AIDS PREVENTION AND MENTAL HEALTH

PSYCHOSOCIAL AND PUBLIC HEALTH IMPACTS OF NEW HIV THERAPIES

EDITED BY
DAVID G. OSTROW
AND
SETH C. KALICHMAN

Psychosocial and Public Health Impacts of New HIV Therapies

AIDS Prevention and Mental Health

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Foreword

"AIDS is kind of like life, just speeded up."

Javon P., heroin addict with AIDS, Bronx, New York, 1988

"Now I'm not so much scared of dying as scared of living."

Mike D., heroin addict with AIDS, New Haven, Connecticut, 1998

Within little more than a decade, AIDS has been tranformed from an untreatable, rapidly fatal illness, into a manageable, chronic disease. Most of this tranformation has occurred in the past five years, accelerated by the advent of protease inhibitors and the proven benefits of combination antiretroviral therapy and prophylaxis against opportunistic infections. For people living with HIV/AIDS, these developments have offered unprecedented hope, and also new challenges. As reflected in the quotes above, some of the anxieties and anticipation of premature dying have been replaced by the uncertainties involved in living with a long-term, unpredictable illness.

The role of caregivers for people with HIV/AIDS has also changed radically over this time. Earlier in the epidemic, we learned to accompany patients through illness, to bear witness, to advocate, to address issues of death, dying, and bereavement. The arrival of more effective therapy has brought with it new capabilities, but also new complexities, raising difficult problems concerning access to care, adherence, and toxicity. Greater possibilities for success may also mean greater possibilities for failure: "provider guilt" and victim blaming may become more prominent as the vaunted promise of highly active antiretroviral therapy (HAART) fails to be realized in some patients, while others thrive and have to contend with rethinking their future lives. Perceptions of therapeutic efficacy may also translate into decreased concerns about risk-taking behavior.

The ascendance of a virologic model of pathogenesis runs the risk of narrowing the focus of HIV care; the advancement of science brings with it the danger of reductionism. Our ability to elucidate the structure of the virus should not lead us to ignore the important psychosocial issues that will continue to evolve with the epidemic; indeed, the virus and its therapy have little meaning outside of the human and social context in which these are expressed. This reality is particularly important as the epidemic continues to advance in populations that are increasingly disenfranchised, poor, and vulnerable. The availability of effective treatment immediately raises challenges regarding access, affordability, and the emergence

of a "two-tiered" system of care, in which existing social inequalities of race and class become further evidenced in the differential distribution of sought after HIV therapies. Before the advent of HAART, there was a grim form of leveling that occurred in the epidemic, a democratization of death in which all were affected equally. The possibility of improved survival as a result of engagement and adherence with complex HIV therapies has now resulted in a differentiation of outcomes, with the risk that the hierarchy of survival will parallel the hierarchy of the larger society. (This is already glaringly apparent on a global scale, in which it has been repeatedly observed that 90% of the world's HIV-infected population resides in developing countries where virtually no one has access to any HIV-specific therapies.)

Fortunately, this volume, *Psychosocial and Public Health Impacts of New HIV Therapies,* edited by David Ostrow and Seth Kalichman goes a long way toward addressing many of the emerging social, psychological, and behavioral issues that have accompanied the new therapeutic era. This collection of chapters, from a diverse group of experts drawn from different disciplines, helps to define the important theoretical, clinical, public health, and research themes that have arisen in the era of highly active antiretroviral therapy. It will be an important reference for clinicians, policy makers, and public health officials attempting to respond to the new chanllenges that accompany the new possibilities for changing the course of HIV disease in infected individuals.

The book begins with a comprehensive overview of the pathogenesis of HIV infection and the array of current therapies, then a review of some of the complex issues involved in the potential pharmacokinetic interactions between protease inhibitors and psychoactive drugs, including drugs of abuse. It then addresses theoretical and practical questions pertaining to the critical area of adherence with HIV medications, rightfully characterized as the "Achilles Heel" of the new therapeutics. Economic considerations and ethical issues are then explored, with implications for health services as well as clinical practice, and the important relationships between HIV, mental illness, adherence, and risk behavior are discussed. This discussion shows convincingly why it is impossible to consider HIV treatment without taking full account of the mental and physical comorbidities that often accompany it, and the societal arena in which the dynamic interplay among host, agent, and environment is enacted.

The concluding chapters address the novel challenges in HIV prevention raised by HAART's success, including the unanticipated consequence that effective HIV therapy and the prospects for postexposure prophylaxis may contribute, paradoxically, to increased risk-taking in sexual and drug use behaviors. This possibility may only increase over time, as prolonged survival increases both the likelihood of lapses in self-protection and the potential timespan over which viral transmission may occur. Combining this with the recently demonstrated occurrence of the sexual transmission of multidrug-resistant HIV the ominous prospect is raised of a self-sustaining epidemic of HIV infections, which will be less likely

to be treatable by any existing "successful" therapies. These issues are clearly of paramount and immediate importance.

The volume ends with a thorough analysis of the important issues for behavioral research and intervention in the HAART era. The long list of issues is both intriguing and daunting—making it clear that there will be ample material for an ongoing research and prevention agenda in the years ahead. In the early years of the epidemic, when we hoped and waited desperately for any treatment at all to fight back at the virus, we talked optimitistically about looking forward to the time when we would be able to treat HIV/AIDS as a chronic disease. That time has clearly arrived, and, in parallel with our newfound treatment capabilities, we confront new and unexpected challenges. Perhaps that is the best that we can continue to hope for: it is still premature to look forward to a time when AIDS is only a memory, *at least not in the forseeable future.* But we may hope to continue to face new problems that arise from our new and—if we are fortunate—ongoing successes.

Peter A. Selwyn, M. D., M. P. H.

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Preface

Very few events have significantly altered the course of the HIV/AIDS pandemic. Discovery of the virus that causes AIDS, the realization that most persons infected with HIV would ultimately develop AIDS and die, the development of HIV antibody testing, approval of the first antiretroviral medications, and the use of antiretroviral treatments to prevent perinatal transmission of HIV are perhaps the most significant achievements that easily come to mind. Of similar, or perhaps even greater magnitude has been the advent of multidrug combination antiretroviral therapies—most notably combinations of nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and protease inhibitors—and the development of laboratory tests to measure the level of viral replication or viral load.

Within weeks of their proclaimed success in reducing viral burden to below measurable levels and improving the health status of people with HIV/AIDS, combination therapies revolutionized the treatment of HIV. It soon became clear that drug-resistant mutations could be suppressed through multidrug treatments and that successful therapy lengthened the time people would live with HIV and improved their quality of life. For the first time in over a decade, the words "cure" and "eradication" entered the vocabulary of credible experts. For the first time in a long time, there was good news about AIDS. By the time this book went into production, just within 2 years of the widespread availability of protease inhibiting drugs, people with HIV/AIDS were dying at a slower rate than seen before and people with HIV were more concerned about returning to work than selling their life insurance policies. It truly became a whole new ball game in HIV/AIDS care and prevention.

The hope and optimism of new HIV treatments, however, did not come without caution and challenge. There were many questions raised in response to new treatments: How do these new drugs work and how do they interact with other treatments? How must clinical services and practice guidelines accommodate the demands of new treatments? What are the psychological ramifications of new treatments that offer such great promise? How do people adjust to an unexpected life extension and how do they adapt to promising treatments that fail? How will new treatments affect existing and future prevention efforts? Are the treatments themselves of preventive value? What are the ethical implications of new treatments that will not be universally accessible? How must care services change in response to new treatments and what policies must be implemented to guide these

adaptations? These and other questions have fueled the development of this book. To these questions, this book offers answers based on the most current scientific information available. And through its answers, the authors attempt to stimulate the next generation of questions for future research agendas.

As medical texts were rewritten to embrace the treatment revolution in HIV/AIDS, the editors and authors saw the need for a single source of information on the social-behavioral aspects of treatment advances. Each chapter of this book provides the most current information from basic and applied sciences. Because the development and refinement of new HIV treatments is not an event, but rather an ongoing dynamic process, the authors have emphasized general principles derived from their areas of expertise. Attending too closely to the details of a specific drug or the challenges of a particular treatment regimen would surely date any book on HIV treatments before its ink was dry. Thus, by highlighting context as well as content,and focusing on general principles in addition to specific details, the authors were able to achieve a book that will be of value even as the newest treatment advances become available. Chapters by the field's leading researchers provide essential information concerning the pharmacology, clinical use including adherence to treatment guidelines, prevention implications, mental health ramifications, and ethical and policy issues of combination therapies for HIV/AIDS. It is our hope that this and future generations of students, clinicians, researchers, and policy makers will find value in this book. We hope that we have achieved our original purposes of putting together a comprehensive book on this rapidly evolving field that will be as up to date as possible and will serve researchers, clinicians, public policy makers, and even consumers of the new therapies. We invite your comments, reactions, and requests for further information.

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Combination Antiretroviral Chemotherapy

Shifting Paradigms and Evolving Praxis

KENNETH H. MAYER

INTRODUCTION

Definitive milestones in the HIV epidemic were initially few and far between since the first description in 198 1 ofwhat came to be known as AIDS. Today, more than 17 years later, a wide consensus of opinion suggests that significant progress has been made, resulting in increases in survival as well as in the quality of life of HIV-infected people. The first milestones were the initial determination of HIV as the etiologic agent of AIDS in 1984 (Barre-Sinoussi *et al.,* 1983; Gallo *et al.,* 1983), and the first effective antiretroviral treatment, zidovudine (ZDV, AZT), was available by 1987 (Fischl *et al.,* 1987). However, it soon became apparent that the benefits of zidovudine were severely limited in duration because of the ability of HIV to develop resistance to individual antiretroviral agents.

The introduction of other nucleoside analogs, such as ddI, ddC, D4T, 3TC, allowed clinicians more choices, enhancing the management of patients who became clinically resistant or intolerant to AZT. However, many individuals continued to have progressively worsening HIV infection even after these drugs were widely available. Clinical experience suggested that the use of combinations of antiretroviral drugs and earlier intervention in the course of the disease tended to result in better clinical outcomes (Hammer *et al.,* 1996), but the natural history of HIV and the therapeutic options continued to be significantly circumscribed until the mid-1990s.

Two types of advances led to the enhanced rate of survival and improved quality of life that recently has been reported. The use of newer, more precise diagnostic methods, such as reverse transcriptase polymerase chain reactions (RT-PCR), branch DNA technology (bDNA), and nucleic acid sequence based analyses

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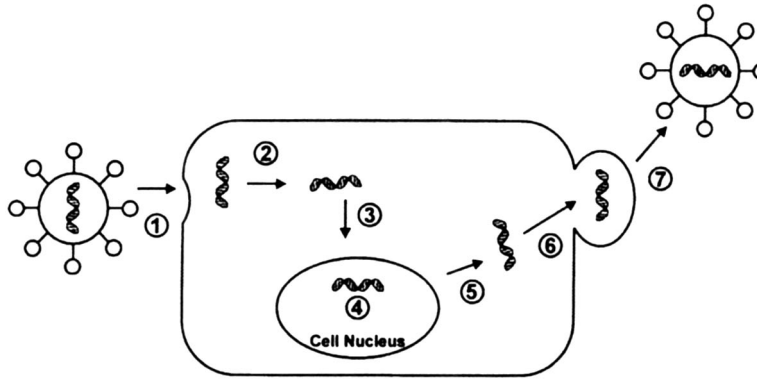
(NASBA), has resulted in an increased appreciation of the high HIV burden present in infected individuals from the onset of the illness (Ho *et al.,* 1995), just after acquiring the virus (see later discussion). These tests greatly improved the understanding of the natural history of HIV infection by providing an important surrogate marker that directly correlated with the onset of HIV-associated immunodeficiency (Mellors *et al.,* 1995). Decreases in the magnitude of the HIV load after the initiation of antiretroviral therapy directly correlated with a salutary clinical response.

The other major milestone in the clinical management of people living with HIV infection was the demonstration that addition of protease inhibitors to nucleoside analog antiretroviral therapy resulted in significant decreases in circulating plasma viremia, and was correspondingly associated with marked improvements in the survival and clinical status of people living with HIV infection (Deeks, Smith, Holodniy, & Kahn, 1997). In this chapter, the evolution of the understanding of the natural history of HIV because of the newer diagnostic imaging techniques is reviewed and the utilization of these techniques for the prognosis and clinical management of HIV-infected people is examined. Specific antiretroviral drugs are reviewed with regard to their efficacy, side effects, and their optimal utilization in combination chemotherapy. The use of antiretroviral drugs for postexposure prophylaxis by HIV (–) persons who come in contact with HIV via occupational, sexual, or drug-sharing risks is also reviewed. Finally, the challenges for clinicians in managing HIV as a chronic immunosuppressive viral infection are reviewed, because the improvement in therapy has created new challenges.

HIV IMMUNOPATHOGENESIS AND CLINICAL COURSE

The main targets for HIV infection are CD4+ lymphocytes, monocytes, tissue macrophages, and dendritic cells (Dalgleish *et al.,* 1984). In order to replicate, HIV first binds via a viral envelope glycoprotein, gp120, to cells expressing the CD4 surface protein and to one of several coreceptors, either CXCR-4 (fusin) or CCR-5 (Figure 1). Following fusion, the virus enters the cell, the viral particle is degraded, and the viral RNA is transcribed by the viral enzyme, reverse transcriptase, into the double-stranded complementary DNA provirus. This genetic material is transported into the cell nucleus as part of the preintegration complex, where the DNA is processed by viral enzymes, then integrated and incorporated into the host genome.

In an activated cell, such as one exposed to cytokines because of an intercurrent infection or other immunologic stimulus (e.g., vaccination), the viral genome is transcribed into multiple messages, which direct the production of multiple copies of viral components, that are subsequently assembled in the cytoplasm of the host cell (Haynes, 1996). Viral messages are then translated into polyproteins, that is, precursor proteins that need further processing in the cells' cytoplasm to produce the components for reassembly into new, mature virions. The HIV pro-



LIFE STYLE TARGETS	INHIBITORY DRUGS
1. VIRAL ENTRY	SOLUBLE CD4
2. REVERSE TRANSCRIPTION HIV RNA Õ DNA	AZT, ddI, ddC, D4T, 3TC, NEVIRAPINE, DELAVIRIDINE
3. INTEGRATION INTO HOST GENOME (LATENCY)	INTEGRASE INHIBITORS
4. TRANSCRIPTION OF NEW REGULATORY GENES	TAT, NEF, REV INHIBITORS
5. HIV RNA TRANSLATION	----------
6. HIV ASSEMBLY	SAQUINAVIR, RITONAVIR, INDINAVIR, NELFINAVIR
7. HIV BUDDING	INTERFERON

Figure 1. HIV life cycle and opportunities for intervention.

tease and integrate enzymes are necessary for the formulation of mature viral particles that are subsequently released from the host cell, resulting in circulating plasma viremia and the ability to infect new CD4 lymphocytes and other CD4-bearing cells (Wei, Ghosh, & Taylor, 1995).

The clinical course of HIV infection varies extensively between individuals even in its earliest phases. Many individuals may be asymptomatic at the time of acquiring HIV infection. However, between 30% and 70% of patients may have a primary infection syndrome, which can include fever, headache, rash, pharyngitis, gastrointestinal disturbances, and lymphadenopathy (Cooper *et al.,* 1985; Shacker, Collier, Hughes, Shea, & Corey, 1996). A clinically asymptomatic phase generally follows, since less than 1% of HIV-infected individuals develop life-threatening opportunistic infections within the first years after their initial infection. At the time that individuals first become HIV+, they may develop an extremely high HIV titer in their blood (plasma viremia) within days after their relevant exposure; they may also have freely circulating HIV antigens, particularly the P24 core antigen. However, within weeks to months after their acquisition of HIV, the host usually develops an immune response which is associated with specific anti-HIV antibodies and cytotoxic T-cell activity. In the early stages of HIV infection, there may be a transient immunosuppression as evidenced by a drop in the number of CD4 lymphocytes but, with the stabilization of this immunologic set point, patients generally maintain a normal level of CD4 lymphocytes (between 500 and 1500 cell/mm^3) for many years. A clinically latent period was thought to be associated with viral quiescence because it was difficult to identify viral-infected cells *in vivo,* so it was initially thought that very few cells actively produced new HIV RNA at any given time.

However, subsequent improvements in viral diagnostic techniques including co-culture and the increasing use of newer diagnostic assays such as PCR and the branch DNA techniques (bDNA) suggested that the amount of infectious virus in both circulating mononuclear cells and plasma was much higher than previously estimated, and could be correlated with clinical status (O'Brien *et al.,* 1996). Newer studies suggested that 1 in 50,000 cells harbored virus that was culturable during the asymptomatic phase; this proportion went up to 1 in 400 cells harboring culturable virus in patients who had symptomatic HIV disease. The advances in newer diagnostic technologies suggested that HIV infection was a much more dynamic process that had previously been appreciated (Ho *et al.,* 1995). Given that only 2% of the body's lymphocyte population circulates at any given time, subsequent studies indicated that the burden of HIV infection was predominately in the lymphoid tissues of the bone marrow, liver, spleen, and peripheral nodes. Over the course of the asymptomatic phase, an increase in progressive viral replication in lymphatic tissue has been reported; this increase results in a loss of lymphoid tissue, alterations in nodal architecture, and progressive lymphocyte depletion.

Newer dynamic studies have suggested that productively infected CD4+ lymphocytes have a half-life of 1.6 days in the circulation and that the kinetics of infection mean that more than 10^9 viral particles are produced daily. The average half-life of plasma free virus is approximately 6 hr. The majority of HIV-infected cells and viral particles are turned around over the course of each day. A persistent source of virus resident in lately infected cells has been found in monocyte/

macrophages, dendritic cells, and other potential reservoirs of longer-term infection (Pantaleo *et al.,* 1991). However, because the preponderance of viral burden is usually actively replicating, with high rates of turnover, the new paradigm has become one of using combinations of antiretroviral agents to rapidly inhibit the huge amount of viral replication and to avoid the ability of the large and dynamic viral burden to develop resistance mutations to individual agents.

This newer dynamic model of HIV suggested that following primary infection, a balance between viral production and clearance is achieved, such that there is a relatively steady state maintained over a long period of time: the viral set point. The major determinants of the plasma viremia set point are thought to be due to both viral and host factors, and may vary between individuals, but the usual set-point levels range between 10^2 and 10^6 copies/ml (Coombs *et al.,* 1989). Data from prospective cohort studies, such as the Multiple AIDS Cohort Study (MACS), in which gay men were recruited prior to the age of antiretroviral therapy, suggested that the set-point level, achieved shortly after HIV seroconversion, was highly associated with subsequent clinical outcome (Mellors *et al.,* 1996). Other studies based on therapeutic trials suggested that changes in HIV plasma viremia in response to antiretroviral therapy explained the major part of any treatment benefit, compared to the CD4 lymphocyte count. CD4 levels also explained part of the therapeutic benefit, but were not as potent a predictor of clinical outcomes as a decrease in plasma viremia (O'Brien *et al.,* 1996). Subsequently, multiple other studies have corroborated the value of assessing the plasma viremia to monitor HIV infection and evaluate the response to antiretroviral therapy.

The high level of HIV replication throughout the course of HIV infection explains how the virus has been able to exert progressive direct and indirect destructive effects on the host immune system (Fauci, 1993; Ho, 1995). As HIV infection progresses, there is a selective loss of naive T cells, which had been activated and infected as a result of the chronically stimulated lymphoid micro-environment, resulting from ongoing HIV replication (i.e., a vicious cycle). Naive T lymphocytes are generated from thymic-derived precursors in the bone marrow, and their ability to regenerate is significantly limited in adults. The major group of surviving cells are memory T cells, which can maintain the CD4 lymphocyte count during long-term asymptomatic HIV infection by proliferative expansion, but the selective loss of naive cells limits the host's subsequent ability to respond to new opportunistic infections once the CD4 lymphocyte count falls below the critical threshold, of 200 cells/mm^3.

The goal of early antiretroviral therapy is to limit the loss of multipotential T lymphocyte naive precursors, which allow for the maintenance of intact immunologic function. The institution of highly effective antiretroviral combination chemotherapy in patients with chronic HIV infection usually leads to an impressively prompt arrest of viral replication, resulting in increases in CD4 lymphocyte counts within weeks after starting these regimens. Initially, the preponderant number of new T lymphocytes that are measured in the blood are memory T helper

lymphocytes, which are functionally capable of replicating to antigenic stimuli to which they have been previously sensitized. However, the posttreatment expansion of circulating CD4 lymphocytes does not result in immune system reconstitution; if antiretroviral therapy is started in individuals with advanced HIV-associated immunocompromise, it is generally recommended that opportunistic infection prophylaxis not be discontinued (Carpenter *et al.,* 1997).

However, newer data suggest that over longer periods of time, naive T helper lymphocytes may be generated from bone marrow precursors and thus some mobilization of immune reconstitution may occur with sustained, intensive antiretroviral chemotherapy (Autram, 1998). This preliminary data might suggest an optimistic interpretation but these findings are not sufficiently well developed to warrant discontinuation of antiretroviral therapy when patients have a rise in CD4 counts, or the assumption that opportunistic infection prophylaxis, once initiated, can be terminated in patients with HIV disease.

Recent studies have demonstrated that when newly infected persons receive highly active combination chemotherapy, they have mounted immunologic responses that resemble those of long-term nonprogressors (persons who have been HIV infected for over a decade who show no signs of immunocompromise) (Rosenberg, 1997). These persons were so recently infected that they have not yet mounted an antibody response, but they were found to be HIV infected by viral load monitoring. Unfortunately, the same impressive immune responses have not been noted in persons with chronic HIV infection who constitute the majority of HIV+ persons, so other approaches to maximal viral suppression or eradication will be needed.

Several investigators have now shown that the suppression of viral replication to below detectable levels in blood using new ultrasensitive assays (i.e., below 20 copies/ml) does not equal eradication (Faints, Hermankova, & Pierson, 1997; Wong, Herzareh, & Gunthand, 1997). HIV has been detected in latent DNA forms in white blood cells in lymph node, bone marrow, or genital fluids in patients who have undetectable blood levels (Mayer, 1997). In several "undetectable" patients, HIV was readily detectable in the blood after antiretroviral therapy was discontinued, suggesting that once HIV infection has been well established, current antiretroviral regimens must be continued indefinitely.

Future treatment regimens may need to add even more potent antiretroviral combination, immunotherapy, or both, if eradication of HIV in chronically infected patients is contemplated. On the other hand, recent studies of patients who received highly active therapy in the midst of acute HIV infection have suggested a level of immunostabilization and viral suppression that might allow for future treatment regimens of limited duration (6 months to several years) if the newly established infection is immediately treated aggressively (Rosenberg, 1997). Even this optimistic hypothesis is speculative; for the time being, one must presume that HIV treatment involves a long-term commitment on the part of the patient and provider.

The possibility that the less than 1% of CD4-bearing cells that are latent reservoirs of HIV DNA and RNA might slowly turn over and be eliminated from the system has led to the development of bold clinical trials that are currently under way. These studies evaluate whether medications may be discontinued after several years of highly effective antiretroviral therapy promptly started soon after patients initially became infected. There is no data to support this interesting speculation; thus, the initiation of combination antiretroviral chemotherapy must be considered the beginning of a lifelong process of viral suppression.

PRINCIPLES AND GUIDELINES OF ANTIRETROVIRAL THERAPY

Over the past few years, the development of a better understanding of the immunopathogenesis of HIV disease, the enhanced ability to detect plasma viremia, and improved antiretroviral chemotherapy have led to the development of a new clinical paradigm for HIV care: the evaluation and management of HIV infection. In an attempt to develop guidelines and standards and to place the new scientific information in the appropriate clinical context, two independent panels met over the course of 1997, one under the aegis of the International AIDS Society–USA (IAS-USA) and the other was convened by the Department of Health and Human Services (DHHS) in conjunction with the Kaiser Family Foundation. The two panels developed parallel benchmarks for consideration of several basic clinical questions, including when to initiate antiretroviral therapy, which drugs to utilize, and when to consider changing antiretroviral regimens (Carpenter *et al.,* 1997) (Table 1).

The scientific rationales for the recommendations were based on several insights, including the increasing recognition of the high level of HIV-productive infection a daily turnover of at least 10 billion HIV particles. More recent studies suggest that plasma viremia is sustained at much lower levels than the HIV-related

Table 1. Comparison of Guidelines of when to Initiate Antiretroviral Therapy: International AIDS Society and Health and Human Services Panels

International AIDS Society—USA panel	Health and Human Services panel
Recommend initiation always	
Symptomatic HIV CD4 < 500 cells/mm^3 HIV RNA > 5000 (bDNA)[a] copies/ml	Symptomatic HIV CD4 < 500 cells/mm^3 HIV RNA > 10,000 (bDNA)[a] copies/ml
Consider initiation	
Any detectable HIV RNA	CD4 > 500 cells/mm^3 and HIV RNA > 10,000 copies

[a]Assay levels using PCR are generally twice as high.

tissue burden at each stage of infection, so viremia is only a marker for the dynamic, sustained, extensive replication of HIV in infected individuals. The panels also noted the utility of monitoring HIV infection utilizing viral quantification by reverse transcriptase PCR (RT-PCR) or the branch DNA technique (bDNA). They noted data from natural history and treatment studies that very few patients progress to AIDS or die with HIV RNA levels greater than 5000–10,000 thousand copies/ml detected by the branch DNA technique, or twice that level when utilizing RT-PCR.

The two panels agreed that HIV therapy should always be initiated in patients with any signs or symptomatic HIV infection, including major AIDS-defining opportunistic infections or more subtle symptoms such as the presence of thrush, oral hairy leukoplakia, *Herpes zoster,* chronic constitutional symptomatology, or several of these (Table 1). The panels also agreed that the studies of the natural history of HIV suggested that clinical progression was inevitable among individuals with CD4 lymphocyte counts less than 500 cells/mm^3, and thus they recommended starting therapy in such individuals regardless of HIV viral load. The IAS-USA panel suggested a lower threshold for starting asymptomatic people on therapy, that is, peripheral viral loads of more than 5000 copies/ml independent of CD4 count, whereas the DHHS panel used 10,000 viral copies/ml as their threshold. Similarly, the IAS-USA panel suggested one might consider starting therapy at any detectable level of HIV RNA, whereas the DHHS panel suggested that only for individuals with more than 10,000 copies/ml of HIV RNA by bDNA would the initiation of therapy would be warranted. Because plasma viremia may be altered because of immunostimulatory events that may lead to cytokine release, for example, an intercurrent infection such as tuberculosis, herpes simplex reactivation, or influenza vaccination, the panels felt that no decision regarding the commencement of therapy or alteration in antiretroviral therapy should be based on a single plasma viral load (or CD4 count) determination. Rather, both panels suggested that any important decision should be based on obtaining at least two measurements in close proximity in order to establish a stable baseline on which to base important clinical decisions.

Recent studies suggest that patients are most likely to do well if they have complete suppression of plasma viremia below limits of currently available detection (generally below 400 to 500 copies/ml with second-generation testing). More recently ultrasensitive assays may detect levels as low as 20–50 copies/ml, but these assays are not yet widely available; thus, both panels recommended that initial antiretroviral therapy should include two nucleoside reverse transcriptase inhibitors (NRTIS) and a protease inhibitor with high in vivo potency (indinavir, ritonavir, or nelfinavir). (Table 2). Alternative regimens may include two NRTIS plus the nonnucleoside reverse transcriptase inhibitor (NNRTI) Nevirapine, and for the DHHS panel two NRTIS and Saquinavir was an alternative regimen. The panels felt that a less desirable alternative would be two NRTIS and that monotherapy at this point and time was contraindicated.

Table 2. Initial Therapy Comparison of Antiretroviral Therapy Guidelines: Health and Human Services vs. International AIDS Society Panels

	IAS-USA	HHS
Preferred	2 NRTI[a] + PI[b]	2 NRTI[a] + PI[b]
Alternative	2 NRTI + NVP	2 NRTI + NVP
Alternative #2	2 NRTI[a]	2 NRTI[a] + SQV
Not recommended	Monotherapy	Monotherapy

[a]AZT + 3TC, AZT + ddI, AZT + ddC, 3TC + d4T, d4T + ddI
[b]Indinavir, ritonavir, nelfinavir
NVP = nevirapine
NRTI = nucleoside reverse transcriptase inhibitor
PI = protease inhibitor

Prior to initiating any complex chemotherapeutic regimen, a detailed discussion between the patient and provider is necessary to assess the patient's ability and willingness to adhere to a complex regimen (Table 3). Recent studies suggest that nonadherence to complex combination chemotherapy may result in the rapid development of viral resistance and the limitation of future therapeutic options. Because reverse transcriptase inhibitors (RTIs) and protease inhibitors may select for cross-resistance to similar agents in their respective drug categories, nonadherence leading to resistance for one drug may foreclose multiple options for the patient in the future. The provider needs to emphasize the advantages of viral suppression, which may preserve immune function, decrease the emergence of drug resistance, and ultimately prolong the patient's quality and quantity of life. Balanced against these advantages are the risks of developing adverse drug reactions, the need to rigorously adhere to the regimen in order to avoid the emergence of resistance, and lack of long-term data regarding efficacy and potential toxicity.

Prior to the initiation of therapy, routine laboratory examinations are performed, including a complete blood count, chemistry profile, and screening for

Table 3. Factors in Decision to Treat Asymptomatic HIV Infection

For	Against
Viral suppression	Risk of adverse drug reaction (ADR)
Preserve immune function	Potential for resistance
Decrease resistance	Limit future options
Drugs may be better tolerated in early infection	Unknown durability
Prolong health and life	Possible long-term toxicity
Consider	
Patient's feelings about initiating medication	
Patient's willingness to be adherent	
Degree of immunosuppression and viral burden	

potential future opportunistic infections such as toxoplasmosis and tuberculosis (Table 4). Once the patient is started on antiretroviral therapy, the CD4 lymphocyte count and plasma viral load are usually determined 1 month after therapy. It is hoped that there will be a drop of at least one log of plasma HIV RNA by 1 month after the initiation of the new antiretroviral regimen. The ultimate goal of antiretroviral therapy is a continued drop in the plasma viral load, with the hope that by 6 months the plasma HIV would be undetectable, utilizing current techniques that have a threshold between 400 and 500 copies/ml. Lower levels can now be detected using the newest modifications of PCR or bDNA technology, which can detect as low as 20 HIV copies/ml. Recent studies suggest that utilizing ultrasensitive PCR or bDNA techniques that can detect down to HIV plasma RNA concentrations of 20 copies/ml may be even more desirable (Montaner, 1998), but the long-term clinical significance and feasibility of this more stringent goal has not yet been fully studied.

Both panels felt that failure to suppress HIV RNA was a source of concern, although the specific criteria used evaluate the time to initiate a change differed slightly between the two panels. Rising HIV RNA, failure to achieve undetectable levels by 16–24 weeks, and a viral burden greater than 10,000 copies at 12–24 weeks (IAS-USA panel) or greater than 10,000 copies at 16–24 weeks (DHHS panel) were indications to change therapy (Table 5). In addition, both panels recognized that independent of viral load changes, declining CD4 counts were an indication for changing antiretroviral therapy. Other factors that the IAS-USA panel suggested for consideration as in changing therapy included clinical progression, unacceptable drug toxicity, nonadherence, and recognition that a regimen was subtherapeutic.

In general, both panels felt that single drug changes in antiretroviral therapy were inappropriate and that one would need to change at least two drugs, and in some cases three, in order to avoid cross-resistance which would likely have occurred in the context of a failing regimen (Table 6). The most common suggested change was to go from one set of nucleoside analogs and protease inhibitors to a

Table 4. Laboratory Testing Prior to the Initiation of Antiretroviral Therapy

CBC, Chemistry Profile
Opportunistic disease screening
Serology: toxoplasma, CMV, HBV, HCV, VDRL
Chest x-ray, ophthalmic exam, PAP smear
$CD4^+$ count
Plasma HIV-RNA viral load
Immediately prior to antiretroviral therapy
4 weeks to assess initial efficacy (goal undetectable, > 1 .0 log)
Continued every 3–4 months or 1 month after changing therapeutic regimen
6 months—reassess therapy
$CD4^+$ count
At DX and 3–6 months thereafter or 1 month after changing therapeutic regimen

Table 5. Comparison of Guidelines of when to Change Antiretroviral Therapy

Indications to change therapy		
	IAS-USA	HHS
Failure	Rising HIV-RNA	Detectable HIV-RNA at 16–24 weeks
	Failure to achieve undetectable HIV	[a]VB > 10K at 16–24 weeks
	[a]VB > 2–10K at 12–24 weeks	Declining $CD4^+$ cell count
	Declining $CD4^+$ cell count	
	Clinical progression	
Other	Unacceptable toxicity	
	Nonadherence	
	Use of suboptimal therapy	

[a]VB = viral burden

different, comparable three- or four-drug regimen. However, other types of changes was also noted as acceptable by the panels, including switching from a protease inhibitor–containing regimen to one that included a nonnucleoside reverse transcriptase inhibitor (NNRTI) or vice versa, or switching to an NNRTI plus a new protease inhibitor.

There are five nucleoside reverse transcriptase agents that are FDA approved and one available by expanded access utilization (Abacavir); there are two nonnucleoside reverse transcriptase agents (NNRTI) that are FDA approved and another available by expanded access utilization (Efavirenz). There are four protease inhibitors currently available with several others in advanced stages of development in clinical trials. Current principles and guidelines that are generally based on three drug combinations will undoubtedly change over the next few years as current clinical trials mature. Patients who have failed triple drug therapy may currently be on four or more drug combinations. Recent studies have suggested that certain antiretroviral combinations are undesirable because of cross-resistance, additive toxicity, incompatible dosing schedules, or a combination of these factors. However, key principles of the newer paradigm will remain: initiating therapy at earlier stages of infection to preserve immune function, utilization of plasma viral load as a key marker of the efficacy of antiretroviral ther-

Table 6. Comparison of Guidelines for Changes of Antiretroviral Therapeutic Regimen

What to change to	
IAS-USA	HHS
2 new NRTIs + new PI	2 new NRTIs + new PI(s) or NNRTI
Not IDV – RTV; ? IDV or RTV – NLF	NLF – RTV or SQV + RTV or NVP + RTV or NVP + IDV
2 new NRTIs + NVP	RTV – SQV + RTV or NLF + NVP
	IDV – SQV + RTV or NLF + NVP
RTV + SQV + nucleoside	SQV – NLF or RTV or RTV + SQV or NVP + IDV

Table 7. Currently Available Antiretroviral Agents[a]

Generic name	Proprietary name	Other names	Manufacturer
Nucleoside reverse transcriptase inhibitor			
Didanosine	Videx	ddI	Bristol-Myers Squibb
Lamivudine	Epivir	3TC	GlaxoWellcome
Stavudine	Zerit	d4T	Bristol-Myers Squibb
Zalcitabine	Hivid	ddC	Hoffman–La Roche
Zidovudine	Retrovir	ZDV	GlaxoWellcome
Abacavir	—	1592	GlaxoWellcome
Adefovir	—	bis-pom PMEA	Gilead
Non-nucleoside reverse transcriptase inhibitor			
Delavirdine	Rescriptor	DLV	Pharmacia Et Upjohn
Nevirapine	Viramune	NVP	Roxane Laboratories (Boehringer Ingelheim)
Efavirenz	Sustiva	DMP-266	Dupont–Merck
Protease inhibitor			
Indinavir	Crixivan	IDV	Merck
Nelfinavir	Viracept	NFV	Agouron Pharmaceuticals
Ritonavir	Norvir	RTV	Abbott Laboratories
Saquinavir	Invirase	SQV	Hoffman–LaRoche

[a]Includes both FDA-approved drugs and those available by expanded access protocols.

apy, and the utilization of combination chemotherapeutic regimens. Salient features of each of the key building blocks of antiretroviral therapy are summarized in the following sections (Table 7).

SPECIFIC ANTIRETROVIRAL THERAPY

Nucleoside Analog Reverse Transcriptase Inhibitors

Zidovudine

Zidovudine (3'-azido-3'deoxythymidine; ZDV; AZT) in 1987 was the first antiretroviral agent to be approved (Fischl *et al.,* 1987). Once absorbed into the body, the drug is taken up by cells, and it is phosphorylated by cellular enzymes to an active metabolite for incorporation into the growing viral DNA chain by HIV reverse transcriptase. Once inserted into the chain, no further nucleotide can be added and therefore viral replication ceases. ZDV's active metabolite is ZDV triphosphate, which competitively inhibits the incorporation of thymidine into proviral DNA by reverse transcriptase. *In vitro,* ZDV exhibits potent antiviral activity with an IC_{50} around 1 micromole, depending on the test system used.

In the first antiretroviral clinical trial of ZDV, there was a greater death rate in the placebo arm, compared to advanced patients receiving ZDV. Subsequent trials

indicated that ZDV improved survival, decreased the incidence of opportunistic infections, and increased CD4 counts, compared with nontreated controls (Volberding *et al.,* 1994). Unfortunately, the benefits of ZDV monotherapy are limited; this limitation was clearly shown in the Concorde study, which suggested that after 1 to 2 years, the benefits of AZT disappeared (Concorde Coordinating Committee, 1994). Markers of viral replication immunologic activity returned to baseline and this was subsequently associated with the emergence of ZDV-resistant viral strains (Larder, Darby, & Richman, 1989).

The most common side effects of ZDV are anemia and neutropenia, which tend to be dose dependent and reversible by 2–4 weeks if the drug is withdrawn or if the dose is reduced. Earlier studies utilized doses of ZDV greater than 1 gram a day which was much more highly associated with side effects. The current dosing regimen of 500–600 mg a day is much less commonly associated with hematologic abnormalities. Nonhematological side effects include headache, myalgia, nausea, vomiting, asthenia, and insomnia, which generally resolve in a few weeks after initiation of treatment.

ZDV is the only antiretroviral that has been approved for the prevention of perinatal transmission of HIV from pregnant women to their newborns (Connor *et al.,* 1994). In the AIDS Clinical Trial Group, an NIH-funded network of academically-based HIV clinical trial units, 076 trial, the use of ZDV in the third trimester of pregnancy, intravenously in the course of delivery, and for 6 weeks postpartum by the infant resulted in a threefold reduction in HIV transmission from mother to infant. ZDV has also been shown to cross the blood–brain barrier and has been demonstrated to be effective in decreasing HIV-associated encephalopathy (Gray *et al.,* 1994).

ZDV has been shown to be better in combination with other nucleosides such as ddI and 3TC than in monotherapy in several recent clinical trials (Delta Coordinating Committee, 1996; Eron, 1996). It is frequently administered as part of combination chemotherapeutic regimens because of the relative ease of administration (currently as a twice daily regimen), its effectiveness against neurologic aspects of HIV, and because of the familiarity of clinicians who have used the drug for more than a decade. In combination with other nucleoside analogs and protease inhibitors, ZDV has been shown to reduce plasma HIV levels to below detectable for prolonged periods of time, approaching 2 years in some individuals.

Didanosine

Didanosine (2',3'-dideoxyinosine; ddI) is an analog of adenine and has exhibited significant anti-HIV- 1 and anti-HIV-2 activity in cell culture, ranging from 1 to 10 micromolar. ddI has greater activity in resting peripheral blood mononuclear cells infected with HIV than in activated cells, whereas the opposite is true or ZDV and D4T, providing a rationale for combination therapy (Burger, Meenhorst, & Beijnen, 1995). ddI is formulated with either a citrate/phosphate buffer or with an antacid such as calcium carbonate and magnesium hydroxide, since it is rapidly

degraded in gastric acid to hypoxanthine and dideoxyribose, which are inactive. To reduce this effect, it is recommended that ddI be taken on an empty stomach at least one hour before a meal.

Early studies indicated that in ZDV-experienced patients, switching to ddI resulted in the development of fewer opportunistic infections (Kahn *et al.,* 1992). This led to its recommendation as a second-line drug in patients who were intolerant to ZDV However, subsequent studies compared monotherapy of each of the agents to combination, and found that the combination of AZT/ddI resulted in much better clinical outcomes. ddI has also been shown to be safe and well tolerated in pediatric patients, with improvements in surrogate markers and clinical course (Englund *et al.,* 1997). It is highly active in combination with other nucleoside analogs and protease inhibitors and in combination with other nucleoside analogs and NNRTIS. In addition, studies have indicated that ddI and hydroxyurea, a ribonucleotide reductase inhibitor, have significant synergistic effects against HIV *in vitro* and *in vivo* (Lori, Foli, & Matteo, 1997). Although hydroxyurea does not inhibit HIV replication directly, it can effectively lower plasma levels of dATP, the cellular competitor of ddI, thereby favoring the incorporation of ddI into the growing viral DNA chain and resulting in enhanced efficacy.

The major clinical toxicity associated with ddI is pancreatitis, which has been fatal in rare individuals (Pike & Nicaise, 1993). In early studies, the incidence of pancreatitis ranged from 7% to 13%, but enhanced clinical awareness of this complication has decreased its frequency because patients are better educated to look for premonitory signs of gastrointestinal discomfort. Treatment by ddI has also been associated with peripheral neuropathy, which appears to be dose related and is generally reversible. Other side effects include diarrhea, nausea, and vomiting, which tend to be self-limited. The diarrhea may be associated with the citrate/phosphate buffer in the powder formulation, and thus may abate when the patient is switched to another drug formulation.

Zalcitabine

Zalcitabine (2',3'-dideoxycytidine; ddC) is a cytidine nucleoside analog which is phosphorylated by cellular enzymes to its triphosphate form, which competes with 2'-deoxycytodine-5'-triphosphate for incorporation into viral DNA by reverse transcriptase and subsequently results in chain termination (Broder, 1990). Early clinical studies of ddC in patients with AIDS and other advanced HIV disease revealed a transient benefit on surrogate markers of disease (Merigan *et al.,* 1989). The combination of ddC and ZDV has additive activity in some assays and clinical trials, and has been synergistic in others. When the drug is given in combination with ZDV and protease inhibitors, such as saquinavir, impressive effects on surrogate markers and clinical outcomes have been noted, with the triple regimen being found to be significantly more efficacious than any of the dual drug combinations.

The major clinical toxicity of ddC is peripheral neuropathy, which occurred in 17% to 3 1% of patients treated in the early phase studies (Merigan & Skowron,

1990). The risk of developing peripheral neuropathy on ddC therapy is increased in individuals with advanced HIV infection. Pancreatitis has been described with ddC, but this a rare complication occurring in less than 1% of patients. Other adverse effects that have been reported in monotherapy trials include: oral ulcers, nausea, vomiting, and abdominal pain.

Stavudine

Stavudine (2',3'-didehydro-2'3', deoxythymidine; D4T) is a thymidine nucleoside analog that is phosphorylated to stavudine-5'-triphosphate by cellular enzymes (Riddler, Anderson, & Mellors, 1995). This active form inhibits reverse transcriptase by competing with the enzyme for substrate and by blocking viral DNA synthesis through chain termination. Dose-ranging studies reveal that D4T generally increases CD4 counts and decreases viral load in patients at various stages of disease, including patients who have received prior ZDV therapy. D4T produced similar results in children who had failed or who were intolerant to other therapies, and has been shown to be safe and well tolerated in combination with ddI when administered to children and adults with advanced HIV infection.

D4T was initially used as a second-line treatment for patients who were failing or intolerant to ZDV, until the advent of combination therapy (Petersen *et al.,* 1995). It is antagonistic to ZDV and has overlapping toxicity profiles with ddI and ddC. However, pilot studies of D4T-ddI in patients with advanced HIV infection who had received extensive prior ZDV showed that D4T-ddI was well tolerated and produced substantial benefit in terms of virologic and immunologic markers (Durant *et al.,* 1997). Newer studies have demonstrated the safety and efficacy of D4T and 3TC as dual therapy and in combination with the new protease inhibitors. D4T is also able to cross the blood–brain barrier.

The major toxicity associated with D4T is peripheral neuropathy, which tends to be dose dependent and is generally reversible if caught in its early stages. In one early clinical trial, the rate of development of mild peripheral neuropathy was 9 per hundred patient years and that for severe peripheral neuropathy, 5 per hundred patient years. Other uncommon adverse events associated with D4T therapy include headache, chills and fever, diarrhea, and rash, none of which have progressed once the drug has been discontinued.

Lamivudine

Lamivudine (2',3'-dideoxy-3'-thiacytidine; 3TC) is phosphorylated by cellular enzymes and competes with 2'-deoxycytidine-5'-triphosphate for incorporation into HIV proviral DNA, thereby inhibiting the viral reverse transcriptase (Eron, 1996). It is highly active against HIV-1 and HIV-2. 3TC is more active in resting peripheral blood mononuclear cells than actively dividing ones.

Lamivudine monotherapy has transient clinical activity but in combination with ZDV it has been associated with substantial CD4 cell increases and decreases

in viral load. However, by 6 months, the changes seen in combination therapy have frequently not been sustained and virologic analyses suggest that the rapid emergence of resistance to 3TC is part of the reason. 3TC is also active when combined with d4T (Katlama *et al.,* 1997). However, in several large studies in triple combination therapy with ZDV and protease inhibitors, viral suppression has been shown to persist for almost 2 years in the majority of patients who receive the combination chemotherapy (DeTruchis *et al.,* 1997). 3TC is generally well tolerated both adults and children across a range of doses. Diarrhea, malaise or fatigue, and headache are the most commonly reported side effects in monotherapy trials, but these effects were usually mild and transient (Katlama, Ingrand, & Loveday, 1996; Staszewski, Loveday, & Picazo, 1996). 3TC is also well tolerated in children. Rare case reports of mania and other psychological disorders have been reported in patients receiving 3TC but the drug is generally well tolerated.

Abacavir

Abacavir (1592U89) is a carbocyclic guanosine nucleoside analog with good central nervous system (CNS) penetration and good oral absorption. Preliminary studies suggest great potency, with plasma viral load decreases over 1.5 logs when used as monotherapy, and greater decreases when used in combination regimens. Side effects include acute allergic reactions with fever and rash, and nausea in other patients. The rash may not occur at the outset of therapy, but once it does, the drug should be discontinued, since rechallange has been associated with hypersensitivity reactions. The drug is expected to be licensed by the end of 1998.

Adefovir

Adefovir dipivoxil (bis-pom PMEA) is an adenosine nucleotide analog RTI, which means that it does not have to undergo triphosphorylation to be active against HIV intracellularly. It has broad spectrum antiviral activity, including anti-CMV and other herpes virus activity. In previously treated patients, the addition of adefovir resulted in 0.5 to 1 log decreases in plasma viral load. The most common symptomatic side effects include nausea, anorexia, and flatulence, but metabolic abnormalities including temporary to moderate renal impairment have been described. The drug is expected to be licensed soon.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine

Nevirapine has potent anti-HIV-1 activity in cell culture, with IC_{50} values of 40 nanomolars, although it is inactive against HIV-2 because of its specificity for the HIV-1 reverse transcriptase enzyme (Cheesman *et al.,* 1995). Nevirapine is not

incorporated into the growing strain of HIV DNA, but directly inhibits HIV reverse transcriptase by binding to it noncompetitively. Because it interacts with the specific binding site on the enzyme, any slight variation brought about by single point mutations has a significant impact on the sensitivity of the viral strain to nevirapine and high levels of resistance may develop rapidly.

In early phase clinical trials, a transient antiviral effect was seen with monotherapy but was associated with the rapid emergence of resistant strains, which were detectable by 8 weeks (Havlir, 1997). Subsequent studies utilizing two nucleoside analogs plus nevirapine have resulted in viral suppression in the majority of asymptomatic HIV-infected individuals receiving this "cocktail" (De Jon *et al.,* 1997). The drug is also well tolerated in children (Luzuriaga *et al.,* 1997). Nevirapine reduces cytochrome p450 metabolism of substrates and when used in combination with protease inhibitors, which are metabolized by the same hepatic enzyme system, increased doses of some of the protease inhibitors may be necessary.

The drug is well tolerated in patients, but rashes have been described in 17% of early trial participants. The rash is generally nonpruritic and self-limited once the drug is withdrawn; however, rare cases of Stevens–Johnson syndrome have been associated with the administration of nevirapine. Other side effects have generally been transient, including sedation, fatigue or somnolence, headache, fever, nausea, and vomiting.

Delavirdine

Delavirdine is structurally a bisheteroarylpiperazine compound. *In vitro,* the compound is active against HIV grown in peripheral blood lymphocytes and against HIV strains that are highly resistant to ZDV or ddI. Delavirdine, like other NNRTIS is inactive against HIV-2 (Davey *et al.,* 1996). Delavirdine monotherapy in HIV-experienced patients resulted in transient immunologic and virologic responses, but generally viral load and CD4 count returned to baseline by week 12. This was probably due to the selection of resistant virus *in vivo* (Dueweke *et al.,* 1993). However, combination chemotherapy using delavirdine with two nucleoside analogs or protease inhibitors, or both is active, with favorable alterations of surrogate markers, that is, plasma RNA and CD4 count (Morse, 1997).

Overall, delavirdine is well tolerated, although a mild-to-moderate erythematous maculopapular rash is commonly seen. The rash has been less frequently associated with evolution to Stevens–Johnson syndrome compared to nevirapine, but the overall prevalence of rash is more common with delavirdine. In many cases, the medication can be continued without further progression of the rash and the rash frequently resolves spontaneously. Delavirdine is bound extensively to plasma proteins, particularly albumin, and this may have implications with regard to the level of the drug achievable in different body compartments (Chaput, Dambrosio, & Morse, 1996). Many clinical studies currently under way will enable clinicians to better assess how to use this drug optimally.

