been successful and small, preliminary studies in humans have shown an HPV-specific antibody response, HPV-specific cytotoxic T lymphocytes, and wart clearing.^{141–143}

■ STD VACCINES IN DEVELOPMENT

Of the remaining STDs, vaccine research is most advanced for HSV, *N. gonorrhoeae*, *T. pallidum*, and *C. trachomatis* (Table 99-1).

Herpes simplex virus

Research into herpes vaccination has been ongoing for over 80 years. Predictably, the optimal vaccine would induce both humoral and cellular immunity; however, for HSV, the principal humoral and CMI mediators of infection are poorly understood and the key immunogenic proteins have not been well delineated.^{67,144,145} The virus rapidly enters neurons and nerve ganglia which are immunologically protected sites. Finally, some HSV immune evasion mechanisms are effective only in primates, compromising the reproducibility of research findings from animals.¹⁴⁵

The primary goal of a prophylactic HSV vaccine is sterilizing immunity, the prevention of infection. Failing that, the prevention of latent infection would be highly desirable. The most important goal of a therapeutic HSV vaccine would be to eliminate latent infection or, at least, to prevent recurrent clinical disease and/or asymptomatic viral shedding. No vaccine candidates have achieved any of these goals. Therefore, HSV vaccine trials have adopted more modest objectives, including a reduction in the amount of virus necessary to infect and establish latency, prevention and/or decreased severity of primary clinical herpes, decreased severity and frequency of clinical recurrences, partial protection of the ganglia (decreased magnitude of latent infection leading to less frequent recurrences), shedding less virus and shedding less often.¹⁴⁶

Killed virus vaccine candidates have failed and the focus for HSV vaccine development has shifted to (1) replication-incompetent mutants, (2) replicating vectors with HSV genes encoding immunogenic proteins, (3) subunit vaccines, and (4) DNA vaccines.

Replication-incompetent mutant virus vaccines are derived from infectious HSV viral strains missing a gene essential to the reproductive cycle. After infection, viral replication proceeds until the missing gene product is required. By then, a broad immune response will have occurred since the mutant has intact immunogenic proteins.¹⁴⁷ An early study failed¹⁴⁷ but two later trials using a mutant with a Th2-polarizing gene deletion demonstrated promising therapeutic results in animal trials and phase I/II human trials. Previous research demonstrated that recurrent HSV disease is prevented by virus-specific Th1 cytokines, especially IFN- γ , but facilitated by Th2 cytokines, especially IL-10.⁶⁶ In 2 randomized, double-blind trials involving persons with ≥ 5 recurrences in the previous year, recurrences were prevented in 37.5% and 43.5% ($p = 0.068$ and 0.024 , respectively) and significantly reduced in the remainder.^{66,148}

Replicating vector vaccine candidates involve HSV gene insertion encoding immunogenic proteins into a replication-competent viral or bacterial vector, such as vaccinia, adenovirus, and *Salmonella*.⁶⁸ The vaccine recipient develops humoral and cellular immunity to the HSV proteins encoded

by the vector. Animal studies have been successful but human trials have not been completed. These candidates have three drawbacks: (1) the HSV-specific immune response is limited to a single protein or epitope; (2) individuals may already be immune to the vector and eliminate it prior to HSV-protein immune responses; and (3) safety concerns. Nonetheless, new attenuated-virus vaccine vectors are under development.¹⁴⁴

Recombinant DNA technology has permitted the safe production of HSV glycoprotein free of virus and viral DNA. Subunit vaccine research has centered on glycoproteins D and B. Both are highly conserved in the majority of HSV strains (over 98% in the case of gD) and both stimulate neutralizing antibody, antibody-dependent cellular cytotoxicity, and CD4⁺/CD8⁺ virus-specific immune responses.¹⁴⁷ Although protective in animals, only one or two glycoproteins may not produce broad or durable immunity in humans.¹⁴⁷ In two randomized, double-blind trials of a gD2gB2 glycoprotein vaccine with the adjuvant MF59, decreased HSV-2 acquisition was not achieved. However, a transient 50% protection for 5 months and a difference in efficacy by gender was noted (24% less infection in females vs. 4% in males).^{72,147}

Two additional subunit vaccine trials followed using a gD2 glycoprotein candidate with the adjuvants alum and MPL (3-de-O-acylated monophosphoryl lipid A), a potent inducer of humoral and cellular immunity.¹⁴⁹ Both studies demonstrated significant protection from symptomatic herpes (73%, $p = 0.01$ and 74%, $p = 0.02$) in women without preexisting antibody to HSV-1 or HSV-2.⁶⁸ There was a nonsignificant trend to reduced HSV infection in HSV-1 and HSV-2 negative women (46% and 39%) but no effect in HSV-1 seropositive women or men. The vaccine was safe, well tolerated and induced both gD-specific neutralizing antibodies and Th1 CMI responses.⁶⁸ The adjuvant appears to be the critical difference between these two sets of studies. A larger NIH trial using the latter formulation is underway. Mathematical modeling suggests a more substantial effect for reduced asymptomatic viral shedding than for prevention of disease. In the model, disease prevention without reduced viral shedding may result in increased HSV incidence, confirming previous predictions.^{146,150} The authors recommended universal herpes immunization.

Finally, research is underway into DNA vaccines consisting of bacterial plasmids that express HSV proteins.^{144,145} This approach could stimulate multiple arms of the immune system using a mixture of plasmids encoding various peptides and proteins involved in both CMI and humoral immune responses.¹⁴⁴ An effective HSV vaccine will provide additional benefits for nongenital HSV disease including neonatal herpes, oral-facial herpes, herpetic keratitis, herpetic encephalitis, and eczema herpeticum.¹⁴⁶ These effects would be optimized by universal childhood immunization.

Neisseria gonorrhoeae

Progress in *N. gonorrhoeae* development has been hindered by the lack of a credible animal model of mucosal disease, marked antigenic diversity between strains, and antigenic variation within strains over time.¹⁵¹ Trials of a formalin-killed, pilated whole organism vaccine, a gonococcal purified pilus vaccine, and a recombinant protein I (Por) vaccine have all failed.¹⁵²

Piliation, a virulence factor, has been the focus of vaccine research. Anti-pilus antisera reduce gonococcal adhesion to epithelial cells, opsonize gonococci for phagocytosis, and protect cells in vitro from gonococcal cytotoxicity. Human studies showed antibodies in serum and genital secretions, and protected volunteers from homologous but not heterologous challenge. This protection was easily overwhelmed by increasing the inoculum.¹⁵³ Because of antigenic variation, pilus vaccine research has been temporarily abandoned.¹⁵⁴ However, more stable pilus-associated proteins may be future vaccine candidates.¹⁵²

Por is the major gonococcal outer membrane protein. Although genetic variation occurs in the surface-exposed loops, the membrane-spanning regions are conserved.¹⁵⁵ The protein is encoded by a single copy gene, *por*, and there are two structurally distinct types, PIA and PIB, each with several serotypes.¹⁵² Antibodies to Por promote complement-mediated killing and opsonization, and inhibit interaction with epithelial cells.¹⁵⁵ The immune response to Por during salpingitis may stimulate serotype-specific protection against recurrences with the same serotype.¹⁵² For these reasons, Por is considered a good vaccine candidate. A failed Por vaccine human trial may have been due to contamination with blocking antigen Rmp⁷⁹ which stimulates antibodies that block killing of serum resistant strains.^{79,153} Por vaccines may also be inhibited by sialylation of lipooligosaccharide (LOS) blocking surface exposure of Por epitopes and inhibiting complement fixation.¹⁵³ Encouragingly, recent research supports one dominant PIA type, a common PIB type, and similarity in individual Por variable regions.¹⁵⁵ This suggests vaccines targeting a limited number of Por protein epitopes might provide protection against several strains.¹⁵⁵ Recombinant strains of *Salmonella typhimurium* that express Por and stimulate both humoral and CMI are considered oral vaccine candidates.¹⁵⁴

Many outer membrane components have been considered vaccine candidates including Opa proteins (Protein II), LOS core sugars, H.8 antigen, IgA protease, anaerobically expressed proteins (Pans), transferrin, and lactoferrin. Ultimately, the ideal gonococcal vaccine antigens should have little antigenic variation, not be protected by anti-Rmp blocking antibodies, not masked by LOS sialylation and contain epitopes that are both conserved and stimulate protective antibodies.¹⁵⁴ Por remains the leading candidate.

Chlamydia trachomatis

Despite active preclinical research and development for over 20 years, no vaccine for the prevention of sexually transmitted *C. trachomatis* has entered clinical trials. Vaccines for trachoma prevention have shaped the current approach to vaccines for sexually transmitted chlamydia.

Three important lessons were from trachoma vaccine trials in both humans and primates.¹⁵⁶ Human trials demonstrated that parenteral immunization with whole inactivated chlamydial elementary bodies induced short-lived (<1 year) protection. Primate trials demonstrated protection when the vaccine immunotype matched the challenge strain immunotype (homotypic immunity) and showed that mismatch of immunotypes not only resulted in infection but also enhanced inflammatory responses. Heterotypic infection was associated with immunopathology. These observations suggest that a chlamydia vaccine must be molecularly defined (containing only protective not disease-enhancing antigens) and have better immunogenicity than whole bacterial cells. This has become the central paradigm of chlamydia vaccinology.

The molecular basis for the immunotype (or serovar) classification of *C. trachomatis* appears to be due to allelic variation in a single copy gene that specifies the synthesis of MOMP. MOMP is rich in T and B cell epitopes. Interestingly, T cell epitopes cluster in sequence-constant regions, while B cell epitopes cluster in sequence-variable regions. Monoclonal and polyclonal antibodies to MOMP can neutralize *C. trachomatis* in tissue culture and MOMP antibody-coated organisms cannot infect experimental animals. Neutralizing antibodies to MOMP are directed to conformational epitopes. Because of these favorable immunological properties, MOMP has been extensively studied as a vaccine with disappointing results. Using denatured MOMP extracted from *C. trachomatis* elementary bodies, primates were parenterally and mucosally immunized but made poor antibody responses and were fully susceptible to challenge infection.¹⁵⁷ Possible reasons for failure include the denatured state of the vaccine protein and the need for better adjuvants. More promising results were obtained using the mouse model of *C. muridarum* genital infection and MOMP in its native conformation. This suggests that conformationally intact MOMP is essential for a *C. trachomatis* vaccine.¹⁵⁸

Genomics has made substantial contribution to the search for more broadly conserved antigens that induce protection. Eight different chlamydiae strains and species have been sequenced in their entirety including human immunotypes A, D, and L2 of *C. trachomatis*, the mouse strain *C. muridarum*, and the guinea pig strain *C. caviae*. These animal systems in which host-adapted chlamydia produce infection have strong immune correlates to human *C. trachomatis* infection. This includes the essential role of CD4⁺-dependent CMI in clearing infection and the role of CD4⁺ T cells and B cells in resistance to reinfection.

Based on these animal models, a new regulatory roadmap for chlamydia vaccine research is being defined. Vaccines that have successfully passed evaluation in two animal model systems can enter human trials for phase I and II immunogenicity and safety evaluation. Thus, vaccine candidates that induce immunity in the mouse model can be confirmed in the guinea pig model. If the antigen protects both animals, the orthologous protective antigen in *C. trachomatis* is eligible for testing in phase I/II human trials. This roadmap, while offering a way forward, is clearly labour-intensive since nearly 800 proteins are, in principal, vaccine candidates. Seiving these candidates by using bioinformatics to identify surface proteins, secreted proteins and virulence factors will narrow the list. Alternatively, using proteomics to identify chlamydia proteins able to enter the major histocompatibility complex antigen processing and presentation pathway can focus vaccine research on the few proteins that are T cell antigens. Since primates can be infected with human strains of *C. trachomatis*, primate studies may also be useful to evaluate immunotype restriction of immunity and vaccine hypersensitivity.

Identifying protective antigens for a molecularly defined *C. trachomatis* vaccine is necessary but not sufficient. Delivery of vaccine to dendritic cells, polarizing the immune response to generate appropriate protective effectors and triggering B and T effector/memory cell migratory patterns to genital mucosal surfaces are all important but unanswered research questions. As discussed previously, adjuvant will be critical to a fully immunogenic *C. trachomatis* subunit vaccine. Alum, a currently licensed adjuvant for human vaccine, is likely to be inappropriate since it polarizes to a Th2 helper phenotype for antibody responses. A *C. trachomatis* vaccine must elicit a Th1 response. Promising adjuvants include CpG oligonucleotides and other defined ligands which trigger TLRs and induce polyclonal Th1 responses. While both systemic and mucosal responses are essential to protective immunity, a *C. trachomatis* vaccine will probably be initially evaluated via parenteral delivery.

Treponema pallidum

Achieving effective acquired immunity to *T. pallidum* is strongly supported by four lines of evidence: (1) only one-third of the untreated human syphilis patients develop late complications;¹⁵⁹ (2) “chancre immunity” to reinfection is observed during the early stages of active, untreated infection and is associated with strong humoral and CMI responses;¹⁶⁰ (3) human experiments have shown that, after intradermal challenge, the development of lesions and changes in syphilis serology were dependent on the length of prior infection and that untreated, infected subjects developed no lesions or serologic changes;⁸³ and (4) supporting evidence exists in animal models.¹⁶⁰

The cloning of genes subsequent to the sequencing of the *T. pallidum* genome, recombinant technology, and new outbreaks of infectious syphilis in industrialized countries have renewed interest in a syphilis vaccine.^{154,161,162} Our inability to cultivate the organism presents a significant challenge to vaccine development. Because DTH appears to be a dominant protective immune response in chancre resolution, an effective vaccine needs to induce DTH as a primary effect.^{154,163} In animal models, vaccine candidates protect against infection with homologous but not heterologous strains. *T. pallidum* repeat protein K (TprK) may be the source of this antigenic variability.^{163,164}

Vaccine research is focused on recombinant treponemal antigens and proteins especially TROMPS (Treponema rare outer membrane proteins) which mediate attachment, invasion, acquisition of nutrients and cell stability. Candidates include Tp92 which promotes opsonization and phagocytosis and is 95–100% conserved across strains, TprK which demonstrates some cross-reactivity between strains, recombinant endoflagellar proteins, TpN47, TpN19, and TmpB. All have demonstrated at least partial protection in animal models. TpN47 may be involved in upregulation of HIV replication in monocyte precursors infected with HIV and in upregulating expression of the HIV receptor CCR5.⁸⁴ Interestingly, Tp92 shares sequence similarity with *N. gonorrhoeae* and *C. trachomatis* membrane proteins.¹⁶⁵ Treponemal components in some rabbit syphilis vaccines may cause downregulation of the immune system requiring neutralization.¹⁶⁶ Finally, BCG has been proposed as an ideal vaccine vector because it generates a strong DTH response.¹⁵⁴

THE FUTURE OF STD VACCINES

Several factors will impact the effectiveness of any STD vaccination deployment strategy. First, is the vaccine candidate a take-type or a degree-type vaccine? A take-type vaccine results in either full protection or no protection whereas a degree-type vaccine protects all of those vaccinated from a percentage of challenges.¹⁶⁷ Second, STD vaccine targeting is affected by the reproductive rate (R_0) of the STD involved. Low efficacy vaccines can reduce endemic prevalence because most new hosts are at low risk. However, elimination is problematic because most infectious reservoirs are difficult-to-access, high-risk, core group transmitters.¹⁶⁷ To eliminate STDs with a high reproductive rate (e.g., >4), the critical threshold of coverage (vaccine coverage multiplied by vaccine efficacy) needs to be high and may not be attainable with low efficacy vaccines.¹⁶⁷ Mathematical modeling supports universal vaccination or vaccinating the two highest risk populations.¹⁶⁷

A third consideration is vaccinating only women because of (1) their greater risk of disease, (2) better opportunities

to deliver vaccines (prenatal and family planning clinics), (3) the usual necessity of a female reservoir or host for ongoing transmission, and (4) evidence that women respond more vigorously to some vaccines, e.g., HSV vaccines. A more vigorous immune response in women may also be the cause of more severe STD complications. Modeling supports the targeting of take-type vaccines to one gender.¹⁶⁷

Finally, HBV vaccine programs suggest combined approaches for STDs broadly distributed within the population. For STDs highly concentrated in core transmitter groups, vaccination of groups with the highest risk and the second highest risk may be more cost-effective. This strategy is reminiscent of circle vaccination, which helped to eradicate smallpox. The final answer will come from mathematical modeling combined with practical considerations around delivery and follow-up. The answers may differ for different STDs.

Acquiring an STD is accompanied by social stigmatization and public health STD programs run the risk of increasing this discrimination for individuals and populations. Additionally, the structural nature of stigma and discrimination can negatively affect access to vaccines for marginalized groups such as sex workers and drug users. The criminalization of sex workers, the lack of resources for the poor and the paucity of user-friendly care for street youth and drug users may block vaccine delivery reducing coverage and effectiveness. These are often the same populations

with the highest risk and prevalence. The general population may be reluctant to accept STD immunization and parents may find it difficult to admit that their children may not always make the safest sexual decisions.

On the positive side, research consistently shows that the decision to be vaccinated or to allow vaccination of children or dependents relates to an understanding of the risk of the disease targeted, perceived vaccine efficacy and safety, cost and affordability, and recommendations from health-care workers.^{134,136,137,168,169} Universal infant and school-mandated vaccine programs are the least stigmatizing. Universal infant vaccination has been the most successful strategy in the United States for increasing 19–35-month-old infant coverage with all three HBV vaccine doses (from 16% in 1991 to 92% in 2004).¹⁷⁰ A California law requiring seventh grade students to have documented receipt of three doses of HBV vaccine as of July 1, 1999 was associated with an increase in coverage from 15.8% to 68.5%. Ninety percent of the students not in compliance were in the process of completing the three-dose series.¹⁷¹

Combining STD vaccines with other routine vaccines may also be effective. A combination vaccine containing diphtheria-tetanus-whole cell pertussis-hepatitis B, extemporaneously mixed with a Hib vaccine (DTPw-HBV/Hib) administered at 6, 10, and 14 weeks of age after a birth dose of HBV vaccine was highly immunogenic and well tolerated in a large study from the Philippine.¹⁷² The seroprotection rate to hepatitis B was 94.3%. Noninjection routes of

Table 99-2. Lessons Learned from Hepatitis B Vaccination Programs That Can Inform Vaccination Efforts for Other STDs

1. An STD vaccine which evokes primarily a humoral immune response can be highly effective at preventing a disease for which the natural immune response involves innate, humoral, and *CD4*.
2. There is no harm or benefit in immunizing persons already infected.
3. Protection continues after protective antibodies have fallen below detectable levels.
4. Acceptance of STD vaccines by parents, young people, and persons at risk depends on an understanding of the disease, recommendations by health workers vaccine effectiveness, safety, and affordability.
5. Properly implemented STD vaccination programs can be highly successful.
6. Vaccinating infected mothers can prevent perinatal infection.
7. Noncompletion of the recommended vaccine series can still result in some level of protection.
8. STD vaccination programs in developing countries need not negatively impact other vaccine programs.
9. When an STD vaccine is costlier than childhood vaccines, developing countries may need financial assistance.
10. Mistrust of vaccines and inadequate infrastructure are significant challenges in developing countries.
11. STD vaccine risks may not materialize. HBV vaccine did not result in autoimmune disease, diabetes, optic neuritis, chronic fatigue syndrome, demyelinating diseases, or reactions to thimerosal or aluminum.
12. Vaccine escape mutants are not necessarily important. HBV mutants were seen infrequently in highly endemic areas, involved one genome region, rarely caused vaccine breakthroughs, and did not disrupt vaccination efforts.
13. STD vaccine nonresponse factors may include male gender, age over 40 years, obesity, tobacco use, hemodialysis, buttock or subcutaneous injection, vaccine freezing, accelerated schedules, HIV, and compromised immunity.

administration or shorter courses can also increase coverage but effectiveness, safety, and cost will be the critical factors in vaccine acceptance. Herd immunity will hopefully protect those who decline vaccination.

STD vaccine programs might provide a disincentive to safer sexual behavior and result in an increase rather than a decrease in STD incidence. This has impacted HIV spread where it is called treatment optimism. Highly active antiretroviral therapy (HAART) has made AIDS appear less serious or even curable resulting in increases in unsafe sex among gay men.^{173,174} This may prove especially important for low efficacy vaccines since the public is most familiar with high efficacy childhood vaccines. Pre- and postvaccination counseling will need to make the average person aware of the importance of postvaccination safe sexual behavior, especially when vaccine efficacy is not high.¹⁷⁴

For a degree-type vaccine, a simple inverse relationship exists between vaccine efficacy and increases in unsafe sex.¹⁶⁷ If a vaccine is 75% efficacious, a concomitant 75% increase in unsafe sex will cancel its effect. If, however, unsafe sex increases beyond the vaccinated cohort, an increase in STD incidence can result. Take-type vaccines are less susceptible to changes in sexual behavior. STD vaccination in combination with nonvaccine control interventions can have an additive or synergistic effect depending on the effectiveness of the other interventions and whether the vaccine is degree-type or take-type.¹⁶⁷

HBV vaccination programs have given us valuable insights into STD vaccine issues (Table 99-2).^{91,175–177} An immunization program for persons at high-risk in the United States and Canada quickly expanded to universal infant immunization and routine vaccination of adolescents. Because of the subsequent increases in acute HBV infection in 20–39-year-old males, and in men and women older than 40 years, a national immunization program for adults may be the next step.¹⁷⁵

Humanity has shown the capacity to eliminate globally endemic and epidemic diseases through the use of childhood vaccines. However, the potential benefit from STD vaccines is highest in countries and communities where vaccine access is likely to be the lowest. The equitable distribution of STD vaccines within countries and globally may represent a far greater challenge than vaccine development itself.

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In 2006, the HIV/AIDS pandemic marked its 25th year. To date, roughly 60 million people have been infected and 20 million have died of AIDS. Approximately 15,000 people become infected with HIV every day. Although a number of prevention strategies have been implemented (such as education, counseling, behavioral interventions, early detection and treatment of STDs, and prescreening of blood products) they have proven inadequate for controlling the spread of HIV in many populations.¹ The past decade has seen the introduction of effective antiretroviral therapies (ART) in industrialized nations and the first stages of their dissemination to developing countries, the “heartland” of the epidemic. This effort, however, has been woefully inadequate at meeting the needs of those who require treatment.

Even if one were able to reach all those in need, however, the pandemic can never be fully addressed by treatment alone. Treatment will not prevent events that happen very early after infection, such as transmission to sexual partners during the postinfection peak of viremia² and the massive destruction of CD4 cells that occurs in the gut within weeks of infection.³ Transmission also carries with it real risks for complications, such as ART-induced lipodystrophy.⁴ Thus, there is an urgent need for effective and affordable prevention strategies that can be widely implemented. The most feasible and promising of these strategies is an HIV vaccine.

Designing and developing an effective HIV vaccine has been a major scientific challenge. Despite initial optimism, the search for an HIV vaccine has continued for more than 20 years without reaching its goal. HIV infection offers few clues to guide the search: there are no established correlates of immunity, no documented cases of spontaneous recovery from AIDS or HIV infection, and no animal models that faithfully predict HIV disease and vaccine responses in humans. However, several experimental and biological

models and insights suggest that developing a useful vaccine is possible, and several novel concepts are in clinical trials.

CHALLENGES TO HIV VACCINE DEVELOPMENT

■ GENETIC COMPLEXITY OF HIV: GLOBAL VARIATION

The global variation in HIV poses a formidable challenge to vaccine development, since the prevention of infection with diverse viruses requires the development of either a small number of broadly protective vaccines or a large number of vaccines that protect against a more limited range of viruses. Compared with other infectious disease pathogens, such as influenza, HIV exhibits extraordinary genetic diversity and complex molecular epidemiology (Fig. 100-1).

Rapid viral evolution and founder effects have contributed to heterogeneity in the global distribution of HIV. Based on full-length genome sequence analysis, HIV is classified into three main groups: M (main), O (outlier), and N (non-M, non-O). The vast majority of HIV subtypes identified to date belongs to M group. Group O is found predominantly in Central Africa; group N isolates are very rare and all have come from Cameroon. The M group contains 22 circulating genetic forms. Of these 22 forms, 9 are designated HIV subtypes (subtypes A-D, F-H, J, and K); these subtypes differ by roughly 25–35% in *env* sequences and by roughly 15% in the *gag* gene.⁵ There are 13 circulating recombinant forms (CRFs) that are identified by number in the order of their discovery followed by the letters of the parental subtypes. These CRFs are thought to have arisen by intersubtype recombination in an individual infected with two or more subtypes. All HIV subtypes are thought to have arisen in central Africa, where genetic diversity is greatest. In most other regions of the world, one or a few subtypes or CRFs predominate. On a global scale, the predominant genetic forms are subtype C (southern Africa, India), A (east and central Africa, Eastern Europe), B (North and South America, Europe, Australia), and CRF02_AG (west and central Africa) (Fig. 100-2).

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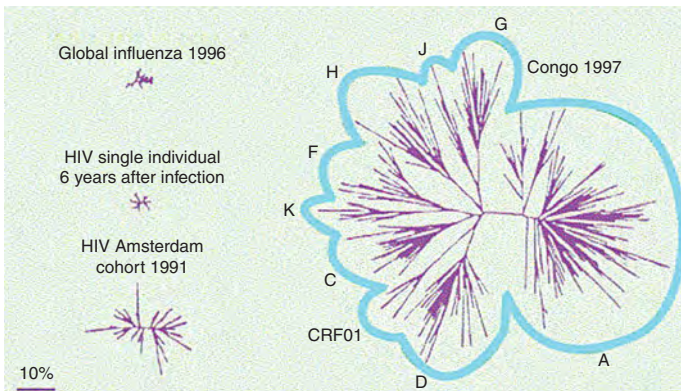


FIGURE 100-1. Influenza virus vs. HIV. (Reproduced with permission from Garber DA, Silvestri G, Feinberg MB. Prospects for an AIDS vaccine: Three big questions, no easy answers. *Lancet Infect Dis* 2004; 4: 397–413.)

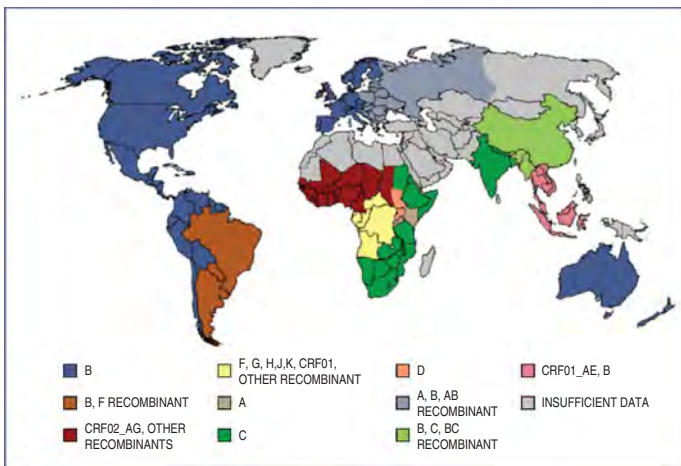


FIGURE 100-2. Global distribution of HIV-1 subtypes and recombinants. (Reproduced with permission from Duerr A, Wasserheit JN, Corey L. HIV vaccines: New frontiers in vaccine development. *Clin Infect Dis* 2006; 43: 500–511.)

■ SUBTYPE SPECIFICITY OF THE IMMUNE RESPONSE

The challenge of achieving cross-subtype protection in human vaccine trials is foreshadowed by studies in nonhuman primate models, which generally fail to show protection against challenge with heterologous simian immunodeficiency virus (SIV) isolates. The antibody response to most vaccine immunogens is nonneutralizing; these antibodies bind to HIV but do not prevent it from infecting target T cells or macrophages. Even if protein immunogens elicit neutralizing responses, the responses are limited. Vaccine candidates generally fail to elicit neutralizing antibody against primary isolates (recent clinical viral isolates) or against viruses of subtypes other than that of the immunogen, despite the fact that shared epitopes have been identified. Neutralizing antibodies can be identified in sera from infected individuals. Human monoclonal antibodies that neutralize isolates of multiple subtypes have been isolated, although such broadly neutralizing antibodies are very rare.^{6,7} In general, neutralization serotypes do not correlate with HIV subtypes, and insights

into a classification system that defines serotypes of HIV-1 infection might therefore provide insights into the development of an effective HIV vaccine.

Cellular responses to natural infection or immunization are generally broader than humoral responses. Cross-clade cytotoxic T lymphocytes (CTLs) are detected in individuals infected with a single HIV subtype.⁸ Vaccination with subtype B vectors results in CTL responses that recognize multiple subtypes, although intraclade responses are generally stronger.^{8–16} This cross-clade recognition is due not only to generation of CTL that recognize conserved epitopes common to several clades but also to the promiscuity of the T cell receptor (TCR), which can accommodate variability in the epitope peptides it recognizes. CD8 epitopes are typically linear sequences of 9–11 amino acids; these amino acids are presented to the TCR in conjunction with the major histocompatibility complex (MHC) molecule, which accounts for up to 65% of the contact with the TCR.¹⁷ The interaction with the TCR and the epitope is not uniform across all amino acid residues of the epitope. Recognition of the primary and secondary TCR contact residues is most important for binding of the epitope to the TCR; binding is relatively unaffected by amino acid substitutions at noncontact residues or by conservative amino acid substitutions in contact residues.¹⁷ In theory, promiscuity in TCR binding could result in recognition of up to 10^6 sequence variants.¹⁷ TCR flexibility in recognizing HIV epitopes has been demonstrated using cloned CTL lines from infected individuals.^{15,18} Similar results were seen in macaque CTLs elicited by infection or immunization.^{19,20} CTLs generated to 5 parent epitopes in human leukocyte antigen (HLA) transgenic mice recognized between 50% and 97% of variant epitopes (from clades A, B, C, D, F, G, H, J, and K as well as CRFs and groups N and O viruses). Conservative amino acid substitutions and those that did not disrupt the HLA-binding motif were more likely to be tolerated.¹⁷ Recognition of epitope variants was also demonstrated by peripheral blood mononuclear cells (PBMCs) from HIV-infected individuals and by CTL lines derived from human PBMC. Epitopes varied considerably in both predicted and actual epitope cross-recognition; these data are currently being used to design vaccine candidates that incorporate broadly recognized epitopes.

■ STRATEGIES FOR ADDRESSING VIRAL DIVERSITY

A variety of approaches have been proposed to design immunogens that will elicit B and T cell responses capable of recognizing a broad array of isolates. The importance of inducing broad immunity is underscored both by the extent of global viral diversity and by recent reports of superinfection of individuals with established HIV infection after exposure to HIV from a second source.^{21,22} The three most common immunogen-design strategies to address this issue are the use of consensus, ancestral,

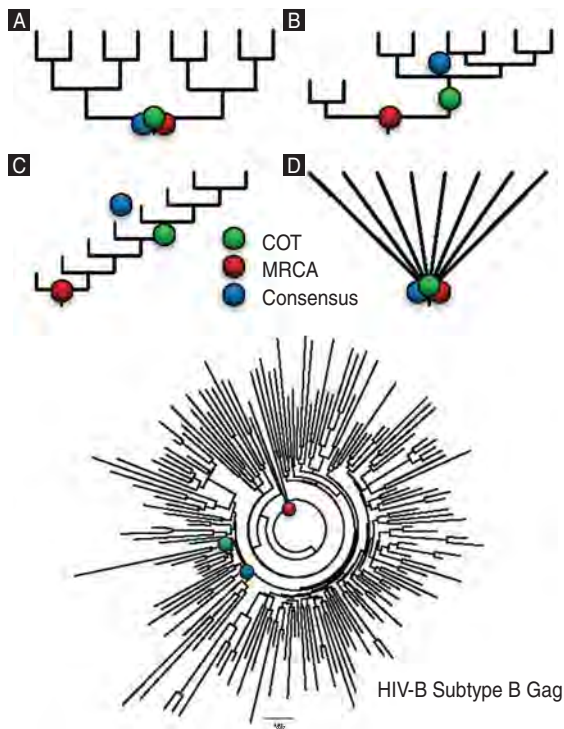


FIGURE 100-3. Top: A-D: 4 Hypothetical phylogenetic trees, each constructed using eight isolate sequences, demonstrating the relative positions of the center of tree (COT), most recent common ancestor (MRCA), and consensus sequences. Bottom: Position of COT, MRCA, and consensus placed on the maximum likelihood phylogenetic tree constructed using subtype b gag sequences. Reproduced with permission from Mullins JI, Nickle DC, Heath L, Rodrigo AG, Learn GH. Immunogen sequence: The fourth tier of AIDS vaccine design. (Figure provided by David Nickle.)

or center-of-tree (COT) sequences (Fig. 100-3). The goal of strategies utilizing these three centralized sequences, all of which preserve many known CTL epitopes, is to reduce the “distance” between the immunogen sequence and the infecting (challenge) virus isolates.^{23,24} The simplest and arguably more representative are the subtype consensus sequences, which are based on the most common amino acid at each position of the aligned available naturally occurring sequences. M group consensus sequences can be built by generating consensus sequences for individual subtypes and then generating a consensus sequence of all subtype consensus sequences.²⁵ Ancestral sequences are built using the phylogenetic trees constructed from known contemporary sequences; the hypothetical ancestral sequence is recreated using maximum likelihood phylogenetic analysis. Centralized (consensus or ancestral) sequences for a given subtype (e.g., C) are closer to the sequences of other subtype isolates than a natural subtype C isolate sequence would be. The centralized sequences lie at the root of the subtype so one saves the distance from the root to the individual contemporary isolates.²³ The final type of consensus sequence is COT, which minimizes the evolutionary distance to all isolates in the data set.^{23,24}

The genes produced from these centralized sequences are artificially made and may not retain important structural

features and biologic functions (Table 100-1). One such sequence has been tested to date: a group M consensus envelop glycoprotein.²³ Because the evolution of hypervariable regions proceeds via insertion and deletion, a consensus sequence was difficult to generate. Instead, a single-isolate sequence was used for five highly variable regions (V1, V2, V4, V5, and a region of the gp41 cytoplasmic domain) to facilitate proper folding; M group consensus was present in the constant and V3 regions. This test-of-concept study showed that the consensus gene retained at least some biologic activity (e.g., CD4 and coreceptor binding, ability to form dimers/trimers) and cross-reacted with patient sera of multiple subtypes. When injected into mice, the synthetic immunogen DNA-induced T cell responses (in an IFN- γ ELISpot assay) against subtypes B, C, and consensus peptides. In guinea pigs, synthetic peptide antigen was able to elicit neutralizing activity against selected primary strains, although neutralizing activity was of limited breadth and strength. A second consensus sequence—a full-length ancestral *env* sequence—was generated using 38 HIV-1 subtype B sequences. This sequence coded for a 160 kDa glycoprotein that was able to bind to and fuse with cells expressing CCR5.²⁶ When used in a DNA-prime, protein-boost regimen, it elicited only weakly neutralizing antibodies in rabbits. Thus, this analysis appears to offer more promise in defining methods to induce more broadly reactive T cell epitopes than neutralizing responses, likely related to the greater dependence of neutralization on the conformational aspects of the HIV-1 virion.

■ HIV VARIABILITY WITHIN INDIVIDUALS

A very high degree of viral diversity is generated by HIV secondary to the high error rate of reverse transcriptase and its inability to correct these errors, coupled with the extremely high level of viral replication (billions of new virions are generated each day).¹⁰ It is estimated that this level of mutation could produce variants with a single nucleotide change at every position in the genome thousands of times per day during chronic infection.²⁷ This high mutation rate is ultimately responsible for the global variation in HIV subtypes discussed above and also results in a high degree of intrahost variability. In other words, high variability exists within the viral swarm in a given individual. The implications of ongoing replication and resultant intrahost variability for successful drug treatment have been clear for some time. Treatment regimens that successfully “shut down” viral replication limit the production of progeny HIV virions. Treatment regimens that permit ongoing replication allow the generation of new virus, some of which will harbor mutations conferring resistance to antiretroviral drugs. These regimens fail when the fitness cost of the resistance mutation is low enough to allow the mutant virus to replicate successfully in the presence of an antiretroviral drug.

Table 100-1. Strategies for Addressing Viral Diversity

Vaccine Source	Differences (%)	Construction	Advantages	Disadvantages
Single-subtype isolates	5–15		<ul style="list-style-type: none"> Genes are derived from a viable virus; likely to adopt native conformations Properties of the isolate are known Furthest along in development 	<ul style="list-style-type: none"> Poor cross-reactivity possible with isolates from same or different subtypes
Subtype consensus	3–8	Most common amino acids at each position among subtype isolates	<ul style="list-style-type: none"> Easy to construct; Most representative of known isolates 	<ul style="list-style-type: none"> Derived consensus is influenced by sampling – only reflects isolates that have been sequenced. This may limit utility if sampled sequences not representative Relationship to newly transmitted strains unclear
M-group consensus	5–15	Consensus of subtype consensus constructs		<ul style="list-style-type: none"> May be unable to assume appropriate structure
Subtype ancestral	3–8	Inferred from phylogenetic tree	<ul style="list-style-type: none"> More likely to include epitopes uncommon during chronic infection (due to escape) Unlikely to change as new sequences are added to database 	<ul style="list-style-type: none"> Including such uncommon epitopes is only important if they are seen currently among recently transmitted isolates Influence of outlier sequences may cause divergence from center of sequence distribution
Subtype center of tree (COT)		Inferred from phylogenetic tree	<ul style="list-style-type: none"> Influence of outliers reduced Reduces distance to circulating strains when phylogenetic tree is asymmetric 	<ul style="list-style-type: none"> May be unable to assume appropriate structure

Similar scenarios are relevant for vaccine strategies that do not induce sterilizing immunity but that, after infection, ameliorate clinical course by eliciting anti-HIV CTL responses. Experiments in nonhuman primate models indicate that the CTL response limits viral replication in vaccinated animals. The degree of suppression varies; in some animals, viral replication appears to be completely suppressed, while limited residual viral replication continues in others. Viral escape from the selective pressure exerted by initial cellular responses is also seen in infected humans. Several investigators have documented mutations within HIV CTL epitopes that allow “CTL escape.”²⁸ These mutations allow the viral variants to circumvent the established CTL response directed towards the wild type epitope and are associated with the disease

progression.^{29–31} Recent experiments in macaques have documented vaccine failure associated with similar mechanisms of CTL escape. In one experiment, CTL responses were elicited in macaques using DNA vaccines in combination with IL-2 protein or plasmids.^{32,33} All controls and vaccinated macaques became infected; six of eight controls died within 2 years. Of the eight macaques receiving the DNA vaccine plus IL-2, seven controlled viremia and remained healthy for 2 years. One animal initially controlled viremia but showed late clinical vaccine failure, went on to develop simian AIDS, and died. Virologic studies showed initial suppression of viremia to undetectable levels. However, by 20 weeks postinfection the initial viral swarm had been replaced with a variant with a mutation in the immunodominant CTL epitope.

A single point mutation was associated with a 100-fold decrease in affinity for the histocompatibility locus (Mamu-A*1) and a 1000-fold decrease in recognition by the dominant CTL elicited by the vaccine. While additional CTL responses were seen subsequently, they were insufficient to contain viral replication and the animal went on to develop an AIDS-like syndrome. Thus, in a manner analogous to the evolution of drug resistance, the emergence of escape mutations led to the clinical failure. Vaccines that elicit high-level CTL responses to multiple epitopes are more likely to avoid failure due to CTL escape, just as the use of combination antiretroviral therapy is more likely to prevent drug resistance. In addition, strategies that elicit CTL and are capable of recognizing large numbers of variant epitopes (through promiscuous binding) may more successfully control infection.

Immune selection pressure may also drive viral variation among individuals within a population (interhost variability). An analysis of HIV variation suggests that viral evolution within a population is driven by a process of mutation within individuals that gives rise to CTL escape mutants that are limited by functional considerations within that individual (fitness cost) and selection pressures in the subsequent host.³⁴ These opposing forces help shape the consensus wild-type variant in the population. The efficacy of HIV vaccines that elicit CTL responses could be limited if transmission of CTL escape mutants from one host to another results in a predominance of these variants in the population. Longitudinal studies in humans suggest that CTL escape mutations may be maintained in the original host despite a fitness cost due to immune selective pressure by CTL directed to the wild-type epitope. Population level studies show both positive (increased heterogeneity) and negative (maintenance of consensus sequence) associations with different HLA class 1 alleles.³⁴ Positive associations presumably arise due to CTL escape in the manner described above. Leslie and colleagues studied such negative associations in clade C- and clade B-infected populations and suggested that negative associations also arise when CTL escape mutations are stably transmitted.³⁵ A negative association is seen when the escape mutation accumulates in a population to a level that defines a new consensus sequence. The loss of the original epitope and fixation of the variant sequence has important implications for vaccine development, as it would render ineffective strategies targeting such epitopes.

In experiments in nonhuman primates, a cloned SIV containing three mutations associated with CTL escape was used to study reversion of CTL-escape variant viruses. Virions carrying the escape mutations showed reduced replication kinetics *in vitro*, suggesting that the escape mutations carried a fitness cost. Two mutations reverted rapidly to wild type when introduced into a new histocompatibility-mismatched host.³⁶ These latter experiments suggest that reversion of CTL escape mutations does occur, especially if the CTL escape

mutation is associated with reduced fitness, and that vaccine strategies that elicit CTLs to epitopes that extract a high fitness cost for escape will be more successful. Replication of the less fit escape mutant will be more easily controlled within the vaccinated host and the escape variant will be more likely to revert to wild type in a new host.

APPROACHES TO PROPHYLACTIC VACCINES

■ NEUTRALIZING ANTIBODIES

More than 85 HIV vaccine trials involving over 30 products have been conducted to date. Initial HIV vaccines targeted the production of neutralizing antibodies. These antibodies not only bind to infectious HIV but do so in a manner that prevents productive interaction with target cells, thereby “neutralizing” HIV infectivity. This approach is appealing because subsequent exposure of the vaccinee to HIV would be expected to stimulate an anamnestic response, resulting in rapid production of antibodies that would block infection. Several licensed vaccines, such as those against polio, mumps, and rubella, elicit antibody-mediated protective immunity³⁷ and, while cellular immunity may be an important protective element for many vaccines, neutralizing antibody is recognized as the immune correlate of sterilizing immunity.

Neutralizing antibodies in HIV-infected persons

Much of the antibody response to natural infection with HIV is nonneutralizing and the role that neutralizing antibodies play is still being elucidated. Strong, broadly cross-reactive neutralizing antibodies have been detected in some but not all long-term nonprogressors who remain disease-free for 10 years or more without treatment.³⁸ In other individuals, neutralizing antibody responses were thought to develop slowly and to be of low titer.^{39,40} However, newer assays that measure responses to autologous virus, rather than heterologous primary isolates or laboratory adapted strains, show rapid development of significant neutralizing responses.⁴¹ These cell-based infectivity assays employ recombinant viruses expressing HIV envelope proteins derived from the same plasma sample being tested for neutralizing activity and thus measure antibody responses to autologous contemporaneous virus. Examination of 14 study participants shortly after infection revealed that only 2 developed negligible neutralizing activity against autologous isolates; the remaining 12 showed moderate- to high-level neutralization. These responses appeared to develop rapidly (within 8 weeks) and initial responses were narrowly focused (i.e., they did not neutralize heterologous virus).⁴² Serial sampling showed ongoing viral evolution in a manner consistent with escape and replacement of neutralization-sensitive virus with successive populations of resistant virus. Although the

neutralization responses are insufficient to limit replication in an infected individual, the authors speculate that even this level of humoral immunity might effectively prevent infection from the small amounts of virus expected to cross the mucosa during sexual transmission.^{41,42}

A number of HIV envelope proteins' features help it evade effective surveillance by the humoral immune system. The HIV envelope is a trimer of heterodimers; each heterodimer comprised a surface subunit (gp120) and a transmembrane subunit (gp 41) that are noncovalently bound to each other. Maintenance of this native trimeric structure may be necessary to elicit neutralizing antibodies. Conversely, the native structure shields many potentially neutralizing epitopes such as the coreceptor binding site, which becomes accessible only after CD4 binding.⁴² Longitudinal follow-up of infected patients revealed an additional potential means of escape from neutralization. The mutations associated with immune escape were not clustered within known neutralization epitopes but instead involved changes in surrounding glycosylation sites. Mutational substitution studies demonstrated that changes at these sites affected neutralization of distant epitopes.⁴³ The authors postulated that the extensive N-linked glycosylation found on the outer surface of the HIV envelope spike sterically hinders antibody binding to neighboring neutralizing epitopes on V1/V2, V3, and receptor binding sites and termed this phenomenon the "glycan shield" mechanism of immune escape.⁴² Subsequent studies of transmission within couples found little variability in sequences obtained from the newly infected partner, consistent with the transmission or outgrowth of a single sequence. Variable loops (V1–V4) in this partner were generally shorter and had a decreased number of glycosylation sites compared to sequences in the "donor" partner.⁴⁴ Virus from the recently infected partner appeared to be up to 10 times more sensitive to neutralization, suggesting that there is a transmission fitness cost associated with the resistance to antibody neutralization seen in the donor partner. If this is the case, protective humoral immunity may be more easily elicited than studies in chronically infected individuals might imply.

Despite the difficulty of inducing broadly neutralizing antibodies that react with multiple primary isolates and/or laboratory-adapted strains, they have been detected (albeit rarely) in infected individuals. The construction of monoclonal antibodies derived from such individuals has allowed more detailed study of these broadly neutralizing epitopes. The best-characterized examples include the following: F105 and b12, which are specific for the CD4 binding site on gp120; 2G12, which recognizes a complex epitope on gp120; and 2F5 and 4E10, which recognize linear epitopes on gp41 (Fig. 100-4). The ease with which these epitopes could be incorporated into a vaccine is unclear. For example, the b12 monoclonal has an unusual extended antigen-binding finger that accesses a normally recessed epitope on gp120 and

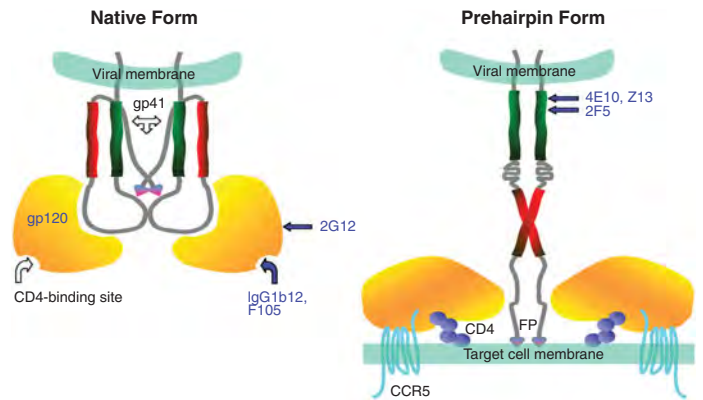


FIGURE 100-4. Schematic revealing the location of neutralizing antibody epitopes on gp120 and gp41 (shown in the native form and the transient, prehairpin form). (Reproduced with permission from Ferrantelli F, Ruprecht RM. Neutralizing antibodies against HIV—back in the major leagues? *Curr Opin Immunol* 2002; 14: 495–502.)

blocks CD4 binding.⁴³ The feasibility of targeting gp41 domains involved in virus fusion with the target cell, as 2F5 and 4E10 do, may be limited by steric hindrance and by the rapidity of the fusion process.^{27,43,45}

When three of these monoclonals were tested in vitro against a panel of newly transmitted clade B isolates, 4E10 alone neutralized all isolates, 2F5 neutralized 80%, and 2G12 neutralized 37%.⁷ The combination of b12, 2G12, 2F5, and 4E10 has shown strong cross-clade neutralization against clades B, C, A, and D in vitro.⁴⁶

Passive transfer studies in nonhuman primates

Several groups have used these monoclonal antibodies to block infection in test-of-concept trials in nonhuman primate models. Initial trials showed that HIV immunoglobulin (HIVIG) or individual monoclonal antibodies failed to protect macaques against the subsequent IV challenge with SHIV 89.6P (a chimeric SIV virus with an HIV envelope). In contrast, double and triple combinations of monoclonal antibodies that were delivered 24 hours before IV challenge resulted in protection against infection or ameliorated clinical course in infected animals.⁴⁷ Ruth Ruprecht and her colleagues have used combinations of three or four neutralizing monoclonal antibodies given to neonatal rhesus macaques before or immediately after oral exposure to SHIV. Thus far, 22 of 31 treated infant macaques were completely protected while all controls were infected.^{6,46,48–50} In separate experiments, monoclonal antibodies (alone or in combination with HIV immune globulin) were infused into female macaques prior to intravaginal challenge with SHIV 89.6PD. All control animals were infected and showed high viral load and CD4 depletion. Complete protection was seen in 8 of 14 passively immunized macaques; the remainder became infected but showed low-level viral replication and only modest declines in CD4 count.⁴⁷

Clinical trials INVOLVING ANTIBODIES

Phase 1 safety studies have been conducted with four of these monoclonals. They have been found in adults to be safe and well tolerated, with in vivo concentrations in the range of those that cause >99% neutralization in vitro.^{46,51} Initial clinical studies of passive immunization with broadly neutralizing monoclonal antibodies in HIV-infected individuals have not resulted in significant reduction in viral load.⁵² The potential utility of passive immunization for the prevention of HIV transmission has been widely discussed. The feasibility of this approach using monoclonal antibodies has recently been questioned due to concerns about low neutralization capacity for nonclade-B HIV, which predominates in areas of high mother-to-child transmission, and concerns regarding the implications of the polyspecific activity associated with some monoclonals.⁵³

Initial trials using recombinant monomeric HIV envelope proteins (gp160 or gp120) to elicit neutralizing antibodies yielded disappointing results. While the products proved very safe in phase 1 and 2 trials,^{54–56} the antibody response was generally low titer and, while it was capable of neutralizing the vaccine strain or lab-adapted HIV, it could not neutralize primary isolates (virus isolated from recently infected individuals), which are thought to most closely resemble infecting virus.⁵⁷ Two phase 3 trials of recombinant gp 120 (rgp120) products have recently been completed: a clade B candidate was tested in the United States, Canada, Europe, and Australia; and a clade B/E mixture was tested in Thailand. Neither vaccine prevented infection nor ameliorated postinfection course.^{58–61}

Current vaccine approaches to eliciting broad neutralization include the construction of immunogens that preferentially expose epitopes capable of inducing neutralizing antibodies. Selective mutagenesis has been used in an attempt to increase the response to neutralizing epitopes, while diminishing that to other, often more dominant, nonneutralizing epitopes.⁶² Another approach seeks to reduce the impact of nonneutralizing epitopes by shielding them by selective addition of n-glycosylation motifs.⁶³ The immunogenicity of monomeric gp120 engineered using these 2 approaches has been tested in rabbits. While the former approach appeared more effective than wild type gp120 in eliciting neutralizing activity against primary HIV isolates, the latter approach did not show appreciable neutralization of any of the primary isolates that were tested.⁶⁴ Deletion of hypervariable loops to expose conserved epitopes⁶⁵ and exposure of highly conserved epitopes in the membrane proximal region are also being explored.⁶⁶

■ CELLULAR IMMUNITY

Most ongoing trials of HIV vaccine candidates involve products that aim to induce HIV-specific CTLs. These cells recognize HIV epitopes displayed on cell surfaces in conjunction with

HLA. Thus, these immune effector cells recognize infected cells but not free virus. They limit the spread of infection by destroying infected cells via apoptosis, or by secreting chemokines and cytokines that interfere with subsequent rounds of infection. Experimental challenge studies suggest that this type of approach is less likely to reduce acquisition of infection than a vaccine that elicits broadly neutralizing antibodies. It is anticipated, instead, that HIV-specific cellular immunity will limit HIV replication and reduce plasma viral load—specifically setpoint viral load, the relatively stable plasma viral load typically seen after acute infection. A number of studies have shown that setpoint peripheral viral load is predictive of subsequent disease course.⁶⁷ In addition, plasma viral load predicts transmission to sexual partners; transmission decreases with reductions in plasma viral load and may be completely prevented when viral load drops below 1500 copies/mL.⁶⁸ Thus it is anticipated that CTL induced by HIV immunogens may limit the effects of HIV infection at both the individual level (disease progression) and the population level (HIV transmission).

T cells in HIV-infected persons

The role of HIV-specific CTL in the control of HIV infection is supported by observations in HIV-infected individuals. During primary infection in humans, control of viremia is temporally correlated with the development of CTL responses.^{69,70} CTLs may also operate to control viral replication in long-term non-progressors, who maintain low viral loads and high CD4 counts over long periods without treatment and who often have high levels of CTLs.⁷¹ A longitudinal study of a single patient documented the effects of CTL escape through the accumulation of mutations in five CTL epitopes; these changes were accompanied by loss of T cell reactivity to 4 of the 5 epitopes and increases in HIV viral load.³⁰ Although observational studies of CTL in infected individuals generally support their role in limiting viral replication, two recent studies failed to demonstrate a relationship between level of HIV-specific CD8⁺ cells in vitro and HIV viral load.^{72,73} This apparent discrepancy may be explained by HIV-induced immune dysfunction and decreases in cytolytic activity of CD8⁺ cells during chronic infection.⁷⁴ These in vivo changes may not be detected by in vitro assays for HIV-specific T cell activity.

CTL Vaccine studies in nonhuman primates

Perhaps more compelling evidence for the role of CTL comes from studies of SIV-infected macaques. In these experiments, depletion of CD8 cells from chronically infected animals was followed by rapid increases in SIV viral load and reconstitution with CD8 cells resulted in suppression of viremia.^{75,76} In addition, longitudinal follow-up studies of infected macaques demonstrated that CTL escape is associated with the loss of control of viremia.³²

Vaccine studies in nonhuman primates also point to a role of CD8⁺ CTL in control of viremia after infection. More direct evidence of a role for vaccine-induced CTL in controlling viremia comes from a recent study in rhesus macaques vaccinated with attenuated SIV mac 239 Δ3.⁷⁷ This vaccination strategy did not prevent infection of animals upon challenge with SIVmac251 but did result in lower postinfection viral loads compared to controls. CD8 depletion at the time of challenge resulted in higher levels of viremia compared to nondepleted vaccinated animals.

While HIV-1 specific CTL are present in HIV infected persons, a wide variety of CTL functions are impaired even in LTNP with HIV-1. At present, it appears that CTLs stimulated by CTL-based vaccines appear to have many of these functions restored. As such, it is hoped that vaccine-induced cellular immunity will control viral replication in the vast majority of individuals. Two outcomes of vaccination may contribute to the relative success of CTLs induced by immunization. T cell help is necessary for generating and maintaining an effective CD8 response. This process is limited in HIV infection, as HIV preferentially destroys CD4⁺ cells. Vaccination of HIV-uninfected individuals should elicit a fully functional T-helper response, which should in turn assist in the development of an anti-HIV CD8 response that is qualitatively better than that seen in a natural infection.²⁷ Second, the fact that exposure to the vaccine immunogen is limited, and not continuous as it is in natural infection, will allow for the generation of CD8 memory T cells, which are anticipated to be most effective in controlling the subsequent infection.²⁷

Clinical trials of CTL vaccines

In 2007, the majority of HIV vaccines in clinical testing elicit primarily CTL-based responses. Many vaccines based on viral vectors, such as poxviruses, adenovirus, and alphaviruses, have been tested in humans and found to be safe.^{54–56} While many of these products have shown limited immunogenicity in humans, in phase 1 and 2 trials several adenovirus candidates induce high-level CTL responses as measured in chromium-release CTL assays, or in ELISpot or intracellular cytokine staining assays, which measure HIV-specific T cell activity. HIV vaccines based on DNA plasmids also show a favorable safety profile, although these vaccines have been less immunogenic in vitro than was predicted by preclinical tests in nonhuman primates. (These and other CTL vaccines will be discussed further in the “HIV Vaccine Design Strategies” section.)

Measuring the effects of CTL vaccines in clinical trials

Based on their effect in animal models, it is anticipated that current vaccine candidates aimed at eliciting cellular immunity will have only a modest effect, if any, on acquisition of HIV infection but will ameliorate clinical course in vaccinees who become infected. Therefore, no effect may be seen using traditional measures of vaccine efficacy, which are based on

reduction in infection rates. A variety of alternate or surrogate endpoints have been proposed for vaccine candidates of this type. These endpoints include vaccine efficacy for delaying disease progression among vaccinees (VEp) or vaccine efficacy for preventing transmission to sexual or needle sharing partners by reducing infectiousness (VEi).^{78,79}

Many surrogate endpoints are based on reductions in peak viremia during the acute infection period and/or in setpoint viral load. Reductions in HIV viral load, in turn, are expected to result in amelioration of clinical course and reduced transmission to partners. Trials could potentially compare mean viral load 1–3 months after diagnosis of infection in vaccine versus placebo recipients. Marked initial suppression of viral replication suggests reductions in both progression and transmission, and viral load during this early time period could be used as a surrogate for either. Potential limitations of this approach include the fact that the initial effect may not be durable due to immune escape and viral replication, leading in turn to parallel increases in progression and transmission.

Because of the limitations of early viral load, it is unlikely that vaccine trials will rely solely on it. Potential surrogate endpoints that occur later after infection (6–24 months) relate to disease progression and include laboratory markers such as viral load, absolute CD4 count, and the number of CD4⁺ memory T cells. Because many individuals may have initiated ART at later timepoints (>24 months after first detection of HIV infection), it may be helpful to use composite endpoints such as time to CD4 count <350 or initiation of antiviral therapy. Another potential comparison at late timepoints is median HIV viral load in HIV-infected vaccinees versus placebo recipients.⁷⁹ Early clinical markers other than AIDS-defining illness among all individuals, including those taking ART, may provide additional surrogate endpoints. These late endpoints can be used to confirm conclusions drawn from earlier surrogates. Because of the ethical obligation to provide ART for infected trial participants, it is unlikely that vaccine effects on late outcomes, such as AIDS-defining illnesses or death, will occur in HIV vaccine trials.^{80,81}

■ MUCOSAL IMMUNITY

Most HIV transmission occurs sexually and therefore involves the transmission of HIV across the epithelium of the vagina, rectum, or penile urethra. Vaccine approaches that generate mucosal immunity to HIV should consist of several immunological steps. First, a vaccine should systematically generate and expand HIV-specific adaptive immune responses. Second, the vaccine, adjuvant, or delivery mechanism should support the generation of HIV-specific cells that migrate to mucosal sites. Finally, HIV-specific cells must be expanded within the mucosal tissue, where they would most likely be effective.

The biology of HIV transmission at mucosal surfaces is not completely understood. M cells (specialized epithelial cells), dendritic cells, or epithelial cells can mediate HIV entry into the mucosal lamina propria. M cells may mediate the transport of virus in the oropharynx, small intestine, and rectum, but are absent in the genital mucosa.⁸² HIV-infected cells can also cross epithelial barriers in the human small intestine by transcytosis in vesicles. HIV may most efficiently gain access to potential host cells in the female genital mucosa (T cells, dendritic cells, and macrophages) through microabrasions in the epithelium. Transmission involving dendritic cells likely also occurs in the intact female genital tract mucosa, where these cells bind HIV-1 gp120 through DC-SIGN and perhaps other cell surface receptors. Experiments in nonhuman primate models show intra- and subepithelial dendritic cells or CD4⁺ cells as primary targets of viral replication shortly after cervicovaginal SIV infection.^{83,84} Dendritic cells that capture HIV at the epithelial surface (e.g., the vaginal lumen) can deliver it to underlying T cells in the subepithelium and disseminate it to lymphoid organs.

Transmission across mucosal surfaces can be inhibited at various points by either antibody or cytotoxic T cells. HIV-specific antibody at mucosal surfaces might inhibit HIV infection in a number of ways. Antibody present in secretions can block attachment of pathogens to the epithelial surface in a process known as immune exclusion. Even nonneutralizing antibodies influence transmission at this stage by cross-linking antigen, enhancing pathogen entrapment in mucus, and preventing contact with mucosal surfaces.

Mucosal immunity in uninfected persons exposed to HIV

Natural history studies and challenge studies in nonhuman primates have shown that mucosal responses are of potential importance in protection against HIV acquisition. Observational studies conducted in highly exposed persistently seronegative (HEPS) women have reported the presence of HIV-specific IgG and IgA in vaginal secretions,^{85–89} but this finding is not universal.^{90–92} Much of the controversy in the field results from the lack of validation and standardization of the assays used to measure antiviral immunity and the lack of unexposed control subjects in some studies. In *ex vivo* transcytosis assays, IgA (but not IgG) isolated from Kenyan commercial sex workers (CSWs) resulted in a decrease in transmission of nonsyncytium-inducing (NSI) HIV across polarized epithelial monolayers.⁹³ Inhibition of transcytosis was also seen *in vitro* when isolated HIV-specific immunoglobulin (secretory IgA, IgG, and IgM) was preincubated with HIV prior to assay or when dimeric HIV IgA was added to the basolateral surface of epithelial monolayers.⁹⁴ However, the extent to which this *in vitro* assay mimics events *in vivo* is uncertain, as the IgA in most assays was monomeric and therefore not the form normally present at these surfaces

(dimeric IgA at the basolateral surface and dimeric IgA plus secretory component at the apical surface).⁹⁵

The detection of HIV-specific T cells in mucosal samples from highly exposed HIV-uninfected CSWs in Africa and Asia, as well as in discordant couples, also points to the potential role of mucosal responses in influencing HIV acquisition. Several investigative groups have demonstrated HIV-specific T cells using ELISpot assays in cervicovaginal specimens of such subjects.^{96,97} These reactions appeared to be mediated by CD8 cells and often responded to the same epitopes in cervix and blood.⁹⁶ These findings of mucosal T cell responses in seronegative persons have suggested that eliciting immune responses in cells that migrate into mucosal surfaces will be important in enhancing vaccine protection. Whether such responses can be effectively elicited from systemically administered vaccines (as seen with measles or hepatitis B) or will require mucosal administration is one of the most critical unanswered questions in the HIV vaccine field.

Studies in nonhuman primates

There is a significant body of literature in animals and some in humans that suggests that vaccines delivered onto mucosal surfaces are more likely to elicit mucosal immune responses than those given systemically. Mucosally applied vaccines also offer greater protection against mucosally applied experimental challenge.

Studies of mucosally administered HIV vaccines in nonhuman primates have demonstrated high levels of protection from infection or disease progression after the subsequent experimental challenge. These vaccines include intranasal immunization with *nef*-deleted SHIV,⁹⁸ Sabin poliovirus vectors,⁹⁹ replication-competent Adenovirus serotype 5 (Ad5) (oral, nasal, or intramuscular administration),¹⁰⁰ DNA plasmids with or without IL-2/Ig DNA boosted with MVA (prime and boost administered nasally),¹⁰¹ or a DNA prime/MVA boost delivered rectally.¹⁰² Conceptually, such studies indicate that mucosally applied vaccines can be protective. The mechanism by which mucosally applied vaccines establish immunity remains unclear. It is also possible that vaccines administered parenterally can elicit mucosal immune responses, if trafficking and local expansion of HIV specific cells occurs.

Clinical trials of vaccines delivered mucosally

Clinical development of these vaccines must balance the need to induce immunity at mucosal surfaces with safety concerns that limit some mucosal applications, such as potential neurotoxicity of replication-competent viral vectors delivered nasally. Initial clinical studies using mucosal delivery of canarypox HIV vaccine (ALVAC 205) to the nose, mouth, vagina, or rectum followed by gp120 delivered intramuscularly (IM) demonstrated that this approach was safe but not

effective for eliciting a mucosal immune response.¹⁰³ This area remains one of active research; several candidates, including a replication-competent adenovirus vector, are under development.

HIV VACCINE DESIGN STRATEGIES

Initial attempts to produce vaccines that protect against infection with HIV followed strategies that have been used

successfully to eliminate or control other pathogens (Table 100-2, Fig. 100-5).

■ LIVE, ATTENUATED VACCINES

Perhaps the most successful example is the use of attenuated viral vaccines against smallpox and polio. Attenuation of the pathogenic effect is achieved by repeated passage of the virus in vitro. The attenuated viruses produced in this manner

Table 100-2. Potential Advantages and Disadvantages of Major HIV Vaccine Design Strategies

Immunogen	Advantages	Disadvantages
Live, attenuated SIV/HIV	<ul style="list-style-type: none"> • Successfully used for other pathogens • Protective in some NHP systems 	<ul style="list-style-type: none"> • Safety concerns • Attenuated variants cause disease in juvenile, and some adult, macaques • Attenuated viruses cause disease in humans
Inactivated SIV/HIV	<ul style="list-style-type: none"> • Successfully used for other pathogens 	<ul style="list-style-type: none"> • Safety concerns re. consistent inactivation • No/few neutralizing antibodies • No CTLs
Envelope proteins	<ul style="list-style-type: none"> • Successfully used for other pathogens • Safe • Targets humoral immunity 	<ul style="list-style-type: none"> • Narrow neutralizing specificity • No CTLs • No protection in two efficacy trials
Peptides	<ul style="list-style-type: none"> • Safe • Inexpensive • Potentially useful for wide antigenic diversity 	<ul style="list-style-type: none"> • Poorly immunogenic in human trials • Formulation/adjuvant development required
DNA	<ul style="list-style-type: none"> • Presents immunogen in conjunction with HLA • Immunogenic in mice, NHP • Safe • Able to give multiple doses 	<ul style="list-style-type: none"> • Poor immunogenicity in humans • Concerns about DNA integration
Viral vectors: (a) poxviruses	<ul style="list-style-type: none"> • Widely used in vaccines (vaccinia/smallpox vaccine) • Can be highly immunogenic • Induces cellular immunity 	<ul style="list-style-type: none"> • Safety concerns (vaccinia) • Response to vaccinia limited by preexisting immunity (smallpox vaccination) • Limited immunogenicity (canarypox) • Limited/narrow neutralizing antibody response
(b) adenoviruses	<ul style="list-style-type: none"> • Highly immunogenic • Robust CTL response • Safe 	<ul style="list-style-type: none"> • Response limited by preexisting immunity (especially Adeno serotype 5)

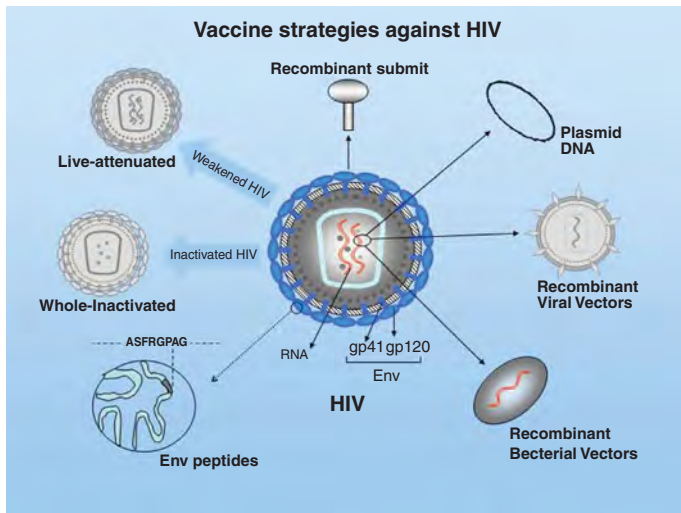


FIGURE 100-5. Overview of AIDS vaccine designs. (Reproduced with permission from Singh M. No vaccine against HIV yet—are we not perfectly equipped? *Virology* 2006; 3: 60.)

replicate in the vaccinee but do not cause disease. In vivo replication often elicits broad durable immune responses that, in many cases, are associated with sterilizing immunity and/or complete protection from disease. Early attempts to replicate these successes in HIV vaccine development investigated the efficacy of attenuated SIV vaccine candidates. The first of these candidates, SIV1A11, was produced by protracted passage in vitro.¹⁰⁴ Vaccination with this attenuated strain did not result in disease but showed limited efficacy in protecting vaccinated macaques against the challenge with pathogenic SIV.

Subsequent experiments using attenuated SIV built on the observation that development of simian AIDS was reduced in animals infected with SIV variants harboring *nef* deletions. Infection of macaques with experimentally constructed *nef*-deleted variants appeared to lead to CD4 preservation. Vaccinees were reported to resist challenge with pathogenic homologous or heterologous SIV.^{105,106} These observations were apparently replicated in humans; a benign clinical course was reported for a group of six individuals who were exposed through blood transfusion to HIV carrying a deletion in *nef*.^{107,108} However, the safety of this approach was called into question by late-onset immunosuppression in three of the transfusion recipients¹⁰⁹ and by progression to AIDS in infant and adult macaques infected with *nef*-deleted SIV, apparently related to recombination in vivo and emergence of more pathogenic variants over time.¹¹⁰ In addition, durability of the vaccine effect was questioned due to lack of protection against challenge of macaques 3–6 years after vaccination with *nef*-deleted SIV.¹⁰⁴ Thus, although attempts to produce appropriately attenuated SIV strains are still ongoing, this approach has largely been abandoned due to concerns relating to safety, especially since ongoing replication

of these attenuated virions may provide opportunities for mutations restoring pathogenicity.

■ INACTIVATED HIV VACCINES

Another approach that had been used successfully for other vaccines, such as rabies and polio, was the use of inactivated or killed HIV. Initially, this approach also appeared promising. Of the nine macaques immunized with formalin-inactivated SIV and adjuvant, eight were protected when challenged with 10 animal-infectious doses of SIV 2–3 weeks after boosting.¹¹¹ These promising results were not replicated, however, when similarly immunized animals were challenged with SIV that varied slightly from the immunizing strain or when challenge occurred after the peak response.¹¹² Further investigations revealed that the immune response in early nonhuman primate experiments was directed against xenoantigens on the surface of inactivated SIV. That is, immunity was directed against cell surface antigens retained in virions as they bud rather than against antigens specified by SIV itself.^{113,114} An additional problem with this approach has been the loss of HIV- or SIV-specific antigens from the viral surface in the process of inactivation. A novel approach has recently been proposed by Poon et al., who used low-dose formaldehyde fixation of HIV prior to heat-inactivation of HIV to produce immunogen that retains envelope in a manner that preserves at least some neutralization epitopes.^{115,116} Vaccination of mice with an immunogen based on a full-length infectious clone HIVsx treated in this manner resulted in low-level neutralizing activity against primary isolates of several clades. Vaccination of macaques with these constructs resulted in sporadic low-level responses.¹¹⁶ Whether such work can effectively result in preserving conformational structures that elicit the levels and breadth of neutralization required is unclear. Safety concerns relating to residual infectivity in the inactivated product are also issues associated with this approach.

■ PEPTIDES/SUBUNITS

Given the problems with the two traditional vaccine approaches mentioned above, attention turned to the use of peptide or subunit vaccines to elicit neutralizing antibodies. Early efforts focused on use of gp120 immunogens to elicit anti-envelope antibodies. Experiments in nonhuman primates indicated that neutralizing antibodies were elicited by this route, and it was hoped that this approach could be used to induce sterilizing immunity (i.e., that it would prevent infection completely).^{117–119} However, the majority of experiments indicated that the antibody response was narrowly limited to the HIV strain used in the vaccine (or one that resembled it closely) and that this approach did not offer protection from challenge with primary isolates or other heterologous strains.^{120,121}

Despite these discouraging results, two phase 3 efficacy trials were launched in the late 1990s using recombinant gp120 immunogens produced from cell-line adapted HIV strains. The first trial used envelop antigens from two different subtype B strains and was tested among 5403 volunteers in the United States, Canada, and Europe. This vaccine did not provide protection against infection (vaccine efficacy = 6%, 95% CI = [-17%, 24%]) and did not affect HIV disease course in participants who became infected.⁶¹ A similar trial using subtype B and subtype E immunogens did not demonstrate protection from infection or HIV disease progression among injection drug users in Thailand.¹²² The failure of these trials to show a protective effect strengthened the argument against empirical testing of vaccine candidates without better understanding of how the candidate might elicit protective immunity. It is widely held that development of immunogens that elicit broadly neutralizing antibodies is simultaneously critical for the field and its major challenge. A formal collaboration of scientists (The Neutralizing Antibody Consortium [NAC]) began in 2003 to address this scientific challenge. Current approaches include (1) use of immunogens that maintain or mimic the native trimeric structure of envelope proteins, (2) use of immunogens that favor presentation of neutralizing epitopes over nonneutralizing epitopes, (3) protection of stable intermediates that present conserved epitopes that are exposed during virus entry, and (4) use of epitopes identified by studies of broadly neutralizing monoclonal antibodies such as 2F5, 4E10, and 2G12 (see above).⁴⁵

■ DNA VACCINES

Another recent approach involves the use of DNA plasmids to deliver DNA coding for HIV proteins or HIV epitopes. These plasmids do not integrate into the host cells of vaccinated individuals but rather remain episomal and act as expression vectors, producing peptides that can induce cellular immunity. They may contain sequences coding for large peptides or polyproteins produced by creating fusions of several HIV genes, or may code for individual HIV epitopes. Inclusion of strong promoters and enhancers, as well as codon optimization (substitution of common human amino acid codons for less frequent codons found in the HIV insert) of the inserts, help ensure high-level HIV protein expression. In contrast to viral or bacterial vectors, protein production in response to DNA vaccines is limited and can focus the immune response more narrowly on the HIV insert sequences. The HIV peptide immunogen synthesized within antigen-presenting cells after uptake of the plasmid is presented on the cell surface in conjunction with MHC class I antigens. Peptide immunogens produced within cells that do not present antigen are released at cell death and can be taken up by antigen-presenting cells, which in turn, present them on their cell surface in conjunction with HLA class I.