Newer Nonnucleoside Reverse Transcriptase Inhibitors

Efavirenz has been the next NNRTI to be FDA approved. Efavirenz (DMP-266, Sustiva) is a newer NNRTI that has been associated with more than a 2-log decrease in plasma HIV load when given in combination with indinavir. In combination with two nucleosides, it has been shown to be active in reducing plasma HIV RNA as a protease inhibitor-containing regimen. The most commonly associated side effect is a mild rash, which may not recur when therapy is interrupted and the patient is rechallenged. Hepatic abnormalities are not frequent and have rarely led to drug discontinuation. Other NNRTIS that are currently in clinical development include loviride and MKC-442.

Protease Inhibitors

Saquinavir

Saquinavir is a peptide derivative of carboxamide methanesulphonate which is a transition-state mimetic of the phenyl–proline peptide bond (Galpin, Roberts, O'Connor, Jeffries, & Kinchington, 1994). Saquinavir completely inhibits the viral protease of HIV-1 and HIV-2, resulting in the formation of immature noninfectious viral particles. In previously untreated HIV-infected patients, a maximum reduction of 80% in HIV RNA was observed after 8 weeks but resistance rapidly developed in patients who received monotherapy (Kitchen *et al.,* 1995). *In vivo* and *in vitro* studies suggest that saquinavir may be used effectively with two nucleoside reverse transcriptase inhibitors (NRTIS). In advanced ZDV-experienced patients, the combination of ZDV, ddC, and saquinavir resulted in decreased plasma viral load, increased CD4, and decreased clinical progression compared to any dual therapy combination (Collier, Coombs, & Schoenfield, 1996).

The initial formulation of saquinavir as a hard gel resulted in a less bioavailable product that was felt to be less active than other protease inhibitors, but a newer formulation using a soft gel capsule resulted in greatly enhanced plasma levels and initial studies showed enhanced antiretroviral effects. The major side effects of saquinavir are gastrointestinal problems, particularly diarrhea, abdominal pain or discomfort, and nausea; elevated aminotransferase levels; and ulcerations of the buccal mucosa. Saquinavir absorption is enhanced with food intake and grapefruit juice. Fewer drug interactions have been noted with saquinavir compared to other protease inhibitors (Table 8).

Ritonavir

Ritonavir is a congener of tetraazatridecan- 13-oic acid, 5-thiazoloyl-methylester that inhibits the HIV protease with a high level of antiviral activity. When given at 600 mg twice a day as monotherapy, the drug has a potent but transient antiretroviral effect (Markowitz *et al.,* 1995). However, in combination with

Table 8. Common Interactions between Protease Inhibitors and Other Medications

	Indinavir	Ritonavir	Saquinavir	Nelfinavir
Rifabutin[a]	Use 1/2 dose	Use 1/4 dose	Consider alternative	Use 1/2 dose
Oral contraceptives	In levels, but no change needed	Ethinylestradiol; use additional contraceptive method	No data	Ethinylestradiol and norethindrone; use additional contraceptive method
Other interactions	Grapefruit juice – indinavir levels by 26%	Desipramine level theophylline level	Grapefruit juice – saquinavir level	

[a]Rifampin is contraindicated for use with indinavir or ritonavir, and not recommended with saquinavir or nelfinavir. Other common drugs do not interact sufficiently with protease inhibitor metabolism to warrant dose modifications.

two nucleoside analogs, the drug has been shown to be highly potent with viral load reductions of more than two logs in the majority of patients receiving the medication (Hoen *et al.,* 1997). The addition of Ritonavir to nucleoside analog–containing regimens has been associated with enhanced survival rates in patients with advanced HIV infection (Cameron *et al.,* 1996). Ritonavir is highly active in combination with two nucleoside reverse transcriptase agents and when given in combination with saquinavir and other protease inhibitors. Part of the explanation for this may be synergistic inhibition of the HIV protease by two protease inhibitors acting at different binding sites for the enzyme. However, another possible explanation is that ritonavir is a potent inhibitor of the cytochrome p450 enzyme system and will raise saquinavir levels more than fivefold.

The most commonly reported adverse events for patients participating in the early studies of ritonavir were diarrhea (62%), nausea (30%), asthenia (17%), and vomiting (15%). Circumoral paraesthesia and taste perversion have also been reported. Taste perversion has diminished now that the unpalatable liquid formulation has been superseded by a capsule form. Progressive dose acceleration over a 2-week period enhances hepatic metabolism of ritonavir and thus decreases the acute onset of the side effects noted with the usual recommended dosage of 600 mg twice a day.

Laboratory values associated with adverse events with ritonavir have included raised plasma levels of hepatic transaminases, elevations in the CPK and triglycerides, and hyperglycemia, which may occasionally require the use of antihyperglycemic drugs. Rare reports of renal failure have also been made, which suggests that periodic screening of renal function is important, particularly if other nephrotoxic drugs are being given (Duong, Sgro, Grappin, Biron, & Boibieux, 1996). Ritonavir is as well tolerated by children as it is by adults, i.e., no increased incidence of side effects.

Indinavir

Indinavir is a member of the class of hydroxyaminopentaneamide isosteres (Vacca *et al.,* 1994). Its efficacy has been studied in wide range of clinical trials, with evidence suggesting that by itself it is highly effective but that resistance develops rapidly to monotherapy. In combination with ZDV and 3TC, the drug in several trials was highly effective in decreasing viral load, increasing CD4 count, and decreasing the rate of HIV-related clinical progression. After 24 weeks on combination chemotherapy with indinavir, from 65% to almost 90% of participants had undetectable plasma viral loads (Gulick *et al.,* 1997). The use of indinavir in combination chemotherapy regimens was beneficial, regardless of whether the patient was antiretroviral therapy naive and regardless of their state of immunologic function (Hammer *et al.,* 1997).

Indinavir is moderately well tolerated (Deeks *et al.,* 1997). It is best taken on an empty stomach. The drug is usually taken three times a day but recent studies suggest that twice daily use may result in comparable clinical efficacy. The most important side effect is the occurrence of nephrolithiasis in about 5% of users over the first year of therapy, caused by crystallization of the drug in the urine. Patients are advised to drink large quantities of fluid to avoid this complication (greater than 48 ounces per day). Other side effects of indinavir include liver function test abnormalities. Recent reports have suggested, in rare cases, abnormal intermediary metabolism, with the appearance of truncal obesity (known colloquially as Crix belly), the so-called buffalo hump or other features that are associated with Cushing's syndrome, although early reports suggest normal serum cortisol levels. Although indinavir is not as potent an inhibitor of the cytochrome p450 enzyme system as ritonavir, drug interactions with indinavir have been noted, and several drugs that are hepatically metabolized, such as the rifamycins, must be dose adjusted when patients are taking them concomitantly with indinavir. Many of the mutations that confer resistance to indinavir can cause cross-resistance to ritonavir and vice versa, so that the use of one of the agents may preclude the subsequent use of the other.

Nelfinavir

Nelfinavir is a member of the butylcarboxamide methanesulphonic acid group with high *in vitro* activity against HIV-1 and HIV-2 (Moyle *et al.,* 1995). In several pivotal phase II and III trials, the safety and efficacy of nelfinavir has been demonstrated alone and in combination with other antiretroviral agents. In monotherapy, resistance rapidly develops. Nelfinavir is usually given three times a day, but recent studies suggest that twice daily dosing may be equally effective. After 24 weeks of antiretroviral therapy, more than 80% of individuals receiving nelfinavir plus nucleoside analog treatments were found to have plasma viral levels below the limits of detection, compared to 18% in patients receiving only ZDV

and 3TC. The drug has also been approved for pediatric usage (Powderly, Sension, Conant, Stein, & Clendeninn, 1997).

Nelfinavir appears to be generally well tolerated; the most commonly described side effects include diarrhea and fatigue, which are usually not severe enough to require drug withdrawal (Henry *et al.,* 1997). *In vitro* and *in vivo* drug resistance have been reported. However, there appears to be less cross-resistance between nelfinavir and other protease inhibitors, suggesting that if this drug is used as initial therapy and patients develop resistance, they may be able to be switched to other combination therapies with new protease inhibitors with some success. Clinical experience suggests variable success with other protease inhibitors as part of salvage regimens for patients who fail on nelfinavir-containing regimens.

Newer Protease Inhibitors

Amprenavir (VX-478, 141W94) is a potent inhibitor of HIV-1 and HIV-2 protease with excellent bioavailability, achieving plasma viral load reductions between 2 and 3 logs when used in combination with RTIs or other PIs. The most common side effects reported thus far have been diarrhea or rash, which have usually not resulted in drug discontinuation. Multiple other protease inhibitors are in early clinical trials (e.g., ABT-378) or later phases of *in vitro* testing. Many have different chemical structures which may allow them to be used in combination that might avert the development of cross-resistance, However, several like amprenavir are also metabolized by the cytochrome p450 system, so that clinicians considering combination protease inhibitor therapy will need to assess complex drug interactions.

ANTIRETROVIRAL DRUG INTERACTIONS

It is now accepted that the treatment of HIV infection with monotherapy is suboptimal because of limited efficacy and the rapid emergence of resistance; invariably combination chemotherapy means that astute clinicians must pay attention to antiretroviral drug interactions (Gerber, 1996). Certain combinations of nucleoside analogs are beneficial because of either reciprocal suppression of the emergence of deleterious mutations or direct viral synergism. The most commonly utilized dual nucleoside combinations are ZDV + 3TC, ZDV + ddI, ddI + D4T, D4T + 3TC, and ZDV + ddC. Combinations of dual nucleosides that have been shown *in vitro* or *in vivo* not to be clinically efficacious include ddC + D4T, ddC + ddI, and ddC + 3TC. In addition, certain combinations of nucleosides and other drugs are to be avoided because of potentially overlapping drug toxicities. An example of such a combination is ZDV + gancyclovir (administered for cytomegalovirus infection),

which can result in increased leukopenia, compared to giving either drug alone (Hochster *et al.,* 1990). On the other hand, certain potential synergistic toxicities, such as peripheral neuropathy when D4T and ddI are combined, have been shown not to be significant after clinical trials were completed.

The nucleoside analogs do not appreciably alter each other's metabolism, nor do they alter the metabolism of the protease inhibitors. On the other hand, the protease inhibitors and the nonnucleoside reverse transcriptase agents are metabolized by hepatic cytochrome p450 isoenzymes (Kempf *et al.,* 1997). The cytochrome p450 group includes at least 27 related enzyme families composed of a large number of individual isoenzymes that are responsible for the metabolism of specific substrates. Rifamycins (e.g., rifampin) are metabolized by the same isoenzymes and are significantly affected by protease inhibitors (particularly ritonavir). The effects of PIs on other drugs commonly used for the care of HIV+ patients is shown in Table 9. Delavirdine is also a cytochrome p450 inhibitor, whereas the other two available nonnucleoside reverse transcriptase drugs (nevirapine and efavirenz) are inducers of cytochrome p450 metabolism.

Because of the inhibition of cytochrome p450 isoenzymes, particularly by ritonavir, combinations of other protease inhibitors, particularly saquinavir and ritonavir or nelfinavir but also indinavir enhance the plasma levels of the latter drugs (Table 10). This result has led to the finding that twice daily dosing of ritonavir with saquinavir without other drugs has clinical efficacy. Other dual protease regimens taking advantage of this metabolic inhibition are under clinical study.

Because the nonnucleoside reverse transcriptase agents nevirapine and efavirenz are metabolized by the liver and induce cytochrome p450, protease inhibitor dose adjustments may be required when using combinations of nonnucleoside RTIs and protease inhibitors (Carptenter, 1997). As previously mentioned, delavirdine inhibits cytochrome p450 and thus current clinical studies are evaluat-

Table 9. HIV Drug Interactions Protease: Inhibitors and Nonnucleoside Reverse Transcriptase Inhibitors

	Affected Drug						
Interacting Drug	IDV	RIT	SQV	NLF	NVP	DLV	EFV
IDV	–	NE	↑	↑	NE	NE	NE
RIT	↑	–	↑	↑	NE	NE	↑
SQV	ND	NE	–	↑	NE	ND	↓
NLF	↑	NE	↑	–	NE	↑	NE
NVP	↓	NE	↑	↑	–	ND	ND
DLV	↑	NE	↑	↑	ND	–	ND
EFV	↓	↑	↑	↑	ND	ND	–

NE = No effect
ND = No data
IDV = Indinavir
RIT = Ritonavir
SQV = Saquinavir (soft gel)
NLF = Nelfinavir
↑ = Increase AUC
↓ = Decrease AUC
AMP = Amprenavir
NVP = Nevirapine
DLV = Delaviridine
EFV = Efavirenz

Table 10. Daily Pill Burden or Available Antiretroviral Agents[a]

Class/drug	Usual adult daily dosing =	Total number of tablets/capsules per day
Nonnucleoside reverse transcriptase inhibitors		
Nevirapine	1 x 200-mg tablets twice daily	2
Delavirdine mesylate	4 x 100-mg tablets three times daily	12
Nucleoside analogues		
Lamivudine	1 x 150-mg tablet twice daily	2
Stavudine	1 x 40-mg capsule twice daily	2
Zalcitabine	1 x 0.75-mg tablet three times daily	3
Didanosine	2 x 100-mg tablets twice daily	4
Zidovudine	2 x 100-mg capsules three times daily or	6
	1 x 300-mg tablet twice daily	2
Protease inhibitors		
Indinavir	2 x 400-mg capsules three times daily	6
Saquinavir nesylate	3 x 200-mg capsules three times daily	9
Nelfinavir mesylate	3 x 250-mg tablets three times daily	9
Ritonavir	6 x 100-mg capsules twice daily	12

[a]Based on manufacturer's prescribing information.
Based on adults weighing ≥ 60 kg.

ing whether delavirdine given in combination with protease inhibitors can result in decreased frequency of dosage to enhance patient adherence and decrease cost.

Other drugs that are metabolized by the cytochrome p450 system include rifamycins (i.e., rifampin, rifabutin), macrolides (e.g., clarithromycin, azithromycin), azole antifungal drugs (e.g., ketoconazole, fluconazole, itraconazole), and oral contraceptives (Borin, Chambers, Carel, Gagnon, & Freimuth, 1997). Thus, very often in the process of evaluating patients with advanced HIV infection who are on multiple other drugs that are hepatically metabolized, careful consultation with clinical pharmacologists is in order. For example, women on oral contraceptives are generally advised to use barrier methods of contraception if they are taking protease inhibitors, particularly ritonavir. Certain other drugs should be avoided by people taking protease inhibitors because of their extensive cytochrome p450 metabolism, particularly the antihistamines terfenidine and astenizole, which can cause fatal cardiac arrhythmias, and benzodiazepine anxiolytics because of increased sedation (Acosta & Fletcher, 1995).

Protease inhibitors, particularly ritonavir, induce enzymes involved with hepatic glucuronidation and may actually decrease the circulating levels of ZDV in the blood. This has not been found to be clinically relevant and therefore patients receiving ZDV and protease inhibitors do not need to have their doses adjusted. However, other protease inhibitor–nucleoside interactions may need monitoring. For example, ritonavir and ddI each increase serum uric acid levels and can increase triglycerides; these values should be routinely monitored in patients receiving these medications.

Depending on to the type ofbuffer used in formulating ddI, its administration can reduce absorption of co-administered drugs such as ciprofloxicin, tetracycline, itraconazole, ketoconazole, and dapsone. Therefore, it is important that patients be instructed to take these medications within an hour before or an hour after receiving ddI. As additional newer agents are added to therapeutic regimens, careful monitoring of complex pharmacologic interactions in patients receiving combination chemotherapy will be warranted.

POSTEXPOSURE PROPHYLAXIS (PEP)

The rationale for using combinations of antiretroviral drugs after occupational, sexual, or recreational parenteral exposure to potentially infectious blood or genital tract secretions is based on several lines of thinking. In a retrospective case-control study, public health researchers found a fivefold decrease in the likelihood that HIV-exposed health care workers would become infected when they received ZDV shortly after their exposure (Cardo *et al.,* 1997). Because of the nature of the study, issues such as the duration of the "window of opportunity" to intervene, the optimal regimen, and duration of treatment were not definitively addressed. However, this analysis was supported by animal evidence of the biological plausibility (Black, 1997) of PEP and the success of antiretroviral treatment in interrupting maternal–infant transmission.

These data led to the establishment of guidelines for the use of PEP after occupational exposure (Centers for Disease Control [CDC], 1995; Gerberding, 1996). Because the per contact risk of HIV infection after a sexual or shared needle exposure is on the same order of magnitude as the per contact risk after an occupational exposure (e.g., around 0.3%), recent recommendations have been developed for PEP use for persons who have sustained nonoccupational exposure (Katz & Gerberding, 1997, 1998). Like the guidelines for occupationally related PEP, the recommendations for PEP after these other exposures suggests that most exposures can be managed with dual nucleoside RTIs (usually ZDV and 3TC) and PEP should be initiated as soon after the exposure as possible, generally within 48–72hr. However, if the source of exposure is known to have advanced HIV infection (i.e., high viral load) or is already taking antiretroviral therapy, and the exposure is judged to be particularly high risk (e.g., unprotected receptive anal sex, traumatic vaginal rape), then three-drug regimens are appropriate, with the choice of specific RTIs and the protease inhibitor based on knowledge of the source patient's clinical history, if available. Because persons with advanced infection often have higher genital tract HIV levels (Anderson *et al.,* 1992) and AZT-resistant HIV is sexually transmitted, the use of a three-drug regimen is thought to optimize protection against a greater viral inoculum at the time of exposure that might already be resistant to a more conservative prophylactic regimen.

Questions about PEP, particularly for nonoccupational exposures, extend beyond the quandary of how many, and which, drugs constitute an optimal regi-

men. Not all sexual exposures involve exposure to blood or genital tract secretions, and those that do not would not qualify for PEP use. In addition, for PEP regimens to be effective (based on animal data), they need to be started promptly and those who use them need to be adherent. Unfortunately, the motivation of uninfected persons to remain adherent to a full month's course of multidrug regimens that may alter their lifestyle (e.g., indinavir must be taken on an empty stomach and requires increased fluid intake to avoid kidney stones) or cause side effects (e.g., diarrhea with nelfinavir) may be limited. Gerberding (1996) noted that more than one third of health care workers did not adhere to two- or three-drug PEP regimens.

In order to have public health utility, community-based PEP programs will need to accommodate the complex psychosocial milieu in which these exposures occur. Some exposures will occur in the context of committed relationships between serodiscordant partners (e.g., condom breakage), whereas others may be associated with sexual assault, necessitating rape crisis intervention and a discussion of the use of emergency contraception of exposed females. An additional concern has been raised regarding the behavioral consequences of the belief that chemoprophylaxis can supplant the adoption of safer sexual or injection practices. First responders will need to develop increased sophistication in the assessment of who are appropriate candidates for PEP, so that disenfranchised persons are not denied PEP capriciously, but so that the net effect of its availability will not be an increase in risk-taking behavior. People who have engaged in risks that make them appropriate candidates for PEP will need sensitive acute counseling and triage into appropriate risk-reduction interventions and supportive care.

They will also need to know that PEP is unlikely to be foolproof. The CDC has noted that at least 11 health care workers who received antiretroviral therapy after occupational exposure subsequently became HIV infected. Other authors in this volume will address these behavioral implications in more detail. The evolving rationale for the availability of PEP after nonoccupational exposure presents new opportunities to acutely limit HIV transmission but has also raised complex public health concerns.

CONCLUSIONS

In less than 15 years, the AIDS epidemic has moved from a poorly understood terror to the elucidation of the pathogenic virus, HIV, to the development of highly effective antiretroviral therapy. However, none of the medications currently in use can be construed to be a cure. The advances in newer diagnostic methodologies to measure the plasma viral burden have enabled laboratory scientists to better understand the immunopathogenesis of HIV infection and have enabled clinicians to more readily assess the efficacy of antiretroviral therapy. The combination of better clinical monitoring and more effective antiretroviral therapeutic regimens has led to an appreciable decrease in HIV-associated morbidity and

mortality. However, the era of this "new paradigm" is just beginning, and the emergence of strains that are resistant to current complex and oftentimes cumbersome regimens underscores the need to continue research toward the development of more highly effective and simpler means of antiretroviral chemotherapy that can result in long-lasting HIV suppression, if not eradication.

Other promising approaches for attacking HIV include defining new targets for antiviral activity, such as the HIV integrase enzyme, the development of gene therapy, immune reconstitution, and nucleic acid–based therapeutic vaccines. Over the next year, half a dozen new drugs that will be effective against HIV are likely to be approved; these include highly active nucleoside RTIs (e.g., abacavir), nucleotide RTIs (e.g., adefovir), and protease inhibitors (e.g., amprenavir). However, most of these drugs represent modifications of the two major targets of the current antiretroviral therapy. Some of these newer regimens may be more efficacious and may offer greater simplicity for HIV-infected individuals, thereby enhancing adherence to chronic regimens. However, it must be anticipated that the majority of individuals currently on highly effective antiretroviral therapy, using what is currently available and in the pipeline will need to take multiple medications several times a day over the long term. The challenge to clinical researchers and care providers is to develop systems of treatment and behavioral reinforcement that will enable patients to remain adherent to these complex regimens, while continuing to seek definitive cures.

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Pharmacokinetics of Protease Inhibitors and Drug Interactions with Psychoactive Drugs

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INTRODUCTION

Polypharmacy is common in the treatment of HIV infection, with numerous drug classes being used concurrently (McDonald & Kuritzkes, 1997). The medication list of a typical HIV patient may include antiretrovirals for HIV infection; antimicrobials, antifungals, and antivirals for prophylaxis or treatment of opportunistic infections; antidepressants, antipsychotics, anxiolytics, or sedative-hypnotics for psychiatric disorders or drug dependence; and a variety of other agents for other manifestations of AIDS (e.g., peripheral neuropathy, cytopenia, wasting, neoplastic process) or for the adverse effects associated with antiretroviral agents (e.g., diarrhea, peripheral neuropathy). With polypharmacy comes the potential for drug interactions.

In a report based on a chart review, the hypothetical probabilities of one or more drug interactions were 3 1 %, 42%, and 77%, respectively, if these patients had been started on indinavir, saquinavir, or ritonavir (Van Cleef, Fisher, & Polk, 1997). These estimated percentages were even higher for patients with CDr counts < 100 cells/μL due to the increased usage of drugs for prophylaxis against opportunistic infections. Another chart review revealed that patients who are initiated on protease inhibitor therapy have a high likelihood of concurrently receiving an agent with a potentially serious drug interaction (Preston *et al.,* 1997). Prescribers

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recognized only a minority (31%) of potential adverse drug interactions at the time of protease inhibitor initiation. Screening and appropriately managing drug interactions has been suggested as an effective method to reduce the incidence of serious drug interactions with indinavir (Everson, Weidle, Perdue, & Bozek, 1997).

Substantial literature is available on drug interactions involving antiinfective agents (i.e., antimicrobials, antifungals, and antivirals) and psychoactive agents (i.e. antidepressants, antipsychotics, and anxiolytics) with other agents (Carson, 1996; Ereshefsky, 1996; Gillium, Israel, & Polk, 1993; Harvey & Preskorn, 1996a, 1996b; Lopes, 1995; Shader *et al.,* 1996). However, the literature examining drug interactions with antiretrovirals is sparse and limited to abstracts in the majority of cases (Shader & Greenblatt, 1996a). At the 1997 conference on Retroviruses and Opportunistic Infections, Jerry Collins of the FDA pointed out that the compilation of laboratory findings and *in vivo* interaction data produces a "drug label which is highly informative for prescribers and patients, but very challenging for practical use"(Collins, 1997, p. 221).

The goal of this chapter is to review the pharmacokinetics of the protease inhibitors and examine drug interactions between protease inhibitors and psychoactive agents. The cytochrome P450 system and its role in drug interactions will be reviewed using examples involving other classes of drugs interacting with protease inhibitors and psychoactive agents.

PROTEASE INHIBITORS

General

The HIV life cycle starts with virions infecting lymphocyte cells and is propagated by the production and release of infectious virion to infect other lymphocytes. Protease inhibitors work by inhibiting the HIV protease enzyme responsible for transforming immature HIV virion to infectious virion. By interfering at this step, protease inhibitors interupt or dramatically slow the cycle and are the most potent weapon in our drug armamentarium against HIV infection. Protease inhibitors can dramatically reduce HIV viral load and when used in combination with reverse transcriptase inhibitors they delay disease progression (Barry, Gibbons, Back, & Mulcahy, 1997; Carpenter *et al.,* 1997; Deeks, Smith, Holodniy, & Kahn, 1997). There are four protease inhibitors currently FDA approved for the treatment of HIV infection (Kakuda, Struble, & Piscitelli, 1998). These agents, saquinavir (Invirase® and Fortovase®—Roche Pharmaceuticals Inc.), ritonavir (Norvir®—Abbott Laboratories), indinavir (Crixivan®—Merck), and nelfinavir (Viracept®—Agouron Pharmaceuticals), have become available only during the past 3 years. Because of the accelerated approval process, data continue to be published regarding their efficacy, adverse effects (e.g., hypoglycemia, diabetes, hypoprothrombinemia), pharmacokinetics, and drug interaction potential. For

example, the product monograph of ritonavir has been updated since its initial release in February 1996 because additional information became available including data regarding drug interactions. In addition, the manufacturer has alerted prescribers of these potential interactions.

Pharmacokinetics

A description of common pharmacokinetic parameters and their mean values for oral protease inhibitors are summarized in Figure 1 and Table 1, respectively. The original formulation of saquinavir, a hard gel capsule (HGC), has an average bioavailability of 4%. Even with the substantial increase in absorption observed when taken with food, saquinavir has the poorest bioavailability of the protease inhibitors. Incomplete absorption and extensive first-pass metabolism account for saquinavir's poor bioavailability (Fitzsimmons & Collins, 1997). To overcome this problem, saquinavir was reformulated as a soft gel capsule (SGC) resulting in a threefold increase in bioavailability.

Similar to saquinavir, the bioavailability of ritonavir and nelfinavir is increased when administered with meals. The bioavailability of ritonavir is increased by 15% when ingested with food. Nelfinavir should be taken with meals since area-under-the-concentration curve (AUC) is increased by two- to threefold compared to administration in the fasting state. Indinavir absorption is also affected by food; however, a standard meal results in a 70% to 80% reduction in AUC of indinavir. Indinavir should be taken on an empty stomach or with a low-fat light meal (e.g., dry toast with jam, cereal with skimmed milk, coffee, tea, fruit juice).

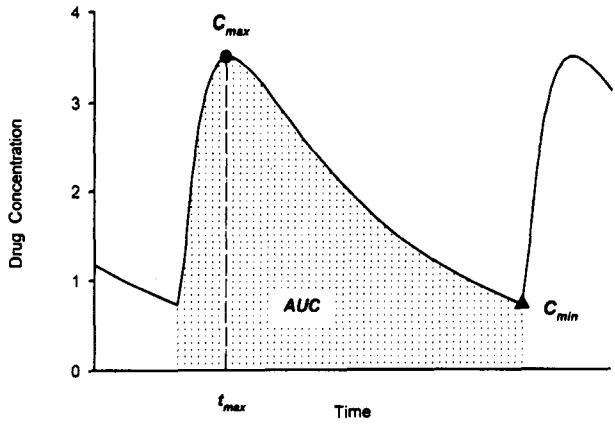

Figure 1. Concentration-time profile of an oral drug and common pharmacokinetic parameters. [C_{max} = maximum drug concentration; t_{max} = time to achieve C_{max}; C_{min} = minimum drug concentration; AUC = area-under-the-curve (illustrated by the dotted area underneath the solid concentration-time curve).]

Table 1. Pharmacokinetic Parameters of Protease Inhibitors

Drug	Indinavir	Nelfinavir	Ritonavir	Saquinavir SGC	Saquinavir HGC
Brand name (manufacturer)	Crixivan (Merck)	Viracept (Agouron)	Norvir (Abbott)	Invirase (Roche)	Fortovase (Roche)
F (%)	60	17-47	> 60	4	~12
C_{max} (mg/L)	3–8	3-4	11.2 ± 3.6	253.3[a]	2477[a]
C_{min} (mg/L)	0.15	1–3	3.7 ± 2.6	0.04[a]	N/A
t_{max} (hours)	0.8 ± 0.3	2-4	2 fasting 4 non-fasting	2.4 fasting 3.8 non-fasting	N/A
Protein binding (%)	60	> 98	98–99	97	97
AUC (mg*h/L)	15-45	22	129 ± 47.1 capsule 129 ± 39.3 solution	866[a]	7249[a]
$t_{1/2}$ (hours)	1.8 ± 0.4	3.5–5	3–5	12	12
CL/F (L/h)	6–14	40	4.6 ± 1.6 single dose 8.8 ± 3.2 steady state	80	80
CL_R (% of total CL)	10–15	1–2	1–2	1	1

Abbreviations: SGC = soft gel capsule; HGC = hard gel capsule; F = bioavailability; C_{max} = maximum (peak) concentration; C_{min} = minimum (trough) concentration; tmax = time to C_{max}; AUC = area-under-the-curve; $t_{1/2}$ = elimination half-life; CL/F = total body clearance; CL_R = renal clearance.

[a] = values of C_{max} and AUC for saquinavir are in units of ng/ml and ng*hr/ml, respectively.

References: Lea & Faulds, 1996; Perry & Benfield, 1997; saquinavir, ritonavir, nelfinavir, and indinavir product monographs; personal communication with Merck & Co. and Roche Pharmaceuticals.

Ritonavir is the only protease inhibitor available as a solution and requires refrigeration. The pharmacokinetics of the oral solution is similar to the capsules. However, it should be noted that the oral solution contains 43% ethanol and the capsules contain only a limited quantity.

Nelfinavir is available as a powder for oral suspension and can be mixed with water, milk, pudding, ice cream, or formula for up to 6 hr before drug administration. However, the powder should not be mixed with acidic food or juices because of resulting poor taste.

The protease inhibitors are highly protein bound (≥97%) except for indinavir (Table 1). All protease inhibitors are metabolized into inactive compounds through the cytochrome P450 system. Less than 5% of unchanged protease inhibitors are found in the urine. Ritonavir has three metabolites; the cytochrome P450 3A (CYP3A) isoform is responsible for the formation of M1 and MI 1; both CYP3A and CYP2D6 are involved with the formation of M2 (Kumar, Rodrigues, Buko, & Denisson, 1996). Six metabolites of indinavir have been identified with the major excretory route through feces (Balani *et al.,* 1996). Saquinavir and nelfinavir are metabolized into numerous inactive compounds.

Intestinal metabolism of indinavir plays a minor role in the first-pass metabolism (Chiba *et al.,* 1996; Chiba *et al.,* 1997), but gut metabolism may be contrib-

utory for those protease inhibitors that are 3A substrates. Data on the importance of intestinal metabolism are not available for the other protease inhibitors. The AUC of indinavir is 60% higher in patients with mild to moderate hepatic insufficiency and a dosing reduction from 800 mg to 600 mg three time daily is recommended. Preliminary data also suggest that the AUC for ritonavir is increased by 40% (range: 17% to 66%) in HIV-infected patients with underlying liver disease (Hsu, Cameron, *et al.,* 1998). Dosing adjustments in hepatic insufficiency have not been recommended for the other protease inhibitors.

Protease inhibitors were developed to be used in combination with reverse transcriptase inhibitors. More recently, protease inhibitors are now being combined for dual therapy of HIV infection (Carpenter *et al.,* 1997; Kakuda *et al.,* 1998). This combination takes advantage of the pharmacokinetic drug interactions (Kempf *et al.,* 1996). When protease inhibitors are used in combination, the hepatic or gastrointestinal clearance of one or both agents is decreased resulting in significant increases in peak blood concentrations (C_{max}) and AUC. All possible two-drug combinations of the four protease inhibitors (indinavir, nelfinavir, ritonavir, and saquinavir HGC) have been studied. Co-administration of saquinavir HGC (600 mg t.i.d.) and ritonavir (300 mg b.i.d.) results in a 30-fold increase in C_{max} and 58-fold increase in AUC for saquinavir (Hsu, Granneman, Cao, *et al.,* 1998; Merry, Barry, *et al.,* 1997). Indinavir co-administration with saquinavir HGC results in a 5- to 8-fold increase in saquinavir C_{max} (McCrea *et al.,* 1996; McCrea *et al.,* 1997). Ritonavir with nelfinavir resulted in a 1000% increase in nelfinavir AUC (Kempf *et al.,* 1997). When indinavir and nelfinavir are combined, the AUC of nelfinavir increases from 32.3 to 59.4 μg*h/mL and the AUC of indinavir increases modestly from 17.9 to 27.0 μg*h/mL (Yuen, Anderson, Daniels, & Kerr, 1997). Nelfinavir increases saquinavir SGC concentrations 4- to 5-fold (Kravcik *et al.,* 1997). Based on a pharmacokinetic study, combining indinavir and ritonavir could allow less frequent dosing of indinavir (b.i.d. instead of t.i.d.) and result in comparable indinavir AUC, higher trough concentration (C_{min}), and lower C_{max} (Hsu, Granneman, Japour, *et al.,* 1997).

Nelfinavir and ritonavir have been studied with the new formulation of saquinavir (SGC). Nelfinavir AUC increased 18%; the increase in saquinavir AUC was substantial at 392%. Ritonavir AUC did not change significantly; saquinavir (400 mg b.i.d.) AUC increased 121% compared to the AUC of saquinavir SGC when given alone (Fortovase® monograph, 1997).

CYTOCHROME P450 SYSTEM

Drug interactions can be classified as pharmacokinetic or pharmacodynamic in nature. Alteration of the absorption, distribution, metabolism, or excretion of one drug by another drug is termed a pharmacokinetic interaction. Pharmacodynamic interactions involve one drug altering the pharmacologic effect of another

drug. For the purposes of this chapter, the focus will be on pharmacokinetic interactions, more specifically those interactions relating to changes in metabolism. Thus, interactions involving interference with absorption, changes in protein binding, or altered renal excretion will not be covered. Before discussing the *in vitro* and *in vivo* data on drug interactions involving protease inhibitors and psychoactive agents, it is important to have a good understanding of the cytochrome P450 system responsible for metabolizing many of these agents.

Drugs are metabolized in the liver into polar, water-soluble metabolites to allow excretion via the kidney or through the biliary system. Drug-metabolizing enzymes are divided into two types: phase I (functional activation processes) and phase II (conjugation reactions). Phase I reactions include dehydrogenation-hydrogenation, hydrolysis (e.g., esterases), reduction (e.g., alcohol dehydrogenase), mono-oxygenation, and oxidation (e.g., xanthine oxidase, monoamine oxidase, and cytochrome P450). Phase II reactions include conjugation (e.g., glucuronide, sulfate, glutathione), acetylation, methylation, and GSH-conjugation. The cytochrome P450 system is responsible for the oxidation of many drugs and endogenous compounds.

Cytochrome P450 is a superfamily of enzymes divided into families (designated by CYP followed by a number, e.g., CYP2), subfamilies (designated by a capital letter, e.g., CYP2C), and individual members (designated by a number, e.g., CYP2C19) based on amino acid sequence homology. Families are at least 40% related based on amino acid sequences and 55% related for subfamilies.

Shimada and colleagues (1 994) evaluated the cytochrome isoform content of human livers. CYP3A4 was found to be the major CYP isoform accounting for 28% of total hepatic CYP enzymes. The other isoforms account for the following percentages of hepatic CYP enzyme: CYP2C = 18%, CYPIA = 13%, CYP2E1 = 7%, CYP2A6 = 4%, and CYP2D6 = 2%. The proportion of drugs metabolized by the major isoforms is about 55% for CYP3A4, 25% for CYP2D6, 20% for CYP2C, and less than 10% for CYP2E1 and CYPlA (Figure 2). Substrates of the various CYP isoforms are found in Table 2.

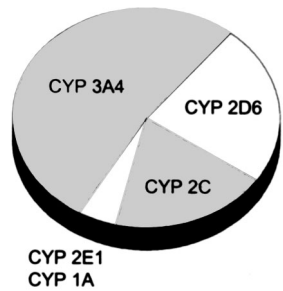

Figure 2. Proportion of drugs metabolized by the major CYP isoforms. Adapted from Benet, L. Z., Kroetz, D. L., & Sheiner, L. B. (1 996). Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination. In J. G. Hardman, L. E. Limbrid, R B. Molinoff, R. W. Ruddon, &A. C. Gilman (Eds.), *Goodman & Gilman 's The Pharmacological Basis of Therapeutics* (9th ed.). New York: McCraw-Hill.

Table 2. CYP Substrates, Inhibitors, and Inducers

Isofon	Protease inhibitors	Psychoactive agents		Other substrates	Inhibitors	Inducers
CYP1A1/2	—	Clomipramine Clozapine Fluvoxamine	Imipramine Mirtazapine Zolpidem	Acetaminophen Caffeine Theophylline	Fluvoxamine	Ritonavir
CYP2C9	—	Fluoxetine Sertraline		Ibuprofen Naproxen Phenytoin Tolbutamide Warfarin	Ritonavir Saquinavir Fluvoxamine	—
CYP2C19	Ritonavir	Amitriptyline Clomipramine Citalopram	Diazepam Imipramine	Omeprazole Propranolol	Fluvoxamine Omeprazole Ritonavir	—
CYP2D6	Indinavir Nelfinavir Ritonavir	Amitriptyline Bupropion Clomipramine Clozapine Chlorpromazine Desipramine Fluvoxamine Haloperidol Imipramine Maprotiline	Mirtazapine Nortriptyline Olanzapine Paroxetine Perphenazine Resiperidone Sertindole Thioridazine Trimipramine Venlafaxine	Amphetamines Codeine Encainide Flecainide Metoprolol MDMA (Ecstasy) Ondansetron Propafenone Propranolol Timolol	Cocaine Fluoxetine Methadone Norfluoxetine Paroxetine Perphenazine Quinidine Ritonavir Sertindole Sertraline	—
CYP2E1	—	—		Acetaminophen Ethanol	—	Ethanol Isoniazid

(continued)

Table 2. *(Continued)*

Isoform	Protease Inhibitors	Psychoactive agents		Other substrates		Inhibitors	Inducers
CYP3A	Indinavir	Alprazolam	Diazepam	Acetaminophen	Itraconazole	Fluvoxamine	Barbiturates
	Nelfinavir	Amitriptyline	Imipramine	Alfentanil	Ketoconazole	Indinavir	Dexamethasone
	Ritonavir	Buspirone	Midazolam	Amiodarone	Lidocaine	Itraconazole	Rifabutin
	Saquinavir	Carbamazepine	Nefazodone	Astemizole	Loratadine	Ketoconazole	Rifampin
		Citalopram	Pimozide	Cisapride	Losartan	Macrolides	
		Clomipramine	Trazodone	Clarithromycin	Lovastatin	Nefazodone	
		Clonazepam	Triazolam	Cocaine	Nifedipine	Nelfinavir	
		Clozapine	Zolpidem	Codeine	Nimodipine	Norfluoxetine	
				Corticosteroids	Nisoldipine	Ritonavir	
				Cyclophospharmide	Propafenone	Saquinavir	
				Cyclosporin	Quinidine	Sertinodole	
				Dapsone	Sulfamethoxazole	Thioridazine	
				Dextromethorphan	Sulfentanil		
				Diltiazem	Tamoxifen		
				Dronabinol	Taxol		
				Erythromycin	Terfenadine		
				Estrogen	Verapamil		
				Felodipine	Vinblastine		
				Hydrocodone	Warfarin		

References: Li *et al.,* 1995; Schmider *et al.,* 1996; Shader & Greenblatt, 1996b; Wilkinson, 1996; Ereshefsky, 1996; Ereshefsky, Rieseman, & Lam, 1996: Bertz and Grannman, 1997.

Drug-Metabolizing Cytochrome Isoforms

CYP3A is the major isoform responsible for drug metabolism with CYP3A4 as the dominant CYP3A isoform. CYP3A possesses broad substrate specificity oxidizing diverse compounds. Its binding site is capable of accommodating both small and large molecules with a range of charge and lipophilicity. Biotransformations that have been attributed to CYP3A include hydroxylation, N-dealkylation, aromatization, dehydration, nitroreduction, and N-oxidation. A 10- to 40-fold interindividual variability of CYP3A expression exists.

CYP3A activity can be modulated by inducers and inhibitors. CYP3A are present in the liver, kidney, placenta, intestine, lung, and brain. The duodenum, jejunum, and ileum contain 50%, 30%, and 15% of hepatic CYP3A levels, respectively (deWaziers *et al.,* 1990). Thus, it is not surprising that intestinal CYP3A plays a role in first-pass metabolism, accounting for the low bioavailability of some drugs (e.g., cyclosporin). P-glycoprotein (an exit pump) in intestinal enterocytes may also contribute to the low bioavailability of protease inhibitors.

Although CYP2D6 plays an important role in drug metabolism, it accounts for only 2% of the total hepatic CYP enzymes. CYP2D6 has specific substrate structural requirements: extended hydrophobic region, positively charged basic nitrogen, and the ability to accept hydrogen bonds 5 to 7 Åfrom the nitrogen atom. CYP2D6 activity can be modulated by inducers and inhibitors. A small fraction of the population are very rapid CYP2D6 metabolizers. An inhibitor may convert a genetically extensive metabolizer to a poor metabolizer phenotype. The prevalence of poor metabolizer phenotypes varies by race: 5% to 8% in Caucasians and about 1% in Asians. Adverse reactions are more frequent in poor metabolizers.

CYP2C9 and CYP2C19 are the two important CYP2C isoforms involved in drug metabolism. Genetic polymorphism has been identified with CYP2C 19; 5% of Caucasians and 20% of Asians are poor metabolizers (May, 1994).

In Vitro and *in Vivo* Studies

In vitro studies with human liver slices, liver homogenates, microsomal fractions, or expressed cDNA lines can be used to evaluate which isoforms are responsible for drug metabolism and changes in pharmacokinetic disposition based on inhibition or induction of hepatic metabolism (Moltke, Greenblatt, Schmider, *et al.,* 1998). *In vitro* studies are not without problems (Bertz & Granneman, 1997). Concerns include what drug concentration to study. Should free drug concentrations that account for protein binding be used? Should a liver to plasma concentration ratio to account for hepatic drug concentrations be used? Physiologic pH is used in *in vitro* studies; however, phospholipid content is not considered. *In vitro* studies also overlook the first-pass effect and the role of *p*-glycoprotein transmembrane protein in prehepatic drug clearance.

In vivo studies usually involve healthy volunteers who ingest the drugs of interest for a short time (as monotherapy and in combination) and undergo numerous blood draws to determine pharmacokinetic parameters (e.g., peak and trough concentrations, AUC, elimination half-life, volume of distribution). Any observed differences in the pharmacokinetic parameters are attributed to a drug interaction. When examining the results of an *in vivo* pharmacokinetic study it is important to question whether the study findings can be applied to the clinical setting. Issues of importance include the dosing regimens and duration of dosing. Were single or multiple doses used? Was steady state achieved to mimic chronic dosing? Was the study duration long enough to determine whether accumulation of parent drug or metabolite would occur? If the metabolite is active, then were metabolite concentrations measured? Was the dosing regimen similar to that used in clinical practice?

DRUG INTERACTIONS

Pros and Cons

Specific isoform activity may be reduced either genetically (i.e., poor metabolizer phenotype) or by exogenous factors such as enzyme inhibition by a coadministered drug. Supratherapeutic drug concentrations due to enzyme inhibition can result in an exaggerated clinical response, toxicity, or both. Subtherapeutic drug concentrations due to enzyme induction can result in loss of efficacy, the development of resistance, or both. To highlight these implications, examples of drug interactions involving protease inhibitors are described in the following sections.

Guibert and colleagues studied the effect of protease inhibitors on methadone metabolism using healthy human liver microsomes (Guibert, Furlan, Martino, & Taburet, 1997). Ritonavir caused a twofold increase in methadone AUC, indinavir a 30% increase, and saquinavir had no effect on methadone metabolism. Based on this *in vitro* study, it is theoretically possible that patients initiated on ritonavir or indinavir while receiving maintenance methadone therapy would require close monitoring of methadone plasma concentrations to avoid excessive sedation and possible respiratory depression with usual therapeutic doses of methadone. However, because neither the inhibition constant (k_i) value nor the inhibitor concentration (IC_{50}) is established for this inhibitor–substrate interaction, such a conclusion remains speculative.

In contrast to the *in vitro* data just mentioned, a human volunteer *in vivo* study has suggested that the net effect of ritonavir on methadone disposition is because of induction rather than inhibition (Hsu, Granneman, Carothers, *et al.,* 1998). The dose-normalized C_{max} and AUC for methadone after a single 5-mg dose were decreased by 36.3% and 37.8%, respectively, after 10 days of ritonavir dosing compared to no ritonavir administration. The authors advise clinicians to exercise caution in the prediction of drug interactions from *in vitro* data only.

Concurrent therapy with ritonavir and clarithromycin is a common practice since clarithromycin has become the preferred agent for *Mycobacterium avium* complex prophylaxis. However, when co-administered, the C_{max} and AUC of ritonavir are increased by 12%–15% whereas the C_{max} and AUC of clarithromycin are increased by 77% and 31%, respectively (Ouellet *et al.,* 1996). However, the 14-hydroxy metabolite of clarithromycin is dramatically decreased to undetectable concentrations. This metabolite is responsible for anti-infective activity of clarithromycin against bacterial pathogens, specifically *Hemophilus influenzae* (Hardy *et al.,* 1990). Again, the potential clinical implications are that patients given clarithromycin for respiratory tract infections are likely to fail due to inadequate concentrations of the active metabolite (Piscitelli *et al.,* 1996), but this concern remains theoretical in the absence of data. In this example, the effect of the drug interaction on the AUC of the metabolite may be more important than the changes in AUC of the substrate (i.e., clarithromycin) or inhibitor (i.e., ritonavir).

Drug interactions may have beneficial effects by inhibiting first-pass metabolism to improve bioavailability, reducing clearance to allow less frequent drug administration, increasing active metabolite concentration, and displacing highly protein-bound drugs from plasma protein-binding sites (Flexner, 1996, 1997). Examples of these beneficial effects include combination protease inhibitor therapy such as ritonavir plus saquinavir. These examples were described in more detail earlier in the pharmacokinetics section.

Thought Process in Identifying Potential Drug Interactions

The list of psychoactive agents that may be prescribed for HIV patients is extensive (Anonymous, 1997a). In one university HIV clinic, 33% of patients were prescribed at least one psychotropic drug (McDonald & Gerber, 1997). The likelihood of drug interactions can be predicted with knowledge of the metabolic disposition (i.e., contribution of hepatic clearance to total clearance, cytochrome isoforms involved, and dominant isoforms) and the inhibiting-inducing ability and potency of the drugs of interest. The reader is referred to a review of psychoactive drug metabolism for a more thorough discussion of the different classes (Harvey & Preskorn, 1996a, 1996b; Ketter, 1995; Moltke, Greenblatt, Hanrmatz, & Shader, 1996).

There are four important steps in the process for identifying potential drug interactions. The first step requires collecting data on metabolic disposition of drugs. This information is summarized in Tables 2,3, and 4 for the psychoactive agents and protease inhibitors, respectively. The protease inhibitors differ based on which cytochrome isoform is used for clearance and in their potency of enzyme inhibition. CYP3A is involved in the elimination of all the protease inhibitors and is the major elimination pathway for indinavir, ritonavir, and saquinavir. CYP3A inducers will potentially increase the metabolism of all the protease inhibitors. This has been documented with the CYP3A inducer rifampin; saquinavir and nelfinavir AUCs decreased by 80% and ritonavir AUC decreased by 35% when co-

Table 3. Metabolic Disposition of Protease Inhibitors

Drug	Hepaticclearance (%)	Metabolicdisposition (% oftotal clearance)	CYP inhibited	CYP induced
Indinavir	>80	CYP3A (major) > 2D6 (minor), GT	CYP3A4	—
Nelfinavir	>90	CYP3A4 (52%) > 2Cl9,2D6 possibly 2C92E1	CYP3A4 2C19,2D6, IA2-weak+	unknown
Ritonavir	>90	CYP3A (major) > 2D6 (minor)	CYP3A4-potent CYP2C9/19 CYP2D6	CYP1A2
Saquinavir	>90	CYP3A (major)	CYP3A4 CYP2C9-weak[a]	—

+Nelfinavir is a weak inhibitor of CYP2C19, 2D6, and 1A2 with Ki values 10- to 40-fold higher than average maximal nelfinavir mesylate plasma levels of 5 μM (Lee *et al.*. 1997).
[a]Saquinavir is a weak inhibitor of CYP2C9 at high concentrations (Eagling *et al.,* 1997).
References: Hsu, Granneman, Cao, *et al.,* 1998; Kumar *et al.,* 1996; Bertz & Granneman, 1997; Eagling *et al.,* 1997; Kerr, Yuen, *et al.*. 1997; Lee *et al.,* 1997; Perry & Benfield, 1997; Moltke, Greenblatt, & Grassi, 1998.

administered with rifampin (Centers for Disease Control [CDC], 1996; Kerr, Lee, Yeun, *et al.,* 1997a; Kerry, Yuen, Daniels, *et al.,* 1997; Crixivan®, Fortovase®, Invirase®, Norvir®, Viracept® monographs).

In general, CYP3A and CYP2D6 substrate metabolism are likely to be affected by ritonavir, and CYP2C9/10/19 to a lesser extent, due to ritonavir's inhibition of these elimination pathways (Kumar *et al.,* 1996). The other protease inhibitors also inhibit CYP3A but to a lesser extent. The order of rank potency against CYP3A4 is ritonavir > indinavir > saquinavir based on inhibition of

Table 4. Documented Protease Inhibitor–Psychoactive Agent Interactions

Drug and dosage regimen (reference)	Protease inhibitor dosage regimen	No. of subjects	Drug affected AUC %	Drug affected C_{max} %
Desipramine 100-mg single dose (Bertz *et al.,* 1996)	Ritonavir 500-mg Q12H	14	Desipramine— 145% increase Metabolite— 15% decrease	Desipramine— 22% increase Metabolite— 67% decrease
Fluoxetine 30 mg Q12H x 8 days (Ritonavir product monograph)	Ritonavir 600-mg single dose	16	Ritonavir Increase 19%	Ritonavir No change
Alprazolam 1-mg single dose (Frye *et al.,* 1997)	Ritonavir 500-mg Q12H	12	Alprazolam Decrease 12%[a]	Alprazolam Decrease 15%[a]

[a]Unexpected result discussed in the text.
Also review the *in vitro* results of Moltke, Greenblatt, Grassi, *et al.,* 1998 for further information regarding triazolam and desipramine.

testosterone 6β-hydroxylation (Ki of 0.019 ± 0.004 μM, 0.17 ± 0.1 μM, 2.99 ± 0.87 μM,respectively) (Eagling, Back, & Berry, 1997). Nelfinavir CYP3A4 inhibition is less potent than ritonavir and indinavir (Lee *et al.,* 1997). Nelfinavir and saquinavir have the ability to inhibit other CYP isoforms *in vitro;* however, high concentrations which are not clinically achievable with current doses are needed to exert an inhibitory effect (Moltke, Greenblatt, Grassi, *et al.,* 1998).

Ritonavir is an inducer of CYP1A2 and glucuronosyl transferases. When ritonavir is co-administered with a substrate using either of these elimination pathways a decrease in substrate AUC may be observed if these pathways account for a large part of the substrates' elimination. The theophylline–ritonavir interaction is an example of CYP11A2 induction by ritonavir (Hsu, Granneman, Witt, Cavanaugh, & Leonard, 1996).

The majority of the data in Table 5 originates from a database compiled by Bertz and Granneman (1 997) or directly from pharmaceutical companies. These data assist in the semiquantitative prediction of the magnitude of potential drug interactions. An important caveat about any database of this kind is that for many drugs the CYP isoform involved in the metabolism has not been identified and substantial uncertainty exists with the current knowledge base (Bertz & Granneman, 1997). For newer agents, this information may be obtained from the medical information department of the pharmaceutical company. Another recent resource is a web site (www.healthcg.com/hiv) which provides an interactive online program offering immediate feedback on drug–drug and drug–food interactions.

The second step involves using the metabolic disposition data to predict changes in substrate metabolism, specifically, what happens to drug exposure (AUC) and clearance. Factors that play an important role in determining the magnitude of changes in substrate metabolism include single or multiple substrate elimination pathways, existence of dominant elimination isoforms, and the inhibition-induction potency. In addition, some substrates are also inhibitors or inducers of the elimination pathway that is affected. This may magnify or diminish the expected effect of an inhibitor or inducer. Another consideration is whether the alternative elimination pathways for the substrate are affected by the inhibitor or inducer. Simultaneous therapy with both inducers and inhibitors of CYP isoforms may have unpredictable effects. There are no dosage guidelines that address these competing effects. It is suggested that close monitoring for toxicity or alternative agents that do not interact be used.

Clinical Consequences and Significance of Potential Drug Interactions

The third step is predicting the clinical consequences or pharmacodynamic effects of the changes in substrate metabolism, specifically, determining the result of changes in drug clearance and AUC. Supratherapeutic drug concentrations can result in an exaggerated clinical response, toxicity, or both; subtherapeutic drug concentrations can result in loss of efficacy, the development of resistance, or both.

Table 5. Metabolic Pathways for Psychoactive Agents

Drug (brand name)	Hepatic clearance (%)	Partition of metabolism by enzyme (% of total clearance)	Active metabolite [route of elimination]	CYP inhibited
Tricyclic antidepressants				
Amitriptyline (Elavil/Endep)	>90	CYP2D6, 2C19, 3A > GT	Nortriptyline [CYP2D6]	—
Clomipramine (Anafranil)	>90	CYP2D6, 1A2, 2C19, 3A	Desmethyl [CYP2D6y]	—
Desipramine (Norpramin)	>90	CYP2D6 (~85-90) >> GT, sulfitase	—	—
Doxepin (Sinaquan)	>90	CYP?	?	—
Imipramine (Tofranil)	>90	CYP2D6, 1A2, 2C19, 3A>GT	Desipramine [CYP2D6]	—
Nortriptyline (Pamelor/ Aventyl)	>90	CYP2D6 (>50)	—	—
Trimipramine (Surmontil)	>90	CYP2D6, CYP(?)	—	—
SSRI				
Fluoxetine (Prozac)	≥90	CYP2C9	Nortluoxetine [CYP2DY6, renal]	2D6 (potent), 3A (norf), 2C19?; norfluoxetine: 3A4,2D6,2C9/19
Fluvoxamine (Luvox)	>90	CYP2D6 > 1A2 >> NAT 2D6	—	1A2 (potent), 3A (mod), 2C9/19, (weak)
Paroxetine (Paxil)	>90	CYP2D6 (≥80)> COMT (minor)	—	2D6 (?fluoxetine), 2C19?
Sertraline (Zoloft)	>90	CYP2C9>CYP3A>others	Desmethyl metabolite	2D6 (weak), 2C19
Miscellaneous antidepressants				
Bupropion (Wellbutrin)	>90	CYP2B6	Hydroxyl [GT]	—
Nefazodone (Senone)	>90	CYP3A	Hydroxy, m-CPP [2D6] and triazole-dione	3A
Maprotiline (Ludiomil)	>90	CYP2D6 (−60)> others	Aromatic hydroxyl [GT]	—
Mirtazapine (Remeron)	25	CYP2D6, 1A2,3A	Uncongugated metabolites [?I	—
Trazodone (Desyrel)	>90	CYP3A	m-CPP [2D6]	—
Venlafaxine (Effexor)	>90	CYP2D6 (55-60) > others	O-desmethyl or ODV [GT, renal]	2D6 (weak)

Mood stabilizer				
Carbamazepine (Tegretol)	>90	CYP3A (primary) > 2C819 (minor)	10,11-epoxide [epoxide hydroxylase]	—
Lithium (Lithobid/Eskalith CR)	0	None	—	—
Valproic acid (Depakene/ Depakote)	>90	GT (560) > Poxidase (≤45) > CYP?	Unclear	—
Neuroleptics/antipsychotics				
Chlorpromazine (Thorazine)	>90	CYP2D6, 1A2?, GT	7-OH-CPZ [GT + others]	—
Clozapine (Clozaril)	>90	CYPlA2 (prim) >> GT,2D6,3A	Norclozapine [renal, GT]	—
Fluphenazine (Prolixin)	n/a	N/A	N/A	—
Haloperidol (Haldol)	>90	Ketonereductase,2D6>3A >>GT	Reduced haloperidol	—
Loxapine (Loxitane)	n/a	N/A 800-272-5525	8-hydroxy [?]	—
Mesoridazine (Serentil)	n/a	N/A	N/A	—
Molindone (Moban)	n/a	N/A	Yes [?]	—
Perphenazine (Trilafon)	high	CYP2D6 (60–70)> others	N/A	2D6
Pimozide (Orap)	>90	CYP3A (primary) + others	Yes [?]	—
Quetiapine (Seroquel)	30	CYP3A4	—	—
Risperidone (Risperdal)	>90	CYP2D6 (>80) > 3A? (minor)	9-hydroxy [renal]	—
Sertindole (Serlect)	>90	CYP2D6,3A	N/A	2D6,3A (weak)
Thiothixene (Navane)	n/a	N/A	N/A	—
Trifluoperazine (Stelazine)	high	N/A	N/A	—
Thioridazine (Mellaril)	>90	CYP2D6 (75) > 2C19?	Mesoridazine [CYP?], sulforidazine [CUP?]	2D6

(continued)

Table 5. *(Continued)*

Drug (brand name)	Hepatic clearance (%)	Partition of metabolism by enzyme (% of total clearance)	Active metabolite [route of elimination]	CYP inhibited
Benzodiazepines				
Alprazolam (Xanax)	≤90	CYP3A (primary)	—	—
Chlordiazepoxide (Librium)	99	N/A	—	—
Clonazepam (Klonopin)	>90	Nitroreductase (CYP3A?)	—	—
Clorazepate (Tanxene)	>90	Acid hydolysis in GIT	Desmethyldiazepam [3A, 2C 19], oxazepam [GT]	—
Diazepam (Valium)	>90	CYP3A > 2C9	Nordiazepam [3A], oxazepam & temazepam [GT]	—
Flurazepam (Dalmane)	>90	CUP (?)	Desalkyl [CUP?], N-a-hydroxyethyl [GT]	—
Lorazepam (Ativan)	>90	GT (primary)	—	—
Midazolam (Versed)	>90	CYP3A	α hydroxy [GT]	—
Oxazepam (Serax)	>90	GT (primary)	—	—
Temazepam (Restoril)	>90	GT (90%) > CYP (?)	Oxazepam [GT]	—
Triazolam (Halcion)	>90	(≤90) CYP3A	—	—
Miscellaneous sedative				
Buspirone (Buspar)	>90	CYP3A (primary)	1-PP	—
Chloral hydrate (various)	100	Alcohol dehydrogenase	Trichloroethanol [GT]	—
Olanzapine (Zyprex)	<50	CYP1A2, 2D6	—	—
Zolpidem (Ambien)	>90	CYP3A (primary) > 1A2, 2D6	—	—

References: Anderson *et al.,* 1994; Shader & Greenblatt, 1996b; Bertz & Granneman, 1997.

The fourth step is determining the clinical significance of the potential drug interaction. For inhibition, the clinical consequence may be amplification of known adverse effects (e.g., diarrhea with ritonavir) or the occurrence of a concentration-related toxicity (e.g., sedation with benzodiazepines). The therapeutic index, type of concentration-dependent toxicity, and the dosage that the patient is receiving when the enzyme inhibitor is added to the treatment regimen are all important considerations (Preskorn, 1997). With this knowledge, one can decide whether the drug interaction makes co-administration potentially hazardous. For induction, a hypothetical clinical consequence may be loss of metabolite antibacterial activity or possible development of protease inhibitor resistance (e.g., protease inhibitor–rifampininteraction). In both of these examples, co-administration would not be advisable. Alternatively, these interactions may be overcome with higher doses. However, higher doses have not been studied in most cases and unless recommended in the product monograph this is not advisable. Van Cleef and colleagues noted that dosage adjustment recommendations are based on mean changes in substrate clearance and in most *in vivo* drug interaction trial doses utilized were less than currently recommended (van Cleef *et al.,* 1997). They conclude that it is unknown whether product monograph dosage adjustment recommendations will result in safe and therapeutic substrate concentrations.

Predicted Drug Interactions

The first example using the thought process to predict drug interactions will deal with CYP2C19 substrates (Table 2). CYP2C19 in conjunction with other CYP isoforms is responsible for the metabolism of amitriptyline (CYP2D6, CYP3A), clomipramine (CYP2D6, CYP1 A), and imipramine (CYP2D6, CYP 1 A). Diazepam deserves consideration here. Although 2C 19 is important to diazepam metabolism at very low drug concentrations, 3A isoforms are predominantly important at most clinical dosage regimens (Anderson, Miners, Veronese, & Birkett, 1994; Schmider, Greenblatt, von Moltke, & Shader, 1996). This is based on the metabolic disposition database (Table 5). Ritonavir is an inhibitor of CYP2C 19, CYP2D6, and CYP3A (Tables 2 and 3). Co-administration of ritonavir and any one of these agents represents combining a multi-CYP inhibitor (i.e., ritonavir) with a substrate with multiple CYP elimination pathways. Theoretically, the majority of substrate elimination pathways will be inhibited resulting in decreased substrate clearance and an increase in substrate AUC. These changes in substrate metabolism would be expected to be associated with substrate toxicity. The clinical consequences of the ritonavir–diazepam interaction for some patients may be excessive sedation and possible respiratory depression. Co-administration is possible with ritonavir and amitriptyline, clomipramine, and imipramine using lower doses and monitoring for adverse effects.

CYP2D6 is responsible for metabolizing numerous substrates. As previously mentioned, in substrates with multiple CYP elimination pathways, co-administra-

tion with ritonavir will result in decreased substrate clearance and an increase in substrate AUC. Ritonavir-bupropion co-administration is contraindicated in the ritonavir product monograph. The original hypothesis for understanding this interaction was based on the presumption that bupropion is a CYP2D6 substrate. Recent package inserts have suggested, based on data known to the manufacturer, that bupropion is actually a CYP2B6 substrate. Further work will be needed to clarify this putative interaction.

CYP3A is the major isoform involved in drug metabolism (Li, Kaminski, & Rasmussen, 1995; Maurel, 1996; Wilkinson, 1996). When co-administered with a CYP3A inhibitor, greater increases in AUC would be predicted to occur with substrates for which CYP3A is the primary elimination pathway (e.g., alprazolam, midazolam, triazolam, buspirone, carbamazepine, zolpidem, trazodone, nefazodone) compared to substrates with multiple CYP elimination pathways of which CYP3A plays only a minor role (e.g., clomipramine, imipramine, mirtazapine). Large and moderate increases in the AUC of substrates might be expected with the former and latter groups of substrates, respectively. Intrinsic clearance for a given drug also plays a role. For example, alprazolam is a low clearance drug and midazolam and triazolam are high clearance drugs. Inhibitory potency also plays a role in determining the magnitude of changes in substrate metabolism. Based on the order of inhibitory potency for the CYP3A isoform, ritonavir > indinavir > nelfinavir ≥ saquinavir, the greatest effect would be expected with ritonavir and the least with saquinavir (Moltke, Greenblatt, Grassi, *et al.,* 1998). Co-administration of ritonavir should be undertaken only with extreme caution with the following drugs due to the seriousness of the possible clinical consequences: pimozide, alprazolam, midazolam, triazolam, diazepam, and zolpidem. Co-administration of these substrates with the other protease inhibitors (indinavir, nelfinavir, and saquinavir) is predicted to result in increases in substrate AUC but to a smaller extent. The product monographs of indinavir and nelfinavir suggest that co-administration with triazolam or midazolam be avoided based on the potential drug interaction and clinical significance. Ritonavir contraindications to CYP3A substrates should apply to the other protease inhibitors based on the clinical significance of potential drug interactions.

The CYP1A in conjunction with other CYP isoforms are responsible for the metabolism of clozapine, fluvoxamine, clomipramine, imipramine, mirtazapine, and zolpidem. Ritonavir is a CYP1A inducer. Theoretically substrate clearance should increase in the presence of an inducer. The expected outcome of substrate-inducer co-administration is altered since ritonavir is a potent inhibitor of the other CYP isoforms (i.e., CYP2C19, CYP2D6, CYP3A) which are also responsible for the metabolism of these particular CYP1A substrates. For all these CYP1A substrates except fluoxetine, a decrease in substrate clearance is expected with ritonavir. Because of the seriousness of the possible clinical consequences of co-administration of ritonavir-clozapine, the manufacturer of ritonavir has suggested that this combination is contraindicated. For the ritonavir-fluvoxamine combina-

tion the effect (primarily 1A2 and 2D6) on substrate metabolism are unknown. Fluvoxamine has multiple CYP elimination pathways; ritonavir inhibits CYP2D6 and induces CYP1 A. However, this situation is further complicated by the fact that fluvoxamine is itself a potent inhibitor of CYP1A2. The overall effect of ritonavir-fluvoxamine co-administration is impossible to predict.

Established Interactions: Psychoactive Agents and Protease Inhibitors

Several authors have summarized the drug interactions seen in patients infected with HIV (Geletko & Dudley, 1995; Heylen & Miller, 1997; Lee & Safrin, 1992; Lopes, 1995; Piscitelli *et al.,* 1996; Sahai, 1996; Tseng & Foisy, 1997). However, drug interactions between protease inhibitors and psychoactive agents are rarely discussed because of the paucity of data (Shader & Greenblatt, 1996a). Table 4 summarizes the existing data, all three interactions involving ritonavir.

Theoretically, even though ritonavir is not as potent an inhibitor of CYP2D6 as quinidine, it may inhibit CYP2D6 and alter the pharmacokinetics of co-administered CYP2D6 substrates (Moltke, Greenblatt, Grassi, *et al.,* 1998). The result of co-administration would be diminished metabolism of CYP2D6 substrates, elevated substrate concentrations, and decreased substrate metabolite concentrations as seen with desipramine. Saquinavir and nelfinavir are weak inhibitors of CYP2D6, thus no effect to very minimal effects would be expected. The ritonavir–desipramine interaction results in a significant increase in the AUC of desipramine, a CYP2D6 substrate. Decreased desipramine dosages with monitoring of desipramine concentrations and adverse events are recommended during the first several weeks when co-administration with ritonavir begins (Bertz & Granneman, 1997).

Ritonavir is itself a CYP2D6 substrate and co-administration with inhibitors of CYP2D6 would result in increased ritonavir concentrations. However, the elevation in ritonavir concentration would not be substantial since ritonavir has an alternative elimination pathway (i.e., CYP2C9/19). The ritonavir–fluoxetine interaction is an example of such a result. These findings are in agreement with *in vitro* studies on ritonavir metabolism (Kumar *et al.,* 1996).

The ritonavir–alprazolam interaction is of interest. When co-administered, the C_{max} and AUC of alprazolam were decreased instead of being increased as might be expected when a CYP3A inhibitor and CYP3A substrate are co-administered (Frye *et al.,* 1997). A prolongation in sedation with no effect on peak sedation was observed. These findings as noted above are best explained by the fact that alprazolam has low hepatic clearance. In addition, some form of induction may occur.

In addition to pharmacokinetic studies, an important source of data is post-marketing experience. The ritonavir product monograph notes that cardiac and neurologic events have been reported in postmarketing experience with nefazadone and fluoxetine. These events with nefazadone might be attributed to accumulation of parent drug (primarily eliminated by CYP3A) and metabolite m-CPP (a

CYP2D6 substrate). However, because mCPP concentrations are quite low, this explanation is unsatisfactory. Similarly, it is tempting to attribute the events with fluoxetine to accumulation of the parent drug and the active metabolite since both are dependent, at least in part, on CYP2D6 for elimination; however, this explanation does not take into account that norfluoxetine is a 3A inhibitor.

A recent case report describes the saquinavir–midazolam interaction (Merry, Mulcahy, Barry, *et al.,* 1997). Without co-administration of saquinavir, a 5-mg midazolam dose was given intravenously and the patient awoke spontaneously and was free of sedation 2 hr later when discharged home. Eight weeks later, after saquinavir therapy was initiated, the same midazolam dose resulted in prolonged sedation lasting greater than 5 hr and requiring intravenous flumazenil. This is another example of co-administration of a CYP3A inhibitor (i.e., saquinavir) and a high clearance CYP3A substrate (i.e., midazolam).

Drugs of Abuse

Literature pertaining to drug interactions involving drugs of abuse is extremely limited. Undoubtedly, the literature will remain limited to case reports due to ethical and legal issues of performing drug interaction studies with illegal substances.

The most noteworthy case report involved ritonavir and ecstasy, an amphetamine derivative also known as MDMA. The death of a British AIDS patient due to an overdose of ecstasy was widely publicized in the HIV-activist press (Anonymous 1997b; Baker & Bowers, 1997; Cox, 1997; Mirken, 1997). Ritonavir inhibits CYP2D6 metabolism of ecstasy resulting in moderately (2- to 3-fold) increased plasma concentrations. A similar interaction would be expected with other amphetamines (CYP2D6 substrate) when taken concurrently with ritonavir (CYP2D6 inhibitor) with increases about the same order of magnitude. Although cocaine (rock or crack) is a CYP3A substrate, 90% of cocaine is metabolized by esterases; thus, no interaction is likely to occur with the protease inhibitors. Dronabinol, a CYP3A substrate, is a capsule formulation of marijuana indicated for HIV-related cachexia. Heroin and codeine are converted to morphine which undergoes glucuronidation and is not metabolized by the cytochrome P450 system. Ritonavir, an inducer of glucuronidation, may decrease the AUC of morphine due to accelerated elimination. A 50% decrease in heroin plasma concentration has been reported when given with ritonavir (Cox, 1997).

Interactions with Other Drugs

Other important protease inhibitor drug interactions involve the nonnucleoside reverse transcriptase inhibitors (NNRTI), azole antifungal agents (e.g., itraconazole, ketoconazole), erythromycin, rifampin, estrogen-based contraceptives, warfarin, and anticonvulsants. These interactions will not be discussed because they are not the focus of this chapter; the reader is referred to the product mono-

graphs and articles on drug interactions in HIV patients (Flexner, 1996; Geletko & Dudley, 1995; Heylen & Miller, 1997; Lee & Safrin, 1992; Lopes, 1995; Piscitelli *et al.,* 1996; Sahai, 1996; Tseng & Foisy, 1997).

STRATEGIES FOR DEALING WITH DRUG INTERACTIONS

Strategies recommended for reducing and managing drug interactions are minimizing the number of drugs prescribed, titrating doses to use the lowest effective dosages, obtaining a careful drug history that might suggest sensitivity for certain drug classes, considering drug interactions when adverse effects occur, and monitoring more closely for adverse effects, using therapeutic drug monitoring when the therapeutic index is narrow (Ereshefsky, 1996; Rosenbaum, 1996). The expert group report on antidepressants and drug-metabolizing enzymes recommended that practice-oriented information about potential drug interactions based on *in vitro* studies be included in product monographs (Meyer *et al.,* 1996).

CURRENT AND FUTURE STUDIES

During the past decade, several useful and promising *in vitro* systems have been developed to predict drug interactions *in vivo* (Moltke, Greenblatt, Schmider, *et al.,* 1998). Studies with human liver microsomes in vitro have been applied to antidepressant and antipsychotic agents to improve our knowledge of their drug metabolism and drug interactions (Greenblatt *et al.,* 1996; Moltke *et al.,* 1994; Moltke, Greenblatt, Court *et al.,* 1995; Moltke, Greenblatt, Schmider *et al.,* 1996; Schmider *et al.,* 1996; Venkatakrishnan *et al.,* 1998). The research on biotransformation is incomplete and more *in vitro* and *in vivo* studies are needed to demonstrate the metabolism of each psychoactive drug in terms of cytochrome enzymes.

The application of *in vitro* metabolic models to antiviral agents such as the protease inhibitors has only recently occurred (Moltke, Greenblatt, Grassi, *et al.,* 1998). Further evaluation of these predictive models and *in vivo* studies of drug interactions of the therapeutic agents used to treat HIV are desperately needed. "Only through additional study and careful observation will the true risk:benefit ratio of these agents become known" (Van Cleef *et al.,* 1997, p. 777).

CONCLUSIONS

HIV-infected patients are burdened with having to take numerous medications for their HIV infection, with potential opportunistic infections, associated psychiatric disorders, and other associated comorbidities. With this needed polypharmacy comes the possibility of drug interactions. Because of their inhibitory effects on the

cytochrome P-450 system, the protease inhibitors are associated with numerous drug interactions. Of the protease inhibitors, ritonavir is the most potent inhibitor of CYP3A, followed by indinavir, nelfinavir, and saquinavir in order of decreasing potency (Moltke, Greenblatt, Grassi, *et al.,* 1998). The inhibitory potency corresponds to the magnitude of change in the substrate C_{max} and AUC. Drug interactions are most notable with ritonavir because, in addition to being a CYP3A inhibitor, it inhibits both CYP2C9/19 and CYP2D6 and induces CYP1A2.

Drug interactions may be beneficial or detrimental. Examples of beneficial interactions include the substantial increase in saquinavir bioavailability when given with ritonavir and the possible decrease in indinavir dosing frequency when coadministered with ritonavir. Detrimental effects may include loss of efficacy, development of resistance, and severe or serious toxicity. Drug interactions that have serious clinical consequences must be thoughtfully considered in the context of risk and benefit. They cannot simply be considered contraindicated when treating a life-threatening disease, when possible alternative agents should be utilized. On the other hand, the majority of drugs may be co-administered with close monitoring and careful dosage titration. In only a handful of cases do sufficient data exist to allow for dosage adjustment recommendations when the drugs are coadministered.

The thought process for identifying potential drug interactions involves four steps that were discussed in detail. This process can predict the changes in substrate metabolism based on the metabolic disposition data. With knowledge of the expected magnitude of change in substrate metabolism and clinical effects associated with supratherapeutic and subtherapeutic substrate concentrations the clinical consequences and significance can be predicted.

In summary, little information is available from peer-reviewed scientific studies about the potential drug interactions associated with protease inhibitors and psychoactive agents. Most of the information appears as warnings in product package inserts of protease inhibitors. Despite this lack of data, the psychoactive agents that must be used with extreme caution with ritonavir based on predicted drug interactions are benzodiazepines, which utilize CYP3A (e.g.. alprazolam, clorazepate, diazepam, midazolam, triazolarn), bupropion, clozapine, pimozide, and zolpidem. Whether these agents are also contraindicated with the other protease inhibitors is unknown. Erring on the cautious side is recommended in these cases because of the associated serious clinical consequences. The product monographs for indinavir and nelfinavir list midazolam and triazolam as contraindicated drugs based on drug-interaction potential (i.e., no studies have been done). Ritonavir is predicted to cause moderate increases in the AUC of tricyclic antidepressants. Nefazodone may possibly lead to inhibitory effects similar to those expected from ritonavir in some patients. Large increases in AUC are expected with carbamazepine and nefazodone when co-administered with ritonavir.

Due to the FDA's accelerated approval process of the protease inhibitors, the product monographs continue to be updated as postmarketing data on adverse

events and further studies of efficacy, safety, and drug interactions are completed. For this reason prescribers should be cautious in viewing the information on drug interactions from product monographs as complete. An "important drug warning" letter was mailed to health care providers in November 1996 to advise of new predicted or suspected drug interactions with ritonavir. The list of drugs contraindicated with ritonavir was expanded based on the occurrence of adverse events and on predicted pharmacokinetic interactions. These predictions were made by the manufacturers using a method similar to the one described in this chapter to identify potential drug interactions.

Knowledge of the metabolic disposition of a drug is essential in predicting drug interactions. This information is available from the medical literature, product monograph, and the medical information department of the pharmaceutical company. The accuracy and completeness of this information is questionable. Understanding the limitations to our knowledge is important; however, this does not diminish the ability to predict potential drug interactions. These limitations should alert the prescriber to carefully monitor pharmacodynamic effects (i.e., efficacy and toxicity) when any new drug is initiated in a patient receiving a protease inhibitor or when a protease inhibitor is to be initiated.

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Treatment Adherence to HIV Medications

The Achilles Heel of the New Therapeutics

JUDITH GODWIN RABKIN and MARGARET CHESNEY

BACKGROUND

In 1996, the practice of HIV medicine was substantially altered. "Combination therapy," also known as highly active antiviral therapy (HAART), that includes at least one protease inhibitor and two or more antiretroviral drugs, has become the standard of care when any antiviral therapy is initiated. HAART replaces monotherapy (AZT or another antiretrovial drug alone) which is now considered ineffective and ill advised because of the likelihood of resistance developing within weeks or months.

This new treatment strategy has emerged because of the almost simultaneous appearance of two major medical breakthroughs. The first was the development of a measure to quantify HIV RNA in plasma. This HIV RNA viral load assay, together with CD4 cell count, is now considered the best available marker of HIV illness progression and is a tool for making treatment decisions. The assay became commercially available in spring 1995 and was approved by the FDA and thus covered by Medicaid and other insurance (so that it became accessible to patients) in May 1996.

The second major breakthrough was the approval of drugs in a new class of antiviral medications—protease inhibitors—between December 1995 and April 1997. Used with at least two other antiviral agents, these drugs dramatically reduce the rate of viral replication for many but not all patients, limiting further proliferation and minimizing the opportunity for new random mutations to occur (Molla *et al.,* 1996; Nelson, 1996).

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STATEMENT OF THE PROBLEM

These exciting treatment advances bring with them major problems with respect to adherence. It has long been recognized that medication adherence is problematic for virtually all conditions and treatments, even when the regimen is simple and the patient is recognizably ill (Blackwell, 1973). Combination therapy for HIV illness is perhaps the most rigorous, demanding, and unforgiving of any outpatient oral treatment ever introduced, and may be prescribed for some patients without any current symptoms. Other patients will have chronic severe medical conditions for which they are already taking multiple medications. Because of limited bioavailability and short half-life of the protease inhibitors currently available, each must be taken at intervals of either 8 or 12 hr around the clock, for years if not forever, either with meals (saquinavir, ritonavir, nelfinavir) or on an empty stomach (indinavir). These drugs are combined with two or more additional antiviral drugs which may have different schedules for a total of up to 22 pills a day. Other medications, either prophylactic or for symptomatic illness, also are prescribed, often increasing the number of pills in each daily regimen even further.

Side effects are common and often severe, including more transient reactions such as nausea, vomiting, diarrhea, and fatigue, and more lasting side effects such as metallic taste, oral numbness, and peripheral neuropathy (Baker, 1996). Metabolic disturbances and new-onset diabetes recently have been reported among patients taking all of the marketed protease inhibitors and the FDA sent a warning to all physicians about this unexpected and apparently rare side effect ("F.D.A. Warns of Diabetes Risk in AIDS Drugs," 1997).

A further complication is that all protease inhibitors have the unfortunate characteristic of early resistance after even a week of missed medication, irregular use, or inadequate dosing (Condra *et al.,* 1995; Jacobsen *et al.,* 1996). Even more problematic, drug resistance that develops often spans several marketed protease inhibitors and possibly those in development as well, thus reducing treatment options (Deeks, Loftus, *et al.,* 1997, Hirsch, 1997). For example, a multisite (ACTG 333) trial was designed to compare the efficacy of a new soft gel formulation of saquinavir with indinavir or continued hard gel saquinavir (the original formulation) for patients who had been on long-term (hard gel) saquinavir and who were not doing well. The study was stopped after 8 weeks because none of the therapies met the study criteria for effectiveness; in other words, patients who failed on one marketed protease inhibitor did not respond adequately either to another marketed protease inhibitor or to the new soft gel formulation ("Roche Racks Up Millions . . . ," 1997). Accordingly, failures of adherence not only delay viral suppression during the unsuccessful trial with one particular combination, but can eliminate this entire category of treatment forever. Of public health significance, the drug-resistant individual is then likely to transmit a resistant virus to any people he or she subsequently infects. Since most

patients have only one or two chances to make this treatment work, adherence is not only a personal but also a public health issue.

In the United States, antiviral combination therapy (HAART) has become the standard of care for all patients with symptomatic HIV illness, those with CD4 counts under 350 cells/mm and those with measurable viral activity (more than 5000–10,000 copies/mL of plasma HIV RNA concentrations) regardless of CD4 cell count (Carpenter *et al.,* 1997), which probably includes the majority of HIV+ patients seen in medical settings. As noted by Bartlett (1995) in an annual review of progress in infectious diseases, there has been a "dramatic shift in strategies [of treatment] with sudden enthusiastic endorsement of an aggressive attack on HIV, using combination therapy with viral burden measurements to assess results. . . . Compliance is both difficult and crucial, and toxic effects are problematic. Most important, resistance appears to be a potential Achilles heel of the entire effort" (p. 1865).

Even under the nearly ideal conditions of premarketing randomized clinical trials, whose highly motivated, informed patients were screened for concomitant problems such as substance abuse or significant psychiatric disorder, not all patients have benefited from HAART. One study citing the efficacy of indinavir, 3TC, and AZT reported success (undetectable viral load) in 85% of subjects, and another, with AZT-experienced subjects with CD4 counts less than 50 cells/mm succeeded with 65% (Carpenter *et al.,* 1997). Although promising for those who respond these figures also indicate that between 15% and 35% of these "model" patients did not show the desired benefit in these clinical trials. News stories and clinical reports about initial failure, or early response followed by loss of efficacy, have appeared during the past year. One such story appeared on the front page of The New York Times in August 1997. One of the first retrospective studies of relapse was reported in September 1997 at the American Society for Microbiology; charts of 153 patients who had started on HAART in March 1996 were reviewed: Although the virus levels of most patients had dropped to undetectable levels, detectable levels of virus subsequently were found in 53% (Deeks, Loftus, *et al.,* 1997). It should be noted, however, that some of the patients in this sample had been heavily pretreated with serial monotherapy; others had very low CD4 cell counts and very high levels of viral load, factors that lessen the likelihood of robust viral suppression. In general, then, HAART does not work for everyone, and when it does initially have an effect, this benefit can be lost.

Factors contributing to initial or subsequent treatment failure include medication history such as serial antiviral monotherapy with resistance developing to each antiviral one at a time; current medical condition such as gastrointestinal disease or severe diarrhea interfering with drug absorption, or liver disease; or medication nonadherence. Of these factors, the last is most amenable to modification. We review the general medical literature, together with a smaller body of work specifically focusing on HIV+ patients, to identify correlates and predictors of adherence.

ADHERENCE: OVERVIEW OF THE LITERATURE

Medication adherence (earlier referred to as compliance, a term now regarded as patronizing) has been the subject of numerous studies for over 30 years, with several comprehensive reviews available (e.g., Besch, 1995; Dunbar-Jacobs, Dwyer, & Dunning, 1991; Ickovics & Meisler, 1997; Meichenbaum & Turk, 1987). Particular attention has been devoted to chronic diseases such as diabetes, arthritis, and severe and persistent mental disorders, although acute infectious illnesses such as tuberculosis also have been extensively studied with respect to correlates of adherence (e.g., Sumartojo, 1993).

Since 1990, at least a dozen studies have examined potential or actual facilitators and barriers to adherence among HIV+ patients. Earlier studies focused on adherence to AZT, and collected their data between 1985 and 1993, more recently with the abstracts presented at AIDS meetings have addressed combination therapy.

In most studies, adherence is defined as more than 80% of doses taken or more than 80% of prescriptions filled on time. It is not known whether this level of adherence reliably will prevent breakthrough of HIV viral reproduction. Moreover, such global estimates do not take into account the timing between doses or meal restrictions.

The general medical literature suggests that adherence is almost universally less than 100%, with most estimates in the range of 30% to 60% and somewhat lower rates for prophylactic medications (Meichenbaum & Turk, 1987; Sumartojo, 1993). Adherence rates vary as a function of illness seventy and patients' perception of the effect that their adherence is likely to have. An early study dramatically illustrates this situation: Glaucoma patients attending a specialty clinic were told that they must use eyedrops 3 times a day "or they would go blind." The adherence rate was 42%. After a subset of patients became legally blind in one eye and they were again cautioned about the medication schedule, their adherence rate increased to 58% (Vincent, 1971).

Among five studies of AZT adherence, successful adherence (defined as more than 80% of doses taken) ranged from 42% using a time frame of the past month (Singh *et al.,* 1996) to 67% in the past week (Samet *et al.,* 1992). These rates are consistent with findings reported in the general medical literature (Ickovics & Meisler, 1997). It is important to note that the treatment regimens studied in these investigations were far less complicated than today's combination therapies.

Several studies of adherence to protease inhibitor regimens recently have been presented. Outpatients seen at an AIDS clinic in San Francisco were asked how many medications doses they had missed in the past three days and blood was drawn for HIV RNA plasma levels. Of the 134 patients, 22% reported missing 20% or more of their protease inhibitor doses over the 3-day period. A higher proportion of adherent patients than nonadherent patients had undetectable levels of virus (Hecht *et al.,* 1998).

Two large national telephone surveys of medication adherence were conducted in the spring of 1998 among patients on combination therapy including a protease inhibitor. The first, sponsored by Dupont Merck, included 665 HIV+ patients of whom 5l% were white and 76% were male. 26% reported missed doses "yesterday,"and 43% reported misses in the past week. The second study, conducted by Community Prescription Services (CPS), included 400 respondents, 91% male, 78% white, and 83% gay. In this study, 8% reported missed doses for "yesterday" was 19% in the past week. Altogether 18% made some error (missed, timing, food error) yesterday and 37% in the past week. A third national study, conducted in 1997 by the CDC included 1294 patients in 12 states taking HAART (Nakashima, 1998). When asked how often they took their antiretroviral medications, 67% said, "always," 23% said "usually," and 9% said "sometimes, rarely or never." Several dozen posters presented at the Geneva AIDS Conference from around the world reported equivalent or worse adherence rates (e.g., Gir *et al.,* 1998) in an international study including Brazil, Norway, England, and U.S.A. found that 46% of their combined sample reported forgetting to take their HIV medications). These three large studies document substantial rates of nonadherence but also indicate that patients are willing and able to report errors, suggesting that self-report methods of elicitation may be more reliable than previously believed.

BARRIERS AND FACILITATORS OF ADHERENCE

Patient Characteristics

As summarized by Meichenbaum and Turk (1987) in their comprehensive review, patient variables are generally poor predictors of adherence: "No consistent relation with adherence has been found for such variables as age, sex, social class, marital status or personality traits" (p. 42). A similar conclusion was reached by Besch (1995) in her literature review, and she further noted that race-ethnic group, religion, and educational level also were not useful predictors. Studies of adherence to AZT also produced negative or inconsistent findings with respect to demographic characteristics (Besch, Morse, Simon, Hodges, & Franhino, 1997; Eldred, Wu, Chaisson, & Moore, 1997; Muma, Ross, Parcel, & Pollard, 1995; Singh *et al.,* 1996).

Beliefs and Expectations

Patients' beliefs, knowledge, and expectations, sometimes shared by friends, family, and community, clearly influence medical decision making and willingness to begin and then adhere to antiviral therapy. In studies of HIV patients, it has been observed that adherence is greater when patients perceive the need for treat-

ment (Stall *et al.,* 1996), believe the treatment will be helpful (Blumenfield, Milazzo, & Wormser, 1990; Muma *et al.,* 1995), and understand the purpose of the medications (Elred *et al.,* 1997). Attitudes of friends and trust in doctors are also associated with adherence (Stall *et al.,* 1996).

Lack of belief in the efficacy of treatment may lead either to treatment refusal or inadequate adherence once initiated. For example, AZT in particular was regarded with suspicion by many HIV+ patients in urban black communities who refused antiviral therapy when AZT was the only option. This suspiciousness was fueled by an early, subsequently refuted report suggesting that AZT might be less effective for African Americans. A patient put it this way: "I've never taken the meds. I been diagnosed so long and my friends who took 'em died. Fear is my major reason. I know more than 200 people who died, and it was related to those medications."

Many formerly reluctant patients have changed their minds following efforts to correct misconceptions and with the advent of combination therapy. A literal measure of relative value is apparent in the street price of these medications: In Washington Heights, New York City, sales of AZT used to be negligible because there were so few buyers; today, a bottle of indinavir sells on the street for $100 or more. Beliefs, even when deeply felt, are mutable.

Beliefs and knowledge also play a central role in adherence to a treatment program initially accepted. Patients who have the conviction that combination therapy can save their lives are generally scrupulous in following their daily regimen. A man with very advanced HIV illness, who had been prescribed perhaps the most complex possible regimen of indinavir, ddI, and 3TC described his appraisal this way: "Initially the problem seemed insurmountable. But the essence of the issue is quite simply this: do or die. A managed drug protocol can lead to longer life, a better quality of life and hope for the future that didn't exist as recently as two years ago. Living with AIDS successfully boils down to one irrefutable equation: one must accept responsibility and participate in one's care." Unsurprisingly, this man doesn't miss a dose.

Another patient who reluctantly agreed to take "all those pills" said she took her indinavir only twice daily, with meals, because otherwise the medicine "bothered her stomach." Since indinavir needs to be taken three times a day, on an empty stomach, this schedule is likely to fail.

Circumstances

Some patients who do believe that combination therapy "works" nevertheless feel they cannot follow the regimen either because their daily lives are disorganized, because they continue to use street drugs, or because they cannot regulate the times of their meals. As one man said, "my doctor, she's *really* pushing me on it and I'm like, 'hey, look at my life! I'm in a crazy residence, I'm using [street drugs], I got things going on, I gotta think a little' and she says there's no time and I say well I'm

making the time. What if I be slipping and wind up selling them [protease inhibitors] on the street to get high? The whole thing ain't no aspirin, man."

Occasionally well-meaning physicians urge reluctant patients to start treatment, despite the patients' reservations, often with unfortunate effects. For example, a patient we interviewed about medication adherence became very embarrassed and stopped the interview. He explained that he really was not taking the medication except for indinavir which he took once a day (instead of three times a day) because he was essentially homeless, was being lent space in New Jersey but traveled to be with his street buddies in the Bronx, and ate when he could. He was supposed to be taking indinavir 3 times a day, every 8 hr, on an empty stomach, plus two other antivirals. When asked whether he had discussed difficulties in adherence with his doctor, he said, "Oh, yes, but she doesn't want to change the medications and says to try harder."

In the foregoing instances, the first patient, who refused to start combination therapy despite physician pressure probably has a better prognosis than the second patient, who agreed with his insistent physician that he should initiate a regimen that he could not plausibly carry out.

Homelessness

In studies of HIV+ patients, unstable social environment (Morse *et al.,* 1991) or homelessness (Samet *et al.,* 1992) were associated with less adherence to AZT. However, some patients living in tenuous settings (such as welfare hotels) can be meticulous about taking their medication if it has been appropriately prescribed (e.g., their prescriptions do not require refrigeration) and if the person is convinced of its efficacy (Broers, Morabia, & Hirschel, 1993).

Substance Abuse

Current drug users or former drug users as well as those who are current heavy drinkers may have particular problems with medication adherence (Mannheim, 1998; Weidler, 1998). Those in recovery sometimes are doubtful about taking any drugs at all, and may need more time to actively accept treatment. Current drug users may have more difficulties with adherence than others because of the instability of their lives and possible concomitant social problems such as homelessness. When such patients come into contact with the medical system, the first priority may not be combination therapy but rather medical stabilization, arrangements for housing and health insurance, and treatment of acute illnesses or prophylaxis for opportunistic infections. As Bangsberg, Tulsky, Hecht, and Moss (1997) argued, "It is ethical to withold [combination] treatment until the patient's life is stabilized" (p. 65). Once this is achieved, and their medical condition warrants it, combination therapy should be an option for drug users as it is for others with concurrent social, psychiatric, or medical problems.

Neuropsychiatric Complications

Even with the best will and motivation, barriers may impede adherence. Among the most significant barriers are neurocognitive impairment and severe psychiatric illness. Surprisingly little attention has been devoted to the neurocognitive status of patients for whom complex medication regimens are prescribed. In neuropsychological assessments of HIV+ patients, the most common areas of impairment on these tests are memory, executive function, and visuomotor coordination. In a longitudinal study of HIV+ men with absent to moderate symptoms and HIV – gay men, the HIV+ men performed more poorly on memory tests (Stern *et al.,* 1991). Among HIV+ patients, those with more advanced illness (CD4 cell count under 200 or AIDS-defining conditions) are more likely to have functional difficulties in activities of daily living, although functional status may fluctuate considerably over time (Crystal & Sambamoorthi, 1996). These are the patients most likely to warrant combination therapy. Prescription of complex medication regimens for patients with memory problems is likely to be most successful when social or institutional resources (e.g., family member, home health aide, day program) are available to help with medication scheduling.

Severe and Persistent Mental Disorders

Psychiatric disorders independent of HIV infection also constitute a significant source of functional impairment. Even mild conditions such as depressed mood as measured on self-report rating scales such as the Profile of Moods Scale (POMS) or Beck Depression Inventory may be associated with decreased medication adherence (Singh *et al.,* 1996). Among patients with severe and persistent mental illness, including schizophrenia and bipolar disorder, noncompliance with psychotropic medication is often a contributing factor to relapse (Buchanan, 1992; Pool & Elder, 1986). HIV infection rates are substantial among men and women with severe and persistent mental illness, ranging from 4% among long-stay inpatients to as high as 23% among dually diagnosed patients admitted to a municipal hospital (Cournos *et al.,* 1991; Silberstein *et al.,* 1994; Susser, Valencia, & Conover, 1993). Prescription of combination therapy to patients with severe and persistent mental illness may pose major adherence problems if they also have additional risk factors for nonadherence such as living alone, having unstable housing, and not participating in day treatment programs.

Treatment Characteristics

Complexity of the therapeutic regimen—number of times a day pills must be taken, whether with meals or not, and nature and severity of side effects—is associated with adherence. The studies documenting these associations, however, may

not generalize directly to combination therapy. In most cases the regimens on which these studies were based were far simpler than those of current combination therapies. At the same time, these previous studies did not have the critical features of the possibility of dramatic improvement coupled with the threat of early resistance that characterize highly active antiretroviral therapy. Thus, the burden (complexity and side effects) must be weighed in relation to the potency of the prescribed regimen, which can vary considerably. As a general rule, the simpler and more benign the regimen, the more likely it is to be followed. Unfortunately, for antiviral medications, the more potent (effective) the compound, the more frequent, severe, and varied the side effects are likely to be.

In terms of regimen complexity, each protease inhibitor requires between 9 (nelfinavir) and 18 (soft gel saquinavir) capsules or tablets a day, in divided doses. All but nelfinavir have meal requirements as well. Ritonavir capsules must be refrigerated so that doses can be prepared only for the day, not sorted by week in pill boxes. Indinavir similarly should not be sorted by the week because it is susceptible to humidity and should be kept with a dessicant in its original container.

Side effects of nearly all antivirals are often significant. The "d"nonnucleoside reverse transcriptase inhibitors (ddI, ddC, D4T) and AZT may cause painful neuropathy; all but 3TC are likely to have noticeable side effects. Until November 1997, only three of the four marketed protease inhibitors were considered "potent" (Carpenter *et al.,* 1997): ritonavir, indinavir, and nelfinavir. Although active *in vitro,* the hard gel formulation of saquinavir that was initially marketed has a bioavailability of only 4%; a soft gel formulation was approved in November 1997 and the earlier hard gel capsule is being phased out in. Ritonavir is the most likely to cause distressing side effects, both relatively transient (e.g., nausea, vomiting) and chronic (circumoral numbness, metallic taste). Its dosing is simpler than the others (twice daily, every 12 hr), but must be taken with meals containing fat to minimize side effects, which is difficult in the presence of nausea. Indinavir has fewer side effects, but because of the risk of kidney stones must be accompanied by large quantities of liquid daily (48 to 64 oz a day). This drug also has had a demanding schedule (every 8 hr around the clock, on an empty stomach, 1 hr before or 2 hr after eating). A trial designed to assess the efficacy of indinavir taken twice instead of three times daily was stopped because of high failure rates on the twice daily dosing arm, and Merck sent a letter (September 25, 1998) to clinicians advising them of this finding. The side effects of nelfinavir are less well known because it is the newest; it may cause diarrhea or rash. The regimen requires three pills three times a day with food, but the timing is more flexible and the food content is not prescribed. Trials are under way to assess the efficacy of combining two protease inhibitors (e.g., saquinavir and ritonavir) while reducing the daily number of capsules and occasions, to retain potency while reducing side effects and simplifying regimen complexity (Farthing *et al.,* 1997).

Rapidly Changing Treatment Options

As of late 1998, three new reverse transcriptase inhibitors (Glaxo Wellcome's 1592U89, abacavir; Gilead's adefovir; and Janssen's Loviride) and two more protease inhibitors (Glaxo's amprenavir, and Abbott's ABT-378) are in human trials. A new nonnucleoside reverse transcriptase inhibitor, Dupont-Merck's efavirenz (Sustiva), was approved for marketing in September 1998. It is particularly attractive since the daily dose is a single tablet. When prescribed with Combivir (AZT plus 3TC), which entails one tablet twice a day, a patient need take only 3 tablets a day. While this combination does not include a protease inhibitor, it may be a sensible choice for patients who cannot, or will not, take more complicated regimens.

At least another half-dozen drugs are in earlier trials. While some of these simply provide alternatives to existing drugs, others promise more potent effects. Given these rapidly changing circumstances of HIV therapy, strategies for adherence cannot be specific to a fixed regime. For example, instead of identifying specific side effects, scales of assessing degree of toxicity are needed; instead of studying adherence to a specific drug combination, various combinations can be scaled in terms of overall burden that take into account number of pills and occasions per day as well as the rigor of food restrictions.

Other Treatment Options

It is not entirely clear whether adherence is increased or decreased when patients already are taking other medications when they start highly active antiretroviral therapy, and it may depend on both the individual and the schedule of the other medications. Stone (1979) found that adherence was 85% when one drug is prescribed, 75% when the patient is asked to take two or three medications, and 65% or less if more than five drugs are prescribed. Number of doses per day similarly has been associated inversely with adherence (Chesney *et al.,* 1995).

Another predictor is the extent to which the regimen interferes with a patient's daily life. The number of times per day that medication must be taken (intrusiveness) rather than the absolute number of pills was found to be the best predictor of nonadherence (Malahey, 1966). In studies of AZT adherence, inconsistent findings have been reported regarding the impact of concomitant medications on adherence. Samet and colleagues (1992) found better adherence among HIV+ patients who were already taking at least one medication regularly; others found the number of HIV medications was negatively associated with adherence (Eldred *et al.,* 1997; Morse *et al.,* 1991). Apart from inconvenience, the chances of misunderstanding the required schedules, making errors of omission or timing, increase as the number of drugs does.

Alternatively, if HIV+ patients have been taking medications for many months or years, it may require less behavior change to add one or two new med-

ications to an existing pattern of adherence than for patients who never have done so, or only needed to remember one medication once a day.