Although immunization using DNA plasmids with HIV inserts elicited substantial cellular responses in mice and nonhuman primates, these products have been poorly immunogenic in humans. One attempt to increase immune response has included the use of genetic adjuvants, specifically the coadministration of DNA vectors coding for cytokines, most notably IL-12 and IL-15. In a second approach, DNA is used as the prime in a heterologous prime-boost strategy, with a protein or vector vaccine as the boost. Initial experiments using this approach in nonhuman primates were very promising. Animals primed with DNA and boosted with pox-virus vaccines (MVA or fowlpox) showed strong CD8 T cell responses.^{123,124} While this approach did not prevent SHIV infection in vaccinated animals after parenteral or mucosal challenge, it was associated with control of viral replication and amelioration of clinical course.^{125,126}

■ VIRAL VECTORS

Perhaps the most widely used approach at present is the use of recombinant viral or bacterial vectors as “Trojan horses” carrying HIV genetic sequences. These vaccine candidates enter the host cell, where they elicit immunity to the vector and to the product of the HIV gene they carry. This approach is useful for eliciting cellular immunity since the HIV genes are transcribed within the targeted cell and thus enter the HLA class I processing pathway.

Poxviruses

The prototype for this approach is vaccinia, a poxvirus used as a vector in the global smallpox campaign. Recombinant HIV vaccines constructed using this replication-competent vector elicited cellular immune responses to SIV and HIV antigens in nonhuman primate models.¹²⁷ However, vaccinia was abandoned in favor of more attenuated strains following a case report of vaccinia dissemination and death in an immune-compromised, HIV-infected individual.¹²⁸ Among the attenuated vaccinia strains, modified vaccinia Ankara (MVA) and the New York strain (NYVAC) have been most widely studied. The strain that gave rise to MVA was used initially in Turkey in smallpox vaccine production. In the 1950s, this strain was brought to Germany where it was further attenuated by repeated passage through chick embryo fibroblasts, a process that resulted in accumulation of multiple mutations and deletion of about 15% of the genome.¹²⁹ A very favorable safety profile was seen in the 120,000 vaccinees who received this product in Turkey and Germany as part of the smallpox campaign; MVA has subsequently been used in experimental HIV, malaria, and cancer vaccines.¹²⁹ NYVAC was developed through deletion of 18 open reading frames and is blocked at an early stage of replication.

These attenuated viruses retain little or no ability to replicate in human cells but can elicit humoral and cellular responses to the vaccine inserts (and to viral sequences). As with DNA constructs, attempts to enhance immunogenicity include repeated dosing, administration with costimulatory molecules such as cytokines, and use in heterologous prime-boost regimens. In nonhuman primate models, vaccination with MVA-based SIV vaccines decreased SIV viral load and ameliorated disease course after challenge.¹³⁰ Priming with SIV DNA plasmid followed by MVA or NYVAC boosting elicited SIV-specific cellular immunity^{123,131} and ameliorated postinfection course in animals that become infected upon challenge.^{125,132} Initial prime-boost trials in humans have been disappointing: only 10–20% of participants in trials of a DNA/MVA regimen showed anti-HIV cellular responses by ELISpot.¹³³ Several phase 1 trials of both MVA and NYVAC are ongoing or in the planning stages, and preliminary results show improved immunogenicity with second-generation MVA and NYVAC constructs.

Canarypox is the HIV vaccine vector studied most extensively in humans to date. These viruses are host-range restricted and undergo abortive replication in human cells. Engineered foreign genes in vector inserts are transcribed and translated, allowing immunogen expression and presentation without vector replication in the host cell. Data from 1126 HIV-uninfected volunteers indicate that HIV vaccines using these vectors are safe and well tolerated with a reactogenicity profile similar to that of existing vaccines licensed for use in adults.⁵⁵ Additionally, canarypox vectors showed no significant safety concerns when tested in over 400 HIV-infected volunteers.¹³⁴ During the past 15 years, over 30 phase 1 and 2 trials involving more than 1500 participants have been conducted with first- and second-generation canarypox HIV vaccines (such as ALVAC), mostly in the United States through the AIDS Vaccine Evaluation Group (AVEG).¹³⁴ These trials were initially met with enthusiasm because the vaccine candidates were not limited by preexisting vaccinia immunity, could be used in homologous or heterologous prime-boost regimens, and appeared to induce both humoral and cellular immunity. However, as with other approaches, the neutralizing antibody response was limited and did not neutralize primary isolates.¹³⁴ These poxvirus vectors were the first to convincingly demonstrate a T cell response to HIV antigens after vaccination. Initial studies that utilized in vitro stimulation to enhance detection of T cell responses suggested that in up to 30–40% of such responses could be detected from volunteers if multiple samples were obtained during the course of vaccination. Recent assays using a more stringent stimulation directed at defining circulating memory T cells suggest the responses are present in 8–10% of persons, well below the amount seen with recombinant adenovirus vectors.^{9,56,134–136} Because of initial encouraging cellular responses, a pivotal trial was conducted in 2001–2003 using a

second-generation ALVAC prime (vCP1452) and a recombinant gp120 (AIDSVAX™ B/B subunit) boost to qualify this regimen for efficacy testing. Responses seen in this trial did not meet the preset immunogenicity criteria and plans for an efficacy trial of this regimen were therefore abandoned.¹³⁷ Several preclinical and clinical studies are ongoing with the aim of optimizing the immunogenicity of these vectors. In Thailand, a phase 3 trial of a canarypox vector (vCP 1521) containing the HIV-1 clade B *env*, *gag*, and protease genes, in combination with gp120 (clades B and E) completed enrollment in January 2006; follow-up is ongoing and is expected to end in mid-2009.¹³⁸

Adenoviruses

The most promising candidates at present are HIV vaccines constructed using adenovirus vectors. These viral vectors are rendered replication-defective by mutations and the deletion of an adenovirus gene. HIV genes are inserted in its place under the control of exogenous promoters and regulatory elements that drive high-level expression of the HIV insert and adenovirus genes. The replication-incompetent adenoviruses retain the ability to infect cells and to deliver their genome to the nucleus.

Two different products are in advanced clinical testing at present. The first, produced by Merck, contains an admixture of three adenoviruses containing codon-optimized subtype B *gag*, *pol*, or *nef* genes, respectively. These three HIV genes are conserved (80% to >90% conserved) across subtypes. The Merck adenovirus vectors containing *gag* alone or a trivalent preparation containing *gag*, *pol*, and *nef* produce robust cytotoxic CD8⁺ T cell responses in macaques (500–1000 γ -interferon-producing cells/10⁶ PBMCs after vaccination with 10¹¹ viral particles).^{139,140}

The Merck trivalent adenovirus vaccine provided protection in animal models. Vaccinated macaques were intravenously challenged with SHIV 89.6P, a pathogenic SIV/HIV chimeric virus. Although there was no protection from infection, HIV replication was suppressed. Test animals experienced a mild course of infection, which did not progress to AIDS during the follow-up period.^{141,142} Although there is debate about how accurately these experiments will predict results in humans, these results are promising.

In phase 1 testing, the Merck Ad5 HIV vaccines have been safe and well tolerated in 1200 study participants to date.¹⁴³ T cell responses have been elicited in 70% of trial participants, with slightly lower response rates among participants with prior adenovirus immunity.¹⁴³ Interestingly, compared with Merck's monovalent product, their trivalent Ad5 vaccine appears to increase the frequency and breadth of responses and to reduce the response disparity between participants with and without preexisting Ad5 immunity (Table 100-3).¹⁴³ A test-of-concept efficacy trial of the Merck Ad5 product

Table 100-3. Comparison of ELISpot Responses Elicited by MRK *gag*-Only and Multigene Ad5 Vaccines

Dose level	Ad 5 Titer	Week 30 ELISpot Response											
		Monogene						Multigene					
		Gag		Gag		Pol		Nef					
		<i>N</i>	%	GM	<i>N</i>	%	GM	<i>N</i>	%	GM	<i>N</i>	%	GM
1 × 10 ⁹ vp/d	≤200	32	72%	207	20	75%	281	20	45%	490	20	60%	196
	>200	14	21%	105	17	35%	219	17	18%	233	17	24%	223
1 × 10 ¹⁰ vp/d	≤200	32	53%	221	22	73%	205	22	59%	342	22	68%	177
	>200	24	29%	287	14	71%	405	14	43%	641	14	57%	401

Dose level for the trivalent represents the *gag*-only component.

vp/d, viral particles per dose; *N*, number in each group; %, percentage of responders; GM, geometric mean ELISpot response for responders only.

ELISpot responder: ≥55 SFC/10⁶ PBMCs and ≥fourfold over media control.

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began in late 2005 and is fully enrolled. This 3000-person phase 2B trial (the STEP study), is being conducted by Merck and the HIV Vaccine Trials Network (HVTN) in the North and South America, Australia, and the Caribbean to evaluate efficacy in reducing either HIV acquisition among all trial participants or viral load setpoint among vaccinees who become infected with HIV.¹⁴⁴ A second 3000-person, cross-clade, test-of-concept trial began enrollment in early 2007 to assess the safety, immunogenicity, and efficacy of this same clade B vaccine in the Republic of South Africa, where clade C HIV predominates.

The second Ad5 candidate, developed by the U.S. National Institutes of Health's (NIH) Vaccine Research Center (VRC), is designed to provide multiclade protection. It is an admixture of four adenoviruses, one of which contains a subtype B *gag-pol* gene fusion. The other three adenoviruses contain subtype A, B, or C envelope genes. This VRC construct has also elicited strong humoral and cellular responses in macaques. The magnitude and breadth of the response was improved by prior priming of the product with the DNA plasmids discussed above.^{145,146} In nonhuman primate studies, the VRC DNA prime/adenovirus boost vaccine did not protect animals from infection. However, viral replication was suppressed and vaccinated macaques experienced a mild course of infection, which did not progress to AIDS during the follow-up period.^{141,146,147} In recent experiments in non-human primates, ameliorated course and prolonged survival in vaccinated animals after SIVmac251 challenge was associated

with preservation of central memory cells.¹⁴⁸ In phase 1 trials, both the DNA product and the adenovector candidate were safe and immunogenic when administered individually.^{149–151} The VRC prime-boost vaccine regimen, consisting of three doses of DNA boosted with a single dose of Ad5, elicited greater humoral and cellular responses in the majority of trial participants.¹⁵² Of note, the VRC Ad5 candidate seems to stimulate more frequent CTL responses to *env* antigens than to structural gene products. Phase 2 testing of the VRC DNA-adenovirus prime-boost regimen was conducted in the United States, the Caribbean, South America, and Africa. This regimen is being evaluated in a large test-of-concept trial that began in these same regions in late 2007. This trial will enroll 8500 participants and is being conducted collaboratively by the NIH VRC, the HVTN, the International AIDS Vaccine Initiative (IAVI), the U.S. Military HIV Research Program (USMHRP), and the Centers for Disease Control and Prevention (CDC). Safety and preliminary efficacy will be evaluated in three regions, where clades A, B, and C predominate, respectively.

A blunted immune response to Ad5 HIV vaccines because of prior exposure to Ad5 (a common respiratory virus)^{139,140,146,147} presents a potential problem for use of this approach in some of the regions that are hardest hit by the HIV pandemic. In these regions, high-titer Ad5 seroprevalence increases rapidly during childhood to 50–80%.¹⁵³ A number of strategies to overcome this problem are currently being investigated, including use of adenovirus vectors of

uncommon serotypes, production of chimeric adenoviruses, priming with DNA, or prime-boost combinations of Ad5 with other adenovirus or poxvirus vectors.^{139,140,146}

■ ADJUVANTS

Another area of ongoing research is adjuvanting of HIV vaccine candidates. Many of the current vaccine strategies do not produce immune responses that are robust, long-lived and appropriately focused on production of neutralizing antibodies or cytotoxic responses. Adjuvants could overcome this by targeting the antigen to antigen-presenting cells or increasing immune response by stimulating production of cytokines and costimulatory molecules or both. Adjuvants such as polymeric microspheres (e.g., polylactide-coglycolide or PLG) have been tested with HIV vaccine candidates to increase immune response through facilitating interactions with antigen-presenting cells.¹⁵⁴ The complementary approach, induction of relevant cytokines and upregulation of costimulatory molecules, is used by other adjuvants such as CpG, unmethylated cytosine-guanine dinucleotides, which acts as a ligand for toll-like receptor 9 (TLR9).¹⁵⁵ Stimulation of TLRs in turn enhance and direct immune response. A related approach is the administration of vaccine candidates with costimulatory molecules such as IL-12, IL-15, or granulocyte-macrophage stimulating factor (GM-CSF) in an attempt to manipulate the immune response and increase cell-mediated immunity to the coadministered HIV vaccine antigen.¹⁵⁶

CONCLUSIONS

Major advances in the HIV vaccine field have been made in the last 3 years. Most of this progress has been in the development of recombinant vector-based immunogens directed at producing memory T cell responses to HIV-1 in order to reduce the effects of the acute, rapid immunodeficiency that accompanies initial HIV infection, a universal feature of acute infection regardless of symptoms. Advanced clinical trials are underway to evaluate whether the first generation of these vaccines is efficacious. These studies will determine whether the current viral vector vaccines are capable of eliciting the quantity and quality of T cell responses that are needed to alter the course of HIV-1 infection for individuals and populations around the globe. If these trials are successful, the world will enter a new phase of defining the strategies through which these vaccines can be used to control the HIV pandemic.

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PART 15

Special Aspects of STI/HIV Prevention and Control in Developing Countries

- 101.** Prevention and Control of STD and HIV Infection in Developing Countries 1957
- 102.** Approach to the Management of HIV/AIDS in Developing Countries 1977
- 103.** Approach to Management of STIs in Developing Countries 1993
- 104.** The Laboratory in the Management of STDs, HIV, and Opportunistic Infections in Developing Countries 2015

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Prevention and Control of STD and HIV Infection in Developing Countries

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INTRODUCTION

Sexually transmitted infections (STIs), a diverse group of infections, are responsible for a large burden of morbidity and mortality in the developing world because of their role in facilitating HIV transmission and because they have a significant adverse impact on reproduction and child health.^{1,2} In the 1990s, STIs were the focus of considerable attention from international donors interested in both HIV control and women's health.³ These efforts were supported by evidence of strong links between STIs and HIV transmission and the political agenda where family planning was put in the context of broader reproductive health initiatives.³ The international focus on and funding for STI control has decreased recently for several reasons. The global focus on HIV prevention was overshadowed by the large international efforts and funding shifts to scale up treatment and mitigation programs for persons with AIDS.⁴ Three community-based randomized clinical trials provided conflicting results on the impact of STI treatment on HIV transmission, leading to more nuanced recommendations.⁵⁻⁹ In addition, syndrome management, a case-management approach promoted widely for settings with limited resources, had poor performance characteristics in women, especially in low prevalence settings.¹⁰⁻¹² Existing STI control efforts are hampered in many countries by failure to implement basic management principles. Moreover, advocacy efforts to gain political and financial commitment to address the burden of STIs and their sequelae are hindered by stigma and lack of data on disease burden and documentation of intervention effectiveness.¹³

STIs AND HIV IN THE DEVELOPING WORLD

SEXUALLY TRANSMITTED INFECTIONS

Incidence and prevalence rates of STIs are significantly higher in the developing world but can vary widely across sites.¹⁴ Global estimates of the impact of STIs, however, underestimate their importance because STIs are extremely

underdiagnosed, underreported, or their sequelae are classified under maternal, child, or cancer morbidity and mortality statistics and not under the broad category of STIs.¹³ There is evidence that bacterial STIs are decreasing in many countries as a result of the implementation of STI case management, including syndromic management, along with overall HIV prevention efforts.¹⁵⁻¹⁷ Viral STIs are now more common in many areas.¹⁸⁻²²

In developing countries, STIs are inadequately treated for a myriad of reasons. Low priority in strategies and plans and consequent low budgets leave these programs under-resourced in the public sector.²³ There are limited efforts to engage and improve private sector services where the majority of patients will seek care initially.²⁴⁻²⁶ Diagnostics and drugs are not available either due to cost or poor logistics systems.^{18,27,28} Delays in patients seeking care because of lack of symptom recognition, stigma associated with genital symptoms, the asymptomatic nature of many STIs, and lack of access to services also contribute.^{29,30}

SEXUAL TRANSMISSION OF HIV

In addition to the stage of HIV infection, STIs are an important determinant of increased genital HIV viral shedding.^{2,31,32} The most compelling evidence that STI treatment impacts HIV transmission are the studies that document declines in genital tract HIV shedding after treatment.³³⁻³⁶ Yet three of the four clinical trials done to examine the question as to whether STI treatment reduces HIV transmission have shown no impact.^{5,6,8,37} These disparate results are felt to be due to underlying differences in the study populations with respect to the prevalence of curable STIs, the stage of the HIV epidemic, and the sexual risk behaviors of the population.³⁸⁻⁴⁰ In addition, these four clinical trials examined the role of treating curable STIs only; the role of HSV-2 and its treatment were untested.

The biological relationship between HIV and STIs is little disputed. However, the programmatic implications of STI treatment to reduce HIV transmission at the community

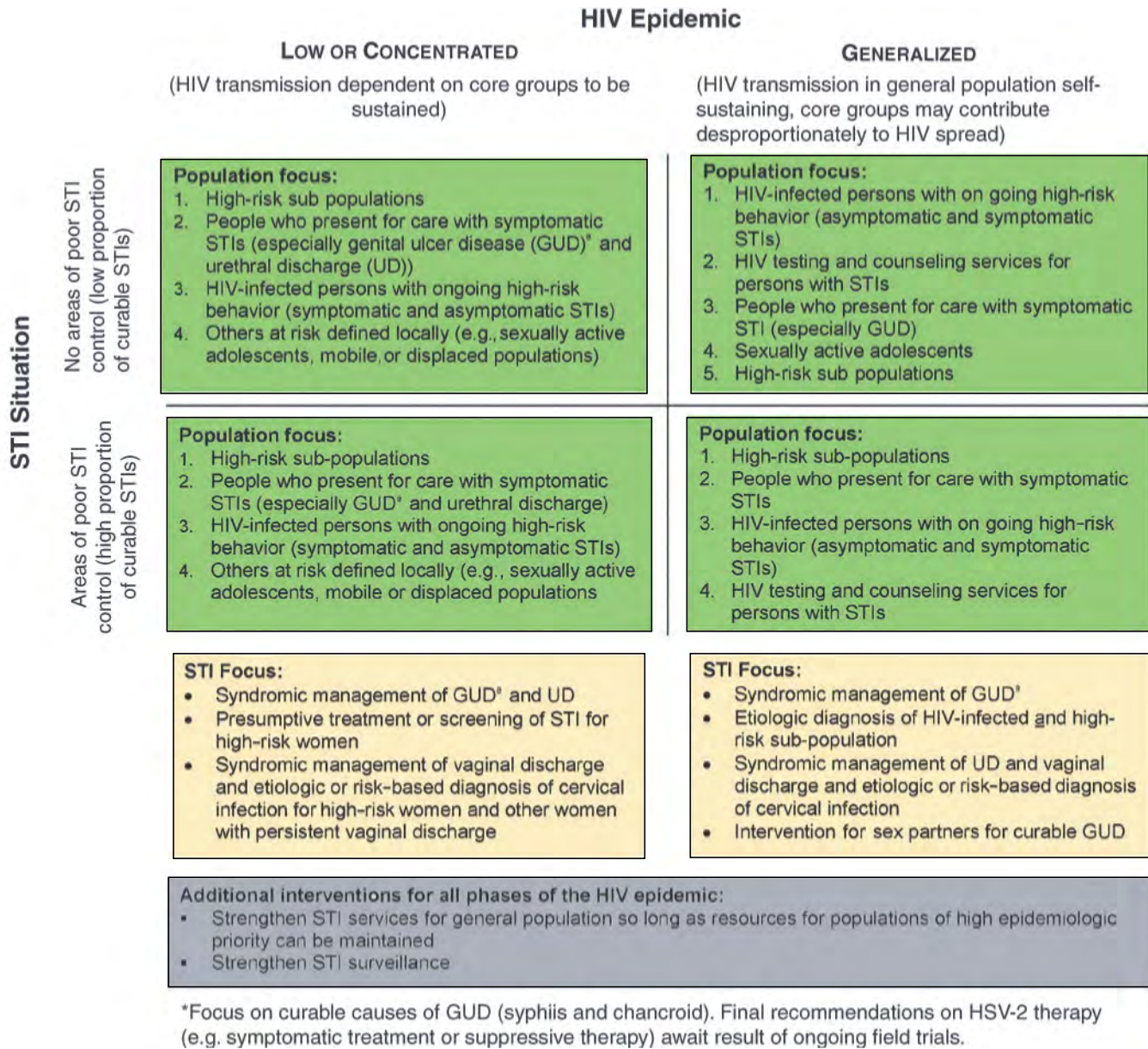


FIGURE 101-1. Framework for priority setting of subpopulations for STI control measures with consideration of the HIV epidemic and STI situation. (Adapted from WHO/UNAIDS. *Consultation on STI Interventions for Preventing HIV: Appraisal of the Evidence*. World Health Organization and Joint United Nations Program on HIV/AIDS, in press.)

level have been difficult to prove. Recommendations for directing how STI control should be instituted for HIV prevention depend on the detailed knowledge of the stage of the HIV epidemic and the state of STI control.^{9,41} These recommendations are outlined in Fig. 101-1⁹.

PRINCIPLES AND PRIORITIES FOR STI CONTROL AND HIV PREVENTION

STI control programs aim to reduce the rate of incident infections through a combination of prevention and treatment strategies. These include behavior change to reduce sexual risk, increase use of barrier methods, and treatment of

persons with STIs. Additional insights into transmission dynamics, new technologies and approaches such as suppressive or prophylactic therapies, male circumcision, vaccines for STIs, and microbicides, when available, will add additional tools and program demands to current control efforts.

Comprehensive STI prevention and control in developing countries should include a wide range of approaches to address STIs at all levels of health system and within targeted communities according to national priorities as outlined in Table 101-1. Ideally, these approaches should be incorporated into a comprehensive STI strategy with implementation plans that clearly state the goals and priorities of the program based on knowing the local STI and HIV epidemic, the

Table 101-1. Government's Role in Comprehensive STI Prevention and Control Program

<p>National-level policy</p> <p>Setting goals and prioritization</p> <p>Allocation of resources on:</p> <ul style="list-style-type: none"> • prevention and treatment of STIs • additional data needs <p>Political advocacy for a supportive policy and legal framework</p> <p>Leadership on community discourse on sexual matters, stigma, and discrimination</p> <p>National program evaluation</p> <p>National-level normative functions</p> <p>Development and distribution of guidelines</p> <ul style="list-style-type: none"> • case management guidelines for general population and high-risk subpopulations • laboratory and quality assurance • surveillance system <p>Planning and guidance of specific activities for STI control</p> <ul style="list-style-type: none"> • focused interventions for high-risk subpopulations (usually with HIV program) • syphilis screening and treatment and ophthalmia prevention in antenatal clinic settings • HPV immunization program • chlamydial screening and treatment for women • private sector partnerships • other as prioritized <p>Articulation of an evaluation plan with indicators</p> <p>Development of monitoring and evaluation system</p>	<p>Operationalization functions</p> <p>Organization of health services to meet goals</p> <ul style="list-style-type: none"> • integration of STI clinical service delivery • supervision into primary health care and private providers • establishment of referral systems for more complex management <p>Establishment of special services to meet the needs of key high-risk subpopulations and linking with HIV prevention programs</p> <p>Establishment of links with sexual and reproductive health services, HIV services, and others per priorities</p> <p>Design of behavior change communication to:</p> <ul style="list-style-type: none"> • reduce stigma and discrimination • reduce STI risk behaviors • increase health-seeking behavior <p>Organization of logistic management systems to ensure uninterrupted supplies of commodities, antimicrobials, condoms, water based lubricants, and laboratory reagents</p> <p>Establishment of training systems to train health-care providers on:</p> <ul style="list-style-type: none"> • clinical management including quality • functioning of the clinic infrastructure • monitoring system <p>Provision for ongoing information about technical issues</p> <p>Establishment of supportive supervision and monitoring feedback system</p> <p>Fostering of a culture of data use at all levels</p>
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implementation mechanisms to reach the goals, and an articulation of what other actors will be involved and their role in meeting the goals.⁴²

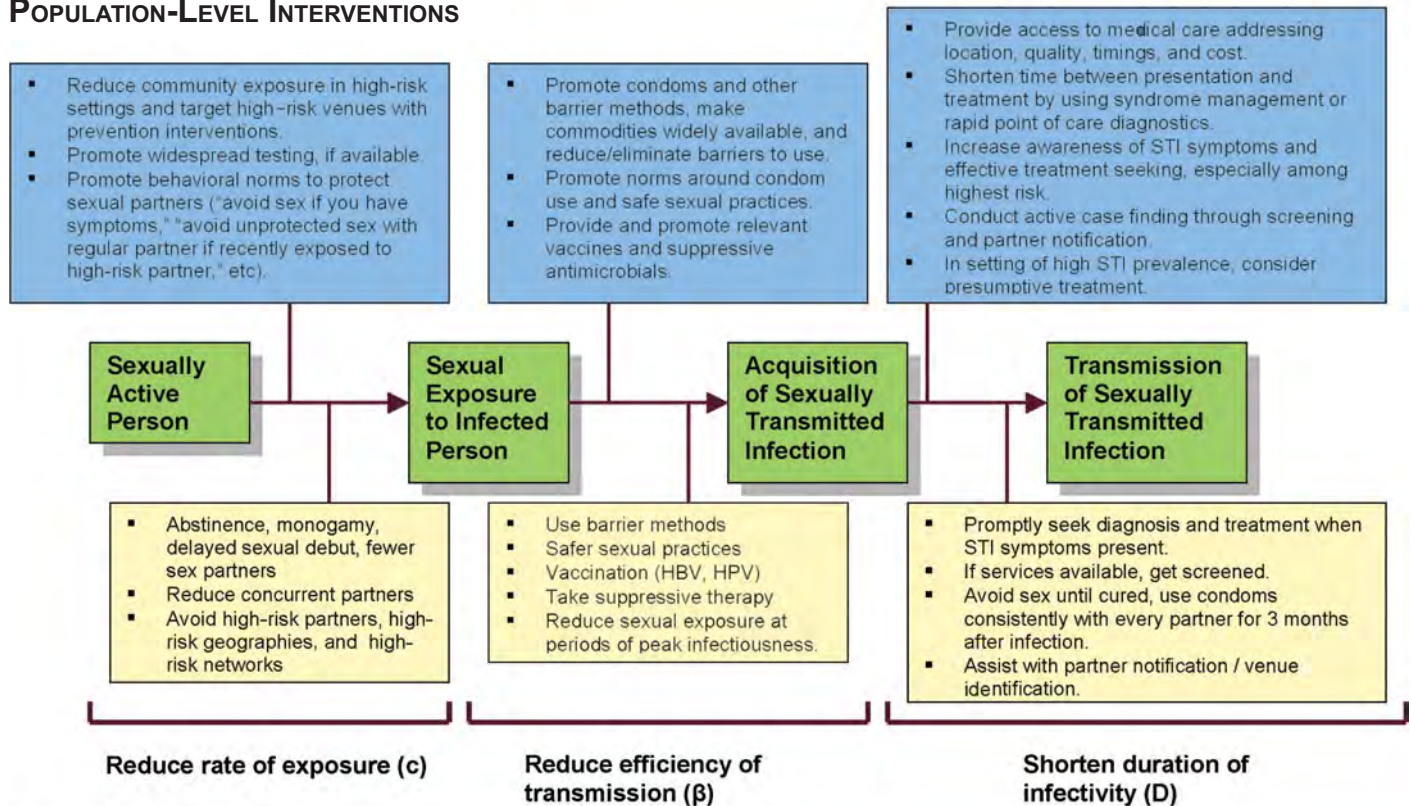
■ STI TRANSMISSION DYNAMICS

The epidemiology of STI transmission has defined the basic strategies for prevention interventions for STIs. Following from the classic model of Anderson and May, $R_0 = c \times \beta \times D$, interventions can prevent spread of an STI within a population by (1) reducing the rate of exposure to STI by lowering the rate of partner change; (2) by reducing the efficiency of transmission; or (3) by shortening the duration of infectiousness for

that STI through treatment. These approaches are summarized in [Fig. 101-2](#).⁴³

Recent research reveals a more complex picture of STI epidemiology. This complexity is based on the fact that populations consist of diverse subpopulations each with distinct subpopulation characteristics and consequent infection patterns.⁴⁴ Sexual networks and concurrency are important in STI transmission dynamics, and an individual's position in the network is important in determining risk of transmission or acquisition.⁴⁵ Characteristics of specific STI pathogens (transmission probability and duration of infectiousness), partner numbers and duration of relationships, and the effectiveness of the health system also impact how specific STI epidemics evolve.⁴⁶

POPULATION-LEVEL INTERVENTIONS



INDIVIDUAL-LEVEL CHOICES

FIGURE 101-2. Individual and population-level interventions for STI control. (From Holmes K, DeLay P, Cohen M. STD control: A public health priority. In: Dallabetta G, Laga M, Lamptey P, eds. *Control of Sexually Transmitted Diseases: A Handbook for the Design and Management of Programs*. Arlington, VA: Family Health International, 1997.)

■ PRIORITIES FOR STI PROGRAMMING

Ideally, all decisions about prioritization of STI control efforts to control STIs and to impact HIV transmission should be based on understanding the STI and HIV epidemic in the specific country. In most developing country settings data are limited. Nonetheless, population-level behavioral data is becoming increasingly available as a result of HIV prevention programming, and special surveys are being done in countries or special modules for men and HIV are being added to other large behavior surveys.⁴⁷ The surveys often provide information on sex worker contact by men or reported numbers of sexual partners by men and women. Similarly, information on prevalence levels of specific STIs and HIV coupled with some behavioral data is more available.

High-risk subpopulations play a disproportionate role in STI and HIV transmission and should be a primary focus of STI prevention and treatment interventions. Second, individuals with STI-related symptoms, particularly genital ulcer disease and urethral discharge, presenting for care represent individuals from a high-risk subpopulation or network and should be provided effective services. A disproportionate number in individuals with acute HIV infection, the most infectious stage of HIV infection, are identified among STI patients suggesting

that the STI and HIV are cotransmitted.⁴⁸ In addition, STI services can impact potential transmission from current HIV-infected individuals by providing prompt, effective treatment.⁴⁹ Individuals with STIs should be involved in finding and treatment of partners and can also be utilized to identify high-risk locations where prevention interventions should be focused.

After focusing on high-risk subpopulations, on individuals with presenting with symptoms and HIV-infected persons, the program will need to decide what, if any, specific STI pathogens should receive program resources and attention. These decisions will depend on several factors:⁵⁰ (1) their overall incidence, prevalence, distribution, and public health impact of specific STI pathogens; (2) clinical characteristics (e.g., symptomatic or not) and sequelae; (3) availability of prevention tools and technologies such as rapid, accurate diagnostics; affordable, preferably single-dose treatments; and vaccines; (4) ability of the health system to absorb the new interventions in terms of training, logistics, monitoring, and surveillance; and (5) the political and cultural acceptability of the intervention among the general population as well as the affected communities. Congenital syphilis prevention, for example, should be implemented by every program.^{51,52} The recent licensing of a human papillomavirus (HPV) vaccine to prevent cervical cancer offers great possibilities to prevent

disease, but cost and politically positioning a vaccine for STIs will need to be addressed.⁵³ The vast majority of chlamydial infections are asymptomatic, especially in women, but account for considerable individual morbidity and mortality as well as profound social and economic impact in women in terms of divorce, stigma, and poverty induced by infertility.⁵⁴

■ HUMAN RIGHTS AND GENDER EQUITY

STI control programs including HIV prevention interventions work with subpopulations who are already marginalized and are least able to realize their human rights. Central to all programming for these groups is a respect for human rights with institution of policies around confidentiality and respect.⁵⁵ Programs, in order to provide services to these subpopulations, may have to address a wider range of health and safety issues within a human rights framework to help ensure active participation of marginalized groups and to prevent coercion. Women and girls are more vulnerable to STIs including HIV infection due to gender inequalities. In some settings, gender norms and relations around marriage, harmful traditional practices, and barriers to women's education increase their risk. Ensuring equal opportunities for women to access prevention and sexual and reproductive health services, reducing violence against women, and protecting their rights is essential for STI control. It is important to engage men and boys in efforts for a long-standing impact on gender inequalities.

PRIMARY PREVENTION STRATEGIES FOR STI AND HIV CONTROL

Keeping individuals and communities uninfected from STI and HIV is fundamental to STI and HIV control. Primary prevention interventions are a crucial component for control, especially in resource-poor settings with limited treatment and diagnostic options, and in the face of a shifting pattern of STIs from curable bacterial STIs to noncurable viral STIs. Moreover, primary prevention strategies to decrease exposure to infectious persons through partner reduction or decrease efficiency of transmission through condoms or other barrier methods would have impact over all, or most, of the STIs, as opposed to vaccines, suppressive therapy, or screening tests which are pathogen-specific. As a result of HIV prevention programming and HIV awareness, there appears to be a change in sexual risk behaviors in some developing countries with specific behavior changes being reported such as delayed sexual debut, increased monogamy, reduced number of partners, increased condom use, and avoidance of sexual contact with sex workers.^{15,56–58}

■ BEHAVIOR CHANGE PROGRAMMING

Effective behavior change programs, or sexual health promotion activities, have multiple aims. At the individual level, the

goal is to reduce risk behaviors that can allow individuals to acquire and transmit HIV and other STIs. This includes safer sexual behaviors such as remaining sexually abstinent or delaying initiation of sexual activity, decreasing the number of sexual partners, decreasing the number of concurrent sexual partners, and using condoms consistently and correctly.⁵⁹ In addition, programs attempt to stimulate open discussion on the underlying factors for risk, risk behaviors and settings and local solutions, counter stigma, and influence the social responses. The ultimate goal is to change social norms around preventive behaviors, making them more normative.⁶⁰

For subpopulation groups who may have higher risk behavior and may have less access to health services because of social issues (e.g., sex workers, men who have sex with men (MSM), injecting drug users (IDUs), migrant workers, and sexually active adolescents), communication strategies using outreach and peer education have been the cornerstone of interventions. Through active outreach, access to those who are at increased risk of STIs has been possible.⁶¹

Additional behavior change goals are to change community attitudes and reduce stigma and discrimination, to create a demand for information and services related to STIs and HIV, to improve symptom recognition by individuals in order to seek appropriate care earlier, and increase overall knowledge and understanding of specific STIs.

Finally, behavior change goals converge with advocacy goals of (1) informing policy-makers and key opinion leaders about the consequences and burden of specific STI pathogens; (2) advocating for intervention options and cost-effective approaches; and (3) articulating policy and legal reforms that would enhance prevention and control efforts.

■ STRUCTURAL INTERVENTIONS

Structural and environmental interventions have the potential to alter the prevention environment making it supportive of behavior change objectives, be it at the level of availability of services, social or political.⁶² Such approaches can focus on ensuring the availability of commodities, equipment, materials, or settings that are necessary to practice healthy behaviors. These may include ensuring availability of condoms, lubricants, STI services, HIV counseling and testing, or developing policies to ensure condoms in venues associated with sexual encounters. The 100% condom use policy of Thailand, where government policy required that condoms be used in brothel-based commercial sex encounters and made establishment owners responsible for condom use by their clients, is one such example.⁶³ Condom social marketing, another example, uses a mix of marketing strategies to motivate and encourage individuals to use condoms while making condoms more accessible by distributing to nontraditional sales outlets and making them more affordable.^{64,65} Other structural interventions at the policy level have included changes

in laws to decriminalize or legalize sex work or MSM sexual behavior, or levy legal penalties against hotel or brothel owners if preventive regulations are not implemented.⁶² Policy interventions such as safe work policies for brothels, antistigmatization efforts for marginalized groups, alcohol taxes, and media campaigns to reduce violence against women have also been done. Where assessed, structural interventions were found to be cost-effective, especially in addressing populations with low HIV prevalence but high vulnerability.^{66,67}

At a more local level, increasing the social, economic, and political power of marginalized groups by empowering them to alter their local environment, and consequently their risk for STIs and HIV, has resulted in more sustainable prevention interventions in a brothel area in Kolkata (Calcutta), India.⁶⁸

■ PREVENTION TECHNOLOGIES

Barrier methods

Male latex condoms. There is strong evidence that male latex condoms reduce transmission of HIV by 80–85%, gonococcal and chlamydial infection, herpes simplex virus (HSV), HPV, and reduce the risk of unintended pregnancy.^{69–72} Condom failures occur due to method or device failures as well as user failures. Key to effective condom promotion is a focus on ensuring quality condoms in the programs, getting them where they are needed, and education on proper and consistent condom use.⁷³ Enhancing skills to negotiate condom use, to use condoms, and intensifying risk reduction counseling can increase acceptability to sexual partners.⁷³

Female controlled barrier methods. Female controlled methods where partner negotiation during sexual intercourse could be avoided and methods that could be used without detection during sex would be powerful tools for women. Studies show that availability and use of female condoms offer at least as much protection as male latex condom use and may increase the overall number of protected sex acts.⁷⁴ There are several constraints to large-scale implementation of female condom use. First is the higher cost of the female condom compared to the male condom and limited data to assess the cost-effectiveness of female condom programs. Second are the program requirements of introducing the female condom that are more complex than for male condoms.⁷⁵

Observational studies on the effectiveness of the diaphragm to prevent STIs have shown evidence of protection from gonorrhea, pelvic inflammatory disease (PID), and cervical dysplasia.⁷⁶ A randomized controlled trials on the HIV prevention effectiveness of the diaphragms in southern Africa showed no added benefit in addition to condoms and HIV prevention services in prevention of HIV transmission.^{76a} Several microbicides are in various stages of development; there is currently none available for use.⁷⁷

Other prevention technologies

Vaccines. Cervical cancer is the second most common cancer in women in the world.⁷⁸ In 2006, a quadrivalent HPV-associated cervical cancer vaccine was approved for use in the United States, the UK, and elsewhere.⁷⁹ The current cost is prohibitive in developing countries although several efforts are underway to make it available.⁵³ Sexual transmission of hepatitis B has been documented mainly in developed countries.⁸⁰ Hepatitis B vaccine has been available for many years and preexposure vaccination is recommended for individuals at risk. For HSV-2, both preventive and therapeutic vaccines are under development. HIV vaccines, similarly, are under development.

Male circumcision. Circumcised men appear to be at lower risk of syphilis (although there was a significant heterogeneity among the syphilis studies), chancroid, and borderline significant reduced risk for HSV-2 infection.⁸¹ Recent randomized controlled trials from sub-Saharan Africa have had remarkably consistent results across three trials showing that male circumcision reduces risk of acquiring HIV from a female partner by about 50–60%.^{82–84} Whether this new prevention intervention will be positioned as a public health intervention and widely promoted or provided on an as needed or targeted basis will depend greatly on the country's overall circumcision rates, HIV rates, as well as cultural and religious considerations.

Herpes simplex virus type 2 (HSV-2) suppressive therapy. HSV-2 is the major cause of genital ulcers in both the developed and developing countries.⁸⁵ Viral shedding of HSV-2 occurs frequently in infected individuals with clinical or sub-clinical disease and is a significant risk factor for transmission. Suppressive HSV-2 therapy has been shown to decrease transmission to uninfected heterosexual partners, and daily suppressive therapy and condoms are recommended for HSV-2 serodiscordant couples.⁸⁶ In a recent report, HSV-2 suppressive therapy reduced HIV both in the genital secretions and plasma in dually infected women.⁸⁷ Several ongoing randomized controlled trials are investigating the effect of symptomatic and suppressive therapy on HIV transmission and acquisition.⁸⁸

STI MANAGEMENT APPROACHES

Experiences in some low- and medium-income countries such as Thailand, Nairobi, Botswana, and parts of South Africa have shown that it is possible to control the common curable STIs, even in settings with high transmission dynamics, through a comprehensive strategy of prevention and treatment.^{9,16,89,90} Prompt, effective, and comprehensive STI case management (see [Table 101-2](#)) remains an important pillar of STI control within existing networks of health-care facilities, both public and private.

Even the most well equipped STI clinics will have limited impact on STI control if there is poor utilization of STI services.

Table 101-2. Elements of Comprehensive STI Case Management

Prompt, accurate diagnosis
Provision of effective treatment for STIs (preferably single-dose treatment) with minimal delay after presentation
Education and counseling on <ul style="list-style-type: none"> • the nature of infection • mode of transmission • the need for adherence to treatment • risk reduction measures • proper use of condoms • need for treatment of all sexual partners • recommendations for HIV testing • the need to use condoms with all partners for 3 mo and (re)test for HIV
Provision of condoms and demonstration of condom use
Partner treatment
The opportunity for follow-up examination to assess treatment outcome

An operational model for estimating program effectiveness for tuberculosis was adapted to STIs and highlights the major barriers to STI case management as illustrated in [Fig. 101-3](#)⁹¹.

The degree and severity of symptoms associated with various STI pathogens greatly influence treatment seeking behavior. The difference in percentage between infected and symptomatic would be small in men with gonorrhea and would be large in women with chlamydial infection. As such, different control interventions would be necessary for each disease; prompt access to effective services for men with gonorrhea would be an important approach, while for women with chlamydial infection screening and treatment would be needed.⁵⁰

Approaches to addressing each level of “drop-off” from infected person to cure and partner treatment are outlined in [Fig. 101-3](#). While improving STI care provided in health-care facilities can address some of the barriers, workplace and flexible community-level interventions are needed to increase the coverage and use of STI services by those who are infected. Linking STI services to ongoing outreach programs being implemented by HIV prevention programs is one way to address access of high-risk subpopulations.⁹²

■ STI MANAGEMENT OF SYMPTOMATIC PERSONS

Provision of effective services to symptomatic STI patients and their partners should be among the top priorities of an

STI control program. Symptomatic STI patients may be aware that they are infected and are more likely to seek care. While bacterial and protozoan STIs can be cured, viral STIs can only be treated to reduce the severity of an episode and suppress recurrence. Nonetheless, individuals with viral STIs can still benefit the STI services by receiving counseling on safer sex, partner notification, counseling regarding HIV testing, and general health information. Ultimately, the goals of STI case management are to (1) provide appropriate treatment to cure and decrease infectivity; (2) reduce risk-taking behavior; (3) ensure that sexual partners are treated to break transmission; and (4) to decrease HIV transmission.

Syndrome case management

The syndromic case management endorsed by WHO/UNAIDS in the early 1990s still remains the standard of care in resource-poor settings for the management of the most common STI syndromes. This approach addresses the limitation of etiologic and presumptive clinical diagnosis.^{93,94} Syndrome management was originally designed and promoted to help clinicians manage symptomatic patients. It was never intended to be used as a tool for case finding or for screening asymptomatic patients and predictably, this misuse of the approach led to disappointment. Syndrome management was most commonly misapplied in settings servicing women (e.g., family planning clinics and antenatal care settings). Most gonococcal or chlamydial cervical infections in women are subclinical or asymptomatic, so there would be no syndromic presentation. The second misconception around syndrome management was that it was implemented as the key, and sometimes only, strategy in STI control programs and was viewed and promoted as a simplistic solution to a complex problem.³ While service provision to symptomatic individuals is a core component to comprehensive STI control programs, it cannot stand alone. Approaches to STI control need to be more multifaceted working across multiple programs to achieve the goals.⁴²

STI syndromes are easily identifiable groups of symptoms and signs. Syndrome management provides treatment for the most common organisms causing the syndrome.¹¹ Algorithms (flowcharts) have been developed for the management of the major STI syndromes: urethral discharge, genital ulcer disease, vaginal discharge, scrotal swelling, and lower abdominal pain. Risk assessments that are locally adapted are utilized to improve the diagnostic validity for gonococcal and chlamydial cervical infection. The advantages and disadvantages of syndrome management are outlined in [Table 101-3](#).

The syndromic approach is effective and cost-effective for urethral discharge and genital ulcer disease syndromes.^{95,96} However, most algorithms do poorly in detecting herpes infection.⁹⁶ Vaginal discharge algorithms are not highly effective in managing gonococcal and chlamydial cervical infection, the majority of which are asymptomatic.

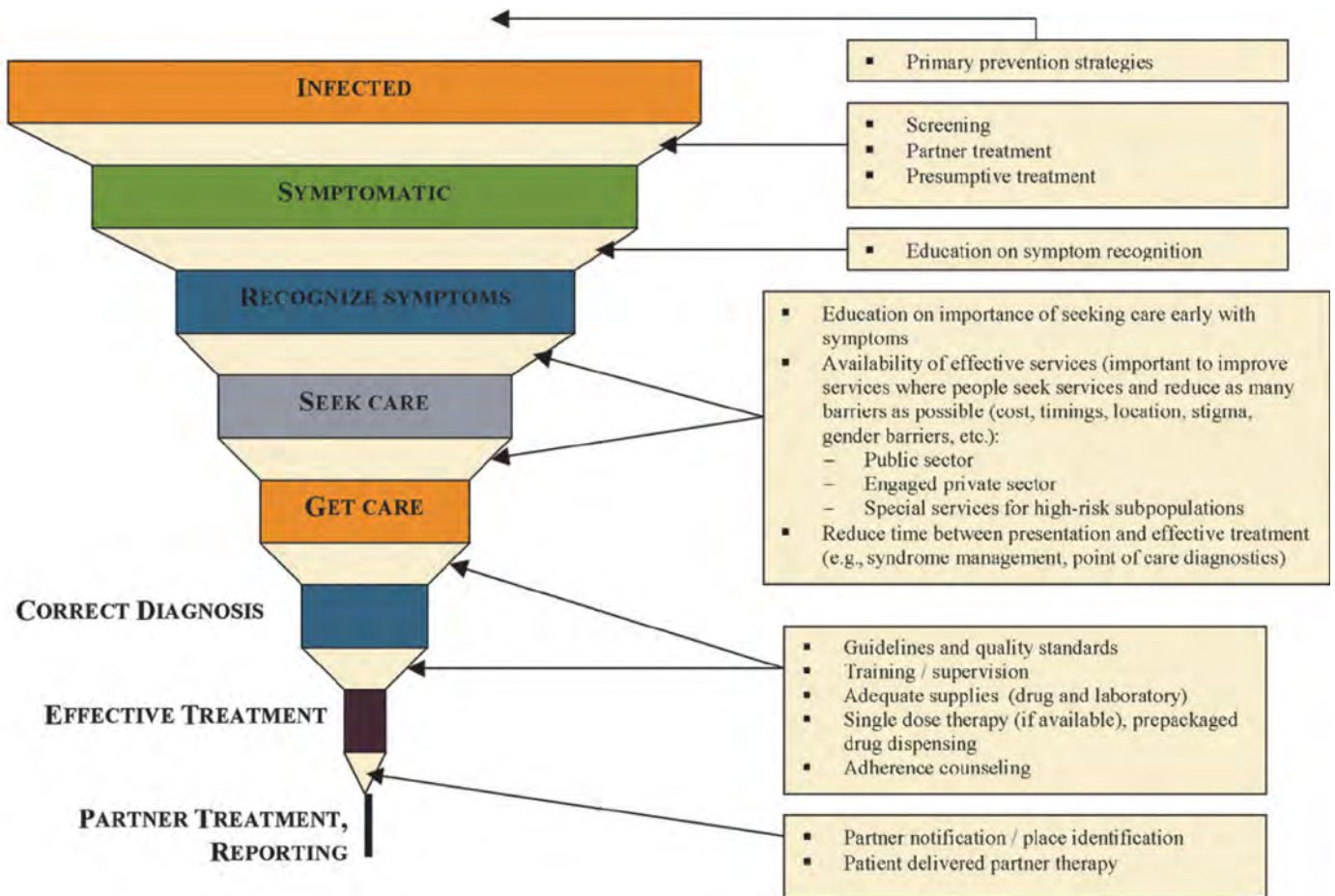


FIGURE 101-3. STI clinical services operational model.

Combining risk assessment and clinical signs of cervical inflammation has a higher positive predictive value for cervical infection.¹¹ Vaginal discharge symptoms are more likely a manifestation of vaginal infection, trichomoniasis, bacterial vaginosis, or candidiasis. In female populations where gonococcal and chlamydial infections are low, syndromic treatment for vaginal infections only is recommended. In high prevalence settings, syndrome management or presumptive treatment could be considered. Moreover, in settings of medium prevalence of infections, selective screening may be appropriate. Given the limited tools available for screening women for gonococcal or chlamydial infections, strategies should be centered on finding symptomatic men and improving counseling and partner notification.⁹⁷

Algorithms should be adapted to the local patterns of STIs, syndrome etiologies, antimicrobial susceptibility, sexual behavior and other risk factors, health-care seeking behavior, availability of point of care tests, and programmatic capacity. They should be validated and updated on a regular basis. The changing etiologies of STI syndromes, increasing HSV-2 in genital ulcers, for example, also need to be considered in developing and revising the algorithms.¹⁶

Syndromic management is not a perfect strategy but is better than the clinical practices that it replaced and more cost-effective than clinical and laboratory diagnosis.⁹⁸ Until inexpensive, simple, and accurate STI diagnostics are developed and made available for use in developing countries, a modified, adapted syndromic approach is still the most feasible symptomatic case management approach.

■ SCREENING AND CASE FINDING

Many STIs are asymptomatic and this can lead to serious sequelae if they are not treated early. STI case finding or screening are required to detect subclinical and asymptomatic STIs. A two-tier screening process of identifying individuals at highest risk of infection through a risk assessment with high sensitivity, based on local risk factors for cervical infections, and testing those identified to be at higher risk reduces the cost of STI screening programs.⁹⁹ Besides screening asymptomatic individuals, symptomatic STI patients seeking care should also be screened for other STIs, such as syphilis in men with urethritis and through routine offers of HIV testing.

Table 101-3. Advantages and Disadvantages of Syndrome Management**Advantages**

- Responds to patient's complaint
- Provides for immediate treatment at presentation
- Treats for most possible infections (depends on algorithm design)
- Avoids costs of laboratory tests
- Can be implemented at primary care levels
- Standardizes reporting for improved case reporting, supervision, quality assurance, and stock management
- Can be modified to incorporate simple laboratory tests
- Sensitive and specific for urethral discharge and genital ulcer disease

Disadvantages

- Overtreatment leading to increased drug costs, and possible adverse drug events, alterations in vaginal flora, and potential for increased antibiotic resistance
- Limited applicability in women with vaginal discharge (recommended for vaginal infections only in populations with low STI prevalence)
- Requires staff training or retraining
- Physicians resist using it
- Health programmers fail to understand purpose of syndrome management
 - Do not plan for syphilis screening
 - Use inappropriately for screening

Antenatal syphilis screening and treatment programs should be implemented by all STI control programs given its cost-effectiveness described below. Screening of high-risk subpopulations is cost-effective because a case treated or prevented in a person from these subpopulations prevents the person from infecting several others.¹⁰⁰ One analysis reported that the “dynamic” benefits of treating bacterial STIs in high-risk subpopulations were about 10 times more than the “static” benefits as measured in disability adjusted life years (DALYs) because of the impact of preventing ongoing transmission.²³

Antenatal syphilis screening

The cost-effectiveness of antenatal syphilis screening has been well documented.⁵¹ Adverse pregnancy outcomes occur in

Table 101-4. Interventions at Clinic-Level to Improve Efficiency of Syphilis Screening

- **Promote** early antenatal attendance before the fourth month of pregnancy
- **Train** personnel on syphilis testing and treatment
- **Integrate** syphilis screening in antenatal care
- **Ensure** a functioning commodity and reagent logistics management system
- **Provide** point of care testing so that results are immediately available and treatment provided without the need for a return visit
- **Implement** epidemiologic treatment of sexual partners of pregnant women who test positive
- **Revise** protocols to add an additional second test at the last trimester to screen for incident cases
- **Improve** quality of care during pregnancy, delivery, and neonatal period

80% of women with active syphilis including stillbirths, perinatal death, and serious neonatal infection. Syphilis screening is cost-effective even in low prevalence settings because of the high medical and societal cost of congenital syphilis.

Despite the cost-effectiveness of this intervention, antenatal syphilis screening and treatment programs and congenital syphilis screening control programs remain inefficient and several clinic-level remedies have been proposed (Table 101-4).¹⁰¹ All of these remedies for improved syphilis screening and treatment require priority setting from public health authorities and accountability for implementation through the health system.

Several studies have documented that point of care screening and treatment can increase the percentage of women screened and treated using nontreponemal tests (RPR or VDRL) or newer point of care testing methodologies using immunochromatographic strip (ICS) tests.^{102–105} This simple and relatively inexpensive test has a great potential to increase coverage for antenatal screening to prevent congenital syphilis and has been shown to be cost-effective.¹⁰⁴ These point of care approaches remove only one of the many barriers to effective syphilis screening and treatment programs for pregnant women.

Screening of high-risk subpopulations

Female sex workers. High rates of curable STIs have been observed worldwide in commercial sex settings where condom use rates are low and where there is limited access to effective

STI treatment services.¹⁰⁶ Effective prevention and treatment of STI among sex workers requires attention to both symptomatic and asymptomatic infections. Regular screening for asymptomatic infections among sex workers using laboratory tests is cost-effective given the high rates of STIs and can result in reduced STI prevalence over time.^{89,107,108} However, this is often not possible because of the limited availability or poor quality of available screening tests and functioning laboratories.

Numerous sex worker interventions implemented under HIV prevention programs are currently providing clinical services for sex workers including regular screening and treatment of symptomatic STIs coupled with behavior change programming and condom promotion. These interventions have reported increases in condom use and some have documented decreases in STI and HIV prevalence.^{17,107–110} Most STI management protocols for sex workers utilize a combination of syndromic treatment of symptomatic STIs, regular STI screening using algorithms with risk scoring, clinical examination with speculum examination to detect signs of cervicitis, and simple laboratory tests to identify leukocytes or gonococci on cervical smears by Gram staining. In addition, they provide regular syphilis screening and treatment. Though this is less than ideal, it is feasible in most settings and can be implemented in a scaled manner. Regular screening of sex workers provides opportunities for regular clinic-based health education and risk reduction counseling, condom promotion, and distribution.

Some developing countries use registration of sex workers and required health check-ups to control STIs.¹¹¹ Where this has been investigated, STI prevalence rates are higher in the unregistered sex workers as a result of severely limiting access to STI care for sex workers who are not registered because of age or other legal constraints such as lack of identity papers or “entertainment” licenses. A more appropriate approach is to ensure high quality and accessible services to all sex workers.

Men who have sex with men (MSM). STI and HIV rates in MSM populations in developing countries indicate that they are at increased risk.^{112,113} There are, however, no reports on impact of treatment and screening strategies for MSM or on any evaluation of STI syndromic algorithms for management of anal STIs. Most treatment guidelines for MSM in these settings, if they exist, are based on a paper of STI syndromes in MSM in the United States and clinical experience of clinicians.¹¹⁴

Injecting Drug Users (IDUs). HIV interventions for IDUs often focus solely on decreasing risk from injecting. IDUs are also at risk for STIs and in many countries act as an amplifier of HIV risk into heterosexual networks through commercial and transactional sex.¹¹⁵ Interventions working with IDUs need to provide sexual health services, condoms, and STI treatment, as part of comprehensive prevention services.

Sexually active adolescents. Sexually active adolescents are an underserved group with high incidence of STIs and HIV. They have several additional barriers to getting sexual health service because services are oriented to older adults or they are inadvertently discouraged from doing so by judgmental provider attitudes, cost, or clinic timings. Health-seeking behavior is also a significant obstacle in some settings. Tailoring existing services to address adolescents’ specific reproductive health needs or developing new services accessible to them have been successful in reaching youth, although few interventions have been implemented at scale.^{116,117}

■ EPIDEMIOLOGIC/PRESUMPTIVE TREATMENT

Epidemiologic treatment, or presumptive treatment, of individuals or populations is given when there is a high likelihood of having that infection(s). Treatment is not dependent on the presence of symptoms or signs, or on results of laboratory tests, but on an identified increased risk of current infection. Epidemiologic or presumptive treatment addresses the problematic issue of asymptomatic infection. An example is the epidemiologic treatment of sex partners of patients with an STI whereby the partner is at a much higher risk of having the same infection.

Presumptive treatment is currently being implemented, either as a one-time intervention at the first contact with services, or on a periodic basis, as an STI control intervention in high-risk subpopulations such as sex workers.¹⁰⁶ The experience in Madagascar and the Philippines, where one-time presumptive treatment for gonococcal and chlamydial infection was provided to female sex workers in existing STI services at first visit, resulted in a rapid reduction of STI rates.^{118,119} The reduced STI prevalence was sustained through ongoing provision of routine STI services. In Laos, where STI services for sex workers are being established, presumptive treatment provided a short-term intervention to rapidly decrease STIs.¹²⁰ Periodic presumptive treatment among female sex workers in South Africa achieved a decline in gonococcal and chlamydial prevalence among them and a documented reduction in bacterial genital ulcer diseases and urethral discharge among miners in the area.⁹⁰ A South African study has shown that such programs for sex workers are highly cost-effective and that periodic presumptive treatment actually improves their cost-effectiveness.¹²¹ Experience in Zimbabwe and the Philippines indicates that prevalence reverts back to preintervention levels without ongoing service provision.^{119,122}

Presumptive treatment cannot stand on its own as an STI control intervention. Implicit in the logic of employing epidemiologic or presumptive treatment is that it is a temporary measure to reduce prevalence that will be sustained through more routine STI service provision.^{123,124}

OTHER ELEMENTS OF COMPREHENSIVE CASE MANAGEMENT

■ HEALTH EDUCATION AND COUNSELING

The STI consultation provides an opportunity not only to diagnose and treat STIs but also to educate on ways to prevent infections in future. A patient's decision to come to a clinic suggests that they would be more receptive and provides the opportunity to counsel about partner treatment, to educate on condom use, the treatment regimen, and about HIV infection risk. As part of STI and HIV risk reduction counseling, each individual should be given information that allows him or her to decide voluntarily about HIV testing. Given the potential for STI and HIV coinfection and the disproportionate impact of acute HIV infection in sexual transmission dynamics, patients with STIs should be counseled accordingly.¹²⁵

Counseling, as opposed to health education, is essential for risk reduction and psychosocial support.¹²⁶ Counseling requires specific skills and considerable time, both of which are often not available in the routine clinical setting. A qualified health-care provider should be designated specifically and adequately trained to provide counseling. In some settings, individuals from high-risk subpopulations are trained to be counselors and work in specific clinics with high numbers of patients from these subpopulations. These counselors are often more acceptable to patients, although large investments in training and ongoing supervision are sometimes necessary.

■ PARTNER NOTIFICATION

Partner notification is a well-established component of comprehensive STI case management but is often difficult to implement.⁹³ Partners of the index patient, the person identified with an STI, are reached through several different strategies: (1) patient-led—the index patient finds and refers (enhanced through provision of a referral card); (2) provider led-based—on information provided by the index patient, the provider notifies the partner; and (3) conditional (contractual) referral—index patients are asked to notify and refer partners by a specific date after which the provider will notify.¹²⁷ Provider referral for developing countries has the disadvantage of more restricted avenues of access to potential partners, such as telephone numbers and addresses, in addition to the additional program costs and concerns about confidentiality that limit the disclosure of information identifying partners. Additional barriers to partner referral include fear of partner discord or violence, multiple partners or casual partners, as well as financial barriers and acceptability of the treatment location to the partner.¹²⁷

Patient delivered partner therapy evaluated in Uganda was shown to be more effective than the enhanced patient referral

through contact cards in the treatment of sexual partners.¹²⁸ This approach may overcome some of the difficulties to partner notification described above such as accessibility of clinical services or costs and may be more acceptable to the index patient.

Given the limitations of the syndromic approach and diagnostic options for women, partner notification by men with urethritis, both men and women with genital ulcers and individuals with reactive syphilis serology should be prioritized. Because of the poor sensitivity and specificity of syndrome management algorithms for vaginal discharge in women, partner notification for male partners is not warranted. The harm and negative social consequences resulting from partner notification should be weighed carefully in the recommendation to refer partners. Partner notification should be voluntary and confidential, and treatment of the index case should not be withheld in efforts to treat partners.

■ ANTIBIOTIC PRESCRIBING AND PATIENT ADHERENCE

In many developing countries, there is inappropriate prescription drug use initiated by both providers and patients.¹²⁹ From the patient perspective, there are the misperceptions that antibiotics are necessary for every illness or that injections are more effective than oral medication. Additionally the widespread, unregulated, over-the-counter use of antibiotics results in self-medication often for both treatment and also for prophylaxis before a risky sexual encounter. When medication is prescribed, poor adherence to dosage regimens is common as a result of poor understanding by patients and financial constraints. On the provider side, lack of knowledge and training, perceptions of patient demands, economic pressure, and social norms, among others have been described.¹²⁹

To address some of these issues, STI syndrome packets have been developed. Prepackaged STI syndrome blister packs have been shown to increase patient adherence (when antibiotic dosing is multiday) and improve provider prescribing habits and overall STI treatment advice in the clinical setting.^{130,131} Prepackaged syndrome treatment packets have been enhanced with partner referral cards, condoms, and STI educational material. Two reports in the literature describe the positioning prepackaged urethritis treatment kits to be sold by private physicians or in nearby pharmacies by prescription.^{132,133} In the evaluation of both these efforts, there was high reported adherence to the antibiotic regimen as well as reported partner referral and condom use during treatment.

■ ROLE OF STI CLINICAL SERVICES FOR HIV PREVENTION

STI clinical services have an important responsibility to address HIV infection prevention both in the management of HIV-infected individuals and in the counseling about HIV

and referral for HIV testing of STI patients of unknown HIV status. Persons presenting with STIs have already demonstrated that they are in sexual networks with high-risk behavior. From numerous HIV prevalence studies globally, HIV prevalence in STI clinic attendees is consistently higher than HIV prevalence in antenatal or general population settings. Treating STIs in dually-infected persons, given the impact of STIs on genital HIV shedding, is a priority.^{49,134} Where resources exist, routine screening of HIV-infected persons who have ongoing high-risk behavior should be considered.

The recent data from Malawi suggesting that STIs and HIV are cotransmitted makes high quality counseling and access to HIV testing services more urgent.⁴⁸ Acute HIV infection would not be detected on routine HIV serological tests at the time of presentation with an STI, but since acute HIV infection is hyperinfectious, consistent condom use with all partners and repeat testing in 3 months should be emphasized at STI clinics.¹²⁵ In an STI clinic in Malawi, investigators were able to identify 90% of acute HIV infections by taking serum samples from discordant rapid HIV tests and testing with a standard p24 antigen assay.¹³⁵ This approach potentially offers a way to identify acute infection in well-equipped developing country settings. In the vast majority of settings, however, HIV testing and counseling services at STI clinics simply do not exist, or are underemphasized in national plans.

STI PROGRAM SUPPORT COMPONENTS

An effective program management system is critical to setting-up and maintaining efficient STI prevention and care. The STI program should have a clear understanding of the HIV epidemics and an overview of the STI situation in the country, key areas of activity, and the spectrum of interventions being undertaken. It is essential that both government and externally supported interventions are coordinated to avoid duplication and ensure that they are directed toward the priority strategies of the country. This coordination is more easily accomplished if there is a national STI prevention and control strategy, STI case management guidelines, training curricula for staff at different levels of the health service, and well-defined reporting and monitoring indicators.

As HIV prevention interventions are similar to many program activities in STI prevention, there needs to be close coordination and coplanning between the two programs. The STI program should have access to expertise in technical, program management, and policy issues related to STI control through an STI technical advisory group. Efficient logistics management is necessary for preventive and care services to maximize the use of limited resources. Availability of essential STI drugs, condoms and lubricants, laboratory diagnostics tests, medical supplies, and communication materials requires trained personnel and a functioning logistics system.

CAPACITY BUILDING

Capacity building to improve human resources and operational capacities of institutions is a prerequisite for effective STI programming. Capacity building is not just training of staff but refers to the strengthening of the full range of supporting systems and activities that allow for staff to be fully effective in their work from good physical infrastructure to adequate supplies to supportive supervision to respect.¹³⁶ A systematic approach to capacity building consisting of developing operational guidelines and supervisory tools, training, regular supportive supervision and monitoring, and good management support in India resulted in a rapid scale-up of quality and standardized STI services that had reached about 70% of the 183,000 estimated female sex workers in the coverage area with clinical STI services in a short time frame.¹³⁷

Training of staff should be based on adult learning principles, targeted and competency-based. Refresher trainings should be conducted to reinforce previous learning and provide opportunities for networking of trainees. Ongoing dissemination of technical and programmatic updates can be done through involving professional associations and through the Internet. These strategies could also reach private practitioners, who are commonly providing STI care.

There has been very limited focus and investment on supervision. It is presumed, or hoped, that training will ensure the desired performance of staff. Supportive supervision should be established to direct and support staff so that they can perform their duties more effectively. Supervision with clear evaluation criteria is one of the most important mechanisms to assess performance and outputs.

QUALITY ASSURANCE

Providing quality services at the primary health-care facilities will encourage STI patients to seek care at these facilities. Quality services are technically sound, based on evidence-informed standard guidelines and procedures, efficient, cost-effective, accessible and acceptable to the client-base, ensure ethical standards, maintain confidentiality, and result in patients reporting their satisfaction. Clinic guidelines and standard operating procedures should be developed to provide guidance on STI case management and other aspects of clinical services. An example of the spectrum of areas covered in such guidelines is presented in [Table 101-5](#). Supervisory tools to monitor quality can be developed based on the adopted guidelines and standards.

When STI clinical services have laboratory testing on-site, internal and external laboratory quality assurance systems should be in place.

Table 101-5. Spectrum of STI Clinic Operations Needing Written Guidelines and Standards**Clinic operations**

- community approach
- coordination with outreach services
- clinic structure and setup
- clinic equipment
- staffing and operations
- staff training and skills

Clinical management of sexually transmitted infections

- STI management of sex workers
- STI management of men who have sex with men
- STI management of symptomatic patients
- Standard treatment
- medications and commodities
- allergic reactions and anaphylaxis
- referral of patients
- documentation

Education and counseling of patients

- components of health education and counseling
- lubricant and condom promotion and distribution
- information, education, and communication materials
- counseling and referral for HIV testing

Laboratory services

- simple laboratory tests
- higher-level laboratory tests
- laboratory standard operating procedures and quality control systems

Infection control

- universal precautions
- cleaning, disinfecting, and sterilizing equipment
- disposal of hazardous waste
- postexposure prophylaxis

Ethical standards, confidentiality and right of refusal**Monitoring, evaluation, and reporting****Technical support and supervision**

at all levels are an essential element of good program management but are often neglected. Information for decision making can be categorized into four groups that include formative assessments, process monitoring, effectiveness evaluation, and special studies (Table 101-6).

Formative assessments

Formative assessment is the first step in the program cycle where current data on HIV prevalence, STI prevalence and incidence, quality of services, current use of services, and acceptability and accessibility issues are considered. Formative assessments can also involve community-mapping efforts to identify high-risk subpopulations and estimate their size. This information is necessary to identify program goals and set targets, to develop program implementation plans and budgets, and to plan data collection activities.

Experience globally has shown that it is possible to find and access high-risk subpopulations and provide services. Recent work has found that targeting sex partner meeting places may complement traditional STI control tools.^{140,141} Several methodologies have been developed and modified to identify high-risk subpopulations or high-risk venues including information supplied by index patients in clinical services, geographic and social mapping, participatory situational assessments, and the PLACE methodology. Most of these approaches entail using members of the community or target population as key-informants and as guides. Number and locations, where high-risk sexual activity takes place or “hotspots” are mapped, sizes of subpopulation are estimated and baseline behavioral data are obtained.¹⁴² The approaches are also important opportunities to promote trust and participation of high-risk subpopulations.

These mapping and size estimation exercises need to be repeated at regular intervals, annually or semiannually to recognize and adapt to the fluidity in sex work typologies and locations including “hotspots” that are influenced by police pressures and social and economic changes. Additionally, access to high-risk subpopulations increase over time as trust is gained. More formal methods of size estimation have also been developed.¹⁴³

Process monitoring

Attention to service delivery, quality, and coverage through monitoring program inputs and outputs is essential for program management. The indicators, for the most part, are collected as part of routine program activities and should be linked to important program activities. Indicators should be reviewed with project staff on a regular basis while managers can be presented key indicators or “dashboard” indicators. Routine process indicators should be reported by every implementing unit providing data “at scale.” In contrast, evaluation activities described below can only be done in

INFORMATION FOR DECISION-MAKING

In order to effectively plan, manage, and evaluate a national STI program, several streams of information are needed at different levels of the program.^{138,139} Monitoring and data use

Table 101-6. Information for Decision Making in STI Control Programs—Examples of Types of Data

Formative Assessment	Process Monitoring	Effectiveness Evaluation	Special Studies
<ul style="list-style-type: none"> • HIV prevalence by population groups • STI prevalence by population groups • Service quality assessments • Health-care seeking behavior • Mapping and size estimation of prioritize subpopulations 	<ul style="list-style-type: none"> • Quality and coverage of training • Outreach and education efforts • Service utilization • Duration of symptoms • Estimated coverage of high-risk subpopulations with STI services • Estimated uptake (number of new attendees) • Number of clinic visits (new vs. repeat/follow-up), age, and sex of clinic attendees • Number and distribution of STI syndromes • Number of condoms distributed, number of condom outlet sites • Percentage days of stock out of antibiotics • Service quality—routine and special assessments 	<ul style="list-style-type: none"> • Sentinel site reporting • Intermittent surveys of health-seeking and sexual behavior in multiple subpopulation groups • Intermittent surveys of HIV prevalence and incidence in multiple subpopulation groups • Intermittent surveys of STI prevalence in multiple subpopulation groups • Intermittent STI syndrome-etiology assessments • Case reporting • Antimicrobial resistance (should be routine but often special studies) 	<ul style="list-style-type: none"> • Evaluation and updating of STI syndromic management algorithms for general populations, sex workers, and MSM • Costing, cost-benefit, and cost-effectiveness • Incidence and prevalence of STI-related complications such as PID or congenital syphilis • Prevalence assessments of viral STIs such as HSV-2, HPV, and HBV • Outbreak investigations • Estimation of the economic costs of STIs • Field evaluation of new rapid diagnostics • Health systems research to investigate practical solutions to current constraints of implementation within the current health systems • Operations research on detection of acute HIV infection in prevention programs (e.g., utility, approaches, cost, etc.)

fewer sites because of expense and difficulty, so the effectiveness of the entire STI program must be inferred based on process indicators from all sites. Monitoring the quality of STI services is essential. Tools or checklists used by supervisors on quality of critical components in STI case management services both collect the information in a systematic manner and ensure that quality issues are immediately addressed in the field. Protocols for systematic quality assessments also exist.¹⁴⁴

Effectiveness evaluation

Evaluating the effectiveness of an STI control program involves assessing or estimating the impact of the program on the prevalence and incidence of STIs, the sequelae of various STIs, and STI-related behaviors such as treatment seeking, condom use, and HIV-test acceptance. Because this information is difficult and expensive to collect, STI control efforts are evaluated using a combination of passive data collection, case reporting, supplemented with special surveys of STI and HIV prevalence, assessment of STI syndrome etiologies, antimicrobial resistance monitoring, and risk behavior prevalence together forming

some of the components of an STI surveillance system. Surveillance data are not only used for program evaluation but also used to determine the need for public health action.

Special surveys are done to supplement the information from passive reporting systems that includes information from all reporting units supplemented with sentinel site reporting and includes behavioral, STI, and HIV prevalence in various subpopulations and syndrome etiologies. Many HIV prevention programs do behavioral surveillance monitoring. Including STI testing and relevant STI questions in these studies has been shown to be possible.¹⁴⁵ Most developing countries do not have a functioning routine system to monitor antimicrobial susceptibility of *Neisseria gonorrhoeae* although there are regional efforts.¹⁴⁶ Given the increasing resistance of *N. gonorrhoeae* globally, susceptibility of the organism to recommended therapy should be assessed on a regular basis.

Special studies

To complement process monitoring, evaluation activities, and formative assessments, special studies including clinical,

microbiological and socio-behavioral research, and operations research are necessary to improve STI programming and inform priority setting. See [Table 101-6](#).

■ LABORATORY SERVICES

While syndromic management was developed to address the needs of health-care settings in the developing world where laboratory services were inaccessible or not affordable, the intent was not to preclude the development of laboratory services. Laboratory services must be continued to be strengthened in STI programs. Basic laboratory testing such as syphilis serologic testing, HIV testing, and basic microscopy should be available in peripheral health-care centers, with increasing diagnostic capability as services become larger.¹⁴⁷ Since laboratory services are often viewed as expensive and unnecessary, this basic support is often lacking.

The availability of nucleic acid amplification tests have allowed for simpler biologic specimens to be taken (e.g., urine or vaginal swabs) and for sensitive and specific diagnosis.¹⁴⁸ Their expense and the need for sophisticated laboratory infrastructure have limited their use for routine diagnosis in developing countries. Instead, these diagnostics have been used mainly to study the epidemiology of STIs and to support population-based surveillance activities, enlarging the database for policy-makers. One of the urgent needs in STI control is the development of sensitive and specific “bedside” or point of care diagnostic tests, particularly for *N. gonorrhoeae* and *Chlamydia trachomatis* to detect lower genital tract infections in women. A fuller discussion of laboratory management in developing countries is discussed in Chapter 104 in this volume.

CHALLENGES TO STI/HIV CONTROL PROGRAM IN DEVELOPING COUNTRIES

■ EFFECTIVELY UTILIZING THE PRIVATE SECTOR

A vast range of providers deliver STI services in developing countries. Patient choice depends on availability of services, needs, and perceptions of the patients about disease seriousness, cost, confidentiality, user-friendliness, and efficacy as well as overall market forces. There have been a handful of documented attempts evaluating how private providers can be incorporated into achieving STI public health goals.

Many observers report that pharmacists and drug clerks are an underutilized resource for STI syndrome management, at least for urethral discharge and vaginal discharge and prevention messaging as they provide private, accessible, rapid, well-stocked, and to some extent anonymous services.^{149–151} Three studies implemented syndrome management training of

pharmacists and showed modest improvement in treatment for assessed syndromes, promotion of partner treatment, and/or condom use but performance deteriorated with time after training.^{151–153} One report suggested that training of pharmacists in syndrome management would be a cost-effective intervention, although the analysis was hindered by lack of information on what proportion of the population used pharmacies.¹⁵⁴ Social marketing of male urethritis treatment kits with drugs, condoms, partner referral cards, and STI educational material is being attempted in several countries (Myanmar, Laos, Nepal, Cambodia, Pakistan, India, Madagascar, Dominican Republic, Benin, and Togo) to address the treatment seeking behavior of symptomatic men and poor drug dispensing habits of pharmacists.¹⁵⁵ In one reported study of socially marketed urethritis kits from Uganda, cure rates compliance and reported condom use were higher than in a control group.¹³² Utilization of pharmacies as legitimate providers, however, will require policy modifications with pharmaceutical regulatory boards, infrastructure to support training, supervision and enforcement, and approval from the medical establishment.¹⁵¹

Voucher schemes have been utilized as a means of involving the private sector by increasing the affordability of specific health-care treatments. On a large scale, however, they are prohibitively expensive to manage if there are large numbers of service delivery points.¹⁵⁶ However, in high-risk subpopulations, vouchers appear to be cost-effective in increasing STI service coverage.¹⁵⁷

Health franchising, where private providers are grouped under a branded name and supported by training, supervision, advertising, and other assistance such as supplies, has been used as a way to increase access to and assure quality of reproductive health services for women and adolescents.¹⁵⁸ Where these efforts have been evaluated, the franchised services appeared to have increased client satisfaction and shown some health improvement, although there were ongoing challenges associated with quality assurance and costs associated with demand generation.¹⁵⁸ One franchise network in India is working with private providers to improve case management of STIs in men. In addition to quality assurance issues, one challenge in this STI franchise has been the positioning of demand generation for STI services in such a way so as to not stigmatize the private practitioners participating in the program (personal communication, Krisila Benson).

Other interventions have worked with the private commercial employers (e.g., trucking and oil companies and construction sites) who employ large numbers of single-sex workers who are usually away from home and are at higher risk for STIs.^{90,159,160}

Other considerations for involving the private sector include postgraduate education, but skills need to be maintained through systems that support regular engagement.¹⁵⁶ Public-private partnerships, where the government encourages

referrals to private providers and/or provides private providers with free treatment, have been used for tuberculosis control.¹⁵⁶ There is no documentation of similar efforts for STIs.

■ COLLABORATIVE IMPLEMENTATION

The new draft global strategy for prevention and control of STIs now calls for collaborative implementation with other programs.⁴² Successful implementation of this vision can be informed by the more or less unsuccessful attempt at integration of HIV/STI programs with family planning and maternal and child health programs that was promoted to control the spread of HIV and STIs and improve women's reproductive health.¹⁶¹ Analysis of this integration attempt by vertical programs found that while policy formulations were often clear, implementation was disjointed and disorganized, hindered both by a failure to allocate responsibilities clearly between program staff associated with the numerous programs involved and a lack of clear communication.¹⁶² There was, in addition, little commitment organizationally to improving quality and equity. Donor activities exacerbated some of these problems when they would support selective components of reproductive health. At the implementation level, additional responsibilities were being added to programs that were already functioning poorly.¹⁶¹ In fact, integrated services have shown limited evidence of having any effect on

STI prevention or STI risk behaviors and condom use, and there is a call for more systematic appraisal of the benefits and the costs, and less ideology.¹⁶³

■ SCALING

Many STI and HIV control programs have limited to no impact because they provide services to only a small proportion of the populations that need them. There is an urgent need for optimal coverage and intensity of programs for STI and HIV in all settings to have an impact.⁵⁵ Scaling up interventions involve expanding geographic and target coverage, reaching additional target populations, broadening the scope and intensity of the intervention, and influencing national policies.¹⁶⁴

In most developing countries, there are major constraints to scaling up effective interventions.¹⁶⁵ Nonetheless, experiences in some countries have shown that it is possible to scale up effective and innovative interventions.^{166,167} Key components of scaling up include: (1) strong political commitment with multisectoral involvement; (2) adequate community involvement and mobilizing communities to act collectively to ensure that the initiatives are owned and responded to by all levels of the community; (3) sound technical design with interventions that can be adopted in the public and private sector; (4) adequate capacity building and technical support; (5) effective, decentralized management systems; and

Table 101-7. Core Elements of Comprehensive STI Control Package

Primary prevention package of reducing sexual risk

- barrier method promotion and provision
- behavior change in sexual partner choice and number

Comprehensive STI case management for symptomatic patients in primary health-care settings and where people seek care (if possible)

- treatment at presentation
- risk reduction counseling
- condom use and provision
- medication instruction including adherence
- partner notification or place identification
- HIV test offered
- special efforts to offer STI services to persons with HIV infection

Focused STI case management services for high-risk subpopulations aiming for high coverage

- active high-risk venue finding
- flexible service delivery

- links with groups for persons living with HIV and AIDS

Special services for specific STI pathogens

- syphilis screening in pregnant women
- neonatal eye prophylaxis for neonatal conjunctivitis
- other interventions based on data

General population educational issues

- about STIs and consequences
- promotion of appropriate treatment seeking behavior

Assessment, monitoring, evaluation, special studies

- managing against targets
- scaling with quality for high coverage
- knowing the epidemic

(6) clear objectives, focused targeting based on strong monitoring and evaluation systems and formative assessment on the needs of the community.¹⁶⁶

CONCLUSIONS

The limited success of STIs control in developing countries is not solely because programs lack point of care diagnostics, increasing antibiotic resistance, shifting pathogens, poor treatment seeking behavior, or complex transmission dynamics. More fundamentally, it is a lack of political will to invest in appropriate control measures and to maintain and strengthen existing basic health systems and lack of data on burden, sequelae, and effectiveness.¹³ That political will shall be even harder to achieve because of politically motivated erotophobia, i.e., the inability of senior leaders to find the courage to guide healthy, constructive public discussion about sexual matters. Without attention to these fundamentals, no new prevention development, be it a diagnostic, a microbicide, or suppressive therapy, will have a major impact because there will be no functioning system to deliver it at the necessary scale.

The effective and cost-effective interventions that are being recommended in this chapter are essentially the same as have been recommended for the last 10 years (Table 101-7)—STI treatment of high-risk subpopulations, comprehensive case management of symptomatic STIs, antenatal syphilis screening and treatment and ophthalmia neonatorum prophylaxis, condom promotion, and risk reduction counseling. There is also increasing emphasis on the role STI clinics can play in identifying and counseling HIV-infected persons and STI diagnosis and management of HIV-infected individuals. For STI prevention and control, attention to scaling up these interventions with quality and prioritized, based on knowledge of the local situation, is the need of the hour.

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Approach to the Management of HIV/AIDS in Developing Countries

Mauro Schechter and Robin Wood

INTRODUCTION

Since the identification of HIV as the cause of AIDS in the early 1980s, the standard of care and treatment has changed markedly in the developed countries, resulting in substantial improvements in HIV-associated mortality and morbidity. In contrast, treatment and care in developing countries has evolved more slowly. In resource-poor countries, before the full extent of the demographic and social impact of the epidemic became manifest, the emphasis of public health and international agencies focused on prevention. As the number of patients with HIV-related disorders began to overwhelm already overstressed health systems, care for persons with HIV/AIDS was perceived as an infinite demand yielding little public health benefit. However, the humanitarian need to alleviate the plight of increasing numbers of people living with HIV/AIDS led to debates pitting care versus prevention. Care was initially limited to chemoprophylaxis and treatment of certain opportunistic infections (OIs) and excluded treatment with antiretroviral drugs that were considered unaffordable. In 2002, price reductions of branded antiretroviral drugs and increasing competition from cheaper generic formulations decreased the cost of first-line antiretroviral therapy (ART) from over U.S.\$10,000 per year to as low as U.S.\$150 per year,¹ thereby increasing the feasibility of their use in resource-poor settings.

In recent years, an international consensus has emerged on the need to address HIV/AIDS with a comprehensive response including treatment, care, and prevention. In March 2004, the United Nations General Assembly declared that the failure to deliver antiretroviral treatment for HIV/AIDS is a global health emergency. The WHO subsequently launched a global effort, in collaboration with other international agencies, to provide ART to 3 million people living with AIDS by the end of 2005.² On September 2005, at the World Summit of the United Nations, Heads of State called for universal access to HIV treatment.

The statistics describing the HIV pandemic are mind numbing with the present reality far exceeding projected

estimates made in the early 1990s.^{3,4} HIV/AIDS affects both health and wealth of households, thereby aggravating preexisting poverty.^{5,6}

HIV-related morbidity and mortality is affecting vital services such as healthcare and teaching. As a direct result of HIV, many African countries will suffer shortages of primary school teachers.^{7,8,9,10} The added stress to health systems has particularly affected hospital medical wards. HIV-infected patients have been reported to constitute 52% and 70% of medical admissions to hospitals in Uganda¹¹ and Malawi¹² and 80% of tuberculosis (TB) admissions to a large hospital in South Africa.¹³

In the developed world, ART has dramatically decreased the morbidity and mortality of HIV infection, resulting in a transfer of medical services from predominantly in-patient to outpatient care.¹⁴⁻¹⁶ A similar impact of ART on morbidity, mortality, and health-resources utilization has been demonstrated in Brazil, a middle-income country where free and universal access to ART has been available since 1996.¹⁷ Recently, data from a variety of settings have conclusively demonstrated that the provision of ART in developing countries is feasible, is cost-effective, and complements prevention efforts.¹⁸⁻²⁰

It is the combination of humanitarian imperative to alleviate suffering and the prospect of effective and potentially cost-saving medical management of HIV/AIDS that has fuelled the international efforts to extend the proven individual and societal benefits of ART to resource-poor countries. Focus is now concentrated on the operational challenges that need to be addressed in order to rapidly increase the numbers accessing treatment in the developing world, while continuing to address HIV prevention and other healthcare needs.

THE ROLE OF HIV TESTING

Considerable controversy surrounds the issue of testing for HIV-infection in developing countries due to stigma and the possible infringement of the right to autonomy and privacy. Moreover, in the absence of effective treatment, the benefits

of being aware of one's HIV status may not exceed the real or perceived disadvantages due to stigma. Women are particularly vulnerable and may be subjected to domestic violence, evicted from their homes, and forced into poverty because of their HIV status.^{21–22} However, the benefits of HIV testing include the potential for prevention of transmission, knowledge of prognosis, institution of primary chemoprophylaxis, and accurate diagnosis of the HIV/AIDS-related illnesses,²³ with considerable benefits for both individual and society.

Although universal voluntary knowledge of HIV serostatus is widely considered as an essential prevention tool, HIV testing services in resource-poor countries reach only a small proportion of those potentially exposed to HIV-infection. As access to antiretroviral treatment and to services for the prevention of mother-to-child transmission of HIV infection is scaled up, there is an opportunity to simultaneously expand access to voluntary counseling and testing programs. To address prevention and care programs, the WHO has estimated that up to 180 million individuals per year will need to be counseled and tested for HIV-infection.²⁴ Community voluntary counseling and testing programs are client-initiated, allowing people to voluntarily learn their status and receive counseling to reduce acquisition or transmission of HIV-infection. Within the healthcare services, an “opt-in” strategy has been the norm but increasingly provider-initiated or “opt-out” approaches are being promoted. As part of the worldwide effort to expand access to prevention of mother-to-child transmission and antiretroviral therapy, routine testing within health-care settings (with the right to refuse) has been recommended in the 2004 joint UN and WHO policy statement on HIV testing.²⁴ The recommendations identify four clearly distinguishable types of HIV testing:

1. Client-initiated testing, to learn HIV status through voluntary counseling and testing.
2. Diagnostic testing as part of medical investigation of persons with signs and symptoms consistent with HIV/AIDS, including all tuberculosis patients.
3. Routine HIV testing at sexually transmitted diseases (STDs) clinics and antenatal services and in high prevalence settings where ART is available.
4. Mandatory screening of blood, tissue, or organ donors, including semen donation for artificial insemination.

In 2004, in order to increase uptake of national maternal-to-child prevention and treatment programs, Botswana began routine “opt-out” HIV screening in perinatal and other health-care settings. Early results indicate routine testing increased uptake of HIV testing without any reduction in the number of women seeking antenatal care; nonetheless, many women did not learn their status because laboratory testing was offsite.²⁵ On-site rapid testing reduces the logistics of returning results to the site and the inevitable drop out due to clients failing to return. HIV testing remains open to

potential abuse and must always be performed within a framework that is cognizant of human rights.

THE NATURAL HISTORY OF HIV/AIDS IN DEVELOPING COUNTRIES

■ NATURAL HISTORY OF HIV INFECTION

Knowledge of the natural history of HIV-infection in developing countries is incomplete. Nonetheless, there are considerable data to suggest that progression to AIDS and/or death may be faster in developing countries. Many factors may potentially result in shorter survival of HIV-infected patients in resource-poor settings, including more frequent exposure to primary pathogens such as *Mycobacterium tuberculosis* and *Salmonella* spp., limited access to health-care services, under-resourced medical services, quality of water supply, and poor nutritional status.

Information on early events soon after HIV infection comes primarily from studies of persons infected with subtype B in North America and Europe. Symptomatic acute HIV infection is often referred to as the acute retrovirus syndrome and is reported to occur in the vast majority of recently infected individuals from developed countries. The acute retrovirus syndrome is often described as a mononucleosis-like syndrome with the onset of symptoms occurring around the time of seroconversion. There are very few reports on early events after acute infection from developing countries. In studies conducted in Brazil, Kenya, and India, in comparison with reports from developed countries, a significantly lower frequency of symptomatic seroconversion was reported. Although the majority of seroconverters in these lower income countries reported at least one symptom attributable to seroconversion, a minority reported three or more symptoms.²⁶ There are also scant data on early virologic and immunological events following seroconversion in developing countries. In a study conducted in Brazil involving seroconverters who were followed for up to 36 months, viral load dynamics were similar to those observed in developed countries, but CD4 counts appeared to decline at a faster rate.²⁷

The spectrum of some major HIV-related conditions in the various regions of the world is shown in [Table 102-1](#). However, besides the likely existence of considerable local variation within regions, the cohorts on whom present knowledge is based are probably subject to selection biases. Additionally, data may be further distorted due to the use of variable diagnostic criteria.^{28–39} Factors influencing regional variations include the prevalence of infectious conditions, particularly localized tropical diseases, and the proportion of individuals surviving with advanced immune suppression. Opportunistic diseases associated with advanced immune suppression such as cytomegalovirus disease are less

Table 102-1. Regional Variation in the Spectrum of HIV-Associated Disease^{25–36}

Disease	Europe, North America	Africa	South America	Asia
Tuberculosis	+	+++	++	+++
Toxoplasmosis	+ / ++	++	++	++
PCP	+++	+ / ++	++	++
Bacterial infections	++	+++	++	++
Kaposi's sarcoma	++	++	++	- / +
Cryptococcosis	+	++	+	++
MAC	++	+	+	- / +
HIV wasting	+	+++	++	+
HIV encephalopathy	++	+	+	- / +
CMV disease	++	+	+	+
Lymphoma	++	+	+	+
Leishmaniasis	- / +	+	++	++
Penicilliosis	-	-	-	++
Paracoccidioidomycosis	-	-	++	-

frequently reported in developing world cohorts whereas TB and bacterial infections, which can cause disease in individuals with relatively intact immune systems, are overrepresented. Thus, it is necessary to be aware of local variations in HIV/AIDS-associated conditions, particularly among returning travelers, or when presumptive diagnoses are made.

While the availability of ART has greatly modified the natural history of HIV-1 infection and despite the rapid expansion of access to therapy, there are very few reports on the spectrum of disease in individuals on ART in developing countries.

■ VIRAL DIVERSITY

Human immunodeficiency virus type 1 (HIV-1) has considerable diversity and at least 10 different subtypes and multiple subtype recombinants having been described. Additionally, there are a growing number of reports of individuals infected with more than one subtype. Subtypes differ from each other by at least 25–35% of amino acid sequences in the envelope proteins.⁴⁰ The biological relevance of HIV-1 subtypes is still undefined, although it may be of importance for the pathogenesis of HIV-1 infection, vaccine development, transmission, and diagnostics.⁴¹ Much of the current information on the geographic distribution and prevalence of HIV-1 subtypes are based on small cross-sectional studies.

The results of longitudinal studies assessing the role of viral subtype on disease progression have given variable results. Comparative studies of serotypes A and D, which are

very prevalent in East Africa, have shown no differences in survival of perinatally infected Ugandan children.⁴² However, in one study adults infected with subtype D had a 29% faster progression to death.⁴³ In Senegal, where subtypes A, C, D, and G are prevalent, the hazard ratio for progression to AIDS of female sex workers infected with non-A-subtype was eightfold higher than those infected with subtype A.⁴⁴ In a study conducted in Southern Brazil, where subtypes B and C dominate, no difference in progression to AIDS was discernable between the main subtypes.⁴⁵ In Brazil, molecular studies have shown that subtype B encompasses two variants. The first corresponds to the B subtype variant that predominates in the United States and Europe. The second variant (B-Br) bears a characteristic motif at the tip of the V3 loop glycine/lysine/glycine/arginine (GWGR) that substitutes for the glycine/proline/glycine/arginine (GPGR) usually present in the prototypic US and European variant. In a study conducted in Rio de Janeiro, it was shown that infection with serotype B-Br was associated with lower rates of progression to AIDS or death than infection with the prototype USA and European serotype B.⁴⁶ Presently available data indicate that infecting subtype does not significantly affect response to ART.⁴⁷

■ HIV-2 INFECTION

Infection with HIV-2 is common in West Africa, Portugal, and countries with close historical links to Portugal. Although HIV-2 infection is associated with similar (OIs) as HIV-1, the virus is considered less pathogenic than HIV-1

and the natural history is characterized by a more prolonged asymptomatic phase, resulting in more favorable prognosis. Additionally, HIV-2 viruses are not susceptible to non-nucleoside reverse transcriptase inhibitors (NNRTIs).

■ PREVENTION OF HIV-RELATED DISEASE

HIV-related morbidity and mortality is due to infections and neoplasms, which tend to occur with increasing frequency as immune suppression progresses. Primary pathogens, such as *M. tuberculosis*, *Streptococcus pneumoniae*, and *Plasmodium falciparum*, which can cause disease even in individuals with intact immune systems, occur over a wide range of CD4 counts, whereas less pathogenic organisms, such as *M. avium intracellulare* (MAC) and Cytomegalovirus are true OIs and thus occur almost exclusively in individuals in advanced stages of immune deficiency. The best prophylaxis for HIV-related illnesses is the reversal of immune deficiency through the use of ART. However, OIs will still occur, especially if ART is instituted at very low CD4 counts or if the response is suboptimal. Factors influencing choice of preventive strategies include the frequency and severity of the OI, the proven efficacy of the intervention in clinical trials, and cost and ease of delivery.

Preventive strategies include avoidance of exposure to pathogen, immunization, and chemoprophylaxis. Pathogen avoidance measures include access to clean water, sanitation, food-hygiene, and vector control. HIV services should minimize exposure of HIV-infected persons to *M. tuberculosis* by performing sputum collection in the open air or in well-ventilated areas. Those with positive *M. tuberculosis* smears or multidrug resistance should not be in general waiting areas.

The high recurrence rate of conditions such as *Pneumocystis jirovecii* pneumonia (PCP), cerebral toxoplasmosis, cryptococcal meningitis, and disseminated MAC infection require lifelong secondary prophylaxis after initial therapy. Secondary prophylaxis can be safely discontinued in those receiving ART who maintain a sustained (at least 3–6 months) increase in CD4 count above the threshold for which primary prophylaxis for that particular infection is routinely recommended.^{48,49}

Immunization

Immunization against infections that commonly affect HIV-infected individuals is an attractive strategy. However, the potential effectiveness of this strategy is undermined by the progressive reduction of vaccine efficacy as the immune deficiency progresses. Additionally, viral replication may be temporarily increased following vaccination, an event of uncertain importance.

Pneumococcal disease has a worldwide distribution and is a major contributor to HIV-related morbidity and mortality. In developed countries, vaccination against pneumococcal infection is widely recommended. Nonetheless, in a randomized

controlled trial conducted in Uganda, the use of the 23-valent polysaccharide vaccine not only failed to prevent pneumococcal disease or death but was also associated with an increase in cases of pneumonia in general.⁵⁰ Since trial participants had relatively advanced disease, this vaccine should not be used in similar populations. Data are awaited on the effectiveness of the newer conjugated pneumococcal vaccines and on response to vaccination in those receiving ART.

Hepatitis B coinfection is very common in Africa, Asia, and South America. To date, no controlled trials of hepatitis B vaccines have been conducted in HIV-infected developing world populations. Nonetheless, it is recommended to offer the vaccine to hepatitis B seronegative individuals with CD4 count >200/ μ L.⁵¹

Influenza has a worldwide distribution. However, the role of influenza vaccine in reducing developing world morbidity and mortality is undefined.

■ PREVENTION OF TUBERCULOSIS

The HIV pandemic presents a massive challenge to the control of TB and is the primary reason for the failure of TB control programs in resource-poor countries where HIV prevalence is high.⁵² TB is also a major cause of death among people living with HIV/AIDS,²⁸ and may lead to increased HIV disease progression.⁵³ TB is more common in those with advanced immune suppression but can present at CD4 counts above the threshold presently recommended for ART initiation.⁵⁴ Randomized controlled studies have shown that a 6-month course of isoniazid reduces the risk of active disease in HIV-infected individuals with latent infection with *M. tuberculosis*⁵⁵ indicated by a positive tuberculin skin test (TST) in the absence of active TB disease. The TST reaction does not distinguish between active and latent infection and also does not have optimal sensitivity and specificity. Although in several trials primary prophylaxis was shown to decrease the incidence of active TB in TST-positive HIV-infected individuals, in only one placebo-controlled trial conducted in Haiti prior to the availability of ART, isoniazid prophylaxis was associated with increased survival.⁵⁵ A similar impact on survival was also reported in an observational study conducted in Brazil.⁵⁶

WHO recommends that HIV/AIDS programs provide isoniazid preventative therapy as part of the package of care for people living with HIV/AIDS. However, exclusion of active TB is critically important before chemoprophylaxis is started. If isoniazid monotherapy were given to individuals with active disease, this would lead to the development of drug resistance. The recommended regimen is isoniazid 5 mg/kg up to a maximum of 300 mg daily for 6–9 months during which time patients should be clinically monitored for toxicity and for active TB.⁵⁷

Programmatic uptake of TB prophylaxis has usually been low, probably because of fear that drug resistance will emerge

and concerns about the short duration of efficacy. The concept of TB preventative therapy is predicated on the assumption that most of the TB disease burden is due to reactivation of latent infection. However, molecular epidemiological evidence suggests that recent infection makes an important contribution to active disease in HIV-infected people living in societies with high TB prevalence.⁵⁸

■ MALARIA PROPHYLAXIS

Malaria and HIV cause more than 4 million deaths per annum, of which 90% occur in tropical Africa where *P. falciparum* is the predominant species.^{59a,b} HIV infection is associated with a higher risk of acquiring malarial infection, with higher parasite density, and with increased risk of clinical malaria in adults, especially those with advanced immunosuppression. In regions with unstable malaria, HIV-infected individuals are at increased risk of complicated and severe malaria and death. There are also data to indicate that antimalarial treatment failure may be more common in individuals with low CD4 counts. Although malarial infection, in turn, temporarily increases HIV replication and viral load, there is no evidence that it affects HIV-disease progression, transmission, or response to antiretroviral drugs. Nonetheless, since malaria is associated with anemia, its presence may affect the choice of antiretroviral drugs.

Coinfected pregnant women are particularly vulnerable, since parasitemia tends to be higher during pregnancy and plasmodia can infect the placenta, resulting in increased risk of anemia, preterm birth, intrauterine growth retardation, low birth weight infants, and high early mortality. HIV-infected pregnant women also tend to have a poorer response to both prophylaxis and treatment of malaria.

People living with HIV/AIDS in malaria endemic areas are considered particularly vulnerable to malaria and should be provided with insecticide impregnated nets. HIV-pregnant women at risk of malaria should also receive intermittent preventive therapy with 3 doses per week of sulfadoxine-pyrimethamine or daily cotrimoxazole. However, malarial resistance to chloroquine and sulfadoxine-pyrimethamine is increasingly diminishing the effectiveness of these prophylactic agents. Additionally, widespread use of cotrimoxazole for primary prophylaxis of OIs may favor development of resistance to sulfadoxine-pyrimethamine in malaria parasites. In regions where both infections occur, special attention must be given to the need for etiological diagnosis for febrile patients.

■ COTRIMOXAZOLE PRIMARY CHEMOPROPHYLAXIS

Cotrimoxazole is recommended as the chemoprophylactic drug of choice for prevention of PCP in individuals with less than 200 CD4 cells/ μ L in developed countries. It has also been shown to significantly decrease morbidity and mortality

in studies conducted in three trials in Africa.^{60,61} Despite some contradictory results; the possible lower frequency of PCP in developing countries, the possibility of promotion of drug-resistance, and controversies relative to the design of published trials, the WHO recommends its use in HIV infection and its efficacy is greatest in those with symptomatic HIV infection or CD4 cell counts less than 200/ μ L.⁶² The survival benefit associated with primary prophylaxis with cotrimoxazole is due to prevention of PCP together with a reduced incidence of cerebral toxoplasmosis, bacterial infections, and isosporiasis. The dose usually recommended is one double strength tablet (160 mg of trimethoprin/800 mg of sulphamethoxazol) daily, which is generally well tolerated. Nonetheless, cutaneous rashes can occur and may require substitution with dapsone, 50–100 mg daily. While dapsone has some anti-PCP activity, it is not effective against cerebral toxoplasmosis and bacterial infections.

THERAPY AND CARE IN DEVELOPING COUNTRIES

■ TUBERCULOSIS

The global burden of TB is increasing in large part because of the HIV pandemic. A third of the world population is infected with *M. tuberculosis*. Coinfection with HIV accelerates progression to active disease after exposure to *M. tuberculosis* and increases reactivation of latent tuberculous infection. TB is the main cause of HIV-related deaths in developing countries, being responsible for 30% or more of in-hospital deaths in some settings. Nonetheless, a premortem diagnosis of TB is confirmed in only approximately 50% of the cases.

In a prospective study conducted in Brazil, the overall annual risk for the development of TB among HIV-infected individuals was 5.4%, being 6.5%, 3.2%, and 10.2% in TST positive, TST negative, and anergic patients, respectively.⁶³ In Cape Town, South Africa, a city with a high prevalence of TB, risk of TB increases with declining CD4 cell count (Fig. 102-1), and 25% of patients with advanced HIV develop TB per annum.⁶⁴

The clinical presentation of TB is greatly modified by immune deficiency. Smear-negative pulmonary disease is more frequent in HIV-infected individuals. Early in HIV-infection, TB presents with a classic reactivation pattern of pulmonary upper lobe infiltrates with cavitation. With increasing immunodeficiency, the chest radiographic picture often resembles tuberculous primary infection with adenopathy and mid or lower lobe infiltrates; dissemination to lymph nodes, meninges and pleural, pericardial, and peritoneal cavities is also more frequent.^{65,66}

A TB diagnosis should be sought in all HIV-infected patients with a cough present for 3 or more weeks, night sweats, fever, or unexplained weight loss. Diagnosis should be sought with a minimum of three sputum smears for acid-fast

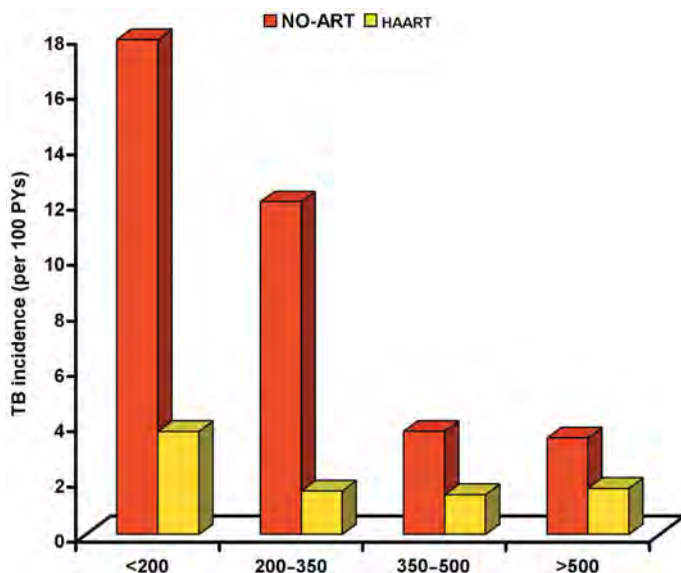


FIGURE 102-1. Tuberculosis incidence per 100 patient years for 4 strata of CD4 counts: <200, 200–350, 350–500 and >500 cells/mm³; 1 in patients not receiving antiretroviral therapy (No-ART) and those on highly active antiretroviral therapy (HAART). (Data from Badri M, Wilson D, Wood R. Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; 15(359): 2059–2064.)

bacilli (AFB) and a fine needle aspiration biopsy of asymmetrically enlarged lymph nodes. Diagnostic yield can be increased by saline sputum induction and mycobacterial culture. Patients with suspected smear-negative pulmonary disease should receive treatment with broad-spectrum antibiotics before a diagnosis of smear-negative TB is entertained.

In settings with very limited resources, empiric TB therapy is frequently resorted to in patients with advanced immune suppression. In these situations, it is crucial that assessment of response to TB empiric therapy is reviewed after 1 month, by which time an unequivocal clinical response is expected to have occurred. The differential diagnosis of pulmonary infiltrates includes bacterial and fungal pneumonias and Kaposi's sarcoma. Many recommend the use of cotrimoxazole prophylaxis by patients with active TB, since it has been associated with an approximately 40% increase in 2-year survival.^{60–62}

TB impacts greatly on the implementation of ART programs. Screening for TB is particularly important when ART is implemented in resource-poor settings. In a community ART service in Cape Town, 57% of those commenced on ART reported a prior history of TB, 14% were referred to the service on TB therapy, and 5% were found to have active TB (Wood, unpublished data). In cohort studies from both developed and developing countries, ART reduced the incidence of TB by 70–90%.^{64,66,67} However, patients receiving ART retain a heightened risk of TB, which remains higher than in the HIV-negative population. In a large study involving over 4,000 HIV-infected patients treated in low-income settings, after 3468 person years of follow-up there were 258 new TB events in the first year of highly active antiretroviral therapy (HAART). The

incidence of new TB events in months 1–2, 3–6, and 7–12 were 13.7/100 (6.4–29.6), 6.0/100 (2.8–12.4), and 4.1/100 person years (2.1–8.4), respectively [manuscript in preparation]. While coexistence of other risk factors for TB, including exposure to patients with TB at HIV treatment facilities may play a role, it seems that persistent deficits in immune function are the principal cause.⁶⁸

M. africanum, a member of the *M. tuberculosis* complex, is endemic to West Africa, where it causes a considerable proportion of pulmonary TB. Sporadic cases of *M. africanum* have been identified outside West Africa. The clinical presentation or disease course is identical to *M. tuberculosis*, although in animal models *M. africanum* appears to be less virulent. Recently it has been suggested that *M. africanum*-infected patients are more likely to be HIV positive than *M. tuberculosis*-infected patients. The data also suggest that *M. africanum* is more of an opportunist than *M. tuberculosis*. It was hypothesized that in areas where rates of HIV are low, *M. africanum* is probably out-competed by *M. tuberculosis*, while increasing HIV prevalence would be associated with an increase in *M. tuberculosis* strain diversity, including lower virulence strains such as *M. africanum*. This, in turn, highlights new complexities associated with the changing pattern of important infectious diseases in the presence of an expanding HIV epidemic.

■ SALMONELLA SEPTICEMIA

Infection with nontyphoidal *Salmonella*, leading HIV-infected persons to severe septicemia, has been reported in Africa⁶⁹ and Asia.⁷⁰ Bacteremia is more frequent when the CD4 counts fall below 200/μL and is associated with significant mortality (35–60%). Among the survivors, 25–45% have recurrences due to recrudescence of the original infection.⁶⁹ Antibiotic resistance patterns vary but fluoroquinolones are particularly useful when there is resistance to other antibiotics. Although secondary chemoprophylaxis is necessary, ART also prevents recurrence.

■ KAPOSI'S SARCOMA

Kaposi's sarcoma is the commonest cancer in HIV-infected individuals. In the USA, Europe, and Latin America, Kaposi's sarcoma almost exclusively affects male homosexuals. In Africa, it affects males and females equally, often running an aggressive course involving skin, lymph nodes, lungs, and the gastrointestinal tract. Skin lesions are variable and can be macular, papular, or nodular, with considerable localized edema when lymph nodes are involved. Diagnosis is usually made by clinical appearance although biopsy can be necessary in atypical cases. Although skin lesions frequently resolve after commencement of ART, there are anecdotal reports to indicate that disseminated Kaposi's sarcoma does not respond so well to ART.

■ TOXOPLASMOSIS

Infection with *Toxoplasma gondii* is acquired through the ingestion of rarely or partially cooked lamb, beef, pork, or game. Prevalence rates vary considerably worldwide.⁷¹ In HIV-infected individuals, cerebral toxoplasmosis is the commonest clinical presentation, usually presenting with seizures or a focal neurological deficit in patients with less than 100 CD4 cells/ μ L. In the Cape Town AIDS cohort, cerebral toxoplasmosis is the third commonest neurological presentation (0.46/100 persons year) after cryptococcal meningitis (1.37/100 persons year) and HIV encephalopathy (0.76/100 persons year) [Wood, unpublished observations]. An autopsy study from Cote d'Ivoire found that in 10% of the cases toxoplasmosis was the likely cause of death.²⁸

Diagnosis should be entertained in those with focal neurologic signs and ring enhancing lesions demonstrated through computerized tomography or magnetic resonance imaging. In the absence of radiologic facilities, the presence of recently developed focal neurologic signs in the absence of meningeal signs in patients with evidence of advance immune deficiency is highly suggestive of cerebral toxoplasmosis. In developing countries with a high prevalence of TB, cerebral tuberculomata constitutes the primary differential diagnosis and more rarely bacterial abscesses, cryptococcoma, lymphoma, and progressive multifocal leukoencephalopathy.

Response to therapy is usually rapid (7–14 days), and a clinical and/or radiological response to a trial of antitoxoplasma therapy confirms the diagnosis. The recommended standard therapy is with pyrimethamine and sulfadiazine. However, in resource-poor settings there is increasing experience with cotrimoxazole 320/1600 mg twice daily for 4 weeks then 180/800 mg twice daily for 3 months.^{72–74}

■ LEISHMANIASIS

Leishmaniasis is a parasitic disease transmitted by the bite of infected sand flies. It is estimated that *Leishmania* spp. infect 12 million people worldwide. Leishmania-endemic regions are expanding and include areas of Central and South America, southern Europe, Asia, the Middle East, and East Africa. Leishmania/HIV coinfection is emerging as a new serious condition, which is expected to continue to increase in frequency.⁷⁵

Three principal clinical forms of leishmaniasis occur: cutaneous, mucocutaneous (espundia), and visceral leishmaniasis (kala azar). HIV-infection increases the risk of visceral leishmaniasis by 100–1000 times in endemic areas and leishmaniasis accelerates the progression of HIV-disease, thus decreasing life expectancy.⁷⁵

It is estimated that 500,000 new cases of visceral leishmaniasis occur annually, 90% of them in five countries, Brazil, Bangladesh, India, Nepal, and Sudan.⁷⁵ Visceral leishmaniasis presents in patients with advanced HIV-infection with fever, hepatosplenomegaly, and pancytopenia.⁷⁵ Serological

diagnosis in HIV-infected individuals lacks sensitivity. Definitive diagnosis depends on isolation of the parasite, primarily from bone marrow aspirates, but also from spleen, liver, and peripheral blood. Treatment is based on a number of chemotherapeutic agents that are toxic and/or expensive and are rapidly becoming ineffective. The use of pentavalent antimony is limited by toxicity and resistance, and in some settings the first-line drug is now amphotericin B; alternatives include pentamidine and liposomal-amphotericin B; the latter is prohibitively expensive. There are contradictory data whether highly active ART prevents visceral leishmaniasis relapses in HIV-infected individuals. Secondary prophylaxis should be continued until CD4 count reaches 350 cells/ μ L.⁷⁶

■ CRYPTOCOCCOSIS

Meningitis caused by *Cryptococcus neoformans* was reported as the cause of death in 2% of a Cote d'Ivoire autopsy study²⁸ and 11% in a Ugandan rural cohort.³² Cryptococcal meningitis (CM) presents as a subacute meningoencephalitis. Diagnosis of CM is confirmed by a positive cerebro-spinal fluid (CSF) cryptococcal antigen (positive in >95%), CSF culture (positive in >95%), or Indian ink test (positive in 60–90% of cases). In addition, there may be pleocytosis and an elevated CSF pressure. CM is the commonest neurological AIDS illness in several African and Asian settings.⁷⁷ It can also occur as a devastating immune restoration disease (see below) that occurs in the first 2 months after ART is introduced, at rates of 18.2 (95% CI 8.2–40.6) and 6.2 (95% CI 1.6–25.1) cases/100 persons year in the first and second months, respectively.⁷⁸

The usual recommended therapy is amphotericin B (0.7 mg/kg/day IV) for 14 days, with or without flucytosine (100 mg/kg/day), followed by 8 weeks of fluconazole (400 mg/day), and then fluconazole 200 mg/day as secondary prophylaxis.⁷⁹

The high rate of cryptococcal immune recovery syndrome (see below) in ART programs in sub-Saharan Africa may be the result of the exclusive use of fluconazole for the treatment of CM. Fluconazole is a fungistatic drug, which is effective as secondary prophylaxis but has less-efficacy than amphotericin B in clearing the organism during the initial treatment phase.⁸⁰

■ HISTOPLASMOSIS

Histoplasmosis is the most common of the endemic mycoses in patients with AIDS. Although it occurs predominantly in the Americas,⁸¹ histoplasmosis has also been reported in Africa⁸² and Asia.⁸³ Disseminated histoplasmosis usually occurs among persons with CD4⁺ T lymphocyte counts <150 cells/ μ L. The most common clinical presentation is a disseminated multiorgan disease, characterized by fever, fatigue, and weight loss. Respiratory tract symptoms of cough, chest pain, and dyspnea might occur in

up to 50% of patients.⁸⁴ Detection of Histoplasma antigen in blood or urine is a sensitive method for rapid diagnosis of disseminated histoplasmosis. Histoplasma antigen is detected in the urine or blood in 85–95% of patients with disseminated disease.⁸⁵ *H. capsulatum* can be cultured from blood, bone marrow, respiratory secretions, or localized lesions in >85% of cases but isolation takes 2–4 weeks. Patients with severe disseminated histoplasmosis should be treated initially with intravenous amphotericin B followed by oral therapy itraconazole for 12 weeks, followed by secondary prophylaxis.⁸⁶

■ PNEUMOCYSTIS PNEUMONIA

The reported frequency of PCP in Africa is highly variable and appears dependent on geography, cohort selection, and diagnostic methodology. The reported incidence of PCP was 0.5/100 persons year in South African miners, 2.28/100 persons year in individuals with less than 200 CD4 cells/ μ L in the Cape Town AIDS cohort, and it was present in 33% of Zimbabweans with radiographic changes compatible with PCP.^{87,88} Clinical presentation is a classic triad of dry cough, mild fever, and increasing dyspnea on effort in patients usually, but not exclusively, with less than 200 CD4 cell/ μ L. Treatment is with cotrimoxazole 15/75/kg/day in divided doses for 21 days; supplemental prednisone (80 mg/day, reducing over 3 weeks) is also recommended for those with hypoxia.

■ PENICILLIOSIS

Caused by *Penicillium marneffeii*, this systemic mycosis occurs exclusively in South East Asia, Guangxi province of China, Hong Kong, and Taiwan. The incidence of this fungal infection has increased in recent years in parallel with rising HIV-1 seroprevalence. The usual presentation is with fever, anemia, weight loss, skin lesions, generalized lymphadenopathy, and hepatomegaly and occurs in patients with advanced immunosuppression.⁸⁹ Treatment is with amphotericin B (0.6 mg/kg/day) followed by itraconazole 400 mg/day for 10 days.⁹⁰ Recurrences occur in approximately 50% of treated cases and secondary prophylaxis with itraconazole 200 mg/day is recommended.

■ PARACOCIDIOIDOMYCOSIS

This deep systemic fungal infection, caused by *Paracoccidioides brasiliensis*, is rare worldwide but common in Brazil and other endemic areas of South and Central America and has been reported in travelers to these areas.⁹¹ In HIV-infected patients, the disease can present with acute lymphohematogenous dissemination or with chronic mucocutaneous lesions, particularly affecting the oral cavity. Diagnosis is confirmed by demonstration of the fungus, culture, or histology. Initial treatment is with antifungal agents,

including amphotericin B, ketoconazole, or itraconazole and subsequent maintenance therapy with ketoconazole or sulfonamides.

ANTIRETROVIRAL THERAPY

In 2003, the WHO and UNAIDS launched a strategy for expanding antiretroviral treatment to 3 million people living with HIV/AIDS in low- and middle-income countries by the end of 2005.^{92–94} As a result of this strategy, by mid-2005 there were an estimated 1 million people on ART in those countries where the burden of disease is greatest (Fig. 102-2). In 2004 and in the first half of 2005, progress of roll out programs in Africa and Asia has resulted in a tripling of numbers of patients receiving ART to 50,000 and 155,000, respectively. In most African countries, reported demand is outstripping supply due to infrastructural constraints. In Eastern Europe and Central Asia, the numbers have doubled to 20,000 people. In Latin America and Caribbean, the number of patients on treatment increased to 290,000, which represents coverage of approximately 66% of estimated need.

Concerns have been raised that expanded access to ART in resource-poor settings will lead to “antiretroviral anarchy,” characterized by poor adherence to therapy, widespread viral resistance to medications, and poor clinical outcomes.⁹⁵ However, emerging data indicate that adherence in developing countries is as good as or even better than in developed countries.⁹⁶ Additionally, data are fast accumulating to indicate that virological and immunological responses at 6 and at 12 months, which have been shown to predict long-term outcome, are similar to those achieved in developed countries.^{97,98} For example, in a study conducted in Southern Brazil, among 454 antiretroviral naïve patients starting HAART, 72% had undetectable viral load at 6 months. When analyses were restricted to the 309 patients who started therapy in 1999 or later, when use of efavirenz and boosted protease inhibitors became more common, success rates were 90% or more for all CD4 strata.⁹⁹ While it is encouraging that similar virologic outcomes can be achieved in resource-poor settings, some have expressed concerns that these results may not necessarily be representative of those presently starting therapy or entering programs.¹⁰⁰

The primary goals of ART programs are the prevention of HIV-related morbidity and mortality. Early on-treatment mortality in resource-poor settings appears to be considerably higher than in developed countries.^{101–103} In one large study, mortality during the first year on HAART in approximately 5,000 HIV-infected patients treated in low-income settings was compared to 22,000 adult patients from developed countries. Compared to high-income countries, patients starting HAART in low-income settings had lower CD4 cell counts, were more likely to be female, and to start treatment with an NNRTI. Mortality was higher in low-income settings. Compared with high-income settings, the adjusted hazard

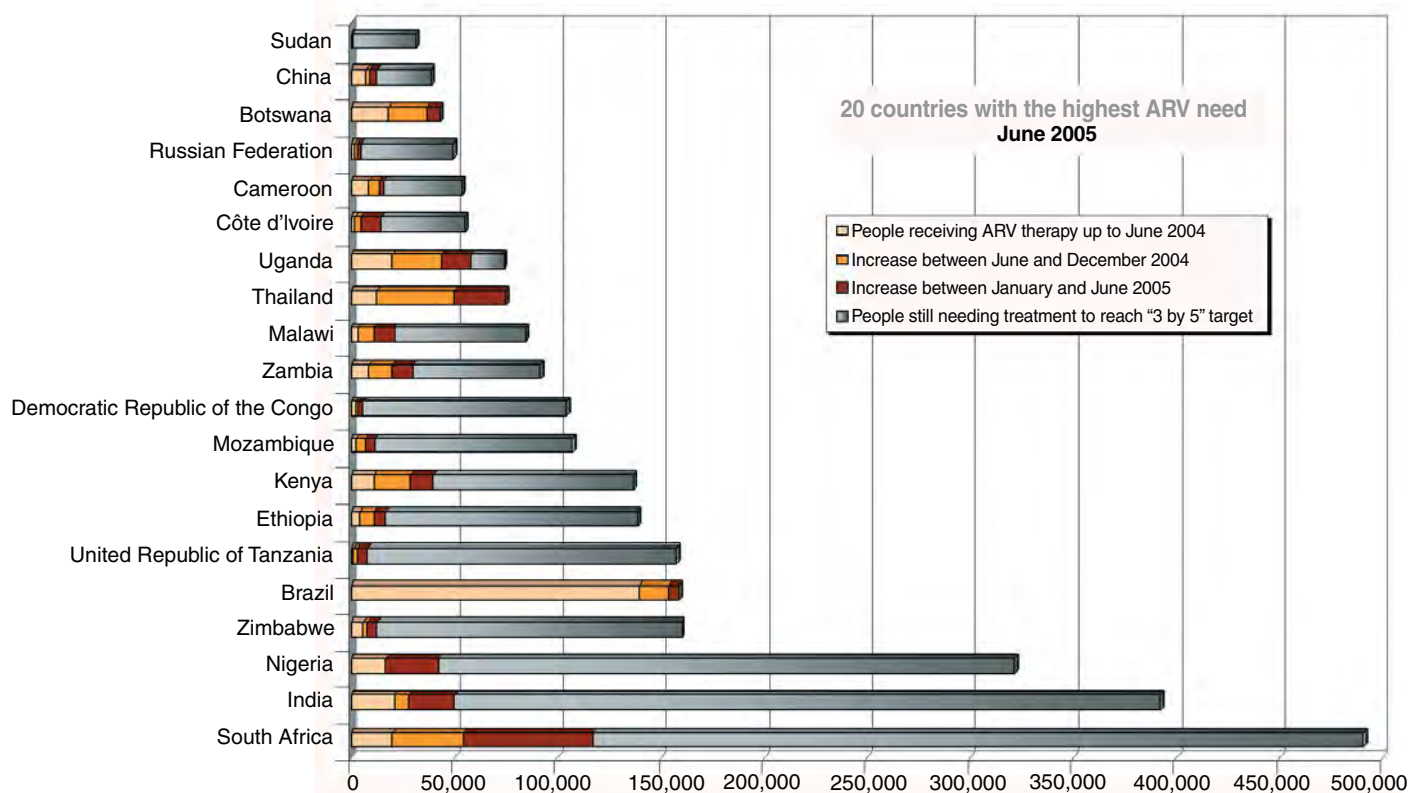


FIGURE 102-2. Progress toward "3 by 5" targets, WHO 2005.

ratio of mortality in low-income settings declined from 3.6 during the first month to 1.5 during months 7–12. At 1 year, cumulative mortality was 4.8% and 2.3% in low and high-income settings, respectively. Interestingly, the provision of treatment free of charge to patients was associated with lower mortality in low-income settings.¹⁰² Higher early mortality may reflect more advanced immune suppression, programmatic delays in accessing treatment, and higher incidence of severe immune reconstitution syndromes (IRS).^{103,104} Due to underreporting, mortality may be even higher due to high rates of program loss to follow-up.^{105,106}

The global scaling-up of HIV access has been achieved as the result of a broad range of national and international efforts. Individual programs depend on these initiatives to finance physical infrastructure and to maintain a reliable supply of drugs. Additionally, many programs are dependent upon local human resources, including trained doctors, nurses, pharmacists, and counselors, which are scarce in most settings. The outcomes of programs are, therefore, constrained by many variables but are still primarily dependent on each individual patient's ability to remain within a treatment program and to maintain a high degree of adherence to the prescribed drug regimens. Patient retention on programs, even within the same city can be highly variable^{107,108} and adherence within a program may also worsen over time.¹⁰⁷

CHALLENGES IN IMPLEMENTING ANTIRETROVIRAL THERAPY IN DEVELOPING COUNTRIES

Until recently, high-drug costs were a major constraint to widespread implementation, but now that drug costs have decreased, the lack of infrastructure and adequately trained health-care workers may be the major constraints. The need to manage a program within a limited national infrastructure has resulted in the exploration of several public sector delivery models. Explored models to date have included distribution of drugs at district hospitals, community clinics, and TB services.

The need for high levels of adherence has led some to make parallels with TB control programs and proposed use of directly observed therapy. The logistics of delivery of lifelong directly observed therapy to large numbers of people is likely to be very challenging. High levels of adherence with directly observed ART in rural Haiti were achieved by integration of community health workers (*accompagnateurs*) into the treatment program.¹⁰⁹ A variety of other adherence strategies have been used in resource-poor settings. In Gugulethu, Cape Town, high adherence to ART, with corresponding high levels of viral suppression, has been achieved using community adherence monitors.¹¹⁰ Elsewhere in Africa, patient-centered approaches, including the identification of "treatment buddies" for ongoing program support, have resulted in high levels of adherence to ART.^{103,111}

STARTING ANTIRETROVIRAL THERAPY

In 1987, 6 years after the first AIDS cases were recognized and 4 years after the etiologic agent, HIV, was first identified, the first antiretroviral drug, zidovudine, was approved for clinical use. In the following decade, AIDS changed from a universally fatal disease to a chronic, medically manageable condition. This extraordinary and unparalleled pace of progress has led to frequent modifications of guidelines on when to start therapy (Figs. 102-3 and 102-4).¹¹²

ART initiation guidelines used in developing countries are based on both clinical and laboratory parameters.¹¹³ Developing countries face an urgent short-term need to rapidly expand antiretroviral access to a large number of patients with advanced clinical disease. However, in the longer term, there is also a need to prevent people living with HIV progressing to AIDS. Presently resources are disproportionately consumed caring for those with advanced disease. Within the

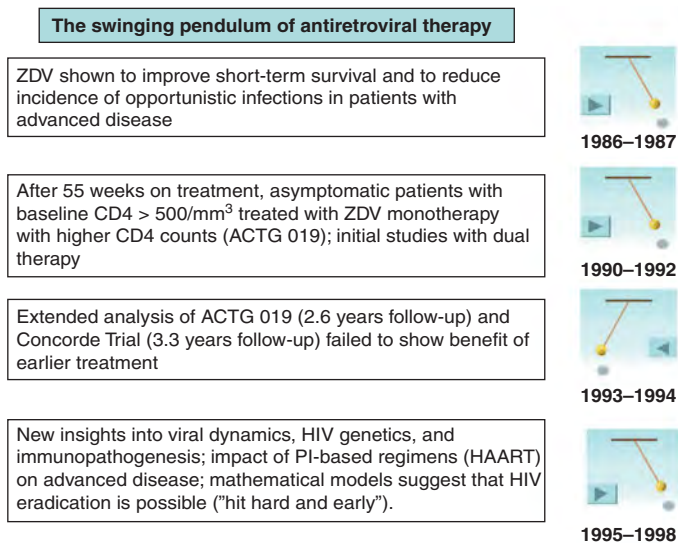


FIGURE 102-3. The swinging pendulum of antiretroviral therapy.

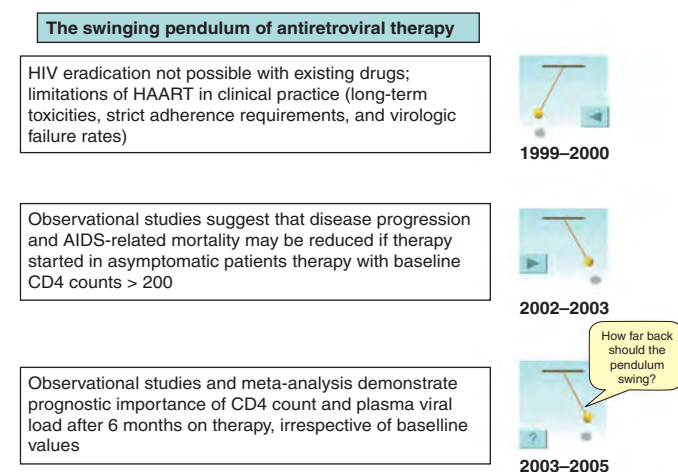


FIGURE 102-4. The swinging pendulum of antiretroviral therapy (continuation).

antiretroviral service in Kampala, Uganda, the majority of patients accessing ART have advanced symptomatic disease with a mean CD4 count at initiation of ART of just 63 cells/ μ L.¹¹⁴ Late presentation is costly in terms of morbidity and mortality,¹⁰⁴ and utilization of health-care resources and also limits the potential for restoration of immune function.¹¹⁵ Treatment of patients with earlier disease is less demanding, results in better outcomes utilizing less health resources, and also decreases the proportion of the population progressing to AIDS. While entry to programs is based on presence of clinical symptoms, it is likely that patients accessing ART will continue to be severely immune compromised. In contrast, CD4 count criteria will only have utility when there is wider access to CD4 counts integrated with voluntary counseling and at all interfaces with the health-care system.

CHOICE OF ANTIRETROVIRAL THERAPY IN RESOURCE-POOR SETTINGS

Scaling-up of antiretroviral treatment programs in the resource-poor settings requires standardization and simplification of treatment regimens. Simplified regimens allow for a limited repertoire of drugs and side effects with which health-care workers need to become familiar with. The maintenance of a secure drug supply is simpler when a limited number of drugs are used. Many factors impact on regimen selections including cost, tolerability, pill burden, safety, the potential for interaction with other commonly prescribed medications, and the need to maintain future treatment options.

TB is the commonest OI in resource-poor settings, and standardized regimens must be carefully chosen to avoid adverse pharmacological interactions with TB drugs. Rifampicin is a potent CYP450 enzyme-inducer, which results in lowered plasma levels of protease inhibitors and has an overlapping hepatic toxicity profile with nevirapine. Rifabutin, the rifamycin of choice in the USA for patients on protease inhibitors, is presently too expensive and largely unavailable in most developing countries. Although further studies are definitely required, some experience has been gained with rifampicin—containing regimens coadministered with ART regimens including three nucleoside reverse transcriptase inhibitors (NRTIs) or two NRTIs associated with either efavirenz or ritonavir-boosted lopinavir.

As women of childbearing potential constitute the majority of patients attending public sector HIV clinics, regimens must be available which are compatible with pregnancy. The need to have "TB and pregnancy friendly" regimens and the constraints of a limited number of antiretroviral drugs presently registered in many developing countries, has resulted in convergence of regimens used in a large number of programs. Quite often, these are based on two standardized

regimens, the first consisting of two NRTIs and a NNRTI and the second of two NRTIs and a boosted protease inhibitor (PI).

Presently registered NNRTIs do not inhibit HIV-2 reverse transcriptase.^{116,117} The protease inhibitors amprenavir and nelfinavir are not active against HIV-2 and protease inhibitors in general may be less robust against HIV-2.

■ INITIATION OF ART IN PATIENTS WITH ACTIVE OPPORTUNISTIC INFECTIONS OR MALIGNANT DISEASE

ART may interact with OIs and their specific therapies in a variety of ways. Initiation of ART may be associated with an improved response to specific therapy of an OI; there may be additive toxicity with specific therapeutic modalities or a worsening of the clinical manifestations of the OI itself. Although, in general, treatment of life-threatening opportunistic conditions should take precedence, ART is the cornerstone of treatment for conditions such as cryptococcal meningitis and disseminated Kaposi's sarcoma when associated with profound immune suppression.

■ IMMUNE RECONSTITUTION SYNDROME

The initiation of ART in individuals with OIs may lead to an increase in clinical severity of the OI and even to the occurrence of an OI for the first time in the first few weeks after ART is started. The temporal association of the worsening (or emergence) of these conditions with control of HIV replication by ART and, in most cases, an elevation in CD4 counts has led to the hypothesis that they result from the restoration of an immune response against the antigens of opportunistic pathogens that causes immunopathology. Supportive evidence has been provided by observations that for some pathogens these conditions are associated with the restoration of pathogen-specific immune responses.

This phenomenon is often referred to as the IRS. The optimal management strategy in terms of timing of the treatment of the OI and initiation of ART is unknown and may vary with the type of OI and level of immune suppression. Prospective randomized studies are clearly required in HIV patients with TB and other OIs to determine the optimal timing of ART after an opportunistic condition is diagnosed in a previously untreated patient.

Data on the incidence of IRS after commencing ART are limited and risk factors still remain to be determined. Globally, mycobacteria are the most significant opportunistic pathogens associated with IRS. In a study conducted in India, the median time to development of clinical IRS was 42 days and the incidence of 15.2 cases per 100 patient years.¹¹⁸ Patients with disseminated TB seem to be particularly susceptible to TB IRS. The most common manifestations of TB IRS are fever and lymphadenopathy, which often require corticosteroid therapy. Some patients develop severe complications that require hospitalization. Immune restoration

syndrome associated with other opportunistic pathogens may also cause inflammation that results in organ failure, hospitalization, or death. Results of studies on the optimal management of IRS, particularly on corticosteroid therapy to treat and to prevent IRS, are eagerly awaited.

LABORATORY MONITORING

Prior to the initiation of ART, identification of current infections and of coexisting medical conditions that may influence choice of therapy (such as TB, diabetes, hepatitis B and/or C, renal failure, pregnancy, etc.) is very important. Nonetheless, the lack of adequate laboratory support for diagnosis and management of most conditions can be an important barrier to the implementation of treatment programs in many resource-constrained settings. Given this limitation, the WHO provided guidance on the minimal laboratory and clinical monitoring requirements.² These requirements were prioritized into 4 categories: absolute minimum tests; basic tests; desirable tests; and optional tests. Absolute minimum tests are prerequisites for introduction of ART in a national program. Basic tests, which are commonly used in the clinical setting, were not considered to be essential for program implementation. Desirable tests would make monitoring and evaluation of program effectiveness much more effective, while optional tests can be used in resource-rich settings. The absolute minimum laboratory tests to have before initiating ART are an HIV antibody test (in those persons >18 months of age) and a hemoglobin or hematocrit level. Additional, basic testing should include a white blood cell count and differential (to permit assessment of neutropenic side effects and the total lymphocyte count), serum alanine, and/or aspartate aminotransferase level to assess the possibility of hepatitis coinfection and to monitor for hepatotoxicity, serum creatinine, and/or blood urea nitrogen to assess baseline renal function, a serum glucose, and pregnancy tests for women. Desirable supplemental tests include bilirubin, amylase, and serum lipids. CD4 cell determinations are, of course, very desirable and every effort should be made to make these widely available. Viral load testing is currently considered optional because of resource constraints. [Tables 102-2](#) and [102-3](#) contain recommendations on tiered laboratory capabilities for diagnosis and treatment of HIV/AIDS in resource-limited settings.¹¹⁹

In asymptomatic individuals, CD4⁺ lymphocyte count is the most important laboratory parameter to assess whether ART should be started. They are also important in the assessment of the effectiveness of therapy, with significant rises of CD4⁺ lymphocyte counts in the first several months seen in therapy naïve, adherent patients with drug susceptible virus. The current technology for measuring CD4⁺ lymphocyte counts is too costly to perform and requires flow cytometry; these constraints severely limit the number of laboratories which can perform counts in resource-constrained settings.

Table 102-2. Recommended Tiered Laboratory Capabilities for Diagnosis and Treatment of HIV/AIDS in Resource-Limited Settings¹¹⁵

Diagnosis and Monitoring Laboratory Tests	Primary Care Level	District Level	Regional/Central Level	
HIV antibody testing	Yes ^a	Yes	Yes	
Hemoglobin	Desirable ^b	Yes	Yes	
Pregnancy testing	Desirable ^c	Yes	Yes	
Basic microscopy for TB and malaria (sputum smear for TB and blood film for malaria diagnosis)	Desirable ^d	Yes	Yes	
FBC and differential	No	Yes	Yes	
CD4 ⁺ cell count	No	Yes	Yes	
ALT	No	Yes	Yes	
Diagnostic tests for treatable HIV coinfections and major AIDS-related opportunistic diseases	Full cerebrum spinal fluid (CSF) microscopy (including India ink for cryptococcal meningitis), syphilis, and other diagnostic tests	No	Yes	Yes
	Diagnostic tests for other major treatable HIV coinfections and AIDS-related opportunistic diseases (hepatitis B, hepatitis C serology, bacterial microbiology, and cultures and diagnostic tests and procedures for <i>Cryptococcus</i> , toxoplasmosis, and other major OIs)	No	Desirable	Yes
Full chemistry (including but not restricted to liver enzymes, renal function, glucose, lipids, amylase, lipase, and serum electrolytes)	No	No	Yes	
HIV VL measurement	No	No	Desirable	

^aRapid tests recommended at primary care level and conventional methodologies can be used at district and regional/central levels. For details, see specific WHO recommendations.

^bShould be available if ZDV is being considered for use.

^cShould be available if efavirenz is being considered for use.

^dReferral if microscopy not available.

^eVL test is currently not recommended for decision making on initiation or regular monitoring of ART response in resource-limited settings. Use should be considered primarily for definitive diagnosis of HIV infection in children under 18 months of age who are vertically exposed to HIV during pregnancy and to assist in decision making in more complex cases.

(Data from Lawn SD, Bekker L-G, Wood R. How effectively does HAART restore immune responses to *Mycobacterium tuberculosis*? Implications for tuberculosis control. *AIDS* 2005; 19: 1113–1124.)

Table 102-3. Frequency of Laboratory Tests Needed for Treatment of HIV/AIDS in Resource-Limited Settings¹¹⁵

Diagnosis and Monitoring Laboratory Tests	Baseline	Monthly During First 3 Mo (Wks 4, 8, and 12)	Every 6 Mo	As Required (i.e., Symptom-Directed or if Clinically Indicated)
HIV antibody testing	×			
Hemoglobin ^a	×	×		×
Pregnancy testing				×
Basic microscopy for TB and malaria (sputum smear test for TB and thick blood drop smear test for malaria diagnosis)				×
FBC and differential	×	×		×
CD4 ⁺ cell count	×		×	
ALT ^b				×
Diagnostic tests for treatable HIV coinfections and major AIDS-related opportunistic diseases		Full CSF microscopy (including India ink for cryptococcal meningitis), diagnostic tests for syphilis, and other sexually transmitted diseases		×
		Diagnostic tests for other major treatable HIV coinfections and AIDS-related opportunistic diseases (hepatitis B and C serology, bacterial microbiology, and cultures and diagnostic tests and procedures for <i>Cryptococcus</i> , toxoplasmosis, and other major OIs)		×
Full chemistry (including but not restricted to liver enzymes, renal function, glucose, lipids, amylase, serum electrolytes, etc.) ^c				×
HIV VL measurement ^d				×

^aHemoglobin monitoring during the first weeks of treatment has been recommended by some experts if ZDV is used. However, other experts suggest that the hemoglobin measurement can be monitored in a symptom-directed approach, particularly for ZDV-free regimens.

^bThe predictive value of preemptive liver enzyme monitoring is considered very low by some specialists and they recommend ALT monitoring in a symptom-directed approach in any situation. However, regular monitoring during the beginning of treatment (in monthly schedule during the first 3 months) and symptom-directed monitoring thereafter have been considered by some experts for patients using NVP-based regimens with high baseline CD4 cell count, particularly women with CD4 cells >250/mm³ and patients with hepatitis B or C coinfection, particularly with evidence of active hepatic disease.

^cThe regular monitoring (baseline and thereafter every 6 months) of full chemistry tests, particularly lipids, liver tests, renal function, and glucose, has been recommended for patients using second-line drugs (see Table 102-3).

^dVL measurement is not currently recommended for decision making on initiation or regular monitoring of ART response. Its use should be considered primarily for definitive diagnosis of HIV infection in children under 18 months of age who are vertically exposed to HIV during pregnancy or in special circumstances, as a complementary evaluation of more complex cases.

(Data from Lawn SD, Bekker L-G, Wood R. How effectively does HAART restore immune responses to *Mycobacterium tuberculosis*? Implications for tuberculosis control. *AIDS* 2005; 19: 1113–1124.)

Development of affordable and locally usable CD4⁺ lymphocyte counts testing technology is an urgent priority.

While the total lymphocyte count correlates relatively poorly with CD4 count, in combination with clinical staging it can be a useful marker of prognosis and survival. In cases where CD4 counts cannot be assessed, the presence of a total lymphocyte count of 1200/mm³ or below may be used as a substitute indication for treatment in the presence of symptomatic HIV disease. In asymptomatic HIV-infected individual, the predictive importance of the total lymphocyte count is lower but is significantly increased if hemoglobin levels are low.¹²⁰

The increase in total lymphocyte count on ART correlates well with change in CD4 cell count. At a group level, changes in total lymphocyte counts also correlate with viral load responses. However, changes in total lymphocyte counts have very limited utility for predicting viral load responses for individual patient management.¹²¹ Thus, total lymphocyte counts may have a limited role as a relatively inexpensive monitoring tool of the immunological response to highly active ART in resource-constrained settings.

The level of plasma HIV-1 RNA is arguably the best parameter to monitor response to ART. However, due to its high cost and technical expertise needed, it is poorly available in most resource-constrained settings. Nonetheless, its absence should not deter the implementation of roll out programs. The lack of availability of viral load monitoring implies that treatment failure will need to be assessed immunologically and clinically, rather than virologically, with yet undetermined long-term implications on the individual and societal levels.

CONCLUSIONS

The HIV pandemic continues to expand predominantly in resource-poor countries resulting in increasing numbers of HIV-related deaths. The global community is no longer able to ignore the enormous disparities in life expectancy and access to healthcare between the developed and developing world. The 3 by 5 initiative represents the largest global health efforts in the history of medicine and has already radically changed medical management of HIV in many resource-poor settings. The future of those with this dreadful disease will be determined by the global commitment to maintain and extend the benefits of medical science and technology to the poor.

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Bea Vuylsteke and Marie Laga

WHAT MAKES CASE MANAGEMENT OF STIs IN WOMEN DIFFERENT IN DEVELOPING COUNTRIES?

In theory, appropriate management of STIs could be based on the same criteria worldwide. However, in practice, the approach taken to STI case management may differ according to the realities of a specific setting. We will consider four aspects of STI management that may differ between developing and developed countries, including the aspect of the provision of treatment, the characteristics of the patients, the disease profile, and the national STI policy. Some of these features concern health care in general, while others are specific to STI care.

■ THE PROVIDER

Whether STI case management is provided by a primary health-care worker or a clinician in a categorical STI clinic, logistic problems are often similar. An obvious hurdle for any health-care provision is the poor infrastructure in many developing countries.¹ Bad roads and poor transport facilities make accessibility to the services difficult. In many places, a consultation room is not available or is underequipped and privacy is often lacking. Laboratory facilities may not exist and, where they do exist, they may not be efficient or capable of performing the relevant tests. Clinicians who can provide comprehensive case management must often work without the help of health educators, contact tracers, counselors, or administrative personnel. The maximum time that can be spent per patient is often not more than 5–10 minutes.

Another, and probably a most important, problem is the lack of continuous and sufficient supply of drugs or the absence of the effective, in general more expensive, drugs for the treatment of STI. There is currently, for instance, no single drug for the treatment of gonorrhea in the developing world that combines efficacy and low price.² Cefixime, ceftriaxone, and spectinomycin are recommended by the WHO as first-line drugs for the treatment of gonococcal infections

because they remain highly efficacious all over the world.³ However, their main drawback is their high cost. Ciprofloxacin, also recommended by WHO, has become cheaper in some countries, but resistance in South and Southeast Asia is emerging, which means that it can no longer be universally recommended.⁴ Kanamycin and above all cotrimoxazole are still widely used in Africa where they remain considerably less expensive. However, their use is compromised by a high resistance pattern in almost all regions.⁵

■ THE PATIENT

The patient's belief in the efficacy of treatment by a formal Western-type health service is, in general, weaker in developing countries than in the industrialized world. Many patients continue to consult traditional healers, especially for STI, and self-medication is common.⁶ Some may go first to the informal sector, and only later, when this treatment does not appear to work, present at a clinic.⁷ Seeking treatment in an appropriate health service and compliance with treatment are also related to other social, economic, and cultural factors.⁸ Many people may simply be too poor to pay for the transport to and from the health service, or for a consultation or for the drugs (full treatment regimen). In many developing countries, the dependence of women on men and their inferior social status may also play a major role.⁹ For example, women may not have the time to go to the health center and STI clinics are often stigmatizing for them. Many women cannot afford informing their husband of the presence of an STI for fear of being blamed for infidelity and hence, of being chased away from the family. In a study in Nairobi, Kenya for instance, 6% of pregnant women with a positive syphilis test did not inform their partner for fear of blame and violence, despite the counseling's focus on the well-being of the unborn child.¹⁰ In some societies, women need the permission of their husband to consult a health service. Some women may thus wait too long or never seek treatment.⁹ In another study in Nairobi, Kenya, a major

gender difference in delay of health seeking for STIs was observed, 5 days for men versus 14 days for women.¹¹

Another patient aspect that may compromise effective health-seeking behavior is the patient's perception of symptoms, which may differ in different cultural settings. A good example is provided by Rwanda, where high production of vaginal flow during sex is much appreciated.¹² Vaginal discharge may thus be perceived not as a sign of disease but as an indication of sexual health. However, seeking treatment for STIs presupposes the perception of a problem. In sum, the patient's capacity to seek timely treatment in an appropriate health service is directly affected not only by the availability, accessibility, and affordability of such services but also by his or her capacity to recognize the symptoms correctly; his or her belief in the efficacy of the health service; and by his or her social, economic, and cultural environment. In developing countries, these factors are certainly different from the industrialized world and some remain poorly understood.