Illness characteristics, as noted, are associated with less adherence. The precise relationship depends on a number of factors. For example, if the medication removes symptoms effectively and quickly, adherence will be higher (e.g., Xanax). If an already symptomatic patient starts a new medication with significant side effects such as nausea and diarrhea, the likelihood of adherence is substantially reduced. Overall, factors found associated with lower adherence include chronicity, minimal symptomatology, or no immediate consequences of missed doses. All of these may characterize antiretroviral therapy. The treatment, as now understood, must be continued for life. Many patients for whom it is indicated have no HIV symptoms, and there are no immediate consequences of missed doses, except relief from distressing side effects if they are otherwise present.

In studies of HIV patients, sicker patients were found more likely to be adherent (Eldred *et al.,* 1997; Samet *et al.,* 1992; Singh *et al.,* 1996). This was not found in the Medical Outcomes Study (Sherbourne, Hays, Ordway, Matteo, & Kravitz, 1992), where patients who were more distressed about their health and patients who reported worse physical health reported lower levels of adherence to medical recommendations. Sherbourne and colleagues proposed that sicker patients may be less able to manage complex treatment regimens, or may feel that nothing they do will be helpful and that the medications will not have a beneficial effect on their health.

Doctor–Patient Variables and Organizational Variables

Research on the role of the health practitioner–patient communication in enhancing adherence shows that, regardless of the prevailing model of communication, the patient ultimately is in charge. If the patient does not approve of an action, he or she can simply not adhere. It has been found that patients who report better adherence are more likely than nonadherent patients to report that their doctors are supportive (Barnhoorn & Adriaanse, 1992). A genuine collaboration between patients and providers regarding patient goals and preferences, available options, and care decisions is thus essential for complex regimens (DiMatteo, 1996).

The most important conversation between doctor and patient regarding combination therapy occurs at the outset. Their ability to work together to select a regimen that matches the patient's way of life is a critical component in establishment of adherence. The physician usually can present different options and the advantages and disadvantages can be considered with the patient. The patient needs to understand the requirements of a given regimen in terms of meals and timing of doses; he or she must have a strong sense of commitment to this undertaking and not just go through the motions because the doctor said so. In addition, it is important for the patient to know what to expect in terms of treatment effects, side effects, and the likely duration and management of both. It also is helpful for possible bar-

riers to adherence to be anticipated and strategies for dealing with them reviewed. Since the timing of initiation of combination therapy is seldom urgent, it is usually far preferable for a physician whose patient is hesitant or unconvinced about its necessity to continue a discussion over two or three visits until the patient's doubts and questions are addressed, than to declare the need for such treatment and hand a reluctant patient the prescriptions. Some patients have told us that it has taken 6 months or a year until they are really ready to make the emotional commitment to this exacting schedule, but when they did begin, they have been meticulously adherent. In order for this kind of exchange to occur, the patient must be willing to voice doubts and reservations and the physician must be willing to take the time to respect them, discuss them, and leave the ultimate decision to the patient. Because this process takes time, it is generally unwise for a doctor to prescribe combination therapy to a therapy-naive patient at his or her first or second visit.

Summary

Overall, more than 200 variables have been examined in relation to adherence (Haynes, McKibbon, & Kanani, 1996) and more than 50 have been related to nonadherence (Meichenbaum & Turk, 1987, Table 4, p. 43), but no single variable or combination of variables has been shown consistently to identify either those who will or will not adhere to treatment regimens they initially agreed to follow. This may be partly due to the fact that, although a history of nonadherence is a good predictor of future nonadherence (Sherbourne *et al.,* 1992), this is not a fixed characteristic.

INTERVENTIONS TO PROMOTE ADHERENCE

There are no proven methods for assuring adherence. Perhaps the most critical steps toward achievement of this goal occur at the outset of the proposed treatment. They are engagement of the patient by the health care provider, a sense of commitment on the part of the patient, and negotiation of a regimen that is feasible and acceptable to him or her. Choosing the right combination depends on the pattern of the person's daily life: whether fixed schedules or totally fluid events characterize the day, whether there is access to kitchen facilities, and whether eating on a regular schedule is likely to happen. Patients must be able to live with the regimen, and although some are willing to change their lifestyle in order to accommodate the most potent possible treatment, others will not or cannot.

Interventions to promote adherence range from one-time printed instructions such as medication package inserts, to elaborate schedules of telephone reminding and 24-hour hotlines, electronic caps on pill bottles that beep when not opened on schedule, and directly observed therapy. Even this last approach, which has been used with recalcitrant tuberculosis patients, is the standard in methadone clinics, and has been proposed for HIV treatments despite logistical problems, often has little carryover on the days when it is not performed (Woodward, 1997).

While no studies have yet evaluated the comparative effectiveness of interventions to improve treatment adherence in HIV disease (Sikkema & Kelly, 1996, p. 44), those conducted with other patient groups are typically multicomponent, including both behavioral and educational elements, and usually are based on cognitive-behavioral models (Azjen & Fishbein, 1980; Dunbar-Jacobs *et al.,* 1991). Techniques include behavioral reminders (e.g., weekly or daily pill boxes, alarms on watches or free-standing devices, daily checklists), self-management skill training, identification of lifestyle cues and error triggers, problem solving to circumvent barriers, integration of medication regimens in daily activities, and identification and resolution of dysfunctional attitudes. All may be helpful tools to promote adherence (Cramer, 1995; Maccharia, Leon, Rowe, Stephenson, & Haynes, 1992). It has been shown that help from others, whether medical staff or a friend or relative, achieves better outcomes than either printed reminders or self-monitoring methods (Kirscht, Kirscht, & Rosenstock, 1981). In a meta-analysis of eight studies of HIV+ patients, the effect of video interventions on improving treatment compliance was no better than pamphlets, special pill packaging, or counseling, and none were significantly effective (Healton & Messeri, 1993).

Overall, the number of controlled intervention studies has been small. A 1996 review of the literature sought randomized clinical trials of medication adherence that included comparison groups, measures of both treatment outcome and medication adherence, and at least 80% follow-up of at least 6 months' duration (Haynes *et al.,* 1996). The authors screened 1553 relevant citations, reviewed in detail 252 studies, and located 13 that met their inclusion criteria. These 13 studies were too disparate to warrant meta-analysis because of differences in clinical disorders, interventions, measures, and adherence reports. Seven of 15 interventions (in the 13 studies) found improved adherence, and 6 found improved treatment outcomes in the experimental groups receiving adherence training. Of these, 2 studies found improved adherence but no clinical effect and 2 others found improved outcome but no effect on adherence measures.

In summary, the empirical findings from intervention trials to promote adherence are modest. The available data together with theoretical models suggest that the following strategies are likely to promote adherence: tailoring the regimen to the person's lifestyle; teaching self-monitoring skills; identifying barriers to adherence and working out solutions; reframing health beliefs; enhancing the patient's sense of mastery (self-efficacy); creating a social environment conducive to adherence; and developing a system to maintain adherent behavior. These elements have been incorporated by one of us (MC) into an adherence intervention model, Partnership in AIDS Clinical Trials (PACT), that has been applied to clinical trial participants at San Francisco General Hospital.

In other medical contexts, the goal is to identify the "at-risk" patient (Blackwell, 1973). With HIV combination therapy, *every* patient must be considered at risk, given the burden, complexity, likely toxicity, chronicity of the regimens involved, and the costs of nonadherence, even apart from any predisposing personal or situational characteristics.

MEASURING ADHERENCE

There is no gold standard to assess medication adherence (Rudd, 1979; Sumartojo, 1993). As Rudd noted nearly 20 years ago, "The ideal standard would be simultaneously unobtrusive (to avoid patient sensitization and maximize cooperation), objective (to produce discrete and reproducible data for each subject), and practical (to maximize portability and minimize cost)" (p. 627). These goals remain to be fulfilled, although numerous detection methods and strategies have been developed in recent years (Bond & Hussar, 1991).

Direct Measures

These include direct observation, use of biological markers, tracer compounds, and assessment of drug levels in blood or urine. Direct observation is routinely used in methadone clinics, in institutions such as hospitals and prisons, and in special programs for patients with active tuberculosis presumed to be potentially nonadherent (Sumartojo, 1993). This is both an intervention and a method of measurement.

Urine and blood assays are possible for many medications, although as of early 1998 assays for protease inhibitors are not available from commercial laboratories. In general, the major advantage of measuring drug levels is that the results are not dependent on the patient's memory, cooperation, or candor. Qualitative assays determine whether a given drug is present or absent. Quantitative measurement provides specific blood levels but accurate timing of the test sample in relation to medication ingestion is necessary. Blood levels are less useful for compounds with short half-lives like protease inhibitors, where accurate determination of achieved serum level requires multiple sampling before and at fixed intervals after a dose. On the other hand, for drugs with long half-lives, a blood level may not reflect recent dose omissions. More generally, blood levels are limited measures because their time frame is short and they do not indicate *when* the medication was taken; further, they are influenced by factors such as concurrent medications or medical conditions (e.g., diarrhea, malabsorption) that may alter their metabolism.

Indirect Measures

There are multiple indirect methods of assessing adherence, including physiological markers, clinical ratings, assessment of treatment outcome, pill counts, prescription tracking and electronic monitoring, and patient report.

Physiological Markers

Some medications have physiological markers that indicate whether they have been taken. For example, AZT causes an increase in mean corpuscular vol-

ume of red blood cells, and this measure is routinely available in hematology assays (complete blood count). Patients with HIV illness who have elevated MCV values are likely to be taking AZT, although other causes for elevation including heavy alcohol use or B6 deficiency. Similarly, uric acid levels rise when ddI is taken (Besch, 1995).

Clinical Ratings

Ratings by health care providers are variably accurate. In her review of the literature on compliance with TB treatment, Sumartojo (1993) noted that physicians' predictions of nonadherence are accurate less than half the time, but "are more accurate when the patient is known to be alcoholic or when physicians consider their relationship with the patient unsatisfactory" (p. 1312). In one study of patients with tuberculosis, physicians correctly identified only 32% of nonadherent patients and incorrectly identified 8% of adherent patients as nonadherent (Wardman, Knox, Muers, & Page, 1988). Roth and Caron (1978) found that physicians "grossly overestimated" their patients' intake of antacid for treatment of peptic ulcer, reporting a Pearson correlation coefficient of +.48 between physician estimate and bottle counts. Cummings, Kirscht, Becker, and Levin (1984) found that compliance ratings by nurses familiar with each of the dialysis patients they assessed "contained approximately 50 percent valid variance," which was the best of three methods studied (the others were patient self-report and physiological markers). In this study, nurses rated compliance on a 7-point scale ranging from "poor" to "excellent" compliance. Overall, although clinician assessments are not highly accurate, they may add information to other measures to produce a composite picture of adherence.

Treatment Outcome

Outcome is sometimes used as an indication of adherence, based on the assumption that there is a direct relationship between the treatment and the desired result (Meichenbaum & Turk, 1987). Patients may improve or not for reasons other than treatment adherence, however. Two well-designed placebo-controlled studies found an independent statistical main effect for adherence, regardless of treatment condition (Epstein & Cluss, 1982). In some instances clinical outcome can be unrelated to adherence or even associated with nonadherence. Reiss, Gonzales, and Kramer (1986), for example, found that noncompliant patients with end-stage kidney disease survived longer than those whose laboratory measures (potassium peak and range and mean phosphorus) indicated compliance. In short, as Dunbar-Jacobs and Schlenk (1996) noted, "Data on the effects of adherence to treatment regimen on clinical outcomes are promising, though not easily found. . . . Data supporting the direct effect of adherence on outcomes, although interesting, are inconsistent" (p. 336). Overall, there is not a simple relationship between adherence and treatment outcome.

Pill Counts

Pill counts often are used to gauge adherence because they are easy and inexpensive. Their utility depends on the medication in question and the timing of its distribution. In clinical trials, where patients receive a 1-week medication supply and return the pill container the following week, counting is straightforward. However, if the patient gets monthly supplies, at intervals that do not coincide with study visits, the task becomes more complex. Using the date on the container label as the "start" date may not be accurate since the patient may have had medication left from a previous prescription. Furthermore, counting medications such as ritonovir constitutes a major practical hurdle: a month's supply consists of 360 capsules, distributed by some pharmacies in a single container and by others in two or three for the month. What does the patient bring in to be counted (if he or she remembers to bring the pill bottles at all)? In general, this method's utility depends on the medication and the context; pill counts err in the direction of overstating adherence.

Electronic Pill Monitors

A sophisticated form of pill count entails the use of microelectronic caps on pill bottles. These caps have the capacity to record the time and date of each occasion when the bottle was opened for a period of up to 30 days. As true of pill counts, this method cannot determine whether the medication is actually ingested, or whether food was or was not taken at the same time. More problematic for treatment regimens requiring multiple medications, each microelectronic pill bottle can contain only a single medication; patients would need to carry several of them around with them all day if they were to function as accurate measures of combination treatment. Even if one medication of the combination is used as a "sentinel" measure, the monthly supply (e.g., 270 tablets for nelfinavir or 540 large soft gel capsules for the new formulation of saquinavir) would not fit into a single pill bottle nor would it be portable if it did.

Self-Report

Retrospective patient reports are widely used because of ease and feasibility, face validity, and empirically demonstrated utility. They may be inaccurate because of social desirability (unwillingness to acknowledge "failures"),or what is known as the "dentist effect" (we brush our teeth more regularly right before and after scheduled dental visits). A significant problem for some patients who have cognitive problems or who have no consistent pattern to their day is forgetfulness: as one patient asked, "How can you expect me to remember when I forgot to take my medication?" Overall, however, systematically elicited short-term recall in a face-to-face interview setting can be accurate with cooperative respondents (Ick-

ovics & Meisler, 1997, p. 389). Strategies to motivate patients to tell interviewers what is actually happening and not what they think the interviewer wants to hear have resulted in higher numbers of reports of nonadherence. In addition, the context of adherence errors can be identified for future remediation.

Diaries are sometimes used, if patients can adhere to this task. In some research, patients are asked to mail back their diary entries on a daily basis to prevent retrospective entries as the study visit approaches. This method actually constitutes an intervention since it serves as a reminder as well as an index of adherence.

In summary, no adherence measure is completely accurate with the exception of directly observed therapy of every prescribed dose over extended periods (as in methadone clinics, although even here it is not done 7 days a week), which is both an intervention and a measurement strategy. There is no gold standard against which to compare different measurement strategies, and in many settings it is even difficult to estimate the magnitude of error of various measures performed at the same time. Measurement issues thus continue to pose major challenges in this research field.

Challenges to Adherence Measurement Posed by Antiretrovirals

At least five new antiretroviral agents—nucleoside reverse transcriptase inhibitors such as Glaxo Wellcome's 1592U89 (abacavir), Gilead's Adefovir, and Janssen's Loviride; a nonnucleoside reverse transcriptase inhibitor (Dupont Merck's efavirenz or Sustiva); and two new protease inhibitors (Glaxo Wellcome's 141 W94 and Abbott's ABT-378)—are in clinical trials as of early 1998. Given these rapidly changing circumstances of HIV therapy, strategies for adherence cannot be specific to a fixed regimen. Measures must transcend particularities (e.g., instead of identifying specific side effects, scales of toxicity can be used; instead of studying adherence to a particular drug combination, various such combinations can be scaled in terms of overall burden and adherence).

Discussion

In the United States today, the prevailing opinion is that combination therapy should begin when patients show laboratory indications of significant viral activity or of immunosuppression, and that this therapy should consist of two antivirals plus one of the potent protease inhibitors now marketed. The goal of this treatment is to achieve and sustain undetectable levels of virus.

Three assumptions are embedded in this treatment model; none of these yet has a strong empirical foundation. The first concerns timing of initiation of combination therapy. David Ho's call to "hit hard and hit early" borrows the infectious disease strategy exemplified in treatment for tuberculosis. It is reasoned that preservation of an intact immune system is more feasible than restoration of one

that is severely compromised. In addition, early in infection, the population of virus is maximally homogeneous and therefore most susceptible to treatment. Furthermore, treatment initiated around the time of seroconversion appears to lower the viral set point, which in turn is associated with an extended period of health.

However, it is not yet known whether early initiation of this complex and demanding therapy is demonstrably superior to delayed treatment, whether future medications may be made unnecessary by use of currently available options, and whether it is reasonable to expect sustained adherence by asymptomatic patients for indefinite periods. In Europe, a number of physicians have raised questions about American guidelines, particularly the early onset of combination treatment. Instead of the American guidelines of treatment onset when viral loads are 10,000 copies or more, they propose 50,000 or 100,000 as a signal for treatment initiation (Alcorn, 1997).

Some European physicians also question the need for three antivirals as first-line treatment, and in several European countries, dual therapy is still widely considered the appropriate first regimen. Preliminary evidence suggests, however, that this is ill advised. Two-year follow-up data from the Merck 035 study showed a persistent advantage for patients started immediately on a three-drug regimen (AZT, 3TC, and indinavir) compared to those who were treated for 6 months with two drugs (AZT, 3TC) to which the third was then added. Not only did the two-drug group have a lower response rate at the end of the first 6 months, but also the subsequent addition of a protease inhibitor was less effective than starting with three drugs, when the groups were compared 2 years later (Mascolini, 1997).

Carrying this one step further, some investigators argue that four antivirals are required to sustain viral suppression in the long run. Several clinical trials are under way to explore the effects of long-term use of four antiviral drugs in this country as well as in Europe.

Finally, what does "undetectable" actually signify? What is undetectable is determined by the sensitivity of the laboratory assay, and this changes as assays are improved. In 1998 the most commonly available viral load assays have a lower limit of 400 copies, under which the assay cannot reliably discriminate presence and number of viral copies. But ultrasensitive assays, which are becoming increasingly available, have a cutoff of 20 rather than 400 copies. One small study found that durability of viral suppression is associated with the lowest level of virus reached, and that patients whose viral load dropped below 20 copies had significantly longer duration of effect than patients whose viral load was between 20 and 400 copies (Mascolini, 1997). Even apart from measurement considerations, is this finding generally valid, and is "undetectable" actually necessary to achieve substantial reduction in progression risk? Will "undetectable" mean indefinite extension of health and life? We do not yet have answers to these questions.

If there is no absolute definition of successful outcome, and if the amount of adherence necessary to achieve what is thought to be a successful outcome similarly remains uncertain, it may not be possible at this time to give decisive answers

about what constitutes adherence "success." The best we can do at present is to work within the current standards and guidelines, to accept the goal of "undetectable" viral load but also to measure what patients actually are doing with their prescribed medications, so that, when more has been learned about necessary and sufficient medication use, retrospective adjustments can be made to the definition of what constitutes adherent behavior.

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Combination Antiretroviral Therapies for HIV

Some Economic Considerations

STEVEN D. PINKERTON and DAVID R. HOLTGRAVE

INTRODUCTION

In December 1995 the first protease inhibitor, saquinavir was approved for the antiretroviral treatment of HIV-infected patients. Four protease inhibitors are now available commercially: saquinavir (Invirase), ritonavir (Norvir), indinavir (Crixivan), and nelfinavir (Viracept). Although resistance to these drugs develops rapidly when used as monotherapy (Mellors, 1997), protease inhibitors can be extremely effective when combined with one or more of the available reverse transcriptase inhibitors, which include zidovudine (Retrovir), didanosine (Virex), zalcatabine (Hivid), stavudine (Zerit), lamivudine (Epivir), nevirapine (Viramune), and delavirdine (Rescriptor). The clinical benefits of combination therapy with a regimen of antiretroviral drugs, typically consisting of two or more reverse transcriptase inhibitors with or without a protease inhibitor, may include markedly reduced plasma viral load, decreased incidence of opportunistic infections, delayed progression to AIDS, short-term reductions in AIDS-related mortality, partial restoration of the immune system, and general improvements in overall health status (Carpenter *et al.,* 1997; Deeks, Smith, Holodniy, & Kahn, 1997). In particular, combination antiretroviral therapy can reduce the quantity of viral RNA circulating in the blood by as much as one or two log units (one log unit equals a 90% reduction; two log units represents a 99% reduction).

The most recent guidelines of the International AIDS Society–USA Panel on antiretroviral therapy recommend combination therapy for all patients with plasma

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viral load levels above 5000 to 10,000 copies per mL, or with CD4+ cell counts below 500 per mm^3; the preferred initial regimen is triple combination therapy (two reverse transcriptase inhibitors plus a protease inhibitor) (Carpenter *et al.,* 1997). The potential economic implications of these recommendations are profound. As discussed further later, triple combination therapy can cost $13,000 or more per year, not including the cost of viral load and CD4+ cell level monitoring. The high cost of these drugs puts them beyond the economic reach of the majority of the world's HIV-infected populace, 90% of whom live in developing countries.

The high cost of antiretroviral therapy has also caused some to wonder whether spending millions of dollars per year on these therapies is a cost-effective use of America's limited health care resources. Might not this money be better spent elsewhere? Conversely, the demonstrated effectiveness of combination therapies in limiting viral replication in HIV-infected individuals has led others to call for an expanded, prophylactic role for these therapies, which could be used as a "morning-after" treatment to prevent the establishment of infection following HIV exposure. The suggestion that these therapies might also suppress viral transmission by reducing the infectiousness of patients on effective antiretroviral therapy has further blurred the distinction between HIV prevention and HIV treatment.

This chapter focuses on some of the myriad economic implications of the new combination therapies. In order to provide basic familiarity with some of the terms and techniques of economic efficiency analyses, the chapter begins with a brief review of the methods employed in cost-effectiveness studies. The annual and long-range costs of currently recommended antiretroviral medications, and combination therapies in particular, are discussed in the next section, followed by a review, synthesis, and extension of the literature on the cost-effectiveness of combination therapy. The potential role of combination therapies in HIV prevention is discussed in the next two sections. In the first, a simple model of HIV transmission is developed and is used to examine the interactions of three factors: (1) potential therapy-induced reductions in the infectiousness of HIV-positive patients, (2) increased opportunities for transmission resulting from the improved health and greater longevity experienced by patients on combination therapy, and (3) increased sexual risk taking among both infected and uninfected persons as a consequence of diminished perceptions of infectiousness. The penultimate section discusses the cost-effectiveness of using antiretroviral drugs for prophylaxis in health care workers who have been occupationally exposed to HIV, and for prophylaxis following sexual or injection-associated exposures. The validity and utility of distinguishing and segregating HIV treatment from HIV prevention efforts is debated in the chapter's concluding section.

COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS

A main focus of this chapter is the cost-effectiveness of combination antiretroviral therapy. But what does it mean to say that a therapy or program is "cost-effective"? The brief overview of cost-effectiveness analysis presented in this

section is intended to acquaint the reader with the basic principles underlying this methodology and to provide an answer to this important question.

In the context of this examination, *cost-effectiveness* analysis is a tool that assists public health and health care decision makers to assess the economic efficiency of HIV prevention and treatment programs. The main benefit of cost-effectiveness analysis is that it provides a means to combine the costs and consequences of a program into a single measure of its overall economic efficiency. This permits decision makers to balance the costs and consequences of different programs in order to maximize the impact of their spending on prevention or treatment (or both). For example, a public health department might be interested in choosing between two HIV prevention interventions with very different characteristics, only one of which can be funded. One might be highly effective but very costly to deliver, on a per-client basis. The other might be less expensive but also less effective. Thus, on the basis of costs alone, the second program would be preferred, whereas on the basis of program impact, the first would be selected. Rather than comparing apples and oranges, however, the decision maker can instead use the techniques of cost-effectiveness analysis to derive a cost-effectiveness ratio for each program, and then select the program with the smaller such ratio (alternatively, the costs and consequences of the two programs can be combined into a single "incremental" cost-effectiveness ratio).

The cost-effectiveness ratio is the ratio of net program costs to the expected health outcomes. The numerator of the ratio is always the net cost, which is the cost of the program itself, minus any savings in averted disease, plus the cost of any side effects of the program. The denominator of the cost-effectiveness ratio represents the positive health outcomes that are expected, and may depend on the particular type of health care or health promotion program being considered. For example, in an analysis of a coronary artery bypass graft (CABG) surgery program, the cost-effectiveness ratio would take the form: Net Cost per CABG surgery. The net cost would include the cost of performing the surgeries, minus any surgery-related medical care savings, such as potential reductions in the need for angioplasties, plus the cost of treating any surgical complications. (In most analyses, the numerator also includes items related to the "opportunity costs" associated with undergoing surgery. For example, the patient might need to take time off from work, entailing a loss in productivity. Or he might need to travel a long distance to visit a regional medical center. These costs also should be factored into the cost-effectiveness ratio.)

Although the Net Cost per CABG ratio might be a reasonable measure of the economic efficiency of CABG surgery programs, it cannot be applied to other areas of health care, such as HIV treatment. A more general measure of health outcomes is needed to permit comparisons across health care areas. One popular choice is years of life saved. For instance, suppose CABG surgery extends the lives of patients by 2 years, on average, at a cost of $50,000, whereas kidney transplantation costs $200,000 and saves 5 years per patient (these are hypothetical estimates to be used for the purpose of illustration only). The heart surgery therefore

costs $25,000 per year of life saved, versus $40,000 per year of life saved for kidney transplantation. If a choice were needed between performing four CABGs or a single kidney transplant (both options have a total cost of $200,000), this hypothetical economic efficiency analysis would favor heart surgery.

The years of life saved approach can be generalized by associating to each year spent in a particular health state (such as a year in perfect health, or a year spent rehabilitating from a skiing accident) a weight that represents the quality of life of time spent in that state. The quality of life weights range from 0 (death) to 1 (perfect health). According to one study, at any given time the average health of the American population is about .94 (Patrick & Erickson, 1993). For example, if someone spent 2 years at perfect health, followed by 1 year recovering from a skiing injury (weight = .88, say), and then 2 years at average health, the total number of quality-adjusted life years (QALYs) corresponding to this 5-year period would be $2 \cdot 1.0 + 1 \cdot 0.88 + 2 \cdot 0.94 = 4.76$.

A cost-effectiveness analysis in which the outcome of interest is the Net Cost per QALY saved is also called a *cost-utility* analysis. The use of a general outcome measure such as QALYs in the denominator of cost-effectiveness ratios permits comparisons to be drawn across disparate areas of health care and health promotion. Moreover, because cost-utility analysis explicitly incorporates quality of life considerations, it is able to capture effects on morbidity as well as mortality, which is important because there are many health care interventions and procedures that have little or no impact on the patient's longevity, but significantly improve quality of life (many psychiatric interventions fall into this category). The recently convened Panel on Cost-Effectiveness in Health and Medicine recommends that all cost-effectiveness studies include a "referent case" cost-utility analysis to ensure comparability with other studies (Gold, Siegel, Russell, & Weinstein, 1996).

Because the purpose of cost-effectiveness (and cost-utility) analysis is to permit comparisons between different health care programs, a program can only be "cost-effective" in reference to another program. When an explicit referent is specified, one program can be said to be more cost-effective than the other; in the preceding illustration, for example, CABG surgery was more cost-effective than kidney transplantation. In other instances, a specific referent is not identified and the comparison is implicit. In such cases, a program is considered cost-effective only if it represents a sound expenditure of limited economic resources, compared to other potential uses of these resources. In an environment of unlimited economic resources, all programs would be cost-effective. In the real world, however, only the most economically efficient programs are considered cost-effective.

Although there is no universally agreed-upon cost per QALY threshold below which programs are considered cost-effective, some general guidelines can be drawn by considering the range of health care programs that have been funded in the past. In general, programs that cost less than about $40,000 per QALY are "cost-effective by current standards"; those in which cost-utility ratios exceed $180,000 per QALY are "questionable in comparison with other health care ex-

penditures"; and those with intermediate cost-utility ratios are "possibly controversial, but justifiable by many current examples" (Kaplan & Bush, 1982, p. 74; ratios updated to 1996 dollars by Pinkerton & Holtgrave, 1998). In the special case that the net program cost is negative, the program is called *cost-saving.* As the label implies, a cost-saving program actually saves economic resources in the long run, hence is clearly cost-effective.

Before concluding this discussion of cost-effectiveness analysis, two methodological issues must be discussed. The first is the practice of discounting both the economic and health-related quantities in these analyses. Discounting is a standard technique that is used in economic analyses to devalue expenses that occur in the future; the basis of discounting is the observation that economic resources are more highly valued in the present than in the future, independent of inflation. The Panel on Cost-Effectiveness in Health and Medicine recommends a standard 3% annual discount rate. The "present value" of $100 discounted at 3% is $97.08 after 1 year, $94.26 after 2 years, and $91.51 after 3 years, (The formula for calculating the present value of a quantity A, discounted for n years at an annual rate of r percent is: Present value = $A/(1 + r/100)^n$.) The practice of discounting favors programs in which benefits are realized in the near present but where costs are deferred until the future. In contrast, prevention programs typically exhibit the opposite pattern, incurring costs in the present for benefits in the future, and therefore appear most cost-effective when a small discount rate is used (Phillips & Holtgrave, 1997).

As noted, health outcomes such as QALYs are also discounted in most analyses. Although the practice of discounting health outcomes is not uncontroversial, discounting only economic resources can lead to paradoxical scenarios in which, for example, the implementation of a program is endlessly delayed because its projected future yield is always greater than its present value (Keeler & Cretin, 1983; Weinstein & Stason, 1977). For this reason, the Panel recommends that health outcomes be discounted at the same rate as economic resources (Gold *et al.,* 1996).

When conducting or reporting the results of a cost-effectiveness analysis it is important to specify the perspective from which the analysis was performed. The perspective determines which program costs and consequences are included in the analysis. An analysis conducted from the perspective of a private hospital, for example, would include only those costs borne by the hospital and not reimbursed by a third party. Other valid perspectives include those of the patient, third party payers (for example, insurance companies), and society in general. An analysis conducted from the societal perspective includes all costs and consequences of the program, regardless of who pays the costs and who experiences the consequences. The Panel recommends that the referent case cost-utility analysis (see previous explanation) be conducted from the societal perspective. This perspective is especially appropriate when assessing programs that are either wholly or partially supported by governmental funding.

THE COST OF ANTIRETROVIRAL THERAPY

As indicated in Table 1, combination antiretroviral therapy with two reverse transcriptase inhibitors (RTIs) or two RTIs and a protease inhibitor is very expensive. For example, the average annual wholesale drug costs for dual combination therapy with the nucleoside analogs zidovudine and lamivudine is approximately $6,000 under recommended dosing schedules (Feder & Milch, 1997; "HIVAntiviral Drug Guide," 1998; "New Drugs for HIV Infection," 1996); the addition of a protease inhibitor can increase this cost by approximately $4,000 to $8,000, Thus, drug costs for triple combination therapy with zidovudine, lamivudine, and a protease inhibitor can total as much as $14,000 annually at wholesale prices; the retail price may be 25% to 35% higher (Deeks, Smith, *et al.,* 1997). The inclusion of regular viral load monitoring, CD4+ cell assays, and treatment for therapy-related side effects would drive the overall cost of combination therapy even higher.

It is uncertain, at present, whether complete eradication of the virus is an achievable goal. Recent findings suggest that HIV infection can persist in resting CD4+ cells and other sanctuaries after as long as 2 or 3 years of effective antiretroviral therapy, and therefore that antiretroviral therapy may entail a lifelong commitment (Baker, 1997; Finzi et al., 1997; Wong *et al.,* 1997). The survival benefit of long-term therapy with currently available antiretrovirals is also unknown (Carpenter *et al.,* 1997). Thus, the total cost of combination therapy over a patient's lifetime cannot be ascertained with certainty.

Table 2 lists the cumulative drug cost for up to 30 years of treatment with three representative combination therapies (zidovudine + lamivudine, stavudine

Table 1. Annual Cost of Antiretroviral Drugs

Antiretroviral agent	Class[a]	Usual dosing[b,c]		Approximate annual cost		
Zidovudine (ZDV; Retrovir)	NRTI	200 mg.	3 times a day	$2,900[b]	$3,300[c]	$3,500[d]
Didanosine (ddI; Videx)	NRTI	200 mg.	2 times a day	$1,700	$2,200	$2,200
Zacitabine (ddC; Hivid)	NRTI	0.75 mg.	3 times a day	$2,600	$2,500	$2,500
Stavudine (d4T; Zerit)	NRTI	40 mg.	2 times a day	$2,800	$2,900	$2,700
Lamivudine (3TC; Epivir)	NRTI	150mg.	2 times a day	$2,700	$2,700	$2,800
Nevirapine (Viramune)	NNRTI	200 mg.	2 times a day	$3,000	Not avail.	$3,000
Delavirdine (Rescriptor)	NNRTI	400 mg.	3 times a day	$2,200	Not avail.	Not avail.
Saquinavir (Invirase)[e]	PI	600 mg.	3 times a day	$7,000	$6,900	$7,100
Ritonavir (Norvir)	PI	600 mg.	2 times a day	$6,800	$8,000	$8,100
lndinavir (Crixivan)	PI	800 mg.	3 times a day	$5,500	$4,300[f]	$6,000
Nelfinavir (Viracept)	PI	200 mg.	2 times a day	$3,000	$4,300	$6,000

[a] NRTI = nucleoside analog reverse transcriptase inhibitor: NNRTI = nonnucleoside analog reverse transcriptase inhibitor; PI = protease inhibitor.
[b] Source: "HIVAntiviral Drug Guide"(1998); rounded off to the nearest one hundred dollars.
[c] Source: "New Drugs for HIV Infection"(1996); rounded off to the nearest one hundred dollars.
[d] Source: Feder & Milch (1997); rounded off to the nearest one hundred dollars.
[e] Saquinavir is now available in a soft gel formulation as Fortovase, with an estimated annual cost of $5,700, "HIV Antiviral Drug Guide"(1998).
[f] Direct price available from Stadtlander Pharmacy "New Drugs"(1996).

Table 2. Cumulative Cost of Combination Therapy

Years of therapy	Undiscounted costs			Discounted at 3%		
	ZDV + 3TC	d4T + ddI + indinavir	ZDV + 3TC + saquinavir	ZDV + 3TC	ZDV + 3TC + indinavir	ZDV + 3TC + saquinavir
1	$6,000[a]	$9,400[a]	$12,900[a]	$6,000[b]	$9,400[b]	$12,900[b]
2	$12,000	$18,800	$25,800	$11,800	$18,500	$25,400
3	$18,000	$28,200	$38,700	$17,500	$27,400	$37,600
4	$24,000	$37,600	$51,600	$23,000	$36,000	$49,400
5	$30,000	$47,000	$64,500	$28,300	$44,300	$60,900
6	$36,000	$56,400	$77,400	$33,500	$52,400	$72,000
7	$42,000	$65,800	$90,300	$38,500	$60,300	$82,800
8	$48,000	$75,200	$103,200	$43,400	$68,000	$93,300
9	$54,000	$84,600	$116,100	$48,100	$75,400	$103,500
10	$60,000	$94,000	$129,000	$52,700	$82,600	$113,300
11	$66,000	$103,400	$141,900	$57,200	$89,600	$122,900
12	$72,000	$112,800	$154,800	$61,500	$96,400	$132,300
13	$78,000	$122,200	$167,700	$65,700	$103,000	$141,300
14	$84,000	$131,600	$180,600	$69,800	$109,400	$150,100
15	$90,000	$141,000	$193,500	$73,800	$115,600	$158,600
20	$120,000	$188,000	$258,000	$91,900	$144,000	$197,700
25	$150,000	$235,000	$322,500	$107,600	$168,600	$231,400
30	$180,000	$282,000	$387,000	$121,100	$189,800	$260,400

[a] Source: "HIV Antiviral Drug Guide" (1998); rounded off to the nearest one hundred dollars.
[b] Rounded off to the nearest one hundred dollars.

+ didanosine + indinavir, zidovudine + lamivudine + saquinavir). Costs are shown both undiscounted and discounted at a 3% annual rate. The undiscounted totals for 15 years of therapy range from $90,000 for zidovudine plus lamivudine, to over $193,000 for triple combination therapy that includes saquinavir in addition to zidovudine and lamivudine (the cost of the stavudine + didanosine + indinavir combination is intermediate in cost). The impact of discounting over 15 years is substantial: The corresponding discounted total costs are approximately $74,000 (zidovudine + lamivudine) and $159,000 (zidovudine + lamivudine + saquinavir), both of which represent reductions of nearly 20% from the undiscounted estimates.

In a recent study of the overall cost of treating HIV, including costs associated with ambulatory care, hospitalizations, opportunistic infection prophylaxis and treatment, and monitoring of viral load and CD4+ cell counts, Holtgrave and Pinkerton (1997) estimated that a 26-year-old patient who received dual combination therapy with zidovudine and lamivudine soon after infection was detected, and who was switched to triple combination therapy 3 years later, would incur HIV-related medical care costs of over $195,000 over the course of his or her lifetime (all costs are discounted at a 3% annual rate). The authors also considered

two other, less realistic scenarios in addition to this "intermediate cost" scenario, which was based on the 1996 guidelines of the International AIDS Society–USA Panel on antiretroviral therapy (Carpenter *et al.,* 1996). In the low-cost scenario, the patient receives only zidovudine monotherapy, resulting in lifetime medical care cost just over $87,000. (This scenario, which no longer represents an acceptable level of care in developed nations, was included in the analysis for comparability with previous studies, such as Guinan, Farnham, & Holtgrave, 1994.) At the other extreme (the high-cost scenario), they estimated the lifetime HIV-related medical care costs at $297,000 for a patient who begins triple combination therapy immediately after seroconverting and who lives for 2 1 additional years.

In this analysis, antiretroviral drug therapy was associated with a reduction in the number of QALYs that the patient would lose to HIV disease. The numbers of discounted QALYs lost in the low-, intermediate, and high-cost scenarios are 13.18, 11.23, and 9.34, respectively (Holtgrave & Pinkerton, 1997). There are thus three unique <Cost,QALY> pairs corresponding to these medical care scenarios: <$87,000,13.18>, <$195,000,11.23>, <$297,000,9.34>. When conducting cost-effectiveness analyses of HIV treatment or prevention programs, it is important that paired cost and QALY estimates be considered together.

Clearly, an HIV prevention intervention can be cost-effective with respect to one therapy (<Cost,QALY> pair), but not to another, more expensive or less effective therapy. As new HIV therapies are developed, new <Cost,QALY> pairs will be introduced. As discussed in the following section, whether a particular HIV prevention intervention is more or less cost-effective with respect to the new therapy often depends not only on the <Cost,QALY> pairs for new and existing therapies, but also on the characteristics of the prevention program itself.

Treatment Advances and the Cost-Effectiveness of Prevention

The cost-effectiveness of HIV prevention programs, such as cognitive-behavioral skills training interventions in which participants learn effective safer sex negotiation skills, or needle exchange programs largely depends on the potential for savings in averted medical care costs. At first glance it might appear that the much greater costs of combination therapy would enhance the cost-effectiveness of HIV prevention interventions. But, in fact, whether a particular prevention program becomes more or less cost-effective as a result of advances in HIV treatment depends not only on the costs and consequences of the new therapy and the one it might replace, but also on the specific characteristics of the prevention program.

Suppose that a new therapy for HIV has been developed. In comparison with the existing therapy, four distinct possibilities can be identified: the new therapy is (1) less expensive and more effective, (2) less expensive and less effective, (3) more expensive and more effective, or (4) more expensive and less effective. For possibility (4), a switch to the new therapy cannot be justified on either economic or therapeutic grounds, and therefore can be eliminated from further consideration. Conversely,

switching to a less expensive and more effective therapy (situation (1)) is clearly advantageous. Not surprisingly, the introduction of a less costly and more effective treatment for HIV would make HIV *prevention* relatively less cost-effective.

The interesting situations occur when economic and therapeutic considerations favor different therapies (cases (2) and (3)). First, suppose that the new therapy is both more effective and more costly than the existing therapy (this describes the recent advancement from zidovudine monotherapy to combination therapy). The overall effect of this advance is to make efficient prevention programs more cost-effective and inefficient programs less so (Pinkerton & Holtgrave, under review). Indeed, an exact "efficiency threshold" can be determined that distinguishes prevention programs that become more cost-effective from those that become less cost-effective. For example, Holtgrave and Pinkerton's (1997) medium-level-of-care scenario improves the cost-effectiveness of a particular prevention intervention, relative to the low-level-of-care scenario, only if the program can prevent an HIV infection for less than approximately $800,000 (Pinkerton & Holtgrave, under review). In contrast, switching to a new therapy that is both less expensive and less effective would enhance the cost-effectiveness of *inefficient* rather than efficient prevention programs (Pinkerton & Holtgrave, under review).

Drug Financing Issues

The high per-patient cost of antiretroviral therapy has placed an inordinate burden on publicly funded efforts to ensure access to these drugs. There are an estimated 700,000 Americans currently living with HIV infection (Holmberg, 1996), roughly one half to two thirds of whom are aware of their HIV status (Berrios *et al.,* 1993; Sweeney, Fleming, Karon, & Ward, 1997). A hypothetical drug assistance program that provided dual combination therapy with zidovudine and lamivudine to every seropositive person in the United States would therefore cost between $2 and $3 billion (at $6,000 per annum), not including costs associated with viral load/CD4+ monitoring and treatment for possible side effects of the drug therapy. (The addition of a protease inhibitor would more than double this hypothetical cost.) Even if the drugs could be procured in bulk at a fraction of the wholesale price, such a program would still represent a substantial economic burden. In comparison, the annual cost of providing zidovudine to all HIV-infected persons in Latin America would exceed $200 million (Kimball, Suarez, Gonzalez, Zessler, & Zacarias, 1990), the cost of providing triple combination therapy to 25% of the HIV-positive population in sub-Saharan Africa would exceed 8% of the gross national product of this region (Hogg, Anis, Weber, O'Shaughnessy, & Schechter, 1997; see also Adler, 1998), and the provision of antiretroviral drugs to all people with asymptomatic HIV infection in Thailand would cost between 235% and 630% of the national AIDS budget (Van Praag & Perriens, 1996).

In the spring of 1997, the National Association of State and Territorial AIDS Directors and the AIDS Treatment Data Network surveyed all 52 AIDS service

programs in the United States that are recipients of Ryan White CARE Act Title II funnding to better understand the current status of AIDS Drug Assistance Programs (ADAPs) (National Alliance of State and Territorial AIDS Directors, 1997). ADAPs are designed to increase access to treatments for persons living with HIV disease who lack adequate public or private health insurance. There are an estimated 140,000 to 280,000 persons with HIV in the United States who may be eligible for state ADAP assistance. The average per client expenditure during the last 6 months of 1996 was $506 a month. It would therefore cost approximately $850 million to $1.7 billion, annually, to provide coverage to all eligible HIV-infected persons. To provide coverage to the approximately 80,000 clients served during calendar year 1996 would have cost over $485 million. In contrast, the total funding for the 52 ADAPs in fiscal year 1997 was only $385 million, much of which was provided by the federal government.

In 1997, many states and territories undertook emergency measures to obtain sufficient funding to meet the demand for new treatments. Thirty of the 52 ADAPs surveyed had supplemented federal moneys with state funding and three were forced to "severely limit services in response to increased demand and costs" (these three states were South Dakota, Mississippi, and Florida). There is wide variability among the states and territories in terms of eligibility criteria and coverage types and levels. For example, not all cover the latest available treatments for HIV disease; in particular, in 1997 four states did not include protease inhibitors in their formularies. States are now exploring a wide variety of ways to increase access to treatments, such as health insurance continuity programs and purchasing insurance through state risk pools (National Alliance of State and Territorial AIDS Directors, 1997).

THE COST-EFFECTIVENESS OF ANTIRETROVIRAL THERAPY

Although combination antiretroviral therapy is expensive, it can also be highly effective, at least in the short term, for some people. Moreover, several economic efficiency studies have reported that combination therapy appears cost-effective when the costs and benefits of combination therapy are weighed against one another (Chancellor, Hill, Sabin, Simpson, &Youle, 1997; Cook *et al.,* 1997; Li, Skolnik, & Wong, 1997; Moore & Bartlett, 1996). From an economic resource utilization perspective, the salient benefits of effective antiretroviral therapy include (1) reduced short-term inpatient and outpatient hospital utilization, (2) reduced medical care charges due to decreased incidence of opportunistic infections, (3) potentially increased patient productivity, and (4) improved health-related quality of life.

Much has been made of the potential of effective antiretroviral therapy to reduce short-term costs associated with hospitalization and treatment for opportunistic infections (Stephenson, 1997). According to calculations by a team of

French investigators, for example, the savings due to combination therapy–induced reductions in hospitalization and AIDS-related treatment costs at many (but not all) French AIDS referral centers were probably sufficient to offset the cost of the drugs themselves (Mouton *et al.,* 1997). However, the duration of benefit that can be expected from combination therapies has not been established, and it is presently unknown whether these apparent savings are real or whether AIDS-related hospitalizations and other medical care costs simply have been delayed into the future, as patients eventually develop AIDS (Pinkerton & Holtgrave, in press).

Alternatively, some of these costs may have shifted from inpatient services to ambulatory care. At St. Vincent's Hospital and Medical Center in New York City, for example, there was a sharp reduction in the average inpatient census beginning at the end of 1995, when the first protease inhibitor was approved by the FDA, and continuing through December 1996 (Torres & Barr, 1997). Conversely, there was a 33% increase in outpatient visits by HIV-positive patients from 1995 to 1996. Thus, "it is unclear whether the savings from the decreased use of inpatient services and the decrease in the average length of stay are offset by higher drug costs and the increased use of ambulatory services" (p. 1532).

Of course, simply delaying the onset of AIDS would reduce overall AIDS-related mortality by increasing the likelihood that AIDS patients would succumb first to a competing cause of mortality. Moreover, postponing expenditures associated with AIDS and end-of-life care for persons with HIV could itself produce potentially substantial economic benefits because these future costs would be heavily discounted.

In estimating the cost and quality-of-life consequences of treating HIV disease, Holtgrave and Pinkerton (1997; see the preceding discussion) assumed that combination therapy would delay, but not prevent, the onset of AIDS and the higher costs associated with end-of-life care. According to this conservative analysis of the benefit of combination therapy, initial therapy with two nucleoside analogs followed by triple combination therapy (Holtgrave and Pinkerton's intermediate-care scenario) costs $108,000 more than zidovudine monotherapy (low-cost scenario) and results in 1.95 fewer lost QALYs, after discounting both dollars and QALYs at a 3% annual rate. The cost per QALY saved by combination therapy, relative to monotherapy, is approximately $55,000. Thus, according to this analysis, combination therapy is probably cost-effective by conventional standards (see the preceding section on cost-effectiveness analysis). However, it should be noted that it was not the objective of the Holtgrave and Pinkerton study to assess the cost-effectiveness of combination therapy; moreover, this conservative analysis excludes other potential benefits (such as increased economic productivity) that would further enhance the cost-effectiveness of combination antiretroviral therapy.

Direct assessments of the economic efficiency of protease inhibitor combination therapy provide stronger evidence that this therapy is cost-effective. For example, Moore and Bartlett (1996) compared zidovudine monotherapy to triple

combination therapy with zidovudine, lamivudine, and indinavir in asymptomatic and symptomatic patients with CD4+ counts of less than 500 cells/mm^3 and no previous history of AIDS-defining illnesses. The incremental cost-effectiveness (i.e., the cost-effectiveness of triple combination therapy relative to monotherapy) was estimated at $10,000 per life year saved (discounted at a 4% annual rate) for the first 6 years of therapy. Because the analysis was terminated after 6 years, it is unclear whether the findings of this study—which noted savings for triple combination therapy due to decreased utilization of ambulatory care resources and reduced hospitalizations—would remain unchanged if the analytic horizon were extended sufficiently to better incorporate potential AIDS-related end-of-life costs for patients on triple combination therapy.

When compared to dual combination therapy rather than to zidovudine monotherapy, triple combination therapy appears somewhat less efficient, though still cost-effective by conventional standards. Cook and colleagues (1997), for example, assessed the cost-effectiveness of triple combination therapy with zidovudine, lamivudine, and indinavir compared to therapy with zidovudine and lamivudine alone, in a population of clinical trial participants who had not yet experienced an AIDS-defining illness. They conservatively assumed that the duration of drug-induced viral RNA suppression extended only through the end of the clinical trial follow-up period (approximately 1 year). Under this assumption, they calculated an incremental cost-effectiveness ratio of $30,000 per life year saved (at an unspecified discount rate) for triple combination therapy, relative to dual combination therapy.

Similarly, Li and colleagues (1997) estimated that the addition of ritonavir to a regimen of reverse transcriptase inhibitors for antiretroviral-experienced patients with CD4+ cell counts below 100 cells/mm^3 would increase lifetime treatment costs by $46,600 while increasing quality-adjusted life expectancy by 1.1 years. The resulting incremental cost-effectiveness ratio was about $43,000 per QALY, which falls within the range generally considered cost-effective in comparison with other medical procedures and therapies.

In summary, although the analyses summarized here differ in methodological particulars (such as the discount rate and use of quality-of-life adjustments), they converge in suggesting that triple combination therapy can be cost-effective compared to either monotherapy or therapy with two reverse transcriptase inhibitors.

ANTIRETROVIRAL THERAPY AS PREVENTION

In the preceding sections the main benefits attributed to effective combination therapy have been to extend patients' lives and enhance their quality of life. But highly active antiretroviral therapy may have a prophylactic benefit as well. In theory, antiretroviral therapy could reduce the probability of HIV transmission from an infected person to his or her sexual or syringe-sharing partners by dimin-

ishing the quantity of virus in the plasma, semen, or cervicovaginal fluids. If this preventive benefit of antiretroviral treatment were realized, then therapy would appear even more cost-effective and other forms of prevention (such as behavioral interventions) would appear less so.