■ THE DISEASE

Although the remainder of this chapter deals in detail with case management of the most common STIs, a few general points are highlighted here. Both the prevalence and the incidence of STIs tend to be considerably higher in developing countries than in the industrialized world. In addition, the relative distribution of various STIs takes on a different disease spectrum, such as higher relative frequency of chancroid as a cause of genital ulcer or *Neisseria gonorrhoeae* as etiological agent in urethritis.^{13–15} Some STIs, such as donovanosis, are virtually seen only in developing countries.¹⁶ The high rates of HIV infection in many geographical areas may have repercussions on the incidence and the natural history of STIs.¹⁷ A study in Côte d'Ivoire for instance showed a strong association between genital ulcers and HIV-related immunosuppression in female sex workers (FSW).¹⁸ In a case-control study in the same country, the mean clinical severity score of pelvic inflammatory disease (PID) was significantly higher among HIV-positive than among HIV-negative patients.¹⁹

Finally, in developing countries, patients with STIs tend to present with more severe and higher frequency of STI related complications, which is largely a result of delayed treatment or lack of effective treatment.

■ NATIONAL STI POLICY

Whether people will have access to acceptable and effective STI case management in a given country depends to a great extent on national policy issues, including the quality of first-level health care, the training and supervision of health-care providers, the national promotion of standardized guidelines for STI case management, the availability of effective STI drugs, and the availability of acceptable STI services for vulnerable populations.²⁰

The elaboration of a comprehensive national STI policy may reveal the level of importance a government attributes to STI control. In countries struggling with limited funds and a range of pressing public health problems, STI is often not the priority for allocating resources. Reasons include an association of STIs with perceived discreditable behavior, failure to associate the diseases with the complications and sequelae, and failure to recognize the size of the problem.²⁰ Policy issues that have rather been an obstacle to a successful control of STIs include: control efforts have been concentrated on symptomatic patients (usually men) and have failed to identify asymptomatic individuals (usually women); service delivery has often been through specialized STI treatment facilities that provide inadequate coverage and are stigmatizing; treatment strategies have focused on unrealistic requirements for definitive diagnosis rather than on practical decision making; and ineffective low-cost antibiotics continue to be used for reasons of economy. Moreover, there has been little emphasis on education and other efforts to prevent infection, and there has been a lack of authoritative guidance on a rational, practical, and well-defined package of activities that could be the basis for prevention and care programs.²⁰

Although WHO has made specific recommendations concerning different types and levels of services including public and private service providers and guidelines for STI case management, the implementation of these recommendations is often incomplete, and knowledge on the actual state of STI policies and programs is lacking.²¹

STI SYNDROMIC CASE MANAGEMENT

Since 80–90% of the population depend for their health needs and demands on the basic health services in developing countries, it is clear that STI control activities should be attempted mainly in this framework.²² In order to offer good quality STI care in developing countries, STI case management should be completed on one patient visit, using simple diagnostic methods, that are neither time consuming nor expensive. A clinical approach has the advantage of offering prompt diagnosis and hence prompt treatment. However, a clinical “etiological” guess may be highly inaccurate for STI diagnosis. It is, for instance, very difficult to differentiate between gonococcal and chlamydial urethritis and mixed etiology on the basis of clinical observation only.¹⁵ Similarly, the “typical” clinical presentation of primary syphilis, chancroid, and genital herpes, has a low diagnostic accuracy.^{23–25} Moreover, it is impossible to identify clinically dual or mixed infections, which are both very common.

Medical training emphasizes that one should try to make the diagnosis using microbiological techniques and subsequently give specific treatment. This laboratory diagnosis-before-treatment is not an option at the basic health services level.²² Many laboratory tests for STI diagnosis are too

sophisticated or not cheap enough to be affordable by the patients. Others are time-consuming, and test results are not available in a reasonable amount of time. This leads to a delayed treatment, or no treatment, because the patient is not returning for results. Simple, rapid, and affordable tests for most STIs have been on the priority list for STI research for years but as yet remain unavailable.

A more realistic approach at primary health-care level is a problem-oriented one and problem-solving syndromic approach has been developed.²² The syndromic approach does not require identification of the underlying etiology. Instead, it is based on the identification of a syndrome, i.e., a group of symptoms and easily recognized signs associated with a number of well-defined etiologies. Treatment is provided for the majority of organisms locally responsible for the syndrome.

Adaptation of the syndromic approach to local circumstances will require a validation of the diagnostic algorithms (flowcharts) used.²² This validation consists of a comparison of the diagnostic outcome of the algorithm to a gold standard. As such the sensitivity, specificity, and predictive value of the approach for different STIs will be determined. The sensitivity of the diagnostic algorithm is defined as the proportion of infections detected by the algorithm. A low sensitivity implies a high number of missed cases that results in potential serious complications and in further disease dissemination.²⁶ The specificity of the diagnostic algorithm is defined as the proportion of patients without infection who are correctly identified by the algorithm. A low specificity results in overtreatment, leading to unnecessary side effects, drug costs, and the psychological cost of inappropriate labeling. The positive predictive value (PPV) of the algorithm is the proportion of all diagnoses made by the algorithm that are confirmed by the gold standard diagnosis, or the real positive cases. The negative predictive value (NPV) is the proportion of all cases not infected according to the algorithm that are also not infected according to the gold standard diagnosis, or the real negative cases.

Many developing countries have adopted the syndromic approach in their national STI guidelines. Their algorithms are adapted to the local infrastructure (e.g., availability of laboratory) and examination possibilities (e.g., possibility of a speculum examination) and to the regional epidemiological situation.

There is enough evidence now that the syndromic approach is effective and has an impact on the STI epidemic. Dramatic declines in STI rates have been observed following control strategies based on the syndromic approach, such as in sex workers in Côte d'Ivoire, Senegal, and South Africa, and in STI clinics in Kenya and in Burkina Faso.^{27–29} The studies of Mwanza (Tanzania) and Masaka (Uganda) demonstrated the impact of syndromic management beyond the STI clinic attendees they targeted by decreasing STI prevalences

in the general population: serologic syphilis by 20%, male urethritis by 50% in Mwanza, and gonorrhea by 70% in Masaka.^{30,31} The declining prevalence of bacterial infections in some of the key syndromes in parts of Africa is a testimony of the success of widespread syndromic management use.²⁸

COMMON STI SYNDROMES IN DEVELOPING COUNTRIES

■ URETHRAL DISCHARGE

Urethral discharge is probably the most common STI syndrome in men in developing countries.^{9,26} In many parts of the developing world, the estimated incidence of urethritis is considerably higher than in developed countries. For example, in a population-based study in two cities of Cameroon, 10% of the interviewed men reported at least one episode of urethritis during the past 6 months.³² This proportion was even higher (20%) among male bar clients.³² In a similar study in a rural area of Tanzania, the annual incidence was 7%.³³ These figures stand in sharp contrast with those reported for Europe and North America where the annual incidence of urethritis in men is less than 1%.^{34,35}

Another striking difference in the epidemiology of urethritis in developed and developing countries relates to its etiology [Table 103-1](#). While *Chlamydia trachomatis* and *Mycoplasma genitalium* are the major causes of urethritis in the developed world, *N. gonorrhoeae* continues to be the major cause of urethritis in many developing countries. Mixed infections are also not uncommon in the urethral syndrome. Common causes of nongonococcal urethritis (NGU) in developing countries are *C. trachomatis*, *Trichomonas vaginalis*, and *M. genitalium*.^{15,37} *C. trachomatis* was present in 13% and 14%, *M. genitalium* was present in 10% and 20%, and *T. vaginalis* was present in 14% and 16% of the men with NGU in Central African Republic and West Africa, respectively. *Ureaplasma urealyticum* was detected in 26.2%, 45.6%, and 45.2% of the men with urethral discharge syndrome in West Africa, Central African Republic, and Thailand respectively. However, *U. urealyticum* was not associated with urethral discharge and was equally present in asymptomatic controls.^{15,37,42}

Given these etiological patterns, a syndromic approach of urethritis requires a treatment for both gonorrhea and NGU. [Fig. 103-1](#) shows the algorithm for the management of urethral discharge recommended by WHO. In case the patient complains of persistent or recurrent urethral discharge or dysuria, and the history does not confirm reinfection or poor compliance, then a treatment for *T. vaginalis* should be offered (algorithm “persistent/recurrent urethral discharge in men,” not shown). However, it should be stressed that the clinical sign of urethral discharge is not always present. For example, visible discharge may be absent shortly after urinating

Table 103-1. Etiologies of Urethritis in Selected Developing Countries

Country	Brazil	7 Countries in West Africa	Central African Republic	Malawi	Madagascar	Thailand	Indonesia	China
Site	<i>Multicenter</i>	<i>Various</i>	<i>Bangui</i>	<i>Lilongwe</i>	<i>Antananarivo</i>	<i>Bangkok</i>	<i>Bandung</i>	<i>Hefei</i>
Author	<i>Moherdau et al.</i>	<i>Pépin et al.</i>	<i>Morency et al.</i>	<i>Hobbs et al.</i>	<i>Harms et al.</i>	<i>Kuvanont et al.</i>	<i>Djajakusumah et al.</i>	<i>Liu et al.</i>
Ref	36	15	37	39	38	42	40	41
Year of study	1995	1996–97	1996–97	1996	1992–93	1985–86	1994–95	2000
Total number of men with urethral discharge syndrome	473	659	410	178	124	434	119	290
Pathogens identified								
<i>N. gonorrhoeae</i> (NG)	44.4%	61.9%	69.0%	65.7%	68.5%	29.5%	67.2%	71.0%
<i>C. trachomatis</i> (CT)	7.4%	13.4%	13.7%	1.7%	41.9%	13.6%	32.8%	25.9%
<i>M. Genitalium</i> (MG)	–	10.0%	20.5%	–	–	–	–	–
<i>T. vaginalis</i> (TV)	1.9%	13.8%	16.1%	20.8%	8.9%	–	–	–
Mixed etiologies								
NG + CT	8.2%	7.0%	8.3%	1.7%	0%	3.7%	25.2%	18.6%
NG + MG	–	3.8%	7.6%	–	–	–	–	–
NG + TV	0%	8.5%	10.5%	12.9%	0%	–	–	–
None of the above	37.8%	21.4%	–	26.4%	20.2%	62.9%	25.2%	21.7%
Test for CT performed	Elisa	PCR	PCR	LCR	IF	Culture	Elisa	PCR
Test for TV performed	Wet Mount	PCR	PCR	PCR	Wet Mount	–	–	–

or when the patient has already taken some antibiotics. This is of particular relevance in large parts of Africa where many people combine treatment from a variety of places. In Malawi, for instance, 53% of patients with urethral syndrome reported to have sought treatment elsewhere before consulting the formal health sector.⁷ As such, if urethritis is only treated when discharge is visible during physical examination, infections may be missed and remain untreated.

The algorithm for the syndromic approach of urethral discharge contributed to the first success stories of the syndromic approach in developing countries. Applying the syndromic approach to urethral discharge has resulted in effective case management of urethritis as shown in different studies.⁴⁴ In a study in Indonesia for instance, the PPV of the syndromic approach for gonococcal and/or chlamydial urethritis was between 75% and 97%, resulting in a low cost per

real case treated.⁴⁰ In addition, the cure rate for urethral discharge with the syndromic approach was 99%.⁴⁰

To decrease overtreatment, a simple laboratory test such as a Gram stain may be used for the detection of intracellular diplococci in urethral discharge. This strategy reserves the, at times, expensive treatment for gonorrhea for patients with a confirmed gonococcal infection.³⁶ However, gonococcal infection cannot always be excluded by Gram stain. In optimal conditions, the Gram stain has a sensitivity of 90–95% and a specificity of 95–100% for the detection of intracellular diplococci.⁴⁵ However, its validity and hence the validity of a diagnostic algorithm including Gram stain varies substantially with the experience of the laboratory technician and the field conditions within countries.⁴⁶ Including a Gram stain in a diagnostic flowchart for urethritis should only be advised when appropriate laboratory facilities are available and results can be given within reasonable time delays, i.e., no return visit is necessary for treatment.

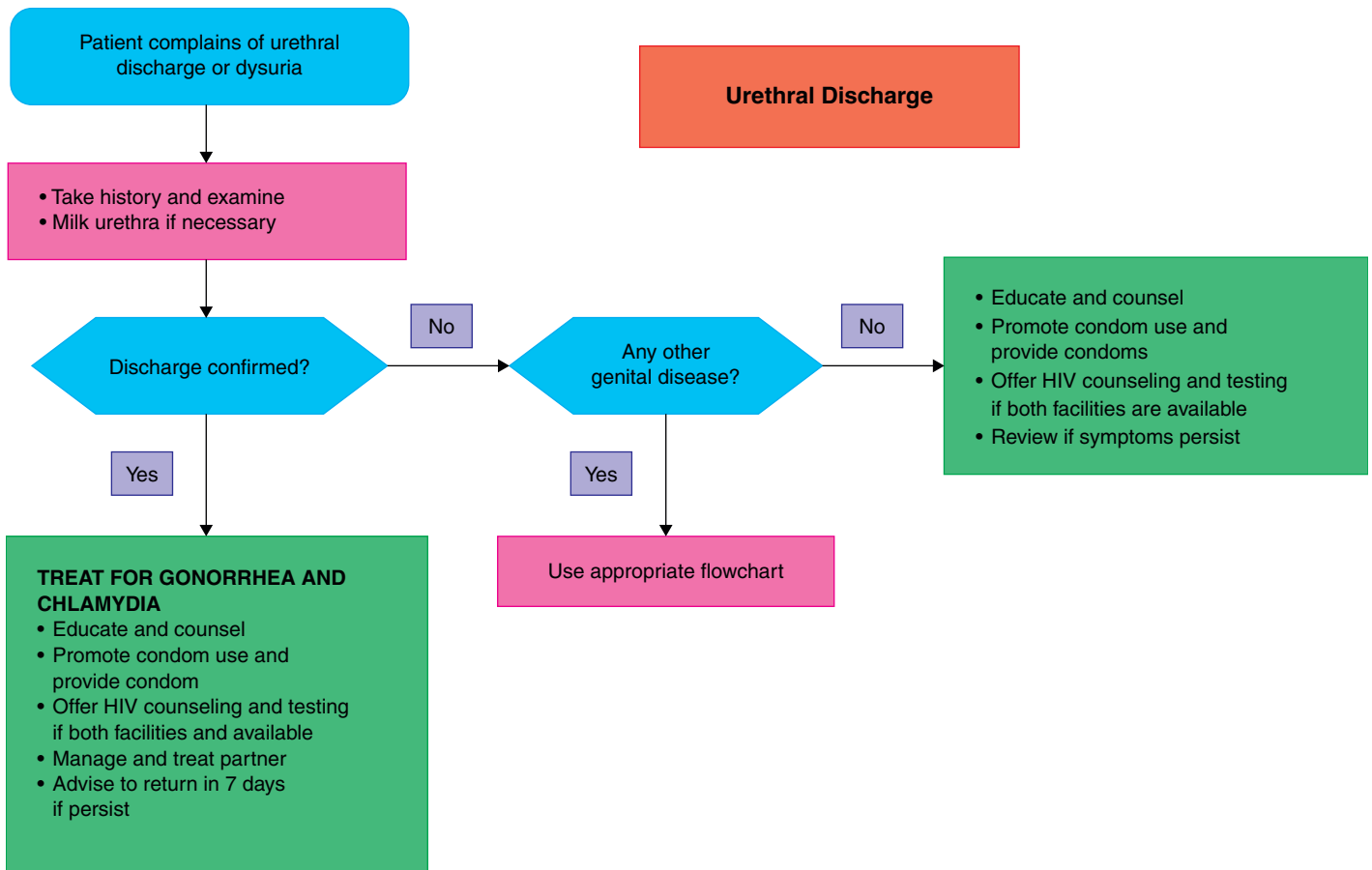


FIGURE 103-1. WHO algorithm for the management of urethral discharge.⁴³

A syndromic approach of urethritis requires a treatment for both gonorrhea and nongonococcal urethritis. A number of studies have demonstrated that gonococcal antibiotherapy is becoming increasingly problematic because of growing drug resistance to the classic antibiotics like penicillin, cotrimoxazole, thiamphenicol, and tetracyclines.^{41–57} These relatively inexpensive antibiotics can, therefore, no longer be recommended as a first choice treatment option.⁵⁸ More worrisome is the increasing resistance that has been recently observed against Ciprofloxacin in Asia and for the first time in Africa (South Africa) [Table 103-2](#). This quinolone has been first-line treatment for gonorrhea in many countries because of its efficacy, single dose oral administration, and relatively low price. The first evidence is also emerging of decreased susceptibility to ceftriaxone, a third generation cephalosporin [Table 103-2](#), but so far, this expensive third generation cephalosporin can still be recommended for the treatment of gonorrhea.

Establishing appropriate treatment strategies is further complicated by the fact that resistance patterns are changing rapidly. In Hong Kong, for example, the proportion of PPNG declined from 25% to 4% in less than 2 years. In this same period, the 4-fluoroquinolone resistance increased from 0.5% till 10.5%.⁵⁹ This illustrates the importance of

monitoring of drug resistance patterns at regular intervals within countries. Updated knowledge of patterns of antimicrobial resistance is essential to arrive at a suitable standard regimen for the treatment of *N. gonorrhoeae* within the syndromic approach.

The current WHO recommendation to give systematically a drug effective against *N. gonorrhoeae* as well as a second drug (tetracycline or doxycycline) effective against *C. trachomatis* to all patients with urethral discharge, will provide adequate coverage not only for these two pathogens but probably for *M. genitalium* as well.⁶⁰ Other studies have indicated, however, that *M. genitalium* is responding much better to azithromycin, which is not readily available in most developing countries.^{60,61}

■ GENITAL ULCERS

Like urethral discharge, genital ulcers are much more common in developing countries than in industrialized countries. However, considerable regional variation exists. There appears to be a higher prevalence of the genital ulcer syndrome (GUS) in southern African countries compared to West and Central African countries. In Zimbabwe, for instance, 63% of the male STI patients presented with genital

Table 103-2. In Vitro Resistance of *N. gonorrhoeae* Against Selected Antibiotics in Africa and Asia⁴⁷⁻⁴⁹

	Ciprofloxacin	Ceftraxone
India		
Hyderabad	57%	20%
Pune	10.6%	10.8%
Delhi	88%	0%
Bangladesh	76%	1.5%
Nepal	11%	0%
China	80%	–
Vietnam	40%	–
South Africa		
2003	24%	–
2005	48%	–
The Gambia	6% ^a	1%

R: resistant; LS/I: less susceptible/indeterminate.

^aStrains showed indications of increase in MIC but remained sensitive.

ulcers.⁶² In this clinic, genital ulcers were the main reason for consultation. Similarly, in rural Mozambique, genital ulcers were the primary reason for consultation in 38% of all STI cases.⁶³ In addition to high levels of GUS in STI patients, patients with a genital ulcer tend to wait a long time before presenting themselves at a health center. In a study in Rwanda, 36% of GUS patients had waited for more than 2 weeks.²³ Similarly, in South Africa, this proportion corresponds to 35–36% among men and women respectively^{64,65} while in the Gambia, 52% of all patients had waited over 2 weeks.⁶⁶ In many cases, patients continued to have sex before consultation.

Table 103-3 illustrates the different etiologies of GUS in different developing countries. Genital herpes, formerly regarded as a minor STI in most developing countries, has now emerged as a leading cause of genital ulceration in many countries where syphilis and chancroid were more prevalent previously. One of the first countries where this phenomenon was noticed was Rwanda. A study in one health center in Kigali showed that in 1986, herpes was the third and second most important cause of genital ulcers in men and women respectively. By 1992, herpes had become the second cause of genital ulcers in men and the leading cause in female patients.^{23,73} During that same period, HIV prevalence among patients with genital ulcers increased from 43% to 67% in men and from 77% to 83% in women,^{23,73} indicating a link between HIV and HSV-2 and explaining the changing etiological patterns for GUS. In

South Africa, the relative prevalence of both syphilis and chancroid among patients with GUS has declined from 1986 to 1998. At the same time, HSV-2 has emerged as the most frequent cause of GUS.¹³ A similar dramatic change in etiology of GUS was noted in Botswana, where the proportion of GUS due to chancroid decreased from 25% in 1993 to 1% on 2002, whereas the proportion of ulcers due to HSV-2 increased from 23% in 1993 to 58% in 2002.⁷⁴ (see Fig. 103-2).

HSV-2 DNA was detected in a significantly higher proportion of ulcer specimens from HIV positive patients than from HIV-negative patients.¹³ Other studies also indicate that both incidence and recurrence of genital herpes are higher in HIV-infected compared with HIV-non-infected patients.⁷⁶⁻⁷⁸ These data suggest that HIV is playing an important role in the increasing prevalence of HSV in GUS in developing countries.

Another reason for this increase may be due to the relative decrease of bacterial STD such as chancroid and syphilis. This may reflect increased condom use and an improved control of chancroid and syphilis in some regions using a syndromic approach. In Thailand, for instance, the incidence of chancroid and syphilis was reduced from nearly 39,000 and 11,855 cases in 1987–1990 and 3645 respectively in 1993.⁷⁹ In Zimbabwe, the number of cases of chancroid diagnosed clinically at the genitourinary center in Harare decreased from 2972 in 1990 to 430 in 1998.^{80,81}

Two rather rare causes of GUS are lymphogranuloma venereum (LGV) and donovanosis. In its primary stage, LGV may manifest itself as ulceration. LGV was detected in 14%, 7%, 6% and 2% of patients with a genital ulcer, in Gambia, Rwanda, South Africa, and the Dominican Republic respectively.^{24,66,67,73} Donovanosis as a cause of genital ulceration is limited to certain regions like Papua New Guinea, Kwa-Zulu-Natal, Eastern Transvaal in South Africa, parts of India, and Brazil.¹⁶ Because the disease is extremely rare in most parts of the world and is often not associated with genital ulcer diseases, donovanosis is

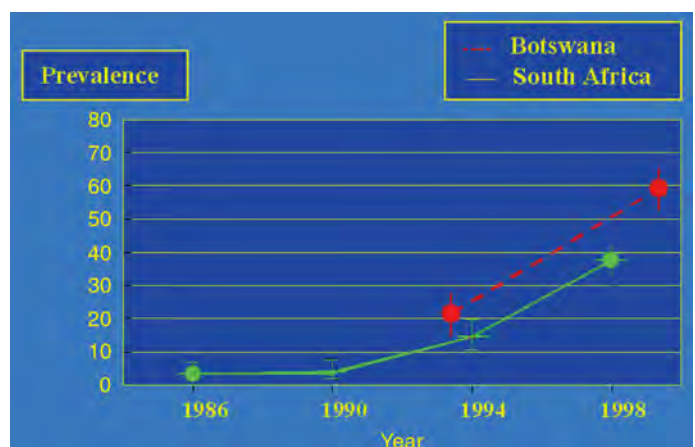
**FIGURE 103-2.** Prevalence of genital herpes among patients with genital ulcers by year of study in South Africa and Botswana.^{74,75}

Table 103-3. Etiologies of Genital Ulcers in Different Developing Countries

Country	Peru	Dominican Republic	Jamaica	Malawi	South Africa	Madagascar	India	Thailand	China	China
Site	<i>Lima</i>	<i>Santo Domingo</i>	<i>Kingston</i>	<i>Lilongwe</i>	<i>Carletonville</i>	<i>Antananarivo</i>	<i>Pune</i>	<i>Chiang Mai City</i>	<i>Shanghai</i>	<i>Chengdu</i>
Author	<i>Sanchez et al.</i>	<i>Sanchez et al.</i>	<i>Behets et al.</i>	<i>Hoyo et al.</i>	<i>Lai et al.</i>	<i>Behets et al.</i>	<i>Risbud et al.</i>	<i>Beyrer et al.</i>	<i>Wang et al.</i>	<i>Wang et al.</i>
Ref	67	67	68	69	13	14	70	71	72	72
Year of study	1994–95	1995–96	1996	1998–99	1998	1997	1994	1995–96	2000–01	2000–01
Total number of patients with genital ulcers	63	81	304	137	186	196	302	38	80	147
Pathogens identified with PCR										
HSV	38.1%	43.2%	52.0%	34.3%	36.0%	9.7%	31.5%	84.2%	38.8%	34.0%
<i>H. ducreyi</i> (HD)	4.8%	25.9%	23.7%	29.9%	50.5%	32.7%	27.8%	0%	0%	0%
<i>T. pallidum</i> (TP)	9.5%	4.9%	10.2%	3.6%	12.4%	29.6%	13.9%	2.6%	75.0%	31.3%
Mixed etiologies										
HSV + HD	4.8%	0%	4.6%	0%	9.7%	0.5%	3.0%	0%	0%	0%
HSV + TP	0%	0%	1.6%	0%	2.2%	1.5%	2.0%	2.6%	20.0%	8.2%
HD + TP	0%	0%	1.0%	1.5%	1.6%	1.0%	1.7%	0%	0%	0%
HSV + HD + TP	0%	0%	0.3%	0%	0%	0%	0.3%	0%	0%	0%
None of the above	47.6%	25.9%	22.0%	33.6%	21.0%	31.6%	34.1%	15.8%	18.8%	42.9%

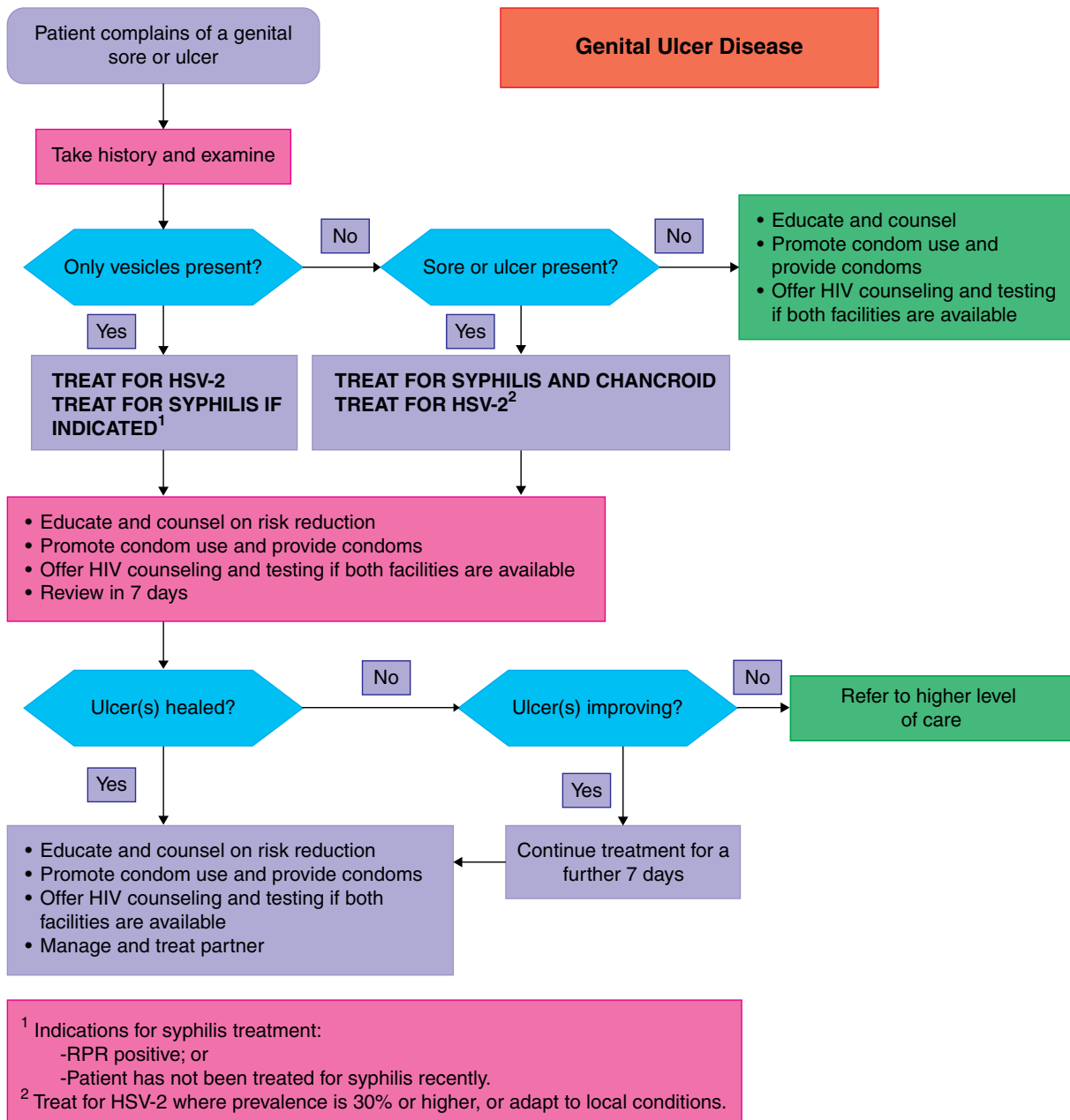


FIGURE 103-3. WHO algorithm for the management of genital ulcers.⁴³

not considered in most flowcharts. The role of sexual transmission of this disease is still controversial. (see Fig. 103-3.)

Determining the underlying causes of GUS is extremely difficult on clinical grounds and mixed etiologies are frequent.^{24,25} Typical vesicles were seen in only 4% of confirmed cases in Rwanda.²³ In a study in Madagascar, the sensitivity of a clinical diagnosis was 93%, 53%, and 0% and specificity was 20%, 52%, and 99% for the diagnosis of syphilis, chancroid, and genital herpes respectively.¹⁴

Until recently, a syndromic approach to the GUS in most developing countries recommended treatment for syphilis and chancroid, and herpes was not addressed by the GUS algorithms. This was due to the relative low prevalence of genital herpes and the unavailability of treatment. In 2001, a WHO

advisory group has recognized the importance of genital herpes, and WHO is currently recommending including the treatment for HSV-2 in the management of genital ulcers, especially in settings where HSV-2 prevalence is 30% or higher.⁸²

Adding a simple diagnostic test such as a RPR test to a diagnostic flowchart is not very helpful, as the test cannot exclude active syphilis. The results of an RPR test are negative in 30–50% of patients with a primary syphilitic ulcer.⁸³

In many parts of the world, patients with syphilis are often coinfecting with HIV. Whereas standard treatment of early syphilis and early latent syphilis in patients with HIV infection may be less effective, a few studies did not find a different clinical or serologic response after 1 dose of benzathine penicillin in HIV-positive as compared to HIV-negative patients.^{84–86}

Antibiotic resistance of *Haemophilus ducreyi* against single dose antibiotic therapy is another observed problem. One study in Kenya suggests that failure of a single intramuscular injection of 250 mg of ceftriaxone is strongly associated with HIV infection.⁸⁷ Increasing resistance to TMP/SMZ and treatment failure have also been documented in Rwanda, and HIV infection and the degree of CD4⁺ depletion were unrelated to clinical and bacteriologic outcome.⁸⁸ In conclusion, a single dose of TMP/SMZ can no longer be recommended for the treatment of chancroid in such regions. In other regions, surveillance data and studies of cost-effectiveness will have to guide therapeutic guidelines.

Giving an antiviral therapy for herpes was not considered for a long time in developing countries because of the high cost of drugs such as acyclovir. Moreover, the therapy was considered to be of limited public health importance since, in any case, it does not cure the herpes but only reduces the duration of symptoms. This picture has changed, in the light of the association between genital herpes and HIV transmission. Treating a person with acyclovir will shorten the duration of genital lesions and may eventually result in decreasing the spread of HIV.⁸⁹ In addition, generic acyclovir has become available at an

affordable price. Adding acyclovir to the syndromic treatment of ulcers, however, will not necessarily lead to higher cure rates.

STI causing genital ulcers are also important causes of inguinal lymphadenopathy in developing countries. A proportion of 8.5% of the male and 4.7% of the female STD patients in Kenya were complaining of genital or inguinal swelling.⁸

Lymph nodes that are 2 cm or larger, and become fluctuant, are considered buboes. The main causes of buboes are chancroid and LGV. Buboes are frequently present in patients with genital ulcers. In Zimbabwe, 20% of the men and 6% of the women with genital ulcers presented with buboes.⁶² In Rwanda, these proportions were 12.4% and 4%, respectively.²³ In women, lymphatic drainage is less superficial than in men. This could explain the fact that in these studies more men than women were having buboes. LGV is usually seen in a secondary stage of acute lymphadenitis with bubo formation, without a sign of the primary ulcer.

As proposed in the diagnostic flowchart shown in Fig. 103-4, a practical way to manage buboes is to consider them as LGV when no ulcer is visible and to manage them as a GUS when an ulcer is present. The aspiration of the bubo (through the healthy skin) may be required.

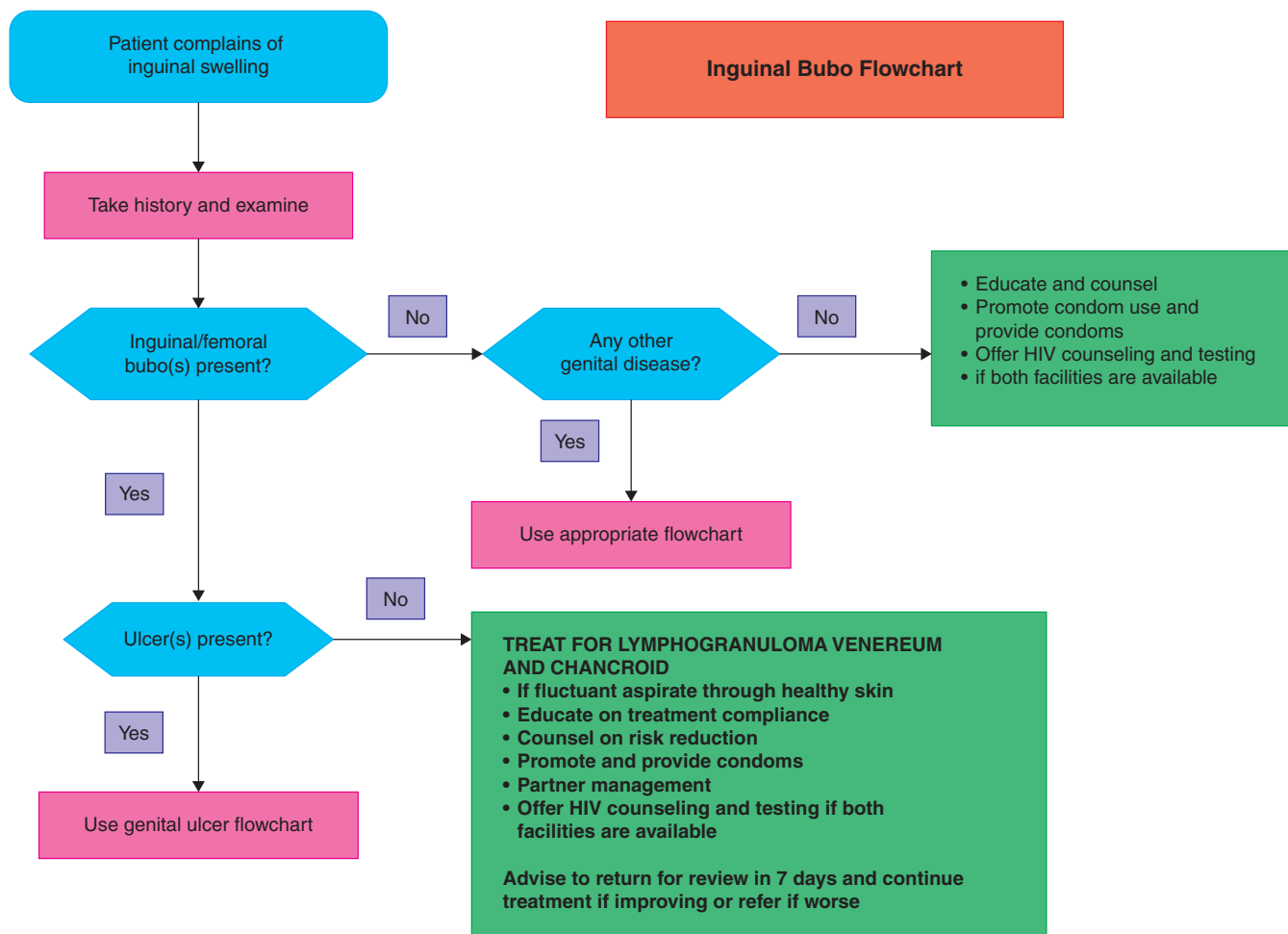


FIGURE 103-4. WHO algorithm for the management of inguinal buboes.⁴³

■ VAGINAL DISCHARGE

Abnormal increased amount or abnormal odor or color of vaginal secretions is a very common symptom and among the most important reasons for women to seek STI care in both developing and industrialized countries.^{8,62,90} These conditions may be related to both cervical and vaginal infections. The underlying causes of cervical infection in women are most frequently *N. gonorrhoeae* and/or *C. trachomatis*, which are usually localized in the endocervix. Although studies from the industrialized world have indicated that *M. genitalium* may cause mucopurulent cervicitis, no such data from developing countries are available.⁹¹ The underlying causes of vaginal infection include sexually transmitted agents such as *T. vaginalis* but also other conditions such as bacterial vaginosis and genital candida infection.

If cervical infection remains untreated, it may cause many serious complications such as acute PID, ectopic pregnancy, and infertility.⁹² A major reason why cervical infections often remain undiagnosed and hence untreated is the complete absence of symptoms and signs in many infected women. Symptomatic cervicitis represents only the tip of the iceberg. In a rural area in Mozambique, up to 89% of infected pregnant women did not report any symptoms.⁶³ In three family planning clinics in Dar es Salaam, Tanzania, 65% of the clients with a gonococcal and/or chlamydial infection reported no symptoms.⁹³ Among prostitutes in Zaire, acute newly acquired infections remained asymptomatic in 69% of all cases.⁹⁴

The asymptomatic character of cervical infections and the failure of many women, including symptomatic women, to seek medical care, may explain the high prevalence of gonorrhea

and/or chlamydia infection and related complications in some developing countries. Prevalence studies of chlamydia infection, for instance, show rates from 1.9% among teenagers in Chile⁹⁵ to 26% in rural women in Papua New Guinea.⁹⁶ Prevalence rates of gonorrhea were as low as 0.02% among pregnant women in Gabon⁹⁷ and as high as 24% in FSW in Thailand.⁹⁸

In primary health-care settings, however, symptoms of vaginal discharge are generally due to vaginal infections and less frequently to cervical infections, as shown in [Table 103-4](#). The most frequent causes of vaginal infection are candidiasis, bacterial vaginosis, and trichomoniasis. The possible complications of vaginal infection are much more limited except for their potential role in facilitating transmission of HIV and maybe their role in causing premature birth.^{104,105} However, vaginal infections cannot be ignored because they are a very common reason why women consult health services. As such, the quality of care for these infections may have a great impact on the confidence that women have in the health service.

Nevertheless, a syndromic approach to vaginal discharge should also take cervical infection into account because of the public health importance of gonococcal and/or chlamydial infections.

However, diagnosis of cervical infections in women is complicated because of the weak association between symptoms/signs and cervical infection and the absence of simple and valid laboratory tests for diagnosis or screening of cervical infections.

Not only the vaginal discharge symptom but also clinical signs such as cervical mucopus, friability or ectopy, and lower abdominal tenderness are of limited use for the clinical diagnosis of cervical infection. Various studies have shown a low

Table 103-4. Infections Identified in Women Attending a Primary Health-Care Center or Gynecology Clinic with the Symptoms "Vaginal Discharge" in Different Settings

Study Site	N	Vaginal Infection			Cervical Infection			Ref
		Candida (%)	BV (%)	Tv (%)	Ng (%)	Ct (%)	Ng and/or Ct (%)	
Tanzania	395	38	37	25	7	5	11	99
Malawi ^a	550	28	23	34	17	4	19	100
Benin	192	32	NA	11	6	2	8	101
Brazil	344	18	15	18	7	8	15	36
Peru	121	NA	39	11	0	12	12	102
Morocco ^b	765	NA	24	7	5	6	10	103

BV = bacterial vaginosis; Tv = *Trichomonas vaginalis*; Ng = *Neisseria gonorrhoeae*; Ct = *Chlamydia trachomatis*.

^aWomen with vaginal discharge, dysuria, lower abdominal pain, or dyspareunia.

^bWomen with vaginal discharge and/or lower abdominal pain.

Table 103-5. Sensitivity and Specificity of Select Symptoms and Signs for the Diagnosis of Cervical Infections in Low Prevalence (*L*) and High Prevalence (*H*) Settings: Results of a Meta-Analysis¹⁰⁶

	Sensitivity		Specificity	
	<i>L</i>	<i>H</i>	<i>L</i>	<i>H</i>
<i>Symptoms</i>				
Vaginal discharge	29.7	29.6	77.9	78.8
Vaginal itching	39.4	35.1	71.9	64.9
<i>Clinical signs</i>				
Vaginal discharge	42.2	58.9	59.6	57.5
Malodorous discharge	30.6	44.1	75.9	64.1
Yellow-green vaginal discharge	23.7	–	79.6	–
Thick or frothy vaginal discharge	45.5	–	68.2	–
Lower abdominal tenderness	38.2	38.3	70.0	65.1
Cervical mucopus	28.6	28.2	91.0	81.6
Cervical friability	24.7	23.7	81.1	82.7
Cervical ectopy	14.5	11.6	94.3	92.9

Sloan NL, Winikoff B, Haberland N, Coggins C, Elias C. Screening and syndromic approaches to identify gonorrhea and chlamydial infection among women. *Stud Fam Plann* 2000; 31: 55–68.

sensitivity and/or specificity of selected symptoms and signs for gonococcal and/or chlamydial cervical infection.

The results of a meta-analysis presented in [Table 103-5](#) showed that none of the symptoms nor clinical signs are at once sensitive and specific for cervical infection.¹⁰⁶ Moreover, there is almost no difference between low-risk and high-risk populations.

Studies in developing countries have demonstrated that risk markers rather than signs and symptoms are predictive for gonococcal and/or chlamydial cervical infections.^{107,94} As a result, WHO has proposed to incorporate a risk assessment for cervical infection in diagnostic flowcharts for symptomatic women [Fig. 103-5](#). This management strategy ensures that a woman with a complaint of vaginal discharge will systematically be treated for vaginal infections but her risk for cervical infection will also be assessed. When her risk assessment is positive, she should receive additional treatment for both gonococcal and chlamydial infection. Risk markers such as a symptomatic partner, being younger than 21 years of age, being single, and having more than one or having a new sexual partner in the last 3 months, have been validated in different settings, including Jamaica, Brazil, Benin, Gabon, Malawi, Tanzania, and Kenya.^{36,90,97,99,100,101,108} Using a risk score assessment in Tanzania, the overtreatment rate for cervical infections decreased from 92% to 17% in pregnant women and from 89% to 36% in nonpregnant women with vaginal discharge.⁹² However, in certain areas it is culturally

not accepted to ask private questions on sexual behavior to women, or the prevalence of cervical infections may be too low to be considered in a syndromic approach.¹⁰⁹ Therefore, the risk assessment should be adapted to local circumstances and STI epidemiology.

Another main obstacle for diagnosis and/or screening of cervical infections is the absence of a simple and valid diagnostic laboratory test for *N. gonorrhoeae* and *C. trachomatis*. The current gold standard laboratory tests such as polymerase or ligase chain reaction are too sophisticated, expensive, and generally not available in most settings. Culture for *N. gonorrhoeae* may be available in some settings, but results are not readily available, which unnecessarily delays treatment. More simple laboratory tests such as Gram stain or Leuco-esterase Dipstick (LED), which are useful in detecting urethritis in men, are not helpful and not specific and sensitive enough to detecting cervical infections.^{90,99} Simple, rapid, and affordable tests for the diagnosis of gonococcal and chlamydial infection have been on the priority list for STI research for years but as yet remain unavailable. The development of such tests is considered by STI control program managers and STI specialists to be an absolute priority in STI research. Major progress has recently been made in this field. A rapid (25 min), cheap (U.S. \$0.85) dipstick for chlamydial infection “First burst” has been recently developed and is awaiting FDA approval. Another duplex (*N. gonorrhoeae* and *C. trachomatis*) test is undergoing evaluation.¹¹⁰ These tests may represent an important

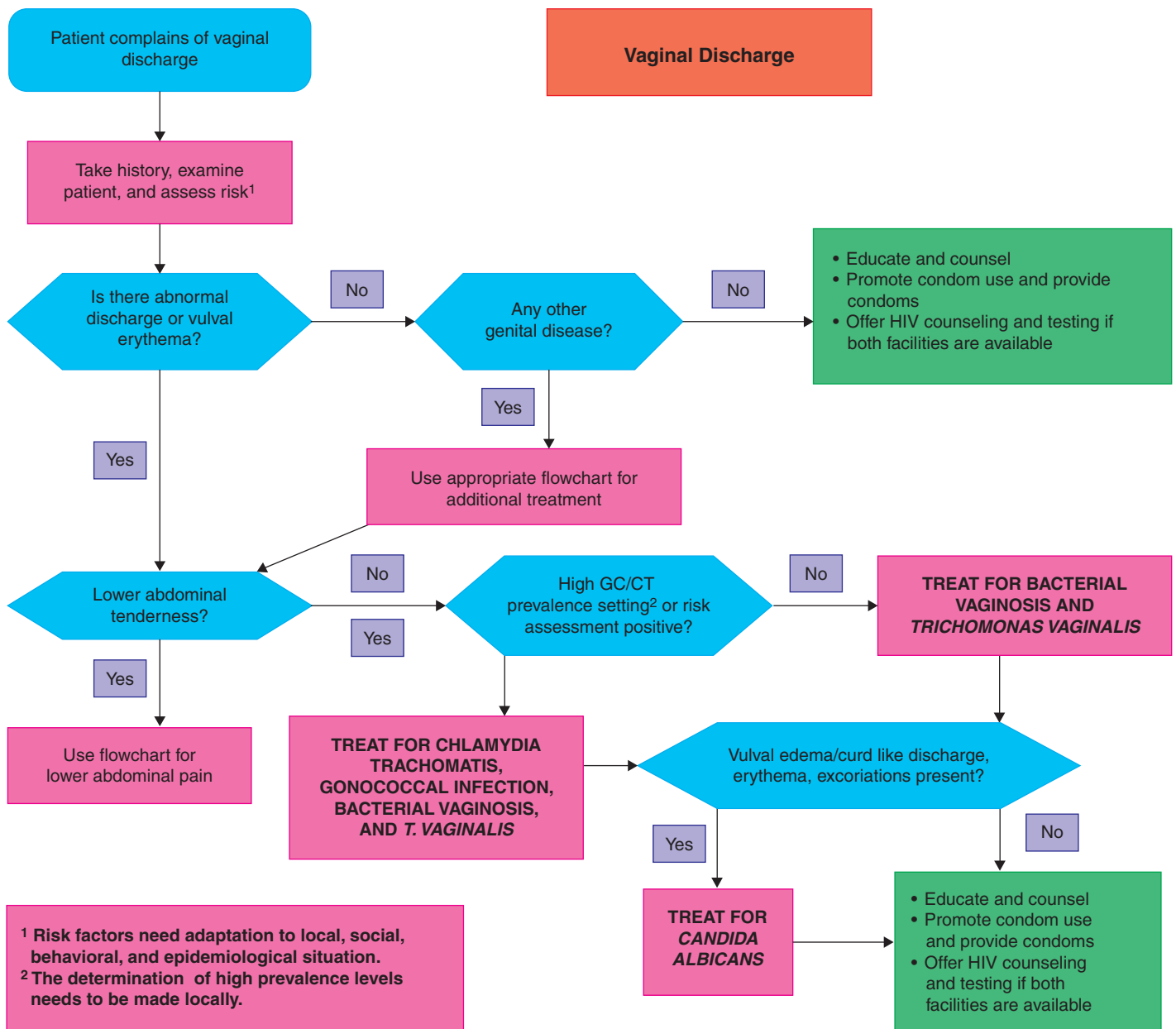


FIGURE 103-5. WHO algorithm for the management of vaginal discharge.⁴³

breakthrough for STI control in symptomatic and asymptomatic women in developing countries.

The recommended treatment for vaginal infection is shown in Fig. 103-5. It includes treatment for both candidiasis and trichomoniasis that covers bacterial vaginosis at the same time. Cervical infections should be treated with antibiotics for gonorrhea and chlamydia infection. The observations regarding the resistance to antibiotics for gonorrhea can be applied to treatment for cervical gonorrhea.

■ LOWER ABDOMINAL PAIN

Lower abdominal pain is a very common symptom in women attending with STI symptoms. It was among the

main complaints in 46%, 48%, and 49% of the women consulting a primary health-care center or STI clinic in Morocco, Kenya, and Malawi, respectively.^{100,103,111}

In most cases, the symptom lower abdominal pain is related with cervical infection due to *N. gonorrhoeae* and/or *C. trachomatis*.^{100–102} However, when untreated, cervical infections may ascend into the upper reproductive tract and cause PID. The role of gonorrhea and of chlamydia infections in PID in Africa has been well documented.^{112,113} The long time sequelae of tubal scarring and occlusion may cause infertility. In Africa, over 85% of infertility in women can be attributed to this infection.¹¹⁴

The most important symptom of PID is lower abdominal pain which may or may not be accompanied by clinical signs

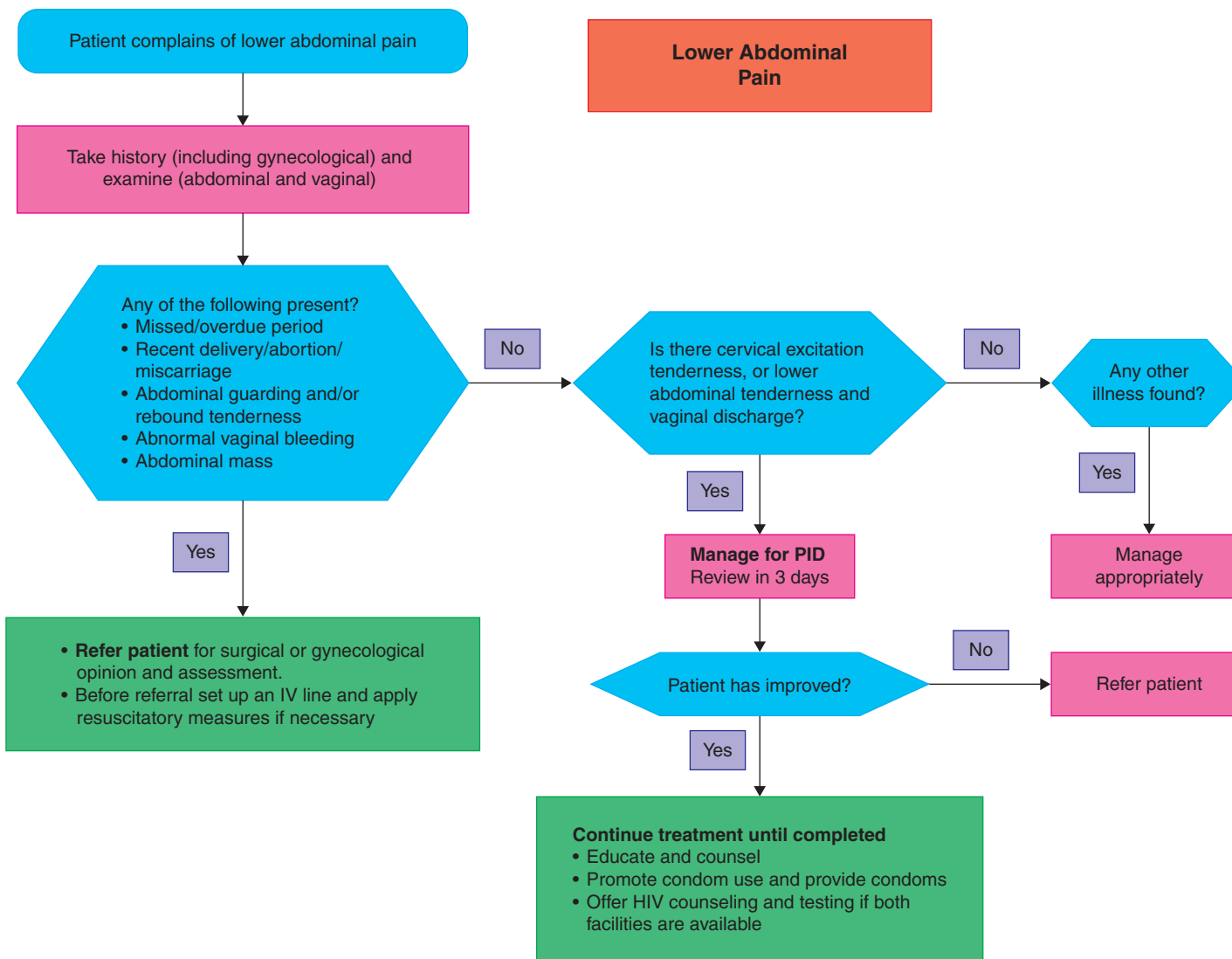


FIGURE 103-6. WHO algorithm for the management of lower abdominal pain.⁴³

like fever, cervical motion tenderness, palpable mass, and vaginal discharge.^{112,115} See also Fig. 103-6 that shows the WHO algorithm for the management of lower abdominal pain.

Lower abdominal pain in sexually active women can also be a symptom of ectopic pregnancy or of other causes of acute abdomen. These emergencies must be excluded before treating for PID. Recommended treatment regimens and indications for hospitalization are discussed in Chapter X.

■ NEONATAL CONJUNCTIVITIS

Both gonococcal and chlamydial ophthalmia neonatorum are still common in many developing countries. Although gonococcal ophthalmia tends to be more severe, more purulent and with an earlier onset than ophthalmia caused by chlamydial infection, the etiological cause (gonococcal or chlamydial) cannot be assumed on the basis of clinical signs only.

An example of a diagnostic flowchart for ophthalmia neonatorum is provided in Fig. 103-7. Effective treatment dramatically changes the course and outcome of the disease, usually with noticeable improvement within 24 hours. The eyes of the baby should be washed with frequent saline irrigations. Unfortunately, the availability of recommended drugs such as ceftriaxone IM or spectinomycin IM for pediatric preparations is a problem in many developing countries. Kanamycin (25 mg/kg as a single IM dose) can be given as a suboptimal alternative. Management should also include the treatment of the mother and her partner.

CASE FINDING AND SCREENING FOR STI IN DEVELOPING COUNTRIES

Because of the asymptomatic nature of many infections, particularly in women, and of the serious complications resulting from untreated infections, active case finding or screening for

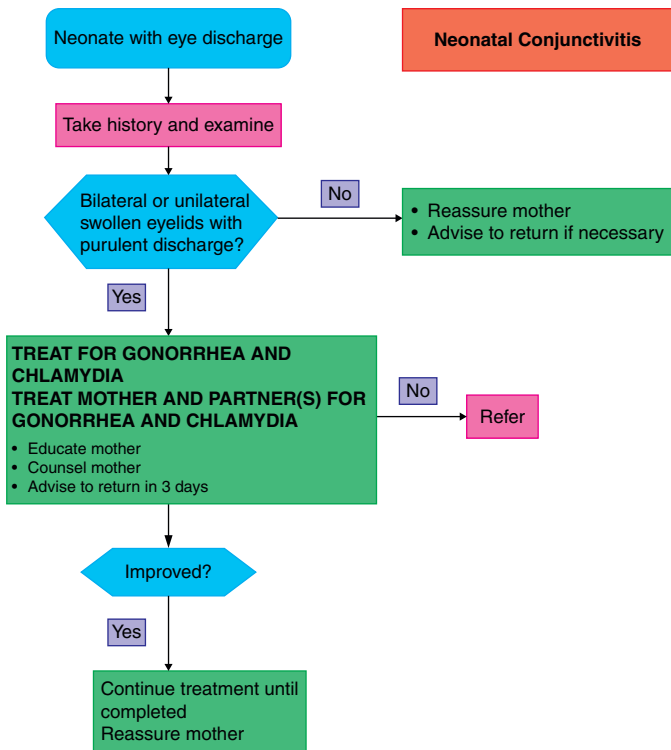


FIGURE 103-7. WHO algorithm for the management of ophthalmia neonatorum.⁴³

STIs is an obvious public health strategy. Global strategies for case finding and/or screening may vary according to the target population. If the aim is to reach a maximum coverage, all women of reproductive age should be targeted. It seems logical to integrate STI services in Mother and Child Health services and Family Planning services because these are often women's primary contact with the health-care system. In many developing countries, these services have a good coverage of women of childbearing age. Another strategy is to target particularly vulnerable groups such as sex workers for screening.

■ STI SCREENING AS PART OF REPRODUCTIVE HEALTH PROGRAMS

The provision of reproductive health, including STI care, was put high on the agenda at the 1994 International Conference on Population and Development (ICPD) in Cairo, and new questions were arising about how to attend reproductive tract infections (RTIs), including asymptomatic STIs in women attending family planning centers or antenatal services.¹¹⁶

Syphilis prevalence rates between 3% and 19% have been reported in pregnant women from developing countries, with the highest rates found in southeastern sub-Saharan Africa.¹¹⁷ Rates of congenital syphilis as high as 3200 per 100,000 live births have been described in Addis Ababa, Ethiopia, and 850 per 100,000 in Lusaka, Zambia.^{118,119} In Porto Alegre, Brazil, 2.3% of the newborns had clinical and/or laboratory

incidence of congenital syphilis.¹²⁰ Adverse pregnancy outcome due to syphilis is preventable through routine serological screening by a simple RPR (or equivalent) test and early treatment of both partners. Screening and treating pregnant women for syphilis is known to be a highly cost-effective, inexpensive, and feasible intervention for congenital syphilis, as demonstrated in Nairobi, Kenya,¹²¹ and in Lusaka, Zambia.¹¹⁷ In the latter study, the cost of preventing an adverse pregnancy outcome due to maternal syphilis was around U.S. \$12 at a seroprevalence level of 10%. Even in countries with seroreactivity rates lower than 1 per 1000 syphilis screening in pregnant women was reported to be cost-effective.¹²²

For gonococcal and/or chlamydial cervical infections, however, no such simple test is currently readily available. Given the success of the syndromic approach including risk assessment for symptomatic patients, it was appealing to test the validity of the approach for STI screening in asymptomatic women.^{93,123,124} However, it soon became evident that the approach has some limitations when used for STI screening in asymptomatic women, especially in low prevalence settings.^{93,109} It should be stressed that the syndromic approach was developed as a diagnostic tool in symptomatic patients and it was never meant to be a screening tool.¹²⁵ Traditionally, screening tools are used to minimize the number of (more expensive) standard diagnostic tests by identifying a group of people with a higher-than-average prevalence of infection. In the absence of such a test, the risk score approach should not be used as a substitute for standard diagnosis because of its poor discriminative ability. The current picture may change, however, when simple, cheap, and rapid diagnostic tests for *N. gonorrhoeae* and *C. trachomatis* are available in developing countries. The development of such tests is considered by STI control program managers and STI specialists to be an absolute priority in STI research. Major progress has recently been made in this field. A rapid (25 min), cheap (U.S. \$0.85) dipstick for chlamydial infection "First burst" has been recently developed and is awaiting FDA approval. Another duplex (*N. gonorrhoeae* and *C. trachomatis*) test is undergoing evaluation.¹¹⁰ These tests may represent an important breakthrough for STI control in symptomatic and asymptomatic women in developing countries.

■ STI SCREENING FOR HIGHLY VULNERABLE POPULATIONS, INCLUDING SEX WORKERS

For some specific populations and settings, STI management using the syndromic plus risk assessment approach alone may not be sufficient and alternative strategies are warranted.

Because of high infection rates and large numbers of sexual partners, sex workers have been considered a core group for the transmission of STIs, especially in developing countries.¹²⁶

Standard diagnostic approaches are often not sensitive enough to detect most infections in high-risk groups such as FSWs. In addition, treatment of symptomatic STI alone will not be sufficient for lowering the infection rate in this population. If affordable, regular laboratory screening of sex workers for the common curable STIs using sensitive tests would identify both symptomatic and asymptomatic STIs.¹²⁷ These expensive high-tech laboratory tests are not available in most situations and alternative strategies are needed. Such an alternative strategy is presumptive or periodic mass-treatment of STIs in high prevalence populations. Presumptive treatment of individuals or populations with a high likelihood of having disease is dependent not on the presence of symptoms or signs, nor on the results of laboratory tests, but on increased risk of exposure.¹²⁷ Because of high prevalence rates and frequent reexposure, sex workers can be treated presumptively for the common curable STI on a one-time or periodic basis. Such an approach may be an effective emergency measure to rapidly reduce high prevalence rates over the short term.^{127,128} The Lesedi project started in October 1996 in a South African mining community. FSWs attended a mobile clinic monthly for examination and counseling and were treated presumptively for bacterial STIs with a directly observed 1 g dose of azithromycin. After 9 months of intervention, gonococcal and chlamydial rates decreased from 25% to 10% and from 11% to 6% and genital ulcers decreased from 10% to 4% and from 6% to 1% among FSW and miners, respectively.¹²⁹ By the end of the first year, costs of the periodic presumptive treatment component of the intervention were tracked and a cost-benefit analysis was carried out based on estimates of averted morbidity and mortality. A model was used to estimate the number of HIV infections averted in women using the services and among miners in the area.¹³⁰ Hospital costs for inpatient and outpatient care of miners with HIV-related illness were determined from hospital records. The calculated benefit ratios were high, even when only considering the direct medical costs, with estimated annual savings of U.S. \$539,000.¹³¹

Since the end of the first phase, services for women at high risk have been expanded and covered all the high-risk areas in the original town by 2001. Antibiotic resistance studies were conducted in 2000 on samples from the project area and no resistance to azithromycin was found (R. Steen, personal communication).

The prevalence of STI drops quickly among women who are attending services regularly. The difference in infection rate between first-time attendees and returning clients prompted some program managers to design two different strategies. In FSW clinics in Kinshasa (Democratic Republic of Congo) and Sihanoukville (Cambodia), for instance, all first-time attendees are given treatment for cervical infections, whereas returning clients are treated according to a strict algorithm (N. Ségué and F. Crabbé, personal communications). In an FSW clinic in Abidjan, Côte d'Ivoire, women

are managed differently if the time since their last visit exceeds 3 months.

Other high-risk male populations who may need special attention regarding STI screening include military personnel, long-distance truck drivers, and in general clients of sex workers. Results from several studies suggest that a significant proportion of men with positive laboratory tests for *N. gonorrhoeae* or *C. trachomatis* are asymptomatic.^{132,133} The LED has been proposed as a cheap nonspecific test that could allow the detection of polymorphonuclear cells in asymptomatic men and also be used to confirm symptomatic urethritis.^{133–135} In a study among clients of FSW in Benin for instance, the positive predictive value of the LED test for urethritis in asymptomatic clients of sex workers was 37.5%.¹³⁵ In another study in Kenya, a positive LED test on urine predicted infection with a sensitivity of 55% and a specificity of 83% in asymptomatic transport workers.¹³³ These results suggest that LED could be a useful case finding tool for STIs in high-risk asymptomatic men in developing countries.

STI CASE MANAGEMENT AS PART OF STI CONTROL PROGRAMS IN DEVELOPING COUNTRIES

Even if 100% sensitive and 100% specific algorithms or simple inexpensive laboratory tests for STI diagnosis were available, they are not likely to reduce the number of STI infections on their own. Simple and valid diagnostic tools are the cornerstones of effective STI case management, but many other factors play a role in a successful STI control program. A model developed in the sixties to evaluate case finding and treatment in tuberculosis control programs¹³⁶ has been adapted to assess the performance of STI case detection and management (Fig. 103-8). It uses a series of steps from number of infected people in the community to number of patients eventually cured by the health system. At every step

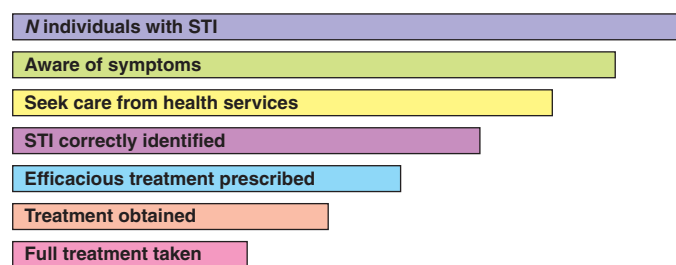


FIGURE 103-8. Operational model to illustrate the different steps involved in STI case detection and treatment. (Adapted from Waaler HT, Piot MA. The use of an epidemiological model for estimating the effectiveness of tuberculosis control measures. Sensitivity of the effectiveness of tuberculosis control measures to the coverage of the population. *Bull World Health Organ* 1969; 41: 75–93; Buvé A, Changalucha J, Mayaud P, et al. How many patients with a sexually transmitted infection are cured by health services? A study from Mwanza region; Tanzania. *Trop Med Int Health* 2001; 6: 971–979.)

between infection and cure, the number of cases lost to the health services is calculated, in order to identify where interventions might have the greatest impact. This model has helped to illustrate that patients with STI have to overcome several hurdles before they are cured. Issues such as being aware of the STI and become motivated to seek correct and appropriate care are as important in terms of “losses of proportion of STI cured” as correct diagnosis and treatment. This was illustrated by Buvé and colleagues in Mwanza (Tanzania) where this model was applied to a real-life situation.¹³⁷

■ CURE RATE ACHIEVED BY THE HEALTH SYSTEM

The cure rate not only depends on the diagnostic tools used but also on the correct application of the tools, the availability of efficacious STI drugs, and the patient’s compliance with the treatment. During a study in a sex worker clinic in Abidjan, Cote d’Ivoire, for instance, all necessary steps to diagnosis were correctly performed in only 68% of the cases.¹³⁸ This shows the importance of training of health-care providers in the correct application of the algorithms, ongoing supervision, and reinforcement after training. In Rwanda, for instance, nurses were able to correctly apply the syndromic STI management guidelines with adequate post-training supervision and a high degree of clinical improvement was achieved.¹³⁹

The accessibility and availability of affordable, effective drugs are further critical conditions for appropriate STI case management. Bulk purchasing by governments and other, more innovative partnerships between multilateral and bilateral agencies, the pharmaceutical industry, and country programs should be put in place urgently.¹⁴⁰ Another step to correct treatment is the patient’s compliance with the treatment prescribed. During an observational study in rural Tanzania, for instance, 69% of the returning women said that they took the full treatment.¹³⁷

■ HEALTH SERVICE DELIVERY

In order to achieve cure through the health system, people with STI have to get in touch with the health system (Fig. 103-8). However, not all men and women who contract an STI are aware of their infection or are worried enough to seek care. Even if they are aware and worried, not all attend a health facility. The literature from developing countries confirms that a substantial proportion of people seek STI treatment in the informal sector from traditional healers, unqualified practitioners, street drug vendors, or pharmacists.^{6–8,141} From a study in Mwanza, Tanzania, it was estimated that in the catchment area of health centers offering improved STI services, 51–72% of patients with STI symptoms sought care from those health centers.¹³⁷ Reasons for not attending a health

center when having an STI include fear of stigmatization and inaccessible and unaffordable services. People may be too frightened to make use of health services because they fear abusive attitudes of health workers and often experience a lack of privacy and confidentiality.¹⁴² A study was performed in South Africa to determine factors associated with delay in seeking healthcare for symptoms of STI. Patients who delayed were those who held misconceptions regarding the STI cause, who perceived STIs not to be serious, whose friends waited before seeking treatment, and who valued personal autonomy in sexual behaviors less.¹⁴³

In ensuring universal access to appropriate STI care programs, it should be recognized that patients seek care from a range of public and private sources. In many countries most STI care is obtained outside the public sector. Planning of a balanced and comprehensive program will need to consider strengthening any health-care providers that are able to provide a quality service.¹³⁷

For vulnerable women such as sex workers, it is even more difficult to access good quality services. Even when they are available, there are a number of reasons for poor utilization of services, such as stigmatization, inconvenient opening hours, and economic, language, or other cultural barriers. Different projects have tried to increase the accessibility of services by promoting sex-worker-only clinics.¹²⁶ These clinics could provide them with additional safe and confidential options for sexual health services. In addition, specialized services may offer better opportunities for targeted educational sessions and regular screening activities. A regular visit by the sex worker will enhance the relationship of trust with the health-care workers and provide a forum for prevention messages.

As mentioned previously, the most critical step in effectively implementing STI control programs for youth is reaching the group and convincing individuals of the value of the intervention.¹²⁷

■ PREVENTION STRATEGIES

Early diagnosis and treatment of STI is an important strategy to reduce the pool of infected people and to prevent secondary infections. In addition, behavioral interventions are designed to prevent the acquisition of infection and disease by promoting abstinence, safer sexual behavior, and the use of condoms for penetrative sexual acts.²⁰

Providing STI clinical care offers an important opportunity for health education to persons who are, by definition, at increased risk of infection. A patient’s decision to come to the clinic signals a level of concern that may provide the teachable moment. Evidence suggests that people are more willing to learn about a disease when they or someone close to them experiences its symptoms or consequences.¹⁴⁴ Patient education in

STIs can be divided into the categories of preventing future infections and managing the current infection. Preventing future infections requires sustained behavior change or the consistent practice of low-risk sexual behavior. Managing the current infection both prevents further transmission to others and prevents complications in the patient.

Behavior change messages include messages on prevention of STI by reducing the number of partners and promoting the use of condoms but also messages to promote health-seeking behavior.¹⁴⁵ In order to increase their coverage at general community level, behavior change message may be delivered by mass media. Mass media can be used to raise general awareness, but a combination of mass media campaigns and interpersonal communication seems most promising to maintain safe sex behavior or prevent and change unsafe behavior.¹⁴⁶ Wide availability of condoms, e.g., through condom social marketing further supports the preventive components of an STI control program.¹⁴⁷

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The Laboratory in the Management of STDs, HIV, and Opportunistic Infections in Developing Countries

Rosanna W. Peeling, David Mabey, Jimmy Whitworth, and Andrew Ramsay

INTRODUCTION

Developing countries bear by far the greatest burden of disease due to HIV and other sexually transmitted infections (STIs). At the same time, the human and material resources at their disposal to control these infections and to provide care for those affected by them are less than in rich countries. In the most severely affected countries, the HIV epidemic has itself had a profound impact on the availability of trained staff in the health sector.

The laboratory is important in the management of STIs, HIV, and opportunistic infection (OI). Its role in the provision of laboratory services in support of patient management and disease control is similar in both developed and developing countries. The main difference is that, in developing countries, the burden of disease is greater but resources are more limited. In the least developed countries, where there is a lack of trained personnel, few resources to buy consumables, old and poorly maintained equipment, and an unreliable electricity supply, there may be few if any fully functioning microbiology laboratories.^{1,2} In these circumstances, only the simplest diagnostic tests can be used. On the other hand, even in the poorest countries, there is often a flourishing private market in health care, at least in major cities, although this is often poorly regulated and of variable quality.

Allocation of resources to laboratory services has not been a high priority in developing countries. In resource-limited settings, health service providers have to prioritize their scarce monetary and human resources to accommodate many competing demands. Even where there is political commitment and resources are available, there are often operational and administrative difficulties in delivery of health services due to an inadequate health-care infrastructure plagued by staff shortages, lack of proper training and supervision, inconsistent supply of laboratory reagents and medicines.³ This has led to demoralization of staff and failure to pay adequate attention to essential aspects of a diagnostic laboratory service: staff training, regular supervision, and quality control. This has affected the quality of results, leading

to a lack of confidence in laboratory diagnosis, resulting in a reduced quality of clinical care. It has also fuelled the perception that laboratories are of little value.²

In some developing countries such as Malawi, the essential health package developed by the Ministry of Health includes a package of essential medical laboratory services.⁴ Such a package includes

- emphasizing the importance of laboratory testing for accurate diagnosis;
- ensuring sufficient financial resources are made available;
- implementation of laboratory training programs;
- regular supervision of laboratory staff;
- routine monitoring of test quality;
- establishing a system for laboratory accreditation;
- evaluation of affordable, rapid diagnostic tests.

This chapter discusses the role of the laboratory in the management of STI, HIV, and OIs and approaches to laboratory diagnosis for these infections according to the resources available. We will focus on public sector services in countries with the greatest burden of disease due to HIV and other STIs, e.g., those in sub-Saharan Africa.

We will discuss the role of the laboratory at three levels of health care:

- peripheral level, such as a health center which serves a number of dispensaries or health posts
- district level, such as district hospitals which serve health centers within a district
- tertiary level, such as regional or referral hospitals

The facilities available at each level will vary from country to country. For the purposes of this chapter, we define them as follows:

At *peripheral* (health center) level, there is unlikely to be a trained microbiology technician, and little likelihood of future staffing with technicians in the short term, nor is there likely to be a member of staff who will be able to interpret and conduct complex investigations appropriately. Tests at the health center level need to be those which will benefit the

Table 104-1. Laboratory Capacity at Different Levels of Health Care

Level of Care	Staff	Equipment	Tests
Peripheral centers	Health worker, nurse	Light microscope at some centers	Rapid tests for STIs and HIV; Smear microscopy for malaria and TB
District hospitals	One or more trained technicians	Light microscope, centrifuge, shaker for syphilis serology, incubator in some facilities	Smear microscopy for malaria and TB; Serological tests for syphilis, HIV; Limited bacterial cultures for tuberculosis and gonorrhea
Tertiary hospitals	Fully functional laboratory with two or more trained technicians	Light microscope, centrifuge, shaker for syphilis serology, incubator	Smear microscopy for malaria; Serological tests for syphilis and HIV, including confirmation; Blood cultures; Antimicrobial susceptibility testing

management of a patient who is not so sick as to need referral to hospital. Testing at these peripheral centers may be useful for protecting therapies from massive overuse or abuse. Laboratory equipment is likely to be restricted to a light microscope.

At *district* level, it is expected that there will be at least one trained technician. Tests performed at this level should be those that will provide clear treatment direction for serious infections. In addition to a light microscope, equipment may include a centrifuge and facilities for simple serological testing and bacterial culture.

At the referral hospital, or *tertiary* level, culture techniques (including blood culture) should be routinely available. If an organism is cultured, then it should be feasible to determine antimicrobial sensitivities. The laboratory at this level should be able to conduct periodic assessment of the etiological cause of common syndromes and of antimicrobial sensitivities of common pathogens to guide syndromic management. The facility and capacity at different levels of health care are summarized in [Table 104-1](#).

Laboratory services need to be organized and quality-assured through a well-defined framework defining roles and responsibilities for STI/HIV laboratory management at different levels of health care. These can include for

tertiary level

1. implementation of national programs and policies;
2. technical support and training for district level laboratory procedures and biosafety issues;
3. providing logistics to ensure the availability of tests, drugs, and other supplies such as needles, reagents, and consumables for diagnostic tests;

4. making recommendations on which tests and equipment to purchase;
5. quality assurance provision and supervision for district and peripheral health centers.

district level

1. technical support and training for peripheral level laboratory procedures and biosafety issues;
2. implementing logistics to ensure the availability of tests, drugs, and other supplies such as needles, reagents, and consumables for diagnostic tests;
3. quality assurance provision and supervision for peripheral health centers.

peripheral level

1. liaise with district regarding program priorities, supply needs and training;
2. performing quality control for rapid tests (if applicable) to ensure test validity.

THE ROLE OF THE LABORATORY IN THE MANAGEMENT OF SEXUALLY TRANSMITTED INFECTIONS

Diagnostic tests for STIs and HIV may be used to improve the clinical management of patients seeking care, to screen asymptomatic individuals at risk of infection, for surveillance, or to screen blood for transfusion. Prompt diagnosis and treatment of infected individuals is a cornerstone of STI control, especially in the case of the curable STIs. In the case of incurable viral STIs (e.g., herpes, HIV infection) diagnosis of infection can help to prevent transmission to sexual partners,

from mother to child, and through blood products, and can allow patients to access effective therapy.

The requirements for test performance may differ depending on the reason for doing the test. For example, in screening blood for case finding or transfusion, high sensitivity is essential, but specificity is less important as confirmatory testing can be performed on those who are positive on the screening test. In voluntary counseling and testing for STI and HIV infection, for psychosocial reasons and to avoid gender-based violence when a woman is wrongly diagnosed with a STI, it is important to avoid a false-positive diagnosis. High specificity is therefore also required.

■ ROLE OF THE LABORATORY IN THE MANAGEMENT OF SYMPTOMATIC PATIENTS

Three alternative approaches may be used to manage patients presenting with symptoms suggestive of an STI:

- **Clinical diagnosis:** The health care provider makes a specific diagnosis, e.g., syphilis or gonorrhea, based on clinical findings. Several studies have shown that this method is unreliable even in the hands of experienced physicians.⁵
- **Etiological diagnosis:** Specimens are sent for laboratory testing to identify the pathogen(s) present and, in some cases, to determine their antimicrobial susceptibility. This is the method of choice but is expensive, and may lead to delay in treatment, resulting in further transmission and development of complications. If those who are tested do not return for their results, they are not treated, resulting in a waste of resources, adverse clinical outcomes, and continued transmission of infection.
- **Syndromic management:** Patients with well-defined syndromes such as urethral discharge or genital ulcer are treated for all the likely causes of that syndrome.

Syndromic management of STIs is recommended by WHO in settings where access to laboratory services or resources is limited.⁶ Flowcharts are available for the management of six syndromes: urethral discharge and scrotal swelling in men, vaginal discharge and lower abdominal pain in women, and genital ulcer and inguinal adenopathy in either sex. The advantages and disadvantages of syndromic management are shown in [Table 104-2](#). The principal disadvantage is that it leads to overtreatment.

The laboratory has two important roles in supporting syndromic management: at the **tertiary level**, studies should be conducted periodically to determine the major causes of the common syndromes and to measure the antimicrobial susceptibility of local isolates of *Neisseria gonorrhoeae* and *Haemophilus ducreyi*. Syndromic management algorithms should be modified according to the results of these studies. At the district or **peripheral level**, simple tests (e.g., microscopy) can reduce the number of patients receiving unnecessary treatment.

Microscopy

- Gram stain for *N. gonorrhoeae* for patients with urethral discharge (not recommended for vaginal discharge because of poor sensitivity)
- Gram stain for bacterial vaginosis (BV) and candidiasis
- Wet preparation for *Trichomonas vaginalis*

Syphilis Serology

- nontreponemal tests such as the Rapid Plasma Reagin (RPR) or Venereal Disease Reference Laboratory (VDRL) test
- rapid, point-of-care treponemal tests

Use of simple diagnostic tests can increase specificity, and hence reduce overtreatment, as shown in the urethral discharge flowchart ([Fig. 104-1](#) depicts flowchart).⁶ Since the sensitivity of a Gram-stained smear of urethral

Table 104-2. Advantages and Disadvantages of Syndromic Management of STIs

Advantages

- Problem-orientated (responds to patient's symptoms)
- Highly sensitive and does not miss mixed infections
- Treatment given at first visit
- Provides opportunity and time for education and counseling
- Avoids expensive laboratory tests
- Avoids unnecessary return visit for laboratory results
- Curtails referral to specialist centers
- Can be implemented at PHC level

Disadvantages

- Overdiagnosis and overtreatment with the following consequences:
 - Increased drug costs
 - Possible side effects of multiple drugs
 - Changes in vaginal flora
 - Potential for increased drug resistance
 - Difficulties with partner notification
- Requires (re)training of staff

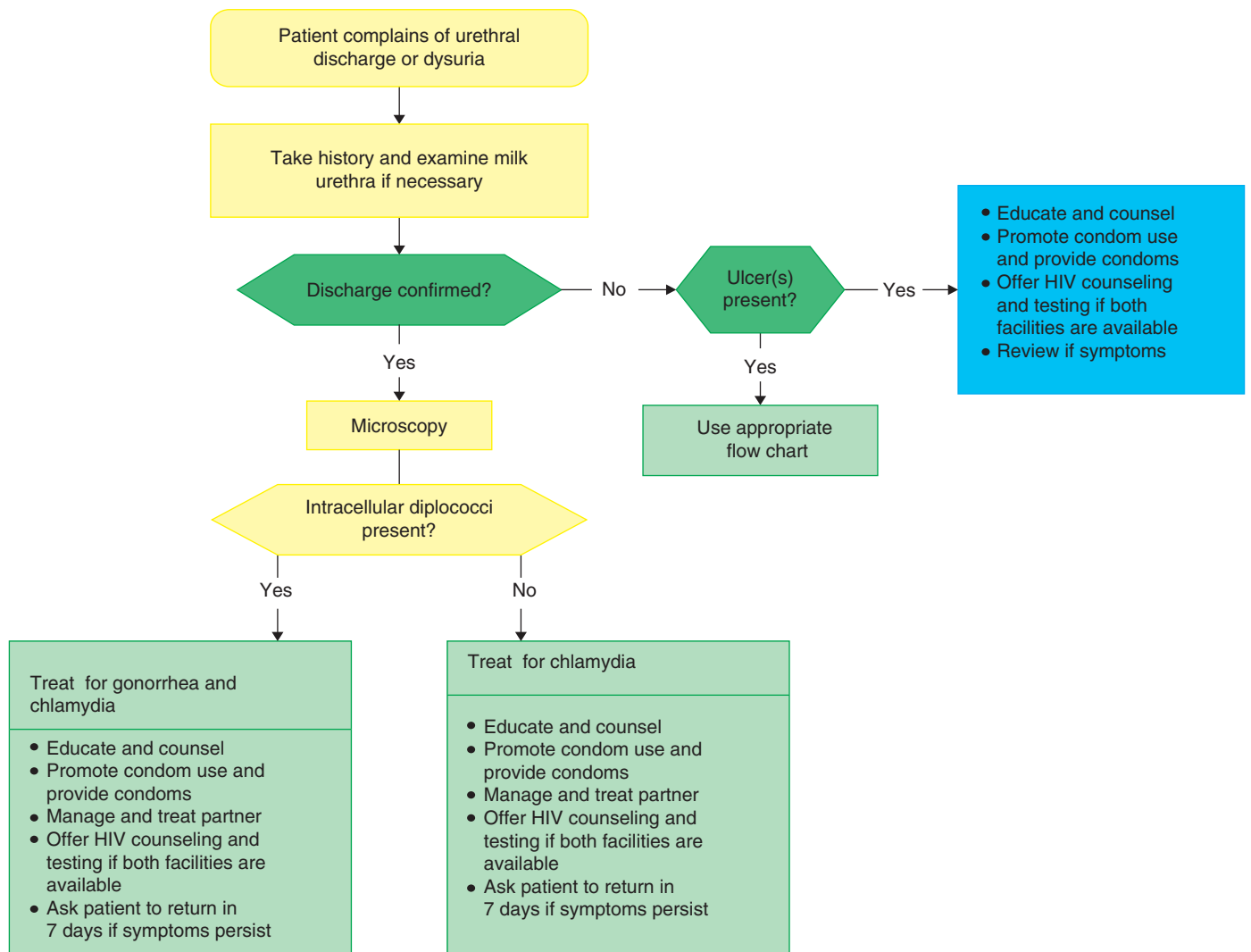


FIGURE 104-1. Flowchart for urethral discharge with microscope.

discharge for the detection of gonococcus is above 90% compared to culture, the use of a microscope in this case avoids unnecessary treatment for gonorrhea in patients who are not infected.

Evaluations of the WHO flowcharts have shown that the algorithm for vaginal discharge lacks both sensitivity and specificity for the identification of women with *Chlamydia trachomatis* and *N. gonorrhoeae* infection^{7,8} (Fig. 104-2 depicts flowchart for vaginal discharge with microscopy).⁶ The sensitivity of microscopy for the detection of gonococcus in vaginal discharge is much lower than that for urethral discharge and is therefore not recommended. Most women with this symptom do not have these cervical infections but suffer from vaginal infections (candidiasis, BV, or trichomoniasis). Vaginal infections can be diagnosed microscopically (by Gram stain or wet preparation), but this may not always be required since symptomatic candidiasis can usually be diagnosed clinically by speculum examination and presumptive treatment with

metronidazole for both BV and trichomoniasis is safe and inexpensive.

Unfortunately, it is not possible to diagnose gonorrhea or *C. trachomatis* infection in women at peripheral health services in most developing countries since facilities are not available for culture, antigen detection, or nucleic acid amplification tests. Gram stain of an endocervical swab can be used to diagnose gonorrhea, but this technique is at best only about 50% sensitive in specimens from women. In many cases, no infectious cause can be found for the symptom of vaginal discharge, even using the most sensitive diagnostic tests. In these cases, the symptom may be attributable to cultural or psychological factors.^{9,10} This leads to problems in both treatment and partner notification. The use of microscopy to exclude vaginal infections can avoid repeated unnecessary treatment in such cases and suggest more appropriate therapeutic interventions.

Whereas presumptive treatment for these infections may be given to women at risk, it is important in all cultures to

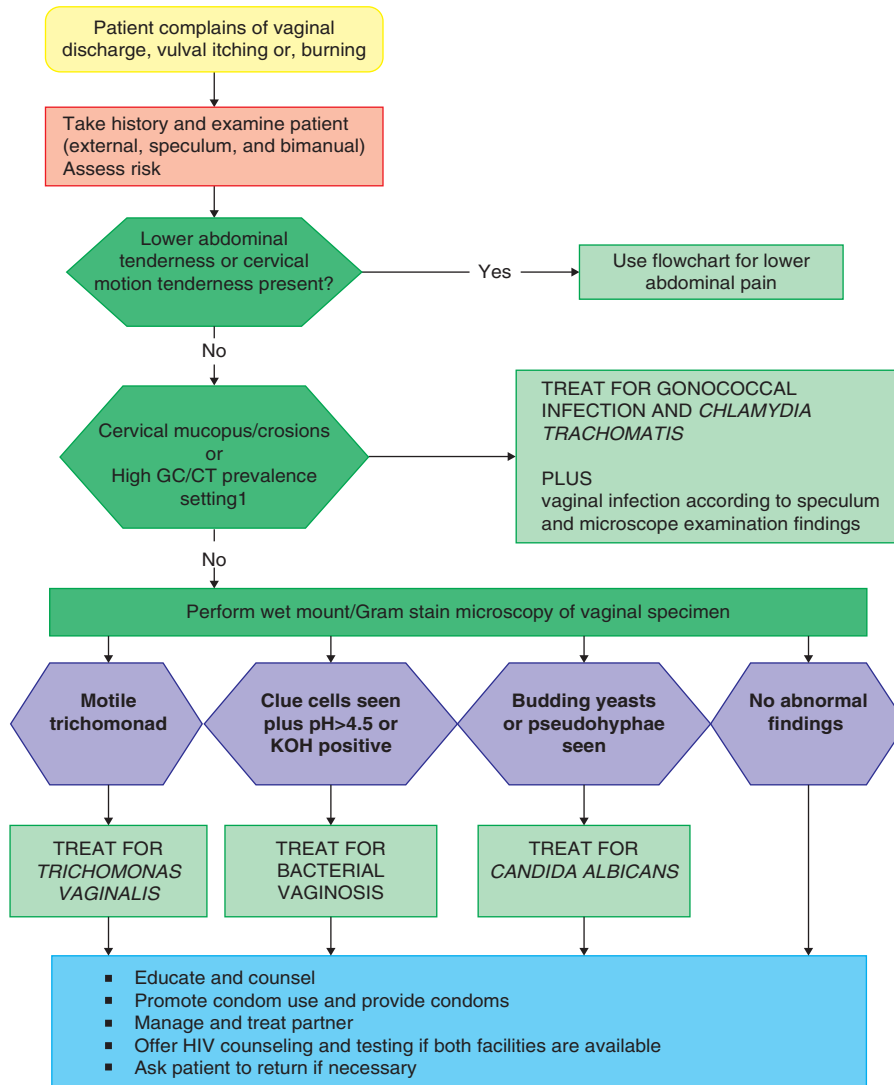


FIGURE 104-2. Flowchart for vaginal discharge with microscope.

avoid informing uninfected women that they should refer their partner for STI treatment. There is a great need for simple, cheap, point-of-care tests for these infections in women.^{11,12} These tests should meet the criteria developed by the WHO STD Diagnostics Initiative (SDI) which can be defined by the acronym “ASSURED” (www.who.int/std_diagnostics). They should be Affordable, Sensitive, Specific, User friendly, Robust and Rapid (results available in less than 30 minutes), Equipment-free, and Deliverable to those who need them.

■ ROLE OF THE LABORATORY IN CASE FINDING AND SCREENING

Case finding

Patients presenting to health facilities with one STI are at increased risk of other STIs, which may be asymptomatic. The laboratory has an important role in identifying such

infections in patients seeking STI care. In particular, all STI patients who will not be treated for syphilis through syndromic management should be screened for syphilis. This approach is known as *case finding*.

A range of STI diagnostic tests are available for use at different health-care levels. Most of these tests require a laboratory facility.^{13,14} At the peripheral level, patients may be screened with the RPR or VDRL tests for syphilis and treated if positive. At the district level, a positive RPR or VDRL test may be confirmed with a treponemal test such as the *Treponema pallidum* Hemagglutination Assay (TPHA) or *T. pallidum* Particle Agglutination Assay (TPPA) before treatment is given. Culture for gonorrhea and enzyme immunoassays (EIAs) for genital chlamydial infections may be available at district or tertiary level. Rapid tests for chlamydial and gonococcal infections are commercially available but they are costly and their sensitivity is too low to be recommended for use as tools for case finding or screening.^{15–17}

Screening

Screening for syphilis and HIV infection is generally offered to pregnant women attending antenatal clinics to prevent transmission of these infections to the fetus or neonate. Screening for other STIs is rarely offered, even to high-risk groups, although screening programs for female sex workers have been successfully implemented in some countries using a combination of clinical findings and simple laboratory tests.^{18,19}

Syphilis in pregnancy is a major cause of adverse pregnancy outcome in many developing countries.^{20–23} A recent study in Tanzania found that it was responsible for some 50% of all stillbirths.²⁴ In most countries the RPR is used to screen pregnant women. Women who test positive at peripheral clinics are treated without recourse to a confirmatory treponemal test. Given the importance of early treatment and the efficacy and safety of intramuscular benzathine penicillin, this is a sound strategy, even though it may lead to unnecessary treatment in some cases. Screening and treatment of pregnant women for syphilis remains cost-effective even when the prevalence is low. In Tanzania, where the prevalence of syphilis in pregnant women was found to be approximately 8%, it is among the most cost-effective health interventions available, at less than US \$11 per disability-adjusted life year (DALY) saved.²⁵

In almost all countries it is official health policy to offer screening for syphilis to all pregnant women. The reality is, unfortunately, rather different. It has been estimated that less than 30% of pregnant women are screened for syphilis in sub-Saharan Africa.^{20,26,27} A study in Bolivia showed that although 76% of the study population received antenatal care, only 17% were screened for syphilis during pregnancy.²³ There are many reasons for the low rates of antenatal screening for syphilis, of which a major barrier is that current screening using a nontreponemal test requires a laboratory with

1. trained personnel;
2. refrigeration for storage of reagents;
3. electricity to run equipment: refrigerator, centrifuge to separate serum from whole blood and a shaker to perform the serology.

Since such facilities are generally not available in remote areas, blood or serum samples have to be transported to regional or central facilities for testing. Results are therefore often available only days or weeks after testing. Studies showed that even when this simple policy was followed, only a small proportion of infected women received treatment when RPR testing was performed off site, since many did not return for their results or specimens or results are lost in transit.²⁸ The delay in obtaining test results not only results in delay in treatment for the patients but also continues transmission of infection until they and their partners are treated. A series of demonstration projects showed that decentralization

of syphilis screening followed by immediate treatment can be effective in reducing perinatal mortality.^{29–33}

However, in rural areas, there are technical difficulties associated with performing serological tests at primary health care settings. In particular, maintaining trained personnel and assuring quality standards and supplies of tests and treatment are problematic in many settings.^{34,35} Where laboratory services are not available, the new, simple, point-of-care treponemal tests provide an important opportunity to improve coverage. Recent evaluations have shown that a number of simple, point-of-care tests for syphilis in a dipstick or cassette format, have sensitivities of 85–99% and specificities of 93–100% compared to laboratory-based treponemal tests.^{36–40} The advantage of these tests is that, unlike RPR or VDRL, they can be stored at room temperature in any health facility including mobile clinics, do not require any equipment, and can use whole blood obtained by finger pricks. Field trials showed that they are useful at district or peripheral level.⁴⁰ As treponemal antibodies persist for years, treponemal tests cannot be used to distinguish between recent active infection and past treated infection. But given the serious consequences of failure to detect and treat infected pregnant women and the rarity of adverse drug effects, the benefits of a rapid test that is simple to perform and enable immediate treatment clearly outweigh the risks of overtreatment. Their greatest value is likely to be in increasing the coverage of syphilis screening in rural areas of developing countries where access to laboratory services is a problem and in increasing the proportion of cases treated when return rates are low. More information on the performance and operational characteristics of these rapid tests can be found on the SDI website: www.who.int/std_diagnostics.

The role of the tertiary and district level laboratories is critical in assuring the proficiency of the health workers performing the testing and the quality of the rapid tests being stored in conditions where test quality can be compromised by long-term storage in conditions of high heat and humidity.

For large scale screening, enzyme immunoassays have been shown to be highly sensitive and specific compared to standard treponemal tests and are useful for detecting all stages of syphilis.⁴¹ These assays are relatively simple to perform in district or tertiary facilities and have the advantage of automation and high throughput. They are therefore suitable for case-finding and screening.

■ INTEGRATION OF STI AND HIV LABORATORY SERVICES

STIs have been shown to play a role in increasing the risk of HIV transmission.^{42–44} In developing countries, the prevalence of HIV is high in STI clinics. Hence opportunities for integration of STI and HIV screening at all levels of health care must not be missed.^{45–47} This approach gives at-risk

populations a single point of access to information and services. For program managers, integrated services are more cost-effective than if the training and quality assurance of testing were provided independently. In particular, rapid syphilis screening can be integrated into rapid HIV testing for prevention of mother-to-child transmission (PMTCT) programs to avoid the tragedy of babies avoiding HIV but dying of syphilis,⁴⁷ as was observed in one clinic in Haiti. A mother sought prenatal care at the clinic, accepted HIV voluntary counseling and testing and, after testing HIV-positive, took short course antiretroviral therapy for PMTCT. Postpartum, she gave her baby antiretroviral therapy and provided artificial milk to protect against HIV transmission through breast-feeding. The baby died at 3 weeks from congenital syphilis.

THE ROLE OF THE LABORATORY IN THE DIAGNOSIS AND MANAGEMENT OF HIV INFECTION

Laboratory tests are needed for the diagnosis of HIV infection to determine the need for antiretroviral treatment, to monitor the response to treatment, and to diagnose OIs in HIV-infected patients. When testing is done outside of laboratory settings, the laboratory plays an essential role in providing quality assurance.^{48–51}

■ DIAGNOSIS OF HIV INFECTION

The capacity for HIV serological diagnosis is required at all levels: for laboratory confirmation of suspected HIV-related illness, for screening antenatal clinic attenders to prevent mother-to-child transmission, for voluntary counseling and testing, and for screening of blood for transfusion. HIV screening should also be offered to STD patients and to all clinic and hospital attenders in high HIV prevalence settings (http://data.unaids.org/una-doc/hivtestingpolicy_en.pdf). Because of the serious consequences of an incorrect HIV result, attention to methodological detail is extremely important.

When the number of specimens is small and the staff available are not highly trained, rapid tests are the most attractive option, which makes them suitable at the peripheral level. These tests can use whole blood and are simple to use but they are relatively expensive. Regular supervision is especially important for relatively untrained staff working in health centers. Rapid tests and EIAs are appropriate at district and referral hospital levels where larger numbers of specimens are tested⁴⁸ (www.who.int/hiv/amds/diagnostics). Western blot, if used at all, should be done at reference laboratories.

When routinely offering HIV testing, in the voluntary counseling and testing (VCT) setting, in screening pregnant women to prevent vertical transmission (PMTCT programs), or where HIV infection is suspected clinically, a confirmatory test

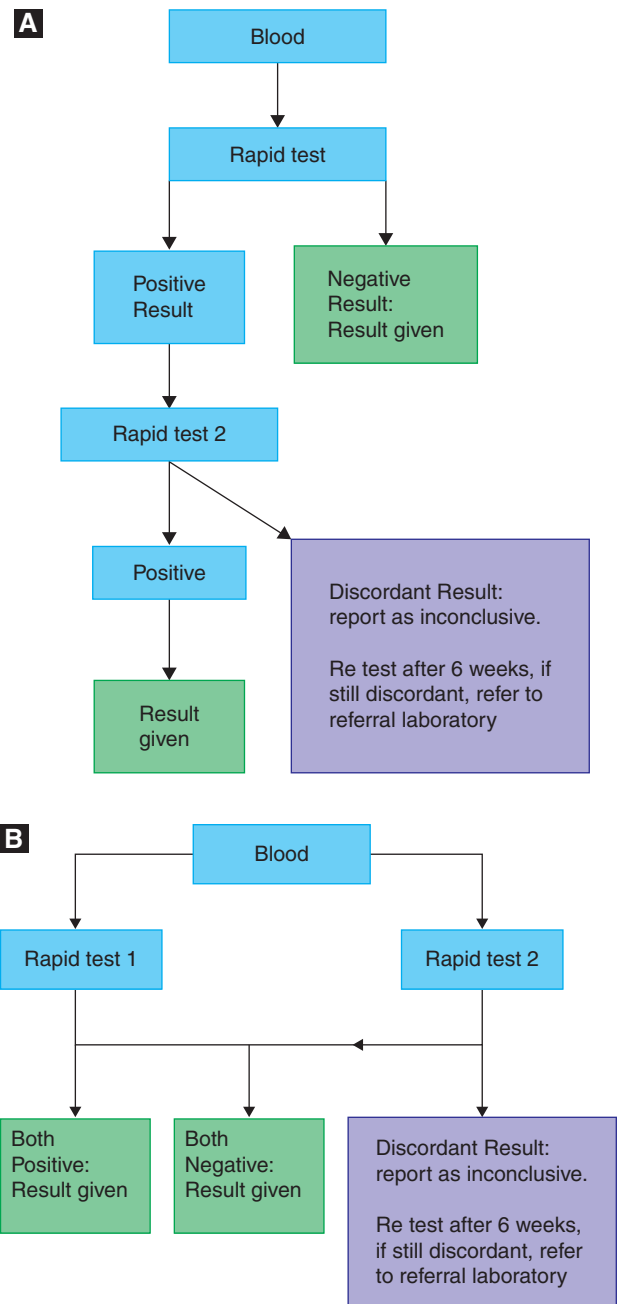


FIGURE 104-3 Schema for parallel versus serial testing for HIV. **A.** Serial testing. **B.** Parallel testing.

should be performed on all positive samples before a patient is informed of his/her result. WHO and CDC have proposed algorithms for parallel testing and sequential testing using two different tests^{49–50} (Fig. 104-3). Parallel testing, in which all samples are tested with two assays, is more expensive than sequential testing. Evaluation of different algorithms for testing and confirmation have been studied for a variety of settings.^{52–55}

In screening blood for transfusion, a single highly sensitive serological test may be used, if possible after excluding high-risk donors who may be in the “window period” associated with HIV seroconversion. Blood testing positive is discarded and,

unless the donor requests the result, a confirmatory test is not generally required.

■ THE ROLE OF THE LABORATORY IN HIV TESTING

Diagnosis of HIV infection in people aged >18 months

A positive HIV antibody test (by either a rapid test or EIA) of high sensitivity should be confirmed by a second antibody test (rapid test or EIA) using an antibody test of different operating characteristics with good sensitivity and high specificity.^{49–50}

Given the potential for false-positive results in low prevalence populations, in populations with an expected prevalence below 5%, a third HIV-positive antibody test to confirm positive cases from two tests is recommended for clinical purposes.^{49–51,56}

The performance of serological tests for HIV infection has been evaluated by WHO using panels of positive and negative sera from different regions of the world. Performance may vary in different populations. Ideally, before being introduced, a new test should be evaluated against a reliable gold standard in the population in which it is to be used. Further technical information on HIV testing by WHO can be found at: www.who.int/hiv/amds/diagnostics.

Diagnosis of HIV infection in children aged <18 months

HIV infection cannot be diagnosed in this age group by the detection of antibodies to HIV since maternal antibodies may be detected even in uninfected babies. Positive reactions for HIV nucleic acid (RNA or DNA) are required, or enhanced HIV p24 antigen in blood on two separate determinations, from specimen(s) taken more than 4 weeks after birth. Where the infant has had antiretroviral prophylaxis HIV RNA nucleic acid testing is not reliable until 4 weeks after cessation of the antiretroviral therapy (ART) used for prophylaxis. Ideally, two separate specimens are required.

The World Health Organization (WHO), as part of efforts to scale up ART treatment for children with HIV/AIDS, particularly in resource-limited settings, has developed simplified standardized recommendations for diagnosis and treatment of HIV that can be used by countries for adaptation and to support development of national treatment recommendations,⁵⁷ www.who.int/hiv.

■ ROLE OF THE LABORATORY IN DETERMINING THE NEED FOR ANTIRETROVIRAL TREATMENT

The need for ART in HIV-infected patients may be determined by clinical stage or by CD4 cell count. The WHO clinical staging system for HIV disease is given in another chapter in this book. The laboratory may play a role in diagnosing stage-defining OIs, including the following: pul-

monary or nonpulmonary TB, *pneumocystis carinii* pneumonia (PCP), cryptococcosis, cryptosporidiosis, isosporiasis, disseminated mycosis, pneumococcal bacteremia, recurrent nontyphoid *Salmonella* septicaemia, and visceral leishmaniasis.

The CD4⁺ lymphocyte count is an important determinant of the need for antiretroviral treatment in HIV-positive individuals. WHO defines advanced HIV infection according to the following laboratory criteria:

- In an adult: CD4 count less than 350/mm³.
- In a child: CD4% <35% in those less than 12 months, <25% in those 12–59 months, and <20% in those 5 years or over (subject to review by technical working group).

WHO laboratory criteria for the diagnosis of AIDS are

- in an adult or adolescent >15 years: CD4 count less than 200/mm³ or CD4% <15%
- in a child: CD4% <25% in those less than 12 months of age; CD4% <20% in those 12–59 months; CD4% <15% or <200/mm³ in those 5 years or over

Performing a CD4 count is currently technically demanding, although the promise of CD4 counts at district level hospitals may soon be a reality as there has been substantial funding for development and optimization of point-of-care tests for CD4 count.^{58–70} Quality control and maintenance of equipment will be important challenges in this setting. The total lymphocyte count has been suggested as a surrogate marker for CD4 cell count, but a recent systematic review found that the correlation between the two was poor, with correlation coefficients varying between 0.23 and 0.74.^{71–72}

■ ROLE OF THE LABORATORY IN MONITORING THE RESPONSE TO ART

ART is likely to fail if adherence to treatment is <95% or if the infecting strain is resistant to one or more of the drugs used. This is best monitored by changes in viral load, which should fall to undetectable levels in those on effective treatment.⁷³ However, viral load measurement is unlikely to be available outside reference centers (see [Table 104-3](#)). CD4 cell counts should rise as the immune system is reconstituted in those taking effective treatment, though this may not be the case in those with very low CD4 levels at the start of treatment. The WHO has established a network for monitoring ART resistance in those who fail treatment, HIV *ResNet*.⁷⁴

THE ROLE OF THE LABORATORY IN THE MANAGEMENT OF OPPORTUNISTIC INFECTIONS in HIV-POSITIVE PATIENTS

In developing countries laboratory facilities are usually limited, such that the scarce resources that are available need to be used to maximum effect. A general problem at all levels with

most microbiology services, including what should be simple microscopy, is a serious lack of trained staff.^{2,3} Also, microbiology does require a good supply of quality assured media and reagents, of which there are usually many to consider, and which may be costly.

In many situations, microbiology is not going to affect patient management. Firstly, any microbiological investigation other than microscopy usually takes more than a day to produce a result, by which time the patient might have recovered, died, or simply become untraceable. Secondly, a specific diagnosis might not affect clinical care if there is no treatment available or if the treatment given on clinical grounds is unaffected by the microbiological diagnosis. Microbiological investigation therefore needs to be targeted to situations where a specific diagnosis will lead to effective treatment, or where a diagnosis of an untreatable condition will prevent further fruitless investigation.

A critical factor in a health system is the need for a reference laboratory. In addition to the clinical care aspects required, in a tertiary level hospital, these facilities would form the basis of surveillance systems. Thus, it would be expected that they would intermittently be responsible for performing

assessments of blood stream infections (BSIs), identifying common etiologies such as identifying causes of community acquired pneumonia, of diarrhea, and of fevers. This information would be used to provide advice and to modify and support syndromic approaches at more peripheral levels.

There are two main approaches to the management of OIs in HIV-infected individuals in developing countries. These are based on either etiological diagnosis of specific conditions or on investigations of particular syndromes. These two approaches are described in more detail below.

THE ROLE OF THE LABORATORY IN CLINICAL MANAGEMENT OF CASES

The major OIs that need to be identified are tuberculosis, causes of chronic diarrhea, bacteremia caused by *Salmonella* spp. or *Streptococcus pneumoniae*, and cryptococcal disease. In some regions (e.g., Sudan, Kenya and part of the Middle East, and the Indian subcontinent), visceral leishmaniasis should be considered. In Southeast Asia, disseminated penicilliosis is common in advanced HIV infection. In South America, case reports suggest that disseminated

Table 104-3. WHO Recommendations for Laboratory Capacity for ART Monitoring in Resource-Limited Settings

Tests	Health center	District Hospital	Reference Center
HIV			
–rapid tests	+	+	+
–ELISA		+	+
–confirmatory tests		+	+
–viral load			+
Blood chemistries:			
–CD4		+	+
–total lymphocyte		+	+
–CBC differential		(+)	+
–serum chemistries			+
–electrolytes			+
–renal function			+
–liver enzymes			+
–lipids			+
Pregnancy tests	+	+	+

Trypanosoma cruzi infection occurs in advanced HIV infection.

At the peripheral level, microscopy of direct Ziehl-Neelsen (ZN) stained sputum smears might be feasible, though this may not be possible in all health centers. The ZN smear remains the quickest way to detect acid-fast bacilli (AFB); it may be possible to produce a result while the patient waits. The sensitivity of direct sputum microscopy for AFB is known to be low and variable.⁷⁵

At district level, microscopy for sputum and CSF should be available, with the ability to perform Gram, ZN, and Indian ink stains. If a centrifuge is available, the sensitivity of the microscopy techniques can be improved by concentration. Stool microscopy should be feasible and can identify treatable causes of chronic diarrhea such as *Giardia* or *Strongyloides*, which are not considered OIs, and *Cryptosporidium* and *Isospora*, which are. Diagnosis of *Cryptosporidium* or *Isospora* infection defines stage 4 disease, which may have implications for eligibility for ART. Concentrated preparations of stool and staining for *Cryptosporidium* spp. improves the clinical value of stool microscopy but involves the use of formaldehyde and ether. *Cryptococcus neoformans* can be quite easily demonstrated in cerebral spinal fluid (CSF) by direct microscopy with India ink. Cryptococcal antigen testing of CSF or serum may also be valuable at this level.

If culture facilities are available, this should focus on

- blood cultures, to differentiate sepsis due to *Salmonella* spp. and *S. pneumoniae*. This is often impossible clinically, and in regions of high HIV prevalence blind treatment may be unsuccessful or lead to a rapid rise in antimicrobial resistance.
- cultures of pleural effusions, joint fluids, and pericardial fluids. In these cases, other diagnostic tests are often not able to differentiate between TB and bacterial infection.

At the “reference” or tertiary level, it should be possible to culture bacteria (including *Mycobacterium tuberculosis*) and to perform antimicrobial sensitivity testing on a range of clinical specimens—sputum, CSF, blood, pleural fluids, and genital discharge. Mycobacterial susceptibility testing is likely to be highly centralized in a national center.

■ APPROACHES TO SYNDROMIC MANAGEMENT AND TREATMENT REGIMENS

Investigation of HIV infected patients needs to focus on the major clinical syndromes:

- fever and cough
- fever and headache
- fever with no focus
- diarrhea

It is particularly in these cases that a specific diagnosis will aid clinical management. The three major causes of fever with cough are bacterial (usually pneumococcal) pneumonia, pneumocystis pneumonia, and tuberculosis. Since treatment is different for each, it is important to make an etiological diagnosis. In patients with fever and headache, it is important to exclude meningitis, especially cryptococcal meningitis in immunocompromised patients. In all cases of fever in endemic areas, it is necessary to exclude malaria, which may be more severe in advanced HIV disease.

In patients with fever without an obvious focus, once malaria has been excluded, blood cultures should be taken to identify bacteremia. Ten to twenty percent of febrile admissions are likely to have a BSI. If it is not possible to do blood cultures on all patients, it is nevertheless important to conduct intermittent surveillance of BSI, which can be used to develop clinical algorithms. TB is also high on the list of differential diagnoses. In endemic areas, Giemsa's stain of a buffy coat smear may be used to diagnose visceral leishmaniasis.

The reference laboratory also has important roles to play in response to specific surveillance requests, e.g., identifying causes of community acquired pneumonia, or causes of diarrhea, and in supporting quality assurance for tests performed in health centers and district hospitals. The cause of chronic diarrhea can usually be identified by stool microscopy, especially if concentration techniques are used and a modified ZN stain is used to identify *Cryptosporidium*.

The availability of diagnostic tests to investigate these syndromes is shown in the [Table 104-4](#).

FUTURE OUTLOOK

To increase access to diagnosis and screening for STIs including HIV, ASSURED tests that can be performed outside of laboratory settings have been developed. At present, a number of tests for syphilis and HIV fulfill these criteria and they are available to UN member states from the WHO Bulk Procurement Scheme at negotiated pricing. Improved tests for the diagnosis for genital chlamydial and gonococcal infections will soon be available for evaluation. Investments in development of such tests for monitoring the efficacy of ARTs will soon result in a variety of CD4 tests that can be used at district levels. An important role of the laboratory is in the support of quality control of rapid tests that are being stored and deployed at peripheral sites, often at temperatures above the 30 °C limit specified by the manufacturers. Supervisors of laboratories at district levels need to ensure the proficiency of health care workers in performing these tests at peripheral levels.^{76,77}

The HIV epidemic has imposed an enormous strain on the already fragile health care infrastructure in many developing countries. The contribution of donor agencies to HIV care and treatment has not been accompanied by sufficient capacity building in countries. This is especially true of laboratory capacity strengthening, as it takes time to build up a workforce with advanced skills to provide timely quality-assured laboratory services. In countries already suffering from severe constraints in their health systems, this scarcity of trained staff is compounded by large numbers of vertical programs and the conflicting agenda of various donor agencies and migration of trained workers for better salaries and benefits.

In many countries there are separate programs for HIV and STI control and prevention even though it has been shown that the two are interrelated in that HIV-infected individuals have a high viral load when they acquire an STI. Testing and treatment are provided at different venues by duplicate sets of staff, adding to the problems of strained human and other resources. The integration of laboratory services for STI, HIV, TB, and OIs at all levels would be an important step forward.

However, in many countries a limited primary health care system has meant poor access to health services for many. In a country already suffering from severe constraints in its health system, the poor integration of programs focused on single diseases within the broader health system further hinders health care delivery at local levels.

An estimated 720,000 infants are born HIV-positive every year. In sub-Saharan Africa, only 30% of pregnant women are screened for syphilis even though the disease is responsible for more than 30% of perinatal deaths. An estimated 492,000 cases of congenital syphilis occur annually in Africa.²⁰ Observations in many affected countries indicate that the epidemiology and transmission of HIV and syphilis are closely linked and that screening for both infections would lead to better health outcomes. Yet in many parts of the developing world, PMTCT programs do not routinely include syphilis screening. This is a tragedy as congenital syphilis is preventable if infected mothers are identified and treated by the middle of the second trimester of their pregnancy. The tragedy is even more regrettable given that economical,

Table 104-4. The Role of the Laboratory in the Management of Opportunistic Infections in HIV Positive Patients

Syndrome	Pathogen	Peripheral	District	Tertiary
Fever with no focus	Malaria	Rapid test; blood film	Rapid test;	Rapid test;
	Bacteremia	–	Blood film Blood culture	Blood film Blood culture Antimicrobial susceptibility
Fever + cough	Tuberculosis	Sputum microscopy	Sputum microscopy;	Sputum microscopy;
	PCP	–	TB culture (may be available)	TB culture;
	Pneumococcal pneumonia	Sputum microscopy	– Blood culture	Antimicrobial susceptibility Silver stain of BAL or induced sputum Blood culture Antimicrobial susceptibility
Chronic diarrhea	Cryptosporidiosis	Microscopy	Microscopy	Microscopy
	Isosporiasis			
	Microsporidiosis			
	Giardiasis			
	Strongyloidiasis			
Fever + headache	Cryptococcosis	–	Serology (CRAG)	Serology
	Tuberculosis	–	Microscopy of CSF	(CRAG)
	Bacteremia	–	Microscopy and culture of CSF	Microscopy and culture of CSF Microscopy and culture of CSF

simple rapid diagnostic tests and effective treatment for syphilis are available. The story of effective interventions not reaching those in need, heard many times in the developing world, repeats itself.

Increasingly governments are encouraged, in collaboration with nongovernmental organizations, to provide comprehensive care in the scale-up of HIV treatment programs to include tuberculosis and reproductive health and sexually transmitted diseases services in order to avoid the tragedy of babies being saved from HIV but dying of syphilis.

Clearly, future efforts must be focused on using rapid tests to increase access to diagnosis of STI, HIV, and OIs and on effective laboratory systems to provide accurate surveillance information and to monitor the impact of interventions. For each country, such efforts must be informed by more research to determine the feasibility and sustainability of using appropriate tools at different levels of the health care system.

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PART 16

Special Medical, Legal, and Social Issues

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The FBI reports that while all other violent crime is decreasing in the United States, the number of forcible rapes is increasing.¹ The prevalence of sexual assault depends on how it is defined. In the United States, the Federal Bureau of Investigation Uniform Crime Reporting Program defines rape as “carnal knowledge” (vaginal coitus) of a female forcibly and against her will. Anal or oral assault and sexual assault of males are not included in the FBI statistics. In 2004, the FBI reported 94,635 arrests for rape (32.3/100,000 population).¹ The National Institute of Justice’s National Violence Against Women Survey used a different definition. Rape was defined as forced vaginal, oral, or anal sex experienced by men or women. This survey, done between November 1995 and May 1996, found that in the United States, 18% of women and 3% of men had experienced rape in their lifetime. In the prior 12 months, 0.3% (203,100) of women and 0.1% (92,700) of men experienced a completed or attempted rape.²

Homosexual men may be at increased risk for sexual assault. In one large study, 257 of 930 (27%) gay men reported a history of nonconsensual sex, although only 80 (8.6%) reported assault at age 21 or older.³

Sexually transmitted diseases (STDs) are among the most common medical problems complicating sexual assault. STDs diagnosed at the time of a sexual assault can add to the emotional problems experienced by victims, whether or not the disease was acquired as a result of the assault. In addition, victims often express severe anxiety about the possibility of contracting an STD from the assailant. This anxiety can accentuate the emotional trauma they experience, aggravate any posttraumatic stress, and delay their recovery. The possibility of HIV transmission during the sexual assault has further added to the panic and stress related to sexual victimization.⁴

CHARACTERISTICS OF VICTIMS

Factors that increase the risk of rape include major psychiatric diagnoses, homelessness, alcohol or drugs use, and

physical disability.^{5,6} In adolescents, a history of either initiating intercourse or having an STD at an early age is correlated with experiencing a subsequent rape.⁷ One study of women reporting a history of rape showed them to be much more likely to have multiple sexual partners than women not reporting rape.⁸

Many victims of sexual assault neither obtain medical care nor report the event to police agencies. The proportion of “nonreporters” is estimated as 25–46%.^{9,10} Victims who are assaulted by strangers are more likely to report than those assaulted by an intimate partner or other person known to them.⁹ Men may be more reluctant to report sexual assault than women.¹¹

Victims’ ages range from adolescence to old age but most victims are younger. In one large emergency department study, one-fourth of victims seeking medical care were younger than 18 years, with a median age of 23 years.¹² In females, the greatest percentage of rapes occurs between ages 11 and 17.¹³

Female victims of domestic violence are at increased risk for sexual assault. McFarlane, et al. studied 148 women seeking protection orders from courts because of domestic violence. Sixty-eight percent of the women also reported being sexually assaulted by their domestic partner.¹⁴

One of the factors complicating the care of rape victims is the poor rate of compliance with follow-up care.¹⁵ In one study where follow-up care was aggressively promoted, only 31% of victims returned for further care.¹⁶ This increases the importance of prophylactic treatment at the initial visit because a follow-up visit for diagnosis of STD acquired at the time of the rape is not likely to occur.

One of the major risk factors for being sexually assaulted in adulthood is experiencing sexual abuse as a child or young teen.¹⁷ Sexual abuse in childhood puts men and women at risk for depression, low self-esteem, early initiation of sexual behavior, drug and alcohol abuse, and other social ills.¹⁸ These risk factors lead to a decrease in self-protective behaviors (such as condom use) and an increase in risky behaviors such as having multiple sexual partners and trading sex for drugs.¹⁹ After sexual assault in adulthood, victims of childhood

sexual abuse are at increased risk for revictimization as well as STD and high-risk sexual behavior.^{7,20,21} The end result is a spiral of risk originating in childhood trauma, leading to a high-risk lifestyle leading to further sexual assault and higher STD risk. This points out the importance of preventing childhood victimization in controlling HIV infection and STDs.^{22,23}

CHARACTERISTICS OF ASSAILANTS

Assailants are more likely to be someone known to the victim. In one study, 78% of victims reported assault by a friend, relative, or acquaintance.²⁴

Most rapes involve only one assailant. In about 20% of cases, multiple assailants are involved. Rapes of males are more likely to involve multiple assailants than female rapes.¹²

In 1997, the U.S. Bureau of Justice Statistics produced a comprehensive report on convicted sex offenders.²⁵ On any one day, 234,000 sex offenders are under the care, custody, or control of corrections officers in the United States. About 60% are under supervision in their communities and 40% are incarcerated. Sex offenders account for about 5% of the prison population. Ninety nine percent of convicted rapists are male and 16% are juveniles. When considering all types of sexual offenders (including people committing rape, child molestation, and all other types of sex offenses), 3.8% are female. Among males serving prison time for rape, 64% have a record of a previous conviction for sexual assault. Sex offenders are less likely to be married at the time of their incarceration than other violent offenders. Rapists have other lifestyle risk factors that may increase the likelihood of infection with an STD, including drug use, multiple sexual partners, and history of incarceration.²⁶

CHARACTERISTICS OF SEXUAL ASSAULTS

Vaginal assault is the most common type reported by female victims (83%). 25% of females and 43% of males report oral assault. 15% of females and 67% of males report anal assault. One-third of victims report digital penetration, and 3% report assault with an object.¹² Using visual inspection, genital trauma is seen in 53% of female victims. Genital or anal trauma is seen in 36% of male victims.¹² Use of the colposcope to provide magnification increases the percentage of victims noted to have trauma. With colposcopy, 68–87% of vaginally assaulted females show genital trauma and 56% of anally assaulted females show anal trauma.^{27,28} Compared to females, a higher proportion of male assault victims will show nongenital trauma.¹⁵

Rapes of men and women incarcerated in prisons are unfortunately common.²⁹ Since prison inmates have an increased incidence of STD and HIV infection, victims of

prison rape most likely are at higher risk of infection.³⁰ Prison rapes are rarely reported and until recently, many states have not collected data on the prevalence of rape in their prisons. In 2003, a law was passed in the United States requiring the Bureau of Justice Statistics to collect statistical data on prison rapes. The law also requires yearly public hearings about prisons with the highest and lowest rates of sexual assaults.³¹

The number of victims being given prophylactic antimicrobials varies depending on where they are treated. Some emergency departments report treating as many as 88% of victims.¹² Overall, data from the National Hospital Ambulatory Care Survey from 1992 to 1998 showed that only 49% of U.S. adult sexual assault victims received at least one medication for STD.³²

CHARACTERISTICS OF THE VICTIM, THE ASSAILANT, AND THE ASSAULT AFFECT THE DIAGNOSIS AND TREATMENT OF STD

Many factors complicate the diagnosis and treatment of STD after sexual assault, including the following:

1. Victims often do not know the STD/HIV status of the assailant, making the calculation of risk of STD/HIV difficult in any particular case.
2. High-risk behaviors leading to sexual assault can also put the victims at risk for STD.
3. Genital and anal injuries (including microtrauma) can increase the victims' likelihood of STD/HIV infection.
4. Many victims are reluctant to come forward for treatment because of shame or fear of reprisals.
5. Medical follow-up is difficult because of the victims' reluctance to return for care.
6. Sex offenders often have been previously incarcerated, increasing their risk for STD/HIV. One study showed a high rate of hepatitis B and C infections in incarcerated sex offenders.³³
7. An STD identified at the initial visit after sexual assault could be preexisting rather than a result of the assault.^{34,35} However, with some organisms, such as herpes simplex virus, hepatitis B virus, or HIV, highly specific serologic tests exist to detect seroconversion in the victim which may indicate whether or not infection was recently acquired.
8. Multiple assailants may increase the risk of STD following rape.
9. The presence of a coexisting STD such as syphilis can increase the risk of HIV.
10. Whether or not the assailant ejaculates can affect the occurrence of STD following rape. However, victims' history of whether or not ejaculation occurred can be

inaccurate. In one study, sperm were found in the vaginal cavity of 44% of rape victims reporting that the assailant did not ejaculate.³⁶

11. Studies of sex offenders and reports by victims indicate that during the process of offending, rapists often experience sexual dysfunction, erectile insufficiency, and failure to ejaculate. This could decrease the likelihood of transmitting an STD to the victim.^{37,38}

RISK OF ACQUIRING STD FROM SEXUAL ASSAULT

Most sexual assault victims are seen after a single episode of sexual contact. Little is known about the infectivity of most STDs after a single episode of intercourse, although the relative infectivity of some organisms has been determined. Among regular partners of male patients with gonorrhea and *Chlamydia trachomatis* infection, studies employing culture diagnosis found rates of 80% and 45%, respectively.³⁹ The risk of transmission of *Neisseria gonorrhoeae* from an infected female prostitute in a single sexual exposure has been estimated to be 22–25%.⁴⁰ Although equivalent data from a single male to female exposure are not available, the risk would be expected to be at least that high.^{40,41} Up to 20–27% of monogamous partners of patients with hepatitis B infection are found to be infected.^{42,43} The risk of infection after a single exposure is probably less but is likely to vary with factors such as bleeding during the exposure and presence of hepatitis B antigen in the infected partner. Similarly, 30% of sexual partners of patients with syphilis are found to be infected, but again, the risk of infection after a single exposure, doubtless, varies by stage of syphilis and aspects of the encounter.⁴⁴ Risk of transmission of HIV after a single sexual encounter is discussed below (see “HIV and Postexposure Prophylaxis”).

STUDIES OF SPECIFIC DISEASES AFTER SEXUAL ASSAULT

Studies on STD after rape are difficult to interpret. Many factors differ in these studies including age of the subjects, length of time between the assault and the testing for STD, setting of the testing (STD clinic versus emergency department versus other clinic), sex of the victims included in the study, and types of tests used to diagnose STD. Most studies were done retrospectively; i.e., charts of rape victims were reviewed after discharge. Most studies involved many different practitioners obtaining and processing the specimens. And finally, studies have been reported from many different cities and countries, where the underlying rates of STD in the population differ.

For these reasons, it is difficult to determine the true incidence of STD resulting from rape. Table 105-1 gives the rates of STD diagnosed after rape in adult victims in studies published since 1990.

STDs AS EVIDENCE IN SEXUAL ASSAULT CASES

STDs are often factors in sexual assault cases tried in courts of law in the United States. They have been recognized by criminal courts as proof that sexual contact has occurred, especially where the victim is a child or young adolescent.^{45,46} STD as evidence of sexual assault has been upheld when both the defendant and the victim were infected with the same disease.^{47–50}

When an STD is found in the victim and is thought to be the result of sexual contact with the accused, positive cultures or blood tests for antibodies from the defendant can be helpful as corroborative evidence. The collection of those specimens, however, must be done without violating the defendant's rights. Under the modern Federal rules of evidence for criminal proceedings, cultures, blood tests, and physical examinations for STD can be done on the defendant after court hearings are held before a judge to determine “probable cause” that evidence will be recovered. The defendant's fourth amendment rights to protection from unreasonable search and seizure must be respected.⁵¹

The interpretation of STD evidence requires a thorough knowledge of the epidemiology, natural course of infection, infectivity, and response to treatment of the STD in question. For example, if a victim is found to be infected with an STD at the time of a sexual assault, the accused may not become infected after a single act of intercourse. Negative cultures obtained from the defendant will not necessarily prove he did not commit the crime.

If positive diagnostic studies are obtained from both the victim and the assailant, matching the organisms for various biologic properties could theoretically be useful in linking the assailant to the crime. Matching of victim and assailant strains by serologic typing has been reported.⁴⁵ In epidemiologic studies, tests are used to establish the relatedness of strains of *C. trachomatis* and *N. gonorrhoeae* among sexual partners.^{52,53} An HIV strain suspected of being transmitted from a dentist to his patients was identified forensically using molecular techniques.^{54,55} Such matching can be used if the characteristics studied are stable from generation to generation in *in vivo* and *in vitro* systems. In one sexual assault case, HIV gene sequencing using the pol and gag genes (instead of the env gene used in the dental case) was described. This sequence may be even more stable.⁵⁶

Potentially, these techniques could provide very specific matching of organisms to trace the path of transmittal

Table 105-1. Surveys of Sexually Assaulted Women and Men, Published 1990–2005

Author	City	Number of Participants	NG*	CT	TV	BV	CA	TP	HSV	HIV
Estreich 1990 ⁹⁵	London	124	15(12.1)	6(4.8)	15(12.1)	–	11(8.9)	–	2(1.6)	1(2.3)
Hillman 1990 ⁹⁶	Edinburgh	5	1(20.0)	0	–	–	1(20.0)	–	0	1(20.0)
Jenny 1990 ³⁴	Seattle	Initial 203 F/U 109	13(6.4) 3(4.0)	20(10.1) 1 (2)	30(14.7) 10(12)	70(34.3) 15(19)	– –	0 0	4(2.4) 0	1(0.8) 0
Lacey 1990 ⁹⁷	Manchester	90	10(4.8)	7(7.7)	6(6.6)	17(18.8)	2(2.2)	0	–	–
Sturm 1990 ⁹⁸	St. Paul	Initial 232 F/U 62	10(4.8) 0	13(6.1) 1(1.9)	–	–	–	–	–	–
Glaser 1991 ⁹⁹	Brooklyn	Initial 76 F/U 37–58	2(2.6) 0	13(17.1) 7(9.0)	15(19.7) 2(2.3)	29(38.2) 9(12.0)	– –	0 0	0 0	–
Ross 1991 ⁹⁹	Edinburgh	43	1(2.3)	2(4.7)	1(2.3)	1(2.3)	1(2.3)	–	1(2.3)	–
Davies 1992 ¹⁰⁰	Birmingham	110	2(1.8)	9(8.2)	6(5.5)	14(12.7)	2(1.8)	0	3(2.7)	–
Rambow 1992 ¹⁰¹	Portland	Initial 177 F/U 44–100	18(10.7) 1(1.1)	–	–	–	–	1(0.6) 1(3.6)	–	–
Peipert 1994 ¹⁰²	Providence	227	6(2.7)	13(5.7)	2(1.1)	–	–	–	–	–
Riggs 2000 ¹²	Denver	393–441	12(3.1)	24(5.4)	–	–	–	–	–	–
Reeves 2004 ¹⁰³	London	92	–	1(1.1)	–	–	2(2.2)	–	–	–
McFarlane 2005 ^{**14}	Houston	79	6(8)	9(11)	–	10(13)	3(4)	–	5(6)	–
Thompson 2005 ¹⁰⁴	Edinburgh	100	–	11(10)	–	–	1	–	1	–

Numbers under disease categories represent number of patients positive for the disease and numbers within parentheses indicate their percentages

*NG = *Neisseria gonorrhoeae*; CT = *Chlamydia trachomatis*; TV = *Trichomonas vaginalis*; BV = Bacterial vaginosis; CA = Condyloma accuminata or human papilloma virus infection; TP = *Treponema pallidum*; HSV = Herpes simplex virus; HIV = Human immunodeficiency virus; F/U = Follow-up.

**Infections by patient report. Subjects were assaulted by a domestic partner.

between assailant–victim pairs. Microbial forensic techniques have become standard in other arenas such as bioterrorism research.⁵⁷

TESTING FOR STD AFTER SEXUAL ASSAULT

The CDC's "*Sexually Transmitted Diseases Treatment Guidelines 2002*" recognize that testing for STD and offering prophylactic antimicrobials should be individualized, depending on the circumstances of the victim and the assault.⁵⁸ Rape victims may be at risk for preexisting STD,

and STD resulting from rape can be psychologically devastating. With this in mind, victims' health will most likely be best served by a careful workup for STD detection. The CDC's recommendations for STD testing after rape are found in [Table 105-2](#). In addition to diagnostic testing, patients should be educated on signs and symptoms of STD and urged to abstain from sexual intercourse until STD prophylaxis has been completed.

Care of the sexual assault victim includes careful medical evaluation, counseling, forensic testing, appropriate reporting, and follow-up for physical or mental complications.

Table 105-2. Recommended Diagnostic Testing for STD After Sexual Assault⁵⁸

Initial examination (preferably within 72 h of assault)

1. Cultures for *N. gonorrhoeae* and *C. Trachomatis* from any sites for penetration or attempted penetration.
2. FDA approved nucleic acid amplification tests can be substituted for cultures. Positive results should be confirmed by a second nucleic acid amplification test that targets a different sequence from the initial test.
3. Wet mount and culture of vaginal swab for *T. vaginalis* infection. If symptomatic, wet mount should also be examined for bacterial vaginosis and candidiasis.
4. Collection of serum for evaluating for HIV, hepatitis B, and syphilis.

Follow-up examination 1–2 wks postassault in patients **not** receiving antimicrobial prophylaxis at initial examination

1. Cultures for *N. gonorrhoeae* and *C. Trachomatis* from any sites for penetration or attempted penetration.
2. FDA approved nucleic acid amplification tests can be substituted for cultures. Positive results should be confirmed by a second

nucleic acid amplification test that targets a different sequence from the initial test.

3. Wet mount and culture of vaginal swab for *T. vaginalis* infection. If symptomatic, wet mount should also be examined for bacterial vaginosis and candidiasis.

Follow-up examination 1–2 wks postassault in patients who **received** antimicrobial prophylaxis at initial examination

1. No follow-up testing is required at 2 wks if patient is asymptomatic.
2. Tailor follow-up workup on symptoms displayed and on antimicrobials received and taken.

Follow-up examination at 6, 12, and 24 wks postassault

1. Repeat serologic testing for HIV and syphilis if initial tests were negative.
2. Repeat testing for HBV if patient is not immunized.

Several publications address recommendations for overall care of victims of sexual assault.^{59–63}

ANTIMICROBIAL PROPHYLAXIS AFTER SEXUAL ASSAULT

Rape victims often forego follow-up medical care after an initial evaluation. This increases the urgency of prophylactic treatment of potential STD. If the clinician opts to offer prophylaxis after assault, it is important to explain to the patient the side effects of the drugs and the lack of knowledge about the necessity of prophylaxis after rape. (The special issue of HIV prophylaxis is discussed below.) [Table 105-3](#) lists the CDC's recommendations for STD prophylaxis after sexual assault.⁵⁸

■ HIV AND POSTEXPOSURE PROPHYLAXIS

Victims of sexual assault are at risk for acquiring HIV.⁶⁴ In January 2005, the CDC issued guidelines recommending the use of postexposure prophylaxis (PEP) for HIV in uninfected patients who sustain high-risk sexual exposures to individuals *known* to be HIV infected and who present for evaluation within 72 hours of exposure.⁶⁵ While comprehensive, the guidelines assume knowledge of the source's HIV status. This is rarely the circumstance in sexual assault. Using the recent CDC guidelines as a framework and as an endorsement of nonoccupational PEP, clinicians caring for sexual

Table 105-3. Recommended Regimen for Antimicrobial Prophylaxis After Sexual Assault⁵⁸

1. Postexposure hepatitis B vaccination (without HBIG [hepatitis B immune globulin]) if the patient is previously unvaccinated. Repeat HBV vaccination should be repeated at 1–2 mo and 4–6 mo after the initial dose.
2. If perpetrator is known to be infected with Hepatitis B, consider administering HBIG.
3. For CT, GC, trichomonas, and BV prophylaxis:
 - a. Ceftriaxone 125 mg IM in a single dose; *PLUS*,
 - b. Metronidazole 2 g orally in a single dose; *PLUS*,
 - c. Either azithromycin 1 g orally in a single dose or doxycycline 100 mg twice a day for 7 d.

assault victims must conduct HIV risk assessments and make treatment decisions based on the individual needs of each patient.

One of the justifications for using HIV PEP after sexual assault even if the HIV status of the assailant is unknown is this: The acquisition of a life-threatening and life-changing infection after a forced sexual encounter compounds the trauma inherent in sexual assault and leads to an ongoing violation of the victim's personal integrity and safety.

Chapter 72 discusses the scientific basis for HIV PEP. The risk of HIV transmission resulting from some types of sexual exposure is similar to the risk after needle-stick exposure. Because of the effectiveness of PEP after needle-sticks,⁶⁶ several authors have suggested protocols for HIV PEP following sexual assault.^{67–70} While previous concerns existed that providing PEP after sexual exposures may increase high-risk sexual behaviors, recent data have not supported this concept.⁷¹ There is no evidence that using HIV PEP after sexual assault would encourage high-risk behaviors.

■ RISK ASSESSMENT

The assailant's seropositivity (including viral load and clinical status) greatly influences the risk of HIV transmission to the victim.⁷² Studies estimate that as many as half of rape victims know their assailants,⁷³ while less than 2% know the assailant's HIV status.⁷⁴ Given these facts, the clinician should ask the victim about what, if anything, is known about the assailant's health and habits and develop a risk profile (history of intravenous drug use, male assailant having sex with men, and a history of current or previous incarceration), if possible. When this information is not available, the seroprevalence of the relevant community where the assault occurred should be considered. For example, the incidence of HIV is 14 times higher in prisoners compared to the general U.S. population.⁷⁵ If the assault occurred in an area of high HIV seroprevalence such as a prison, use of PEP may be appropriate.

In addition to quantifying the risk of HIV transmission based on the assailant's seropositivity or risk profile, the clinician can evaluate the level of risk based on the type of sexual exposure. Estimates of risk vary depending on the type of sexual contact that occurred (Table 105-4). In most cases, patients are able to report this information.

Certain factors may increase the risk of HIV transmission during sexual assault compared with consensual sexual activity. Abrasions, mucosal damage, and other physical trauma are more likely to result with forced penetration and may increase the risk of HIV transmission.^{15,76} In addition, sexual assault victims and perpetrators may be more likely to be infected with other STDs compared to the general population.³⁴ These underlying infections increase the victim's susceptibility to HIV.⁷⁷ Having multiple assailants may also increase the risk of transmission and should be considered a significant risk factor. Table 105-5 lists suggested categories of risk for HIV to be considered when evaluating sexually assaulted patients for PEP. This risk assessment tool has not been tested clinically.

■ TREATMENT RECOMMENDATIONS

Sensitive discussion with victims regarding HIV exposure and prophylaxis may alleviate emotional stress for victims. Discussion of avoidance of high-risk sexual behaviors is not

Table 105.4. Estimated Per-Act Transmission Risk of HIV from Unprotected Exposure to an HIV Infected Person, by Exposure Route

Exposure Route	Risk per 10,000 Exposures to an Infected Source	Reference
Receptive anal intercourse	50	72, 105
Receptive penile-vaginal intercourse	10	72, 105, 106
Insertive anal intercourse	6.5	72, 105
Insertive penile-vaginal intercourse	5	72, 105
Receptive oral intercourse	1	72
Insertive oral intercourse	0.5	72
Percutaneous needle-stick	30	107

Estimate of risk for transmission from sexual exposure assumes no condom use.

From Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. *MMWR Recomm Rep* 2005; 54(RR-2): 1–20.⁶⁵

appropriate for the initial visit postsexual assault. Follow-up visits, however, can be used to discuss a variety of risk reduction behaviors, including ways to avoid revictimization and assure safety. Many sexual assault victims will have many psychological and social factors in their lives that put them at risk for *both* STD and sexual assault, including prior victimization, poverty, domestic violence, and unsafe living conditions.^{7,78,79}

If HIV PEP is prescribed, patients should be educated about risks, benefits, and side effects of therapy. Inform patients about the lack of conclusive data on HIV PEP efficacy. The importance of compliance and follow-up should be stressed. Initial laboratory testing should include HIV testing, a complete blood count, blood urea nitrogen and creatinine, and liver function studies. Careful telephone follow-up frequently throughout the course of treatment may increase patient compliance and successful completion of the course of therapy.⁸⁰

Data on the optimal choice and number of antiretrovirals to prescribe after sexual assault are largely empiric. PEP is recommended only for patients who present within 72 hours of the assault. PEP should be started as soon as possible after exposure and continued for 28 days.⁶⁵ All female patients must have a pregnancy test prior to starting therapy, as some regimens are contraindicated in pregnancy.

Table 105-5. Suggested Categories of Risk to be Considered in Cases of Sexual Assault When Evaluating Patients for HIV Postexposure Prophylaxis

Patients at *high HIV risk* after sexual assault:

- Patients were penetrated vaginally, anally, or orally by a known HIV-positive assailant.
- Assailant's seropositivity is unknown but other factors exist that may modify the risk from the exposure such as
 - anogenital trauma is present;
 - multiple assailants are involved;
 - assailant is known to be from a high-risk population; or,
 - victim has coexisting anogenital infections.

Patients at *moderate risk* after sexual assault:

- Patients were penetrated anally, vaginally, or orally, and the assailant ejaculated, and the seropositivity of the assailant is unknown, but there are no factors that modify or potentially increase the risk of exposure.

Patients at *low risk* after sexual assault:

- Assault involved no anal, vaginal, or oral penetration.
- Assault involved oral penetration without ejaculation.
- Assailant is known to be HIV negative.

The current CDC guidelines endorse a 3-drug regimen for nonoccupational exposures to *known* HIV-infected sources.⁶⁵ Favored regimens include a non-nucleoside reverse transcriptase-based regimen such as efavirenz *plus* (lamivudine or emtricitabine) *plus* (zidovudine or tenofovir); or, a protease inhibitor-based regimen such as coformulated lopinavir/ritonavir *plus* (lamivudine or emtricitabine) *plus* zidovudine. While there is no evidence that a 3-drug regimen is more effective than a 2-drug regimen, for patients at *high risk* for exposure (Table 105-5), a 3-drug regimen is recommended.

If the patient is determined to be at *moderate risk* for exposure, the CDC has not offered official recommendations. Other experts have recommended 2-drug regimens because of the decrease in side effects, toxicity, and cost.^{67–69,74} These regimens include coformulated zidovudine and lamivudine, zidovudine and emtricitabine, tenofovir and lamivudine, or tenofovir and emtricitabine. Before any regimen is adopted, consultation should be sought from experts in HIV treatment and prevention. For the latest information on doses and side effects of antiretroviral drugs, refer to the U.S. Department of Health and Human Services website, *AIDSinfo* at: <http://www.aidsinfo.nih.gov/DrugsNew/Default.aspx?MenuItem=Drugs>

Patients at *low risk* for HIV exposure should not be routinely offered PEP. If they are suffering extreme psychological stress related to possible HIV exposure because of sexual assault, they should be counseled, reassured, and referred for follow-up. In the rare case where the patient is unable to accept the provider's recommendation *not* to use HIV PEP, the clinician can reassess prescribing PEP depending on the individual patient's needs.

For patients on PEP, follow-up should include monitoring liver and renal function as well as complete blood count. Whether or not PEP is prescribed, serologic testing for HIV

should be repeated at 4–6 weeks, 3 months, and 6 months. Because adherence to PEP medication regimens is especially poor among sexual assault survivors,⁸¹ patients should be warned of the possible risk of developing drug resistant HIV strains with poor compliance. Ideally all patients on PEP should be seen within 72 hours to answer questions and to address side effect from medications should they arise.⁸⁰

OTHER ASPECTS OF TREATMENT OF RAPE VICTIMS

Rape victims are at risk for impaired physical and mental health. In addition to STD, the sequelae of rape include⁸²

- physical injuries resulting from assault
- assault-related stress on the immune, endocrinologic, or autonomic systems
- assault-related emotional problems
- increase risk of engaging in high-risk unhealthy behavior posttrauma, such as unhealthy diet, smoking, excessive alcohol or drug use, and poor sleep
- increase in psychosomatic and physical symptoms resulting from stress and anxiety

Victims commonly experience posttraumatic stress disorder, anxiety disorders, and depression after sexual assault.⁸³ Health-care facilities caring for rape victims should have counseling and/or referrals available to help mitigate the physical and mental health consequences of sexual assault. Recent work indicates that brief interventions preparing rape victims for their physical examinations and discussing common reactions to rape can reduce exam-related anxiety and may also decrease the development of psychological symptoms posttrauma.⁸⁴

Rape victims often report “secondary victimization” by police and medical personnel who treat them insensitively.⁸⁵

Many areas have volunteer victims' advocates available who respond to emergency departments and support victims through the medical and legal processes. The presence of victims' advocates during the postrape medical exam has been shown to decrease victims' anxiety and distress.⁸⁶ If these services are available, they should be utilized to support victims of sexual assault.

RAPE, HIV, AND VIOLATION OF HUMAN RIGHTS

In many parts of the world where rates of HIV infection are high, women experience sexual inequality, low social status, and little control over their reproductive health. In these societies, violence against women is often rampant. For example, in South Africa, the rate of HIV infection in adults is estimated to be as high as 25%.⁸⁷ The rate of sexual assault is unknown but is thought to be among the highest of any country.⁸⁸ Human Rights Watch estimates that over 1 million South African women are sexually assaulted each year.⁸⁹ Since HIV infection is so common, rape victims face the significant prospect of being infected with HIV as a result of sexual violence.⁹⁰

Gender-based sexual violence is especially a problem during times of armed conflict. During wars in Yugoslavia, Darfur, Rwanda, Somalia, Burma, and many other countries, women have been systematically raped by soldiers as part of 'ethnic cleansing'.^{91,92} In Rwanda, reports emerged of HIV-positive soldiers purposely raping large numbers of women to cause illness and death among their enemies.⁹³ Trafficking of women and children in wartime and peacetime is another human rights violation that threatens the health of the victims and increases risk for STD and AIDS.⁹⁴ These complex political/social issues must be addressed worldwide to stop both sexual assault, STD and AIDS from destroying people's lives.