For therapy to serve a prophylactic function would require that (1) the decreases in blood plasma viral load observed with effective therapy translate into decreases in the quantity of virus present in the genital fluids (this does not apply to injection-associated transmission), and (2) the probability of viral transmission is positively correlated with the amount of virus present in these fluids. The scientific evidence for the first of these assumptions is somewhat equivocal, with several investigators reporting diminished viral burden in the semen and cervicovaginal secretions of patients on antiretroviral regimens, including protease inhibitor combination therapy and zidovudine monotherapy (Anderson *et al.,* 1992; Boswell, *et al.,* 1997; Gilliam *et al.,* 1997; Gupta *et al.,* 1997; Hamed, Winters, Holodniy, Katzenstein, & Merigan, 1993; Lennox *et al.,* 1997; Seage *et al.,* 1993; Speck *et al.,* 1996; Vernazzi, Gilliam, Dyer, *et al.,* 1997; Vernazzi, Gilliam, Flep, *et al.,* 1997; Wiktor *et al.,* 1996) while other investigators failed to find a significant relationship (Hénin *et al.,* 1993; Krieger *et al.,* 1991; Liuzzi, Chirianni, & Bagnarelli, *et al.,* 1996; Melvin *et al.,* 1997; Rasheed, Li, Xu, & Kovacs, 1996). Related studies have found no correlation between blood plasma viral titers and the quantity of virus in the genital fluids of HIV-infected individuals (Jurriaans, Vernazza, Goudsmit, Boogaard, & Van Gemen, 1996; Liuzzi, Chirianni, Clementi, *et al.,* 1996). Moreover, there is genetic evidence that genital and plasma HIV arise from separate viral reservoirs (Byrn, Zhang, Eyre, McGowan, & Kiessling, 1997; Subbarao, Wright, Ellerbrock, Lennox, & Hart, 1998; Zhu *et al.,* 1996).

With regard to the second assumption, little is presently known about the relationship between viral quantities in the genital fluids and the probability of transmission. HIV-infected patients exhibit wide variability in the quantity of virus present in the plasma (and presumably the genital secretions as well), with viral load ranging from millions of copies per mL to undetectable levels. It is unknown whether infectiousness varies with viral load according to a dose–response relationship, or whether the probability of infection depends on the quantity of transmitted virus exceeding some threshold.

Several studies indicate that plasma viral load is positively correlated with increased infectiousness (Fiore *et al.,* 1997; Lee *et al.,* 1996; Operskalski *et al.,* 1997; Ragni, Faruki, & Kingsley, 1998). Moreover, in one study, HIV-infected men who received zidovudine monotherapy were 50% less likely to transmit the virus to their female partners than were untreated men (Musicco *et al.,* 1994). Reductions in the probability of HIV transmission from zidovudine-treated women to their male sexual partners have also been reported (Chirianni *et al.,* 1992). Because protease inhibitor combination therapy is much more effective than zidovudine monotherapy at suppressing viral load, combination therapy could be expected to exert an even greater impact on host infectiousness.

Conversely, it is also possible that, despite reducing host infectiousness, antiretroviral therapy might actually *increase* the frequency of transmission by extending the lives and improving the health of HIV-infected persons, and thereby increasing the opportunity for transmission. Thus, combination therapy might reduce the probability of viral transmission for each act of intercourse, while simultaneously increasing the number of occasions on which such transmission might potentially occur. Too little is known about the long-term effects of combination therapy and about the impact of this therapy on host infectiousness to draw conclusions about whether it will lead to an overall increase or decrease in the number of new infections. Nevertheless, the interaction of these competing influences can be modeled mathematically, as explored later.

Considerable concern has also been expressed in the HIV prevention community that the availability of effective antiretroviral therapy has diminished the perceived severity of HIV illness among some at-risk persons, and that perceptions—accurate or not—that combination therapy renders the virus less infectious might lead some HIV-infected and at-risk individuals to become less vigilant in maintaining safer sex practices (Kelly, Otto-Salaj, Sikkema, Pinkerton, & Bloom, 1998; see also Chapter 7, this volume). Although there have been numerous anecdotal reports on the Internet and in the gay and popular press of increased sexual risk taking, there is very little empirical evidence documenting this phenomenon, as yet. In one of the few studies to date, Dilley, Woods, and McFarland (1997) interviewed 54 HIV-negative men who have sex with men about the impact of recent advances in the management of HIV infection on their perceptions of the severity of HIV disease and the continued need for safer sex precautions. Twenty-six percent reported that they were "less concerned about becoming HIV-positive" because of the new therapies, and 13% "strongly" or "somewhat" agreed with the statement, "I am more willing to take a chance of getting infected when having sex." These results suggest that at least *some* individuals might take greater risks as a consequence of the new treatments.

EXPLORATORY MODEL OF TREATMENT-INDUCED INFECTIOUSNESS REDUCTIONS AND SECONDARY TRANSMISSION

A simple model of the sexual transmission of HIV (Pinkerton & Abramson, 1994, 1998) can be used to examine the issues introduced previously. Suppose first that host infectiousness is proportional to plasma viral load (Pinkerton & Abramson, 1996). Then, the one to two log unit reductions observed in many patients receiving combination therapy would be associated with a 90% to 99% decrease in the probability of transmission (Kelly *et al.,* 1998), which is similar to the reduction achieved through the use of latex condoms (Pinkerton & Abramson, 1997). Extreme caution is warranted here, however. The reader is reminded that the model proposed here is based on a number of as yet unverified assumptions.

Suppose an HIV-infected person has intercourse n times with each of *m* uninfected partners, and let a denote the per-act probability of transmission (or "infectivity"). The expected number of partners who would become infected is

$$R = m\,[1 - (1 - \alpha)^n] \tag{1}$$

Assume that combination therapy results in a longer lifetime, hence greater opportunity for sexual activity. Let $r < 1$ denote the proportionate reduction in infectivity that results from effective combination antiretroviral therapy and let μ denote the number of partners the patient has after initiating therapy. If the number of acts per partner is still *n,* then the number of infections expected among his or her partners is

$$R_c = \mu[1 - (1 - \alpha r)^n] \tag{2}$$

Notice that the total number of sex acts has increased from $m \bullet n$ to $\mu \bullet n$, but the per-act transmission probability has decreased from α to αr.

A number of factors besides viral load can potentially influence HIV infectivity, including the particular sex act (e.g., anal intercourse is riskier than vaginal intercourse, and the receptive partner is at greater risk than the insertive partner), the strain of HIV, genetic factors, and the presence or absence of additional cofactors, especially STDs and genital ulcers (Freidland & Klein, 1987; Holmberg, Horsburgh, Ward, & Jaffe, 1989; Nicolosi, 1992; O'Brien, Shaffer, & Jaffe, 1993; Royce, Seña, Cates, & Cohen, 1997). An additional important factor is, of course, whether condoms are used. A recent meta-analysis of published studies of HIV transmission from HIV-infected individuals to their regular partners suggests that condoms are nearly 95% effective in preventing the transmission of HIV, in practice—that is, even when user errors are taken into consideration (Pinkerton & Abramson, 1997). When used correctly and consistently, the potential efficacy of condoms is much greater.

The special case of no increase in the number of sex partners is illustrated in Figure 1, which shows the proportion of partners who would become infected as a result of *n* acts of receptive anal intercourse with an infected person who is receiving either no treatment or treatment that reduces the per-act transmission probability by one or two log units. The data in this illustration were generated assuming that the per-act probability of transmission for unprotected receptive anal intercourse equals .02 (see Katz & Gerberding, 1997; Pinkerton, Holtgrave, & Bloom, 1998) and that it is reduced to .001 by the consistent use of 95% effective condoms (Pinkerton & Abramson, 1997), and to .002 (a one log unit reduction) or .0002 (a two log unit reduction) by combination therapy. As shown in Figure 1, both consistent condom use and effective antiretroviral treatment substantially reduce the transmissibility of HIV. For maximal suppression, of course, condom use should be combined with treatment.

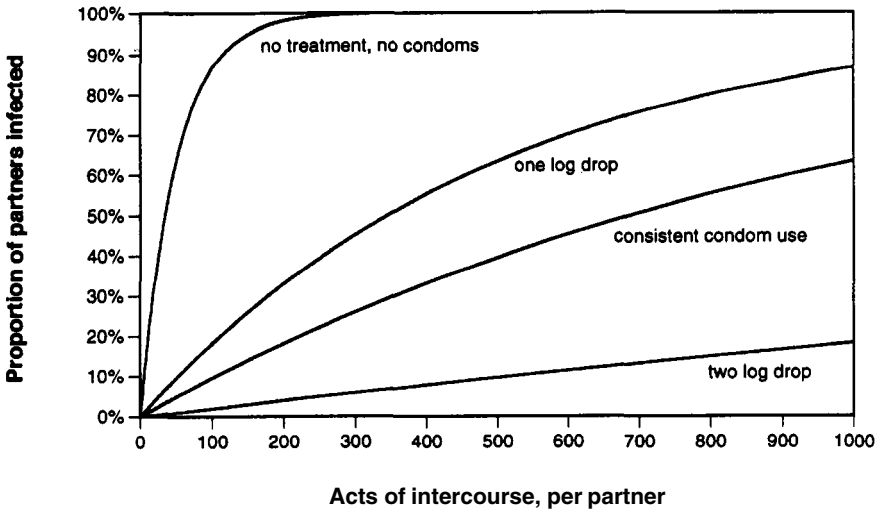

Figure 1. Proportion of partners who would become infected following receptive anal intercourse with an HIV-infected person. Four scenarios are shown: The infected person is receiving effective antiretroviral therapy leading to a one or two log unit reduction in infectiousness, or is not receiving treatment but uses condoms consistently, or is not on therapy and never uses condoms.

If there *is* an increase in the number of sex partners, due to the greater longevity of persons receiving combination therapy, then the question becomes: When is the increase sufficient to negate the preventive benefits arising from the lower infectiousness of infected persons receiving this therapy? The answer is that combination therapy actually results in *more* infections among the partners of the infected person only if the "partnership inflation factor" (μ/m) satisfies the inequality

$$\frac{\mu}{m} > \frac{1-(1-\alpha)^n}{1-(1-\alpha r)^n} \tag{3}$$

The partnership inflation factor represents not only the proportionate increase in the total number of sex partners for a patient on combination therapy, in comparison to a patient who is not receiving therapy, but also the proportionate increase in the total number of sex acts (since the number of acts per partner is assumed to be invariant). We assume that the longer a patient lives, the more partners he or she has and the more sex acts he or she engages in, and therefore the more likely it is that the partnership inflation factor would exceed the threshold in inequality (3).

Figure 2 illustrates how the partnership inflation factor varies as a function of the number of acts per partner for two infectivity values: $\alpha = .02$ (unprotected receptive anal intercourse) and $\alpha = .001$ (condom-protected receptive anal intercourse). Consider first Figure 2(a). In this figure it is assumed that combination therapy produces a two log unit drop in infectiousness. In the high-infectivity sce-

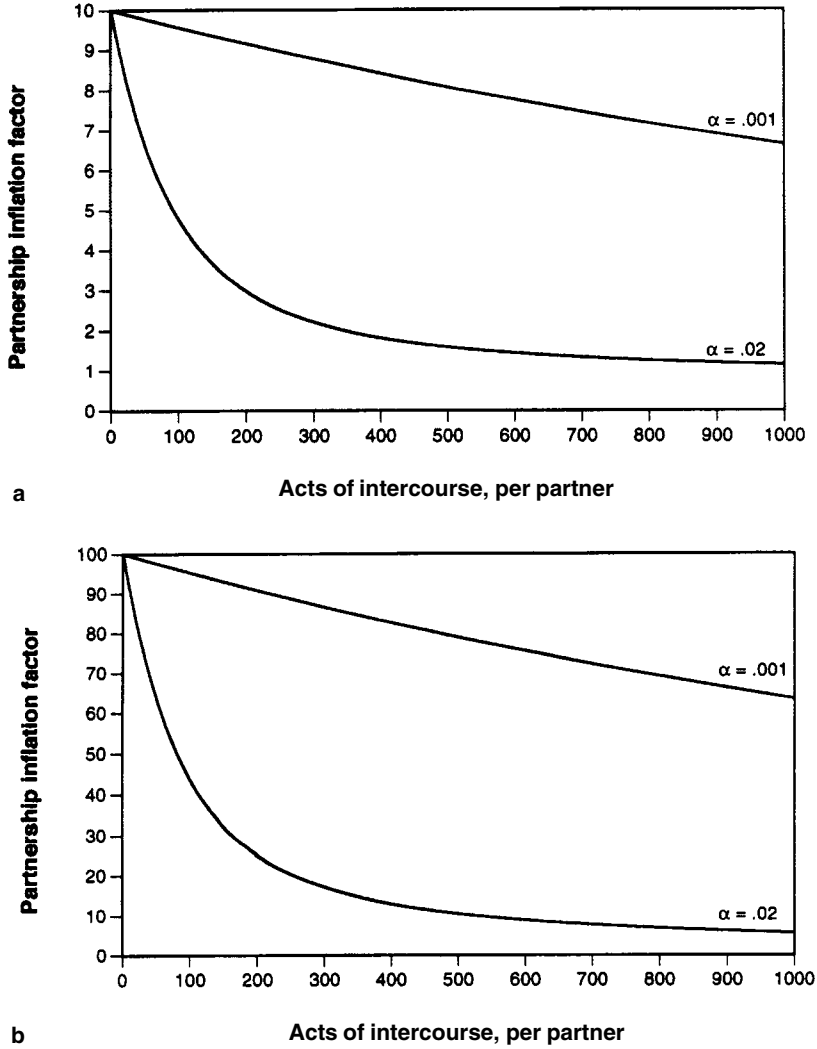

Figure 2. Minimum value of the partnership inflation factor such that combination therapy would increase the expected number of infections among the partners of patients receiving therapy, due to their increased longevity, shown as a function of the number of acts of intercourse per partner, assuming a total of 1000 total acts of either unprotected (α = .02) or condom-protected (α = ,001) receptive anal intercourse. Therapy is assumed to result in either a two log unit reduction (Figure 2a) or one log unit reduction (Figure 2b) in infectiousness. (The partnership inflation factor represents the proportionate increase in the total number of sex partners for a patient on combination therapy, in comparison to a patient who is not receiving therapy, and also the proportionate increase in the total number of sex acts.)

nario ($\alpha = .02$), the inflation factor attains its minimum value when the number of acts of intercourse per partner is at the upper bound of the range of values considered here ($n = 1000$). At that point, the inflation factor is just over 5.5, indicating that an infected person on effective therapy would need to have 5.5 times more partners and 5.5 times more total acts of intercourse than someone who is not on therapy, in order to offset the reduced likelihood of transmission that results from the decreased infectiousness. Assuming that the rates of sexual activity are roughly equal for persons who are or are not treated, this would imply that combination therapy would need to extend the sexually active life expectancy of infected people by a factor of about 5.5 times, relative to the untreated condition. For more reasonable numbers of acts per partner, the inflation factor is much greater. When the number of acts per partner is 10, for instance, the inflation factor exceeds 90. It is quite unlikely that combination therapy would extend individuals' lives sufficiently to permit such a substantial increase in sexual activity. A similar comment applies if condoms are used consistently for all sex acts (so that a = .001), as shown in the figure.

If it is assumed that combination therapy produces a reduction in infectiousness of only a single log unit, the situation is somewhat different, as illustrated in Figure 2(b). For the consistent condom-use scenario, the inflation factor ranges from approximately 6.6 to 10, whereas in the high-infectivity condition, it is just over 9 when the number of sex acts per partner, *n,* is 10; is less than 5 when *n* equals 100; and falls to below 1.2 when *n* equals 1000. In this last (quite extreme) case, the prophylactic benefits of Combination therapy would be negated if therapy increased life expectancy by a factor of just 1.2.

Thus, although it is certainly possible that by decreasing the per-act probability of transmission, combination therapy could reduce the number of partners who become infected, it is also possible that by extending the sex lives of infected people, it could increase this number (see also Anderson, Gupta, & May, 1991; cf. Paltiel & Kaplan, 1991). As Figure 2 illustrates, which of these scenarios occurs will depend on the number of sex acts per partner and the total number of partners, the effectiveness of antiretroviral therapy in reducing host infectiousness, and the per-act transmission probability.

This model can also be used to examine the possible impact of reduced adherence to safer sex practices, such as the consistent use of condoms for every sex act, due to perceptions that persons on effective combination therapy may be less infectious or even noninfectious. (Strictly speaking, the proposed model is not a model of increased risk taking on the population level, that is, by all sexually at-risk individuals, but is instead concerned with the sexual behavior of infected persons and their partners.)

Figure 3 shows the proportion of sex partners who would become infected after 100 acts of receptive anal intercourse ($\alpha = .02$) with an infected person who is either not receiving any treatment or who has experienced a one or two log unit drop in infectiousness as a consequence of effective combination therapy. As indicated in this figure, unless condoms are used more than half the time by persons on combination

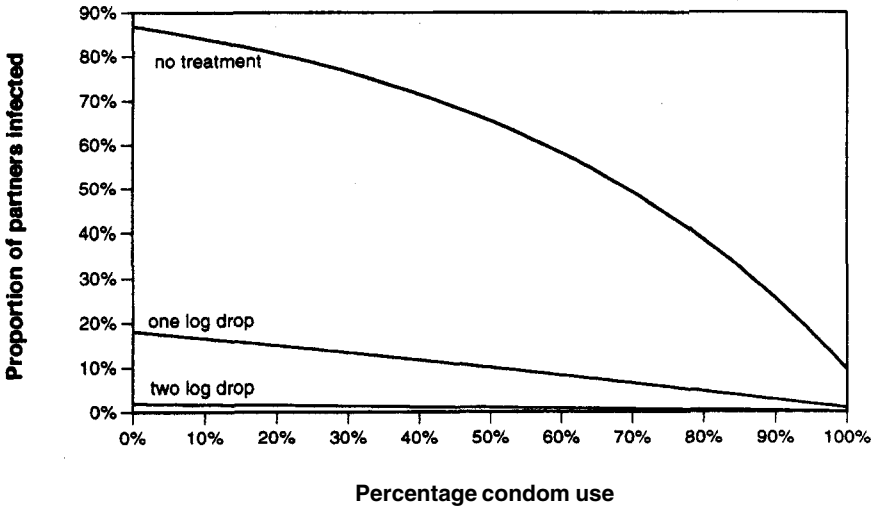

Figure 3. Proportion of partners who would become infected following 100 acts of receptive anal intercourse with an HIV-infected person as a function of the proportion of acts for which condoms are used. Three scenarios are shown: The infected person is receiving effective antiretroviral therapy leading to a one or two log unit reduction in infectiousness, or is not receiving treatment.

therapy, therapy that induces a one log unit reduction in infectiousness would prevent fewer cases of secondary transmission than would the consistent use of condoms in the "no treatment" condition. In other words, patients receiving "one-log therapy" would need to use condoms for at least 50% of all contacts in order to match the protective benefit afforded by consistent condom use in the absence of therapy. In contrast, even consistent condom use cannot match the protection provided by "two-log therapy." Figure 3 also indicates the importance of consistent condom use by HIV-positive individuals on effective antiretroviral therapy. The transmission rate is close to zero when therapy is combined with the consistent use of condoms.

According to another popular model of HIV transmission, early in an epidemic each infected person can be expected to transmit the virus to & other people, on average, where R_0 is given by the equation $R_0 = \beta cD$ in which D denotes the duration of infectiousness, c represents the rate at which new sexual partnerships are formed, and β denotes the probability of HIV transmission occurring at some point during the sexual partnership (Anderson & May, 1988; May & Anderson, 1987; see also Pinkerton & Abramson, 1994, for a discussion of the relationship of this model to the one just presented). Both effective antiretroviral therapy and condom use reduce the per-partnership probability of transmission, β, and therefore R_0. Let $r < 1$ denote the proportionate reduction in infectiousness resulting from effective combination antiretroviral therapy or the consistent use of condoms, so that reduced probability of transmission, per partnership, is $r\beta$. For

therapy that induces a one or two log reduction in infectiousness, $r = .9$ or .99, respectively, while for consistent condom use, r is approximately .95 (Pinkerton & Abramson, 1997). Because this is a linear model, the duration of infectiousness (roughly, patient longevity) would need to increase by 1000% (e.g., from 10 to 100 years) to offset the epidemiological benefits of a 90% (one log unit) reduction in infectiousness, and by 2000% (e.g., from 10 to 200 years) to eliminate the epidemiological benefits of a 95% (two log unit) reduction in the per-partnership probability of transmission.

However, a note of caution is warranted for both these models. There is considerable uncertainty regarding the "correct"values of several of the parameters appearing in these models, most notably, the per-act or per-partnership probability of transmission and the effectiveness of combination therapy in reducing this probability. In the present analysis a fairly high per-act infectivity estimate was used (see Brookmeyer & Gail, 1994; Mastro & de Vincenzi, 1996; Royce *et al.,* 1997, for additional infectivity estimates). According to one model of HIV dynamics, a much lower infectivity value (perhaps as low as ,001) holds during the long asymptomatic period that follows the brief burst of viral replication at initial infection and precedes the development of AIDS-defining symptoms; during this time, plasma viral load remains relatively constant, fluctuating about the "viral set point" (Jacquez, Koopman, Simon, & Longini, 1994; Pinkerton & Abramson, 1996). Also, the infectivity of activities other than receptive anal intercourse is much less, as is the infectivity for condom-protected sex. Finally, as discussed earlier, the extent to which combination therapy reduces infectiousness remains uncertain. In light of this uncertainty, the results presented here should be interpreted very cautiously.

POSTEXPOSURE PROPHYLAXIS

General Considerations

In 1996 the U.S. Public Health Service issued updated guidelines on the use of antiretroviral medications for prophylactic use in health care workers who suspected that they had been occupationally exposed to HIV (Centers for Disease Control, 1996); this superseded their previous recommendations regarding the use of zidovudine monotherapy for postexposure prophylaxis (Centers for Disease Control, 1990). According to the revised guidelines, 1 month ofprophylactic treatment with a combination of zidovudine, lamivudine, and indinavir should be recommended to health care workers reporting high-risk exposures, including percutaneous exposure to HIV-infected or potentially infected blood. For lower risk exposures, including mucosal or skin contact with blood or percutaneous exposure to potentially infectious fluids other than blood, prophylactic treatment with zidovudine, zidovudine plus lamivudine, or zidovudine, lamivudine, and indinavir, should be offered to the health care worker. The guidelines did not recommend

prophylaxis for health care workers who reported very low-risk exposures, such as contact with noninfectious bodily fluids.

The goal of postexposure prophylaxis (PEP) is to eliminate the virus before it can become established as a persistent infection. Ideally, an exposed individual would seek prophylactic treatment shortly after a suspected exposure to HIV-infected blood (or semen or cervicovaginal fluids). Data from nonhuman primate models suggest that the effectiveness of PEP wanes quickly, and therefore that treatment should be initiated within hours of the suspected exposure (Centers for Disease Control, 1996; Martin, Murphey-Corb, Soike, Davison-Fairburn, & Baskin, 1993; Mathes *et al.,* 1992).

There is little empirical evidence regarding the effectiveness of PEP in humans. In a case-control study of zidovudine prophylaxis for occupationally exposed health care workers in the United States, United Kingdom, and France, PEP was associated with a 79% to 81% reduction in the risk of seroconversion following percutaneous exposure to HIV-infected blood (Cardo *et al.,* 1997; Centers for Disease Control, 1995). Given the substantially greater antiviral activity of protease inhibitor combination therapy in comparison with zidovudine monotherapy, it is reasonable to assume that combination therapy, if initiated promptly, would be at least as effective as zidovudine monotherapy at preventing the establishment of sustained infection in HIV-exposed individuals.

Studies have demonstrated that zidovudine monotherapy PEP for health care workers can be a cost-effective prevention strategy (Allen, Read, & Gafni, 1992; Ramsey & Nettleman, 1992). Because combination therapy is much more expensive than zidovudine monotherapy, but the effectiveness of combination therapy PEP is unknown, the cost-effectiveness of PEP in accordance with the Public Health Service's revised recommendations is also uncertain. However, the results of a recent study suggest that triple combination therapy would be cost-effective even if it is no more effective than zidovudine monotherapy at preventing the establishment of HIV infection in exposed individuals (Pinkerton, Holtgrave, & Pinkerton, 1997). According to this cost-utility analysis, PEP that is provided within Public Health Services guidelines costs about $400,000 per infection averted, or about $37,000 per QALY saved, which is within the range conventionally considered cost-effective. Moreover, a supplemental analysis comparing combination therapy to zidovudine monotherapy indicates that if the former is just slightly more effective than the latter, then the added expense of combination therapy with lamivudine and indinavir in addition to zidovudine is clearly justified (Pinkerton, Holtgrave, & Pinkerton, 1997).

PEP following Nonoccupational Exposures

The development of much more effective antiretrovirals has led many members of the HIV prevention community to question whether these drugs might also be suitable for prophylaxis following a suspected sexual or injection-associated

exposure to HIV (American Health Consultants, 1996; Carpenter *et al.,* 1996; Katz & Gerberding, 1997). According to anecdotal reports, some physicians have already begun prescribing short-course antiretroviral regimens for HIV-exposed patients (Gorman, 1997; Zuger, 1997). Moreover, the San Francisco Department of Public Health recently initiated a program to assess the feasibility of providing postexposure prophylaxis to exposed individuals (Katz & Gerberding, 1997).

Although ethical considerations support the use of PEP following sexual abuse or assault (Gostin *et al.,* 1994) or for use by HIV-discordant couples who may experience accidental exposure to HIV (e.g., when a condom breaks), making PEP available on demand to all who request it remains controversial. Beyond the obvious economic inefficiency of potentially providing treatment to men and women who are at no or little risk of actually becoming infected, some commentators have expressed concern that the availability of PEP could result in increased sexual risk taking by some people, that it could facilitate the development of antiretroviral-resistant strains of HIV due to lax adherence to complex antiretroviral regimens, or that patients might needlessly suffer side effects from antiretroviral treatment (American Health Consultants, 1996; Katz & Gerberding, 1997; Macready, 1997).

There are also substantial uncertainties regarding the effectiveness of PEP following sexual or injection-associated exposures. There are no data at present on the effectiveness of PEP at preventing infection via mucosal exposure, including sexual exposure (Katz & Gerberding, 1997). Moreover, delays of several hours to a few days between exposure and the initiation of prophylactic chemotherapy are likely following sexual exposure, which could substantially diminish the effectiveness of PEP. Finally, it is unknown whether adherence to the complicated antiretroviral regimens would differ in the occupational and nonoccupational settings.

Because the cost of providing 1 month of antiretroviral therapy to potentially uninfected individuals is so great, it is important to assess whether the provision of PEP to individuals reporting suspected sexual or injection-associated exposure to HIV is cost-effective or whether the resources that a PEP program would consume would be better directed to other HIV prevention efforts (Pinkerton & Holtgrave, 1998b). In a recent study of the cost-effectiveness of PEP following suspected sexual exposure to HIV, Pinkerton and colleagues (1998) examined a number of different scenarios, comprising receptive anal, receptive vaginal, and insertive (anal or vaginal) intercourse with a partner who is either known to be infected or of unknown HIV status, but with a probability of being infected equal to the prevalence of HIV infection in the associated reference group (men who have sex with men or high-risk heterosexuals). In general, the results suggest that PEP would be cost-effective for men who have had receptive anal intercourse with a male partner of unknown HIV status (assuming that the probability that such a partner is infected is .18), or for receptive vaginal intercourse with an HIV-infected heterosexual male, or when it is extremely likely that the partner is infected. PEP for insertive anal and vaginal intercourse does not appear to be cost-effective, even when it is

known that the partner is infected. The authors conclude that "providing PEP to all who request it does not appear to be an economically efficient use of limited HIV prevention and treatment resources" (Pinkerton *et al.,* 1998). A related analysis suggests that PEP might also be cost-effective for injection-associated exposures, especially when there is a high probability that the partner is infected (Pinkerton, Holtgrave, & Bloom, 1997).

CONCLUSION

The advent of protease inhibitor combination therapy has ushered in a new era of effective antiretroviral treatment for HIV disease. However, the high cost of these drugs, which can total $13,000 or more per year, puts them out of the economic reach of all but the wealthiest countries, where only a small fraction of the world's HIV-infected people live. Even in the wealthiest nations, many people are unable to afford these therapies. In 1997, drug assistance programs in several states suffered financial shortfalls due to the high costs of combination therapy, forcing them to restrict the number of patients enrolled in the program or tighten eligibility criteria, institute waiting lists, reduce the number of drugs covered, or transfer money from other programs into the drug assistance program (which in some cases may have meant diverting funding for prevention programs to pay for antiretroviral medications) (National Alliance of State and Territorial AIDS Directors, 1997). The cost of a 1-year supply of the drugs may also exceed the cap that some managed care organizations place on annual medication expenses (Pear, 1997).

In summary, combination therapy is very expensive, but is it worth it? Thus far, the available evidence suggests that it is. Combination therapy can be highly effective, substantially reducing viral load, decreasing short-term mortality and progression to AIDS, and improving the clinical health and quality of life of treated patients (Carpenter *et al.,* 1997; Collier *et al.,* 1996; Deeks, Smith, *et al.,* 1997). As reviewed earlier, a number of economic efficiency studies have demonstrated that triple combination therapy is cost-effective, compared either to zidovudine monotherapy or to dual combination therapy with nucleoside analog reverse transcriptase inhibitors. These analyses should be viewed as preliminary, however, due to present uncertainty in the duration of benefit from combination therapy.

A substantial minority of patients (as many as half according to one report) do not respond to combination therapy with the dramatic reductions in viral load and improved clinical health touted in the popular media (Deeks, Loftus, Cohen, Chin, & Grant, 1997); others may respond initially, only to find the beneficial effects of treatment waning with time, as resistance to one or more drugs develops. For patients who have developed resistance to one or more of the currently available antiretrovirals, experimentation with alternative drug combinations may be necessary to determine which combination, if any, is effective (the problem of re-

sistance is especially acute among patients with a history of monotherapy with a nucleoside analog, such as zidovudine).

It appears that drug resistance can develop quickly in patients who do not strictly adhere to the complicated and demanding medication regimens that combination therapies entail (Mellors, 1997). Combination therapy may require a patient to take 20 or more pills each day (in addition to whatever other medications he or she might be taking); some need to be taken every 8 hr, others every 4; some should be taken with food, others on an empty stomach; some need refrigeration; and so on. Side effects of the drugs may include nausea, uncontrollable diarrhea, headache, dizziness, and kidney stones. For many infected people, adherence to these difficult regimens is complicated by additional life stressors, such as unemployment or poverty, drug use, or the need to take care of sick friends or relatives (Kelly *et al.,* 1998; Rabkin & Ferrando, 1997).

Although challenging, strict adherence to prescribed combination therapies is necessary to inhibit the development of drug resistance and to maximize the effectiveness and cost-effectiveness of these therapies. Combination therapy is maximally effective only when the component medications are taken as prescribed. Subclinical or irregular dosing substantially reduces the therapeutic benefits of these drugs, in an apparently sublinear fashion. Thus, although taking only half the prescribed dosage might cut drug costs in half, it might also reduce clinical benefits by much more than half, thereby reducing the overall ratio of benefits to costs. Hypothetically, at least, lax adherence could also lead to the genetic evolution and subsequent spread of drug-resistant HIV strains, with disastrous and costly consequences for the public health. For these reasons, behavioral interventions to promote adherence among patients receiving combination therapy might themselves be cost-effective.

Economic evaluation research indicates that interventions to reduce HIV risk behaviors can be highly cost-effective (Holtgrave, Qualls, & Graham, 1996; Holtgrave & Pinkerton, 1998a, 1998b). The cost-effectiveness of these interventions, which help prevent people from becoming infected and therefore obviate the need for HIV-related medical care, is intimately tied to the cost-effectiveness of the treatments themselves. Improvements in the treatment of HIV can make prevention either more or less cost-effective, depending on the particular characteristics of the prevention program and the nature of the improvement in therapy.

Indeed, it no longer seems correct to draw a sharp distinction between prevention and treatment. Prevention, in a sense, is preemptive treatment. Combination therapy, meanwhile, might have a prophylactic effect by reducing the infectiousness of persons receiving effective therapy; conversely, it might adversely affect viral transmission dynamics by increasing the duration of infectiousness, or by reducing some individuals' adherence to safer sexual practices as a consequence of diminished perceptions of the need for behavioral HIV prevention measures. The postexposure use of antiretroviral drugs to prevent the establishment of sustained infection in HIV-exposed individuals is another example of

the blurring between prevention and treatment (as is the use of antiretrovirals to inhibit vertical transmission of HIV).

As the distinction between HIV prevention and therapy grows ever murkier, the need for greater coordination among those concerned with the treatment, control, and prevention of HIV infection grows apace. Combination therapies offer great promise to improve and extend the lives of HIV-infected individuals, and as such should form an important component of future coordinated efforts to combat HIV.

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5

Ethical Issues in the Use of New Treatments for HIV

ELIZABETH HEITMAN and MICHAEL W. ROSS

INTRODUCTION

The appearance of HIV occurred at a remarkable point in the history of medicine, when many researchers were confident that science was on the brink of conquering infectious disease and the emerging field of biomedical ethics had defined both the ideal interaction between medical practitioners and patients and the ideal way in which both parties should face terminal illness. HIV provided an ironic counterexample to many of the newly established truths of medical science and medical ethics. It demonstrated the limits of the previous generation's ability to control and cure infection and challenged the limits of the new ethical standards for the care of the seriously ill.

The development of protease inhibitors has been heralded as the beginning of the end of AIDS as an acutely fatal disease. Despite, or perhaps because of, their complexity, protease inhibitors offer the possibility that medicine will regain its problematic status as the science of miracles (Johnson, 1997). The ethical issues that these new pharmaceuticals will raise will almost certainly be as complex as the science, because the projected success of protease inhibitors will be attended by a variety of unresolved social, ethical, and legal questions from the past 15 years' experience with HIV: These issues will be particularly important for those whose work with HIV/AIDS involves questions related to mental as well as physical health.

After a brief introduction to some relevant conceptual issues in ethics, this chapter focuses on four areas of ethical concern for mental health and primary care providers that are likely to be affected by the availability and use of protease inhibitors: confidentiality and disclosure of HIV status; consent and adherence in treatment and research; competence, capacity, and surrogate decision making; and prejudice against people with HIV/AIDS.

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CONCEPTUAL ISSUES IN ETHICS

In the professional and lay literature and commentary on ethical issues in health care, the concepts and language of morals, ethics, and the law are often used interchangeably. In this discussion, "morals" and "morality" refers to the framework of personal values that are shaped by religious and sociocultural tradition and experience and which typically define right and wrong behavior for the individual. "Ethics" as used here will refer to the systematic consideration of moral values and their relationship to standards of right and wrong in a social context, particularly in the context of a professional activity like health care. Such a distinction can be important in the case of HIV/AIDS, where private convictions about the morality of individuals' health-related behavior can both inform and distract attention from broader questions of social and professional ethics.

A number of components are essential to ethics' broader view in health care, including (1) concern for the benefits and harms that may come from research and treatment, and how and by whom harms and benefits are defined; (2) the role of the patient and respect for his or her voice in decision making; and (3) the fair distribution and appropriate use of the varied resources of health care. These three dimensions of ethical focus are often expressed as the philosophical principles of *beneficence* and *nonmaleficence, respect for autonomy,* and *justice* (Beauchamp & Childress, 1994). Although ethics is one of the primary disciplines of philosophy, in health care it is a multidisciplinary field that also draws on the theory and experience of medicine, psychiatry, nursing, sociology and social work, pastoral care and religious studies, health education, and law to establish standards for practitioners' behavior, social policy, or both. This approach is widely recognized as one of the strengths of biomedical ethics.

Despite the multidisciplinary view taken by medical ethicists, many clinical caregivers interpret ethics primarily in terms of formal legal standards and precedents (DeVille, 1994; Hazard, 1995). Clinicians and administrators worried about malpractice litigation focus on legal standards in hopes of preventing claims. Many look to the law for definitive answers, often perceiving ethics to be abstract discussion of opinion that raises more questions than it answers. However, caregivers who rely strictly on the law for guidance will rarely find comprehensive or conclusive answers to complex questions such as those raised by HIV/AIDS.

As experience with HIV/AIDS has demonstrated, new developments in health care often outpace society's capacity to address the ethical issues they raise. The law typically lags well behind the appearance of ethical problems, due in part to the administrative processes through which both case law and legislation are created and in part to the difficulty of predicting events and their consequences. Thus, even after almost two decades, there are still significant questions about the prevention and treatment of HIV/AIDS that the law does not address, including many issues involving mental health providers or mental health care for persons with HIV.

Where law does exist, case law may be too specific to extend beyond particular questions and broader legislation may still require court interpretation in a specific context. Both case law and legislation on health care often emphasize the practice of hospital-based physicians and may not apply well to important differences in other practitioners' work. Laws and their interpretation may also vary dramatically from state to state, because of differences in political or socioeconomic climates. And, as has been seen in AIDS law across the country, laws established by misinformed or politically motivated judges and legislators may create, rather than prevent, ethical conflict (Osborne, 1988).

The law often provides an indication of public awareness and sentiment on ethical issues. Nonetheless, the solutions proposed in the law often represent the lowest common denominators of ethical debate, rather than ideal approaches to interpersonal relations. The US. experience with legislation and case law has shown that vital ethical dimensions of social and professional interaction, such as trust, compassion, fear, and prejudice, remain outside the practical reach of the law (Blendon & Donelan, 1988; Press, 1984). As the potential for successful treatment with protease inhibitors begins a new phase in HIV care, consideration of their consequences and rightful use should thus take a broad but practical ethical view.

CONFIDENTIALITY AND DISCLOSURE

Since the original identification of HIV-1 (the predominant HIV infection in the western hemisphere, hereafter referred to simply as HIV) confidentiality has been a primary ethical concern in its diagnosis and treatment. Confidentiality is one the oldest ethical principles in western health care, first seen in the Hippocratic Oath's vow not to reveal patients' secrets (Hippocrates, 1923). Without trust in the caregiver's promise of confidentiality, many persons would not reveal information essential to their diagnosis and treatment. Without protection of their confidentiality, many persons affected by stigmatized conditions such as HIV/AIDS and mental illness might never seek needed treatment. Because of the centrality of confidentiality to effective care in HIV/AIDS, the law typically does emphasize its importance: In many states caregivers may not legally disclose a patient's or client's HIV status without his or her consent.

Disclosure and the Duty to Warn

The protection of patients' confidentiality has always been weighed against caregivers' duty to warn others about potential harm that a patient may pose to them. The standard for appropriate disclosure of confidential information is the duty to warn identified in the *Tarasoff* case (*Tarasoff,* 1976). In *Tarasoff,* a clinical psychologist and his employer, the University of California at Los Angeles, were held liable for the death of a woman whom the therapist's client had openly threat-

ened to kill during a counseling session. While *Tarasoff* appears to set a precedent for caregivers to disclose a patient's diagnosis of HIV infection to those to whom the patient may transmit the virus (Dickens, 1988), practitioners often may not know who is at risk, and the law typically permits disclosure only when others are clearly identified.

In 1987, the Council on Ethical and Judicial Affairs of the American Medical Association recommended that specific statutes be drafted to protect confidentiality while providing (1) a means for warning unsuspecting sexual partners, (2) protection for physicians from liability for failure to warn when prohibited by state law, and (3) clear standards for physicians reporting to public health authorities (American Medical Association [AMA], 1988). Subsequently many state laws were drafted to permit physicians to warn a patient's legal spouse, but they typically created a *right,* not a *duty* to warn, and limited the right of disclosure to the individual's physician. Whereas the *Tarasoff* ruling held that a non-M.D. psychotherapist was liable for failing to warn a third party of an imminent risk of harm, the legal duty and authority of mental health professionals and other nonphysicians with respect to HIV typically appears to be limited, even if they have conclusive knowledge of a patient's HIV status and specific high-risk behavior.

Required Reporting and Partner Notification

Traditionally, the public health response to sexually transmitted disease has included a structured system of testing, physician reporting, and contact tracing, now known as *partner notification.* In this process, physicians are required to report to the local health department the names of anyone found to have certain infections. Health department officials, rather than the individual patient's physician, then attempt to identify and contact everyone whom he or she may have exposed, encourage them to be tested, and, as necessary, provide opportunities for treatment (Fleming, 1980). Because partner notification depends on the voluntary cooperation of reported individuals, it endeavors to safeguard their confidentiality by not disclosing the names of original sources to anyone they identify as sexual partners (Katzenstein, 1991).

Since the enzyme-linked immunosorbant assay (ELISA) was first used to detect HIV infection, many ethicists and public health practitioners have advocated voluntary testing and disclosure of HIV status instead of widespread screening and partner notification (Bayer, Levine, & Wolf, 1986; Gostin, Ward, & Baker, 1997; Rutherford & Woo, 1988). Both screening and partner notification have been restricted in most states, The emphasis on voluntary testing and disclosure stemmed from two considerations that have been essential to the ethics of HIV care, The first was concern about at-risk individuals' fear of the disclosure of their seropositivity and its potentially disastrous consequences. The second was the absence of effective treatment that would benefit the person who received the disclosed information.

The effectiveness of protease inhibitors may well change the ethical calculus that has valued protecting the confidentiality of HIV status over the ability to warn others of their possible exposure. To the extent that combination therapy provides effective control of viral load, the arguments for screening, name-based reporting, partner notification, and physician disclosure to those at known risk are considerably strengthened (Gostin *et al.,* 1997). Failing to inform persons likely to have been exposed to HIV could readily be equated with the harm of denying them a chance for early intervention. This rationale first gained currency when triple-drug therapy was shown to reduce maternal–fetaltransmission of HIV: The prospect of saving children's lives has led some states to mandate offering HIV testing to all pregnant women, and others to require screening in order to begin therapy as early as possible in pregnancy (Grimes, Helfgott, Watson, & Eriksen, 1996). Recent headlines about infected individuals who have intentionally exposed multiple sexual partners to HIV have also increased public calls for partner notification and its use in public health and criminal prosecution (Gegax, 1997).

Many states already require clinicians and testing centers to report the names of asymptomatic people who test positive for HIV as well as those who have AIDS (Gostin *et al.,* 1997). However, most current legislation limits the duty to report a patient's HIV or AIDS to physicians who have firsthand knowledge of the diagnosis. Whether and how the availability of effective intervention for the control of HIV will affect existing law on reporting or disclosure for nonphysicians is unclear. However, it will almost certainly create a professional responsibility for nonphysicians working with persons with HIV to address the conflicting demands of patient confidentiality and the protection of others.

Disclosure and Invisibility

Because protease inhibitors appear to reduce both symptoms among persons with AIDS and the risk of developing symptoms for the asymptomatic, they raise the possibility that HIV infection could become an increasingly invisible disease as it becomes more manageable. Such invisibility could potentially either increase or reduce the importance of professional reporting and disclosure. In the rosier scenario, HIV-infected persons could be more open about their diagnosis because its social impact would be less severe; deception would not be necessary to protect one's interests. The overall probability of transmission of HIV would be reduced because anyone for whom persons with HIV/AIDS might pose a risk of infection could take suitable precautions to prevent it, conscious of the presence of the virus and the risk of transmission. Moreover, by reducing viral load, protease inhibitors might make some forms of risky sexual behavior safer.

Alternatively, however, the ability to conceal HIV infection could translate into more deception and an increased risk of transmission. A recent study of individuals receiving treatment for HIV infection found that many had not told their sexual partners about their infection, and that these nondisclosers were not more

likely to use condoms regularly than were subjects who had disclosed their conditions (Stein *et al.,* 1998). The absence of symptoms and an imperceptible viral load could make it easier for persons affected by HIV to deny their infection, both to themselves and to others. So long as they keep their symptoms under control with medication, no one apart from the prescribing doctor would need to know that they are affected. Just as persons diagnosed with other controllable chronic diseases, such as cancer or epilepsy, often elect to keep their stigmatized conditions a secret (Sontag, 1978), people with HIV infection could reinforce the stigma by keeping their infection hidden.

Moreover, as discussed in Chapters 6 and 7 in this volume, misplaced faith in the power of protease inhibitors, among both the infected and uninfected, may also lead to an increase in risky behavior, with the increased risk of the development and transmission of drug-resistant strains of HIV. In the absence of data on the transmissibility of HIV by people using combination therapy, caregivers must continue to emphasize prevention through safer sex and drug-use practices. When patients or clients with HIV/AIDS attempt to justify unsafe practices with magical thinking about protease inhibitors, practitioners need to counsel them carefully about the therapy's limits and engage them in sincere preventive efforts.

In all likelihood, the effectiveness of protease inhibitors will not affect the importance of confidentiality in only one direction: The transformation of HIV infection into "another chronic disease" will require openness about the diagnosis, just as openness has been essential to promoting public awareness about the treatment and survivability of many cancers. However, there will be many who will seek to preserve the confidentiality of their seropositivity precisely because the stigma associated with fatal disease cannot be eliminated overnight (Sontag, 1978). Moreover, as HIV/AIDS continues to affect poor and nonwhite populations disproportionately, the stigma associated with the disease may shift from its association with death and homosexuality to more general prejudices about the chronically disadvantaged.

Beyond the question of disclosure to individuals at risk of exposure, appropriate confidentiality about treatment of HIV with protease inhibitors will remain an ethical issue. If their treatment with protease inhibitors is effective, people who once left the workforce because of their AIDS-related symptoms may be well enough to return. Whether and how to reveal a diagnosis of HIV/AIDS to a prospective employer will remain difficult questions, despite the legal protections, such as the Americans with Disabilities Act (ADA), intended to prevent discrimination in the workplace. Persons using combination therapy who are insured through their work may come to the rapid attention of their employers due to the costs of treatment and related coverage (Hopper, 1996).

The complex dosing schedule for combination therapy may itself make individuals' diagnosis of HIV/AIDS evident in some environments. Some degree of disclosure may be necessary in the workplace in order to make effective treatment

possible. Companies that have sound workplace wellness and disease management programs already recognize that they can increase their employees' productivity by protecting their confidentiality and by providing time for workers to address on-the-job health needs (Zablocki, 1997; Ziegler, 1997). As combination therapy makes possible even greater mainstreaming of school-aged children with HIV/AIDS, their confidentiality, and thus that of their parents with HIV, will also be affected by school officials' need to monitor or administer medication.

Counseling about Disclosure

Irrespective of the availability of effective therapy, one essential part of counseling will be helping the seropositive individual determine who needs to know about his or her condition and when disclosure might be harmful (Lippmann, James, & Frierson, 1993). Primary care physicians and mental health professionals working with HIV/AIDS should consider it a central therapeutic goal to help their patients come to terms with their diagnosis and reveal it appropriately to others, particularly to sexual partners whom they may put at risk. Laws that permit the physician to disclose a patient's HIV infection to others give the clinician leverage in helping a reluctant patient reveal this information.

Nonetheless, the ability of physicians and other caregivers to establish trust with their patients and clients with HIV/AIDS is central to helping them acknowledge how they may put others at risk of infection. Building trust is similarly essential to helping patients and clients work through the shame, guilt, and fear associated with HIV infection to disclose their condition appropriately, and in dealing with the potential rejection and fractured relationships that may result. Such trust is ultimately more powerful than the coercive powers granted by the law, as it permits caregivers to work with their patients and clients, rather than against them.

Creating trust may be caregivers' most difficult ethical challenge. In clinical environments where long-term therapeutic relationships are rare and where financial pressures and workloads limit the time that clinicians spend with their patients and clients, therapeutic trust may be difficult to establish. Moreover, persons from poor and ethnic minority populations may be inherently mistrustful of medical and mental health professionals, as the legacy of their marginalization and the historical effects of the Tuskegee syphilis trial remain strong (Gamble, 1997). Because some AIDS research has been publicly compared to the Tuskegee trials by prominent physicians and ethicists (Angell, 1997), African-American HIV patients may have even greater fears about the nature of their own treatment. In turn, patients' mistrust may foster resentment among clinicians who feel maligned by their patients' negative assumptions. Overcoming the mutual suspicion of health care practitioners and ethnic minority patients is an issue where more research is sorely needed.

CONSENT AND ADHERENCE IN TREATMENT AND RESEARCH

Respect for patient self-determination or autonomy is the central principle in mainstream biomedical ethics and health law in the United States; individuals have a right to determine what treatment they will accept, and a responsibility to themselves and to their caregivers to participate in their treatment. The ethical values of self-determination and respect for others' autonomy are derived primarily from Euro-American political tradition and experience, and their primacy may not be accepted among nonwhites and the poor. Nonetheless, facilitating patients' self-determination and empowering patients to make autonomous life choices are essential components of much of primary care and mental health practice. One of the mental health professional's most important activities is to help patients and clients take appropriate responsibility for themselves and their behavior, for their own benefit and to prevent harm to others that their behavior may cause.

Standards of Informed Consent

Among ethicists, respect for patient self-determination and the empowerment of patients to be self-determining are the cornerstones of the concept of *informed consent,* which is essential to all health care (Beauchamp & Faden, 1986; Katz, 1984). In this view, informed consent refers primarily to an ongoing process of patient education and the communication of information and advice, discussion of questions, negotiation of options, and support for difficult decisions that the patient may be called to make. The standard for such informed consent is the individual patient's confident understanding of the meaning and ramifications of his or her condition and its treatment, and the ability to make decisions consistent with personal intentions and values. Secondarily, informed consent refers to a short-term process in which the patient agrees to undertake a specific treatment after having been informed of its nature, benefits, risks, and alternatives. The standard for this second meaning of informed consent is the disclosure and discussion of information that a "reasonable patient" would find important or useful in making specific treatment choices.

Achieving the first standard for informed consent can be a time-consuming and emotionally intense process for practitioners, especially in relation to a complex condition like HIV infection. Such informed consent requires not only providing health education tailored to the needs and comprehension of the individual patient, but also a careful appraisal of the individual patient's abilities to understand and integrate health information into his or her patterns of decision making and daily activities. This approach to informed consent ultimately involves the negotiation of clinical understanding and negotiation of a treatment plan that both the patient and caregiver will accept and support.

The second level of informed consent, although generally easier to achieve than the first, still requires evaluation of the individual's ability to understand and

act on health information, skilled provision of that information in a form that the patient can actually use, and negotiation of a treatment plan that is acceptable to both parties. Although this process is based on legal assumptions about the needs of a "reasonable patient," many members of disenfranchised and vulnerable populations most affected by HIV/AIDS have little in common with the reasonable patient whom practitioners and the law may envision, and their views of "reasonableness" may be quite different.

Respect for patient autonomy and the ethical demands of informed consent require that the caregiver seek to reach individual patients or clients on their own level. The spread of HIV has demonstrated the difficulty of providing even basic information about the disease, its prevention, and its treatment in populations from the lower socioeconomic levels of society. Patient literature, one of the most commonly used approaches to health education, is virtually useless to the estimated 25% of the U.S adult population who are functionally illiterate (Weiss & Coyne, 1997). The proportionally higher rate of illiteracy among the urban poor, ethnic minorities, prisoners, and other disadvantaged populations now experiencing dramatic increases in HIV infection poses a tremendous challenge to the reasonable-patient standard for informed consent. The growing use of protease inhibitors in such populations will require specific attention to the problems of teaching patients with low literacy skills and limited education in health-related matters (Doak, Doak, & Root, 1985). Although health education specialists may be available in some clinical settings, all caregivers who prescribe protease inhibitors to potentially illiterate patients must become competent in the diagnosis of illiteracy in order to provide even minimally effective treatment information.

Ethical Aspects of Adherence to Treatment

Respect for patient autonomy also requires that the practitioner accept the uncomfortable fact that, even after careful in-depth education on the prevention and treatment of HIV and the negotiation of a therapeutic alliance, patients' and clients' own views of appropriate intervention and behavior may not conform to the professional's recommendations. *Adherence to treatment* prescribed by the physician, also known as compliance, has been perceived to be the patient's ethical responsibility since the earliest days of medicine. Adherence became a major issue in HIV treatment with the advent of nucleoside analogues, and its significance has grown with the introduction of protease inhibitors. Rabkin and Chesney address the practical complexities of adherence to treatment with protease inhibitors at length in Chapter 3, this volume.

The ethical issues surrounding adherence are similarly complex. Adherence is commonly understood as "the extent to which a person's behavior adheres to medical or health advice, particularly with respect to taking prescribed medications, following recommended diets or other regimens, or making other changes in health-related behaviors" (Conrad, 1987). An individual's level of adherence is

typically defined by practitioners giving advice or researchers investigating the patient's responses to medical intervention. The relationship between caregivers and their patients and clients, as well as the success of treatment, often depends on the degree to which the latter accept and follow their practitioners' advice.

A predominant ethical concern in all of health care is the clinician's attitude toward patients and their role in treatment. The word "compliance,"still in wide use today, portrays the patient as an ignorant, passive recipient of medical advice in an unequal system, rather than as an informed, active agent in treatment. Replacing the term "compliance"with the more neutral "adherence"or the more positive "participation in treatment" is intended to change the way the patient's or client's role is viewed. Such a change is particularly appropriate in the treatment of HIV, where AIDS activists and others affected by the virus have been integral to defining the treatment issues and appropriate efforts in research (Arras, 1990). Nonetheless, the diversity of persons with HIV requires that caregivers recognize and work with each individual's willingness and ability to participate in treatment, especially before prescribing protease inhibitors as part of a complex, multidrug regimen.

Adherence to protease inhibitor–based regimens is ethically important on several fronts. First, lack of adherence will engender drug-resistant forms of HIV that may be transmitted to others. Second, the prediction of an individual's likely adherence may affect whether he or she will receive antiretroviral therapy, which raises a number of questions of social justice in access to treatment. Third, the development and refinement of new generations of protease inhibitors is dependent on research that demands participants' strict adherence to the study regimen; if study subjects' lack of adherence causes confounding and loss of statistical power, the drug's effects may be misrepresented and the cost of research and treatment may rise, potentially pricing effective therapy outside the reach of all but a few who could benefit.

The ethical aspects of adherence are closely related to the issues of consent and access to treatment. Research on factors associated with adherence to medical recommendations has focused on how well the practitioner's advice corresponds to the patient's explanatory models of health and illness and the patient's self-image (Conrad, 1985, 1987; Press, 1984), and on communication and rapport between patient and practitioner (Ley, 1985; Roter, 1977; Roter & Hall, 1994). Ethicists typically consider the discourse that elicits key information about the patient's or client's view of health and illness and that provides intelligible information about his or her condition and possible treatment, to be indispensable to the informed consent that every medical intervention requires (Beauchamp & Faden, 1986; Katz, 1984).

Unfortunately, in many contexts informed consent has been reduced to a legalistic process of signing a form that discloses little other than the risks of treatment. Because the law typically does not require patients to sign consent documents for drug regimens, clinicians may not even formally disclose the risks

of the combination therapy that they prescribe. Both treating physicians and mental health professionals who provide education and counseling for persons with HIV can make a significant contribution to their patients' understanding and adherence to prescribed treatment by employing a fuller ethical model of informed consent in this work. By talking with each person early in the treatment about what he or she "knows" or has heard about the disease and possible treatment, it may be possible to understand and work with the patient's explanatory models of HIV infection and its treatment in a way that enhances the patient's autonomy. When asked for their views, many patients will give the practitioner insight into their perspectives and the extent to which they are likely to accept and adopt the treatment as recommended.

Effects of Conceptual Models on Consent and Adherence

Lay or folk models of the mechanisms of HIV and its transmission are quite important to the adoption of preventive behaviors (Lowy & Ross, 1994). Protease inhibitors are most effective when their use follows a preventive model that supports the regular taking of medication in the absence of symptoms, even when some side effects occur. Although this model makes sense to health care practitioners, its internal logic may be unintelligible to many lay people whose use of health care, and medication in particular, is based on another view of therapeutic action.

A few lay models of HIV treatment that are relevant to adherence to protease inhibitor therapy include the *symptom-based model,* in which medication is titrated to respond to the appearance of the symptoms the drug is intended to address; the *self-medication model,* in which patients assume the existence of a prompt feedback loop in which the need for medication is signaled by a craving; the *"uncertainty of effects"* model, in which professional debate and clinical research into the best use of the drug are interpreted as a justification for modifying its prescribed dose or schedule; the *"overdose model,"* in which the fear of adverse side effects or toxicity may lead patients to take a subtherapeutic dose; and the *"hoarding model,"* in which patients hoard their drugs for a time when they may be sicker or unable to afford them or to give or sell to others without access to effective treatment. Other more complex lay models may involve the metaphor of illness as a punishment (Heitman, 1992; Kopelman, 1988; Sontag, 1989), the effects of which may be quite difficult to address without psychotherapy (Ross, 1990).

Because the social worlds of many persons affected by HIV are radically different from that of most medical professionals, additional research into the experience and understanding of health, illness, prevention, and effective therapy among groups at risk for HIV will also be essential to their successful treatment with combination therapy. Moreover, although the development of drug-resistant strains of HIV is serious for the individual, the greater threat is that such strains will be transmitted to others, Thus, improving adherence to combination therapy

will also require caregivers' attention to their patients' and clients' adherence to safer sex or drug-use practices and additional research into the conceptual frameworks that underlie interpretation of these practices. This broader understanding of adherence, not simply the effects on the individual, must also figure in any decision to provide access to new treatment regimens.

Adherence and Access to Treatment

Consideration of adherence to treatment raises disturbing issues of social justice. Deciding whether an individual will adhere sufficiently to combination therapy with protease inhibitors may mean deciding whether he or she will receive significant medical intervention. For many patients nonadherence results from sincere efforts to take control over their disease through the management of its treatment (Conrad, 1987). Nonetheless, many caregivers equate nonadherence with irresponsibility, and may reject nonadherent patients and clients as being unwilling or unable to participate in their own care (Conrad, 1987; Sontag & Richardson, 1997).

Those patients most often identified as "noncompliant" are members of ethnic minority and other disempowered groups, including African Americans, Hispanics, illegal drug users, immigrants, and the poor. Not surprisingly, doctors are less likely to spend needed time talking with patients from these groups than they are with middle-class Caucasian patients (Waitzkin & Stoeckle, 1976). Hart's Inverse Care Law (Ross, 1994) holds that those in most need of medical treatment have the least access to services, a phenomenon that is evident in the context of HIV/AIDS. If classes of people, usually those most disadvantaged and stigmatized, are to be denied access to combination therapy on the grounds that they are less likely than others to adhere to treatment, then these groups may be consigned to an even more difficult future (Sontag & Richardson, 1997).

There is a real danger that practitioners will make judgments about individuals' likely adherence to treatment based on stereotypes and their membership in particular categories, rather than on the basis of the individual's personal characteristics. All patients should be assumed to be eligible for treatment involving protease inhibitors until determined to be otherwise; group affiliation and behavioral patterns should be viewed as a place to start to evaluate the patient's ability and willingness to adhere to a treatment regimen, not as the only criteria.

Individual patients and clients may also be good judges of whether they are able to be adherent, and their perspective should be elicited as part of the evaluation. Meaningful conversation about the treatment will not only provide information to the patient but also build his or her confidence in the caregiver, thus improving the likelihood of adherence (Roter & Hall, 1994). Enhancing patients' adherence to treatment ultimately requires two-way communication and trust, both of which are difficult to establish in an environment of mutual suspicion (Gamble, 1997; Press, 1984). There are probably no easy answers to the difficulties of main-

taining adherence to treatment regimens and to safer sex and drug-use regimens, but the potential ethical dilemmas may be reduced if practitioners consciously seek their patients' fuller participation in the planning and execution of the treatment plan. People typically perceived to be adherent and those typically perceived to be nonadherent should be engaged in equally strenuous efforts to maximize their active adherence.

The Prescriber's Role in Appropriate Drug Use

The unidirectional view of adherence with treatment as the patient's problem needs to be replaced with a focus on the ethical interaction of patient and practitioner and research to improve adherence and therapeutic outcomes. Physicians have a professional duty to keep up to date on the standard of care for the conditions that they treat, and may be held both ethically and legally liable for prescription practices that lead to harm. However, as the treatment for HIV/AIDS grows more complex, optimal care may be difficult to define at any one time, and physicians are at increased risk for suboptimal prescription and prescription errors. As a recent study of hospital-based prescription errors concluded (Lesar, Lomaestro, & Pohl, 1997), it can be quite difficult for physicians to keep up a comprehensive knowledge of the drugs that they prescribe, and errors may lead to serious harm.

The development of practice guidelines (Bartlett, 1997; U.S. Department of Health and Human Services [DHHS], 1997) has done much to reduce the potential variability in treatment for HIV/AIDS across different types of medical practice. However, guidelines in other areas of medicine have received mixed reviews, as they not only do not eliminate variability among physicians but also may introduce new problems (Farmer, 1993). Guidelines may give a false impression of consensus among practitioners and are often compromises between different treatment philosophies. Guidelines may be interpreted by patients and inexperienced clinicians to mean that the defined "gold standard" is the only appropriate regimen for any individual diagnosed with HIV/AIDS. Physicians who are unaccustomed to treating patients with HIV, and who may be unfamiliar with the difficulties of undertaking the recommended regimen, may rush patients into combination therapy before evaluating their individual ability to participate fully in treatment. Ironically such haste to get patients on standard treatment may foster nonadherence.

Beginning a likely noncompliant patient with HIV/AIDS on a new drug regimen poses not only the risk of harm to the individual but also the serious public health problem of the development of drug-resistant strains of HIV. Given that potential, starting patients on complex regimens and then deciding whether to continue on the basis of their demonstrated adherence is not a practical option. However, as Rabkin and Chesney observe, there are few if any circumstances in which protease inhibitors must be started immediately. Where there are questions about an individual's ability to undertake combination therapy successfully, whether due to such environmental factors as homelessness or the inability to re-

frigerate medications, or to such personal factors as impaired memory or difficulty swallowing, the prescribing physician and other caregivers should work with the patient to identify and, wherever possible, overcome the barriers to effective treatment.

Consent and Adherence in Research

All pharmaceutical research is marked by tension between the need to establish efficacy without confounding, the need to evaluate the drug's effectiveness as used by patients outside the research setting, and the cost and supply of the study drugs. In the late 1980s, before significant therapy was available for HIV infection, adherence to interventions prescribed through drug trials was a major ethical issue with tremendous political ramifications (Arras, 1990). Desperate for access to treatment of potential value, many educated subjects reportedly lied to get into trials, and after enrollment circumvented the scientific safeguards on the research process to get the drugs that they personally believed held the greatest therapeutic potential.

Since the early 1990s, ethicists, researchers, and AIDS activists concerned about the trade-offs between scientific validity and subjects' self-interest have urged more collaboration between subjects and investigators, particularly with respect to community participation in the design of studies and increased access to nonvalidated treatments (Arras, 1990). Although mistrust and manipulation are still present in AIDS trials, the level of collaboration between AIDS investigators and people with HIV has increased remarkably. More recently, the demonstrated benefits of combination therapy and the greater availability of effective treatment outside of trials have eliminated much of the motive for calculated nonadherence in protease inhibitor research. Nonetheless, ongoing research into the mechanisms of protease inhibitors and their most effective use means that informed consent and adherence remain important ethical issues in AIDS research.

Informed consent is particularly important, and often particularly difficult, in randomized controlled trials (RCTs), the "gold standard" in pharmaceutical research. The purpose of an RCT is to evaluate the efficacy of two or more interventions that are presumed to offer equal benefit (Freedman, 1987). In an RCT participants are assigned to one of two or more tightly controlled treatment protocols based on a lottery system intended to eliminate selection bias. Although a control group typically receives the standard of care, by definition one or more groups in an RCT will receive less beneficial or more harmful treatment than that which is ultimately shown to be the most effective.

Because research protocols are not primarily intended to meet the individual needs of each subject, and because they rely on subjects' close adherence to a standard regimen, RCTs require a stricter standard of informed consent than does basic patient care. As part of the consent process in any RCT, potential subjects should be fully informed about the process of and rationale for randomization, the

range of treatments provided in the trial and those available outside the study, and that the protocol typically prevents clinicians from modifying individuals' treatment significantly unless they withdraw from the research.

In practice, informed consent in research, much as in clinical patient care, typically emphasizes the documentation of the disclosure of the risks of research over the communication that the paperwork is meant to document (Beauchamp & Faden, 1986; Katz, 1984). Unfortunately, HIV trials'consent forms are often so complex that formal education in science and the law may be necessary to understand what they propose. Evaluation of the consent document used in one HIV drug study determined that it was written at a college science level (Tindall *et al.,* 1994) and that it was clearly unintelligible to many of the protocol's subjects. Without meaningful dialogue on the nature of a drug trial and the subject's role in research, complex consent forms not only prevent many people from understanding the clinical information that researchers need to convey, but also they may ironically foster misunderstandings that compromise adherence to prescribed treatment (Applebaum, Roth, Litz, Benson, & Winslade, 1987).

Moreover, even after a thorough explanation of a protocol, many clinical research subjects demonstrate what has been called the "therapeutic misconception" (Applebaum *et al.,* 1987), the assumption that they have been assigned to the "best" arm of the study for their particular needs and that the researcher's goal is their personal welfare. Others continue to assume that participation in research offers individuals cutting-edge interventions that will, by virtue of being new, be an improvement over the standard of care. The therapeutic misconception and its consequences in HIV research have been noted by Chesney and colleagues, who observed that participants in a phase 1/11 vaccine trial were less likely to maintain safer sexual practices because they presumed that the experimental vaccine had a protective effect (Chesney, Chambers, & Kahn, 1997). These findings call into question the possibility of subjects' truly informed participation in clinical research from which they hope to benefit significantly.

Since combination therapy became available outside research protocols, controversy about the meaning of informed consent in AIDS research has been particularly focused on developing countries, where various pharmaceutical trials have been conducted with populations whose need for medical care is dire but for whom informed consent is a foreign concept (Levine, 1991). In particular, many have questioned the ethics of trials that assign some subjects to a control group that receives only the nonpharmaceutical standard of care for the region (Lurie & Wolfe, 1997). The widespread debate surrounding international AIDS trials that intentionally provide no effective intervention to the placebo control group has renewed general discussion of placebo-controlled trials, which, although they are widely considered to be unethical (Rothman & Michels, 1994), remain an important part of the U.S. Food and Drug Administration's approval process.

Research on the psychosocial aspects of HIV/AIDS should focus on a number of pressing questions about consent and adherence and their ethical conse-

quences. These include (1) the provision of essential knowledge to patients and potential research subjects that will enhance both their true understanding of the intervention proposed for them and their voluntary participation in it; (2) the scope and reasons for variation among ethnic and socioeconomic groups with respect to adherence to treatment regimens, and specifically the attitudes, beliefs, and situational variables associated with adherence across less adherent populations; (3) the origins of specific beliefs and skepticism about pharmaceuticals in general and anti-HIV drugs in particular that may affect consent to treatment with protease inhibitors; (4) attitudes toward HIV disease and its severity, particularly the role of symptoms (and possible side effects) in consent to both therapy and research and adherence to prescribed treatment; and (5) the specific problems of psychological adjustment to HIV/AIDS and treatment that affect adherence. It may be useful to base such research on the premise that, just as the right to informed consent implies the freedom to refuse some aspects of treatment, some nonadherence to prescribed treatment is a valid human response to illness.

COMPETENCE, CAPACITY, AND SURROGATE DECISION MAKING

Persistent nonadherence to prescribed treatment regimens is often a red flag for health care professionals to consider a patient's competence to act in his or her own best interests. Because the possibility of dementia may lie behind the seemingly illogical behaviors of persons with HIV, mental health professionals working with persons who have HIV/AIDS have a particular responsibility to assess the causes and motives for their patients' and clients' unexpected choices or actions. In some circumstances, when the patient's or client's irrationality persists or puts the individual at unusual risk, it may be necessary to find a surrogate decision maker for health care. In cases of demonstrable incompetence, a formal guardian may be necessary.

The terms "competence" and "incompetence" are used differently in the law, in health care, and in everyday life. Legally a person is presumed to be competent until a judge rules that he or she is not able to make meaningful life decisions in his or her best interest. Upon the declaration of incompetence, the court appoints a guardian who is legally responsible for all important decisions about the individual's life, including decisions about appropriate medical intervention, financial arrangements, and living conditions. In some cases the court-appointed guardian may be a friend or relative; at other times the guardian may be a lawyer or government employee who has never known the individual while competent.

In the context of health care, "competence" typically refers to the more specific concept of "decision-making capacity." The individual's understanding of his or her condition, the proposed treatment, his or her role in the treatment, its likely consequences, and any alternatives become the basis for determining capacity. These criteria are also the standard for informed consent. If the individual's ca-

pacity for medical decision making can be determined, the issue of his or her underlying mental status may not be relevant to consent to treatment unless he or she has a legally appointed guardian.

In lay usage, questions of competence often refer to whether an individual is being logical and consistent in his or her behavior and choices. Persons whose lifestyles or patterns of behavior do not comport with those of mainstream society may appear to outsiders to be incompetent, but may be perceived by friends and family as perfectly reasonable in their context. In such circumstances, a sudden shift to "normal" behavior may be interpreted by familiars to be a sign of incompetence.

Over the course of a serious illness, an individual's capacity for making medical decisions and managing other life events may change many times. Little is known conclusively about the effects of protease inhibitors on the prevention or treatment of AIDS-related dementia, and comprehensive research on this issue is needed. Changes in mental status and signs of mental incapacity in an individual being treated with any new therapy should be taken seriously and reported to the prescribing physician. If it appears that the changes in mental status are related to medical intervention, it may be necessary to consider whether the other benefits of therapy warrant continuing the treatment.

Evaluation of mental status is especially important in research. Studies that enroll mentally incapacitated persons, even when the treatment is anticipated to improve their mental status, must ensure that an appropriate surrogate consents to participation, and that the research subject's interests are safeguarded throughout the trial. Researchers and other health care professionals involved in research have a particular responsibility to ensure that when a competent individual's mental status changes in the middle of a study, an appropriate surrogate decision maker evaluates the risks and benefits of remaining in the trial.

Because the legal declaration of incompetence is typically permanent, mental health professionals should be cautious in seeking to have a guardian appointed for persons who may be suffering from dementia. If the individual is functioning appropriately in other ways, and has adequate support at home, a surrogate decision maker for medical purposes can be designated without resorting to the courts. In many states the law outlines a hierarchy of surrogate medical decision makers that focuses on family members. Nonetheless, serious conflict may erupt among family members considering appropriate medical intervention for a loved one, even when the law spells out who has the authority to speak on the patient's behalf. Many more such conflicts emerge when the law excludes members of the patient's family of choice in favor of biological relatives from whom he or she may have been estranged long before becoming ill.

Despite the promise of protease inhibitors to relieve much of the burden of AIDS as an acutely fatal disease, persons diagnosed with HIV are still likely to die of its more chronic symptoms, and may still suffer from dementia and other mentally compromising conditions before succumbing. As part of their coordinated

health care, all persons with HIV need to plan for a time when they will be unable to participate in their own medical decision making. In most states and in Canada, any competent adult may execute a durable power of attorney for health care, a legal document appointing a surrogate decision maker to represent his or her wishes in the event of incapacitation. These documents take effect whenever the individual is unable to make decisions for him or herself, not merely, as required in "living wills," when the cause of the incapacitation is terminal illness (Annas, 1994). As protease inhibitors are already changing the view that equates a diagnosis of AIDS with terminal illness, the durable power of attorney is likely to become increasingly more valuable than the living will to people with HIV.

Mental health care professionals are in a particularly good position to discuss patients' plans for end-of-life care and for preventing strife among family members and significant others who may not agree about the patient's best interests. The encouragement and assistance of health care practitioners is an essential element in such advance planning and its documentation, as even many individuals who want to talk about end-of-life care are unable to bring up the issue themselves (Lo, McLeod, & Saika, 1986). Completing an advance directive can also give the chronically ill a sense of security that their wishes will be followed, thus lessening the anxiety and denial that are typically the focus of counseling for both the patient and family. Directives tailored to address the specific questions that are likely to arise in the treatment of AIDS can also eliminate much of the guilt and second-guessing that create conflicts for decision makers (Singer, Thiel, Salit, Flanagan, & Naylor, 1997). As the apparent success of protease inhibitors at reducing viral load may unreasonably raise patient's expectations of cure, conversations about the inevitable time when everyone must die may also lessen the potential for despair if the expectations are not fulfilled.

PREJUDICE AND LIVING IN THE COMMUNITY

Since their introduction, protease inhibitors have been presented in the lay media as the answer to HIV infection. But whereas the first descriptions of AIDS as an untreatable fatal infection quickly undermined Americans' confidence in the power of medicine, reports about the medical success of protease inhibitors are unlikely to reverse the social effects of HIV as a death sentence so easily. Despite educational campaigns that have increased awareness of prevention of HIV transmission, prejudice against people with HIV disease and fear of the virus remain common. The stigma of death will take many years to eliminate, and may remain long after a cure is found for HIV infection (Sontag, 1989).

People with HIV disease have gained remarkable visibility in the past few years, particularly as progress in AIDS research has provided new therapies. With physical improvement brought on by effective treatment, more people diagnosed with HIV and AIDS will remain in or return to active social lives. How they will

be received remains one of the greatest ethical challenges of the disease, as the causes of prejudice can be difficult to identify and overcome (Blendon & Donelan, 1988). Some seriously ill AIDS patients whose lives have been restored by protease inhibitors have found that the experience of facing death makes returning to life difficult (Hopper, 1996; Rabkin & Ferrando, 1997). Friends and family who have supported someone with AIDS through terrible illness may similarly find protease inhibitors to be a mixed blessing: their initial joy at a loved one's recovery may be combined with fear that symptoms and suffering will return, or anger and resentment that their own involvement with the disease has been protracted.

If new treatments make it possible for many people with AIDS to remain in or return to full- or part-time employment, it will be vital to understand and influence employers' responses to the stigma of HIV infection. As noted earlier, employers' discrimination against persons with HIV is not well covered by the ADA. In some fields, employers may remain reluctant to hire people with HIV for fear that customers' potential knowledge of an employee's HIV status will affect business. Employers may also fear the high insurance premiums likely to result from coverage for combination therapy. Even when employers do want to hire and insure workers with HIV, other employees may resent the rise in insurance premiums that one person's HIV may cause.

Persons who are not employed prior to receiving protease inhibitors may face a potential double discrimination: Prejudice keeps them from working, which in turn may prevent them from having the financial resources to afford protease inhibitors or the social support that makes adherence to the treatment regimen possible. Even combined, Medicare, Medicaid, Ryan White funding, and research protocols cannot provide protease inhibitors for all of the uninsured who might benefit from them (Bayer & Stryker, 1997). If protease inhibitors remain available only to the socioeconomically privileged, the gap between the haves and the have-nots with HIV will only grow, and AIDS will become even more stigmatized as a disease of the vulnerable and marginalized.

AIDS activists contend that disparities in the allocation of public and private funds may reflect the nation's prejudicial view of HIV compared to other critical medical conditions, as well as society's judgment against the mental illness, prostitution, drug abuse, and homelessness that complicates the prevention and treatment of HIV disease. Other critics of AIDS policy insist that "AIDS exceptionalism" has unfairly given special status to HIV and persons with AIDS, including an array of free, highly specialized support services unavailable to people with other serious diseases (Stolberg, 1997). Whatever the level of services, as AIDS becomes more like other chronic diseases, public policy on the funding of combination therapy is likely to have a marked effect on the public perception of HIV/AIDS and those whom it affects.

One final form of professional and social prejudice that may arise with respect to protease inhibitors is the dangerous presupposition that the early positive results of combination therapy research and treatment will continue into the fu-

ture. Because the world has waited so anxiously for the suggestion of any effective treatment for HIV, research indicating a lack of effectiveness of protease inhibitors, unexpected limits to their benefits, or longer-term harms may be subject to undue scrutiny or criticism. Researchers, pharmaceutical companies, clinicians, and patients, motivated by an overwhelming desire for the success of protease inhibitors, may be unable to recognize their limits and drawbacks until longer-term outcomes data make recognizing them unavoidable (McKinlay, 1981).

Although some of this effect may be reduced by double-blinded RCTs, self-deception remains a well-documented phenomenon in the best scientific communities (Barber, 1961). For individual patients whose conditions do not respond as expected to protease inhibitors, presuppositions about the drug's effectiveness may foster the prejudicial assumption that the patient is not adhering to recommended treatment. Such assumptions can have devastating effects on individual patients already distraught about the failure of treatment (Rabkin & Ferrando, 1997), and may prompt caregivers to overlook important clinical signs that warrant follow-up research. Careful documentation of unexpected responses or lack of response to protease inhibitors when the patient reports adherence may point to new areas for research as well as to more successfully tailored interventions for "difficult cases." Even if protease inhibitors become the universal standard of care, systematic reassessment of combination therapy will be essential to understanding their long-term effects and identifying unexpected consequences, positive and negative (Banta & Thacker, 1990).

CONCLUSION

The stunningly rapid growth of the medical and psychosocial knowledge about HIV and its treatment has left many caregivers struggling to incorporate new findings into their work and many patients uncertain about the implications for their future life. This is a period of tremendous expectation, where the rewards of research appear high for AIDS investigators, clinicians, and people living with HIV: High expectations, however, may also lead to profound disappointment if the implied promises of new treatments for HIV are not fulfilled. Broken promises, real or imagined, will ultimately undermine the trust that is the foundation of the ethics of health care and of scientific research.

The AIDS epidemic is widely credited with having tempered the uncritical enthusiasm of U.S. society for medical miracles and unrealistic faith that science holds the key to improving the human condition. AIDS and its treatment have continually reminded us of the importance of human presence and support in illness, even when no effective therapy is possible. This valuable lesson has come at a high price and should remain the centerpiece of the ethics of HIV care, even as we work to interpret and apply the therapeutic breakthroughs of combination therapy.

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6

Mental Health Implications of New HIV Treatments

SETH C. KALICHMAN and BINEETHA RAMACHANDRAN

INTRODUCTION

History shows that news about advances in HIV treatment influence the psychological adjustment of people with HIV/AIDS (Schroder & Barton, 1994). Early in the epidemic, discovery of the virus that causes AIDS led many to believe that a cure would soon be found. Similarly, the advent of antiretroviral medications, most notably the approval of zidovudine (AZT), brought hope that HIV could be controlled. With each new promising therapy, even those that have shown no evidence for efficacy, such as ozone therapy and passive hyperimmune therapy, people have looked to the promise of a treatment breakthrough, albeit with successively less enthusiasm. Skepticism and often cynicism were replacing optimism as the list of HIV treatments grew without meaningful increases in survival. The availability of protease inhibitors, however, appears to have revitalized a hope in AIDS treatment that has not been seen in years. Used in combination with AZT and other reverse transcriptase inhibitors, protease inhibitors are the centerpiece of highly active antiretroviral therapies. These potent combinations of drugs reduce the viral burden of HIV and can increase CD4 cell counts, giving good reason for optimism. However, along with the promise for extending lives and improving the quality of lives of people living with HIV infection, combination therapies pose significant behavioral and psychological challenges.

This chapter overviews the emotional and mental health aspects of combination therapies. Without the benefit of published empirical research, we discuss the psychological ramifications of promising new treatments. Much of our review is therefore guided by the nonempirical literature and emerging clinical experience. First, we examine issues involved in the complex decision making concerning

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when to initiate combination antiretroviral therapies. Second, we examine how the demand for combination therapies, coupled with their cost, raises concerns over who will access new treatments. Third, we explore evidence for how combination therapies have affected the hope and optimism of people living with HIV/AIDS, including their ability to return to work, reevaluate relationships, and redefine themselves as persons living with HIV/AIDS. In contrast, we discuss the psychological implications of failure of combination therapies. We then turn our attention to the potential effects of combination therapies on the sexual practices of people with HIV/AIDS and those at risk. Finally, the implications of combination therapies for mental health services are considered. Before discussing the mental health implications of combination therapies, however, we set a context for the mental health aspects of antiretroviral therapies by briefly describing the psychological dimensions of HIV's disease trajectory.

THE HIV DISEASE AND TREATMENT TRAJECTORY

Effective treatments for HIV offer hope for managing HIV infection and delaying the onset of AIDS. However, the reality of these outcomes is contrasted with those often afforded to people living with other serious medical conditions (Kalichman, 1995). For example, cancer and other life-threatening diseases often have several trajectories with multiple outcomes because of the availability of curative treatments. Holland (1982) discussed four possible clinical courses of cancer: (1) a successful curative attempt that results in no recurrent disease, (2) a curative attempt with response but with later recurrence of disease, (3) a curative

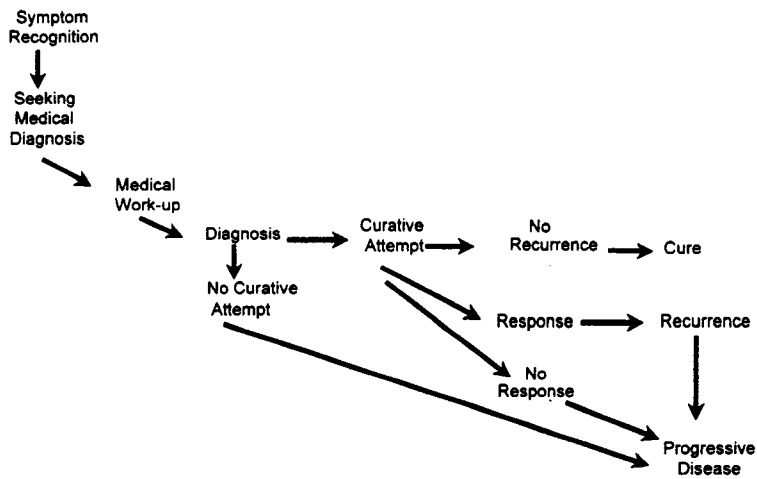

Figure 1. The trajectory of cancer and other life-threatening illnesses that have curative treatments. Adapted from Holland (1982).

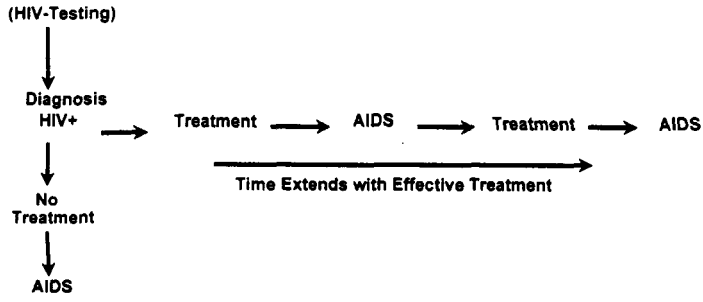

Figure 2. The trajectory of HIV/AIDS where treatments are available to stall the development of AIDS but without potential cure.

attempt and no effective response, and (4) no curative attempt (see Figure 1). A cure is therefore possible in three of the four trajectories, offering hope and motivating treatment seeking and adherence behaviors. Emotional adjustment to life-threatening diseases that have multiple trajectories relies heavily on the degree to which there are real possibilities for cure.

In contrast to life-threatening illnesses such as many cancers that have curative treatments, there are no such possibilities for HIV/AIDS. The clinical trajectory of HIV infection is therefore significantly different from that of other diseases. Although HIV-related illnesses are treated and lives are extended, illness signifies an underlying progressive HIV disease process. At best, people can receive HIV/AIDS treatment in hope that they will live to the next generation of drugs that will further extend their lives and perhaps ultimately live to a cure. Symptomatic illnesses can be treated, but ultimately responses to treatment end (see Figure 2). The prospect of persistent opportunistic illnesses with a degenerating immune system therefore poses a relentless succession of medical and psychological challenges.

The role of combination therapies in HIV disease has modified this trajectory. Adding protease inhibitors to the available treatment arsenal for HIV/AIDS lengthens the overall duration of treatment, delays the onset of symptoms, and extends the spacing between opportunistic illnesses. Combination therapies do not change the trajectory of HIV infection by introducing curative attempts. However, with combination therapies HIV infection can become a long-term chronic condition. A key factor altering the HIV disease trajectory is the timing of initiating combination therapy.

PSYCHOLOGICAL RAMIFICATIONS OF NEW TREATMENTS

Treatment Decision Making

The time to initiate combination therapies is a point of considerable controversy. Starting treatment early may suppress the propagation of mutant strains of HIV that will ultimately undermine treatment. Over the course of infection, HIV

replicates itself millions of times, resulting in as many as 10 trillion virus particles (Ho, 1995, 1996). HIV also rapidly disseminates throughout the body and accumulates in lymphatic tissues and other compartments, including cerebral spinal fluid and the brain. Slowing the early progress of HIV may therefore alter the course of infection. On the other hand, the effects of combination therapies may diminish over time, with risks for nonadherence, treatment resistance, and cross-resistance increasing and potentially restricting later treatment options. The possibility of developing treatment cross-resistant strains of HIV threatens losing sensitivity to an entire class of these agents. Concerns about the long-term use of combination therapies lead some people to delay starting combination therapies until later in infection. The following excerpts from the popular press illustrate these dilemmas.

> Ten years ago, when reports about AZT's curative powers made headlines, people with HIV flocked to the drug; only years later did we come to understand the severe limitations of its elixir. San Francisco's Don Abrams, who has been at the dead center of this epidemic since the early 1980s as clinician, researcher and thirty something gay man, urges publicly that the mistakes of the early AZT euphoria be avoided with the protease inhibitors. "I have a large population of patients who have not taken any antiretrovirals since the very beginning," he says. "They've watched all of their friends go on the antiretroviral bandwagon and die, so they've chosen to remain naïve to drug therapy. More and more, however, are succumbing to the pressure that protease inhibitors are 'it.' We're in the middle of the honeymoon period with these drugs, and whether this is going to be an enduring marriage is unclear. I'm advising my patients if they still have time, to wait." (Barr, 1997).

> Science hasn't yet managed to cure a single viral infection, so I don't think we'll ever have a cure for AIDS. But I do think that within a couple of years, we will be able to classify HIV as a chronic, manageable disease. For those of us positive a long time, I don't think it's an automatic death sentence. The key is how healthy we can keep ourselves for the next couple of years. (Delio, 1996).

Decisions about when to begin treatment are also made in a constantly changing treatment environment, which in turn can be a source of stress. New information comes almost daily, making it nearly impossible for a person to fully experience the sense of internal control that comes with being well informed of one's treatment options. Reports of new drugs can have varied effects on decisions to begin combination therapies. Optimistic individuals may see new drugs as a motivation to start therapy early, hoping that new, non–cross-resistant drugs will be available by the time they develop resistance to currently available agents; pessimists may choose to wait until there are more protease inhibitors available before risking failure on the current drugs. In either case, the availability of promising treatments poses difficult issues for large numbers of asymptomatic people with HIV who are delaying initiation of antiretroviral therapies (Kalichman, Ramachandran, & Ostrow, 1998).

Decisions about when to initiate and when to delay therapy can create significant stress for people living with HIV/AIDS. Similarly, changing drugs after having started one regimen can also cause considerable stress given the risks for

cross-resistance and reduced treatment potency. These decisions can be influenced by how people perceive the relative success of others on similar treatments. In addition, persons may be more or less active in treatment decision-making processes, with some individuals feeling more empowered than others. Individual differences in engaging in medical decisions have been well documented. For example, Miller (1 987) described two general styles of coping with stressful events: information seekers, who monitor stressful situations and information avoiders, who are less included to monitor such situations. People who are high in monitoring are more likely to report illness symptoms than those low in monitoring are. High monitoring is also associated with requesting more medical tests and demanding more information about their medical condition (Miller & Mangan, 1988; Miller, Brody, & Summerton, 1988). Therefore, people who are information seekers may be more closely in tune with their condition and more involved in their treatment decisions. Although these relationships have not been observed in people living with HIV/AIDS, they are likely to affect HIV treatment decisions.

Accessing Treatment

Protease inhibitors and the drugs that must be taken with them are expensive, costing as much as $15,000 per year plus laboratory tests and doctor visits. Because combination therapies are recommended for use early in the course of HIV disease, the cost per person over their extended life with HIV will add billions of dollars to what is already an expensive illness to treat. The lifetime treatment of a person with HIV infection was over $120,000 from time of infection to death before combination therapies became available, with most of the costs incurred later in the HIV disease process. Protease inhibitors may, however, delay the onset of symptomatic illness, potentially reducing or deferring the costs of terminal care. In addition, successful treatment will also reduce hospitalizations and thus cut the costs of HIV infection. For example, Cohen (1997) suggested that combination therapies can lead to a 36% reduction in AIDS diagnoses and over one-third reduction in hospitalizations. Hospitals may downsize or close inpatient services dedicated to AIDS while expanding outpatient services. Therefore, the true costs of protease inhibitors and combination therapies in the scope of long-term care remain to be seen. Like many other treatments that have been available much longer, combination therapies will probably not be accessible to the majority of people in the world who are living with HIV infection, in developing countries and in poverty-stricken areas of developed countries.

Differential access to or acceptance of treatment accounts for most differences between men and women in terms of survival with HIV/AIDS (Kitahata *et al.,* 1996). In an atmosphere of increased hope there is an ever-widening gap in AIDS care between the haves and have-nots in the AIDS epidemic. Although access to care is not a new issue in AIDS treatment, it will likely be exacerbated by the costs of combination therapies.

Revitalized Hope and Optimism

Despite numerous cautions guarding against overly optimistic expectations for combination therapies, people looking for an end to AIDS responded with jubilation to early results from clinical trials. The media reflected and probably fueled the excitement of new treatments, as illustrated in the following examples:

> The power of new treatments is such that a diagnosis of HIV infection is not just different in degree today. It is different in kind. It no longer signifies death. It merely signifies illness. (Sullivan, 1997, p. 54).

> A dramatic new treatment for AIDS is raising hopes the epidemic can be brought under control, at least in North America and Europe. Results of trials of new expensive drugs, called protease inhibitors, have brought a sense of buoyancy at the World AIDS Conference in Vancouver. The trials suggest that when used in combination with other drugs such as AZT, the protease inhibitors can make HIV virtually disappear. (Haysom, 1996).

The impact of increased optimism should not be downplayed; the revitalization of the hope that is offered by protease inhibitors may itself have health-promoting benefits. Hope and optimism are common characteristics of long-term survivors as well as many people who have died with HIV/AIDS (Rabkin, Remien, Katoff, & Williams, 1993). One study even suggested that positive attitudes about one's prognosis may increase survival time (Reed, Kemeny, Taylor, Wang, & Visscher, 1994). People living with HIV/AIDS, many of whom had contemplated their own death, may suddenly start contemplating their survival. Regrouping to restart one's life arouses great uncertainty, particularly for people who have experienced past promises and treatment failures. The prospects of slowing the course of HIV infection, despite the unknown durability of treatments, have led many people to reevaluate their lives and make long-term plans, including those for going back to work, examining relationships and relationship needs, and redefining oneself as a person with HIV/AIDS in a community of people with HIV/AIDS.

Returning to Work

People who had once battled their way through bureaucracies to access disability benefits may suddenly consider reemployment, returning to school, career changes, and other life-redefining decisions. Returning to work is often considered the landmark for successful HIV treatment in the era of combination antiretroviral therapies. AIDS service organizations have found their most popular programs are resume-writing seminars, career options workshops, and job interviewing practice sessions. Issues of disclosing HIV serostatus to employers and co-workers, managing medication adherence while on the job, and avoiding work-related stress are among the areas to be addressed in returning to work. The implications of employment on public assistance and medical benefits must also be sorted through. Decisions to relocate for work will also occur as people feel

healthier and less dependent on particular medical providers. These issues are new in the AIDS epidemic, but will become increasingly common for many people who experience positive treatment outcomes with combination treatments.

Reevaluating Relationships

Relationships are also reevaluated in the context of living longer than one thought (Rabkin & Ferrando, 1997). Relationship partners who had been caregivers may no longer be needed in the same way, and people may end relationships they were staying in because of their dependence on a partner. Similarly, care-providing partners who were unsatisfied in the relationship but felt it wrong to abandon a sick person may no longer feel obligated to remain in the relationship. Family relationships and friendships will also take on different meanings when people are feeling better. The improved health that can result from combination therapies offers opportunities to rebuild relationships and strengthen ties. Relationship roles change for persons receiving and giving care.

Identity and Community

As people respond positively to combination therapies they may redefine their identity as persons living with HIV/AIDS. The self-perception of a person identified as having AIDS rather than being HIV positive–asymptomatic can undergo somewhat of a reversal. Although diagnoses may not officially change, the phenomenology of AIDS undergoes a transformation when the tide of HIV infection is turned. Redefinitions of self must also occur in the context of a community of persons with HIV/AIDS, some of whom may not be doing as well as others. Identities based on disease state have always existed, distinguishing between HIV positive and HIV negative, asymptomatic and symptomatic, AIDS and non-AIDS. But combination therapies and tests for viral load have broadened the scope of HIV infection; people can have high, low, and undetectable viral loads, and people may be treatment resistant or treatment nonresistant. In addition to being either HIV seropositive or HIV seronegative, a person with an undetectable viral load may become considered HIV neutral: positive for HIV antibodies but with undetectable HIV. The implications for personal identities and roles in a community of people living with HIV/AIDS are unknown.

People starting combination therapies have survived to a time with greater treatment options, a goal that many of their friends were not so fortunate to realize. People who respond to combination therapies and survive with HIV longer will experience the loss of others less fortunate. Survivor guilt was common to AIDS before combination therapies were available, but the era of new HIV treatments may create whole new dimensions to survival guilt, as well as a more generalized grief over deceased friends, partners, and children.

When Treatments Fail

Despite the success of combination therapies in treating many people with HIV, between 15% and 35% of participants in clinical trials testing combination antiretroviral therapies do not demonstrate clinical benefits, and the results appear even worse for people treated outside research protocols. For example, Fatkenheuer and colleagues (1997) found that 64% of persons on saquinavir, 38% taking ritonavir, and 30% on indinavir experienced less than one log reduction in plasma HIV RNA levels within 6 months of starting therapy. Treatment failure can occur when (1) combination therapies do not result in clinically meaningful reductions in viral load, (2) side effects of combination therapies become intolerable and lead to discontinued treatment, and (3) initial positive responses to treatment diminish. Rabkin and Ferrando (1997) described the psychological ramifications of each of the possible ways that treatment may fail. Failing to respond when combination therapies are initiated may lead to a sense of injustice. Anger and resentment will likely be targeted to physicians, pharmaceutical companies, and others who have proclaimed the successes of combination therapies. Many people may experience a sense of betrayal over being misled about the promises of combination therapies. Developing significant side effects that require discontinued treatment, on the other hand, may lead to self-blame for not being able to tolerate an effective drug. Internalizing the failure of combination therapies can lead to self-criticism and despair. Finally, initially successful responses to combination therapies followed by decline will probably be interpreted as another false promise for HIV treatments, with the danger of spawning a sense of hopelessness and unwillingness to try new therapies.

Psychological reactions to treatment failures are influenced by prior treatment history. Having had more extensive experiences with antiretroviral therapies will mean that a person has been through the ups and downs of treatments tried and treatments failed. Unfortunately, drug resistance is also more likely to develop for people with more extensive treatment histories, so the expectations for success will differ. Thus, greater experience with treatments may psychologically prepare people for unsuccessful treatment efforts, while creating a greater fear of failure since other available treatment options are few or nonexistent.

The emotional aftermath of treatment failures can be limited by communicating the realistic expectations for combination therapies. Guarding against overoptimism must be balanced with the realistic optimism that is necessary to sustain adherence to these difficult treatment regimens. It is also important to deal with the potential guilt of treatment failure, particularly when drug resistance develops (Rabkin & Ferrando, 1997). Having decided to start treatment early or not having perfectly adhered to a treatment regimen can fuel self-blame for treatment failures.

Implications for Continued Sexual Risk Behavior

It is far more common for people with HIV/AIDS to refrain from sexual intercourse than to practice frequent acts of unprotected sex. Still, a sizable minor-

ity of people living with HIV/AIDS continue to practice high-risk sexual behavior despite the pressures placed on them to take steps to protect themselves and their sex partners. The risks for persons with HIV and their partners vary depending on many factors, including disease state, treatment history, and general health status. The risks for HIV-positive seroconcordant partners are those of reinfection with multiple strains of HIV and co-infection with other sexually transmitted pathogens, such as cytomegalovirus infection. However, the risks of reinfection and co-infection may be traded for sexual pleasure, as exemplified in an article by Gendin (1997) published in *Poz Magazine.* Gendin wrote:

> I know reinfection is a danger. Tons of positive men (including me) are walking storehouses of mutant, multidrug resistant (MDR) virus. . . . Then there is the issue of STDs, some of which are very nasty. Hepatitis B, for example, can kill a person with HIV. . . . But for some of us, that's beside the point, and reinfection isn't a major worry. It's such a vague concept. (p. 64)

A subgroup of HIV-infected persons will therefore disregard the risks posed by unprotected sex and ascribe to what has become known as the bareback sex culture—HIV-positive men who choose to practice unprotected anal intercourse despite the risks. A survey of gay and bisexual men conducted in Atlanta in 1997 found that 54% of HIV-seropositive men had heard of bareback sex and 13% identified with the bareback sex culture (Kalichman, 1998a).

Across several studies with diverse populations, as many as half of men and women living with HIV infection reported practicing unprotected sexual behaviors that pose a high risk for HIV transmission. Self-identified gay and bisexual men recruited through community channels, for example, reported recent unprotected anal intercourse. Kalichman, Kelly, and Rompa (1997) found that 39% of men who have sex with men reported engaging in unprotected anal intercourse in the 3 months prior to participating in the study. None of the men in this study reported using condoms every time that they had anal intercourse, and condoms were used by HIV-seropositive men during an average of only 39% of anal intercourse occasions. Among the 33 HIV-seropositive men in this study who reported engaging in unprotected anal intercourse, one third reported unprotected acts with only one partner, one third reported two partners, and one third had engaged in unprotected anal sex with three or more men.

The tendency to think of new treatments as a cure for HIV/AIDS could give rise to an even greater denial of risk, both among people living with HIV/AIDS and those at risk for HIV infection. Proclaiming to be HIV infected but noninfectious, or HIV neutral, may become a new substatus among people living with HIV. Such untested preventive interpretations of successful protease inhibitor treatment may have grave effects on the spread of HIV. Beliefs in reduced infectivity stem from research showing that combination therapies are associated with reductions in viral load in semen (Vernazza *et al.,* 1997). However, interpreting an undetectable viral load as a noninfectious state is dangerous because of the instability of viral load and the uncertainty of how viral load translates to infectivity.

Evidence for the effects of new treatments on behavior comes from a San Francisco study of 54 men who have sex with men. Dilley, Woods, and McFarland (1 997) found that 26% of men were less concerned about becoming HIV infected because of new treatments. In addition, 15% of men indicated that they were more willing to take sexual risks because of the advent of new therapies. Beliefs that treatment will reduce HIV transmission risk were also examined in a community survey of men who have sex with men, where such beliefs were found associated with HIV-risk behavior. Kalichman (1997) found that men who reported practicing unprotected anal intercourse as the receptive partner were significantly more likely to believe that new treatments for HIV infection reduce the risks for becoming infected; one in five believed that it is safe to have unprotected anal intercourse with an HIV-seropositive man with an undetectable viral load; and 23% stated that new treatments for HIV relieved their worries about unsafe sex.