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Legal and Political Aspects of STI Prevention in the United States: Public Duties and Private Rights

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INTRODUCTION

STI prevention is the most legally and politically complex public health problem. STIs involve the most intimate human behaviors and are intertwined with deeply held religious and moral beliefs. In our modern “age of the condom,” issues of STI control are easily obscured by the rhetoric of personal protection and responsibility. These are key concepts, but there are populations, such as adolescents, which are difficult to convince to behave responsibly, and others, such as the wives of men who are not faithful, who cannot protect themselves. STI control is also complicated by the legal and moral issues posed by prostitution and illegal drug use.

This chapter focuses on public health law and the control and prevention of STIs in the United States. The U.S. experience is unique for legal, historical, and cultural reasons. The U.S. experience is valuable for those outside the United States because the basic legal and social issues posed by STIs are universal. In many ways, the societal response to STIs is similar in different countries, even though the legal approaches differ.

The defining characteristic of the U.S. legal system is that the United States is divided into 50 state governments. The National Congress can override (preempt) state law in most areas, and the U.S. Constitution is binding on the state as well as the federal government. In some areas of health regulation, such as air and water pollution laws, Congress sets national standards that constrain state action. These standards lead to a uniform national environmental policy. Public health law, however, has been traditionally left to the states. In STI control, this has meant that there are significant differences in basic control laws and enforcement in different states. At the same time, the states depend on the federal government to fund state public health services. Congress uses restrictions on this funding to encourage some public health actions and discourage others. This combination of differing state laws and Congressional overrides means that there is no uniform U.S. STI and HIV control and management policy.

PUBLIC HEALTH LAW BASICS

■ THE ROOTS OF PUBLIC HEALTH LAW

Public health law is rooted in the fundamental right of a nation to self-defense from external and internal threats. These threats may be military, demographic, economic, or environmental.¹ Historically, the prime environmental threat was disease. The Black Plague ripped the fabric of European society in the Middle Ages. The diseases carried by Western missionaries and sailors did more to destroy indigenous cultures than did their military, religious, and cultural imperialism.² Epidemic disease has been resisted with quarantines, embargoes, and limitations on travel since the earliest days of international commerce, making the right to close one's borders to outside threats fundamental to international law.³ The risk that communicable diseases pose to national security is what justified the broad public health powers traditionally recognized by the United States and most countries.⁴ STI control also has a direct history as part of the national security law. Disease control is fundamental to maintaining an army in the field. It has only been in the last 100 years that munitions have outstripped disease as a killer of soldiers. STIs have always followed military campaigns. Even in the United States, the first serious political commitments to controlling gonorrhea and syphilis grew out of a concern with military readiness.⁵

Public health law is part of the larger discipline of administrative law; the law governs the formation and operation of government agencies. Boards of health were among the first governmental agencies and figure in many historic constitutional cases that form the basis for administrative law. As applied to public health actions, administrative law has two major tenets. First, decisions should be made by experts, not by lay judges and juries. Second, agencies must be allowed some flexibility in the development and implementation of policy, i.e., the legislature can give agencies broad powers to address threats to the community.

■ JUDICIAL DEFERENCE TO PUBLIC HEALTH AGENCIES

Administrative law recognizes that decisions involving technical or scientific information must be made by persons with proper educational training and experience. The agency will be required to show that it has an expert justification for its decision and a procedure to assure that the regulatory process is carried out in a consistent and even-handed manner. The court will defer to the agency's decision unless it finds that it is arbitrary or capricious, i.e., that it did not follow that agency's procedures or that it was not consistent with the agency's rationale. The court will not allow litigants to contest whether the agency made the correct choice from acceptable alternatives.⁶

Public health authority must be broad and flexible to meet the challenges of new diseases and new knowledge about old diseases. Even in the United States, with its suspicion of unconstrained public authority, state laws generally give health officers the authority to do whatever is necessary to protect the public health. Statutes specify the broad outlines of disease control programs, leaving to the discretion of the health officer the specific details on which diseases will be reported, within what time frame, in what form, and how the infected individuals will be managed. The health officer then promulgates regulations to detail the specifics of the disease control strategies. These administrative regulations give notice of a citizen's obligations but may be quickly modified to reflect changes in disease dynamics. Health officer powers are limited to actions rationally related to improving public health, not, for example, supporting a law enforcement effort to reduce pimping that cannot be empirically connected to STI reduction. As another example, courts have struck down laws that used unfounded public health arguments to support discriminatory actions against racial or ethnic groups; but in general, the courts defer to the expertise of local health officers.⁷

The United States Supreme Court has found few limits on the authority of public health officials to take whatever actions are, in their expert opinion, necessary to protect the public health. These have included imposing quarantines on large geographic areas, holding persons infected with communicable diseases in custody to prevent the spread of the disease, the forced treatment of disease carriers, and the seizure and destruction, without compensation, of any property that threatens the public health.⁸ Most countries have done the same.

Agency expertise and flexibility depend on the courts' standards of reviewing agency actions. If the courts, whose expertise is in law, not public health, substitute their decisions for the decisions of the agency, it will undermine the effectiveness of expert decision making. If the courts require judicial review of all agency actions, it will be impossible to act quickly, and the cost of the review to the agency will limit

the number of actions the agency may take. These transaction costs for decision making are called agency costs. As an example, the Social Security Administration of the United States processes millions of benefits claims each year. If every determination that affected a citizen's rights required court review, the costs of providing a court hearing would be more than many of the claims the agency is asked to pay.⁹ It would also increase the cost of making a claim beyond the means of most claimants. In countries without significant judicial review of agency action, interference by politicians without public health expertise can also raise agency costs and make it difficult for agencies to carry out their mission.

Persons who are restricted through public health orders are entitled to have these actions reviewed by an agency appeals panel or the courts, after the health department has acted. This is a critical distinction: most people will cooperate with the public health restrictions and contest it in court. If they want to contest a restriction of their freedom, the U.S. Constitution guarantees them the right to file a writ of habeas corpus to force the agency to show a court the factual basis for their confinement and the legal authority that allows the confinement.¹⁰ If the state requires a hearing before the health department acts, including rights such as appointed counsel paid for by the state, the number of legal proceedings increases dramatically, as does the delay and cost. Most health departments in the United States operate on limited budgets, and some do not have their own attorneys to represent them in court. They must depend on the city, county, or state attorneys to represent them, and these attorneys are often disinterested in public health enforcement. Increasing the due process rights of individuals will reduce the resources that are available to carry out agency functions and force the agency to reduce or limit its enforcement action.

■ CONSTITUTIONAL LIMITATIONS ON PUBLIC HEALTH POWERS

The major constitutional limit on public health powers is that they may not be used to undermine criminal due process rights. The U.S. Constitution requires that before individuals may be punished, their guilt must be determined by a jury under procedural rules designed to protect their rights. The Constitution does not require that these same protections be provided when the person is being restricted to protect the public health and safety. For example, public health inspectors can enter a private home as part of routine investigations with only limited judicial supervision. In contrast, a police officer looking for evidence of a crime must obtain a warrant from a judge based on a showing that probable cause exists to believe that the evidence is in the home. Since STIs are frequently associated with criminal behavior such as illegal drug use and prostitution, it is important for public health authorities and legislatures to understand this distinction.

The distinction between criminal laws intended to punish and public health laws intended to prevent and ameliorate hazards and behaviors harmful to the public, irrespective of the subjective intent of the individual member of society affected, is crucial in all societies. This was reaffirmed recently by the United States Supreme Court. The case involved pregnant women who were tested for illegal drugs without their consent. This was done as part of their routine prenatal care. The results were used to threaten criminal prosecution if they did not stop using illegal drugs during pregnancy.¹¹ The court found that while testing pregnant women without their consent would be allowable for a legitimate public health purpose, such as a referral to drug treatment or counseling, it could not be done to collect evidence to be used to justify a criminal prosecution.

Active (infectious) tuberculosis is a good illustration of the difference between public health and criminal laws. Assume that a man has active tuberculosis and is at large in the community under no public health isolation orders. This tuberculosis carrier infects a fellow passenger on a bus, and the passenger eventually dies from the infection. The causation is clear—the bus passenger died because of the actions of the disease carrier. If the man did not know he was infected, or did not know the risks his infection posed to others, this would not be a crime because there was no evil intent or reckless disregard of societal rules. Thus, it would be impermissible to incarcerate the tuberculosis carrier as a punishment for spreading the disease. (If he did know, he could be guilty of recklessly endangering others and might also be liable for damages.) It would be a proper exercise of public health authority to restrict this tuberculosis carrier to prevent the spread of disease.¹² He would have no right to bail because of his danger to the public.¹³ When the carrier is successfully cured and rendered noninfectious, the health department's authority to hold him will end.

■ DISCRIMINATION ISSUES

STIs have always carried a social stigma. One of the categories of the old tort of slander per se, i.e., slander which did not require any proof of harm because the accusation was universally seen as unacceptable, was to be accused of having a loathsome disease. In many of these cases, the loathsome disease was an STI, especially syphilis.¹⁴ At the beginning of the AIDS epidemic in the United States, before HIV was discovered and the epidemiology of the disease was elucidated, there was a fear that this was an easily communicable “gay plague.” (This was partially stimulated by the unfortunate first syndromic name—gay related immunodeficiency disease, or GRID.) There were calls to fire gay waiters, gay hairdressers lost customers, and gay men worried, with some cause, about employment and housing discrimination. This was a complex phenomena, at least in the United States, and

it has been misunderstood in ways that have hampered HIV control efforts.

First, the level of public fear fell off as it became clear, through the efforts of the U.S. Surgeon General and others throughout the medical and public health world, that AIDS could not be transmitted through casual contact. By the time the HIV test was available in 1985, the initial wave of public fear of AIDS was past. This did not mean that discrimination was no longer an issue, but this discrimination was not just about possible HIV infection but also about homosexuality, which at that time was not well accepted in most parts of the United States. For many employers, the issue was really about gay employees as much as about HIV.

Second, the irrational organization of the U.S. health insurance system created real concerns about the loss of health insurance for persons diagnosed with HIV. Whereas this was real, it was not an HIV phenomenon. A person diagnosed with any serious or chronic illness faces the same issues. If you are not in a group insurance plan, insurance becomes unaffordable if you are sick. If you are in a group plan, your illness will raise the cost to the plan. If it is a small plan, then the costs can rise very quickly and the employer will feel pressure to push the employee out of the plan, i.e., out of the workplace. Persons with liver disease, heart disease, emphysema, and other chronic illnesses faced the same problem, and, to a great extent, still do. The question for public health is not whether there was discrimination against persons with AIDS or other diseases but whether the measures taken to combat the discrimination, and which stymied public health efforts, were needed or even effective and, if they were, are they still needed?

There are two classes of measures to prevent HIV-related discrimination: keeping the disease secret; and laws to prevent discrimination against persons known or suspected to be infected with HIV. Persons wanted to keep their HIV status secret from their employers, their landlords, and their health insurer. This led to restrictions on the handling of HIV information in medical records, special consent forms for HIV testing that discouraged persons from being tested, anonymous HIV testing, and a failure to require HIV to be reported by name to health departments. The problem with these measures is that they did not address the real problems.

Health departments do not report information to employers, health insurers, or landlords. Whether someone is tested at the health department or whether the individual's HIV status is reported to the health department by their health care provider, the information in the public health report is used for public health purposes only. Health departments have an almost perfect record on keeping public health information private. Ironically, the first wave of persons with AIDS were already known to health departments because almost all of them were reported for other STIs and hepatitis B. Had

health departments wanted to do anything sinister with the reporting data, they would have already known who the usual suspects were. Thus, there was no reason to have anonymous testing and no named-reporting—health departments posed no risk of exposure to anyone.

The most problematic issue was keeping information from health insurers. Health and life insurance is not a game where you get a free pass if you can keep your illness secret. Patients have a duty to be truthful about their medical condition, and keeping HIV status secret is fraud on the insurer. Whereas the health department will protect the information about HIV from tests they administer, the patient is defrauding the insurer by withholding this information from the insurer. Whether this is justified or not, it is not an issue of HIV discrimination, it is an issue of the injustice of the health care insurance system and persons with diseases other than HIV were also doing the same thing. Public health officials should have been talking about everyone who has a serious illness and the need for health insurance reform, not supporting special laws for HIV.

The Americans with Disabilities Act of 1990 (ADA)¹⁵ specifically addressed many of the HIV discrimination issues, other than health insurance, which is excluded from the Act. Employers and others are prohibited from discriminating against persons with a disability or against persons who they think have a disability. Employment decisions have to be based on the individual's ability to do the job safely, not on class-based assumptions about what persons with a disability can do. The ADA also limited employers' access to employee health information to prevent employers from using employee health records to identify disabled employees. The United States Supreme Court, interpreting the ADA, found that HIV was a covered disability, even if the infected individual had no signs of the infection other than a positive HIV test result.¹⁶ Whereas individuals may have many valid reasons for hiding their HIV status, the ADA provides them with more protection if their employer knows they are HIV infected.

■ PRIVATE LAW AND STI CONTROL

The state's role in disease prevention is to prevent the spread of disease, not to compensate those who are infected by others. There is also a private law remedy to compensate persons injured by disease carriers who do not take proper precautions to prevent the spread of their disease. The United States has well articulated liability theories that can be applied to the three types of communicable disease compensation cases: (1) infectees suing infectors; (2) infectees suing physicians for failing to warn them that a patient of the physician was a disease carrier; and (3) patients suing their physicians for medical malpractice. There have been cases awarding compensation for infecting an unsuspecting person with an STI and for malpractice in treating an STI.¹⁷ A physician who fails to report HIV in

a state that attempts to warn persons at risk will be sued for negligence per se—the tort remedy for breaking a law.¹⁸ These are difficult lawsuits to defend because the reporting law sets the standard of behavior.

In general, tort law has not been an effective incentive for disease prevention. There has been little litigation over the negligent transmission of STIs because there is no one to pay the compensation and the attorney's fees. Few STI carriers are wealthy enough to pay a court-ordered award, and all insurance policies exclude coverage for STI transmission. There have been a few awards against physicians for failing to take proper disease control measures, but most litigation involving physicians has been over patient privacy issues. These lawsuits generally attempt to limit the access to information about STIs, creating an incentive for physicians to not conduct proper disease reporting, testing, and disease control. Whereas physicians cannot be sued for complying with public health reporting laws, this is not generally known. This should be specifically stated in all public health codes to encourage STI reporting, as this has proven helpful in encouraging reporting of suspected child maltreatment.

Physicians should expect to see more litigation over failing to make a timely diagnosis of HIV as it has become clear that early diagnosis and treatment with antiviral prolongs life and improves its quality. One court has already awarded in excess of \$1 million in such a case.¹⁹ Physicians must be especially careful to recommend HIV testing to pregnant women. It is now considered standard of care, and if the woman declines, the physician must be careful to document all the circumstances of the refusal. As cases involving other medical tests have demonstrated, juries tend to assume that patients only refuse simple tests because the physician was negligent in informing the patient of the benefits of the test.²⁰ With an innocent baby as the plaintiff, and the mother possibly dead by the time of trial, these will be very difficult cases to defend.

APPLYING THE LAW TO STI CONTROL

■ MANAGING PUBLIC HEALTH INFORMATION

Communicable disease control, including STI control, is driven by epidemiologic information about the medical condition of individuals. Managing this confidential information is a core public health law concern. Medical information occupies a peculiar position in the United States and many other countries. People want information about their medical conditions kept private and worry about it being shared without their knowledge and permission, yet they want access to the best care without delay and they want someone else to pay for it. Since no insurer will pay for care without knowing what it is, and since modern medical care involves many team players, balancing these conflicting expectations is very difficult. The advent of

electronic medical records and widespread electronic transmission of medical information caused the United States and several European countries to enact strict privacy laws controlling the storage, transmission, and sharing of medical information. The United States Department of Health and Human Services has recently promulgated regulations that set a national standard for keeping a patient's medical information private. The law focuses on what it calls Personal Health Information (PHI)—medical information that includes personal identifiers such as the patient name or social security number. These regulations, and all state medical privacy laws, provide exemptions that allow public health personnel access to patient medical records for disease investigation and control programs.²¹ Without such exceptions, the health department could not investigate communicable diseases without the permission of the infected person. More generally, all medical care systems should recognize the general principle of patient privacy but also that this must be tempered for public health investigations.

Since PHI must be managed differently from public health information, it is important to distinguish between the two. Public health information is information about an individual's medical condition that is used for epidemiologic purposes such as vital statistics, or disease investigation, or for determining if the person poses a risk to others. Whereas some public health information may come from interviewing the patient or from the patient's medical or laboratory medical records, it may also include information developed by public health investigations. Thus, there is a critical distinction between personal medical records and public health information: patients need access to their PHI to assure ongoing medical care, but they do not need access to public health information held by the health department. Any PHI held by the health department that is not in the patient's ordinary medical record will be investigational data that includes information on others that should be kept confidential.

More generally, PHI with the patient's name or other identifying information held by public health should be kept confidential from the patient and from everyone else who does not have a specific need to know its contents. This means that access to confidential information within the health department should be restricted to persons involved in disease control or epidemiology record keeping. Outsiders should not be told identifying information about the disease carriers unless it is essential, such as telling an employer that an employee is infected with tuberculosis in order to identify all workplace contacts.

Managing public health information is more complex in dual function health departments that provide STI treatment in addition to their STI epidemiology and investigation functions. When a health department is delivering individual medical care, the patient's individual medical care is subject to the same standards as in private medical practice, and the medical records are subject to the same laws as those held by

other medical care providers. These include the patient's right of access and access by various financial auditors and medical quality inspectors, as well as all members of the health care team. In the United States, access to and transfer of these records is controlled by comprehensive federal regulations and many other countries have similar restrictions. Public health investigation records must be kept completely separate from the patient care records, and patient care personnel should not have access to them unless the department is so small that the same staff provides both clinical and epidemiological services.

Concerns about the privacy of medical information should not deter disease control efforts, including databases created to facilitate the identification and tracing of infected persons. STIs are a special case in that the carriers of these diseases, particularly the incurable ones such as HIV, have a special responsibility not to spread them to others. A measles or tuberculosis patient, who spreads the disease through ordinary activities, will be isolated to prevent the spread of the disease. STI carriers pose no threat through casual contact and can prevent the spread of the STI by not engaging in risky activity. They are not isolated but in return have an obligation to refrain from risky behavior. As an incurable, deadly communicable disease, HIV is the most serious communicable disease routinely encountered in public health practice. Whereas unnecessary breaches of confidentiality should be avoided, the risk of a breach of confidentiality is more than offset by the importance of making all reasonable efforts to control the spread of HIV.

■ STI TESTING

Communicable disease epidemiology begins with a diagnosis of the disease. Some diseases—smallpox, Ebola—announce themselves through their severity and visible symptoms. STIs, at least in their initial phases, are silent, or have ambiguous symptoms that are easily confused with other conditions or ignored. Testing is the first step in STI surveillance and epidemiology. Before 1985, when the HIV test became available, there was little controversy over STI testing and clear legal authority to require testing when epidemiologically justified.²² Most states required pregnant women to be tested for syphilis so that they could be treated to prevent congenital syphilis. STI testing, including syphilis was required for wedding licenses and most hospitals did syphilis screening as part of hospital admission blood work. Many of these requirements were dropped as the decreasing incidence of syphilis made them less cost-effective but not because they were legally questionable. Most states still require syphilis screening for pregnant women without notifying the patient or getting specific consent.²³

STI testing, other than HIV testing, is done in the same manner as other noninvasive diagnostic testing. The tests are ordered, usually based on "medical suspicion," as part of the

general evaluation of the patient and they are covered by the consent to the medical evaluation. Patients are not asked to consent to individual tests. This consent is usually signed by the patient but may be implied by the patient seeking care and allowing the physician's examination. (Since implied consent would not be adequate for releasing information covered by HIPAA, it is not advisable in the United States.) The physician may or may not tell the patient the specific tests being ordered—the automated analysis performed in many clinics may include 40 or more tests, making it difficult and confusing to present the patient with a list of the tests ordered. The patient is contacted when the results are completed and told the results of tests directly related to the evaluation and any abnormal tests.

State laws that require special consent for HIV testing pose a significant barrier to HIV testing. Another barrier is laws that require post and even pretest counseling. Although such counseling is useful, it limits testing and diagnosis and is not required for other potentially devastating diagnoses, such as cancer or multiple sclerosis. States have also failed to require HIV testing for pregnant women, although they do require testing for syphilis. Since both tests for HIV and syphilis have the same medical justification, preventing the development of congenital infection by treating the mother, there is no scientific justification for putting infants at risk of HIV while trying to protect them from congenital syphilis.

■ DISEASE REPORTING

The first step in STI surveillance and epidemiology is making the disease known to the public health authorities. This can come from investigations and voluntary reports to the health department, but most communicable disease epidemiology starts with legally mandated reports by medical care providers, clinical laboratories, and persons in other care situations, such as day care centers. Whereas disease reporting has been mandated by law since the colonial period, it was not reviewed by the United States Supreme Court until 1977. This case arose from a state law requiring that narcotic prescriptions be reported to the state. The reports were used to detect inappropriate drug use and illegal prescribing or selling narcotics.²⁴ The law was challenged by physicians and patients who claimed it was an invasion of their privacy and that it improperly interfered with the physician—patient relationship. This was in the wake of the *Roe v. Wade* decision that recognized a special status for medical privacy related to abortion.²⁵

Rather than extend *Roe v. Wade* into a general medical privacy law, the United States Supreme Court found the reporting law a constitutional exercise of the state's power to protect the public health. More generally, the Court has rejected special privacy rights in medical care that are not related to abortion and birth control. The Court recognized that the state had a duty to keep the information confidential, but that the state

had a right to require the reports and to use them to investigate potential abuses. Despite the fact that a prime purpose of these reports was to identify criminal activity, which merits more constitutional protections than public health investigations, the Court ruled that the state has broad latitude to require disease reports for public health purposes.

Mandatory disease reporting is critical for STIs. Whereas high-quality data on disease epidemiology may be obtained by large-scale surveys of randomly sampled practitioners without requiring routine individual disease reports, such surveys are problematic for STIs. They are expensive and time-consuming, making it virtually impossible to detect short-term changes in disease dynamics. They also depend on the practitioners having the information. Since a major problem with STIs is that physicians do not routinely test for them, especially for HIV where state consent requirements discourage testing, the data is not there for the surveys to reach. Surveys that preserve the anonymity of those surveyed also fail to address the duty to warn, which requires the identification of individual infected patients, and do not allow further investigation of contacts.

Mandatory physician reporting of designated STIs has been a component of STI prevention for more than 60 years in the United States. (Extremely common STIs, such as gonorrhea and chlamydia, are generally not reported by name because they are too common and too easy to treat to justify using limited disease control resources to track.) Unfortunately, epidemiologic information about STIs has been very difficult to collect even with legal persuasion, in part because of the health care providers' concerns with protecting their patients' privacy²⁶ and also because many physicians do not practice public health responsibilities as a core activity in the practice of medicine.²⁷

Statutes and regulations mandating STI reporting should recognize the three functions served by reporting: (1) statistical assessment of disease epidemiology; (2) direct disease control interventions; and (3) discharge of the physician's duty to warn persons at risk of contracting a disease from the patient. The health department must educate physicians about the importance of disease epidemiology and the potential risks they run if they do not comply with reporting laws, thus facilitating the spread of HIV to an innocent third party, especially a newborn.

Public health agencies should also recognize that in modern medical practice, the most important deterrent to physician reporting is time and money. In plain terms, there is no reimbursement code for reporting, and no state health department routinely disciplines physicians for failing to report communicable diseases. For most STIs with a laboratory based diagnostic test, physician reporting is now much less important than laboratory reporting. Laboratories are much more intensively regulated than physician practices, so they are much more likely to comply with reporting laws.

Most laboratories are automated so that reporting can be done automatically as part of the testing and billing process.

The most important barrier to HIV reporting is anonymous testing, which is allowed in most states. This is particularly important because a growing number of women are being infected by male partners who hide their homosexual liaisons.²⁸ It also creates the dilemma of persons who test positive but never return for their test results and who cannot be contacted for follow-up.

■ CONTACT TRACING/PARTNER NOTIFICATION

Contact tracing and partner notification is used in the investigation of all communicable diseases. Despite its effectiveness in controlling diseases such as tuberculosis, measles, hepatitis, and bringing persons with curable STIs to treatment, contact tracing is one of the most controversial issues in HIV prevention. It has been criticized because of coercion, because it is not perfectly effective, and because it might increase the chance of violence toward infected women.

The fears of contact tracing are unfounded.²⁹ First, no jurisdiction in the United States coerces individuals to divulge the names of their contacts. This would not be justified in contact tracing for STIs because effective contact tracing does not depend on perfect reporting.³⁰ The overlapping sexual networks make it likely that the individuals with the most contacts will be identified by at least one contact. Most people infected with an STI cooperate in identifying their contacts.³¹ Although it is a crime to not cooperate with public health investigations, no jurisdiction uses this power in routine disease investigation. (It might be used in an emergency, such as a smallpox outbreak.)

Research showing that contact tracing puts women at risk for domestic violence must be recognized and is troubling, but it is neither new nor limited to HIV. A typical scenario is the woman who is screened as part of her prenatal care and found to be HIV infected. The investigator then notifies her husband, who is often the source of the disease, who assaults his wife for involving him with the public health officers. The best solution, which is used by New York City and some other jurisdictions, is to combine contact tracing with domestic violence services. If the disease investigator believes that the woman (or man) is at risk, they can be referred to domestic violence services as part of the investigation and notification process.

■ INVOLUNTARY SCREENING, TREATMENT, AND RESTRICTIONS

Informed consent to all medical treatment and testing has become a fundamental tenet of the international medical and bioethics communities. For communicable diseases, as opposed to most noncommunicable diseases, endangerment of others is always a consideration. Courts in the United States uphold orders requiring persons who endanger the

public to be isolated unless they agree to treatment that will make them noninfectious. Outside of prisons, it is very unusual for the court to order the use of physical force to overcome the patient's objections to treatment. However, international disease control programs, such as the smallpox eradication program, have found it necessary to use aggressive strategies, including involuntary immunization and bribing villagers to report hidden cases of disease.

What if the patient would be willing to accept the treatment, but for language, educational, cultural, or medical reasons, it is not possible to get a fully informed consent? In these cases it is very important to differentiate between research, and care that is intended to benefit the patient or the community. If the goal of the intervention is solely research, with no potential benefits to the patient, then the international treaties on medical research apply. In these cases, consent is mandatory before testing or treatment.

Isolation and quarantine are venerable techniques in public health. The use of confinement in the case of STIs, however, seems to have little practical use. Unlike many diseases, intimate contact is required for the spread of STIs. In effect, drawing a blood sample or administering an antibiotic under medically indicated circumstances is a less restrictive means of state intervention in the control of STIs than isolation. The fatal and thus far incurable nature of HIV infection may force attention to isolation as a remedy in very rare cases. Depending on the factual situations that arise with HIV infection, for example, associated dementia or an independent mental illness, the courts may well have to consider mental health law and public health law measures for isolating an individual with HIV who is clearly a danger to others or who is gravely disabled and unable to care for himself. Individuals who knowingly expose others to HIV can, and have been, prosecuted under the criminal law and imprisoned.

Given that isolation is a very restrictive approach to STI control, some comparable mechanisms that will ensure participation in examinations and agreements not to expose others are needed. The alternative of health hold orders should be considered. A health hold order means a specific order issued by an authorized public health official to a named individual to cooperate with examination, treatment, or to behave within certain limits necessary to protect the public health.³² Such an order could be appealed to the courts or higher administrative official in a confidential proceeding. The health hold also might be in the form of a voluntary agreement subject to enforcement by court order and result in a very brief detention for examination or a "show cause" contempt proceeding if the voluntary agreement is not likely to be kept or in fact is not being kept. Health holds might also be administered conveniently to persons detained in institutional settings for alleged sexual crimes. Health authorities can avoid having the health hold used for nonhealth matters, such as to compel cooperation in criminal matters, by

focusing strictly on what is required for individual and epidemiologic treatment of STI.

PRIMARY PREVENTION

Primary prevention of STIs in general, and HIV in specific, is complicated by conflicting political agendas in the United States. Conservative politicians and some religious leaders oppose sex education in general and education about safe sexual practice in particular. This opposition is sufficiently widespread that Congress prevents the use of federal funds to support many effective public health education efforts, including those that target poor and minorities, communities at the highest risk for HIV. Unfortunately, the states depend on federal funding for their public health efforts, so even progressive states that support these efforts must limit their actions because of the limits on the federal grants.

Most politicians want to be seen as tough on crime, so efforts to change Draconian drug laws that merely shift HIV-infected persons into the prison system have failed. Few politicians support needle exchange or other efforts to make illegal IV drug use safer, and there is almost no support for the medicalization of drug addiction.

Ironically, at the same time that conservative politicians and religious leaders oppose programs that try to educate about safer sexual practices, politicians in most major urban centers have prevented the closing of gay bathhouses. This is despite evidence that methamphetamine and Viagra use in the bathhouses threatens to dramatically increase new cases of HIV.³³ HIV treatment, at least in the United States, is seen as so effective that it has reduced the effectiveness of HIV prevention messages.

CONCLUSIONS

Effective laws to prevent STIs are based on accurate understanding of available resources, legal and cultural traditions, and intelligent shaping of legislation to meet sound, and probably narrow, disease prevention goals. Laws to organize the reporting of STIs, the screening of persons at greatest risk, and the tracing of the contacts of disease carriers should be a priority of lawmakers concerned with preventing STIs. Personal privacy and liberty must be protected to the greatest extent possible, consistent with the protection of society from STIs. As demonstrated by the contrast between the magnitude of societal risks for gonorrhea and for HIV infection, the milder the disease, the more it can be tolerated for the sake of preserving personal liberties.

Public and private professionals involved in STI prevention must conform their actions to laws governing diagnosis, treatment, reporting, quarantine, and isolation. Law is an

effective device in the prevention of STIs to the extent that it is wielded as one tool in a comprehensive prevention, diagnosis, treatment, and management strategy. Many traditions of public health and legal precedents are valuable standards against which responses to new conditions such as HIV infection must be measured.

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Ethical Challenges of the Global AIDS Epidemic

Ronald Bayer

In a quite fundamental sense the AIDS epidemic has provided the occasion for the effort to articulate an ethics of public health. Although such an effort drew upon the insights and perspectives of bioethics, it was clear that more was needed. Bioethics had taken root in the United States largely in an effort to redress the balance of power between clinicians and patients and researchers and subjects. Central to that effort was an explicit focus on the rights of the individual. Hence, the protection of autonomy became the core commitment of bioethics. Important as was the protection of the individual, it could not serve as the only or even preeminent principal in the context of public health, where the focus was, by definition, on the protection of the community. Nevertheless, as the ethics of public health took shape in the context of the AIDS epidemic, the critical importance of individual rights—claims of privacy, bodily integrity, freedom from unwarranted restraints—was clear. AIDS, too, provided the context within which the ethics of research in a world characterized by deep inequalities became the subject of contentious discussion. Only during later stages of the epidemic, when therapeutic advances made access to care a critical matter, did questions of justice both within nations and internationally take on greater salience. It was the emerging demand for access to care on the part of the poorest people in nations which bore the brunt of the global epidemic that set the stage for vital questions about the moral duties of the world's richest nations to the poorest.

EXCEPTIONALISM, CIVIL LIBERTIES, HUMAN RIGHTS, AND PUBLIC HEALTH: THE ETHICS OF TESTINGS AND CASE REPORTING

In the early and mid-1980s, at the outset of the encounter with AIDS in the United States and Western Europe, it was necessary to face a set of fundamental questions: Did the history of responses to lethal infectious diseases provide lessons about how best to contain the spread of HIV? Should the policies developed to control sexually transmitted diseases or other communicable conditions be applied to AIDS? If AIDS

were not to be so treated, what would justify such differential policies?

To understand the importance of these questions, it is necessary to recall that conventional approaches to public health threats typically provided a warrant, when deemed appropriate, for mandating compulsory examination and screening, breaching the confidentiality of the clinical relationship by reporting to public health registries the names of those diagnosed with “dangerous diseases,” imposing treatment, and in the most extreme cases, confining persons through the power of quarantine.¹ To be sure, many aspects of this public health tradition, forged at the outset of the 20th century, had been modulated over the decades, in part because of changes in the patterns of morbidity and mortality.

Nevertheless, it was the specter of the historically coercive aspects of the public health tradition that most concerned proponents of civil liberties and advocates of gay rights and bioethics as they considered the potential direction of public health policy in the presence of AIDS, a disease that so disproportionately affected disfavored groups, gay men, drug users, and the poor in minority communities. Although there were some public health traditionalists in the United States and elsewhere who pressed to have AIDS and HIV infection brought under the broad statutory provisions established to control the spread of sexually transmitted and other communicable diseases, they were in the distinct minority. In place of the conventional approach to public health threats, there emerged an alternative view, broadly defined as exceptionalist,² that took as its starting point the need to craft policies that were persuasive rather than coercive that viewed the protection of the rights of those who were infected as integral rather than as antagonistic to the goals of disease prevention. For those who advanced this new perspective, privacy and confidentiality were to be accorded great importance. In all, the goal was to avoid, at all costs, measures and practices that might be counterproductive, which might “drive the epidemic underground” by inspiring fear and distrust rather than fostering engagement between public health officials and those most at risk.

In those nations where the language of civil liberties informed the discourse on rights, it was common to assert that there was no tension between public health and civil liberties. Policies that undermined civil liberties would subvert the goals of AIDS prevention. Policies that effectively advanced the cause of AIDS prevention would protect civil liberties. On a global level, this perspective took the form of claims about the deep connection between health and human rights. Indeed, it was at the WHO's Global Program on AIDS, first directed by Jonathan Mann, that a sustained effort was undertaken to face the synergistic relationship between the protection of human rights and the struggle against AIDS.³ Central to that mission was the view that HIV was most apt to spread among the socially vulnerable and that the protection of the socially vulnerable from acts of discrimination, stigmatization, and coercion was integral to effective AIDS protection efforts.⁴ The specter of the Cuban response to AIDS in the late 1980s haunted the discussion of health and human rights. In that nation, a massive all but mandatory HIV-testing program had identified those who were infected. Following what it took to be established health principles, the Cuban government then quarantined the infected.⁵ How the exceptionalist perspective with its commitment to non-coercive approaches to HIV affected the policy is most clearly illustrated in the debates over HIV testing and the reporting of HIV by name to public health registries. From the moment of its introduction in 1985, the HIV test became the subject of intense debate. Fear that those identified as having HIV might be subject to discrimination and stigma; concern about how the diagnosis of HIV infection, in the absence of effective therapy, could produce unbearable psychological burdens; and a belief that testing had little to do with behavioral change, led AIDS activists generally, and gay leaders specifically, to adopt a posture of hostility and/or skepticism regarding the test. On the other hand, many public health officials believed that the identification of infected persons could play a crucial role in fostering behavioral change. Out of their confrontations emerged a broad consensus that, except in a few well-defined circumstances, people should be tested only with their informed, voluntary, and specific consent.⁶

Much of the early discussion of HIV testing occurred in the context of extreme therapeutic limits. And indeed, in the epidemic's early years the primary function of testing was as an adjunct to prevention efforts. As a result of clinical developments—the belief that treatment with zidovudine could delay the onset of symptomatic AIDS and the recognition of the importance of primary prophylaxis against *Pneumocystis carinii* pneumonia—by 1990, the medical significance of identifying those with early HIV disease had become clear. Consequently, the clinical and political context, involving a wide range of constituencies, of the debate about testing underwent a fundamental change.⁷ Gay organizations began to urge gay and bisexual men to have their antibody status determined under confidential or anonymous conditions.

Physicians pressed for AIDS to be incorporated into the medical mainstream and for the HIV-antibody test to be treated like other blood tests, i.e., given with the presumed consent of the patient. In the face of such pressure, those committed to the protection of the rights of the infected continued to insist that testing only occurs with specific informed consent. Whatever, in fact, occurred in the context of clinical settings, public policy in all economically advanced democratic nations continued to reflect a commitment to the voluntaristic premise of the exceptionalist perspective and the enduring influence of the ethical underpinnings first enunciated in the mid-1980s when medicine was all but impotent.

In the United States, pressure to shift the paradigm of testing away from the exacting standard of informed consent continued to mount. It was especially pronounced in the case of pregnant women and newborns.⁸ Diagnostic progress was to make it possible to determine whether HIV-positive newborns were truly infected soon after birth, and the improved prospects of clinical management were to make such determinations for infected infants appear all the more critical. So, it is not surprising that pediatricians became increasingly impatient with the strict regimen of explicit and specific consent that surrounded the testing of newborns for HIV⁹—all the more so because routine and unconsented testing of newborns for inborn errors of metabolism such as phenylketonuria was mandated in virtually every state and had provoked little by way of ethical objection. The 1994 finding that the administration of zidovudine during pregnancy could reduce the rate of vertical transmission by two-thirds¹⁰ only added to the pressure. In June 1996, the American Medical Association's House of Delegates passed a resolution calling for mandatory testing of pregnant women.¹¹ Even the Institute of Medicine, which early in the epidemic had opposed testing policies that abrogated the privacy rights of pregnant women, was, by the end of the 1990s, to endorse routine testing on the basis of an informed right of refusal, a much less exacting standard that specific informed consent.¹²

In the new millennium, the changes that had occurred in Western nations were to find expression in less developed nations.¹³ In 2004, UNAIDS and the WHO issued a policy statement that sought to respond to the fact that “the current reach of HIV-testing services remains poor: in low- and middle-income countries only 10% of those who need voluntary counseling and testing because they may have been exposed to HIV infection have access to it.” To face this challenge, the new policy proposed the routine offer of testing in clinics treating STIs, in the context of pregnancy to facilitate antiretroviral prevention of mother-to-child transmission, in settings where HIV is prevalent and antiretroviral treatment is available. While maintaining the importance of a human-rights-based approach to HIV testing, the policy significantly suggested that an opt-out approach be relied upon.¹⁴

Even more expansive was the proposal of Kevin De Cock and colleagues in 2006 which supported “routine testing

wherever *basic* HIV care and prevention are available.” Here it was not the possibility of treatment that was to drive the move to extended testing but the prospect of preventing HIV transmission. “The ideal that all citizens of high prevalence countries should know their serologic status and should be tested repeatedly over the course of their lives should become explicit targets of preventative efforts.”¹⁵

Indicative of the changing landscape was the fact that in South Africa, for example, advocates for widescale HIV testing, human rights and treatment activists among them, began to argue that exacting standards of informed consent tended to suppress the uptake of testing. Given the growing prospect of gaining access to antiretroviral treatment, they asserted that testing should be routinized with an opt-out provision. Those who feared the prospect of coercion, no matter how subtle, rejected such suggestions, arguing that only the strict standards of informed consent could protect both the rights and interests of people with HIV.

A course similar to that which occurred with testing characterized the debate surrounding case reporting for HIV infection. Given the profound stigma that surrounded AIDS in the epidemic’s first years and the extent to which individuals with or at risk for HIV feared the social consequences of having their diagnoses made public, it is not surprising that confidentiality of AIDS-related information assumed great salience. From the pragmatic perspective of public health officials it was crucial to preserve confidentiality as a way of assuring that those at risk would come forward for testing and counseling.¹⁶ Others objected on grounds of principle. Privacy was a value that should not be lightly set aside.

But, however central were the claims of privacy and the duty to protect confidentiality, they were not absolutes. Among the conventionally accepted limits to those claims occurred when individuals with infectious diseases were reported by name to confidential public health registries. Thus, it was not surprising that despite concerns about privacy, little opposition existed in the epidemic’s first years to making AIDS cases reportable by name.¹⁷ AIDS activists appreciated that such reporting was crucial to the understanding of the epidemiology of the new disease. The acceptance of AIDS case reporting requirements was facilitated by the well-established record of health departments in protecting such records from unwarranted disclosure.

With the inception of HIV testing, however, debate emerged about whether the names of all infected persons, regardless of whether they had received an AIDS diagnosis, should be reported. Activists who accepted AIDS case reporting opposed HIV reporting because of heightened concerns about privacy, confidentiality, and discrimination. For them the potential public health benefits of reporting were too limited and the burden on those who would be the subject of reporting too great to justify an abrogation of privacy.

While many public health officials in Western nations opposed HIV reporting because of its potential effect on the willingness of people to seek testing and counseling, some did become strong advocates of such reporting. Their claims sought to underscore the extent to which the public health benefits of HIV reporting would be like those that followed from more broadly conceived reporting requirements, such as those that applied to syphilis, tuberculosis, and AIDS itself.¹⁸

As therapeutic advances began to emerge in the late 1980s, and as the logic of distinguishing between HIV and AIDS became increasingly difficult to sustain, fissures began to appear in the relatively broad and solid alliance against named HIV reporting in the United States. At the end of November 1990, the U.S. Centers for Disease Control and Prevention declared its support for HIV reporting, which it asserted could “enhance the ability of local, state, and national agencies to project the level of required resources” for care and prevention services.¹⁹ The House of Delegates of the American Medical Association also endorsed the reporting of names as well.²⁰

Nothing more tellingly underscores the change that had occurred and the extent to which the claims of public health necessity had trumped the arguments of privacy than an editorial jointly authored by a CDC official, an AIDS activist, and a lawyer-ethicist long involved in AIDS-related work that appeared in the *New England Journal of Medicine* in 1997. “We are at a defining moment of the epidemic of HIV infection and AIDS. With therapy that delays the progression to AIDS, mental illness, and death, HIV infection or AIDS is becoming a complex clinical disease that does not lend itself to monitoring based on end stage illness. Unless we revise our surveillance system, health authorities will not have reliable information about the prevalence of HIV infection. To correct these deficiencies, we propose that all states require HIV case reporting.”²¹

At the end of 1999, in the face of lingering opposition from most AIDS activists, the CDC finally proposed that all states put in place an HIV-reporting system. And while it left open the possibility of reliance on unique identifiers that met strict performance criteria, it was clear that the use of names was viewed as preferable.²² Remarkably, of those states that adopted HIV case surveillance after the publication of the CDC’s recommendations, virtually all adopted coded systems. By 2002, only a handful of states had not adopted some form of HIV reporting. In other economically advanced democratic countries, the move to HIV name-based case reporting did not follow the American pattern.

THE ETHICS OF RESEARCH

As was true of public health practice, the first years of the epidemic forced a rethinking of the ethics of human subjects research. Such a rethinking extended beyond the United

States as the debate in the late 1990s broadened to questions of research conducted in poor countries under the sponsorship of wealthy nations.

The ethical analysis of research involving human subjects emerged against a backdrop of torture, abuse, and scandal. From the Nuremberg Code, which sought to set out the basic moral principles for research in the wake of the postwar trial of Nazi doctors, to the establishment of the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, created in the wake of the revelations about the infamous Tuskegee syphilis experiment, the need to protect potential subjects captured the attention of those appalled by the practice of science. In 1978 the National Commission issued the Belmont Report, which codified a set of ethical principles that sought to inform and guide the work of researchers.²³ Those principles provided the foundations for regulations subsequently enacted by the Department of Health and Human Services and the Food and Drug Administration. At the core of those guidelines was the radical distinction between research designed to produce socially necessary, generalizable knowledge and therapy designed to benefit individuals. Against the former, the Belmont Report held, individuals, especially those who were socially vulnerable, needed protection against conscription. AIDS forced a reconsideration of this formulation.

The HIV epidemic provided the circumstances for the emergence of a broad and potent political movement that sought to reshape radically the conditions under which research was undertaken. The role of the randomized clinical trial, the importance of placebo controls, the centrality of academic research institutions, the dominance of scientists over subjects, the sharp distinction between research and therapy, and the protectionist ethos of the *Belmont Report* were all brought into question. Although scholars concerned with the methodological demands of sound research and ethicists committed to the protection of research subjects played a crucial role in the ensuing discussions, both as defenders of the received wisdom and as critics, the debate was largely driven by the articulate demands of those most threatened by AIDS.²⁴ Most prominent were groups such as the People with AIDS Coalition and ACT-UP, organizations made up primarily of white, gay men. They were joined by community-based physicians who identified closely with the plight of their patients.

What was so stunning, disconcerting to some, and exciting to others was the rhythm of challenge and response. Rather than the careful exchange of academic arguments, there was the mobilization of disruptive and effective political protest. Most remarkable was the core demand. As one analyst noted, “The shortage of proven therapeutic alternatives for AIDS and the belief that trials are, in and of themselves, beneficial have led to the claim that people have a right *to be* research subjects. This is the exact opposite of the tradition started

with Nuremberg that people have a *right not to be* research subjects.”²⁵ That striking reversal resulted in a rejection of the model of research conducted at remote academic centers, with restrictive (protective) standards of access and strict adherence to the “gold standard” of the randomized clinical trial.

Blurring the distinction between research and treatment, expressed forcefully through the slogan “A Drug Trial Is Health Care Too,” those insistent on reform sought to open wide the points of entry to new “therapeutic” agents both within and outside of clinical trials; they demanded that the paternalistic ethical warrant for the protection of the vulnerable from research be replaced by an ethical regime informed by respect for the autonomous choice of potential subjects who could weigh, for themselves, the potential risks and benefits of new treatments for HIV infection. Moreover, the revisionists demanded a basic reconceptualization of the relationship between researchers and subjects. In place of protocols imposed from above, they proposed a more egalitarian and democratic model in which negotiation would replace a scientific authority. Indeed, research “subjects” were now thought of as “participants.” Furthermore, the role of the carefully controlled clinical trial as providing protection against the widescale use of drugs whose safety and efficacy had not been proven no longer commanded unquestioned respect.²⁶

The new perspective did not go without challenge. Some were concerned that the proposed regime would make the conduct of research, so crucial to the needs of those with HIV/AIDS, all but impossible,²⁷ others feared that desperate individuals would, in the absence of the now discredited (paternalistic) ethos, be subject to deception.²⁸

The AIDS-inspired challenge to the ethics of research was not restricted to issues within the United States. Just as the protective regime surrounding research in the United States was a product of a history of abuse, efforts to enunciate ethical standards for the conduct of research in third world nations were shaped by a history of exploitation, a history characterized by investigations on the poor designed to serve the interests of the privileged. Central to those efforts was the belief that the ethical principles first encountered in industrialized nations had direct bearing on the norms that should govern research in very different settings.²⁹ Such universalism took as a given the need to assume that insights regarding cultural differences not serve as the basis for moral relativism.

Just as individual informed consent was the first principle of the ethics of research in advanced industrial nations, it was at the heart of the codes designed to guide research in the poorest nations. To preclude exploitation, international consensus also existed on the extent to which it was critical that research be responsive to the health needs and priorities of the community in which it is to be carried out.³⁰ What would

remain a matter of uncertainty, however, was whether the needs of the poorest and the requirement of responsiveness could justify research that would be unacceptable in the richest nations, whether the principle of universalism could accommodate research in Burundi that would be prohibited in Brooklyn.

That was the issue that would animate a furious international debate occasioned by the 1994 finding that AZT administered to infected women in the second and third trimesters and to their infants for 6 weeks could reduce by two-thirds the rate of vertical transmission.³¹ Although superficially a conflict over a technical matter involving research design—the role of placebos—the dispute touched on the deepest questions of what ethical conduct meant in a world characterized by great inequalities and profound inequities.

In 1997, an editorial appeared in the *New England Journal of Medicine* denouncing an international trial designed to determine if it were possible to develop an inexpensive clinical intervention that could provide something approaching what had been attained in wealthy nations in reducing the risk of mother-to-child HIV transmission.³² Those trials assumed that even if successful, the more affordable interventions would be less effective than was standard in Europe and America.

Given the burden of pediatric AIDS in Africa and Asia, it was a matter of some urgency that trials begin to determine whether cheaper alternatives to the standard regimen could achieve at least some measure of reduced maternal fetal HIV transmission. In June 1994, a special consultation of the WHO considered the challenge and called for the launching of studies to achieve that goal. The consultation made clear its conclusion that placebo-controlled trials “offered the best option for obtaining rapid and scientifically valid results.”³³

There was no question that a placebo-controlled trial would have been considered unethical in the United States or any other advanced industrial nation. No trial that denied access to the effective standard, or to an intervention thought to hold the promise of being at least as effective as, if not more effective than, the prevailing standard of care, would have satisfied the requirements of ethical review. The question posed by the furious controversy that unfolded was whether it was ethical to conduct such a trial in a poor country. The *New England Journal of Medicine* gave its answer unambiguously: “Only when there is no known effective treatment is it ethical to compare a potential new treatment with a placebo. When effective treatment exists, a placebo may not be used. Instead, subjects in the control group of the study must receive the best known treatment.”³² Given this premise, the *Journal* rejected as irrelevant the fact that health care available in most Third World countries provided nothing like health care available in industrialized countries. Citing the Declaration of Helsinki, the international code of

research ethics adapted by the World Medical Association in 1964, for authority, the editorial noted that control groups had to be provided with the best current therapy, not simply that which was available locally. “The shift in wording between ‘best’ and ‘local’ may be slight but the implications are profound. Acceptance of this ethical relativism could result in widespread exploitation of vulnerable Third World populations for research programs that could not be carried out in the sponsor country.”³²

Those who rejected the *Journal’s* viewpoint made clear that placebo-controlled trials were dictated by the urgency of the situation. Only placebo-controlled trials could provide “definitive,” “clear,” “firm” answers about which interventions worked, thus allowing governments to make “sound judgments about the appropriateness and financial feasibility of providing the intervention.” The failure to employ a placebo would have made it difficult to clearly determine whether the affordable but less effective intervention was better than no intervention at all. In short, placebos were crucial to policymakers required to make relatively costly decisions under conditions marked by profound poverty and scarce public health resources.³⁴

Paralleling the debates over maternal fetal transmission of HIV were those that surfaced over the ethics of AIDS vaccine trials. In this case, the focus was on those research participants who might become infected with HIV during a trial. On the one hand, there were those who argued that such individuals be provided with optimal care—the retroviral therapy available in the developed countries. On the other hand, there were those who asserted that care should reflect that which was consistent with what was available in the host nation.³⁵ So divisive was this controversy that UNAIDS could not come to an agreement on the appropriate ethical norm and indeed had to settle for a procedural rather than substantive solution, a solution that focused on how to reach acceptable agreement rather than one that put forth a standard to guide such deliberations.³⁶

The controversies ultimately provoked an international effort to reconsider ethical standards of research in the Third World. The World Medical Association undertook a series of consultations on the revision of the Declaration of Helsinki; the Council for International Organizations of Medical Sciences (CIOMS) did so as well. Finally, within the United States, which funded much of the international research that had been subject to scrutiny, the National Bioethics Advisory Committee took up the issue of studies in poor nations.

While those who saw in any effort to craft “flexible” standards that reflected the uniquely pressing context of international poverty and inequality the treacherous embrace of moral relativism, their opponents persisted in arguing that a failure to consider the context of investigation is a failure of moral understanding. Principles could be universal; their application could not be rigid.³⁷

How profoundly difficult the issues of research in the context of global poverty were is best demonstrated by conclusions reached by the World Medical Association, the CIOMS, and the National Bioethics Advisory Committee. Despite the fact that each body understood the considerable attention that was focused on their efforts, and the importance of forging a common standard, consensus could not be attained. Only the World Medical Association in its revision of the Declaration of Helsinki adopted the position that once an effective therapy was found it became the standard against which all further interventions had to be measured.³⁸ Regardless of the cost of the intervention, placebo controlled trials were no longer tolerable. The CIOMS recommendations, on the other hand, concluded that there might be sound scientific and ethical reasons to reject the “best current” method standard, if the failure to use a placebo would make the results inapplicable in the host country where the search for affordable alternatives was essential.³⁹ That too was the position adopted by the U.S. National Bioethics Advisory Committee.⁴⁰

In the end then, the AIDS-inspired debate over research ethics opened wide the question of whether ethical principles could serve as a universal standard in a world characterized by gross inequality, whether that very inequality made adherence to universal standards morally imperative.

SECURING ACCESS TO CARE

In the first years of the epidemic there was little that medicine could offer those with HIV disease. Indeed, that was the context, as noted, within which AIDS activists struggled to increase access to experimental trials. As the prospects for clinical intervention improved, first with the use of prophylactic treatment to prevent *Pneumocystis pneumonia* and other opportunistic infections and then with AZT, the first widely prescribed antiretroviral agent, it was inevitable that access would be shaped by the extent to which health-care systems were governed by principles of equity.

In the United States, for example, some who needed treatment had private insurance although they had not infrequently faced efforts on the part of their insurers to deny them coverage for their HIV-related conditions. Those who had very limited resources or who became impoverished because of their disease *could* qualify for Medicaid, the joint federal-state program that covered some of the poor. But many remained unprotected.⁴¹ To meet their needs, special programs were developed. The federal government, through the Ryan White CARE Act, directed significant sums to localities to provide medical services. Among the initiatives under the Act was the AIDS Drug Assistance Program (ADAP), designed to pay for AIDS-related medicines. But the patchwork effort was never adequate and left many without needed protection.⁴²

When the protease inhibitors emerged in the mid-1990s and combination antiretroviral therapy became the standard of care, the system was strained to the limits. Medication costs alone for those receiving care could range from \$10,000 to \$15,000 a year.⁴³ One review of the dramatically improved therapeutic prospects added the caveat that the new achievements were important “at least for those socioeconomically privileged.”⁴⁴ ADAP experienced persistent shortfalls in funding. When that was the case, it was necessary to resort to a host of rationing strategies. At one point, nearly half of state ADAP programs limited access to protease inhibitors.⁴⁵ The U.S. story with regard to treatment of HIV disease simply reflected the broader failure to adopt a system of health-care delivery that guaranteed access to treatment as a matter of social right. Where principles of social solidarity or egalitarianism defined the basic contours of the health-care system, the inequities that characterized the U.S. situation did not prevail.

On an international plane the prospect of effective but extraordinarily expensive antiretroviral treatment would pose far-reaching ethical challenges. What justification was there for a system of pricing that made the cost of drugs beyond the reach of the desperate? Could markets ever respond to need where effective demand was nil? Could the monopoly confirmed by patent rights be compatible with a response dictated by claims of the dying? Was the treaty on intellectual property rights, incorporated into the WTO’s international regime, a barrier to survival in context of the AIDS epidemic? What moral obligation did the wealthiest nations have to the poorest to provide the resources necessary to purchase the new lifesaving agents and build the medical infrastructure necessary for their appropriate administration? Was there any reason to believe that a global community that permitted millions to die each year from treatable and preventable diseases such as tuberculosis and malaria would respond differently in the face of AIDS?

AIDS activists ultimately seized on this issue—Life Over Profits—and began an international campaign to confront the pharmaceutical industry. What might have seemed an utterly quixotic undertaking would, however, ultimately take on worldwide dimensions linking protesters in the United States, France, South Africa, institutional proponents of global health such as the WHO, and a sympathetic public. By the end of the 1990s, the pharmaceutical industry was placed on the defensive, perceived as protecting narrow self-interest when the lives of millions were at stake. Against the claims that high prices were necessary to fuel the engine of research, that patent protections were crucial to spurring investments in drug investigations, those who sought to turn the terms of discourse asserted that urgency demanded that the barriers to drug access tumble. As a leader of the International AIDS Society said in 2001, “This is a war, and when you are in a war as we are worldwide with HIV which will claim more lives

than any other infectious disease in history, the rules of the game have got to change.”⁴⁶

In the face of continuing criticism, drug companies argued that at most the price of drugs was a small part of the problem. The issue, they said, was the fundamental limits of the medical infrastructure of poor nations and the inability of the poorest to pay for even heavily discounted drugs. But such arguments, whatever their merits, carried little weight, as long as prices remained high or as long as the offer to negotiate price reductions entailed protracted processes. In early 2001 *The Lancet* thus wrote, “The time has come for the pharmaceutical industry and the governments who represent them in trade disputes to acknowledge that the world is facing an extraordinary challenge.”⁴⁷

Ultimately, under pressure from generic drug manufacturers, prices began to tumble, and pharmaceutical firms began to accept the notion of differential or equity pricing.⁴⁸

As drug prices began to fall, it became ever more apparent that challenges posed by the international pharmaceutical industry as it resisted pressure by activists, the generic manufacturers and international public opinion, were not without foundation: Even if drugs were to be provided at cost, even if the principle of equity pricing were to guide sales, even if nations pursued the option of compulsory licensing and parallel imports, the cost of providing anti-retroviral therapy was simply beyond the reach of the poorest and most HIV-burdened nations. And even if drugs could be paid for, the necessity of a medical infrastructure that could offer and monitor the use of drugs in a way that was attentive to the needs of individual patients and the risks to public health from drug resistance would require huge investments. This was the context within which a remarkable movement to create a massive funding effort to respond to the threat of AIDS would take shape.

In 2001, a Harvard University group issued a call to the global community. In an era of effective antiretroviral therapy, access to care was a moral imperative.⁴⁹ “We believe that on moral, health, social, and economic grounds the international community should provide new scientific and financial leadership for a rapid scaling-up of AIDS treatment in the poorest and hardest hit countries of the world.” The goal was to treat one million patients in Africa within 3 years. It was simply untrue that the infrastructural capacity of African health-care systems precluded the provision of treatment. There were limits but they could be overcome with appropriate international assistance.

To those who had asserted that efforts to provide treatment would subvert already fragile prevention programs, a claim made by many of the humanitarian foundations that had funded such efforts, the Harvard group responded directly: “Treatment is necessary to optimize prevention efforts. When treatment is not available, less incentive exists for an individual to take an HIV test since HIV positive status not only

is associated with social stigmatization but is tantamount to a death sentence. Ultimately, treatment of infected individuals may become a major tool in AIDS prevention.”

Finally, it was argued that the provision of treatment was necessary to preserve the social fabric of societies affected with high levels of infection—“If the current lack of treatment continues, a demographic shift is predicted...such that teenagers will outnumber their elders by 2020. Further, without treatment, millions of adults in the prime of their working lives will die of AIDS and with them skills and knowledge that are necessary for human and economic development.”

In assessing the potential costs of such an effort the Harvard group calculated that 1 million Africans could be treated for \$1.1 billion a year. Were the program to expand to 3 million individuals, a goal achievable in 5 years, the cost would rise to \$3.3 billion a year. (In considering the extension of care to non-Africans who could benefit from inaccessible treatment, it was estimated that approximately \$1.4 billion would be needed in the first year and \$4.2 billion by year 5.) But even so vast an effort would not cover large numbers of people in need of care. To reach those millions could require significant investments in medical infrastructure that were not calculated. Finally, in addition to the costs of care, it was estimated that for prevention efforts for Africa alone \$3 billion was needed annually. Thus, in all, the first year’s effort in Africa would require \$4 billion. To meet this vast commitment it was proposed that an HIV/AIDS Prevention and Treatment Trust Fund be created. The sum involved, while very large, was not beyond the capacity of the wealthiest nations—0.01% of an aggregate GNP of \$23 trillion.

The moral urgency of AIDS treatment was amplified by UN Secretary General Kofi Annan, who called for a global trust fund that would spend \$7–10 billion a year over “an extended period” to face the threat to the world’s poorest people.⁵⁰ Most striking was his assertion that the care which had for so long eluded men, women, and children in the less developed nations was a matter of right. Speaking to Africa’s lenders he said, “Even a year ago few people thought that effective treatment could be brought within reach of poor people in developing countries. There has been a worldwide revolt of public opinion. People no longer accept that the sick are dying simply because they are poor. Everyone who is infected should have access to medicine and medical care. Now we know that that is possible, it is surely an ethical imperative.”

Strikingly, the idea of a global trust fund not only won the support of editorialists identified with a liberal or social democratic posture but by powerful institutions as well. Within days of Annan’s speech the International Monetary Fund and the governing committee of the World Bank endorsed the fund, in principle.⁵¹ The Gates Foundation pledged \$100 million to the effort.⁵² In less than a year’s time, the Global Fund

had been created. By 2005, AIDS funding for developing countries had reached \$8 billion but even that vast expansion represents a shortfall given the pressing needs.

The gulf between conviction and action has become all the more stark as prevailing and pervasive international inequality has taken on moral significance: What was the unfortunate has become unfair; inequality has become inequity. In that translation, the possibility of human agency of political action to effect change opened wide the shortfall—the deep moral failure in allocating resources for AIDS care.

CONCLUSION

This chapter began with an analysis of ethical and policy issues that emerged in the United States and other economically advanced nations bounded by the liberal political tradition; it has concluded with a discussion of the profound moral challenge posed by the AIDS epidemic in the poorest nations, focusing on the question of access to care. It is in those nations that the epidemic will take its toll in tens of millions of lives.

No ethical analysis of the challenges posed by AIDS will ever again be sufficient if it is restricted to the challenges faced in wealthy developed nations. Indeed, increasingly the analysis will need to be driven by the complexities of an epidemic in the world's poorest nations. Older concerns rooted in a focus on the need to protect the privacy rights of individuals will inevitably be overshadowed by new concerns about equity. It is not that the older ethics will have no relevance. But with life itself in the balance, unless the material requirements of those who need access to care are given preeminence, little else will matter.

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Information and Communication Technologies for Prevention and Control of HIV Infection and Other STIs

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INTRODUCTION

Innovative tools such as the Internet, personal digital assistants, tablet computers, cell phones, and other technologies are a growing arsenal in the effort to prevent and* control HIV and other sexually transmitted infections (STIs). As the price of technology decreases, some of these tools have become more ubiquitous even in resource-constrained settings, and their uses are just beginning to be explored in depth. In this chapter, we review the opportunities and challenges of using information and communication technologies (ICT) for HIV/STI surveillance, diagnosis, partner notification, prevention, clinical management, and provider training, in both resource-rich and resource-constrained settings.

To do this, we conducted a literature review of English-, Spanish-, and Portuguese-language publications and conference proceedings in databases such as MEDLINE (from 1966 to April 2007), the Cochrane Library Database (up to Issue 1, 2007), LILACS (the Latin American and Caribbean Health Science Literature Database; from 1982 to April 2007), as well as the Google search engine. Additional articles were identified from references extracted from relevant articles, reviews, and from experts in the field.

SURVEILLANCE

As the diversity of HIV/STI epidemics around the world becomes more apparent, existing HIV/STI surveillance systems must be able to flexibly capture data to describe emerging infections or to explain changes over time in mature epidemics. Surveillance systems vary from simple systems that collect data from a single source, to electronic systems that receive data from many sources in multiple formats, to complex surveys. For ongoing systematic reporting, public

health agencies increasingly rely on automated electronic laboratory reports of notifiable diseases and Internet-based confidential morbidity reporting from physicians. Other efforts, dubbed “second-generation surveillance systems,” collect data among sentinel populations most at risk of becoming newly infected with HIV/STIs, e.g., populations with high levels of risk behavior or young people at the start of their sexual lives.¹

HIV/STI surveillance often extends beyond case-based reporting to the monitoring of sexual-risk behavior at the population level. Such behavioral surveillance and associated research capture risk factor data, often including sensitive and stigmatized behaviors. This is best done in a way to minimize social desirability, reporting, and other biases.^{2,3} Data collection methods that reduce the need for face-to-face acknowledgment of these behaviors, or that ensure anonymity, provide an important means of reducing these biases.^{4,5} This may be facilitated by use of computer-assisted self-interviews (CASIs). CASIs with audio, video, or telephone enhancements have been used to assess general risks, patient histories, and a variety of health data, such as psychiatric and other clinical and public health data. In particular, using CASI, HIV/STI risks have been surveyed by researchers among populations including blood donors,^{6,7} university students,⁸ adolescents,^{9,10} injection drug users,^{11,12} alcohol users,¹² women at risk of seroconversion,^{13,14} and HIV-seropositive individuals.^{15,16} CASI studies conducted in STI clinics have shown enhanced reporting of some sensitive or stigmatized behaviors, as compared with face-to-face forms of data collection,¹⁷ though not for all behaviors or equally by sex of the respondents.^{18,19} Advantages of CASI-collected data include lower levels of missing data and of data entry errors as well as reduced costs.

In a systematic review of audio computer-assisted self interviews (ACASIs) for assessment of drug use and sexual behavior²⁰ conducted in 2004, it was found that out of 24 reviewed papers, only 3 described research implemented outside the United States. In the time since that review, the literature on use of ACASI in resource-constrained settings

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has grown, showing evidence of usefulness in countries such as Brazil, Vietnam, Thailand, India, Kenya, Zimbabwe, and South Africa, among others.^{21–23} The NIMH Collaborative HIV/STI Prevention Trial conducted a feasibility study of ACASI in convenience samples in China, India, Peru, Russia, and Zimbabwe. The results suggested a high-comfort level among participants. The authors reported that despite variable computer experience and literacy, feasibility study participants reported ease in completing ACASI, and preferred a computer to an interviewer for answering sensitive questions, or had no preference.²⁴

In clinical practice or research, the use of ACASI in conjunction with electronic health records could ultimately provide high-quality surveillance data linking risk behaviors to HIV/STI prevalence¹⁸ and may also have some advantages in terms of systems efficiency. For example, a touch-screen ACASI blood donor interview system developed for blood banks in the United States was found in one study to increase donor time by 4 minutes but reduced staff time by 5 minutes;²⁵ the system also generates automated reports to the Food and Drug Administration. Use of an ACASI HIV counseling and testing tool by staff of a community-based mobile HIV testing organization in Seattle resulted in the agency doubling the number of HIV tests offered, with the same staffing level; the automated generation of required reports to the health department also shortened the billing and payment cycle.²⁶ For busy clinicians, ACASI sexual histories could be a practical tool for identifying persons at increased risk for infection.^{18,27} ACASI interviews done prior to the clinician encounter (e.g., while the patient is in the waiting room) could increase the efficiency of the clinical visit,²⁸ allowing clinicians to triage and tailor counseling messages to the patient's specific situation.²⁹

Telephone modalities have been explored for HIV/STI assessment. Computer-assisted telephone interviews (CATI) have been used in several population studies to collect HIV risk data.^{30–39} These have been conducted at a population level from centralized call centers,⁴⁰ as well as through use of personal digital assistants (PDAs) in venues where higher risk populations may congregate, such as at Gay Pride events.⁴¹ Mobile phone and interactive computer interviewing have been used to measure HIV-related risk behaviors, e.g., in a survey of 2416 adult men returning to Hong Kong from Shenzhen in mainland China during April 1997, who were intercepted at the exit of the checkpoint by systematic sampling.⁴²

Cell phones also have been used to collect data and report sentinel events such as medication side effects. Cell-PREVEN Fig. 108-1 is an interactive computer system using cell phones for real-time collection and transmission of adverse events related to metronidazole administration among female sex workers (FSW) in Peru.⁴³ Curioso et al. developed Cell-PREVEN as an application for cell phones in Spanish, based on a system from Voxiva Inc. Cell phones

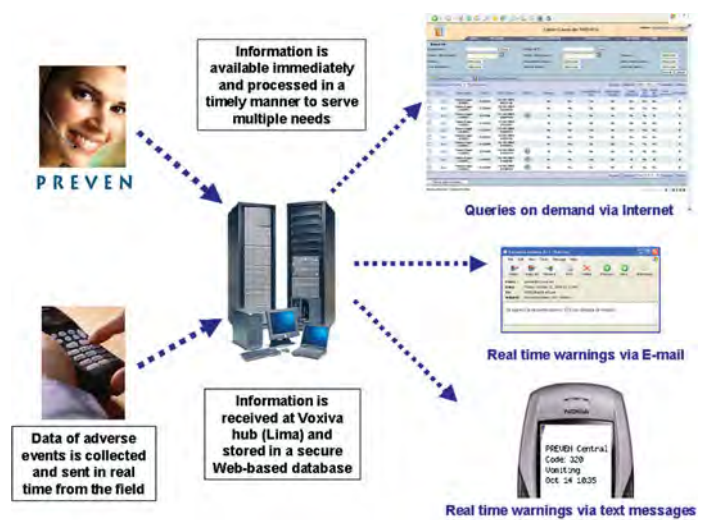


FIGURE 108-1. Description of cell phone and Internet data collection, “Cell PREVEN.”

were used successfully as a method of data reporting for tracking adverse events attributable to medicine given to FSW in three communities. Information was stored in an online database, where it could be immediately accessed worldwide and exported over a secure Internet connection. E-mail and text messages sent to mobile devices alerted key personnel to selected symptoms. Both health-care interviewers and FSW were satisfied with cell phones as a method of data collection, and the system led to much earlier and more complete reports of adverse effects.⁴⁴

Other software applications are being developed so that cell phones and PDAs can be used to transfer disease surveillance data, including for HIV infection, via a General Packet Radio Service connection or Short Message Service data channel into a central database, and to allow health workers to order medication, send alerts, and download treatment guidelines.⁴⁵

Handheld CASI is emerging for data collection and intervention delivery due to advantages such as portability, lower cost compared to laptops, and energy efficiency, which could make handheld computers (e.g., PDAs, cell and “smart” phones) ideal for collecting data in the community. Data collection using handheld computers has been shown to be a faster and more accurate method for transferring data than paper-based methods, including scantron forms.⁴⁶ A 2004 conference on the use of handhelds in Africa concluded that PDAs were cheaper than paper-based health data collection due to reduced data management costs.⁴⁷ One study conducted among adolescents in South Africa to ascertain sexual risk, compared PDA to paper data collection and found reporting was equivalent by modality, but that the PDA format collected more complete data.⁴⁸ Data entry via a pen-based PDA may reduce technology anxiety compared to other forms of computer-aided data collection.⁴⁹

Satellite (<http://pda.healthnet.org/>) are using the cell phone network in Uganda to transfer data to a central site. Local health-care workers collect data on Palm Pilots and then connect to a local, battery-powered server called a "Wide Ray Jack." This server allows data to be sent to and from a central database via a cell phone modem. In Peru, the PREVEN project conducted a cross-sectional field study in 20 cities with an open-source application for PDAs to collect sexual behavior data. The data collected with the PDA application, called PDA-PREVEN, showed very close agreement between paper and PDA responses. The project suggested that PDAs are a feasible alternative to paper forms for field data collection in a developing country.⁵⁰

Computerized data collection for documenting risk behaviors may increase the reliability of sensitive data⁵¹ as well as provide other advantages such as eliminating interviewer bias, ensuring that appropriate questions are asked of respondents, fewer missing data, and reduced data entry costs as compared to paper methods. Resource-constrained countries especially need data collection approaches that are reliable, inexpensive, readily available, and do not require extensive technological expertise to implement or use.⁴⁴ Cell-phone-based systems may best fit these requirements.

DIAGNOSIS AND PARTNER NOTIFICATION

Timely HIV/STI diagnosis and partner notification are important actions to initiate treatment and reduce further transmission in the population. Knowledge of an HIV-seropositive status is an important motivator for changing sexual risk practices and seeking medical care.^{52,53} Additionally, with the current initiatives to provide universal access to antiretroviral therapy in developing countries, participants diagnosed with HIV will benefit from early entry into the health-care system.⁵⁴

To increase HIV/STI diagnosis and improve partner notification, a variety of informatics tools that include the Internet and cell phones are being used. Use of these tools is appealing when they provide anonymity and convenience for the participants. In this section, we will review new technology approaches for HIV/STI testing and partner notification.

■ STI SCREENING

For several years, innovative World Wide Web sites to increase STI screening through on-site or self-collected specimens have been created in developed country settings. Some of these Web sites are www.inspot.org, www.STItest.org, and www.iwantthekit.org. InSPOT (see [Fig. 108-2](#)), an acronym for Internet Notification Service for Partners or Tricks, started on October 2004 in the city of San Francisco.⁵⁵ Although mainly used for partner notification, this Web site also offers information regarding HIV/STI prevention, on-site diagnosis

and treatment, as well as locations of STI clinics in the U.S. cities of San Francisco, Chicago, Los Angeles, Philadelphia, and Portland, in the states of California, Colorado, Massachusetts, Indiana as well as the country of Romania (www.inspot.org).