Because the associations between viral load and infectivity are unclear, decisions to accept reduced risks of unsafe sex because of the presumed lower infectivity also increase the likelihood of transmitting treatment-resistant strains. The potential for transmitting drug-resistant strains of HIV seems even more likely given the overlapping risk factors for treatment nonadherence and continued high-risk sexual practices, including younger age, substance abuse, and emotional distress (Kalichman, Roffman, & Picciano, 1997).

IMPLICATIONS FOR CLINICAL AND MENTAL HEALTH SERVICES

The existential issues posed by promising new treatments are fruitful grounds for mental health services (Rabkin & Ferrando, 1997). Future goals are almost always set with great uncertainty. Considering the possibility of future setbacks can be demoralizing and hamper the enthusiasm that comes with improved health. Therapy can serve to inoculate individuals against disappointing declines in health while encouraging people to move forward.

Unsuccessful combination therapies—patients who do not respond to combination therapies and who are getting sicker—may be dealt with in mental health services using a framework of grief and bereavement (Rabkin & Ferrando, 1997). Mourning the loss of hope as well as the loss resulting from not being a part of widely proclaimed treatment breakthroughs should be facilitated in counseling. Expressing anger, guilt, resentment, and grief should be encouraged. However, clients should be reminded of the astounding pace of new treatments and opportunities to participate in clinical trials. The goal of grief work should be mobilizing the client to move on, and in the case of failed treatments moving on may mean trying new treatment opportunities as they become available.

Mental health providers can assist patients and physicians to address the behavioral aspects of treatment with combination therapies. Working with physicians, nurses, and nutritionists, mental health professionals can help outline optimal meal schedules, dietary considerations, and dosing schedules. For exam-

ple, they can provide memory aids such as timers and alarms for adherence to strict dose schedules; structure daily activities around treatment; and establish treatment plans to assure that such things as work schedules, vacations, and travel do not interfere with treatment. It is likely that support groups and buddy systems designed for people taking combination therapies will also prove useful.

Mental health practitioners can also help people cope with the side effects of protease inhibitors. Cognitive restructuring, relaxation training, and other techniques that have been useful in helping people adjust to other medications can be applied for people taking protease inhibitors. Behavioral interventions for reducing nausea and vomiting that have proved effective with cancer chemotherapy patients may be particularly important for use with persons taking protease inhibitors given the similar side effects of these drugs and the interactions some protease inhibitors have with certain anti-emetic medications. Among the cognitive and behavioral techniques that have been most widely used with cancer chemotherapy patients, progressive muscle relaxation training combined with guided imagery seems most promising for reducing anxiety associated with treatment and the onset of side effects (Carey & Burish, 1988). Individuals may be instructed to practice these techniques before and after administering medications to gain a sense of control and distract their attention from potential side effects.

Because positive outcome expectancies are closely associated with treatment adherence, cognitive therapy and psychoeducational interventions can help enhance optimistic outlooks required of any long-term medical treatment. Cognitive restructuring and disputing negative thoughts about treatment will help clients focus on the promise of treatment and reinforce adherence. Counseling can be useful in improving the relationship between clients and their medical providers. Developing a co-participant role in one's own care is one of the most effective means of achieving consistent adherence to treatment (Sikkema & Kelly, 1996). Modeling interactions, use of role plays, and guided feedback on performance can be used to improve client assertiveness for asking physicians questions and actively engaging in their own care (Besch, 1995).

The potential interactions between protease inhibitors and all classes of psychotropic drugs are unknown but potentially problematic. Medical interventions for HIV infection can overshadow treatment of mental health problems, which often take a lower priority in the eyes of providers and patients. Special attention will be required of mental health professionals to safeguard the integrity of their treatment for clients taking protease inhibitors. The demand for counseling for people taking combination therapies possibly will increase and gain considerable importance.

Several studies have now demonstrated mental health benefits gained from psychological interventions for people living with HIV infection. Stress reduction, interpersonal therapy, and cognitive behavioral coping interventions reduce anxiety and depression in people living with HIV infection (Eller, 1995; LaPerriere *et al.,* 1990).

Therapy groups for people living with HIV have also shown promising results in reducing psychological distress. In one study, men who participated in eight structured cognitive behavioral therapy group sessions that included cogni-

tive restructuring, progressive muscle relaxation, and problem-solving skill development demonstrated reduced levels of depression and overall improvement in other indexes of psychological well-being (Kelly *et al.,* 1993). In that same study, men who participated in semistructured social support groups also demonstrated significant improvement in mental health functioning relative to a no-treatment control group. Thus, consistent with findings from other research, group therapy is a potentially effective strategy for treating mental health problems in people living with HIV infection.

Research has also suggested that individual counseling sessions are effective in treating depression in HIV-infected persons. Markowitz and colleagues (1995) provided evidence for the effects of interpersonal psychotherapy on depression in people living with HIV infection. Depressed clients explored difficulties in one of four problem areas: grief, role dispute, role transition, and interpersonal deficits. Focusing on the here and now, therapists highlighted the client's goals and strategies for achieving these goals. The study demonstrated reductions in depression among treated clients relative to a supportive psychotherapy control condition. Thus, mental health counseling and therapy conducted in both group and individual sessions have demonstrated positive outcomes with people living with HIV/AIDS. These strategies should therefore be considered.

Mental health professionals should pay particular attention to the potential complacency that can be fed by overexuberant hope and optimism in both HIV-positive and at-risk clients. Clients living with HIV will benefit from support to help them maintain a positive outlook over the long-term use of complex drug regimens. Improved treatments may lead to increased sense of control over the course of HIV infection, and a sense of control is associated with increased hope for the future (Remien, Rabkin, Williams, & Katoff, 1992). Uninfected clients who engage in risky sexual or drug-using practices must be reminded that there remains no cure for AIDS, and although new treatments offer people living with HIV hope for a longer life, HIV infection still causes significant deterioration of health and is a life-threatening disease. It will also be important for providers to evaluate the beliefs and perceptions that people hold about protease inhibitors and dispute misperceptions of effective treatments leading to protection against transmitting HIV to sex and drug-using partners.

People who are at risk but uninfected with HIV should be counseled to practice safer sex and refrain from unprotected anal and vaginal intercourse. Behavioral interventions to reduce HIV-risk activities are effective for use with men, women, and adolescents (Kalichman, 1998b; Kalichman, Carey, & Johnson, 1996). State-of-the-art HIV risk–reduction strategies include providing clients with accurate and relevant HIV risk and preventive information, sensitizing clients to their potential risks for infection, and instructing clients in safer behavioral alternatives. Skills building in these interventions includes behavioral self-management skills such as cue identification, problem-solving risky situations, and consistent and correct use of condoms. In addition, clients are instructed in sexual assertiveness, risk-reduction negotiation, and risk-refusal skills. Using a variety of interactive techniques

and activities, information, motivation, and cognitive-behavioral skills are always couched in culturally and personally relevant contexts. Especially in light of the promises offered by combination therapies, it is essential that clients be supported for maintaining behavioral changes that lower their risk for HIV infection.

CONCLUSIONS

The new era of HIV treatment offered by protease inhibitors and combination therapies offers great hope and great challenges. Mental health providers, now as much as ever, are well positioned to aid in the care of people living with HIV infection. To remain optimally effective, caregivers must be well informed about the progression of HIV infection and the progress of medical science in battling AIDS, as well as their potential psychological and behavioral downsides. Protease inhibitors are the most recent of what is hoped will be many new HIV treatments that will bring new challenges to the care of clients living with HIV and AIDS.

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Practical Prevention Issues

DAVID G. OSTROW

> Antiretroviral therapy causes us to reconsider and reconceptualize HIV prevention from a social/behavioral model to a social/behavioral/medical model. Individuals need to be . . . segmented into. . . categories and messages and programs need to address the needs of each group. . . . HIV will become like any other infectious disease with a cure or at least with treatments that slow its progression; individuals will need to find a reason to avoid exposure and those reasons are going to be harder to find as HIV becomes easier to treat. 1) *Those who are exposed* but uninfected need post-exposure prophylaxis (triple combination therapy within 72 hours of exposure to avoid infection). 2) *Those who are in aprimary infection stage.* . . need aggressive treatment to change the natural history of their disease and also to reduce their ability to infect others during this highly infectious stage. . . . 3) *Those with established infection* need triple combination therapy, assistance with compliance, and assistance to help them from spreading HIV to others. 4) *Those with any kind of HIV infection* need to be targeted so that they do not spread HIV. This means programs for early identification of HIV, access to treatment, and strategies to facilitate HIV risk reduction. *This last program is essential as no HIVcan spread unless someone with HIV spreads it to someone who is not infected with HIV.* (Emphasis added)
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INTRODUCTION

This medically based paradigm of HIV prevention made possible by newer protease inhibitor (PI) therapies set out by Thomas Coates (Coates, 1997) and others (Katz & Gerberding, 1997) needs to be further elaborated in the harsh light of clinical and social reality. The purpose of this chapter is to discuss some of the major practical aspects of HIV prevention in the era of highly effective antiretroviral combination therapies (hereafter referred to as "combination therapies"). We must deal not only with the theoretical efficacy of postexposure treatment and preexposure prophylaxis (see Chapter 1, this volume, for a more detailed discussion

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of the state of knowledge of use of combination therapies to prevent infection from nonoccupational exposures), but also the issues of compliance with the costly, lengthy, and potentially toxic treatment protocols (see Chapter 3, this volume, on adherence issues), as well as the hypothesized effects of partial compliance on the emergence of drug-resistant strains and the long-term loss of combination therapy efficacy as these resistant strains become dominant in the communities at risk. The data summarized later in this chapter from our own current behavioral prevention research efforts focuses on the impacts that increased trust in medicine-based HIV prevention may have on risk-related attitudes and behaviors among sexually active persons, predominantly self-identified gay men, and non–self-identifiedmen who have sex with men (MSM). In addition, I argue that the availability of sophisticated medically based treatments and prophylaxis does not automatically lead to their use in STD prevention, as is now clear in the case of hepatitis B and HIV prevention among this same population of high-risk men (Ostrow, Vanable, McKirnan, & Brown, 1998).

It is important for understanding this chapter that the reader have a basic knowledge and understanding of the scientific facts and medical realities that underlie the use of combination therapies to prevent primary or secondary HIV transmission. These can be obtained from the medical chapters at the beginning of this book and from some of the recent review articles cited here (Gulick, 1997; Gulick *et al.,* 1997). Despite the explosion of new information, the primary–secondary distinction is of minimal importance here, because for each new primary HIV infection there is some kind of secondary and tertiary transmission, *ad infinitum.* More important is that we explore the prevention issues from the viewpoints of *both* members of the sexual encounter involved in the transmission of infection, from the perspectives of the participants and couple (or larger group); we must also recognize the impacts of infection risk on their social-sexual networks and communities.

This will be accomplished by focusing on a particular aspect of HIV prevention made theoretically possible by the new combination therapies, namely, the postexposure use of combination therapies to attempt to avert infection of the exposed individual. In talking about postexposure treatment (PET, or "PEP"[postexposure prophylaxis], as it is sometimes referred to) it is important to emphasize that *at this time* there is little if any evidence regarding the effectiveness of PET in decreasing the HIV infection rate from unprotected intercourse or shared blood and other bodily fluids through intravenous drug use (IDU)-related behaviors. Thus we are in the unfortunate position of having to discuss an unapproved intervention of potentially little, if any, therapeutic value thrust upon us by technological advances. Note also that Chapter 8, this volume, explores some of the community and activist issues raised by the new combination therapies, especially as they also relate to postexposure treatment.

As clients, patients, and other caregivers may soon beseech you for PET (if they have not already), it is necessary that we discuss the practical prevention as-

pects of PET and related interventions based on new combination antiretroviral therapies. It is not enough, when dealing with persons who have exposed themselves or others to HIV, to merely say that "they also need social and behavioral strategies to help them to adhere to treatment and to reduce sexual or parenteral risk"(Coates, 1997). Given the lack of time and money for the intense behavioral interventions that would be required to prevent further HIV transmission among gay men, MSM, and parenteral drug users as reviewed in the recent National Institutes of Health (NIH) Consensus Statement on HIV Prevention (1997), and the lack of behavioral counseling expertise among most primary medical and infectious disease specialty caregivers, it is unrealistic to think that such behavioral issues will be adequately attended to in the typical primary care or other limited resource settings (Ostrow, 1997).

Take, for example, the situation we all dread: that of the frequently unsafe HIV individual who requests PET for his or her latest exposure or exposures while having unprotected sex or drug use with multiple partners of unknown serostatus during the latest evening at the local bath or crack house. The 30-day period for which postexposure combination PET needs to be given, under current guidelines, is much longer than the period between this exposure and further exposures, based on the patient's prior history and the person's previous nonadherence to short-term educational and cognitive-behavioral interventions. If we were to attempt to involve this individual in longer term cognitive-behavioral or motivational therapies, the likelihood that they would cooperate or receive benefit is small yet the cost is high, even when compared to the high cost (estimated to be a minimum of $1,000 for the drugs alone) of PET. It is much simpler and so much less confrontational to just give this patient a bunch of pills and walk away from the problem (or rather have this "problem patient" walk away from us). But is it ethical to take such a course of what I consider (non)-action? Or consider the case of the patient with HIV infection who has been noncompliant in his or her prior therapies: Are we justified in denying such a patient triple combination therapy including a protease inhibitor on the grounds that they are likely to do more harm than good? Or are we ethically obligated to provide psychoeducational assistance to that patient to increase the adherence so that the person can responsibly be prescribed combination therapy? These are the sorts of difficult questions that will increasingly confront caregivers, policy makers, economic analysts, and patient advocates, not to mention our increasingly diverse patients themselves. Although there are no right or wrong answers to these difficult questions, professional caregivers will find themselves being forced to make decisions based on inadequate or, in the case of PET, nonexistent information. This chapter concentrates on the practical prevention issues involved in counseling persons whose knowledge, attitudes, and behaviors regarding HIV and its transmission may well be changing as a result of the introduction of combination therapies and the promise of effective PET. The rest of this chapter is organized according to "myths"or barriers to behavioral change that have rapidly grown up in the post–proteaseinhibitor (PI) era of HIV

CHANGING ATTITUDES AND MYTHS ABOUT HIV PREVENTION

Myth #1: "Behavioral Interventions for Sexually Transmitted HIV Don't Work"

The first topic to be discussed here is the myth of the failure of prevention intervention among gay men and MSM. We have heard many voices from within and outside the gay and MSM communities speak up on the subject of the failure of behavioral interventions as the excuse for continuing unsafe sexual and drug-using behaviors in the AIDS era (Odets, 1995; Patton, 1996). If standard, enhanced, and, especially, targeted HIV behavioral interventions have not worked as myth #1 purports, then why has the rate of new infections among gay men decreased so dramatically (Centers for Disease Control [CDC], 1997)? And why are they so cost-effective (see Chapter 4, this volume, for a discussion of the cost-effectiveness of various HIV prevention programs)? Yes, there are relapses and yes, there are recalcitrant individuals, but these are exceptional and often sensational cases. Overall there have been dramatic drops in HIV infection rates shown in all communities where a combination of social, individual, and targeted small-group interventions have been applied systematically and with adequate follow-up and evaluation (Auerbach, Wypijewska, & Brodie, 1994; Fishbein & Coutinho, 1997). These changes have been difficult to demonstrate through controlled clinical research trials, in large part because of the rapid diffusion of interventions perceived as beneficial by the grass roots community organizations where they have been fielded. This is in sharp contrast, at least at this time, to the complete lack of demonstrated efficacy for the more medically based interventions represented by combination PET.

It certainly can be argued that recently proven high rates of prevention of vertical transmission and occupational exposures with a variety of effective antiretroviral regimens suggests that immediate (less than 72 hr) postexposure prophylaxis is a viable option for primary and secondary prevention of nonoccupational or non-vertical transmission. But there are serious enough differences between vertical and occupational exposures on the one hand and sexual and drug use exposures on the other, that extrapolation from the prior situations to sexual and drug exposures is risky at best. The situation for sexual exposure PET is further complicated by the recent demonstration that multidrug-resistant strains of HIV can be transmitted through sexual exposure, and that at least some of these strains will be highly resistant to the commonly used combination therapies (Hecht *et al.,* 1998). This is not to imply that postexposure prophylaxis or treatment of sexual and needle-sharing exposures will not turn out to be effective in preventing nonoccupational transmission, but only that we are once again seeing a rush to use unproven and costly medical prevention strategies *rather than* implementing available and proven behavioral interventions for a sexually transmitted disease. Can it be that our discomfort in discussing sexual and drug-use issues with patients or clients motivates us to recommend unproven medical regimens in place of needed counseling?

A variation on the myth of the failure of behavioral interventions is the idea that it is an "either/or"situation when it comes to the prevention of further spread of HIV in the PI era. In fact, given the certainty of less than 100% efficacy of either PET or preventive HIV vaccines, it will most likely turn out that a combination of behavioral *and* medical interventions will prove to be most effective in the long run. Even more likely, it will be a combination of controlled interventions, grassroots forums, targeted media, medical prophylaxis, and preventive vaccines that will have the best chances of eliminating further HIV infections within any particular network of social, sexual, or drug-use contacts. Here we seem to be up against the normal human trait to envision the solution to societal problems in simple ''eitherlor"terms rather than being aware of the multiple levels within our individual and social behaviors that promote HIV transmission and thus must be altered to terminate its further spread.

Myth #2: "The End of AIDS Is Here"

The next "myth" about HIV prevention that needs discussion is that we are now in the "post-AIDS' era with the advent of effective "cures" and PET (Rofes, 1998; Sullivan, 1996). It is once again very compelling and attractive to accept the "hype"that the combination therapies are so effective that AIDS will never occur in properly treated individuals and that most, if not all, of HIV transmission can be prevented by the timely use of PET. That is either PET alone under some scenarios, or combined with high penetration of early aggressive treatment of all HIV infections as soon as possible following identification, or again with behavioral modification and adherence programs added to address some of the major behavioral issues discussed here. Ignoring the important cost and access issues, which include the assumption that now standard combination therapies and PET are not practical outside the most wealthy societies (see Chapter 4, this volume) and even then only among the adequately insured, it is clearly a myth that the loss of life and livelihood due to AIDS can be stopped and new HIV infections ended by the widespread application of currently available combination therapies and PET. With current medical technologies, the progression of HIV infection and the development of AIDS can be significantly slowed down, but not prevented. We can categorically state to our patients and colleagues that there has *not been a single "cure" as the result of the new therapies.* (American Foundation for AIDS Research [AMFAR] has been taking advantage of this fact in their recent billboard campaign which features a series of zeros followed by the statement "number of cases of AIDS cured to date" or "persons vaccinated against HIV to date," etc.) Nor do we have any idea of just what proportion of new infections can be averted through the widespread and timely use of PET, as discussed earlier. Persons with HIV infection are still developing AIDS and dying from the syndrome, just as before; the major difference is the increased time from infection to disability and death that the combination treat-

ments offer compared to earlier antiretroviral treatments. Some (Philipson & Posner, 1998) have even argued that the existence of better antiretroviral therapies will result in longer life expectancies for PL WHIVS and, as these infected persons increasingly return to an active sex life, we will witness a resurgence of HIV infections and new cycles of AIDS in vulnerable high-risk communities.

A better analogy for the current situation with the new therapies is to diabetes as a chronic manageable disease. With careful and expensive monitoring and treatment as well as significant lifestyle modification to maximize the benefits and longevity of the new treatments, persons can lead nearly normal lives. Yet, with all of the advances in diabetes diagnosis and management, persons with serious diabetes still eventually deteriorate in terms of both health and quality of life (QOL), and diabetes is still a frequent cause or concomitant of death (see Chapter 9, this volume, for a discussion of the research challenges posed by HIV/AIDS as a chronic manageable disease). We also know that the uptake of new therapeutic treatments, not to mention preventive treatments, is very slow even among some of the most medically oriented groups in our society.

For example, we have just presented at the 12th World AIDS Conference, Geneva (Ostrow, Vanable, *et al.,* 1998), data showing that the penetrance of use of the hepatitis B vaccine among a high-risk group of drug-using MSM who engage in unprotected sex (at least once in the past 6 months) is only 22%! Even though more than half of the nonvaccinated men were already hepatitis B infected and some 15% had active chronic or early infections, risk varied markedly by racial-ethnic characteristics. Furthermore, in a proof of Hart's Law of Inverse Care Accessibility (Hart, 1971), we found that the socioeconomic subgroup ordering of men in the study showed HIV vaccination rates to be exactly the reverse of rates of hepatitis B and HIV infection (see Figure 1).

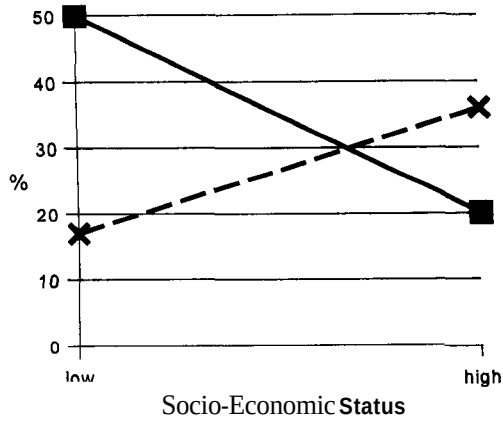

Figure 1. Hart's Inverse Care Law. x —x = rate Hep B vaccination. ■——■= rate Hep B on HIV infection.

Obviously, new technology-based strategies to prevent HIV transmission will not protect the health of vulnerable individuals unless programs to promote the detection and treatment of acute HIV, hepatitis B, and, by extension, hepatitis C, and the early vaccination of all at-risk men and women against hepatitis A and B are promulgated as well. These programs must make strenuous outreach efforts to minority populations to ensure that we correct the disproportionate lack of access to new medical technologies among the most needy (and oftentimes the highest risk) members of our society. And, remembering that health prevention behaviors are difficult to both initiate and maintain (Becker & Joseph, 1988), we should not be surprised when proactive recruitment and incentive-based programs are required to get adequate numbers of the highest risk persons diagnosed, treated, and vaccinated.

Myth #3: "Managed Health Care Emphasizes Preventive Health Care"

While the first two myths have significant negative impacts on prevention efforts by encouraging laxity in the maintenance of safer sex by at-risk persons while reducing the diligence of public health and primary care programs in counseling and preventing HIV exposure, there is another myth that health care reform means increased preventive medicine. Especially at a time of shrinking managed care and public health care dollars for HIV and STD testing and counseling, it is unlikely that we will see a significant increase in support for these activities. For example, many insurance programs will not pay the estimated $150 to $200 required for a series of hepatitis B vaccinations, even though they can avert tens of thousands of dollars in health care costs for those who otherwise become infected and go on to chronic active infection. This sort of institutional behavior suggests that this myth is alive and well even in times when insurance and primary care programs claim that they are really interested in providing preventive rather than just disease model care.

Already private foundations are springing up all over the medical landscape to raise money and campaign for awareness and funding of research for their particular diseases or diseases. Modeled after the tactics of early gay AIDS activists, these new "single health issue" foundations and patient action committees seek to increase funding through any and all means for their particular illness or condition, and all have been amazed at the unbelievable success of HIV/AIDS organizations in raising money for their cause. What better omen for the future of congressional lobbying than to see how effectively these issues are being converted into revised priorities for the NIH agencies responsible for research on the epidemiology and natural history of chronic diseases. But their efforts, and those of advocates for behavioral modification to prevent HIV and other viral STDs, will be insignificant if they stop at the point of discovery of medical interventions and do not actively promote the incorporation of prevention activities into primary care.

Why then the rush to apply an expensive (a full triple regimen of PET over 28 days costs $1000 to $1500), inconvenient (the typical PET regimen calls for be-

tween 500 and 750 pills over the course of 1 month, a far cry from the touted "morning-after pill"), and unproven technologies to HIV prevention? Perhaps it is part of a larger shift in our society's approach to behavioral problems in the past 15 to 20 years combined with myth #2, that the new combination therapies are indeed "cures" for HIV infection and the AIDS pandemics that HIV causes. If indeed we are now in the post-AIDS era, as community sages such as Eric Rofes have suggested (Rofes, 1998), it is a shift in priorities within government and affected communities rather than a true change in medical realities. Many responsible public health officials and gay community leaders have emphasized the need to incorporate HIV prevention and AIDS treatment into the larger contexts of the prevention of sexually transmitted diseases (STDs) or holistic health concerns, thereby ending the era of "AIDS exceptionalism" (Stolberg, 1997). This will be of benefit, again, only if the standard of care for other STDs is raised to the level now being practiced for HIV, rather than lowering HIV care levels to the lowest common denominator so often seen in publicly funded STD services.

Unfortunately, some less responsible or misinformed individuals have interpreted these changes to mean that the need to practice and maintain safer sex and drug use has lessened. This shift in public attitudes can be seen to be causing parallel changes in perceived social noms, such that unsafe or "raw" sex is now accepted and promoted by subgroups within the gay and drug-using communities (Gendlin, 1997; Ostrow, McKirnan, Vanable, & Hope, 1998; Warner, 1995). In addition, we need to examine the commercial pressures constantly applied by drug manufacturers and others to use drugs to solve all our problems. Where are the "detail men" pushing behavioral interventions? If we do not continue to emphasize the importance of behavioral HIV prevention messages and social noms, who will protect our clients, friends, and colleagues from being swept up into a disastrous attempt to halt a sexually transmitted disease epidemic through the use of PET rather than through the maintenance of behavioral change that took a decade of concerted effort at all levels to attain? We should heed the words of King Holmes in 1979, two years before the first reports of AIDS started to appear, on the dangers of relying on medical (at that time the soon-to-be-released hepatitis B vaccine) solutions to behavioral problems:

> I think it is an unrealistic ideal to think that we're going to be able to come up with some magic bullet, whether it is doxycycline prophylaxis or hepatitis B vaccine or gonorrhea or syphilis or herpes vaccine or any other approach to venereal disease control that will eliminate the problem of sexually transmitted disease within any group. It becomes an issue then of trying to develop specific guidelines of sexual responsibility; of counseling an individual who is a carrier; of discouraging oral–anal contact, which carries an enormous risk of enteric infection with a number of really significant diseases. Hopefully this issue can be addressed from within the community. (Holmes, 1980)

Obviously, Holmes was concerned about the dangers of establishing community norms for sexual behavior which relied totally on the "magic bullets" of antibiotics and vaccines, something which we are very much concerned with here as well.

What are the implications of PET for sexual behavior norms within the gay community? To what extent does the belief that some form of postexposure prophylaxis for HIV exists change the dynamics of safer sex education and relapse prevention within the gay and MSM communities? These are questions that urgently need to be addressed as we embark on the social-behavioral-medical model of HIV prevention suggested by Coates and others.

Myth #4: "Medically Based HIV Prevention Interventions Are the Ultimate Answer"

We already know that any treatment or vaccine against the current strains of HIV-1 may be ineffective against HIV-2 or even new types of HIV-1 and that any antiretroviral therapy is limited in terms of the time for which it can suppress viral replication before resistance to that regimen becomes established. These are important considerations in recommending any form of medical prophylaxis or prevention regime to sexually active homosexual men or, for that matter, men and women with multiple sexual partners in general. This section reviews the small amount of published and unpublished research in this area. At the recent 5th Conference on Retroviruses held in Chicago February 1–5, 1998, there was a single poster on PET for nonoccupational exposures by Bouvet and colleagues at Bichat-Claude Bernard Hospital in Paris (Bouvet, Prevot, Matheron, Cremieux, & Laporte, 1998). They attempted to follow 74 persons who presented at their hospital shortly after sexual exposure, and they actually administered PET to 48 of these persons. Although follow-up has been generally short (an average of 3–4months) and much lower among the persons refusing PET (only 40% of those not treated vs. more than 80% of persons given PET returned for follow-up testing), they have yet to observe seroconversions among any of the persons who returned. We await further results from this ongoing study and early results from attempts to perform randomly assigned PET studies in several U.S. cities.

In terms of the use of combination therapies to prevent HIV infection following exposure, all of the published literature involved health care workers accidentally exposed on the job and most involved use of AZT alone or in combination with another reverse transcriptase inhibitor (RTI) rather than the triple protease inhibitor plus RTI "cocktails"now in general use. These published studies of worksite HIV exposure prophylaxis fall far short of demonstrating an unequivocal effect because the assignment to PET was usually not random. In contrast, very strong data is beginning to come out suggesting that providing the newer combination therapies to both pregnant women during the last trimester of pregnancy and their offspring immediately following birth can significantly reduce or eliminate the likelihood that the newborn will be HIV infected (Smith, 1998) but this situation is rather different from that of using PET for sexual exposures. Despite the warnings about using an unproven regimen to prevent HIV infection following sexual or drug-use exposures, it is quite obvious that this will be tried and that

"usual and customary practice" will change based more on the hope that PET works than on any hard scientific data.

For a primary care clinician or mental health caregiver working with someone who reports a recent sexual or drug use exposure to HIV, there are a number of pieces of information that need to be gathered as soon as possible while you and your patient are discussing the rationale for their beginning combination therapy prophylaxis. These include whether the exposure source was someone known to be HIV+, the degree and extent of exposure (e.g., whether oral, vaginal, or anal, and whether the ingestion of semen was involved), and the likelihood that similar exposures will recur within the 30-day period of the PET regimen. Some clinicians and programs are using the answers to these questions to determine not only whether PET will be encouraged or provided, but also to decide what sort of PET (e.g., monotherapy vs. bitherapy vs. triple therapy) is used. For now, most programs are using bitherapy (e.g., ZDV plus a second RTI) unless the index case was known to be HIV+ or already on those particular drugs and then a triple therapy (two RTIs plus a PI) is chosen. As noted previously, if the index case's infection was with a multidrug-resistant strain of HIV, then genotypic or phenotypic testing is required before the correct PET regimen can be prescribed. For casual sex with nonprimary partners, most likely the HIV or treatment status of the partner will be unknown, in which case there are no clear guidelines for deciding on how many or which drugs to use. All current protocols call for a full month of continued prophylactic treatment, so that the "morning-after pill" is more like "the month after and 100s of pills." All current protocols attempt to begin PET within 72 hr of exposure, as that is the assumed window of opportunity for the prophylactic treatment of nonoccupational exposures. The need to continue to emphasize behavioral prevention messages rather than join the PET bandwagon was clearly stated by Lawrence Altman (1998) when he summed up this year's World AIDS Conference by saying "newproblems with anti-AIDS drugs and set-backs in vaccine trials left many participants thinking that their best hope against the epidemic was the strategy they had since it began: prevention"(p. 1).

Myth #5: "Successful Treatment with Combination Therapy Means that One Is Noninfectious to Sexual Partners"

One of the major reactions to the availability of combination therapies that we have observed is the tendency for HIV+ men and women to assume that if their plasma viral load indicates "nondetectable"virus, this translates into nondetectable levels of virus in their semen or vaginal fluids and, therefore, insignificant risk of either transmitting HIV to their susceptible partner or becoming infected from a treated HIV+ partner. Increasingly, there appears to be a tendency to equate successful clinical treatment with elimination of the risk of HIV transmission from sexual exposure. This is turning out to be far from the truth, as studies are begin-

ning to appear indicating that a significant proportion of men successfully treated in terms of their plasma viral load may still have high levels of virus in their semen (for example, see Evans *et al.,* 1998, and Vernazza *et al.,* 1998, but conflicting results in Barroso *et al.,* 1998). This proportion may be anywhere from 10% to 30% of men successfully treated, and even higher among men who do not respond adequately to the combination therapy given. Thus, it is really myth #5 rather than a reality that combination therapies can eliminate the risk of sexual HIV transmission, even among persons who appear to respond optimally, in terms of plasma viral load and CD4 t-helper cell counts, to their treatment. There is as yet no information as to why some men continue to secrete high concentrations of virus into their seminal fluid despite nondetectable levels in their blood, but the need for caution in counseling at-risk persons is obvious. And for those men who think telling their prospective partners that they are HIV+ but have "nondetectable" virus loads and are therefore not going to infect that partner through unprotected sex, very clear and plain language explaining the multiple fallacies inherent in such an approach to risk reduction is justified and necessary. As yet, no one has bothered to compare the blood and vaginal secretions of HIV+ women on combination therapy!

But any of these examples of counseling patients about the continued risk of HIV infection despite successful combination treatment imply that the primary care provider or counselor is able to speak openly and frankly with the patient or client about the individual's sexual behaviors, risks, and expectations about those risks. The usual caveats apply here as well: Helping your patient to open up about their sexual lifestyle requires a nonjudgmental attitude, an openness to hearing about sexual lifestyles that may be very different from the caregiver's own, and ability to provide counseling in a straightforward way and in language that the recipient can understand. Any caregiver who feels that he or she cannot be nonjudgmental or straightforward in discussing intimate details of their patients' sexual and drug-use lives should consider referring these patients to one of their colleagues who can (American Medical Association [AMA], 1997; Montgomery & Ostrow, in press; Ostrow & Obermaier, 1983).

METHODOLOGICAL ISSUES IN CURRENT PREVENTION RESEARCH AROUND THE NEW TREATMENTS

Because of the newness of the issues discussed here and the lack of even formative data on the changing beliefs, practices, and behavioral impacts around the new HIV therapies, we have begun an exploratory investigation of the state of knowledge and attitudes regarding the new therapies among gay men and MSM in the Chicago area. This study utilizes three different data collection formats in order to delineate the major themes, domains-issues of interest, and their potential correlates within gay or MSM communities:

The Quantitative Survey

A six-page survey has been developed, in collaboration with Seth Kalichman (Atlanta) and Michael Ross (Houston), that addresses a broad spectrum of attitudes, concerns, and risk behaviors. The survey takes 10 to 15 min to complete and has been administered, so far, to approximately 900 men attending large community street fairs in Chicago, as well as persons participating in various ongoing research projects and persons signing up on the TAKEAIM web page (discussed later). In addition, a two-page survey has been extracted from the longer survey to collect data from all persons signing onto the TAKEAIM web page. It should be noted that the scale measuring the self-perceived impact of PIs on the individual's concern about engaging in unprotected anal sex (referred to as either "decreasedAIDS-risk anxiety" or "increased comfort with unsafe sex") has both the best psychometric properties of the various scales being developed but also is the strongest predictor of both actual and intended sexual risk taking with HIV+ partners in this initial sample (Ostrow, McKirnan, *et al.,* 1998).

However, it is also obvious that only a small minority of either the HIV+ or HIV– men who have completed the survey admit to either increased comfort with unsafe sex due to the new combination therapies or have actually increased their risk-taking behaviors because of their availability (Ostrow, McKirnan, *et al.,* 1998). We think that we are now at the beginning of the curve in terms of changing attitudes and norms in the gay male community of Chicago, but that these changes will accelerate over time as more persons become aware of the efficacy of these new treatments and the potential for such medical interventions as PET.

The Website: www.TAKEAIM.org

This website is available to anyone with Internet access at home, work, or through public Internet access facilities. In addition to being a site for access to the latest information on combination therapies and prevention research in the community, the TAKEAIM website is linked to several chat rooms that focus on the impact of the new HIV treatments on the individual and their social network. The plan is to have the chat rooms monitored several evenings a week by well-known experts who will attempt to keep the discussion on track in terms of the primary domains of prevention and mental health implications of these new treatments. At other times the chat room will be unmoderated but will have a specific focus issue for comments, such as "How do you feel the new treatments for HIV have affected your sex life?" All participants in the chat rooms are asked to complete the two-page version of the survey questionnaire prior to being allowed access to the chat room. Otherwise, their participation in the chat room is entirely anonymous. Participants decide to what extent they wish to censor the information that they give out regarding their own HIV and treatment statuses, while the moderator can decide when and how to intervene in keeping the chat focused on the topic or is-

sues relevant to combination therapies and their psychosocial impacts. We are advertising the website through gay community newspapers in Chicago as well as nationally, on other existing chat services, and through one or more existing AIDS-related websites that have generously provided their own chat room links to host our discussion groups.

The purpose of this aspect of our qualitative data collection activities is to see if monitored or unmonitored Internet chat is capable of uncovering the same set of issues or domains regarding the prevention and psychosocial implications of the new HIV therapies as the much more laborious and expensive ethnographic interviewing techniques being used in the third data collection activity described in the following section. Since Internet chat is already in the form of computer-analyzable text, we hope to be able to directly feed the edited chat narratives into computer-based ethnographic analysis programs without the necessity for face-to-face interviewing, tape transcription, and correcting required by existing ethnographic research methods. This is a totally new and exciting methodology for us and, if even partially successful, could be easily adapted to a variety of sensitive topics related to HIV prevention and other forms of formative research. On the potential "con"side is the fact that our study population will obviously be limited to those persons on the Internet who are willing to engage in conversation involving their sexual and other intimate activities in a Web-based chat room. We already know that many such individuals exist, as demonstrated by the popularity of M4M chat rooms on America OnLine, IRC, and so on. But we do not know how representative these men are of the larger communities of gay men and MSM, nor whether they will discuss some of the more controversial aspects of their sexual lives, such as increased "bare backing" and the use of combination therapies as prophylaxis or to suppress their own or partner's infectivity. By urging strongly and on multiple occasions that such men volunteer for discussion that might otherwise take place in small groups at their gym or elsewhere, we could actually convert a small percentage of men into collaborators to disseminate the facts about combination therapies and help to dispel the deadly myths described earlier.

Standard Face-to-Face Semistructured Ethnographic Interviews

Finally, we are doing interviews with men selected from the Chicago AIDS Cohort Study (MACS), the AIM project, mental health and primary caregivers, and so forth in the Chicago area. Transcribed and analyzed using standard ethnographic methods, this interview-derived data is compared to the Web chat data and used to better understand the meanings of the findings from the quantitative surveys. All of the men interviewed are asked to complete the long form of the PI survey at the conclusion of their interview; they are selected to represent a cross-section of HIV+ and HIV– men, white–African American–Hispanic men, men on PIs who have positive responses versus men who did not respond or had to terminate their PI treatment because of serious side effects, and caregivers involved in the counsel-

ing and treatment of men in need of combination therapies. This data will form the "gold standard" against which our Web chat data and survey data can be assessed, and also determine the priorities and domains of interest that are most pertinent to our ultimate target populations—people who may engage in unsafe sexual or drug-using behaviors in part as a result of their reliance on the new anti-HIV therapies.

RELATIONSHIP TO CURRENT PREVENTION EFFORTS IN CHICAGO AND ELSEWHERE

These preliminary results provide baseline information for the prospective observation of changes in individual attitudes, behaviors, and social network norms in Chicago among gay men and MSM and indicators for appropriate intervention activities intended to decrease the prevalence of unsafe sex in these communities. What strikes us as most salient are the changes in perceived risk–safety of unprotected anal intercourse that are rapidly taking place in a small but highly vocal subgroup of the gay community and the high rates of interest in learning about and actually having access to PET demonstrated by all of the persons we have surveyed (Ostrow, McKirnan, *et al.,* 1988). Also, these changes seem to be taking place first among those men already taking sexual risks, so it is impossible to determine any causal relationships from this first wave of cross-sectional data. Further studies will be necessary to examine the causal relationship or relationships between changes in risk perceptions and interest in PET and actual sexual risk taking. However, there seem to be several obvious implications of these findings and those of others that bear translation into community intervention activities, discussed in the following paragraphs.

First and perhaps foremost is the need to reintroduce community-based norm preservation activities that can halt or slow the erosion of the safer sex norms established during the first 10 years of gay community prevention efforts. Kelly and colleagues have developed a model for such interventions in their multiple small-city studies which utilize community opinion leaders, usually bartenders and other gay venue personalities, to deliver the message that safer sex is the necessary norm for the community (Kelly *et al.,* 1991; Kelly *et al.,* 1992). It seems that this type of intervention can be easily adapted to the issue of preserving safer sex norms in the face of increasing comfort with unsafe sex. Rather than saying "I believe in safer sex," the required message now seems to be "Stay committed to safer sex for the long run as the cure is not yet with us." This is a relatively long and complicated message in the world of mass media, but similar campaigns have been launched elsewhere. For example, the New Zealand AIDS Foundation for the past 2 years has been using a tattoo logo of a heart with the words "Safe Sex Forever" in the form of a red ribbon over the heart, based on their formative research indicating that men in relationships have to be encouraged to maintain safety over time. We are market testing a similar, derivative tattoo that substitutes the words "Spirit-Health-Fun-

Love" and that can be used in a variety of print advertisements for community forums and educational workshops. And the San Francisco AIDS Foundation quite some time ago used the theme of "Be Here for the Cure" to suggest that gay community preservation is both an individual and collective responsibility.

However, these and other new research findings present us with some tricky and apparently contradictory facts. Whereas earlier in the epidemic, before there were combination therapies, a strong future orientation was correlated with safer sexual practices, it would seem that certain future orientations in the current era can be indicative or even productive of relapse to unsafe practices. More and more of the communications on Internet chat rooms and personal ads refer to "bareback sex" or "raw sex" as the preferred activity, and separate chat rooms and sex clubs have been started exclusively for men looking for partners willing to engage in unprotected anal sex. Whether these apparent changes in peer network norms are the cause or effect of the seeming increase in unsafe sexual activities, it is clear that their relative sanctioning in a variety of media outlets can only encourage further deterioration of community standards regarding safer sex.

Behavioral research projects have just begun to adapt to these changes by providing men the opportunity to define the safety of their sexual activities in terms of the intended use of pre- or postexposure prophylaxis in addition to or instead of the consistent maintenance of safety in the bedroom. However, primary caregivers and mental health care givers are, once again, situated ideally to provide facts and counseling to their patients-clients in a manner that will enforce high standards of maintenance of safer sex while debunking the deadly myths discussed earlier.

Perhaps these are the expected and unavoidable consequences of medical progress, but they still require responsible public education and behavioral intervention campaigns. Scattered responses have begun to emerge, often in the context of arguments over safer sex burnout (Odets, 1995) and the relative safety of alternative forms of sexual expression such as unprotected oral–genital sex. Obviously, some changes in community norms and acceptance of "unsafe" sexual practices were already under way before the advent of combination therapies, most notably the emergence of "negotiated safety" as a strategy whereby seroconcordant couples could enter into agreements limiting their extracouple sexual activities to permit safer unprotected sex within the relationship (AIDS Impact Round Table, 1997; Gold, 1996; Kippax, 1996).

The introduction of combination therapies strengthens the arguments for promoting negotiated safety from the points of view of HIV+ men wanting to live more normal lives (including the right to have unprotected sexual intercourse with their long-term partner) and that of HIV– men finding it difficult to maintain safer sex indefinitely or with all types of partners. But existing data suggest that such strategies are still relatively rare and that, increasingly, unsafe sex is taking place outside of stable primary relationships with seroconcordant partners (see Panel on Negotiated Safety from AIDS Impact Round Table, 1997). In order to understand this phenomenon, we must look at the current determinants of commu-

nity norms and practices and why they seem contrary to the educational campaigns of the past. Has emphasizing the possibility of "Being there for the cure" led us down a path that encourages unsafe sex now that combination therapies which, according to Myth #2, *are* the cure, are available? Has mass media hype around the new anti-HIV therapies led us to believe that unsafe sex and HIV infection are as innocuous as getting gonorrhea and that PET is as easy as taking a morning-after dose of doxycycline? Or are these innovations merely being used as excuses or explanations for behavioral trends in the gay and MSM communities that were already occurring independent of the recent medical advances?

While the research to answer these important questions is taking place, it seems prudent to adopt a conservative attitude and to work hard to prevent further erosions of safer sex norms, shifts toward attitudes accepting of unsafe sex, and the concomitant increases in sexual transmission of HIV that apparently can and are taking place.

CONCLUSIONS

It is obvious from the preceding discussion that there is an urgent need to approach "postmarketing" surveillance of the prevention outcomes resulting from new HIV treatments in a more formal and systematic manner rather than through the anecdotal evidence and "urban myths" that are the current primary sources of information. We have seen how fast potentially deadly myths have grown up around the new HIV therapies and how these myths substitute for scientifically based information in sexual decision making. While cost-efficacy models can be used to estimate the various trade-offs between lowering infectivity and relaxing safer sex standards (see Chapter 4, this volume), they cannot substitute for ongoing surveillance in diverse populations of the levels of correct and incorrect knowledge about these new therapies, their extent of penetration and use, and their impact on attitudes and risk-taking behaviors.

This conclusion emphasizes the need for closer collaboration between behavioral scientists, clinicians, health educators, and public health officials in responding to the prevention challenges of the new treatments. Are our medical students, residents, mental health trainees, and practitioners being educated about the promises and limitations of the new treatments? Have we incorporated sexual and drug-use behavior evaluation and counseling into all types of primary care education and specialty training?

We need to revisit the myth of the "failure of prevention" to see how it relates to the changes taking place now among individual, group, and social norms regarding safer sex, estimated risks of HIV transmission related to specific sexual and drug-use acts, and the future impact of the HIV/AIDS epidemics on our communities. Is the wish that HIV has been "cured" and that we are now in the "post-AIDS era" being driven by our refusal to accept the fact that behavioral modification can

work but that it can be a costly and time-consuming process requiring ongoing maintenance? Or as death rates due to AIDS plummet in large cities, are we all too willing to relegate HIV/AIDS to the category of afflictions of the poor and powerless? As Hart's Law of Inverse Care Access emphasizes, we have never in the past shown a particular concern as a society that the more marginalized segments of the population have adequate access to new medical technologies. Is HIV going to be any different than hepatitis B or tuberculosis are now once it becomes preventable through vaccination or aggressive early treatment?

Studies of how best to adapt community norm–changing campaigns to the preservation of safer sex norms are urgently needed before we witness reversals in the downward trends in HIV infection recently documented. Proposals to shift HIV/STD prevention funds to early treatment programs are premature and particularly misguided. The prevention gains of the past decade are fragile and hard won and should not be abandoned as technology advances. Ultimately it will take a concerted combination of behavioral *and* medical prevention strategies to eliminate the threat of HIV/AIDS, and we will still have to worry about the transmission of other chronic viral STDs such as hepatitis B and C, and herpes.

Although this chapter has focused on the impact of new combination therapies on prevention among gay men, there is very little information on how these issues differ among minorities, women, intravenous drug users, and members of other at-risk communities without the resources and organizations of gay-identified men. Fortunately, most studies currently being initiated include both men and women, have racial and ethnic diversity, and attempt to reflect the fill spectrum of persons living with HIV. Already we have observed that education, income, and other socioeconomic factors can heavily influence access to and utilization of newer medical technologies, such as the hepatitis B vaccine. There is no reason to believe that the new antiretroviral combination treatments, which are more expensive by orders of magnitude than prior STD preventive treatments, will be any different. It is hoped that the emphasis on compassion and support that characterized the best of the early psychosocial and public health responses to the AIDS epidemic will not be lost as we enter this new era of potent biomedical treatments. The epidemic is *not* over, there is *no cure* and *no vaccine,* and AIDS stigma and discrimination against PLWHIVs is still commonplace. But with ever more potent antiretroviral treatments to *accompany* behavioral interventions, not replace them, we can feel ever more confident that HIV prevention can succeed. The challenge is to make sure that this success is shared by *all* persons, regardless of their socioeconomic status.

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Postexposure Prophylaxis
A Community Member's Perspectives

MIKE SHRIVER

We now live in a time where we all have a wish to make things seem possible.

Paul Volberding, January 28, 1998
"Impact of New HIV Treatments on HIV Testing,"
Kaiser Family Foundation Meeting

INTRODUCTION

Over the past 18 months, both within and outside the communities hardest hit by HIV and AIDS, there has reemerged the discussion of postexposure prophylaxis (PEP) to prevent seroconversion for someone potentially exposed to HIV. Regardless of the durability of this conversation, it lacks a strong scientific foundation and context. Many of the attitudes and beliefs surrounding PEP parallel those from the "morning-after pill" used to prevent pregnancy as a consequence of sexual assault and the constituent concerns revolving around HIV vaccine preparedness studies in the United States (Katz & Gerberding, 1997). Yet these issues provide only a cursory glimpse into the problem with the debate surrounding PEP. Even though lacking a strong scientific backing, the concept of PEP is appropriate, but only when placed in a context of a comprehensive health promotion and disease prevention continuum. It is hoped that this article will begin a process of developing both content and context.

A HISTORICAL WHIRLWIND

The concept of a pill or a therapeutic agent that can be administered following an unhealthy or violent sexual interaction and that will reasonably and safely guarantee preventing unintended pregnancy from that assault is not new. However, it is also not without controversy. In a historical context, the "morning-after pill"

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used to reduce the number of unintended pregnancies (and disease) after sexual assault cases remains lodged deeply in the American psyche, and to some it represents a philosophically deeply troubling medical intervention.

With increasing frequency abortion is alleged to be solely a means to escape the consequences of premature or extramarital sexual intercourse, and is sometimes compared to another version of a "morning-after" procedure. Opponents of abortion contend that this medical intervention is primarily used as a means of birth control, hence as a prophylactic strategy. Debate over the importing of RU486, the most prominent morning-after pill, into the United States remains clouded with allegations of the erosion of the moral and cultural fabric of the nation, as opposed to a clear understanding of the science of this therapeutic intervention.

Controversies surrounding a pill, pills, or behavioral-medical interventions aimed at reducing the unintended (negative) consequences of sex remain part of the backdrop of our nation's pressing health crises. This controversy has not so subtly been introduced into the HIV lexicon, specifically regarding the potential to administer triple combination therapy to individuals who have in some fashion themselves been exposed to HIV (unwittingly, accidentally) to stave off a potential new HIV infection. This theoretical drug regimen procedure has been commonly referred to as "postexposure prophylaxis."