STItest.org is a Web site of the San Francisco City Clinic that provides on-site testing, treatment, and information about a variety of STIs. An interesting component of this Web site is the opportunity for participants to create their laboratory requisition slip and receive their syphilis test online (www.STItest.org). During the first year of launching this program, 218 tests were performed and six patients were diagnosed and treated for a new syphilis infection.⁵⁶

Another Web site used for STI screening is www.iwantthekit.org ([Fig. 108-3](#)). This Web site provides an educational Internet-based program to encourage women older than 13 years to request, use, and send back to the laboratory home-sampling kits for self-collection of specimens for *Chlamydia trachomatis* testing. After 1 week, the participants can call to the program and by using their kit's unique ID number and a private password can obtain their results. If the result is positive, the participant is referred to the nearest clinic to receive free treatment. During 7 months, 10% (41/400) of participants were found to be Chlamydia positive and 95.1% received treatment. There was good acceptability of this method: 89.5% of women preferred self-collection and 94% rated collection as easy or very easy. Compared to the community kit pick-up approach, this online program has shown better results: 97.2% of kits were requested by e-mail and 87.5% of kits returned for testing were e-mail requested.⁵⁷

The Internet has been used to advertise kits that involve self-collection of specimens for HIV and STI at home that later are sent to the laboratory for analysis. Frank et al. in 1997 demonstrated that anonymous HIV-1 home specimen collection (HSC) kits with pretest and post-test telephone counseling provided a safe and effective alternative to conventional venous blood HIV-1 antibody testing.⁵⁸ Further studies have shown that HSC kits increase HIV testing among persons not previously tested, 60% of all users and 49% of those who tested HIV positive using the kit had never been tested before. Additionally, this way of testing is an acceptable option in the United States for persons with less access such as ethnic minorities or bisexuals.⁵⁹

Only one HSC kit for HIV, The Home Access HIV-1 Test System manufactured by Home Access Health Corporation, has been approved by the U.S. Food and Drug Administration.⁶⁰ This kit may be purchased over-the-counter or on the Internet. The blood samples are taken at home by finger prick, and the dried blood spots are mailed to a laboratory for testing using an anonymous personal identification number (PIN). The pretest, and posttest counseling and the results are received through a toll-free telephone number using the PIN.⁵⁸

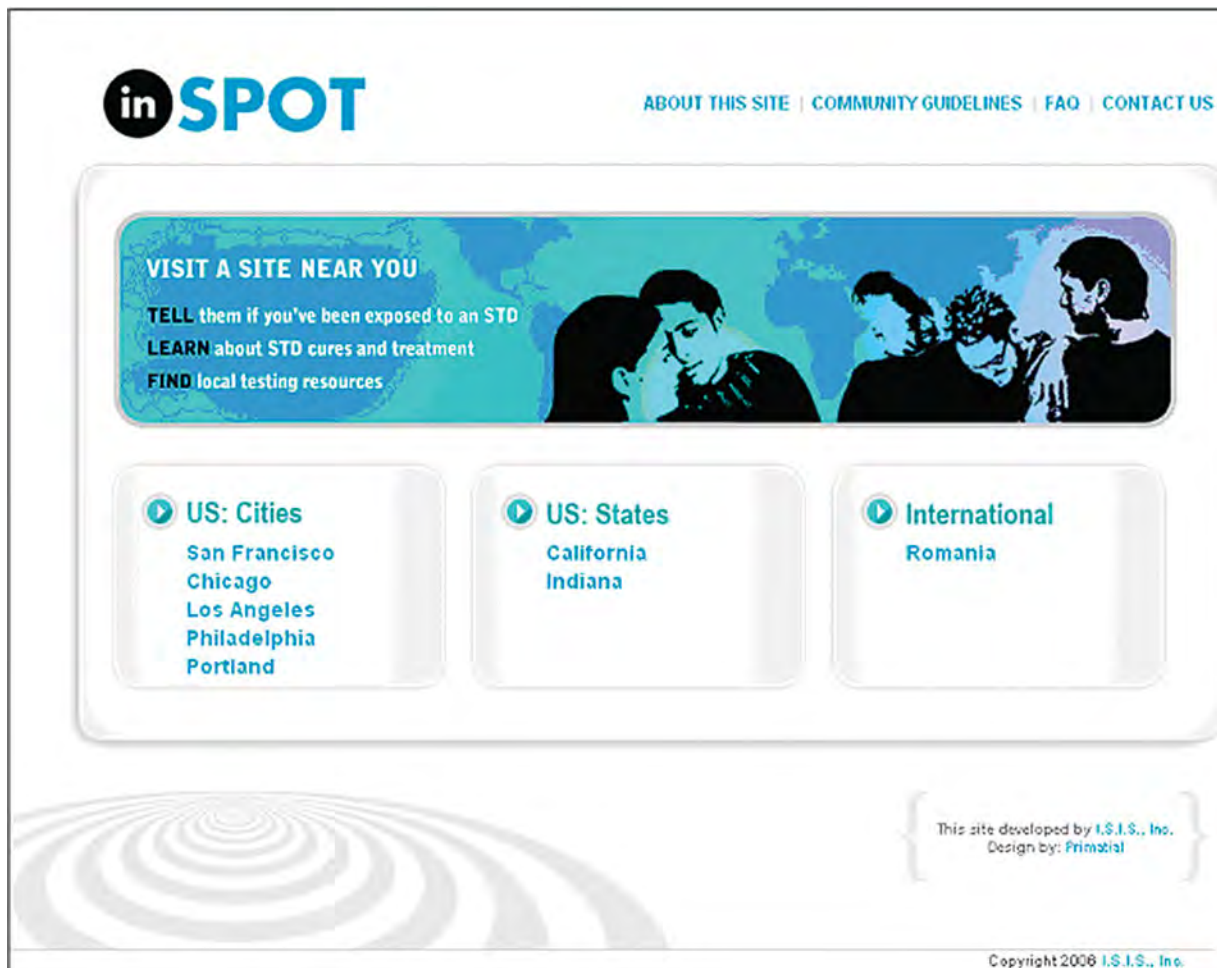


FIGURE 108-2. Screenshot of Internet-facilitated partner notification, “In SPOT” (www.inspot.org).

Evaluation of HIV self-testing is now being studied in the United States; this way of testing requires consumers to collect the sample, run the test, and interpret the results.⁶⁰ Although as of mid-2007, there were no FDA cleared home-use test kits, the existence of rapid HIV testing and HSC make its future implementation feasible. Additional research about the acceptability of the test in high-risk populations, feasibility to perform and interpret self-tests correctly, its impact on confirmatory testing, and on risk behaviors still need to be addressed.⁶¹

■ PARTNER NOTIFICATION: VIA THE INTERNET, VIA E-MAIL, WHAT ELSE IS COMING?

Partner notification—the process by which sex partners of index cases with HIV/STI are informed of their exposure and the need to receive medical evaluation⁶²—traditionally has utilized telephone, mail, or personal contact. Recently, technologies such as cell phones, Internet, email and text messaging have been adopted.⁶³

In the first study addressing the use of the Internet for online partner notification, participants of an Internet chat

room were notified via e-mail messages about a syphilis cluster and encouraged to seek medical evaluation. As a result, 42% of named partners were notified and tested.⁶⁴ Further studies have analyzed different methods to improve partner response rates; some of the recommendations include the involvement of the index patient on the notification, conditional referral of the index patient where he/she is given a distinct time period to notify partners before the provider contacts them, inclusion of personalized messages that reference a specific health matter, the availability of health educators on chat rooms, and the provision of information on STI-testing sites, STIs, and partner referral on Web sites frequently visited by MSM.⁶⁵

The InSPOT Web site was created to allow newly diagnosed patients with an STI/HIV infection the ability to inform anonymously or confidentially their partners through an electronic postcard that they might have been exposed to an STI or HIV. In 2005, this Web site had over 93,000 visitors and approximately 16,000 e-cards were sent to 26,000 recipients; 77% of these e-cards were sent anonymously, 14% notified about Chlamydia, 17% about gonorrhea, and 15% about syphilis.⁶⁶

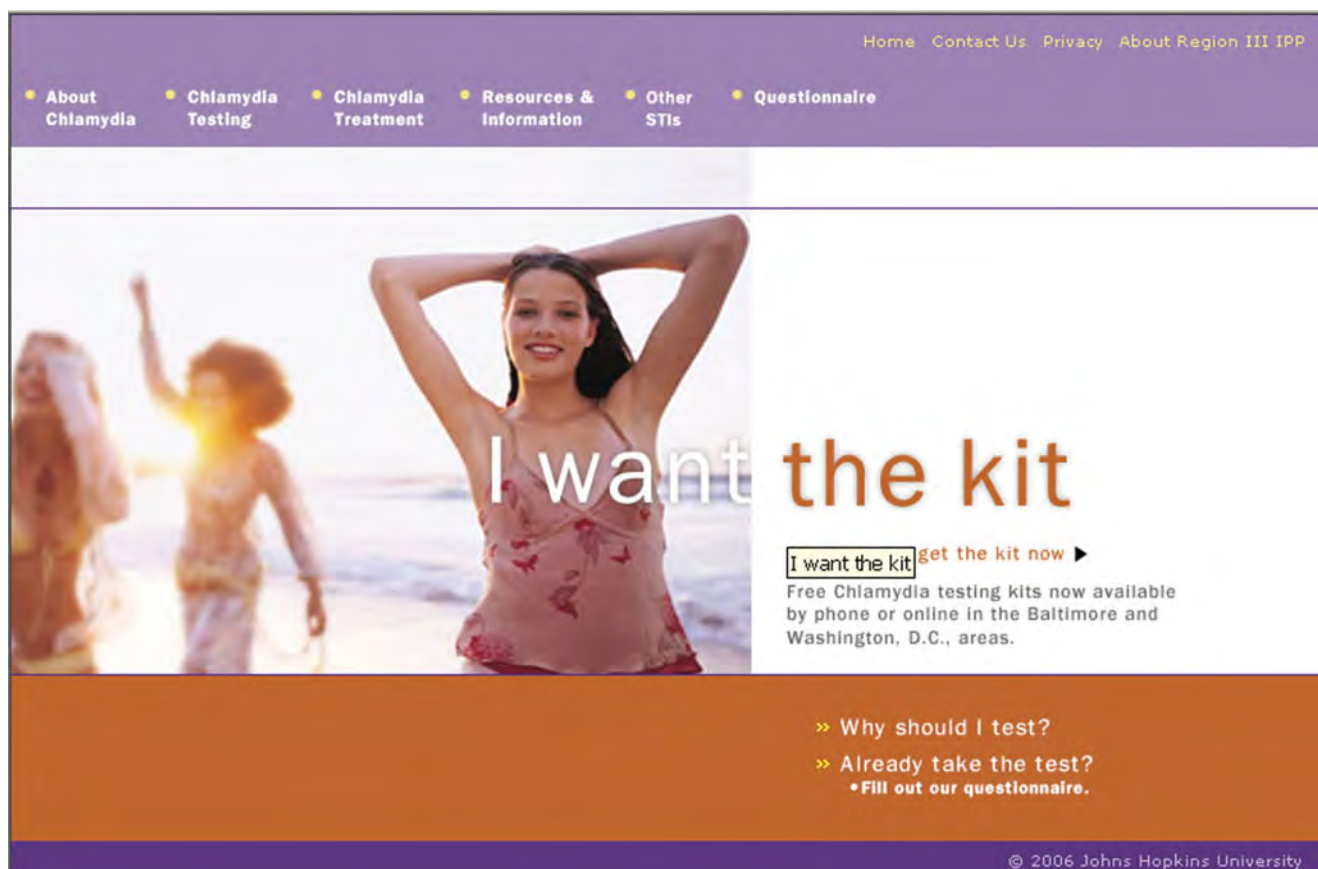


FIGURE 108-3. Screenshot of Internet-facilitated Chlamydia screening, “I Want the Kit” (www.iwantthekit.org).

Other forms of partner notification such as text messaging have been published. A case report of a partner receiving a text message with the diagnosis of trichomoniasis resulted in a timely treatment of this disease.⁶⁷

Future directions for partner notification may involve a text or e-mail message from the health provider’s mobile phone or computer to the partner(s) of the index case. The e-mail or text message could have a Web site address specific to each infection that could provide patients with additional information about the disease. In order to protect confidentiality, the Web site could be designed with mechanisms that ensure each page automatically expires when the user moves to another page or alternatively, the partner could be given instructions on how to erase the history of the visit when logging out. A user ID and password could be given to the partner to enter the site; this would not only protect privacy but also could provide an accurate number of contacts visiting the Web site, which can be useful for program evaluation purposes.⁶³

While there are multiple benefits to the use of technology for partner notification, it nevertheless also has some risks. Internet and cell phone notification are not always confidential, e-mails can be read by others, mobile phones may be used by more than one person, e-mails and phones can change, and phones can be lost.⁶³ For these reasons and

within the context of each public health effort, it is important to balance the risks and benefits of the use of these technologies before deciding their implementation.

PREVENTION

Effective prevention begins with a foundation of awareness and knowledge about HIV and STIs. One recent effort to promote awareness and increase knowledge and access to education about HIV and STIs using a cell phone short message service is SexTextSF in San Francisco (www.sextextsf.org).⁶⁸ This cell phone-based sexual health promotion service was based on a similar service developed by the Brook Charity in the UK. In the San Francisco example, the health department promotes in target communities, the text message “SEXINFO” and the call in number. Users access the discrete service via their text messaging program on their cell phone to reach a variety of topics in sexual health including the following: “What to do about a broken condom?” “If they think they are pregnant?” “Where to go for STI or HIV testing?” The evaluation of that project demonstrated that about 10% of the target population had used the service and use of the service could be associated with increased access to sexual health clinical services.⁶⁹

Brief counseling interventions can reduce incident STIs,⁷⁰ yet not all settings have trained staff counselors or sufficient

clinician time to deliver evidence-based risk reduction. Computerized HIV/STI risk assessment and counseling tools may be an effective way to deliver behavioral interventions in busy clinical settings. Computer-delivered counseling interventions for HIV/STI prevention have been developed by several research groups in the last 15 years. Paperny reported in 1997 on a decade of use in Hawaii of a computerized adolescent health assessment and education tool that had been used by over 5000 adolescents.⁷¹ Roberto and colleagues also developed a computerized HIV education tool for adolescents, testing it in two schools.⁷² Weinhardt found that STI clinic patients were open to the idea of computer counseling delivered in waiting rooms.⁷³ Grimley and Annang's computer counseling tool delivered in an STI clinic waiting room was found in a randomized trial among 430 longitudinal enrollees to result in increased condom use at six months (21% increase in the intervention group vs. 13.3% in the control group, $p = 0.03$). Erbeling and colleagues in Baltimore also utilized an ACASI patient assessment designed to provide tailored, theory-based intervention strategies to the medical provider.⁷⁴ In a study involving 157 college students randomized either to 3 computerized sessions or to an attention-control arm receiving a nutritional tutorial, Kiene and Barta found a significant increase in self-reported condom use at six-weeks follow-up.⁷⁵ Kurth, Spielberg, Fortenberry, and Malotte developed a "Computer-Assisted Risk assessment and Education (CARE) for HIV/STIs" CD-ROM for use in clinical settings⁷⁶ to deliver interactive HIV/STI risk reduction counseling and rapid HIV testing administration, in a format that may allow more behavioral reflection on the part of the user.⁷⁷ A version of this software designed for use among people living with HIV is described in the "Clinical Management" section.

SEX-SEEKING OVER THE INTERNET: PROS, CONS, AND PROMOTING SEROSORTING

The use of the Internet to seek sex partners has been widely reported in developed and developing countries.^{78,79} In some regards, at-risk populations such as men who have sex with men are leading the way in self-directed use of ICT, e.g., using the Internet to seek sex partners,^{79,80} or health information. Offline sex that occurs following online solicitation may result in a disproportionately large risk of HIV and STI transmission.^{81–83} Individuals who seek sex partners through the Internet may report a higher level of sexual risk behaviors such as higher number of partners, more anal sex, and more sexual exposure to partners known to be HIV positive compared to those who do not use the Internet to find sex partners.⁸¹ Studies of patients at STI clinics found also that among this core group, the Internet has been a common venue for meeting and having sex with partners. In San Francisco, MSM with early syphilis infections reported the Internet as the most common place to meet sex partners,

followed by bars, bathhouses, and sex clubs.⁸⁴ Having sexual intercourse with partners met online has also been directly linked to syphilis epidemics and HIV transmission. Klausner et al. in 2000 reported a syphilis outbreak among gay men linked to online chat rooms in San Francisco,⁶⁴ and Tashima et al. in 2003 reported two cases of acute HIV infection acquired through meeting persons over the Internet.⁸⁵

The Internet does provide an environment where individuals may have open and anonymous discussions about their serostatus, preferences for certain sexual practices and condom use. Carballo-Diequez et al. in 2006 found that both HIV-negative and HIV-positive MSM were more likely to engage in sexual negotiation and serostatus disclosure on the Internet than in person and that those who negotiate were also more likely to use condoms for anal intercourse.⁸⁶

Among MSM, certain sexual harm reduction practices such as serosorting, strategic positioning, and withdrawal before ejaculation have been described.⁸⁷ Serosorting is a process by which individuals discuss their HIV status with potential partners and modify their sexual behavior based on the partner's serostatus.⁸⁷ Strategic positioning is a process by which individuals choose certain sexual positions to decrease the risk of transmitting or getting HIV, for example, they may choose to be the receptive instead of the insertive partner if their serostatus is HIV positive.⁸⁸

EDUCATING PATIENTS WITH INFORMATION TECHNOLOGIES

The Internet constitutes an important source of information in health care. Patients can search for information about their diagnosis, seek out health-care providers, explore treatment options, and share opinions about their diseases.⁸⁹ The existence of chat rooms that allow real-time communication, forums, and discussion groups where participants can post messages about a specific topic and Web logs where they can comment, post news, or simply talk about their personal lives have changed the way patients interact with each other and has increased enormously the amount of information each participant shares and receives.

Practical criteria to evaluate Web sites are provided by the PILOT mnemonic, developed by Price,⁹⁰ to remind people what they should look for a trustworthy medical Web site:

- **Purpose:** If the site has a mission statement, read it. If not, read the home page and analyze the site's purpose. Does it inform and educate? Or is designed to persuade, sell, outrage, or entertain?
- **Information:** Truly useful medical Web sites offer valuable information and emphasize facts rather than opinion and testimonials. If the site is selling anything, ask yourself if that influences the content.

- **Links:** The best sites want to inform you and are happy to recommend additional Web sites to further enhance your knowledge in that topic or related topics. The best sites provide links that are rated or reviewed.
- **Originator:** Who is responsible for the information? Best bets for sound medical information are medical societies, consumer-advocacy groups, well-known hospitals, and government and university-sponsored sites.
- **Timeliness:** Medical information is only useful if it is current. Look for sites that update frequently.

The PILOT method has been used by Kalichman et al. to teach HIV-seropositive patients some useful skills for critically evaluating and using health information.⁹¹

The use of the Internet to provide patient education can be useful to target high-risk populations in developed and developing countries. Bull et al. found in a US study that MSM and persons with a history of STI testing were likely to endorse HIV/STI prevention through chat rooms, e-mails, and Web sites.⁸⁰ Alva et al. in 2005 found that among Peruvian HIV-positive persons, who used the Internet to meet sex partners 87.5% also sought information related to HIV, compared to 72.1% of such persons not seeking partners.⁷⁹

Health departments, community-based organizations, and others have long used ICT to reach persons with information about HIV testing, HIV/STI prevention, and advocacy. Rai et al. reported the “Chandigarh AIDS hotline,” a computerized telecounseling service in Chandigarh, India, for AIDS prevention and AIDS awareness. It is a 24 hour computerized interactive voice response service, which is accessible on a four-digit number (1097) by telephone.⁹² Confidentiality and anonymity of the caller are the hallmarks of this service. The HIV/AIDS hotline is a toll-free service that provides information and counseling on HIV/AIDS related issues in English, Hindi (national language), and Punjabi (regional language).

Web-based health information and education may provide new ways to provide better access to difficult-to-reach populations, cities, and regions. Consider, for example, the great popularity and cheap cost of Internet cafes or “cabinas publicas” in Peru.⁴⁴ The unique popularity and low cost of Internet cafes in a growing number of countries open new possibilities to developing future web-based systems to show that effective information management can be possible in poor communities with no modern infrastructure but widespread use of internet cafes.

CLINICAL MANAGEMENT

■ ELECTRONIC HEALTH RECORDS (EHRS)

Electronic health records are evolving rapidly and are influencing clinical practice^{93,94} particularly in chronic disease

management. The EHR can provide data that are essential for implementing continuous quality improvement not only at the individual patient level, but also at the clinic or health system level. This will be useful not only for the chronic viral STIs, but will likely also prove essential for optimizing acute care management as well, for example, in management of bacterial STIs.^{95,96} Clinicians need to monitor HIV patient status carefully and frequently, and intervene with various therapies. Effective health-care delivery requires innovative methods of disseminating medical knowledge and informing the physician about how to provide and monitor high-quality care. Physicians need easy access to patients’ information, simplified reporting, guidelines that improve the quality of care, and methods to facilitate adherence to guidelines. Computer-based patients’ records can provide a useful tool for such efforts.⁹⁴

Since 1989, the U.S. Department of Veterans Affairs has maintained a national HIV registry and contains longitudinal data and detailed resource utilization and clinical information. The registry contains data that are electronically extracted from Veteran Affairs’ computerized comprehensive clinical and administrative databases, called “Veterans Integrated Health Systems Technology and Architecture.”⁹⁷ In France, NADIS 2000 is an electronic health record program for patients with HIV infection and hepatitis that has been in use in centers of Infectious Diseases in France since November 2000. The tool permitted real-time use by the physicians in outpatient and day-care units and was easily handled by all the practitioners. The developers note that its use was facilitated by having clearly defined the system principles before its application, an intuitive interface simulating a consultation, and providing functions that benefit the physician users (graphical visualization of biological variables, printing of prescriptions and letters).⁹⁸

In the United States, the National Institute of Allergy and Infectious Diseases funds the “Center for AIDS Research Network of Integrated Clinical Systems (CNICS);” a system of EHRs in use across seven HIV clinics. This extensive infrastructure will support basic, translational, and multidisciplinary research, allowing longitudinal tracking of patient outcomes and clinical specimens across sites.

AMPATH, the Academic Model for Prevention and Treatment of HIV/AIDS, is a collaboration of Moi University and the Moi Teaching and Referral Hospital in Eldoret, Kenya and the Indiana University School of Medicine. It was the first organization to offer comprehensive ambulatory HIV/AIDS care in Kenya, enrolling its first patient in November 2001 and by mid-2007 was caring for nearly 45,000 HIV-positive individuals. The AMPATH medical record system (AMRS) is sub-Saharan Africa’s first EHR system for the comprehensive management of the clinical care of patients infected with HIV. It was based on an initial “Mosoriot medical record system.”^{99,100} This system,

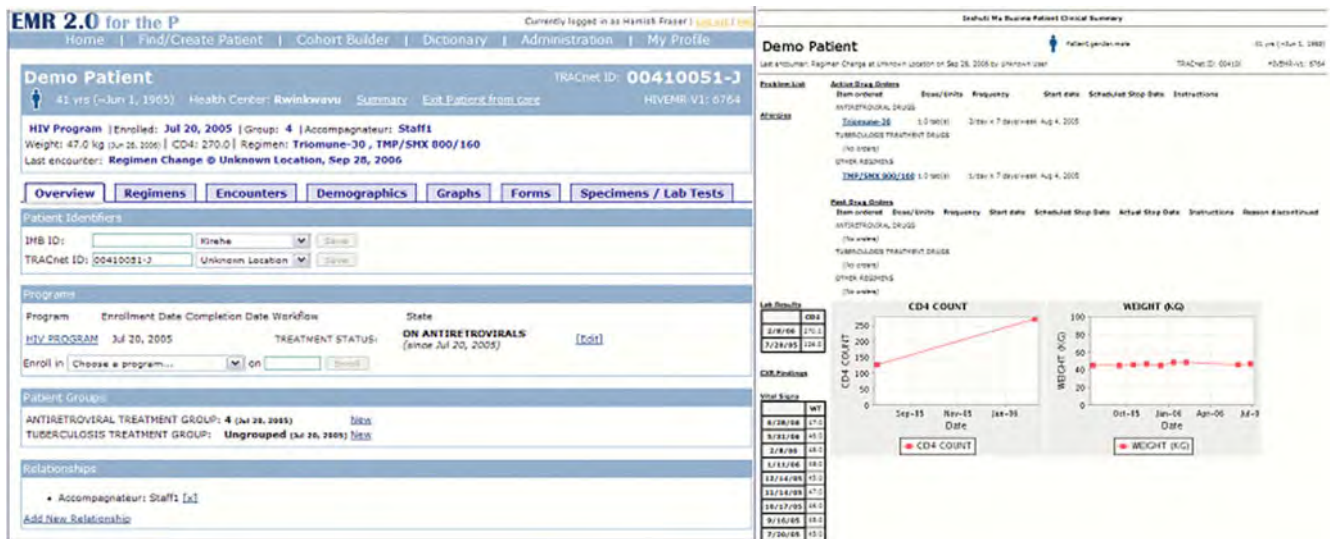


FIGURE 108-4. Example of HIV electronic health record “OpenMRS” architecture.

composed of both paper-based and electronic records, has been found by Siika and colleagues to lead to uniformity in data collection and to facilitate the retrieval of patient data for clinical care and research.¹⁰¹ The AMRS was explicitly designed to use simple technology, in order to aid in the maintenance and sustainability of the system in resource-constrained environments; the tool is now in use in several countries in eastern Africa and elsewhere.¹⁰¹ A Wiki (collaborative development) site for the openMRS system is available at <http://openmrs.org/wiki/OpenMRS>; see [Fig. 108-4](#).

Web-based electronic medical record systems have shown that effective information management is possible in other poor communities without extensive modern infrastructure. In Peru, Fraser et al. described a web-based medical record system to support the management of multidrug resistant tuberculosis.¹⁰² Web-based analyses have been developed to track drug sensitivity test results, patterns of sputum smear, and culture results and time to conversion from positive to negative cultures.¹⁰²

Fraser et al. also described the “HIV-EMR,” a prototype electronic medical record system to support treatment of HIV and tuberculosis in remote and impoverished areas in Haiti. This electronic medical record allows physicians to order medicines and laboratory tests, and provides alerts based on clinical status and test results.¹⁰³ Partners in health have also used web-based EHRs in Rwanda to support anti-retroviral rollout.

Recently, Curioso et al. developed a web-based electronic report system for STI for the PREVEN project in Peru.⁴⁴ Interviewers entered their data directly into a single database as they progress through the reports, thereby saving time and costs over having the data entry done after data are collected. The system collects new participants and generates alert reports defined by the number of missed treatments that must be provided by the health-care interviewers. The system

has the capability of searching so the interviewers can check past laboratory results and medications. The system allows real-time access of the database (only available for the team leaders) via the web.

■ DECISION SUPPORT SYSTEMS

The potential for computerization to improve clinical care has been appreciated for some time.¹⁰⁴ Advances in electronic medical record capabilities enable clinical reminders to inform providers when recommended actions are “due” for a patient. Computerized clinical reminders have been advocated as a strategy to improve adherence with established clinical guidelines. With clinical reminders, the software rather than the human initiates the human-machine interaction. Clinical reminders take advantage of preexisting electronic patient information to alert the provider when an action is recommended. In addition, clinical reminders are “real-time” decision aids in that they prompt providers to consider guideline-based advice when a patient record, and ideally the patient, is in front of the provider. As such, they have the potential to improve quality of care, for example, they can result in increased prevention interventions by busy clinicians.

In HIV care, clinical reminders were associated with more timely initiation of recommended practices. For example, Kitahata et al. demonstrated that HIV clinical reminders delivered at the time that HIV care is provided were associated with improvement in adherence to practice guidelines.¹⁰⁵

Safran et al. demonstrated that when alerts and reminders are linked with a patient’s computer-based patient record, adherence to a set of HIV practice guidelines can be improved.⁹⁴ Despite evidence that they improve adherence to guidelines, the U.S. Veteran’s Health Administration has experienced challenges in having providers consistently use clinical reminders as intended.¹⁰⁶

Creative utilization of hospital data environments may be an inexpensive route to improved compliance with practice guidelines. Shuter et al. reported that after the initiation of a weekly computer-based Pap smear reminder list in an HIV care clinic, the prevalence of scheduled women with up-to-date Pap smears increased from 61.4% to 73.2% ($p < 0.001$) during 1 year. The improved rate of up-to-date Pap smears showed no sign of attenuation over time.¹⁰⁷

■ SUPPORT FOR PEOPLE LIVING WITH HIV

ICTs can help people with chronic diseases such as HIV to self-manage their treatment regimens, as well as to facilitate connection to others for psychological support. Gustafson and colleagues utilized one of the first web-based support sites for people living with HIV, known as the “Comprehensive Health Enhancement Support System.”¹⁰⁸ Others have used the web to create virtual support or affinity groups, such as for HIV-positive adolescents.¹⁰⁹

A randomized trial conducted by Flatley-Brennan et al. involved the use of a home-based computer network connected to the Internet (the ComputerLink) designed for people with AIDS to determine if the program would reduce social isolation and improve confidence and skill in decision making without causing differential decline in health status among people with AIDS. Services available included an online electronic encyclopedia, public and private communication, and a decision support system; a registered nurse coordinated all services. The authors concluded that computer networks provide feasible alternatives for the delivery of health services to homebound individuals. Communication services were used more extensively than other services, suggesting that the primary mechanism of intervention is peer contact. The system use improved confidence, though not skill, in decision making.¹¹⁰

VIHrtual Hospital is a telemedicine web system for improving home integral care of chronic HIV patients through the Internet implemented in Spain.¹¹¹ Using the videoconference, chat, or messaging tools included in the system, patients can visit their health-care providers (physician, psychologist, nurse, psychiatrist, pharmacist, and social worker), and gain access to the electronic patient record. The system also provides a telepharmacy service that controls treatment adherence and side effects, sending the medication to the patient’s home by courier. The system facilitates communication between patients and improves the collaboration between professionals, creating a care plan for each patient. As a complement, there is a virtual library where users can find HIV/AIDS information helping to enhance prevention. This system has been developed using low cost technologies.^{111,112}

Garcia et al. designed CREAIDS (Center of Reference for AIDS), a four-module patient-directed interactive software program for improving adherence to antiretroviral



FIGURE 108-5. Screenshots of a computer counseling tool, “CARE +.”

therapy.¹¹³ Brock and colleagues have used PDAs to deliver medication adherence education; they found a short-term impact on self-reported adherence.¹¹⁴

Figure 108-5 shows computer screenshot examples of a computer counseling tool called “CARE+” that was designed to support ART adherence and HIV transmission risk reduction. A randomized controlled trial among 240 adults with HIV in Seattle, WA, found that among those with detectable viral load at baseline ($n = 90$), the CARE+ intervention participants were twice as likely as controls to have undetectable viral load at the 6-month follow-up visit (RR 1.9, 49% vs. 26%; $p = 0.04$). There was a statistically significant reduction in condom use errors in the intervention arm at 6-month follow-up (RR 0.44, exact $p = 0.05$).¹¹⁵

Several studies utilizing human staff-delivered and automated text messages delivered to pagers and cell phones have been conducted in the United States, with a range of results.¹¹⁶ Some have not found a meaningful impact of telephone-delivered support on outcomes of interest such as measures of depression among HIV-positive participants.¹¹⁷ Others have found that use of interactive voice response-delivered phone calls to HIV-positive problem drinkers resulted in lower drinking levels over time.¹¹⁸ Another study led by Reynolds for the AIDS Clinical Trials Group, found among 109 newly treated HIV-infected patients, a significantly better overall treatment effect at 64 weeks in the telephone group ($p = 0.023$); calls were associated with a promising but nonsignificantly reduced risk (HR = 0.68; 95% CI 0.38–1.23) for treatment failure.¹¹⁹ Another randomized trial among HIV-positive patients who smoked found that participants who received a cellular telephone intervention were 3.6 times (95% CI 1.3–9.9) more likely to quit smoking compared with participants who received usual care.¹²⁰ Potential benefits of phone interventions (accessibility of delivery, potential cost-effectiveness as compared with

in-person delivery) must be weighed against the need for confidentiality (e.g., determining that the cell phone respondent is the participant/patient), targeting (e.g., actively substance-using patients may do better with face-to-face rather than telephone counseling delivery)¹²¹ and sustainability, as effects may wane over time unless maintained, as was found in one study with HIV-positive adolescents.¹²²

Cell phones are being used to support patient medication adherence in resource-constrained settings. In South Africa, the project Cell Life is using cell phones to monitor adherence for the management of HIV disease in patients on antiretroviral therapy. Some of the platforms used by Cell Life include a global system for mobile communications, wireless Internet gateway, and a geographical information system database.¹²³ A cell phone system in use in Rwanda over the course of 2 years connected 75% of the country's 340 HIV clinics and covered 32,000 people. Patient entry data are transmitted centrally to Kigali, and weekly reports are created to monitor various factors such as clinics' stocks of antiretroviral drugs and any relevant notices to providers.¹²⁴ In 2007, Voxiva announced an agreement with the U.S. President's Emergency Plan for AIDS Relief to utilize cell phone systems with HIV patients in 10 African countries.¹²⁵ While some have questioned health intervention delivery models that assume individual cell phone ownership,¹²⁶ such ownership and cell phone penetration are varied by setting, and also are increasing over time; it is estimated that within a few years, 80% of Africans will live in areas that will have cell phone coverage.

■ CONSULTATION USING TELEMEDICINE

Telemedicine supports of health-care delivery in remote areas.^{127–129} Telemedicine holds the promise of improving access to health care, especially in areas where there are geographical barriers, and of reducing costs.¹²⁷ Several studies of telemedicine to support HIV patients are reported in the developed world,^{111,112} but data are limited in developing countries.

In rural areas, telemedicine may support access for teleconsultation. TeleMedMail¹³⁰ is a software application to facilitate store-and-forward telemedicine by secure e-mail of images from digital cameras. TeleMedMail is written in Java and allows structured text entry, image processing, image and data compression, and data encryption. This web-based telemedicine system is currently under evaluation in South Africa and Peru, and Spanish and English versions are available.

The Internet has the potential to enhance collaboration among researchers by facilitating rapid dispersal of information and the coordination of numerous, complex, real-time interactions. One example of a working group was the Great Lakes Regional Center for AIDS Research. The Great Lakes Regional consortium of scientists at Northwestern

University, the University of Minnesota, the University of Michigan, and the University of Wisconsin–Madison consolidated their complementary scientific expertise. Core facilities allowed investigators to join proteomics, genomics, bioinformatics, animal models, and clinical studies into a unified whole.¹³¹ Figure 108-6 summarizes the range of information technology tools that a patient living with HIV might use.

PROVIDER TRAINING

■ COMPUTER-BASED TRAINING PROGRAMS

Digital resources can potentially serve as a powerful medium for the training of clinicians and other HIV/STI workers, delivered via CD-ROMS,¹³² e-mail lists¹³³, and in recent years via the Internet.¹³⁴ Advanced communication technologies can create a cost-effective infrastructure to disseminate new intervention models to service providers worldwide.¹³⁴

Given the necessity to support clinicians in treating patients with antiretroviral therapy, many institutions and organizations are developing computer-training programs for health-care providers working in developing countries.

The International Training and Education Center for HIV (I-TECH), which provides training in 25 countries, offers a wide range of training products tailored to each country's needs to help educate all members of society about HIV/AIDS. I-TECH (www.go2itech.org) has produced a broad spectrum of supportive media products and teaching aids, including videos in multiple languages, CD-ROM toolkit compilations; brochures for patients, and pocket guides and posters for health-care workers. I-TECH has assembled a listserv to include in-country clinicians in the periodic updates e-mailed to the I-TECH Clinical Team. I-TECH posts an electronic library of teaching cases for clinical training on HIV/AIDS care, and treatment with WHO and other partners.

I-Med Exchange, launched in July 2000 by the International Association of Physicians in AIDS Care, is a program directed to physicians and allied health professionals providing HIV/AIDS care in southern African countries—Botswana, Lesotho, Namibia, South Africa, and Swaziland. I-Med Exchange proposed to “bridge the digital divide” between the developing world and the developed world for health information, using information technology. The main, formal activity of physicians enrolled in the program was to participate in interactive online presentations accessed live on the Internet, or viewed as archived seminars either on an I-Med Exchange Web site or CD-ROM.¹³⁵

The Institute of Tropical Medicine, Antwerp set up a computer-aided training program for health-care providers, working in more than 17 developing countries. Expert advice from HIV/AIDS specialists on treatment of HIV infection and

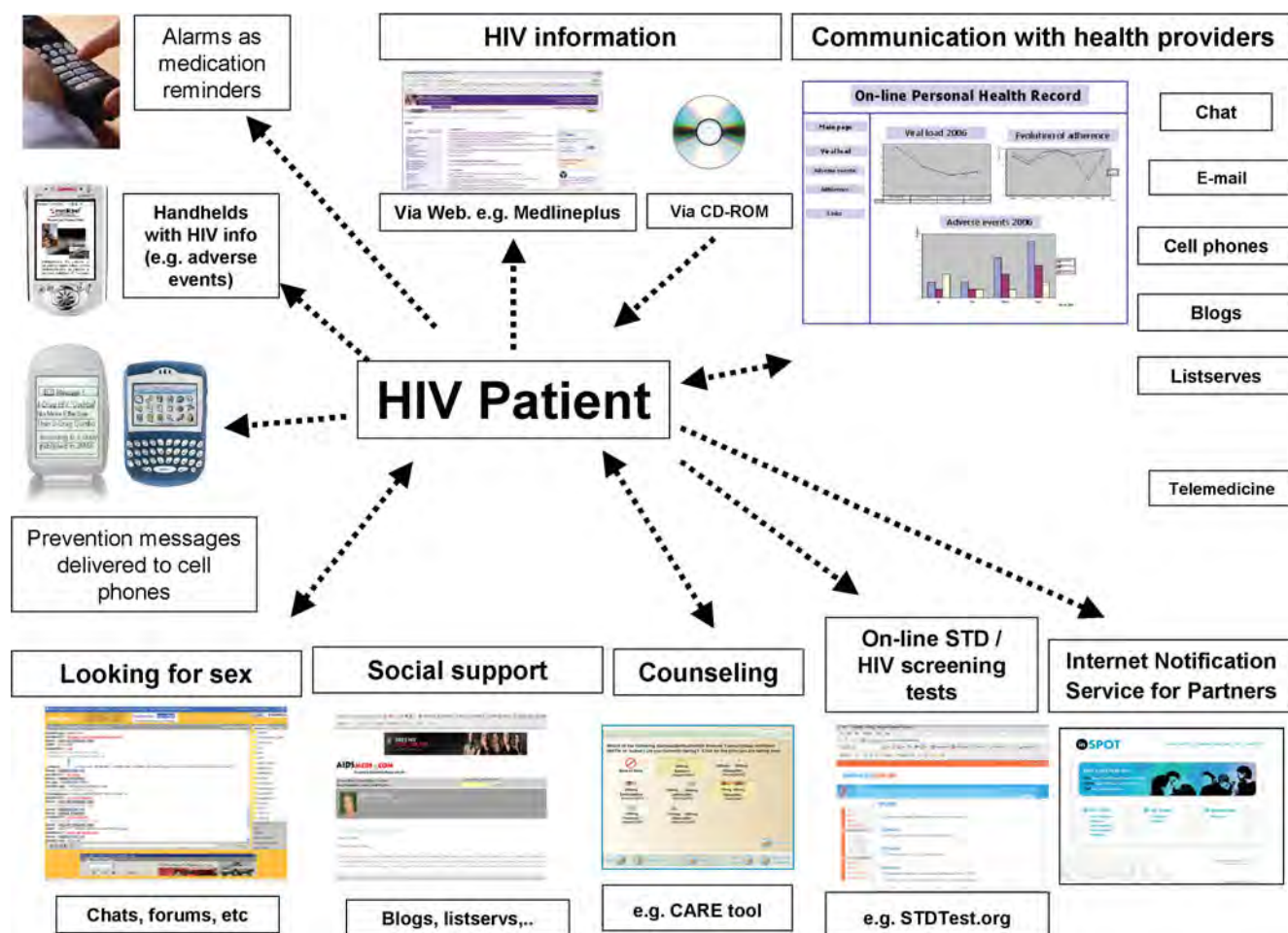


FIGURE 108-6. Overview of information and communication technologies available for HIV patients.

management of opportunistic infections have been offered to colleagues working in different countries. The telemedicine advice was organized initially through an e-mail network on a list server but later, in response to the need of continuous medical education on HIV and treatment, through a discussion forum on a telemedicine Web site (<http://telemedicine.itg.be>). E-mails have been used for years by the Antwerp Institute as a low cost telemedicine support for colleagues working in low resource countries. By giving the opportunity to trained clinicians to access continuous support and education through a discussion forum and policy documents on the Web site, the idea is to lower the threshold to launch HIV treatment projects in low resource settings.¹³⁶

HIVeDucation is an interactive, HIV clinical management course tailored to the needs of clinicians in those regions of the world that have been hardest hit by the HIV epidemic. The course combines computer-based self-study modules, participatory clinical case studies, e-assisted tutoring, on-site workshops, and the building of peer consultation networks to provide an integrated clinical program. HIVeDucation has continuing education courses that can be completed online or with a jump/thumb drive, uploading pre/post test scores to the Web site: <http://www.hiveducation.net>.

Cure4Kids (<http://www.cure4kids.org>) is an Internet learning network that delivers medical education to doctors and nurses on pediatric cancer and AIDS. Cure4Kids also provides web conferencing tools for communication and collaboration.¹³⁷

In China, Tucker et al. developed a HIV/STI training page for the Web site of the Chinese National AIDS Prevention and Control Center (<http://www.aids.net.cn>).¹³⁸

A number of PDA-based resources are available for the HIV/STI clinician, some of them free of charge. Tice and Bhan reviewed many useful PDA-based resources for the infectious diseases specialist.¹³⁹ Additional resources can be found in review articles by Keplar.^{140,141}

■ CONTINUOUS EDUCATION ON THE INTERNET

There is enormous potential to implement web-based continuing education in developing countries through online courses that can train and provide current information to health-care professionals in the management of HIV/STI. Studies have shown that web-based continuing education can improve health-care professionals' practical skills.¹⁴² Technological advances that allow inclusion of interactive

links, video, images, and sounds make it increasingly feasible to illustrate and encourage realistic clinical problem solving.¹⁴² Other advantages of web-based continuing education include absence of geographical barriers, user interaction, real-time interactivity, flexibility and potential low cost, important issues to consider in developing countries.

Most participants who engage in a web-based continued education are satisfied with the experience and find it to be an effective learning format. Barriers to web-based continued education include technical difficulties and lack of computer knowledge.¹⁴³

For any web-based course to succeed, Wong et al. proposed the following 10 overlapping and iterative areas of activity that must be addressed: the market for the course; course aims and intends learning outcomes; choice of software platform; staff training needs; writing high-quality study materials; design features for active learning; technical and administrative challenges; evaluation and quality improvement; mainstreaming the course within the institution; and financial viability.¹⁴⁴

Table 108-1 summarizes some of the free continuing education courses and activities for doctors and other health-care professionals. Of particular interest are learning tools for STI training available from the CDC STD Prevention Training Centers—e.g., Self-study STD Modules for Clinicians; ready-to-use curriculum for the clinical educators; and STD 101-in-a-box—all available at <http://www.cdc.gov/std/training/default.htm>. Also available is a comprehensive Web site developed by Drs. Spach and Marrazzo that features interactive case studies covering a broad array of topics related to hepatitis (<http://www.hepwebstudy.org>).

■ IMPACT OF INFORMATION TECHNOLOGIES RELATED TO HIV/STI IN RESOURCE-CONSTRAINED SETTINGS

Informatics is particularly useful for electronic health records, telemedicine, clinical decision systems, and improving access to information.¹⁴⁵ Yet, resource-constrained countries that can benefit the most from the use of informatics and telemedicine, are the ones that have the least access to them, and the highest burden of disease. Despite growing interest in telemedicine and medical informatics in these countries, issues of affordability, cost-effectiveness, and sustainability remain to be addressed.

Information systems should be carefully planned and integrated across different programs, especially in resource-constrained settings. Prahalad (2005) has reported that health workers in many developing countries spend as much as 40% of their time filling out paper-based forms, and compiling and copying data from different programs (e.g., tuberculosis, malaria, HIV/AIDS).¹⁴⁶ By choosing the most appropriate information technology, duplication can be avoided and appropriate devices—e.g., cell phones, Internet—can be

deployed to report from public health programs. Development and evaluation of practical, low cost clinical information systems should be a priority in rolling out HIV treatment in developing countries.¹⁰³

There is great potential to improve health through the use of ICTs in developing countries. The problems of low Internet diffusion and the digital divide are obstacles that developing countries face in using the Internet for development purposes. In some countries, one user may access the Internet in numerous ways including wireless, Internet cafes, kiosks, home, work, and/or school accounts.⁴⁴ Single accounts may be shared by many users. Some users are heavy users and others light users; some started long ago while others started recently. The diffusion of innovation is contingent not only on willingness to adapt to new technologies, but also on the financial and human resource base able to support these tools.

E-health in developing countries is a nascent reality that offers opportunities that need to be explored. Given the widespread access through Internet cafes in Latin America, there is potential to deploy web-based prevention intervention programs as well as educational interventions for HIV/STI, especially to difficult-to-reach populations and higher-risk groups such as men that have sex with men.¹⁴⁷ Those can be delivered at low cost and can be accessed by a great number of participants in innovative ways. In addition, the Internet also can be used to recruit people for randomized trials (for example, hard-to-reach populations like MSM) and to deliver testing and prevention messages.

In many developing countries, health workers have limited access to the Internet in their workplace. They may instead gain access from Internet cafes and other venues. While countries in Africa have the world's lowest Internet penetration (as a percentage of population), the continent also has the largest absolute growth in Internet usage from 2000 to 2007.¹⁴⁸ Moreover, up to 80% of Africans are projected to live within mobile phone coverage areas by 2010, making cell phone delivered data collection and interventions more feasible. The dramatically falling costs of computers suitable for Internet use should go some way to closing the gap between rich and poor. This price drop and accessibility to computers brings a unique opportunity for health-care delivery and research.

The past few years have witnessed several developments that are making access to information for scientists in the developing world more affordable.¹⁴⁹ These include initiatives promoted by scientists, libraries, publishers, academies, and societies. The WHO Sexually Transmitted Diseases Diagnostics Initiative (http://www.who.int/STI_diagnostics/) posts summaries and critical reviews of key articles related to STI screening approaches and technologies on a Web site to enhance access to the STD diagnostics literature in developing countries.¹⁵⁰ The Public Library of Science (<http://www.publiclibraryofscience.org>) is a nonprofit

Table 108-1. A Selection of Free HIV/STI Continuing Education Resources

Name	Courses, Online Modules
California STI/HIV Prevention Training Center http://www.STIhivtraining.org/	<ul style="list-style-type: none"> – Online Chlamydia course: The training is designed to increase knowledge of asymptomatic Chlamydia infection, the importance of screening young, sexually active women and the management of Chlamydia infected patients and their partners. During the course, you evaluate and treat two simulated patients.
CDC training and continuing education online http://www2a.cdc.gov/phtnonline/	<ul style="list-style-type: none"> – Online STI case series: Presented by the National Network of STI/HIV Prevention Training Centers & Centers for Disease Control and Prevention (CDC). – Incorporating HIV prevention into the medical care of persons living with HIV (web on demand). – Prevention with positives: HIV risk reduction strategies for health-care providers (web on demand). – Rapid testing: advances for HIV prevention (web on demand).
Clinical care options Hepatitis http://clinicaloptions.com/Hepatitis.aspx	A series of text-based or case-based interactive activities concerned with aspects of Hepatitis B and Hepatitis C infection.
Clinical care options HIV http://clinicaloptions.com/HIV.aspx	A series of text-based or case-based interactive activities concerned with aspects of HIV/AIDS.
FreeHepatitisInfo http://www.freehepatitisinfo.com/	HepatitisWATCH news is a monthly CE-accredited newsletter that brings updates on new information on the topics of hepatitis and hepatitis/HIV coinfection.
HCV advocate's online education center http://www.hepeducate.org/quizical/login.php (free registration required)	<ul style="list-style-type: none"> – Diagnosing HCV: Topics covered are the types of tests used to diagnose HCV, antibody tests, HCV viral load tests, the hepatitis C virus and its lifecycle, HCV genotypes and quasispecies, biochemical liver function tests, the significance of ALT levels, liver biopsies, the four histological stages of liver damage.
HIV web study http://depts.washington.edu/hiv aids/index.html	Twelve half-hour modules concerning diagnosis and treatment of HIV/AIDS—initial evaluation; dermatologic manifestations; oral manifestations; opportunistic infections: prophylaxis; opportunistic infections: treatment; antiretroviral Rx; antiretroviral Rx: resistance; antiretroviral Rx: adverse effects; drug-drug interactions; postexposure prophylaxis; perinatal transmission; special populations.
International AIDS Society USA: cases on the web http://www.iasusa.org/cow/	<p>A series of online continuum education (CE) activities sponsored by the International AIDS Society USA, including</p> <ul style="list-style-type: none"> – clinical management of treatment-experienced patients presenting with virologic failure. – diagnosis and management of immune reconstitution syndrome in HIV-infected patients. – the importance of viral fitness and drug resistance in chronic and recent HIV infection. – perinatal HIV: special considerations.

(Continued)

Table 108-1. (Continued)

Name	Courses, Online Modules
Medscape HIV/AIDS http://www.medscape.com/hiv-aidshome	CE activities of special interest to physicians who treat HIV/AIDS. Medscape contains a variety of educational formats: <ul style="list-style-type: none"> – Conference coverage—Reports of advances presented at major medical conferences; typically includes several tracks with news stories, expert interviews, and in-depth topic overviews. – Clinical update—Comprehensive original review article on scientific advances in a clinical topic. – Fast track clinical update—Narrowly focused original review article on scientific advances in a clinical topic. – CE-live—Real-time online events with streaming video, synchronized visuals, and interactive questions and answers; archived for 1 year. – News-CE—Daily reports of major current medical research articles; 0.25 credits each – Journal CE—Articles selected from a wide selection of conference reports and peer-reviewed journals. – Special report CE—Topic-based monthly email newsletter distributed to Medscape’s professional member database by specialty. – Interactive patient cases—Original CE activity presented to the physician in an interactive, clinical case-based format. – CE circle: Multimedia content certified by other accredited professional education providers, typically from live symposia or monographs, and then posted on Medscape and archived for 1 year.
Medscape infectious disease http://www.medscape.com/infectiousdiseaseshome	CE activities of special interest to infectious disease specialists. Educational formats are similar as “Medscape HIV/AIDS.”
MMWR continuing education programs (Centers for disease control) http://www2.cdc.gov/ce/availableactivities.asp	This site contains the PDF versions of several HIV-related articles published in the morbidity and mortality weekly Reports. You download and read the articles, then submit your quiz answers online.
NNPTC online case series (National Network of STI/HIV Prevention Training Centers) http://www.STIhivtraining.org/nnptc/start.cfm .	The series includes case presentations of common STI-related syndromes. The guided interactive process helps you to evaluate each case, arrive at a diagnosis and provide recommended treatment.
STI/HIV case series (In Spanish). Universidad Peruana Cayetano Heredia/University of Washington. http://cursos.redpreven.org/	An interactive course with clinical cases to train health-care workers in the management of patients with STIs.

Updates can be found at: <http://faculty.washington.edu/wcurioso/CE.htm>.

organization of scientists committed to making the world’s scientific and medical literature freely accessible to scientists and to the public around the world for the benefit of scientific progress, education, and the public good. The Open

Archives Initiative (<http://www.openarchives.org>), supported by the Digital Library Federation and National Science Foundation, has its roots in an effort to enhance access to e-print archives as a means of increasing scholarly

communication. PubMed Central (<http://www.pubmedcentral.gov>) is a free-and-unrestricted digital archive of life sciences journal literature, developed and managed by the National Center for Biotechnology Information (NCBI) at the U.S. National Library of Medicine (NLM).

Many journals already have online publishing operations, and there is a growing tendency to publish material online only, to the exclusion of print. This literature must be preserved in a form that ensures open access to it over the longer term.¹⁴⁹ A number of journals and archives are now available free on the web. The Open Society Institute (Soros Foundation, <http://www.soros.org/openaccess>) has supported alternative journals and open archiving initiatives.

There are several nonprofit publishers/distributors of developing country journals and information. These include Bioline International (<http://www.bioline.org.br>), which hosts electronic versions of many developing country journals (most of them at a modest subscription fee); International Network for the Availability of Scientific Publications, or INASP (www.inasp.info/index.html), a cooperative network of partners whose mission is to enhance the flow of information within and between countries, especially those with less developed systems of publication and dissemination; SciELO (<http://www.scielo.org>), which hosts multiple journals published in Latin American countries; and African Journals Online or AJOL (<http://www.inasp.info/ajol/index.html>), which provides free online access to titles and abstracts of multiple African journals and full text on request. HINARI (Health Internet, <http://www.healthinternet.org>), a UN/WHO initiative, aims to provide commercial medical journals free to licensed countries in the developing world. PERI (Programme for the Enhancement of Research Information, <http://www.inasp.info/peri/index.html>) supports information production, access, and dissemination for research partners in developing and transitional countries utilizing ICTs.

HIF-net, launched in July 2000 by the International Network for the Availability of Scientific Publication and the WHO, is an e-mail discussion list (hif-net@dggroups.org) targeted mainly for providers and users of health information in resource-poor settings. It has more than thousands of subscribers spread over 130 countries. Another global networking health group is the Program for Monitoring Emerging Diseases, ProMEDmail (<http://www.promedmail.org>). This is an Internet-based reporting system that provides rapid access to information on outbreaks of infectious diseases and acute exposures to toxins.

IMPLICATIONS AND CHALLENGES OF ICTS IN HIV/STI

In this chapter, we have reviewed some of the published literature regarding the use of ICT applications to HIV/STI control. While a variety of ICT tools are in various stages of use for

HIV/STI prevention, relatively few areas have accumulated a critical mass of evidence-based data about the most effective approaches. However, some of that evidence is compelling, and the potential for future uses appears large. Application to some areas of practice and research are nascent, the impact on disease incidence and economic evaluation data are still very limited, and evaluation of these tools would benefit from rigorous study designs. Nonetheless, these technologies very likely will become more available and potentially, more integrated, into routine HIV/STI prevention efforts. Appropriately, utilized technologies may improve HIV/STI screening, prevention, surveillance, and care for patients and populations in both resource-constrained and resource-rich settings.

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Appendixes

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B. Sexually Transmitted Diseases Treatment Guidelines	2089

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A

APPENDIX

Clinically Significant Drug Interactions with Medications for STDs and HIV

Alice K Pau

Treatment of HIV infection involves use of combinations of medications at the same time. Among the antiretroviral drugs, the protease inhibitors and non-nucleoside reverse transcriptase inhibitors have the greatest propensity of having pharmacokinetic interactions with each other and with other drugs commonly used in the HIV patients, including drugs used for the treatment of other sexually transmitted infections.

The most commonly encountered drug interactions that occur with medications used to treat HIV can be grouped into two major categories: overlapping/additive toxicities and pharmacokinetic interactions. Overlapping/additive toxicities are easily predictable with knowledge of the major side effects caused by each agent. For example, peripheral neuropathy can be a side effect of stavudine, didanosine, and zalcitabine; bone marrow suppression can occur frequently from zidovudine and ganciclovir; when these drugs are used in combination, invariably, increase in frequency and/or intensity of these adverse effects may ensue.

PHARMACOKINETIC INTERACTIONS

These interactions occur when one medication alters the concentrations of another by interfering with its absorption, metabolism, and/or elimination. Not all drug interactions lead to clinically significant events. It is of particular importance for those drugs, which have narrow margin of safety and efficacy. In these cases, increases in drug concentration or exposure may predispose the patient to concentration-related toxicities, whereas reduces in drug concentration may lead to inadequacy of its desired pharmacologic activity. Being able to recognize potentially significant interactions may help the clinicians to avoid these interactions or to manage them accordingly. The table provided in this appendix lists the known interactions and potential management strategies for drugs commonly used in treating HIV and STDs.

■ CHANGES IN DRUG ABSORPTION

The rate and extent of absorption can be affected by many factors, such as the presence or absence of food, gastric pH,

rate of gastric emptying, malabsorption, the presence of metabolic enzymes such as the 3A4 isoenzyme of the cytochrome P450 system (CYP3A4), and efflux proteins such as p-glycoprotein in the gut lumen.

Some drugs may affect the oral absorption of others by alteration of some of the above listed factors. For example, the absorption of the protease inhibitor atazanavir requires an acidic pH. Coadministration of long acting proton pump inhibitors may significantly impair the absorption of atazanavir, resulting in subtherapeutic drug concentrations. On the other hand, the protease inhibitor saquinavir has very poor bioavailability due to the presence of the CYP 3A4 enzyme in the gut lumen, which metabolizes saquinavir before it can be absorbed systemically. Ritonavir given in conjunction with saquinavir can inhibit the CYP3A4 activities in the gut, resulting in substantially improved oral bioavailability. Some of these significant interactions are listed in the table.

■ CHANGES IN DRUG METABOLISM

Most of the significant drug–drug interactions occur when the hepatic metabolism of one drug is induced (hastened) or inhibited (slowed down) by the presence of another drug which can serve as an inducer or inhibitor of the enzymatic pathway. The cytochrome P450 system is the most important of such hepatic metabolic pathway, responsible for the metabolism of many drug compounds as well as endogenous chemicals such as corticosteroids. The HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors, azoles, macrolides, and rifamycins are some commonly used anti-infective agents that are metabolized through this pathway and may result in significant interactions when they are used in combination with each other. Careful evaluation of drug interaction potentials each time a new drug is prescribed is critical in order to avoid untoward reactions. The table provides the reader with some initial management strategy, although the clinicians should be cautioned that some interactions are highly variable from patient to patient,

the recommendations in the table do not preclude close clinical monitoring, and further dosage modification or drug discontinuation may be necessary in some patients.

Even though most significant drug–drug interactions may result in negative or undesirable outcome, the recognition of the potent inhibitory effect of ritonavir has led to the exploitation of this unique property to “boost” or “enhance” the systemic exposure of other protease inhibitors. The addition of low dose ritonavir to another protease inhibitor may result in delay in drug clearance, prolong elimination half-life, thus, allowing for less frequent dosing to improve drug adherence. On the other hand, one should be cautious about other drugs the patients may be taking concomitantly with a ritonavir-boosted regimen, as the concentrations of these other medications may be increased if the concomitant drug is a substrate of the CYP system.

■ CHANGES IN DRUG ELIMINATION

This most commonly occurs when use of a medication that compromises renal function (pentamidine, foscarnet, amphotericin) reduces the kidney’s ability to eliminate renally cleared

medications (such as penicillin, tenofovir). Drug concentrations may then increase and additional toxicities may develop.

■ DRUG INTERACTION TABLE

The following table should serve as a guide in helping to predict the outcome of combining medications used to treat HIV infection and sexually transmitted diseases. Because of the narrow therapeutic range of some of these medications it is critical that someone familiar with HIV care evaluates all medications a patient is taking for any possible drug interactions. Unless this is accomplished in a systematic manner a serious toxicity could result or efficacy of the regimen may be compromised and result in incomplete viral suppression and development of resistance. Clinicians are reminded that the absence of data does not always mean that it is safe to combine two drugs. New drug interaction data emerge frequently, significant interactions, which may lead to safety concerns, are often made public through alerts from the Food and Drug Administration and drug manufacturers. Clinicians should be kept abreast of these new information in order to provide the patients the safest possible drug therapy.

Significant Pharmacokinetic Interactions Between Drugs Used for Treatment of Sexually Transmitted Diseases, Including HIV Infection

Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
<i>Antibiotics used for STDs</i>			
Azithromycin	Contraindicated drugs: none		
	Nelfinavir	↑ Azithromycin level	Monitor for azithromycin toxicities
Cephalosporins	Contraindicated drugs: none		
	Probenecid	↑ Cephalosporin level by inhibition of renal tubular secretion of cephalosporin	May enhance cephalosporin activity; monitor for toxicities
Ciprofloxacin, Gemifloxacin, levofloxacin, and moxifloxacin	Contraindicated drugs: none Antacids with aluminum or magnesium salts; Calcium-containing products; Didanosine buffered formulation Iron supplements Sucralfate	↓ Absorption of fluoroquinolones	Fluoroquinolones should be given at least 2 h before or 6 h after these products
	Drugs causing QTc prolongation, e.g., cisapride, Class IA Antiarrhythmics, Class III Antiarrhythmics, Erythromycin, etc.	May have additive effect in QTc prolongation with all fluoroquinolones—less likely with ciprofloxacin	Avoid these combinations if possible, only use if no alternative treatment

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
Clarithromycin	Contraindicated drugs: astemizole, terfenadine, cisapride, pimozide		
	Atazanavir	↑ Clarithromycin levels, potential for ↑ QT prolongation	Reduce clarithromycin dose by 50% & monitor for cardiotoxicity or use azithromycin
	Darunavir/ritonavir	↑ Clarithromycin levels	Dosage reduction if creatinine clearance <60 mL/min; consider using azithromycin
	Delavirdine	↑ Clarithromycin levels	Monitor for clarithromycin toxicities or use azithromycin
	Efavirenz	↓ Clarithromycin levels	Significance unknown, consider using azithromycin
	Fluconazole	↑ Clarithromycin levels, QT prolongation & torsades de pointes have been reported	Monitor for cardiotoxicity or use azithromycin
	Lopinavir/ritonavir	↑ Clarithromycin levels	Dosage reduction if creatinine clearance <60 mL/min; consider using azithromycin
	Nevirapine	↓ Clarithromycin level	Use azithromycin or monitor for clarithromycin efficacy
	Ritonavir	↑ Clarithromycin levels	Dosage reduction if creatinine clearance <60 mL/min or use azithromycin
	Tipranavir/ritonavir	↑ Tipranavir levels, ↑ Clarithromycin levels	Dose reduction if creatinine clearance <60 mL/min, or use azithromycin
Erythromycin	Contraindicated drugs: astemizole, terfenadine, cisapride, pimozide		
	Gemifloxacin, levofloxacin, moxifloxacin	May have additive effect in QTc prolongation	Use this combination with caution, esp. in at-risk patient; possibly use an alternative fluoroquinolone such as ciprofloxacin
Metronidazole	Contraindicated drugs: none		
	Amprenavir oral solution	Potential for propylene glycol toxicity as patients on metronidazole may not adequately metabolize and eliminate propylene glycol—a solvent in amprenavir oral solution	Use amprenavir oral solution only if fosamprenavir cannot be used
	Ritonavir, lopinavir/ritonavir oral solution	Inhibition of alcohol and aldehyde dehydrogenase by metronidazole. Possible disulfiram-like reaction due to alcohol in these preparations	
Penicillin	Contraindicated drugs: none		
	Probenecid	↑ Penicillin level & half-life by inhibition of renal tubular secretion of cephalosporin	May enhance penicillin activity; monitor for toxicities

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
Tetracycline (mainly doxycycline)	Contraindicated drugs: none		
	Antacids, bismuth, cholestyramine, didanosine buffered formulations, and oral calcium, magnesium, aluminum, and iron products	↓ Tetracycline absorption	Separate doses by giving tetracyclines at least 2 h before these products
	Atovaquone	May ↓ atovaquone level	Monitor for atovaquone efficacy
<i>Antifungal drugs used for STD</i>			
Fluconazole	Contraindicated drugs: astemizole, terfenadine, cisapride		
	Clarithromycin	↑ Clarithromycin levels, QT prolongation & torsades de pointes have been reported	Monitor for cardiotoxicity or use azithromycin
	Nevirapine	May ↑ Nevirapine level	Monitor for nevirapine-associated toxicities
	Tipranavir/ritonavir	↓ Tipranavir level	No dosage adjustment of tipranavir/ritonavir recommended; fluconazole dose >200 mg not recommended
<i>Antiretroviral therapy—nucleoside reverse transcriptase inhibitors</i>			
Abacavir	Contraindicated drugs: none		
	Tipranavir/ritonavir	↓ Abacavir level	No dosage adjustment recommended, monitor antiviral efficacy
Didanosine (ddl) buffered formulations	Contraindicated drugs: none		
	Drugs should not be used with didanosine: Ribavirin (see below), allopurinol, stavudine (during pregnancy—only if benefits outweigh the risk of lactic acidosis/hepatic steatosis/pancreatitis)		
	(Amprenavir/ Fosamprenavir)	Potential for ↓ amprenavir absorption due to ↑ in gastric pH	Separate administration by at least 1 h
	Atazanavir	↓ Atazanavir absorption due to ↑ in gastric pH	Use enteric coated ddl
	Ciprofloxacin & other fluoroquinolones	↓ Fluoroquinolone absorption due to chelation from magnesium/aluminium cations	Use enteric coated ddl. If buffered formulation is used, take fluoroquinolones at least 2 h before or 6 h after ddl
	Delavirdine	↓ Delavirdine—absorption when used with buffered ddl	Use enteric coated ddl or separate administration by at least 1 h
	Ganciclovir (oral and IV)	↑ Didanosine levels	No dosage adjustment recommended. When used together, monitor for didanosine toxicities (pancreatitis, peripheral neuropathy)
	Indinavir	↓ Indinavir absorption when buffered ddl is used; not affected by enteric coated ddl	Use enteric coated ddl or take indinavir at least 1 h before ddl
	Lopinavir/ritonavir	↓ Lopinavir absorption	Take any ddl preparation at least 1 h before or 2 h after lopinavir/ritonavir

(Continued)

Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
	Ribavirin	↑ intracellular concentration of ddl—increased serious ddl-associated mitochondrial toxicities	Avoid concomitant use
	Tenofovir	↑ ddl level—for both buffered and enteric coated formulations	↓ ddl dose to 250 mg/d for pts >60 kg, and to 200 mg/d for pts <60 kg; monitor for ddl-associated toxicities
	Tipranavir/ritonavir + Enteric Coated ddl	↓ Didanosine level	Clinical relevance unknown, no dosage adjustment recommended. For optimal absorption, give didanosine separate from tipranavir/ritonavir by at least 2 h
Emtricitabine	No significant pharmacokinetic interactions		
Lamivudine	No significant pharmacokinetic interactions		
Stavudine	Contraindicated drugs: none		
	Drugs not recommended to use with stavudine: Zidovudine (antagonistic antiretroviral effect), didanosine (additive toxicities—only if benefits outweigh the risk of lactic acidosis/hepatic steatosis/pancreatitis/additive peripheral neuropathy)		
	No other significant pharmacokinetic interaction		
Tenofovir	Contraindicated drugs: none		
	Atazanavir	↓ Atazanavir levels	Add ritonavir 100 mg/d; dose atazanavir at 300 mg once daily
	Didanosine	↑ Didanosine level—for both buffered and enteric coated formulations	↓ ddl dose to 250 mg/d for pts >60 kg, and to 200 mg/d for pts <60 kg, monitor for didanosine associated toxicities
	Lopinavir/ritonavir	↑ Tenofovir level	No dosage adjustment necessary
Zidovudine	Contraindicated drug: none		
	Drugs should not be used with zidovudine: Stavudine—antagonistic antiviral effect		
	Probenecid	↑ Zidovudine levels	Monitor for increase bone marrow suppression
	Rifampin	↓ Zidovudine levels	Monitor for zidovudine efficacy; consider using rifabutin
	Tipranavir/ritonavir	↓ Zidovudine levels	Clinical relevance unknown, no dosage adjustment recommended
<i>Antiretroviral therapy—non-nucleoside reverse transcriptase inhibitors</i>			
Delavirdine	Contraindicated drugs: astemizole, terfenadine, cisapride, pimozide, ergot derivatives, alprazolam, triazolam, midazolam		
	Drugs should not be used with delavirdine rifampin, rifabutin, amprenavir, fosamprenavir, carbamazepine, phenytoin, phenobarbital, St. John's Wort, lovastatin, simvastatin		
	Amprenavir and fosamprenavir	↑ Amprenavir levels, but significant ↓ in delavirdine level (C _{min} ↓ by 88%)	Do not coadminister. Alternative NNRTI (efavirenz or nevirapine) should be used
	Clarithromycin	↑ Clarithromycin level	Use azithromycin. If clarithromycin is used, dose reduce if creatinine clearance <60 mL/min

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
	Didanosine (ddl) buffered formulation	↓ Delavirdine levels	Consider enteric coated ddl; or take delavirdine at least 1 h before buffered ddl
	Indinavir	↑ Indinavir concentration	No dosage adjustment necessary
	Lopinavir/ritonavir	↑ Lopinavir level	Doses not established, monitor for lopinavir/ritonavir toxicities
	Nelfinavir	↑ Nelfinavir level, ↓ delavirdine level	No dosage adjustment recommended; consider using alternative NNRTI
	Saquinavir	↑ Saquinavir level	Effect on ritonavir-boosted saquinavir unknown; no dosage adjustment recommended at this point
Efavirenz	Contraindicated drugs: astemizole, cisapride, midazolam, triazolam, ergot derivatives, voriconazole (see below)		
	Atazanavir	↓ Atazanavir level	Only use with ritonavir boosting
	Clarithromycin	↓ Clarithromycin level	Significance unknown, consider using azithromycin
	Fosamprenavir	↓ Amprenavir level	Only use with ritonavir boosting
	Indinavir	↓ Indinavir levels 30–35%	↑ Indinavir to 1000 mg Q8H or use with ritonavir boosting
	Lopinavir/ritonavir	↓ Lopinavir level	↑ Lopinavir/ritonavir to 600 mg/150 mg (3 tablets) twice daily; once daily lopinavir/ritonavir should not be used with efavirenz
	Ritonavir	↑ Ritonavir, ↑ Efavirenz	Monitor for toxicities of both drugs
	Saquinavir	↓ Saquinavir levels 60%	Use only with ritonavir boosting
	Tipranavir/ritonavir	↓ Tipranavir level	No dosage adjustment recommended
Nevirapine	Contraindicated drugs: none		
	Atazanavir	May result in ↓ Atazanavir level	Concomitant use only if atazanavir is boosted with ritonavir
	Clarithromycin	↓ Clarithromycin level	Use azithromycin or monitor clarithromycin efficacy
	Fluconazole	↑ Nevirapine level	Avoid concomitant use or monitor for nevirapine toxicities
	Fosamprenavir	May result in ↓ Amprenavir level	Not recommended unless with ritonavir-boosting
	Indinavir	↓ Indinavir AUC	↑ Indinavir dose to 1000 mg q8h or add ritonavir to ↑ indinavir level
	Lopinavir/ritonavir	↓ Lopinavir concentration	↑ Lopinavir/ritonavir to 600 mg/150 mg twice daily; once daily lopinavir/ritonavir should not be used with nevirapine
	Saquinavir	↓ Saquinavir levels	Saquinavir should not be used with nevirapine without pharmacokinetic boosting (e.g., with ritonavir)

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
<i>Antiretroviral therapy—protease inhibitors</i>			
Amprenavir (and fosamprenavir) ^a	Contraindicated drugs: cisapride, ergot derivatives, pimozone, midazolam, triazolam Drugs should not be used with amprenavir oral solution or fosamprenavir: bepridil, delavirdine, lovastatin, simvastatin, rifampin, rifapentine, St. John's Wort, tipranavir, ritonavir oral solution (not to be given with amprenavir oral solution—see below)		
	Delavirdine	↑ Amprenavir level; ↓ Delavirdine Level	Do not coadminister
	Didanosine buffered formulations	May ↓ Amprenavir absorption	Separate dosing by at least 1 h
	Efavirenz + Fosamprenavir	↓ Amprenavir level	Only use with ritonavir boosting; if once daily ritonavir + fosamprenavir is used, an additional 100 mg of ritonavir should be added
	Indinavir	↑ Amprenavir level; ↓ Indinavir level	Dosing recommendation not established, monitor for viral efficacy Monitor for toxicity of both drugs
	Lopinavir/ritonavir + Fosamprenavir	↓ Fosamprenavir, ↓ Lopinavir	Doses not established; increased rate of adverse events seen when use in combination
	Metronidazole (with amprenavir oral solution)	Metronidazole inhibits alcohol & aldehyde dehydrogenase—may lead to propylene glycol toxicity (propylene glycol is solvent in amprenavir oral solution)	Use fosamprenavir oral capsule or other protease inhibitor; or avoid metronidazole
	Nevirapine	May ↓ Amprenavir level	Consider alternative therapy; or use ritonavir to ↑ amprenavir level
	Ritonavir oral solution + Amprenavir oral solution	The ethanol in ritonavir oral solution may compete with the propylene glycol in amprenavir oral solution in their metabolic pathway, leading to accumulation of either ethanol or propylene glycol	Concomitant administration of the two products is not recommended
	Ritonavir + Fosamprenavir	↑ Amprenavir level	Low dose ritonavir (200 mg/d) may be used to boost amprenavir level
	Tipranavir/ritonavir	↓ Amprenavir level	Do not coadminister
Atazanavir	Contraindicated drugs: cisapride, ergot derivatives, pimozone, midazolam, triazolam Drugs should not be used with atazanavir: bepridil, rifampin, rifapentine, proton pump inhibitors, indinavir, lovastatin, simvastatin, irinotecan, St. John's Wort		
	Clarithromycin	↑ Clarithromycin level; ↑ Atazanavir level	↓ Clarithromycin dose by 50% (to avoid risk of arrhythmia) Alternative: Azithromycin
	Didanosine buffered formulations	↓ Atazanavir absorption due to ↑ gastric pH	Use enteric coated didanosine

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
	Efavirenz	↓ Atazanavir level	Only use this combination with ritonavir boosting
	Nevirapine	Not studied; potential for ↓ Atazanavir level	Not recommended to be used concomitantly; if combined, add ritonavir and consider therapeutic drug monitoring
	Ritonavir	↑ Atazanavir level	Ritonavir 100 mg/d recommended as pharmacokinetic enhancer
	Saquinavir	↑ Saquinavir level	Appropriate dose for saquinavir + atazanavir +/- ritonavir has not been established
	Tenofovir	↓ Atazanavir level	Use the combination only with ritonavir boosting (ritonavir 100 mg + atazanavir 300 mg—both once daily)
Fosamprenavir (Pro-drug of amprenavir)	See drug interaction information under Amprenavir		
Indinavir	Contraindicated Drugs: Astemizole, terfenadine, amiodarone, ergot derivatives, cisapride, midazolam, pimozide Drugs should not be used with Indinavir: Atazanavir, lovastatin, simvastatin, rifampin, rifapentine, St. John's Wort		
	Clarithromycin	↑ Indinavir level; ↑ Clarithromycin level	No dosage adjustment
	Delavirdine	↑ Indinavir level	No dosage adjustment
	Didanosine buffered formulation	↓ Indinavir level	Use enteric coated didanosine preparation or separate indinavir and didanosine by at least 1 h
	Efavirenz	↓ Indinavir levels	↑ Indinavir to 1000 mg every 8 h or add ritonavir to boost indinavir level
	Ketoconazole	↑ Indinavir level	No dosage adjustment needed
	Nevirapine	↓ Indinavir level	↑ Indinavir to 1000 mg every 8 h or add ritonavir to boost indinavir level
	Ritonavir	↑ Indinavir level	Add ritonavir as pharmacokinetic enhancer—ritonavir 100–200 mg twice daily + indinavir 800 mg twice daily
	Saquinavir	↑ Saquinavir levels	Dosage for this combination not yet established
Lopinavir/ritonavir	Contraindicated drugs: astemizole, terfenadine, cisapride, pimozide, ergot derivatives, midazolam, triazolam Drugs should not be used with lopinavir/ritonavir: rifampin, rifapentine, lovastatin, simvastatin, St. John's Wort, fluticasone, tipranavir/ritonavir		
	Clarithromycin	↑ Clarithromycin level	Reduce clarithromycin dose in patients with creatinine clearance <60 mL/min
	Delavirdine	↑ Lopinavir level	Doses not established, monitor for lopinavir/ritonavir toxicities
	Didanosine	↓ Lopinavir/ritonavir absorption	Take didanosine at least 1 h before or 2 h after lopinavir/ritonavir
	Efavirenz	↓ Lopinavir level	↑ Lopinavir/ritonavir to 533 mg 133 mg twice daily; once daily lopinavir/ritonavir should not be used with efavirenz

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
	Fosamprenavir	↓ Fosamprenavir level, ↓ Lopinavir level	Doses not established; increased rate of adverse events seen when use in combination.
	Metronidazole with lopinavir/ritonavir oral solution	Inhibition of alcohol and aldehyde dehydrogenase by metronidazole. Possible disulfiram-like reaction due to alcohol in lopinavir/ritonavir oral solution	Do not coadminister—may consider oral capsule formulation, at least during concomitant metronidazole therapy
	Nevirapine	↓ Lopinavir level	↑ Lopinavir/ritonavir to 600 mg/150 mg twice daily; once daily lopinavir/ritonavir should not be used with efavirenz
	Saquinavir	↑ Saquinavir level	Reduce saquinavir dose to 800 mg twice daily
	Tenofovir	↑ Tenofovir level	No dosage adjustment
	Tipranavir/ritonavir	↓ Lopinavir level	Do not coadminister
Nelfinavir	Contraindicated drugs: amiodarone, quinidine, astemizole, terfenadine, cisapride, ergot derivatives, pimozide, midazolam, triazolam		
	Drugs that should not be coadministered with nelfinavir: Lovastatin, simvastatin, rifampin, St. John's Wort		
	Azithromycin	↑ Azithromycin level	No dosage adjustment recommended
	Delavirdine	↑ Nelfinavir level, ↓ delavirdine level	Dosage has not been established; monitor for nelfinavir toxicities
	Efavirenz	↑ Nelfinavir	Use standard dose for both
	Indinavir	↑ Indinavir level and ↑ nelfinavir level	No dosage established; monitor for excessive toxicities of both drugs
	Saquinavir	↑ Saquinavir level	↓ Saquinavir to 1,200 mg twice daily
Ritonavir	Contraindicated drugs: amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine, cisapride, ergot derivatives, pimozide, midazolam, triazolam		
	Drugs not to coadminister with ritonavir: lovastatin, simvastatin, St. John's Wort, fluticasone, alfuzosin, rifapentine, and voriconazole (if ritonavir > 400 mg twice daily is used)		
	Atazanavir	↑ Atazanavir level	Low dose ritonavir (100 mg/d) may be used to boost atazanavir level; Atazanavir dose: 300 mg once daily
	Clarithromycin	↑ Clarithromycin level	↓ Clarithromycin dose in patients with creatinine clearance <60 mL/min
	Fosamprenavir	↑ Amprenavir level	Low dose ritonavir (200 mg/d) may be used to boost amprenavir level (fosamprenavir 700 mg + ritonavir 100 mg) twice daily; or (fosamprenavir 1400 mg + ritonavir 200 mg) once daily
	Indinavir	↑ Indinavir levels	Low dose ritonavir (200–400 mg/d) may be used to boost indinavir level; Indinavir dose 800 mg twice daily

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
	Metronidazole	Inhibition of alcohol and aldehyde dehydrogenase by metronidazole. Possible disulfiram-like reaction due to alcohol in ritonavir preparations	Use with caution and monitor for disulfiram-like reactions
	Nelfinavir	↑ Nelfinavir AUC 152%	No dosage recommendation; monitor for nelfinavir toxicities
	Saquinavir	↑ Saquinavir level to therapeutic concentration	Low dose ritonavir should always be used to boost saquinavir level
Saquinavir	Contraindicated drugs: astemizole, terfenadine, cisapride, pimozone, midazolam, triazolam, ergot derivatives, rifampin, amiodarone, bepridil, flecainide, propafenone, quinidine Drugs should not be use with saquinavir: lovastatin, simvastatin, St. John's Wort, garlic capsules, rifapentine, tipranavir/ritonavir		
	Clarithromycin	↑ Saquinavir level	No dosage adjustment necessary
	Delavirdine	↑ Saquinavir level	Appropriate dose of the combination not established
	Efavirenz	↓ Saquinavir level	Saquinavir should not be used with efavirenz without ritonavir boosting
	Fluconazole	↑ Saquinavir level	No dosage adjustment necessary
	Indinavir	↑ Saquinavir levels	Appropriate dosing has not been established
	Lopinavir/ritonavir	↑ Saquinavir levels	↑ Saquinavir efficacy
	Nelfinavir	↑ Saquinavir and ↑ nelfinavir levels	Saquinavir 1200 mg twice daily; nelfinavir 1250 mg twice daily
	Nevirapine	↓ Saquinavir levels	Saquinavir should not be used with nevirapine without pharmacokinetic boosting (e.g., with ritonavir)
	Ritonavir	↑ Saquinavir AUC 20-fold	Low-dose ritonavir should be used to boost saquinavir level
	Tipranavir/ritonavir	↓ Saquinavir levels	Do not coadminister
Tipranavir/ritonavir	Contraindicated drugs: amiodarone, bepridil, flecainide, propafenone, quinidine, astemizole, terfenadine, ergot derivatives, cisapride, pimozone, midazolam, triazolam Drugs should not be used with tipranavir/ritonavir: Rifampin, St. John's Wort, lovastatin, simvastatin		
	Abacavir	↓ Abacavir level	Clinical relevance unknown, no dosage adjustment recommended
	Amprenavir/ fosamprenavir	↓ Amprenavir level	Coadministration is not recommended
	Clarithromycin	↑ Tipranavir level, ↑ Clarithromycin level	For creatinine clearance <60 mL/min, clarithromycin dose should be reduced
	Didanosine (enteric coated)	↓ Didanosine level	Clinical relevance unknown, no dosage adjustment recommended. For optimal absorption, give didanosine separate from tipranavir/ritonavir by at least 2 h
	Efavirenz	↓ Tipranavir level	No dosage adjustment recommended

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
	Fluconazole	↑ Tipranavir level	No dosage adjustment of tipranavir/ritonavir recommended; fluconazole dose >200 mg not recommended
	Lopinavir/ritonavir	↓ Lopinavir level	Coadministration is not recommended
	Saquinavir	↓ Saquinavir level	Coadministration is not recommended
	Zidovudine	↓ Zidovudine level	Clinical relevance unknown, no dosage adjustment recommended
<i>Antiretroviral drugs—fusion inhibitor</i>			
Enfuvirtide	No significant pharmacokinetic interaction		
<i>Antiviral drugs</i>			
Acyclovir/Famciclovir/ Valacyclovir	Contraindicated drugs: none		
	Probenecid	↑ Acyclovir (for acyclovir & valacyclovir) & Penciclovir (for famciclovir) levels by inhibition of renal tubular secretion	Monitor for toxicities of the antiviral drugs
Cidofovir	Contraindicated drugs: coadministration of drugs with high nephrotoxic potential		
	Probenecid	↓ Cidofovir nephrotoxicity by blocking uptake of cidofovir by proximal tubular cells	Probenecid given with saline before and after cidofovir dose can reduce incidence of cidofovir-associated nephrotoxicity
	Nephrotoxic drugs (e.g., amphotericin B, cidofovir, pentamidine, aminoglycosides)	May ↓ Cidofovir renal clearance & ↑ cidofovir accumulation	Avoid concomitant use; if used, monitor renal function and cidofovir-associated toxicities
Entecavir	No significant drug interaction		
Foscarnet	Contraindicated drugs: none		
	Drugs should be avoided: nephrotoxic drugs		
	Nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, cidofovir, pentamidine, etc.)	May ↓ Foscarnet renal clearance & ↑ Foscarnet accumulation	Avoid concomitant use; if used, monitor renal function and foscarnet-associated toxicities
Ganciclovir or Valganciclovir	Contraindicated drugs: none		
	Drugs should not be used with ganciclovir or valganciclovir: Imipenem-cilastatin (reports of generalized seizure, avoid concomitant use unless benefits outweigh the risk)		
	Didanosine	↑ Didanosine levels	No dosage adjustment recommended. When used together, monitor for didanosine toxicities (pancreatitis, peripheral neuropathy)
	Probenecid	↑ Ganciclovir level by competition of renal tubular secretion	Monitor for ganciclovir toxicities

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Primary Drug	Secondary Drug	Interaction Result	Management of Interaction
Interferon alfa (including pegylated formulations)		No significant pharmacokinetic interaction	
Ribavirin	Contraindicated drugs: none		
	Drug should not be used with ribavirin: Didanosine		
	Didanosine	↑ intracellular concentration of didanosine—increased serious didanosine-associated mitochondrial toxicities	Avoid concomitant use

^aAmprenavir capsule is no longer in distribution in the United States—the information is primarily pertaining to the effect of interacting drugs on fosamprenavir (prodrug of amprenavir) or amprenavir oral solution. navir (prodrug of amprenavir) or amprenavir oral solution.

B

APPENDIX

Sexually Transmitted Diseases Treatment Guidelines, 2006

Kimberly A. Workowski and Stuart M. Berman

This abbreviated version of the 2006 STD Guidelines focuses on the treatment and counseling of persons with sexually transmitted diseases and does not include discussion of vaccine preventable STDs, screening for cervical dysplasia, management of persons who have been sexually assaulted, and management of less common manifestations; these issues are addressed in detail in the complete guidelines document.

CLINICAL PREVENTION GUIDANCE

The prevention and control of STDs are based on the following five major strategies: (1) education and counseling of persons at risk on ways to avoid STDs through changes in sexual behaviors; (2) identification of asymptotically infected persons and of symptomatic persons unlikely to seek diagnostic and treatment services; (3) effective diagnosis and treatment of infected persons; (4) evaluation, treatment, and counseling of sex partners of persons who are infected with an STD; and (5) preexposure vaccination of persons at risk for vaccine-preventable STD.

OVERVIEW OF CHANGES IN THE 2006 CDC STD TREATMENT GUIDELINES

For over 30 years, CDC's publication of national guidelines for management of STDs has assisted clinicians with effective guidance on the delivery of optimal STD care. New recommendations in these updated guidelines include the clinical efficacy of azithromycin for chlamydial infections in pregnancy, an expanded diagnostic evaluation for cervicitis and trichomoniasis; a new antimicrobial for trichomoniasis; the role of *Mycoplasma genitalium* and trichomoniasis in urethritis/cervicitis and treatment-related implications; lymphogranuloma venereum (LGV) proctocolitis among men who have sex with men (MSM); revision of the criteria for spinal fluid examination to evaluate for neurosyphilis; the emergence of azithromycin-resistant *Treponema pallidum*;

increasing prevalence of quinolone-resistant *Neisseria gonorrhoeae* in MSM; postexposure prophylaxis after sexual assault; and an expanded discussion of STD prevention approaches. A summary of some of these new recommendations is described below. A complete version of the STD Treatment Guidelines is available at www.cdc.gov/std/treatment.

Annual screening for chlamydia in all sexually active women aged ≤ 25 years is recommended, as is screening of older women with risk factors (e.g., those who have a new sex partner or multiple sex partners). There is insufficient evidence to recommend routine screening for *Chlamydia trachomatis* in sexually active young men, based on feasibility, efficacy, and cost-effectiveness; however, screening should be considered in high prevalence areas (adolescent clinics, correctional facilities, STD clinics). Efficacious therapeutic regimens for chlamydia include azithromycin or doxycycline. Because of the high probability of repeat infection, women should be retested for chlamydial infection 3–4 months after treatment. Clinical experience and limited studies are available to support the efficacy and safety of azithromycin as a recommended regimen in pregnant women.

Selection of appropriate therapy for gonorrhea is guided by a CDC-sponsored surveillance system that has monitored gonococcal antimicrobial susceptibility for the last 20 years (GISP). Ongoing data from GISP demonstrate that fluoroquinolone-resistant gonorrhea is continuing to spread and is widespread in the United States. As a consequence, this class of antibiotics is no longer recommended for the treatment of gonorrhea in the United States (*MMWR*, April 13, 2007). Oral alternatives to fluoroquinolones are limited, as cefixime suspension is the only available formulation. Some evidence suggests that cefpodoxime proxetil 400 mg or cefuroxime axetil 1 g might be reasonable oral alternative regimens.

C. trachomatis, *N. gonorrhoeae*, *Trichomonas vaginalis*, and genital herpes are established etiologic agents for cervicitis, and limited data suggest an association with bacterial vaginosis

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and *M. genitalium*. However, in the majority of cases of cervicitis no pathogen is identified. The evaluation of cervicitis should include nucleic acid amplification testing on cervical or urine specimens for chlamydia and gonorrhea and examination of vaginal secretions for bacterial vaginosis and trichomoniasis. The decision to provide presumptive therapy for cervicitis (chlamydia or gonorrhea) should include an individual risk assessment, the likelihood of follow-up, and the prevalence of infection in the population. There is limited information on the natural history of cervicitis when neither chlamydia or gonorrhea is present. The value of prolonged administration of antibiotic therapy for cervicitis is unknown, as standard management options are undefined.

Sexually transmitted organisms, especially *C. trachomatis* and *N. gonorrhoeae*, aerobic and anaerobic vaginal flora, and genital mycoplasmas have been associated with PID. There are no differences in short- and long-term clinical and microbiologic response rates between parenteral or oral therapy. If parenteral cephalosporin therapy is not feasible, use of fluoroquinolones (levofloxacin 500 mg orally once daily or ofloxacin 400 mg twice daily for 14 days) with or without metronidazole (500 mg orally twice daily for 14 days) may be considered if the community prevalence and individual risk (see “Gonococcal Infections in Adolescents and Adults” in *Sexually Transmitted Disease Treatment Guidelines*, 2006) of gonorrhea is low. Tests for gonorrhea must be performed prior to instituting therapy and the patient managed as follows if the test is positive:

- If NAAT test is positive, parenteral cephalosporin is recommended.
- If culture for gonorrhea is positive, treatment should be based on results of antimicrobial susceptibility. If isolate is QRNG, or antimicrobial susceptibility can not be assessed, parenteral cephalosporin is recommended.

Although information regarding other outpatient regimens is limited, amoxicillin/clavulanic acid plus doxycycline or azithromycin plus metronidazole has demonstrated short-term clinical cure. No data has been published regarding the use of oral cephalosporins for the treatment of PID.

Metronidazole or tinidazole are the recommended regimens for trichomoniasis treatment. Some strains of *T. vaginalis* can have diminished susceptibility to nitroimidazoles; however, most infections will respond higher doses of metronidazole or tinidazole. In vitro data and limited clinical investigation support the efficacy of tinidazole when treatment with metronidazole fails.

Syphilis remains an important problem due to recent increases in primary and secondary syphilis, especially in MSM, and due to biological interactions, with syphilis

facilitating HIV acquisition and transmission. Long-acting preparations of penicillin remain the treatment of choice for all stages of syphilis. Limited data are available on the management of early syphilis in those with penicillin allergy with ceftriaxone or azithromycin and on the appropriate dose and duration of these alternative regimens. However, recent reports have described clinical treatment failure in MSM who received azithromycin for early syphilis. HIV-infected persons who have early syphilis should be managed according to standard treatment recommendations, although there may be an increased risk for neurologic complications and higher rates of treatment failure. The natural history of central nervous treponemal invasion in HIV-infected persons is not well defined, but some investigators have suggested that lumbar puncture be considered in those persons with syphilis who have RPR \geq 1:32 (regardless of stage), especially with concomitant HIV infection with CD4 \leq 350. Abnormalities of the cerebrospinal fluid (pleocytosis or elevated protein) are common in early syphilis and in persons with HIV infection; however, there is no evidence to suggest that these abnormalities reliably predict the need for aggressive treatment regimens.

Suppressive therapy for genital herpes reduces the frequency of recurrences by 70–80% in persons with frequent recurrence (more than six recurrences per year). Treatment with valacyclovir 500 mg daily has been shown to decrease the HSV-2 transmission in discordant heterosexual couples in which the source partner has genital HSV-2 infection. Effective episodic treatment of recurrent genital herpes requires initiation of therapy within 1 day of lesion onset or during the prodrome; new recommendations for episodic therapy include acyclovir 800 mg orally three times daily for 2 days or famciclovir 1 g twice daily for 1 day.

LGV, caused by *C. trachomatis* serovars L1, L2, or L3, most typically presents as a self-limited genital ulcer followed by tender inguinal or femoral adenopathy. However, an increasingly recognized presentation has been recently observed in MSM with proctitis or proctocolitis and a high HIV-coinfection rate. LGV diagnosis should be based on clinical suspicion, local epidemiology, *C. trachomatis* testing, and the exclusion of other etiologies. Genital and lymph node specimens can be tested for *C. trachomatis*, but nucleic acid amplification tests are not FDA cleared for testing rectal specimens, and genotyping (not widely available) is required for differentiating LGV from non-LGV serovars. Chlamydia serology can support the diagnosis in appropriate clinical context, but LGV test interpretation is not standardized; these tests have not been validated for proctitis presentations, and *C. trachomatis* serovars-specific serologic tests are not widely available. Because of the current limitations in LGV diagnostic capabilities (lack of rapid, widely available, standardized

testing), the clinical management of persons with symptoms suggestive of LGV should include presumptive treatment.

Scabies infestation is a common cause of pruritus and skin rash worldwide. Ivermectin represents a new oral therapeutic option for scabies and may hold particular promise in the treatment of severe infestation or in epidemic situations. Lindane should only be used as an alternative therapy due to the risk of neurotoxicity and aplastic anemia. No controlled studies for crusted scabies have been conducted, but combination therapy with ivermectin and topical scabicides may prove to be a useful option. Pediculosis pubis is treated with either permethrin cream or pyrethrins; however, increasing rates of drug resistance to these pediculicides may affect their efficacy in the future. Malathion can be used when treatment failure is believed to have occurred because of resistance.

An important part of STD treatment is the evaluation and treatment of sex partners. Partner management can be provided directly by the provider or with assistance from the health department. The provision of partner services and the specific STDs for which they are offered may vary among providers, agencies, and geographic areas. Expedited partner therapy (EPT) may be an option for management of heterosexual patients with chlamydia or gonorrhea, in which partners of infected patients are treated without medical evaluation or prevention counseling. More information about EPT can be found at <http://www.cdc.gov/std/treatment/EPTFinalReport2006.pdf>. However, certain operational barriers exist including the lack of clarity about the legal status of EPT in some settings. There is no evidence to support the use of EPT in the management of syphilis or among MSM with chlamydia or gonorrhea.

Table B1. The Five Ps: Partners, Prevention of Pregnancy, Protection from STDs, Practices, Past History of STDs

1. Partners

- "Do you have sex with men, women, or both?"
- "In the past 2 months, how many partners have you had sex with?"
- "In the past 12 months, how many partners have you had sex with?"

2. Prevention of pregnancy

- "Are you or your partner trying to get pregnant?" If no, "What are you doing to prevent pregnancy?"

3. Protection from STDs

- "What do you do to protect yourself from STDs and HIV?"

4. Practices

- "To understand your risks for STDs, I need to understand the kind of sex you have had recently."
- "Have you had vaginal sex, meaning 'penis in vagina sex'?"
- If yes, "Do you use condoms: never, sometimes, or always?"
- "Have you had anal sex, meaning 'penis in rectum/anus sex'?"
- If yes, "Do you use condoms: never, sometimes, or always?"
- "Have you had oral sex, meaning 'mouth on penis/vagina'?"

For condom answers:

- If "never": "Why don't you use condoms?"
- If "sometimes": "In what situations or with whom, do you not use condoms?"

5. Past history of STDs

- "Have you ever had an STD?"
- "Have any of your partners had an STD?"

Additional questions to identify HIV and hepatitis risk:

- "Have you or any of your partners ever injected drugs?"
- "Have any of your partners exchanged money or drugs for sex?"
- "Is there anything else about your sexual practices that I need to know about?"

Table B2. Recommendations for the Proper Use of Male Condoms

- Use a new condom with each sex act (e.g., oral, vaginal, and anal).
- Carefully handle the condom to avoid damaging it with fingernails, teeth, or other sharp objects.
- Put the condom on after the penis is erect and before any genital, oral, or anal contact with the partner.
- Use only water-based lubricants (e.g., K-Y Jelly™, Astroglide™, AquaLube™, and glycerin) with latex condoms. Oil-based lubricants (e.g., petroleum jelly, shortening, mineral oil, massage oils, body lotions, and cooking oil) can weaken latex.
- Ensure adequate lubrication during vaginal and anal sex, which might require the use of water-based lubricants.
- To prevent the condom from slipping off, hold the condom firmly against the base of the penis during withdrawal, and withdraw while the penis is still erect.

Table B3. Recommended Screening Tests for Pregnant Women

- All pregnant women in the United States should be tested for HIV infection as early in pregnancy as possible.
- A serologic test for syphilis should be performed on all pregnant women at the first prenatal visit.
- All pregnant women should be routinely tested for hepatitis B surface antigen (HBsAg) during an early prenatal visit (e.g., first trimester) in each pregnancy, even if they have been previously vaccinated or tested.
- All laboratories that conduct HBsAg tests should use an HBsAg test that is FDA-cleared and should perform testing according to the manufacturer's labeling, including testing of initially reactive specimens with a licensed neutralizing confirmatory test.
- All pregnant women should be routinely tested for *Chlamydia trachomatis* at the first prenatal visit. Women aged <25 years and those at increased risk for chlamydia (i.e., women who have a new or more than one sex partner) should also be retested during the third trimester to prevent maternal postnatal complications and chlamydial infection in the infant.
- All pregnant women at risk for gonorrhea or living in an area in which the prevalence of *Neisseria gonorrhoeae* is high should be tested at the first prenatal visit for *N. gonorrhoeae*. A repeat test should be performed during the third trimester for those at continued risk.
- All pregnant women at high risk for hepatitis C infection should be tested for hepatitis C antibodies at the first prenatal visit.
- Evaluation for bacterial vaginosis (BV) might be conducted during the first prenatal visit for asymptomatic patients who are at high risk for preterm labor (history of previous preterm delivery).
- A Papanicolaou (Pap) smear should be obtained at the first prenatal visit if none has been documented during the preceding year.

Table B4. Recommended Screening for Sexually Active MSM

- HIV serology, if HIV negative or not tested within the previous year.
- Syphilis serology.
- A test for urethral infection with *N. gonorrhoeae* and *C. trachomatis* in men who have had insertive intercourse^a during the preceding year.
- A test for rectal infection^b with *N. gonorrhoeae* and *C. trachomatis* in men who have had receptive anal intercourse^a during the preceding year.
- A test for pharyngeal infection^b with *N. gonorrhoeae* in men who have acknowledged participation in receptive oral intercourse^a during the preceding year; testing for *C. trachomatis* pharyngeal infection is not recommended.

These tests should be performed at least annually for sexually active MSM, including men with or without established HIV infection. In addition, some specialists would consider type-specific serologic tests for HSV-2, if infection status is unknown. Routine testing for anal cytologic abnormalities or anal HPV infection is not recommended until more data are available on the reliability of screening methods, the safety of and response to treatment, and programmatic considerations.

^aRegardless of history of condom use during exposure.

^bProviders should use a culture or test that has been cleared by the FDA or locally verified in accordance with applicable statutes.

Table B5. Specific Recommendations for Diagnostic Testing for HIV Infection

- HIV screening is recommended for all persons who seek evaluation and treatment for STDs.
- HIV testing must be voluntary.
- Consent for HIV testing should be incorporated into the general consent for care (verbally or in writing) with an opportunity to decline (opt-out screening).
- HIV rapid testing must be considered, especially in clinics where a high proportion of patients do not return for HIV test results.
- Positive screening tests for HIV antibody must be confirmed by a supplemental test (e.g., Western Blot or immunofluorescence assay) before being considered diagnostic of HIV infection.
- Persons with positive HIV test results (screening and confirmatory) must receive initial HIV prevention counseling before leaving the testing site. Such persons should receive a medical evaluation and, if indicated, behavioral and psychological services be referred for these services.
- Providers should be alert to the possibility of acute retroviral syndrome and should perform nucleic acid testing for HIV, if this syndrome is suspected. Patients suspected of having recently acquired HIV infection should be referred for immediate consultation with a specialist.

Table B6. Initial Evaluation of HIV-Positive Persons

- A detailed medical history, including sexual and substance abuse history, vaccination history, previous STDs, and specific HIV-related symptoms or diagnoses.
- A physical examination, including a gynecologic examination for women.
- Testing for *N. gonorrhoeae* and *C. trachomatis* (and for women, a Pap test and wet mount examination of vaginal secretions).
- Complete blood and platelet counts and blood chemistry profile.
- Toxoplasma antibody test.
- Tests for antibodies to HCV; testing for previous or present HAV or HBV infection is recommended if determined to be cost-effective before considering vaccination.
- Syphilis serology.
- A CD4 T-lymphocyte analysis and determination of HIV plasma viral load.
- A tuberculin skin test (sometimes referred to as a purified protein derivative).
- A urinalysis.
- A chest radiograph.
- Some specialists recommend type-specific testing for HSV-2 if herpes infection status is unknown.
- A first dose of hepatitis A and/or hepatitis B vaccination for previously unvaccinated persons for whom vaccine is recommended (see hepatitis A and hepatitis B) should be administered at this first visit.

Table B7. Specific Recommendations for HIV Counseling and Referral

- Persons who test positive for HIV antibody should be counseled, either on site or through referral, concerning the behavioral, psychosocial, and medical implications of HIV infection.
- Health-care providers should be alert for medical or psychosocial conditions that require immediate attention.
- Providers should assess newly diagnosed persons' need for immediate medical care or support and should link them to services in which health-care personnel are experienced in providing care for HIV-infected persons. Such persons might need medical care or services for substance abuse, mental health disorders, emotional distress, reproductive counseling, risk-reduction counseling, and case management. Providers should follow-up to ensure that patients have received the needed services.
- Patients should be educated regarding what to expect in follow-up medical care.

Table B8. Treatment of ChancroidRecommended regimens^a

- Azithromycin 1 g orally in a single dose
or
- Ceftriaxone 250 mg intramuscularly (IM) in a single dose
or
- Ciprofloxacin 500 mg orally twice a day for 3 days
or
- Erythromycin base 500 mg orally three times a day for 7 days

Other Management Considerations:

Male patients who are uncircumcised and patients with HIV infection do not respond as well to treatment as those who are circumcised or HIV negative. Patients should be tested for HIV infection at the time chancroid is diagnosed. Patients should be retested for syphilis and HIV 3 months after the diagnosis of chancroid, if the initial test results were negative.

Follow-Up:

Patients should be reexamined 3–7 days after initiation of therapy. If treatment is successful, ulcers usually improve symptomatically within 3 days and objectively within 7 days after therapy. If no clinical improvement is evident, the clinician must consider whether (1) the diagnosis is correct, (2) the patient is coinfecting with another STD, (3) the patient is infected with HIV, (4) the treatment was not used as instructed, or (5) the *H. ducreyi* strain causing the infection is resistant to the prescribed antimicrobial. The time required for complete healing depends on the size of the ulcer; large ulcers might require >2 weeks. In addition, healing is slower for some uncircumcised men who have ulcers under the foreskin. Clinical resolution of fluctuant lymphadenopathy is slower than resolution for ulcers and might require needle aspiration or incision and drainage. Although needle aspiration of chancroid buboes is a simple procedure, incision and drainage might be preferred because of a reduced need for repeat drainage procedures.

^aCiprofloxacin is contraindicated for pregnant and lactating women. Azithromycin and ceftriaxone offer the advantage of single-dose therapy. Worldwide, several isolates with intermediate resistance to either ciprofloxacin or erythromycin have been reported.

Table B9. Treatment of Genital Herpes**First Clinical Episode of Genital Herpes:**

Many persons with first-episode herpes have mild clinical manifestations but later develop severe or prolonged symptoms. Therefore, patients with initial genital herpes should receive antiviral therapy.

Recommended regimens^a

- Acyclovir 400 mg orally three times a day for 7–10 days
or
- Acyclovir 200 mg orally five times a day for 7–10 days
or
- Famciclovir 250 mg orally three times a day for 7–10 days
or
- Valacyclovir 1 g orally twice a day for 7–10 days

Table B9. (Continued)**Suppressive Therapy for Recurrent Genital Herpes:**

Suppressive therapy reduces the frequency of genital herpes recurrences by 70–80% in patients who have frequent recurrences (i.e., >6 recurrences per year), and many patients report no symptomatic outbreaks. Treatment also is effective in patients with less frequent recurrences. Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years and with valacyclovir or famciclovir for 1 year. Periodically during suppressive treatment (e.g., once a year), providers should discuss whether or not to continue therapy with the patient.

Daily treatment with valacyclovir 500 mg daily decreases the rate of HSV-2 transmission in discordant, heterosexual couples in which the source partner has a history of genital HSV-2 infection.

Recommended regimens

- Acyclovir 400 mg orally twice a day
or
- Famciclovir 250 mg orally twice a day
or
- Valacyclovir 500 mg orally once a day^b
or
- Valacyclovir 1.0 g orally once a day

Episodic Therapy for Recurrent Genital Herpes:

Effective episodic treatment of recurrent herpes requires initiation of therapy within 1 day of lesion onset or during the prodrome that precedes some outbreaks. The patient should be provided with a supply of drug or a prescription for the medication with instructions to initiate treatment immediately when symptoms begin.

Recommended regimens

- Acyclovir 400 mg orally three times a day for 5 days
or
- Acyclovir 800 mg orally twice a day for 5 days
or
- Acyclovir 800 mg orally three times a day for 2 days
or
- Famciclovir 125 mg orally twice daily for 5 days
or
- Famciclovir 1000 mg orally twice daily for 1 day
or
- Valacyclovir 500 mg orally twice a day for 3 days
or
- Valacyclovir 1.0 g orally once a day for 5 days

^aTreatment might be extended if healing is incomplete after 10 days of therapy.

^bValacyclovir 500 mg once a day might be less effective than other valacyclovir or acyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥ 10 episodes per year).

Table B10. Treatment of HSV Infection in Persons Infected with HIV

Recommended regimens for daily suppressive therapy

- Acyclovir 400–800 mg orally twice to three times a day
or
- Famciclovir 500 mg orally twice a day
or
- Valacyclovir 500 mg orally twice a day

Recommended regimens for episodic infection

- Acyclovir 400 mg orally three times a day for 5–10 days
or
- Famciclovir 500 mg orally twice a day for 5–10 days
or
- Valacyclovir 1.0 g orally twice a day for 5–10 days

Acyclovir, valacyclovir, and famciclovir are safe for use in immunocompromised patients in the doses recommended for treatment of genital herpes. For severe HSV disease, initiating therapy with acyclovir 5–10 mg/kg body weight IV every 8 hours might be necessary.

If lesions persist or recur in a patient receiving antiviral treatment, HSV resistance should be suspected and a viral isolate should be obtained for sensitivity testing. Such patients should be managed in consultation with an HIV specialist, and alternate therapy should be administered.

Table B11. Treatment for Granuloma Inguinale

A limited number of studies on donovanosis treatment have been published. Treatment halts progression of lesions, although prolonged therapy is usually required to permit granulation and reepithelialization of the ulcers. Healing typically proceeds inward from the ulcer margins. Relapse can occur 6–18 months after apparently effective therapy.

Recommended regimen

- Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed

Alternative regimens

- Azithromycin 1 g orally once per week for at least 3 weeks and until all lesions have completely healed
or
- Ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed
or
- Erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed
or
- Trimethoprim-sulfamethoxazole one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed

Some specialists recommend the addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every 8 hours) to these regimens if improvement is not evident within the first few days of therapy.

Table B12. Treatment for Lymphogranuloma Venereum

Treatment cures infection and prevents ongoing tissue damage, although tissue reaction to the injection can result in scarring. Buboec might require aspiration through intact skin or incision and drainage to prevent the formation of inguinal/femoral ulcerations.

Recommended regimen

- Doxycycline 100 mg orally twice a day for 21 days

Alternative regimen

- Erythromycin base 500 mg orally four times a day for 21 days

Some STD specialists believe that azithromycin 1.0 g orally once weekly for 3 weeks is probably effective, although clinical data are lacking. Clinical followup of persons with LGV is necessary until signs and symptoms have resolved.

Table B13. Treatment of Primary and Secondary SyphilisRecommended regimen for adults^a

- Benzathine penicillin G 2.4 million units IM in a single dose

Recommended regimen for children

After the newborn period (aged >1 month), children with syphilis should have a CSF examination to detect asymptomatic neurosyphilis, and birth and maternal medical records should be reviewed to assess whether such children have congenital or acquired syphilis (see Table B18). Children with acquired primary or secondary syphilis should be evaluated (e.g., through consultation with child-protection services) and treated by using the following pediatric regimen.

- Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose

^aRecommendations for treating HIV-infected persons, pregnant women with syphilis, and sexual assault of children are discussed in the full report.

Table B14. Treatment for Latent Syphilis

The following regimens are recommended for penicillin nonallergic persons who have normal CSF examinations (if performed).

Recommended regimens for adults

Early latent syphilis—Benzathine penicillin G 2.4 million units IM in a single dose

Late latent syphilis or latent syphilis of unknown duration—Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-week intervals

(Continued)

Table B14. (Continued)**Management Considerations:**

All persons who have latent syphilis should be evaluated clinically for evidence of tertiary disease (e.g., aortitis and gumma) and syphilitic ocular disease (e.g., iritis and uveitis). Patients who have syphilis and who demonstrate any of the following criteria should have a prompt CSF examination:

- neurologic or ophthalmic signs or symptoms,
- evidence of active tertiary syphilis (e.g., aortitis and gumma),
- treatment failure, or
- HIV infection with late latent syphilis or syphilis of unknown duration.

If dictated by circumstances and patient preferences, a CSF examination may be performed for patients who do not meet these criteria. Some specialists recommend performing a CSF examination on all patients who have latent syphilis and a nontreponemal serologic test of >1:32 or if the patient is HIV infected with a serum CD4 count <350. However, the likelihood of neurosyphilis in this circumstance is unknown.

If a CSF examination is performed and the results indicate abnormalities consistent with neurosyphilis, the patient should be treated for neurosyphilis (see Table B16). If a patient misses a dose of penicillin in a course of weekly therapy for late syphilis, the appropriate course of action is unclear. Pharmacologic considerations suggest that an interval of 10–14 days between doses of benzathine penicillin for late syphilis or latent syphilis of unknown duration might be acceptable before restarting the sequence of injections. Missed doses are not acceptable for pregnant patients receiving therapy for late latent syphilis; pregnant women who miss any dose of therapy must repeat the full course of therapy.

Follow-Up. Quantitative nontreponemal serologic tests should be repeated at 6, 12, and 24 months. Patients with a normal CSF examination should be re-treated for latent syphilis if (1) titers increase fourfold, (2) an initially high titer (>1:32) fails to decline at least fourfold (i.e., two dilutions) within 12–24 months of therapy, or (3) signs or symptoms attributable to syphilis develop. In rare instances, despite a negative CSF examination and a repeated course of therapy, serologic titers might still not decline. In these circumstances, the need for additional therapy or repeated CSF examinations is unclear.

Recommended regimens for children

Early latent syphilis—Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units in a single dose

Late latent syphilis or latent syphilis of unknown duration—Benzathine penicillin G 50,000 units/kg IM, up to the adult dose of 2.4 million units, administered as three doses at 1-week intervals (total 150,000 units/kg up to the adult total dose of 7.2 million units)

After the newborn period, children with syphilis should have a CSF examination to exclude neurosyphilis. In addition, birth and maternal medical records should be reviewed to assess whether children have congenital or acquired syphilis (see Table B18). Older children with acquired latent syphilis should be evaluated as described for adults and treated using the following pediatric regimens. These regimens are for penicillin nonallergic children who have acquired syphilis and who have normal CSF examination results.

Table B15. Treatment of Tertiary Syphilis

Tertiary syphilis refers to gumma and cardiovascular syphilis but not to all neurosyphilis. Patients who are not allergic to penicillin and have no evidence of neurosyphilis should be treated with the following regimen.

Recommended regimen

- Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units IM each at 1-week intervals

Table B16. Treatment for Neurosyphilis

Persons who have neurosyphilis or syphilitic eye disease (e.g., uveitis, neuroretinitis, and optic neuritis) should be treated with the following regimen.

Recommended regimen

- Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units IV every 4 hours or continuous infusion, for 10–14 days

Alternative regimen

- Procaine penicillin 2.4 million units IM once daily plus
- Probenecid 500 mg orally four times a day, both for 10–14 days

Table B17. Management of Neurosyphilis, Other Management Considerations

Follow-Up:

If CSF pleocytosis was present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Follow-up CSF examinations also can be used to evaluate changes in the VDRL-CSF or CSF protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important. If the cell count has not decreased after 6 months or if the CSF is not normal after 2 years, retreatment should be considered. Recent data on HIV-infected persons with neurosyphilis suggest that CSF abnormalities might persist for extended periods in these persons and close clinical follow-up is warranted.

Penicillin Allergy:

Ceftriaxone can be used as an alternative treatment for patients with neurosyphilis, although the possibility of cross-reactivity between this agent and penicillin exists. Some specialists recommend ceftriaxone 2 g daily either IM or IV for 10–14 days. Other regimens have not been adequately evaluated for treatment of neurosyphilis. Therefore, if concern exists regarding the safety of ceftriaxone for a patient with neurosyphilis, the patient should obtain skin testing to confirm penicillin allergy and, if necessary, be desensitized and managed in consultation with a specialist.

Pregnancy:

Pregnant patients who are allergic to penicillin should be desensitized, if necessary, and treated with penicillin.

Table B18. Treatment of Congenital Syphilis

Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women and, therefore, on the routine serologic screening of pregnant women during the first prenatal visit. In communities and populations in which the risk for congenital syphilis is high, serologic testing and a sexual history also should be obtained at 28 weeks' gestation and at delivery.

Scenario 1. Infants with proven or highly probable disease and

1. an abnormal physical examination that is consistent with congenital syphilis,
2. a serum quantitative nontreponemal serologic titer that is fourfold higher than the mother's titer,^a or
3. a positive darkfield or fluorescent antibody test of body fluid(s).

(continued)

Table B18. (Continued)

Recommended evaluation

- CSF analysis for VDRL, cell count, and protein^b
- Complete blood count (CBC) and differential and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver-function tests, cranial ultrasound, ophthalmologic examination, and auditory brainstem response)

Recommended regimens

- Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
- or
- Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days

If >1 day of therapy is missed, the entire course should be restarted. Data are insufficient regarding the use of other antimicrobial agents (e.g., ampicillin). When possible, a full 10-day course of penicillin is preferred, even if ampicillin was initially provided for possible sepsis. The use of agents other than penicillin requires close serologic follow-up to assess adequacy of therapy. In all other situations, the maternal history of infection with *T. pallidum* and treatment for syphilis must be considered when evaluating and treating the infant.

Scenario 2. Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

1. mother was not treated, inadequately treated, or has no documentation of having received treatment;
2. mother was treated with erythromycin or other nonpenicillin regimen;^c or
3. mother received treatment <4 weeks before delivery.

Recommended evaluation

- CSF analysis for VDRL, cell count, and protein
- CBC and differential and platelet count
- Long-bone radiographs

A complete evaluation is not necessary if 10 days of parenteral therapy is administered. However, such evaluations might be useful; a lumbar puncture might document CSF abnormalities that would prompt close follow-up. Other tests (e.g., CBC, platelet count, and bone radiographs) may be performed to further support a diagnosis of congenital syphilis. If a single dose of benzathine penicillin G is used, then the infant must be fully evaluated (i.e., through CSF examination, long-bone radiographs, and CBC with platelets), the full evaluation must be normal, and follow-up must be certain. If any part of the infant's evaluation is abnormal or not performed or if the CSF analysis is rendered uninterpretable because of contamination with blood, then a 10-day course of penicillin is required.^d

Recommended regimens

- Aqueous crystalline penicillin G 100,000–150,000 units/kg/day, administered as 50,000 units/kg/dose IV every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
- or
- Procaine penicillin G 50,000 units/kg/dose IM in a single daily dose for 10 days
- or
- Benzathine penicillin G 50,000 units/kg/dose IM in a single dose

Some specialists prefer the 10 days of parenteral therapy if the mother has untreated early syphilis at delivery.

Scenario 3. Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

Table B18. (Continued)

1. mother was treated during pregnancy, treatment was appropriate for the stage of infection, and treatment was administered >4 weeks before delivery and

2. mother has no evidence of reinfection or relapse.

Recommended evaluation: No evaluation is required.

Recommended regimen

- Benzathine penicillin G 50,000 units/kg/dose IM in a single dose^e

Scenario 4. Infants who have a normal physical examination and a serum quantitative nontreponemal serologic titer the same or less than fourfold the maternal titer and the

1. mother's treatment was adequate before pregnancy and

2. mother's nontreponemal serologic titer remained low and stable before and during pregnancy and at delivery (VDRL <1:2; RPR <1:4).

Recommended evaluation: No evaluation is required.

Recommended regimen: No treatment is required; however, some specialists would treat with benzathine penicillin G 50,000 units/kg as a single IM injection, particularly if follow-up is uncertain.

^aThe absence of a fourfold or greater titer for an infant does not exclude congenital syphilis.

^bCSF test results obtained during the neonatal period can be difficult to interpret; normal values differ by gestational age and are higher in preterm infants. Values as high as 25 white blood cells (WBCs)/mm³ and/or protein of 150 mg/dL might occur among normal neonates; some specialists, however, recommend that lower values (i.e., 5 WBCs/mm³ and protein of 40 mg/dL) be considered the upper limits of normal. Other causes of elevated values should be considered when an infant is being evaluated for congenital syphilis.

^cA woman treated with a regimen other than those recommended in these guidelines for treatment should be considered untreated.

^dIf the infant's nontreponemal test is nonreactive and the likelihood of the infant being infected is low, certain specialists recommend no evaluation but treatment of the infant with a single IM dose of benzathine penicillin G 50,000 units/kg for possible incubating syphilis, after which the infant should receive close serologic follow-up.

^eSome specialists would not treat the infant but would provide close serologic follow-up in those whose mother's nontreponemal titers decreased fourfold after appropriate therapy for early syphilis or remained stable or low for late syphilis.

Table B19. Evaluation and Treatment of Older Infants and Children for Syphilis

Children who are identified as having reactive serologic tests for syphilis after the neonatal period (i.e., aged >1 month) should have maternal serology and records reviewed to assess whether the child has congenital or acquired syphilis.

Recommended evaluation

- CSF analysis for VDRL, cell count, and protein
- CBC, differential, and platelet count
- Other tests as clinically indicated (e.g., long-bone radiographs, chest radiograph, liver function tests, abdominal ultrasound, ophthalmologic examination, and auditory brain stem response)

Recommended regimen

- Aqueous crystalline penicillin G 200,000–300,000 units/kg/day IV, administered as 50,000 units/kg every 4–6 hours for 10 days

If the child has no clinical manifestations of disease, the CSF examination is normal, and the CSF VDRL test result is negative, some specialists would treat with up to three weekly doses of benzathine penicillin G, 50,000 U/kg IM.

Table B20. Management of Male Patients Who Have Urethritis**Confirmed Urethritis:**

Clinicians should document that urethritis is present. Urethritis can be documented on the basis of any of the following signs or laboratory tests:

- Mucopurulent or purulent discharge.
 - Gram stain of urethral secretions demonstrating >5 WBC per oil immersion field. The Gram stain is the preferred rapid diagnostic test for evaluating urethritis. It is highly sensitive and specific for documenting both urethritis and the presence or absence of gonococcal infection. Gonococcal infection is established by documenting the presence of WBC containing GNID.
- or
- Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment demonstrating >10 WBC per high power field.

If none of these criteria are present, treatment should be deferred, and the patient should be tested for *N. gonorrhoeae* and *C. trachomatis* and followed closely if test results are negative. If the results demonstrate infection with either *N. gonorrhoeae* or *C. trachomatis*, the appropriate treatment should be given and sex partners referred for evaluation and treatment.

Empiric treatment of symptoms without documentation of urethritis is recommended only for patients at high risk for infection who are unlikely to return for a follow-up evaluation. Such patients should be treated for gonorrhea and chlamydia. Partners of patients treated empirically should be evaluated and treated.

Table B21. Treatment of Nongonococcal Urethritis

Recommended regimens

- Azithromycin 1 g orally in a single dose
- or
- Doxycycline 100 mg orally twice a day for 7 days

Alternative regimens

- Erythromycin base 500 mg orally four times a day for 7 days
- or
- Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
- or
- Ofloxacin 300 mg orally twice a day for 7 days
- or
- Levofloxacin 500 mg orally once daily for 7 days

Recurrent and Persistent Urethritis:

Objective signs of urethritis should be present before initiation of antimicrobial therapy. In persons who have persistent symptoms after treatment without objective signs of urethritis, the value of extending the duration of antimicrobials has not been demonstrated. Persons who have persistent or recurrent urethritis can be retreated with the initial regimen if they did not comply with the treatment regimen or if they were reexposed to an untreated sex partner. Otherwise, a *T. vaginalis* culture should be performed using an intraurethral swab or a first-void urine specimen. Some cases of recurrent urethritis after doxycycline treatment might be caused by tetracycline-resistant *U. urealyticum*. Urologic examinations usually do not reveal a specific etiology. Approximately 50% of men with chronic nonbacterial prostatitis /chronic pelvic pain syndrome

Table B21. (Continued)

have evidence of urethral inflammation without any identifiable microbial pathogens. If the patient was compliant with the initial regimen and reexposure can be excluded, the following regimen is recommended.

Recommended regimens

- Metronidazole 2 g orally in a single dose
or
- Tinidazole 2 g orally in a single dose
plus
- Azithromycin 1 g orally in a single dose (if not used for initial episode)

Table B22. Management of Cervicitis

Two major diagnostic signs characterize cervicitis: (1) a purulent or mucopurulent endocervical exudate visible in the endocervical canal or on an endocervical swab specimen (commonly referred to as “mucopurulent cervicitis” or cervicitis) and (2) sustained endocervical bleeding easily induced by gentle passage of a cotton swab through the cervical os. Either or both signs might be present. Cervicitis frequently is asymptomatic, but some women complain of an abnormal vaginal discharge and intermenstrual vaginal bleeding (e.g., after sexual intercourse). A finding of leukorrhea (>10 WBC per high power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix. In the absence of inflammatory vaginitis, leukorrhea might be a sensitive indicator of cervical inflammation with a high negative predictive value.

Treatment:

Several factors should affect the decision to provide presumptive therapy for cervicitis or to await the results of diagnostic tests. Treatment with antibiotics for *C. trachomatis* should be provided in women at increased risk for this common STD (age <25 years, new or multiple sex partners, and unprotected sex), especially if follow-up cannot be ensured and if a relatively insensitive diagnostic test (not a NAAT) is used. Concurrent therapy for *N. gonorrhoeae* is indicated if the prevalence of this infection is high (>5%) in the patient population (young age and facility prevalence).

Concomitant trichomoniasis or symptomatic BV should also be treated if detected. For women in whom any component of (or all) presumptive therapy is deferred, the results of sensitive tests for *C. trachomatis* and *N. gonorrhoeae* (e.g., nucleic acid amplification tests) should determine the need for treatment subsequent to the initial evaluation.

Recommended regimens for presumptive treatment^a

- Azithromycin 1 g orally in a single dose
or
- Doxycycline 100 mg orally twice a day for 7 days

^aConsider concurrent treatment for gonococcal infection if prevalence of gonorrhea is high in the patient population under assessment.

Table B23. Treatment of Chlamydial Infections

Treating infected persons prevents transmission to sex partners. In addition, treating pregnant women usually prevents transmission of *C. trachomatis* to infants during birth. Treatment of sex partners helps to prevent reinfection of the index patient and infection of other partners.

Coinfection with *C. trachomatis* frequently occurs among persons who have gonococcal infection; therefore, presumptive treatment of such patients for chlamydia is appropriate. The following recommended treatment regimens and alternative regimens cure infection and usually relieve symptoms.

Recommended regimens

- Azithromycin 1 g orally in a single dose
- or
- Doxycycline 100 mg orally twice a day for 7 days

Alternative regimens

- Erythromycin base 500 mg orally four times a day for 7 days
- or
- Erythromycin ethylsuccinate 800 mg orally four times a day for 7 days
- or
- Ofloxacin 300 mg orally twice a day for 7 days
- or
- Levofloxacin 500 mg orally once daily for 7 days

A recent meta-analysis of 12 randomized clinical trials of azithromycin versus doxycycline for the treatment of genital chlamydial infection demonstrated that the treatments were equally efficacious, with microbial cure rates of 97% and 98%, respectively.

Table B24. Treatment of Chlamydial Infections Among Children

Sexual abuse must be considered a cause of chlamydial infection in preadolescent children, although perinatally transmitted *C. trachomatis* infection of the nasopharynx, urogenital tract, and rectum might persist for >1 year.

Recommended Regimens for Children Who Weigh <45 kg

- Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days

Recommended Regimen for Children Who Weigh \geq 45 kg but Who Are Aged <8 Years

- Azithromycin 1 g orally in a single dose

Recommended Regimens for Children Aged \geq 8 years

- Azithromycin 1 g orally in a single dose
- or
- Doxycycline 100 mg orally twice a day for 7 days

Table B25. Treatment of Uncomplicated Gonococcal Infections of the Cervix, Urethra, and RectumRecommended regimens^a

- Ceftriaxone 125 mg IM in a single dose
or
- Cefixime 400 mg orally in a single dose^b
plus

Treatment for chlamydia if chlamydial infection is not ruled out

Alternative regimens

- Spectinomycin 2 g in a single IM dose^c
or
- Single-dose cephalosporin regimens

Some evidence suggests that cefpodoxime 400 mg and cefuroxime axetil 1 g orally might be additional oral alternatives in the treatment of uncomplicated urogenital gonorrhea; additional information on alternative oral regimens are available at <http://www.cdc.gov/std/treatment>. Cefpodoxime proxetil 200 mg PO is less active against *N. gonorrhoeae* than is cefixime and also does not quite meet the minimum efficacy criteria (demonstrated efficacy with lower 95% confidence interval [CI] of >95% in summed clinical trials) with cure rates, 96.5% (CI = 94.8–98.9%) for urogenital and rectal infection; efficacy in treating pharyngeal infection is unsatisfactory, 78.9% (CI = 54.5–94%). Clinical studies are being conducted to assess whether cefpodoxime 400 mg PO is an acceptable oral alternative. Treatment with cefuroxime axetil 1 g PO does not quite meet the minimum efficacy criteria for urogenital and rectal infection (95.9%; CI = 94.5–97.3%) and its efficacy in treating pharyngeal infection is unacceptable (56.9%; CI = 42.2–70.7%).

^aThis regimen is recommended for all adults and adolescents, regardless of travel history or sexual behavior.

^bThe tablet formulation is currently not available in the United States.

^cSpectinomycin is currently not available in the United States

Table B26. Treatment of Uncomplicated Gonococcal Infections of the Pharynx

Gonococcal infections of the pharynx are more difficult to eradicate than infections at urogenital and anorectal sites. Few antimicrobial regimens can reliably cure >90% of gonococcal pharyngeal infections. Although chlamydial coinfection of the pharynx is unusual, coinfection at genital sites sometimes occurs. Therefore, treatment for both gonorrhea and chlamydia is recommended.

Recommended regimens^a

- Ceftriaxone 125 mg IM in a single dose
plus

Treatment for chlamydia if chlamydial infection is not ruled out

^aThis regimen is recommended for all adults and adolescents, regardless of travel history or sexual behavior.

Table B27. Gonococcal Conjunctivitis

Recommended regimen

- Ceftriaxone 1 g IM in a single dose

Recommended regimen for disseminated gonococcal infection (DGI)

- Ceftriaxone 1 g IM or IV every 24 hours

Alternative regimens

- Cefotaxime 1 g IV every 8 hours
or
- Ceftizoxime 1 g IV every 8 hours
or
- Spectinomycin 2 g IM every 12 hours
or
- Cefixime 400 mg orally twice daily

Recommended regimen for gonococcal meningitis and endocarditis

- Ceftriaxone 1–2 g IV every 12 hours

Therapy for meningitis should be continued for 10–14 days; therapy for endocarditis should be continued for at least 4 weeks. Treatment of complicated DGI should be undertaken in consultation with a specialist.

Table B28. Recommended Regimen for Ophthalmia Neonatorum Caused by *N. gonorrhoeae*

Recommended regimen

- Ceftriaxone 25–50 mg/kg IV or IM in a single dose, not to exceed 125 mg

Topical antibiotic therapy alone is inadequate and is unnecessary if systemic treatment is administered.

Table B29. Gonococcal Infections Among Children

Recommended regimens for children who weigh >45 kg: Treat with one of the regimens recommended for adults

Recommended regimens for children who weigh ≤ 45 kg and who have uncomplicated gonococcal vulvovaginitis, cervicitis, urethritis, pharyngitis, or proctitis

- Ceftriaxone 125 mg IM in a single dose

Alternative Regimen

Spectinomycin: 40 mg/kg (maximum dose: 2 g) IM in a single dose may be used, but this therapy is unreliable for treatment of pharyngeal infections. Some specialists use cefixime to treat gonococcal infections in children because it can be administered orally; however, no reports have been published concerning the safety or effectiveness of cefixime used for this purpose.

Table B29. (Continued)

Recommended regimen for children who weigh \leq 45 kg and who have bacteremia or arthritis

- Ceftriaxone 50 mg/kg (maximum dose: 1 g) IM or IV in a single dose daily for 7 days

Recommended regimen for children who weigh $>$ 45 kg and who have bacteremia or arthritis

- Ceftriaxone 50 mg/kg IM or IV in a single dose daily for 7 days

Table B30. Treatment of Bacterial Vaginosis

Recommended regimens

- Metronidazole 500 mg orally twice a day for 7 days
or
- Metronidazole gel, 0.75%, one full applicator (5 g) intravaginally, once a day for 5 days
or
- Clindamycin cream, 2%, one full applicator (5 g) intravaginally at bedtime for 7 days

Persons should be advised to avoid consuming alcohol during treatment with metronidazole and for 24 hours thereafter. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use. Refer to clindamycin product labeling for additional information. Topical clindamycin preparations should not be used in the second half of pregnancy.

Alternative regimens

- Clindamycin 300 mg orally twice a day for 7 days
or

Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days

Table B31. Treatment of Trichomoniasis

Recommended regimens

- Metronidazole 2 g orally in a single dose
or
- Tinidazole 2 g orally in a single dose

Alternative regimen

- Metronidazole 500 mg orally twice a day for 7 days

Persons should be advised to avoid consuming alcohol during treatment with metronidazole or tinidazole. Abstinence from alcohol use should continue for 24 hours after completion of metronidazole or 72 hours after completion of tinidazole.

The nitroimidazoles comprise the only class of drugs useful for the oral or parenteral therapy of trichomoniasis.

Table B32. Vulvovaginal Candidiasis

VVC usually is caused by *C. albicans* but occasionally is caused by other *Candida* sp. or yeasts. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC can be classified as either uncomplicated or complicated. Approximately 10–20% of women will have complicated VVC, suggesting diagnostic and therapeutic considerations.

Classification of vulvovaginal candidiasis (VVC)

Uncomplicated VVC

- Sporadic or infrequent VVC
and
- Mild-to-moderate VVC
and
- Likely to be *Candida albicans*
and
- Nonimmunocompromised women

Complicated VVC

- Recurrent VVC
or
- Severe VVC
or
- Nonalbicans candidiasis
or
- Women with uncontrolled diabetes, debilitation, or immunosuppression, or those who are pregnant

Table B33. Treatment of Uncomplicated VVC^a

Short-course topical formulations (i.e., single dose and regimens of 1–3 days) effectively treat uncomplicated VVC. The topically applied azole drugs are more effective than nystatin. Treatment with azoles results in relief of symptoms and negative cultures in 80–90% of patients who complete therapy.

Recommended regimens

Intravaginal agents:

- Butoconazole 2% cream 5 g intravaginally for 3 days^b
or
- Butoconazole 2% cream 5 g (Butoconazole1-sustained release), single intravaginal application
or
- Clotrimazole 1% cream 5 g intravaginally for 7–14 days^b
or
- Clotrimazole 100 mg vaginal tablet for 7 days
or
- Clotrimazole 100 mg vaginal tablet, two tablets for 3 days
or
- Miconazole 2% cream 5 g intravaginally for 7 days^b
or
- Miconazole 100 mg vaginal suppository, one suppository for 7 days^b
or

Table B33. (Continued)

- Miconazole 200 mg vaginal suppository, one suppository for 3 days^b
or
- Miconazole 1,200 mg vaginal suppository, one suppository for 1 day^b
or
- Nystatin 100,000-unit vaginal tablet, one tablet for 14 days
or
- Tioconazole 6.5% ointment 5 g intravaginally in a single application^b
or
- Terconazole 0.4% cream 5 g intravaginally for 7 days
or
- Terconazole 0.8% cream 5 g intravaginally for 3 days
or
- Terconazole 80 mg vaginal suppository, one suppository for 3 days

Oral Agent:

- Fluconazole 150 mg oral tablet, one tablet in single dose

^aFor treatment of complicated VVC, see full guidelines report.

^bOver-the-counter preparations.

Table B34. Treatment of Pelvic Inflammatory Disease

All treatment regimens should be effective against *N. gonorrhoeae* and *C. trachomatis* because negative endocervical screening for these organisms does not rule out upper reproductive tract infection. The need to eradicate anaerobes from women who have PID has not been determined definitively. Anaerobic bacteria have been isolated from the upper reproductive tract of women who have PID, and data from in vitro studies have revealed that some anaerobes (e.g., *Bacteroides fragilis*) can cause tubal and epithelial destruction. In addition, BV also is present in many women who have PID. Until treatment regimens that do not adequately cover these microbes have been demonstrated to prevent long-term sequelae (e.g., infertility and ectopic pregnancy) as successfully as the regimens that are effective against these microbes, the use of regimens with anaerobic activity should be considered.

Recommended parenteral regimen A

- Cefotetan 2 g IV every 12 hours
or
- Cefoxitin 2 g IV every 6 hours
plus
- Doxycycline 100 mg orally or IV every 12 hours

Because of the pain associated with infusion, doxycycline should be administered orally when possible, even when the patient is hospitalized. Oral and IV administration of doxycycline provide similar bioavailability.

Parenteral therapy may be discontinued 24 hours after a patient improves clinically, and oral therapy with doxycycline (100 mg twice a day) should continue to complete 14 days of therapy. When tubo-ovarian abscess is present, many healthcare providers use clindamycin or metronidazole with doxycycline for continued therapy, rather than doxycycline alone, because it provides more effective anaerobic coverage. Clinical data are limited regarding the use of other second or third-generation cephalosporins (e.g., ceftizoxime, cefotaxime, and ceftriaxone).

(continued)

Table B34. (Continued)

Recommended parenteral regimen B

- Clindamycin 900 mg IV every 8 hours
plus
- Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every 8 hours. Single daily dosing may be substituted.

Alternative parenteral regimens

- Ampicillin/Sulbactam 3 g IV every 6 hours
plus
- Doxycycline 100 mg orally or IV every 12 hours

Oral therapy can be considered for women with mild-to-moderately severe acute PID, as the clinical outcomes among women treated with oral therapy are similar to those treated with parenteral therapy. Women who do not respond to oral therapy within 72 hours should be reevaluated to confirm the diagnosis and should be administered parenteral therapy on either an outpatient or in-patient basis.

Recommended Oral Regimen

Ceftriaxone 250 mg IM in a single dose

Plus

Doxycycline 100 mg orally twice a day for 14 days

With or without

Metronidazole 500 mg orally twice a day for 14 days

OR

Cefoxitin 2 g IM in a single dose and Probenecid,
1 g orally administered concurrently in a single dose

Plus

Doxycycline 100 mg orally twice a day for 14 days

With or without

Metronidazole 500 mg orally twice a day for 14 days

OR

Other parenteral third-generation cephalosporin
(e.g., ceftizoxime or cefotaxime)

Plus

Doxycycline 100 mg orally twice a day for 14 days

With or without

Metronidazole 500 mg orally twice a day for 14 days

Alternative Oral Regimens

If parenteral cephalosporin therapy is not feasible, use of fluoroquinolones (levofloxacin 500 mg orally once daily or ofloxacin 400 mg twice daily for 14 days) with or without metronidazole (500 mg orally twice daily for 14 days) may be considered if the community prevalence and individual risk (see "Gonococcal Infections in Adolescents and Adults" in *Sexually Transmitted Disease Treatment Guidelines*, 2006) of gonorrhea is low. Tests for gonorrhea must be performed prior to instituting therapy and the patient managed as follows if the test is positive:

- If NAAT test is positive, parenteral cephalosporin is recommended.
- If culture for gonorrhea is positive treatment should be based on results of antimicrobial susceptibility. If isolate is QRNG, or antimicrobial susceptibility can't be assessed, parenteral cephalosporin is recommended.

Although information regarding other outpatient regimens is limited, amoxicillin/clavulanic acid and doxycycline or azithromycin with metronidazole has demonstrated short-term clinical cure. No data have been published regarding the use of oral cephalosporins for the treatment of PID.

Table B35. Recommended Regimens for Treatment of Epididymitis

As empiric therapy is often initiated before laboratory tests are available, it is recommended that all persons receive ceftriaxone plus doxycycline for the initial therapy of epididymitis. Additional therapy may include a quinolone if acute epididymitis is not caused by gonorrhea based on a culture or nucleic acid amplification testing or if the infection is most likely caused by enteric organisms. The goals of treatment of acute epididymitis caused by *C. trachomatis* or *N. gonorrhoeae* are (1) microbiologic cure of infection, (2) improvement of signs and symptoms, (3) prevention of transmission to others, and (4) a decrease in potential complications (e.g., infertility or chronic pain). As an adjunct to therapy, bed rest, scrotal elevation, and analgesics are recommended until fever and local inflammation have subsided.

Recommended regimens

- Ceftriaxone 250 mg IM in a single dose
plus
- Doxycycline 100 mg orally twice a day for 10 days

For acute epididymitis most likely caused by enteric organisms or with negative gonococcal culture or nucleic acid amplification test

- Ofloxacin 300 mg orally twice a day for 10 days
or
- Levofloxacin 500 mg orally once daily for 10 days

Table B36. Recommended Regimens for External Genital Warts*Patient applied:*

- Podofilox 0.5% solution or gel. Patients should apply podofilox solution with a cotton swab, or podofilox gel with a finger, to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated, as necessary, for up to four cycles. The total wart area treated should not exceed 10 cm², and the total volume of podofilox should be limited to 0.5 mL per day. If possible, the health-care provider should apply the initial treatment to demonstrate the proper application technique and identify which warts should be treated. The safety of podofilox during pregnancy has not been established.
or
- Imiquimod 5% cream. Patients should apply imiquimod cream once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6–10 hours after the application. The safety of imiquimod during pregnancy has not been established.

Provider administered:

- Cryotherapy with liquid nitrogen or cryoprobe. Repeat applications every 1–2 weeks.
or
- Podophyllin resin 10–25% in a compound tincture of benzoin. A small amount should be applied to each wart and allowed to air dry. The treatment can be repeated weekly, if necessary. To avoid the possibility of complications associated with systemic absorption and toxicity, two important guidelines should be followed: (1) application should be limited to <0.5 mL of podophyllin or an area of <10 cm² of warts per session and (2) no open lesions or wounds should exist in the area to which treatment is administered. Some specialists suggest that the preparation should be thoroughly washed off 1–4 hours after application to reduce local irritation. The safety of podophyllin during pregnancy has not been established.
or

(continued)

Table B36. (Continued)

- Trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80–90%. A small amount should be applied only to the warts and allowed to dry, at which time a white “frosting” develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate (i.e., baking soda), or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.
- or
- Surgical removal either by tangential scissor excision, tangential shave excision, curettage, or electrosurgery

Alternative regimens

- Intralesional interferon
- or
- Laser surgery

Table B37. Recommended Regimens for Cervical Warts

Recommended regimens for cervical warts

- For women who have exophytic cervical warts, high-grade SIL must be excluded before treatment is initiated. Management of exophytic cervical warts should include consultation with a specialist.

Recommended regimens for vaginal warts

- Cryotherapy with liquid nitrogen. The use of a cryoprobe in the vagina is not recommended because of the risk for vaginal perforation and fistula formation.
- or
- TCA or BCA 80–90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white “frosting” develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.

Recommended regimens for urethral meatus warts

- Cryotherapy with liquid nitrogen
- or
- Podophyllin 10–25% in compound tincture of benzoin. The treatment area must be dry before contact with normal mucosa. This treatment can be repeated weekly, if necessary. The safety of podophyllin during pregnancy has not been established. Although data evaluating the use of podoflox and imiquimod for the treatment of distal meatal warts are limited, some specialists recommend their use in some patients.

Recommended regimens for anal warts

- Cryotherapy with liquid nitrogen
- or
- TCA or BCA 80–90% applied to warts. A small amount should be applied only to warts and allowed to dry, at which time a white “frosting” develops. If an excess amount of acid is applied, the treated area should be powdered with talc, sodium bicarbonate, or liquid soap preparations to remove unreacted acid. This treatment can be repeated weekly, if necessary.
- or
- Surgical removal

Warts on the rectal mucosa should be managed in consultation with a specialist. Many persons with warts on the anal mucosa also have warts on the rectal mucosa and so persons with anal warts can benefit from an inspection of the rectal mucosa by digital examination or anoscopy.

Table B38. Treatment of Acute Proctitis

Acute proctitis of recent onset among persons who have recently practiced receptive anal intercourse is usually sexually acquired. Such patients should be examined by anoscopy and should be evaluated for infection with HSV, *N. gonorrhoeae*, *C. trachomatis*, and *T. pallidum*. If an anorectal exudate is detected on examination or if polymorphonuclear leukocytes are detected on a Gram-stained smear of anorectal secretions, the following therapy may be prescribed while awaiting additional laboratory tests.

Recommended Regimen

Ceftriaxone 125 mg IM (or another agent effective against rectal and genital gonorrhea)

PLUS

Doxycycline 100 mg orally twice a day for 7 days

Persons with suspected or documented herpes proctitis should be managed in the same manner as those with genital herpes. If painful perianal ulcers are present or mucosal ulcers are detected on anoscopy, presumptive therapy should include a regimen for treating genital herpes. In addition, LGV proctitis should also be considered. Appropriate diagnostic testing for LGV should be conducted in accordance with state or federal guidelines, and doxycycline therapy should be administered 100 mg orally twice daily for 3 weeks.

Table B39. Treatment of Pediculosis Pubis

Recommended regimens

- Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes
- or
- Pyrethrins with piperonyl butoxide applied to the affected area and washed off after 10 minutes

Alternative Regimens

- Malathion 0.5% lotion applied for 8–12 hours and washed off
- or
- Ivermectin 250 ug/kg repeated in 2 weeks

Reported resistance to pediculicides has been increasing and is widespread. Malathion may be used when treatment failure is believed to have occurred because of resistance. The odor and long duration of application for malathion make it a less attractive alternative than the recommended pediculicides. Ivermectin has been successfully used to treat lice but has only been evaluated in small studies.

Lindane is not recommended as first-line therapy because of toxicity. It should only be used as an alternative because of inability to tolerate other therapies or if other therapies have failed. Lindane toxicity, as indicated by seizure and aplastic anemia, has not been reported when treatment was limited to the recommended 4-minute period. Permethrin has less potential for toxicity than lindane.

Table B40. Recommended Regimens for Treatment of Scabies

- Permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8–14 hours
or
- Ivermectin 200 µg/kg orally, repeated in 2 weeks

Alternative Regimens

- Lindane (1%) 1 oz of lotion or 30 g of cream applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours

Lindane is not recommended as first-line therapy because of toxicity. It should only be used as an alternative if the patient cannot tolerate other therapies or if other therapies have failed.

Lindane should not be used immediately after a bath or shower, and it should not be used by persons who have extensive dermatitis, women who are pregnant or lactating, or children aged <2 years. Lindane resistance has been reported in some areas of the world, including parts of the United States. Seizures have occurred when lindane was applied after a bath or used by patients who had extensive dermatitis. Aplastic anemia after lindane use also has been reported.

Permethrin is effective and safe and less expensive than ivermectin. One study demonstrated increased mortality among elderly, debilitated persons who received ivermectin, but this observation has not been confirmed in subsequent reports.

Other management considerations:

Bedding and clothing should be decontaminated (i.e., either machine-washed, machine-dried using the hot cycle, or dry cleaned) or removed from body contact for at least 72 hours. Fumigation of living areas is unnecessary.

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