PEP's scientific theory is simple: Administer highly effective anti-HIV drugs to an individual recently exposed to HIV before this person has seroconverted and thereby eradicate HIV before it can proliferate in the individual's body. There is clear resonance between postexposure prophylaxis's theoretical basis and the canon of data on occupational exposure to HIV (Centers for Disease Control [CDC], 1995; Tokars, Marcus, & Culver, 1993), not to mention the now commonly invoked phrase "complete viral eradication." Recently reissued CDC guidelines continue to standardize the most scientifically valid means to chemotherapeutically stave off HIV infection in health care workers who have experienced accidental exposure to HIV through a splash, a needle-stick, or other modes of occupational exposure. However, although the actual numbers of health care workers who have become HIV infected through a direct workplace exposure remains infinitesimally small, a total of 114 confirmed cases in the United States, compliance data for health care workers and mono- and combination therapy for occupational exposure is notoriously poor (CDC, 1997). This particular point has significant implications for extrapolation, especially when considering triple combination therapy as the standard therapeutic intervention for occupational exposure, let alone for PEP. There is sufficient evidence to point out the risks associated with less than excellent adherence for HIV-infected individuals on triple combination therapy (Deeks, Smith, Holodniy, & Kahn, 1997). Given that, the unknown risks associated with PEP's regimen of triple combination, adherence, possible side effects, and long-term impact on treatment strategies are compelling.

The resulting community enthusiasm following the 11th International Conference on AIDS in Vancouver, British Columbia, Canada, in 1996 was based on preliminary and promising data out of New York City that aggressive antiretroviral treatment of early HIV infection could lead to the near-elimination of virus pre-

sent in the body (e.g., Hammer *et al.,* 1996). From this promise of better treatment outcomes for people with HIV disease emerges a corollary premise. If triple combination therapy can lower and even possibly eradicate viral load in blood serum, can it also block HIV infection from taking hold in a recently exposed individual? Not surprisingly, these early, short-term data led the media, the HIV community, and the scientific community to wonder aloud about the possibility of completely eradicating HIV from the patient's body. Consequently, this dialogue has centered on the possibility of postexposure prophylaxis as a means to step in and medically manage—namely, stop—HIV seroconversion.

However, this concept has emerged without data. Although it is not without good intention and good will, PEP remains theory. It is fascinating (some suggest fascination; others suggest science fiction) that even with data highlighting a less than uniform benefit from triple combination therapy for people with HIV disease the discussion about PEP has proceeded. And, to be frank, the concept of PEP is still absent sound science, cost-effectiveness studies, or even an appropriate contextualization within a prevention and care continuum.

The reasoning behind intervening at the point of a potentially life-threatening situation (unwitting or accidental exposure to HIV) and assisting the patient in ridding the body of a harmful agent is laudable and proper. The scientific philosophy of PEP is clearly and reasonably underscored by pragmatism—knowledge of the gravity of HIV infection and its probable fatal nature. Fundamentally nested in the context of PEP is the belief that it is better to remain HIV uninfected, in spite of recent, more effective, and proven treatment interventions, than to seroconvert.

The circular discussion about postexposure prophylaxis has led to a blurring of fact and fantasy, fatalism and optimism, and has ignored fundamental realities of disease management and disease prevention.

In order to understand the theoretical benefit of postexposure prophylaxis and the theoretical risks associated with it, one must first contextualize PEP in a prevention continuum and a care continuum, then suggest its utility, benefit, and place. It is only then that PEP can be reasonably justified, promoted, evaluated, and perhaps even funded.

Finally, to understand the relative value of PEP, a new framing of this therapeutic intervention must be recommended. Rather than refer to this intervention as an act solely of "prophylaxis," it would be more appropriate to refer to this process as a sequence in a course of HIV prevention.

HEALTH PROMOTION, HIV INFECTION, AND ACCESS TO CARE AND PREVENTION

Before moving directly to the issue of PEP, it is important to assert a model of HIV prevention and care that has both utility and practicality. For too long, our organic insistence on a reactive model of health care (as opposed to proactive, preventive health care) has allowed communities and individuals to experience the

consequences of a health care system out of balance. Disproportionate incidences of disease and risk continually precede interventions, as opposed to creating a climate of good, sound, and sensitive health promotion activities. Behavioral science assumes a secondary role in this scenario, oftentimes because either the public or public health personnel do not believe that individuals are capable of behavior change over a period of time.

However, data not only suggest but confirm that individuals and communities, when given appropriate tools, education, interventions, and incentive, can and will modify behaviors that place them at risk for negative consequences (Corby & Wolitski, 1997; Kalichman, 1998). In some instances (such as with traumatic head injury), laws have been passed to further this goal. In other instances, community mobilizations have shouldered part of the bolstering responsibility of such modifications (as with HIV prevention).

For the purposes of this discussion, it is a reasonable assumption that there is neither a national nor widespread (and financially supported) health promotion model and/or philosophy in the United States. Thus, in order to truly and fairly assess PEP, just such a model needs to be suggested and accepted as context.

The end result of this model is to suggest that one must evaluate PEP not just on its scientific merits, but also on its relative effectiveness in contributing to a health promotion paradigm with beneficial health outcomes (i.e., reducing the number of new individuals becoming HIV infected over time).

AN EVIDENT AND NEW MODEL OF HIV PREVENTION AND CARE

It is reasonable to describe any given (index) community (both seronegative and living with HIV disease) as falling into four discrete categories. These categories are the following:

1. Those who are HIV uninfected (both aware and unaware of this status)
2. Those who are HIV infected (both aware and unaware of their status)
3. Those who are HIV infected and seeking care
4. Those who are HIV infected and are in care

This model is based on an assumption that once someone has entered the care system, she or he remains in that system. Individuals and communities obviously move from category to category in this model except that (currently) one cannot become HIV uninfected once seropositive. If one were to construct a mathematical model out of this categorical ideal, there would be rates between these categories. For this discussion, in this model, the rate from category 1 (seronegative) to category 2 (seropositive) is the annual seroincidence for said index community (community-identified jurisdictional risk group).

From a public health (and cost-savings) perspective, one goal of this model is to reduce the rate that an index patient or index community moves from being

seronegative to becoming seropositive. As prevention works, the rate decreases. In addition, this model offers a way to understand the system-capacity continuum and link between HIV prevention and care. Since supply for care has yet to exceed demand for care, public health always operates under stress. One solution to this stress or pressure would therefore be to reduce the number of persons moving from seronegative to seropositive.

There are other practical results from this model, not just in a reaffirmation of the importance of prevention. This model squarely suggests a reconceptualization of the role of HIV counseling and testing. At one point it was (mistakenly) assumed to be a prevention activity, counseling and testing in this model is a critical diagnostic tool. Its meaning as a diagnostic intervention point must neither be undervalued nor underestimated. Clearly, counseling and testing serve to help identify individuals who need care (if HIV positive) and those who need primary prevention services to either maintain a seronegative status or to keep from infecting others with HIV.

STD management, prevention, and treatment move through this system as both primary prevention, making someone less infectable as well as making someone less infectious, and secondary prevention, keeping those with HIV free from other, immune-debilitating infections. The same holds true for activities such as needle exchange programs, even if only to consider hepatitis B and C rates, abscesses, emergency room visits, and drug-related violence, crime, and death.

Reducing the number of infectious and infected individuals (infectious means the number engaging in high-risk behaviors with seronegative and those with indeterminate or unknown HIV status) presumes a commitment to sound, well-funded and effective HIV prevention. There is no known, natural progression for a community or a person to move from a risk-taking behavior to a no-risk-taking behavior without some form of incentive, encouragement, personalization of risk or knowledge, or intervention.

Finally, the rate that individuals and communities move from seronegative to seropositive greatly depends on the ability of the seropositive to no longer place the seronegative and those with indeterminate or unknown HIV status at risk through their behavior. This is the challenge of primary prevention. Primary prevention interventions are thoroughly undervalued across the United States, but they must assume primacy, especially as better and more scientifically valid interventions with documented outcomes become increasingly available.

In a model that promotes preventive health, HIV prevention interventions would assume a primacy along the health care continuum. Significant, early investments of resources at the beginning of the health care continuum would almost assuredly guarantee lowered health care costs for the entire system. Resources, science, public support, infrastructure, and policies would facilitate, not hinder, its goal. However, this is often not the case. Resources for HIV care dwarfs resource allocation for HIV prevention. HIV prevention remains highly politicized. Scientifically proven interventions either are prohibited by law—for example, needle exchange—or remain hamstrung by federal program and content restrictions. And,

in spite of technological advances such as alternative testing technologies for HIV infection, HIV prevention practice and prevention science are not attended to in a comprehensive and robust manner.

Although easier said than done, this model is ultimately about preventive health care—keeping as many people as possible seronegative is about keeping people from becoming infected. PEP can be seen, therefore, as a tool toward this goal, and part of a comprehensive armamentarium against HIV infection and disease progression.

Ideally, health promotion standards would precede the introduction of PEP. These standards include the following:

- *Active support for specific community health activities (i.e., adolescent health, women's health, lesbian-gay health services).* Without culturally competent and available health care services for historically underserved and marginalized populations, health promotion services live in a vacuum. There must be active promotion and support for services that expressly provide services to specific cultural, ethnic, racial, gender, and even age communities.
- *Accessible and available substance and mental health services.* From mental health illness and substance abuse prevention programs through residential and aftercare services, a concerted effort must be made to address the issues of chemical dependency and mental health services in the communities hardest hit by HIV/AIDS.
- *Services to reduce the harm of illicit drug injection (e.g., the provision of alcohol and cotton swabs, needle exchange programs, treatment on demand).* The long-standing debate over the federal ban on needle exchange has inadvertently allowed a "forest for the trees" discussion. Although needle exchange programs are essential to curb the HIV epidemic in injection drug users, they are not a panacea. The entire health needs of injection drug users, including the physical risks associated with improper or unsafe injection (such as abscesses, hepatitis B and C rate) and treatment on demand must be addressed if the epidemic is to be really managed within these communities.
- *Age-appropriate healthy sexuality school-based curricula.* With the signing into law of the Welfare Reform Bill (1996), the single largest increase for HIV prevention, as funded by Congress, has been allocated to enforce abstinence-based education, in spite of scientific evidence that abstinence-only education is dangerous and unhealthy. Incorporating abstinence-based education into comprehensive healthy sex and sexuality curricula is essential to reduce the numbers of unintended teen pregnancies, HIV infections, and other STDs.
- *Behavior-based health promotion campaigns (educational and instruction) for the reduction of sexually transmitted diseases (including both*

viral and bacterial STDs) nested in a system of readily accessible detection and treatment programs. The traditional approach to STD management and control has not succeeded in eradicating sexually transmitted disease in the United States. There is evident need to incorporate behavior change models into STD prevention, treatment, and control if the epidemics of STDs (which are perhaps the most significant co-factor in HIV infection) are to be brought under control. There is a clear need to incorporate prevention science and biomedical interventions to reduce the number of new STD infections.

- *A capacity and public health infrastructure commensurate with its health demands.* Health care systems are not just an amalgam of good interventions run out of relevant and stable community-based organizations that are evaluated and client centered. An integral component of good public health and therefore effective health promotion activities is an infrastructure that allows for stability, timeliness of contracting and evaluation, and sound fiduciary oversight and accountability. The past decade has seen intentional erosion of public health infrastructure. Unfortunately, ultimately, the only entity that suffers from the destruction of the backbone of public health is the consumer.
- *Policies that assist in health promotion (federal, state and local).* Simply put, policies and laws that endanger the public health of the citizenry must be changed. In a paradigm where science drives public policy and programs, the moralizing of public health (and criminalizing index communities) is an unacceptable barrier to healthy communities.
- *Comprehensive HIV prevention interventions.* Comprehensivity incorporates primary and secondary prevention, integrates relevant services when appropriate, and communicates across categorical programs and funding streams to maximize the health of any given community or jurisdiction.

To introduce PEP into a system with any less than the eight listed standards would be to cripple the preventive health model. Yet, this is clearly the threat posed in many communities by this proposed biomedical intervention.

A PLACE FOR PEP IN THE HEALTH SYSTEM

The introduction of the concept of PEP caught many in the community off guard. Some were upset; others urged caution over the lack of a scientific base to justify its use. For many, it proposed a new paradigm that emphasized abandoning behavioral science for that of biomedical science. For others, it struck a dissonant chord echoing back to their experiences with HIV vaccine readiness trials.

In an odd twist, some community advocates held that PEP is racist in its construct, out to replicate lessons never learned from the ill-fated, unethical

Tuskegee syphilis trial. Perhaps the most bizarre dismissal for PEP came from a slight sector of the treatment activist community who felt the source of PEP was the pharmaceutical industry hungry to peddle unsafe drugs to an unsuspecting public.

This is not to say that there were not advocates for PEP; in fact they remain. However, those opposing a rush to lay down guidelines about PEP without a strong scientific justification outnumber the supporters.

What remains absent from the public discourse surrounding PEP is not just reason and science, but balance and logic. At one point, the discussion regarding PEP shifted from a discussion about "prophylaxis"to "treatment"(e.g., PEP to PET). At a public meeting, a government health official was asked why their agency had arbitrarily changed the moniker from PEP (as was indicated in the governmental letter of invitation to a meeting in Atlanta) to PET. Those present at this meeting were informed that the shift was merely semantic and that, for all intents and purposes, PEP (prophylaxis) was the same as PET (treatment).

However, when one culls away the absurdity of such a change being merely "semantic,"one can actually see the calculated logic behind the lexicographic shift. As a community advocate pointed out in this public meeting, if the discussion is about postexposure prophylaxis, the Centers for Disease Control and Prevention (CDC) is the agency responsible for the finding of said intervention. However, if it were postexposure treatment, clearly the Health Resources and Services Administration (HRSA) (primarily through the Ryan White CARE Act's Title 111) would shoulder the cost.

If one is to step back with clarity unobstructed by agency finding responsibility, it becomes apparent that neither prophylaxis nor treatment adequately contextualizes this intervention; neither moniker fits correctly. It is more correct to regard this as postexposure prevention services. Thus, this opportunity to work with an index patient who has not just an identified risk behavior but also an identified risk situation cannot be trivialized.

FROM SCIENCE FICTION TO HEALTH POLICY

When a person enters a medical prevention setting because of accidental possible exposure, a "window of opportunity" opens for helping this person either remain HIV negative (through appropriate prevention service triage) or to rapidly access quality and appropriate medical care. Once this window of opportunity opens, this intervention moment should not be lost.

Clearly, either a primary prevention environment is needed for this person including counseling and support, or a secondary prevention setting is called for, to assist in reducing the onset of illnesses, including opportunistic infections and/or other viral and bacterial sexually transmitted diseases. This moment—when the person has entered the health care continuum—must be seized, and the whole of

the patient's needs must be attended to so that he or she can maintain good health, good health promotion activities, and good caretaking skills.

CONSIDERATIONS AND RECOMMENDATIONS

There remain a great many ethical and community concerns regarding PEP that must first be analyzed and answered before this potentially beneficial intervention could or should be present within a given community.

On the ethical front, one must seriously consider the following issues:

- Is this intervention equally available to all at-risk (and exposed) persons?
- Is this intervention based on a thorough informed consent process with each patient?
- Is this intervention resonant with community-based standards and public health–funded HIV prevention strategies?
- Is there accessible, available health care in the jurisdiction?
- Are prescribing physicians capable of frank, healthy, and prevention-oriented discussions with their patients for whom this intervention might be indicated?
- Are prescribing physicians trained to the current (and evolving) standard of care for the management of HIV disease?
- Are prescribing physicians capable of performing a comprehensive health inventory on the patient that includes (and is sensitive to) issues of domestic violence, substance abuse, and lesbian-gay-bisexual health and sexual health concerns?
- Is the health care setting adequately prepared to provide counseling and care to homeless and indigent individuals?
- Is there a strong referral network already present in the jurisdiction that can actualize a health care referral for either primary or secondary prevention services?

In analyzing community concerns, the following questions must be answered:

- Has the index community been educated as to risks and benefits associated with PEP?
- Is there a community consensus on the importance of PEP?
- Are there data to suggest that a particular at-risk community would be harmed with the introduction of PEP?
- Are there, already in place in the index community, health care norms, basic and advanced education programs, sufficient capacity to provide interventions, and culturally relevant prevention and care programs and evaluative processes to examine the impact of PEP prior to its introduction?

- Does the jurisdiction have the financial wherewithal to support PEP as a nested intervention within its health care (health promotion–disease prevention) continuum?
- Will all at-risk communities be equally educated and have equal access to this intervention?
- Are there meaningful public health partnerships between local health departments, community-based providers, and advocates such that intended and unintended consequences of this intervention can be gauged (and changed if the data direct such a change)?
- Will culturally competent practitioners be administering this intervention in concert with culturally specific community-based service providers?
- What assurances can be given to the community that this intervention is safe? Effective? Cost-effective? Or even cost-saving?
- Are there reasonable safeguards to either discontinue or medically intervene in case PEP inadvertently has adverse consequences for participants, progeny, or partners (spouses, domestic partners)?
- What liability, if any, do the public health and medical establishments have in the event of unintended but adverse effects on participants, their offspring, or both? (And for what length of time following this intervention?) (And what precedent case is there to standardize liability, access to remuneration, length of time before suit is inadmissible, or all of these?)

The discussion on PEP is multifaceted. What appears on the surface to be a simple solution to a simple problem may in fact hide a deeper and more complicated issue. Therefore, much data, planning, investigation, and research are required before PEP can be promoted as an important intervention in our collective struggle against HIV disease.

A cursory review of these events and processes would include the following elements:

- A strong literature review on whether the introduction of an intervention akin to PEP (say a vaccine candidate) has had positive or negative impacts on risk-taking behavior among high-risk individuals and/or high risk index communities;
- A clear and well-constructed case-controlled clinical trial to determine the efficacy of PEP and the impact of PEP on a community's and individual's risk-taking behaviors and beliefs;
- Both biomedical and behavioral research to develop realistic and effective therapeutic treatment dose schedules (such as b.i.d. schedules, incentives for adherence, support structures, and reduction in adverse side effects);
- A thorough analysis of jurisdictional capacity to provide comprehensive health promotion services (both primary and secondary HIV prevention activities);

- Clear support for primary HIV prevention efforts across jurisdictions, including efforts to aggressively promote risk-reduction activities (e.g., condom usage, needle exchange, drug treatment, and STD services) and efforts to promote HIV counseling and testing;
- Integration of HIV prevention messages and counseling into correlative health promotion services (e.g., family planning, mental health, violence prevention, substance abuse prevention and treatment, STD);
- Constructing a meaningful and realistic assessment of individuals (not index communities) and their ability to participate realistically with and adhere to their individualized health promotion regimen (e.g., combination therapy, prevention case management, substance abuse treatment);
- Thoughtful health planning research on how to appropriately nest PEP within a jurisdictional continuum of health promotion services (e.g., cost-effectiveness studies, evaluation research, technical assistance to Ryan White CARE Act grantees, planning councils or consortia and HIV Prevention Community Planning Groups).

CONCLUSION

Clearly, scientific advancements in the effective management of HIV disease are happening at breakneck speed. What was a theoretical possibility less than 5 years ago has become fact for many people living with HIV: increased survival benefit. The drive for a preventive vaccine is under way (although we are not sure that technological advances are disciplining research methodology or vice versa). Nevertheless, it is clear that regardless of therapeutic advances, it is still better to be seronegative than living with HIV disease.

Sadly, in spite of proven, inexpensive, and evaluated HIV prevention interventions, the HIV community continues an overreliance on biomedical advances to assist in the communal management of disease and disease progression. Primary HIV prevention remains the most effective way of decreasing new HIV infections in the absence of a proven and accessible vaccine. And secondary HIV prevention offers reductions in morbidity and mortality that cannot be ignored.

If the dialogue regarding PEP does nothing more than shift the community's understanding of the need for a more robust and comprehensive HIV prevention portfolio based on health promotion rather than crisis management, then it will have served a greater good. It is unlikely that definitive studies proving the efficacy of PEP will surface in the next few months. However, what we have at our disposal (good, proven, replicable, community-specific HIV prevention interventions) persevere.

On a deeper level, PEP challenges the very nature of our belief in HIV prevention (and preventive health). If we really believe that individuals and communities are capable of changing behavior and maintaining this change, then PEP and

its relevance to any health care model assumes its place in a much broader context. If, however, we do not believe science and the best intentions of individuals and communities, then PEP is simply a metaphor of an overreliance upon pills and not people, medications and not behavioral interventions, of science over humanity.

If we do not accept the challenge inherent in the discussion surrounding PEP, we will lose a critical chance to rethink, revamp, and overhaul a health care system that has yet to invest time, energy, and belief in sound health promotion. Ultimately, the choice is clear: either to be prepared, adapt, adopt, and transform or forever to be caught in a reactive mode, lacking both sound context and a comprehensive health promotion system. To accede to the latter is akin to running to stand still.

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9

Behavioral Research Needs and Challenges of New Treatments

AIDS as a Chronic Illness

WILLO PEQUEGNAT and ELLEN STOVER

INTRODUCTION

The efficacy of protease inhibitors, a new category of antiretroviral medications, and potent regimens combining new and old antiretroviral drugs are remarkable achievements in HIV medicine. These new treatments have created experiences in which, after having come to terms with imminent death, persons living with HIV or AIDS (PLHIV/AIDS) have the potential of many more years of life (Rabkin & Ferrando, 1997). Confusion and trauma may result from this situation; this stems from the difficulty of reconciling two contradictory life orientations: an acceptance of a premature death and reenergizing life with new possibilities (Davies, 1997). Living with HIV/AIDS as a chronic illness (like diabetes), which like other serious illnesses intrudes on and reshapes a person's life and priorities, is a new and once unthinkable area for research.

PERSONS LIVING WITH HIV OR AIDS (PLHIV/AIDS)

As the use of protease inhibitors and other new treatments on the horizon become more widespread, the group of PLHIV/AIDS is likely to grow. Because such treatment is new, few studies have examined the extraordinary issues faced by persons who opt for this potent treatment regimen. This chapter calls for research on these issues in order to develop strategies to help individuals re-engage with life and cope with AIDS as a chronic illness. After reviewing the strengths of PLHIV/AIDS, the research directions suggested by other chronic illnesses are dis-

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cussed. Finally, five major areas of research are laid out along with priority research areas.

A small literature has accrued delineating issues faced by persons who have experienced repeated cycles of wellness and illness and the coping strategies that they develop (see especially Callen, 1990; Davies, 1997; Rabkin, Remien, Katoff, &Williams, 1993a; Remien, Rabkin, Williams, & Katoff, 1992; Remien, Rabkin, Katoff, & Wagner, 1993). An article by Jue (1994) provides an excellent overview. To develop effective interventions, it is important to understand the strengths of these individuals and recognize the challenges they face.

Reasons for Survival

Many PLHIV/AIDS attribute their survival to receiving good medical care and being equal partners in their care. They are assertive and well-informed consumers of health care who have accepted AIDS as a permanent part of their life. Other reasons given for survival include a positive attitude, a healthy lifestyle, taking responsibility for oneself, support from others, and prayer, meditation, and spirituality (Davies, 1997; Remien *et al.,* 1992; Remien *etal.,* 1993).

Coping Strategies

The coping strategies seropositive persons adopt include setting short- and long-term goals, remaining active, having a sense of humor, socializing and pursuing pleasurable activities, focusing on aspects of a situation that are within their control, receiving psychotherapy, having a problem-solving approach, and "getting outside'' themselves by giving support to others (Remien *et al.,* 1992).

Cognitive-behavioral and supportive group interventions have been effective in enhancing skills and decreasing psychological distress (Chesney & Folkman, 1994; Fawzy, Namir, & Wolcott, 1989; Kelly *et al.,* 1993). HIV-infected men who have less effective coping strategies are more likely to continue to engage in higher risk behaviors (Kalichman, *et al.,* 1997; Robins *et al.,* 1994).

Personality Characteristics

PLHIV/AIDS seem to share certain personality characteristics or to have strengthened these traits in response to their experience with AIDS. Because they have had to deal with uncertainties about their health, they have a greater tolerance for ambiguity in their lives. They are often highly flexible and thus able to adapt to the changes brought on by the course of their illness. They have confidence in their ability to manage their illness (self-efficacy) and, because they have repeatedly recovered from serious episodic illnesses, many develop an optimism that these difficult times will eventually improve (Chesney & Folkman, 1994).

PLHIV/AIDS speak of learning to appreciate the present moment and finding meaning and pleasure in simple things, especially in connections and shared moments with others (Davies, 1997).

Survivor Guilt and Fear

PLHIV/AIDS face difficult issues because they have "outlivedthe odds." Many have exhausted their financial resources. Some feel that they have made tacit contracts with family and friends about their life span on which they have extracted favors, and by continuing to live, they have broken the contracts and imposed extra emotional and financial burdens on others (Remien *et al.,* 1992). Many encounter resentment and hostility from others who have lost someone to AIDS or from those who have AIDS and are not as responsive to the new therapies. If PLHIV/AIDS are in a period of relatively good health, others may minimize their past health problems and doubt the severity of their illness, which for some survivors may negate the significant achievement and pride they feel in coping well. Some experience survivor guilt and fear disclosing their longevity to others, a situation that for many gays parallels the "closeted" experience.

Social Isolation and Loneliness

Along with the losses of health and previous lifestyle, AIDS has often taken many of their friends, creating an ongoing cycle of loss and grief. They must balance painful feelings of abandonment and bereavement with feelings of hope for themselves and others who have remained relatively healthy. In such a situation, loss of emotional stamina—emotional burnout and exhaustion—may immobilize even the most resilient (Rabkin *et al.,* 1993a). For this reason, and because of ongoing health problems and fears of rejection or of infecting others, many PLHIV/AIDS do not have the emotional energy to invest in a romantic relationship. This may lead to social isolation and loneliness and to problems with self-concepts such as attractiveness and sexuality (Folkman, Chesney, Pollack, & Phillips, 1992).

RESEARCH DIRECTIONS SUGGESTED BY OTHER CHRONIC ILLNESSES

A diagnosis of cancer was once assumed to be a death sentence, as was end-stage heart, lung, liver, and kidney disease. As cancer survival rates have risen and as organ transplantation has become more common, an enormous literature has accumulated on issues faced by survivors, their quality of life (QOL), their illness coping strategies, and the needs of their caregivers. Research on coping with HIV/AIDS as a chronic illness is growing out of this knowledge base which pro-

vides another dimension to understanding the challenges of surviving a life-threatening illness and living day to day.

Shared Problems

PLHIV/AIDS who respond to protease inhibitors share several features with cancer and transplant survivors that may be helpful in research design. Individuals who opt for bone marrow transplant, an increasingly effective cancer treatment, and for transplant of major organs often have no other chance of survival, having failed more conservative treatments. Certain death is the likely alternative, and they may experience the loss of control that accompanies such situations. To prevent their body's rejection of the organ or the bone marrow, they must subscribe to a lifelong intrusive daily regimen of immunosuppressive drugs and other health-maintaining routines. For many cancer and transplant patients, the drugs have a variety of unpleasant side effects that many regard as a new illness.

Some survivors may feel a sense of personal responsibility for continuing to have problems after a successful transplant (Botsford, 1995). They may blame themselves for not being cured by such extensive treatment. Some may experience immobilizing apprehension about resuming life roles after an extended period of being a patient, especially when these roles have been assumed and managed well by partners and other family members.

Uncertainty about the future persists for most cancer and transplant patients, because recurrence of cancer or organ rejection may occur even in those adherent to health regimens. The process of survival is progressive and often undramatic. The long history of illness and treatment experienced by some cancer and transplant survivors has interrupted their careers and strained their finances as well as their families and support systems. The stigma of cancer has led to discrimination on the job and to social isolation from the community.

Shared Strengths

The parallels with PLHIV/AIDS in facing all these difficult challenges are clear. However, research must also take into account the strengths that people develop through the experience of illness. Many survivors of life-threatening illnesses and their families and friends develop a resilience and an ability to cope, spiritual resources, intimate bonds with others, and a strong sense of life's worth and beauty that they claim they did not possess before they became ill.

OVERVIEW OF RESEARCH AREAS

This research agenda is divided into five broad areas for research: (1) medical decision making and adherence, (2) CNS problems of HIV/AIDS, (3) practic-

ing safer HIV-related sexual behaviors, (4) stress and coping, and (5) quality of life. Issues that researchers have found to be important to other survivors of life-threatening illnesses, for example, breast cancer survivors and transplant recipients, are highlighted, and issues relevant for PLHIV/AIDS are discussed. At the end of each section, suggestions for future research are given. (For a discussion of the ethical issues that arise in research in these areas, see Chapter 5, this volume).

Medical Decision Making and Adherence

Background Issues

Treatment with combination therapies can result in inhibition of viral replication and reduction of virus load to a point when it is barely detectable in the blood of seropositive persons. However, the benefits from combination medication regimens can be maintained only if persons are adherent to the complicated dosing schedules and other requirements (see Chapter 3, this volume, for fuller discussion of these issues).

The directions for taking antiretroviral therapy are extremely complex (see Chapter 1, this volume, for a fuller discussion of the issues). Some medications must be taken at room temperature on an empty stomach (indinavir) or with high fat food (saquinavir). Some medicines may require refrigeration (ritonavir) which may complicate mobility. Critical decisions need to be made when the combination of drugs is not achieving the desired results. Monitoring viral load as a guide to medical decision making can also be a complex task which requires learning new information and parameters.

Although in the long run drugs may offer hope for a better life, in the short run they can lead to illness and disability while adjustments are being made in the drugs and the doses. There may be serious side effects that can become new illnesses in themselves, such as diabetes or hypercholesterolemia. People may not want to live with the symptoms and limited QOL if they do not believe in the efficacy claims made for the new therapies. Not taking the therapy as prescribed may not be lack of adherence but a general disagreement with the recommended treatment regimen.

Potential Research Areas

- Develop effective methodologies for measuring direct and indirect adherence to treatment regimens.
- Support research on adherence to treatment regimens and behavioral strategies to manage symptoms associated with treatment and disease progression.
- Study role of cognitive functioning in medical decision making and adherence.

- Identify critical components in process of understanding informed consent and its effects on adherence to drugs.
- Assess the role of patients in medical decision making and adherence and their satisfaction with treatment.
- Study the effect of patient education and different modes of instruction in dosing regimens on adherence to treatment therapies.
- Identify the role of families and other social support systems in ensuring that well thought out medical decision making and treatment adherence occur.
- Assess the predictors of both practicing safer sexual and drug-using behaviors and adherence to drug regimens and beliefs about reduction in viral load.
- Support research on adherence to treatment regimens, including communication techniques to improve shared decision making between health care providers and HIV-infected individuals, and behavioral strategies to manage symptoms secondary to treatment protocols.

CNS-Related Problems of HIV/AIDS

Studies of the neuropathogenesis of HIV infection have contributed to our understanding of the effect of HIV/AIDS on both the central and peripheral nervous systems and its impact on everyday living. As patients begin to live longer on combination therapies, there are likely to be more morbidity and mortality from CNS-related complications.

Quality of Life

Background Issues

Quality of life (QOL) has become an important area of outcome research among long-term survivors of life-threatening illnesses. The measurement of QOL must take into account multiple variables in several dimensions. Early QOL researchers identified more than 800 overlapping dimensions of QOL among Americans; they were able to reduce these to 100 life areas (Andrews & Withey, 1976). A recent review in the *Journal of the American Medical Association* of 75 QOL studies among medical patients stressed the importance of using QOL measures specific to the needs of a patient population and based on patient self-reported QOL concerns (Gill & Feinstein, 1994).

Ferrell and associates (1996) have developed a conceptual framework of QOL among breast cancer survivors that has four dimensions of well-being: (1) physical, (2) psychological, (3) social, and (4) spiritual. Using structured interviews, they found QOL variables specific to breast cancer survivors, such as concerns about fertility after radiation treatment, which they added to the four

dimensions. Several of these variables may be relevant for PLHIV/AIDS receiving protease inhibitors. For example, in the physical dimension of Ferrell's model nausea, appetite, and fatigue were highly important to QOL. In the psychological area, usefulness to others, anxiety, depression, and fear of recurrence were critical. Other important social well-being variables may include family distress, personal relationships, financial burden, and sexuality. In the area of spiritual well-being were hopefulness, life purpose, and religious/spiritual activity.

Although extensive research has yet to be undertaken for the population of interest in this chapter, several areas of quality of life are likely to be important: (1) the side effects and intrusiveness of medication regimens, (2) return to work and financial concerns, (3) role resumption and role retention (the ability to maintain valued social roles), (4) social support and independence, and (5) sexuality and self-concept. Two of these QOL areas—return to work and social support—are addressed here. These two areas have been singled out because research on other illnesses has repeatedly found strong positive correlations between these variables and self-reported quality of life and because PLHIV/AIDS who respond well to protease inhibitors may encounter particular challenges in these areas.

A large research effort has attempted to identify predictors of return to work among survivors (Botsford, 1995). To distinguish between those who are unable to work and those who choose not to, researchers have developed four categories: (1) return to work, (2) retired, (3) medically disabled, and (4) insurance disabled (Meister, McAleer, Meister, Riley, & Copeland, 1986). Those who choose not to work are classified as retired as opposed to disabled. The insurance disabled category may have particular relevance for the population addressed in this chapter. Insurance-disabled individuals are unable to return to work because they would lose their Medicaid or Medicare, which pays for their costly medications. Many studies have found that loss of insurance or disability income is a strong predictor of nonreturn to work.

Better QOL of those who return to work is not guaranteed. Discrimination may be a serious problem, resulting in distress and in ongoing financial problems. A French study found that cancer survivors had great difficulties borrowing from banks (Joly *et al.,* 1996). Studies of cancer survivors have shown that up to 25% of those who return to work experience problems such as dismissal, demotion, denial of wages, and ostracism; about 10% have to deal with hostility such as jokes about their physical appearance (Muzzin, Anderson, Figueredo, & Gudelis, 1994). For blue-collar workers, these figures may be as high as 80%. The Federal Disabilities Act and state laws requiring insurance coverage regardless of pre-existing conditions provide increased opportunities to expand employment for PLHIV/AIDS through legal advocacy and education of employers, patients, and families.

Numerous QOL studies have found that the extent and richness of one's social network is strongly related to good self-reported quality of life. However, it is also well documented by cancer survivor research that illness negatively effects relationships with others, particularly intimate relationships (Taylor & Dakof, 1988).

Families are sometimes broken up by long-term illness, because of divorce or the necessity of finding others to care for young children. Many women who are PLHIV/AIDS have had to give their children to others to raise. Those who respond to protease inhibitors may wish to resume the role of mother, and may require special support. In addition, PLHIV/AIDS may have had their social networks decimated by AIDS. Poverty and substance abuse among the survivor's family and friends may make them undependable in terms of support. It is relatively recently that evidence has been found for the role of psychosocial factors, such as emotional support from others, in increasing the likelihood of survival (Chesney & Folkman, 1994; Spiegel, 1993a).

Much research has shown that families and other caregivers of cancer survivors generally have many needs that are unmet by community resources. Lower-class families have smaller and more concentrated social networks compared with middle-class families, whose networks are larger and looser. Middle-class families are thus often able to call on more resources. The stigma that is associated with AIDS may result in social isolation (both community- and self-imposed), as has been found for cancer survivors and their families; social isolation can have a negative effect on treatment adherence and health status (Muzzin *et al.,* 1994).

Potential Research Areas

- Identify QOL measures specific to the needs and lives of PLHIV/AIDS receiving long-term medical treatments.
- Examine expectations of PLHIV/AIDS in regard to maintaining past quality of life and adapting to current quality of life and its impact on health status.
- Examine predictors of return to work and the role of returning to work in the quality of life of PLHIV/AIDS on multiple treatment regimens.
- Identify workplace issues and problems related to the long-term illness and solutions (e.g., the intrusion of medication schedules, side effects, or both on work performance).
- Examine workplace discrimination in this population, especially for blue-collar workers, and identify avenues for change.
- Identify social support needs specific to this population and examine issues and problems regarding social support, role retention and resumption, family burden, and so on.
- Develop and test interventions for ameliorating stress and improving coping for PLHIV/AIDS and its impact on QOL and disease progression.
- Develop and test interventions to enhance the development of social support from families and friends.
- Develop and test interventions (e.g., job counseling, retraining) to enable return to work by PLHIV/AIDS who are being successfully treated.
- Develop and test interventions for supporting the families of PLHIV/AIDS in adapting to HIV/AIDS as a chronic condition.

- Identify the psychosocial variables that are predictors of adapting to HIV and mediators of change associated with effective secondary prevention programs.
- Test the effectiveness of preventive interventions in improving quality of life and promoting health-enhancing behavior of PLHIV/AIDS.
- Develop and test interventions to minimize the impact of stigmatization of HIV-infected persons, including decisions regarding treatment and QOL.
- Support health services research and evaluation to assess the impact of changes in the health care delivery system on care, disease progression, and QOL.
- Conduct research to identify and remove barriers to effective health care utilization, including access, continuum of care, and health and social services to improve treatment adherence and QOL.

CONCLUSIONS

Although HIV/AIDS is still a mysterious and life-threatening disease, it can be prevented and now it can be treated. Close attention needs to be paid to the changing nature and demographics of the epidemics and the populations that are becoming seropositive and those who are receiving treatment. As the treatments become more efficacious, the need to attend to the possible CNS complications from HIV/AIDS and their sequelae, such as dementia and other HIV-related neuropsychological and psychiatric impairments becomes even more pressing. As HIV/AIDS is now viewed as a chronic illness, considerations of how to teach people to manage their treatment regimens and maintain a good QOL throughout are paramount.

Despite the baffling nature of HIV/AIDS, researchers in behavioral science, neuroscience, immunology, and molecular biology are continuing to ask and answer more specific questions. The striking growth of HIV-related prevention and treatment research during the last decade encourages us to believe that many of the research questions laid out in this research agenda will be successfully addressed in this next decade.

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AIDS Treatment Glossary

Abscess an isolated accumulation of pus associated with a localized infection.

Accelerated Approval expedited FDA approval of a new treatment based on early surrogate marker data from clinical studies. The purpose of accelerated approval is to hasten the availability of new drugs for serious or life-threatening conditions. Government approval of a new treatment for sale based on early surrogate marker data from clinical studies.

Active Immunity biological defense to stimulation by a disease-causing organism or other antigen.

Acupuncture An ancient technique of traditional Chinese medicine that stimulates or disperses the natural flow of energy within the body. The technique consists of piercing the skin at specific points of the body with a thin needle,

Adherence the degree to which a patient follows drug schedules. A synonym for *compliance.* The act of following a prescribed therapeutic regimen.

Adjuvant in vaccines, a substance added to increase the immune response to the inoculant.

Adverse Event a toxic reaction to a medical therapy.

Adverse Reaction (side effect) an unwanted negative reaction to an experimental drug or vaccine.

Aerosolized a form of administration in which a drug, such as pentamidine, is turned into a fine spray or mist by a nebulizer and inhaled.

AIDS Clinical Trials Group (ACTG) a nationwide consortium of medical centers carrying out clinical trials to study therapies for HIV/AIDS, sponsored by the National Institute of Allergy and Infectious Disease (NIAID).

Alkaline Phosphatase an enzyme produced in the liver as well as in bone and other tissues. Elevated serum levels of the enzyme are indicative of liver disease, bile duct obstruction in particular.

Allergic Reaction an extreme sensitivity to things such as drugs. Some allergic reactions can be life threatening.

Alopecia hair loss.

Alternative Medicine a catch-all phrase for a long list of treatments of medicinal systems, including traditional systems such as Chinese or Ayurvedic medicine as well as homeopathy, various herbals and many other miscellaneous treatments that have not been accepted by the mainstream, or Western, medical establishment. Alternative medicine may be referred to as *complemen-*

tary medicine. The designation "alternative medicine'' is not equivalent to "holistic medicine," which is a more narrow term.

Alternative Therapies treatments that are not based in traditional Western medical practice. Also referred to as complementary medicine.

Americans with Disabilities Act (ADA) a federal law passed in 1990 that prohibits employers of at least 15 people from discriminating against people with disabilities (including HIV). Also prevents discrimination with respect to public accommodations, including restaurants, stores, public transportation, and so on. Requires employers to make reasonable accommodations, if necessary, to allow people with disabilities to keep working.

Antibiotic an agent that kills or inhibits the growth of microorganisms, especially a compound similar to those produced by certain fungi for destroying bacteria. An antibiotic is used to combat disease and infection.

Antibodies molecules in the blood or secretory fluids that tag, destroy, or neutralize bacteria, viruses, or other harmful toxins. They belong to a class of proteins known as immunoglobulins, which are produced by B-lymphocytes in response to antigens.

Anticoagulant a substance that delays or counteracts blood clotting.

Antiemetic an agent that prevents vomiting.

Antifungal a substance that kills or inhibits the growth of a fungus.

Antioxidant a substance that inhibits oxidation or reactions promoted by oxygen or peroxides.

Antiprotozoal drugs or other therapies that kill or inhibit the multiplication of single-celled microorganisms called protozoa.

Antiretroviral drugs that treat retroviral infection. AZT, ddI, and ddC are examples of antiretrovirals used to treat HIV infection.

Antisense a complementary piece of genetic material (DNA or RNA) that binds to another piece of DNA or RNA and prevents that DNA/RNA from being used to synthesize new proteins.

Antisense Drug a synthetic segment of DNA or RNA that locks onto a strand of DNA or RNA with a complementary sequence of nucleotides. Antisense drugs are designed to block viral genetic instructions, marking them for destruction by cellular enzymes, in order to prevent the building of new virus or the infection of new cells.

Antiviral drugs that destroy a virus or suppress its replication.

Attenuated Virus a weakened virus with reduced ability to infect or produce disease. Some vaccines are made of attenuated viruses. A weakened virus strain that can no longer infect or produce disease. An attenuated virus might potentially be used as a vaccine.

bDNA (Branched DNA) a test developed by the Chiron Corp. for measuring the amount of HIV (as well as other viruses) in blood plasma. The test uses a signal amplification technique, which creates a luminescent signal. The brightness of the signal depends on the viral RNA present. Test results are calibrated

in numbers of virus particle equivalents per milliliter of plasma. bDNA is similar in results, but not in technique, to the PCR test.

b.i.d. abbreviation for *bis in die,* a Latin phrase meaning twice a day. A drug prescribed this way should be taken approximately every twelve hours.

Bioavailability the extent to which an oral medication is absorbed in the digestive tract and reaches the bloodstream.

Blinded Study a clinical trial in which participants are unaware whether they are in the experimental or the control group.

Blood–Brain Barrier a physical barrier between the blood vessels and the brain that allows only certain substances to enter the brain.

Blood Retina Barrier the barrier that prevents the passage of most substances from the blood to the retina, making it difficult to treat eye disease with systematically administered medicines, e.g., pills and intravenous infusions.

Bone Marrow Suppression a side effect of many anticancer and antiviral drugs, including AZT. Bone marrow suppression may lead to a decrease in red blood cells (erythrocytopenia or anemia), white blood cells (leukopenia) or platelets (thrombocytopenia). Such reductions respectively result in fatigue and weakness, bacterial infections, and spontaneous or excess bleeding.

Booster a second or later dose of a vaccine given to increase immune response to the original dose.

Breakthrough Infection an infection, caused by the infectious agent the vaccine is designed to protect against, that occurs during the course of a vaccine trial. These infections may be caused by exposure to the infectious agent before the vaccine has taken effect, or before all doses of the vaccine have been given.

Bronchoscopy a diagnostic examination in which a fiber optic tube is inserted in the throat to enable a doctor to see the trachea and the lungs. Bronchoscopy is often used to detect PCP

Buffered refers to pills that include a special substance for neutralizing stomach acid. Drugs are buffered to reduce stomach upset or increase absorption by the intestines.

Buyer's Club a nonprofit group that imports AIDS-related therapies available in other countries but not yet approved by the FDA for use in the United States. Many buyers' club products are sold abroad for purposes that are not related to AIDS or HIV infection, and their use in HIV/AIDS remains speculative.

Cachexia general weight loss and wasting.

Catheter a hollow and usually flexible tube, which is inserted into the body to allow fluids to enter or exit the body.

Case Management system under which the patient's health care and social services are coordinated by one or more individuals familiar with both the patient's needs and community resources.

CD4 a membrane protein or receptor of T-helper lymphocytes, monocytes, macrophages, and some other cells; is the attachment site for HIV.

CD4 Count the most commonly used surrogate marker for assessing the state of the immune system. As CD4 cell count declines, the risk of developing opportunistic infections increases. The normal range for CD4 cell counts is 500 to 1500 per cubic millimeter of blood. CD4 count should be rechecked at least every 6 to 12 months if CD4 counts are greater than 500/mm^3. If the count is lower, testing every 3 months is advised.

CD4 Percent the percentage of total lymphocytes made up by CD4 cells. A common measure of immune status that is about 40% in healthy individuals and is below 20% in persons with AIDS.

CD4/CD8 Ratio the ratio of CD4 to CD8 cells. A common measure of immune system status that is around 1.5 (to one) in healthy individuals and falls as CD4 counts fall in persons with HIV infection.

CD8 (T8) a membrane protein found on the surface of suppressor T lymphocytes.

Cell Antiviral Factor (CAF) a so far unidentified soluble substance secreted by activated CD8 cells that inhibits HIV replication within cells.

Challenge in vaccine experiments, the deliberate exposure of an immunized animal to the infectious agent. Challenge experiments are never done in human HIV vaccine research.

Chemokine soluble chemical messengers that attract white blood cells to the site of infection. There are two structural categories of chemokines: alpha (CXC) and beta (cc). Examples of chemokines that interfere with HIV activity are the **B** chemokines MIP-1**a,** MIP-1B, and RANTES and the chemokine SDF-1.

Chemoprophylaxis the use of chemical agents for disease prevention.

Chemotherapy the use of chemical agents in the treatment of a disease.

Chinese Medicine Chinese medicine is based on treatments that enhance the body's natural immunity and eliminate or reduce the potency of pathogens (external harmful organisms). Traditional Chinese medicine includes the use of herbs or acupuncture.

Clinical Trials scientifically governed investigations of medications in volunteer subjects. Their purposals to seek information regarding the product's saftey (Phase I) and efficacy (how well it works) (Phase II/III).

Clotrimazole (Lotrimin, Mycelex) used to treat skin and vaginal fungal infections.

COBRA a federal law requiring employers of at least 20 people to offer to keep in force group health insurance coverage for at least 18 months for people who have left their jobs or who would otherwise no longer qualify to remain covered as part of the group. (People who leave their jobs as a result of disability may be entitled to 29 months, and others losing their coverage as dependents, 36 months.) During the time coverage is extended, it remains the responsibility of the covered individual to make his or her own premium payments. Some states have adopted Mini-COBRA Laws, requiring companies of fewer than 20 to provide similar benefits.

Co-factor a co-factor is anything (microbes, proteins, hormones, genes) that make a disease progress more rapidly. With HIV infection, co-factors are

only suspected but may include other viruses (like cytomegalovirus), age, genetic resistance or predisposition, and certain hormonelike substances, called cytokines, released by lymphocytes.

Combination Therapy (Convergent Combination Therapies) combined administration of drugs that are effective at different stages of the HIV viral cycle or that affect different elements of the virus. Combined approaches reduce potential drug resistance.

Compassionate Access when drugs are made available even though not approved by government agencies.

Compassionate Use a process for providing experimental drugs on an individual basis to very sick patients who have no treatment options. Often, case-by-case approval must be obtained from the FDA for "compassionate use" of a drug.

Compliance the degree to which a patient exactly follows a particular treatment regimen. Noncompliance may jeopardize the effectiveness of a drug and lead to resistance. Adherence is an alternative term.

Complimentary Treatments unapproved substances or procedures used for therapeutic purposes.

Concomitant Drugs drugs that are taken together. Certain concomitant medications may have adverse interactions.

Concorde Study joint French/British clinical trial of AZT in asymptomatic HIV-infected individuals. See AZT.

Continuous Infusion uninterrupted introduction of fluid other than blood into a vein.

Contraindication a specific circumstance when the use of certain treatments could be harmful.

Control Arm the group of participants in a clinical trial who receive standard treatment or a placebo, against which the experimental treatment is compared.

Controlled Clinical Trial a trial in which one group of subjects is administered an experimental drug or vaccine and another group is administered either a placebo or a standard treatment or vaccine. Participants are usually unaware of which group they are in.

Coordinated Care describes care that is planned and implemented so as to form a cohesive therapeutic program.

Correlates of Immunity/Correlates of Protection the immune responses that protect an individual from a certain disease. The precise identities of the correlates of immunity in HIV are unknown.

Corticosteroid any steroid hormone obtained from the cortex or outer portion of the adrenal gland or any synthetic substitute for such a steroid. Corticosteroids are immunosuppressive and include prednisone, corticosterone, and aldosterone.

Cross-Resistance the phenomenon in which a microbe that has acquired resistance to one drug through direct exposure also turns out to have resistance or more other drugs to which is has not been exposed. Cross-resistance arises

because the mechanism of resistance to several drugs is the same, resulting from identical genetic mutations.

Culture a culture, in medical terms, is a medium in which microbes can grow. HIV is grown in cultures containing lymphocytes. If a sample of a person's blood is put into such a culture, and HIV grows, the person is infected with HIV. Other blood tests for HIV are polymerase chain reaction or the p24 antigen test. The usual blood test for HIV detects antibodies to the virus instead of the virus itself. The antibody test is usually preferred because it is less expensive, better standardized, and more readily available.

Curetting scraping of a cavity with a sharp spoon-shaped instrument.

CXCR-4 (Fusin) a seven-looped protein structure on the surface of certain immune system cells that acts as a chemokine receptor site. CXCR-4, which naturally binds to the alpha chemokine SDF-1, is the second receptor necessary for T-tropic, synctia-inducing HIV to enter and infect a cell. The other receptor site for HIV binding and entry is CD4.

Cytochrome P450 System a system that breaks down drugs in the liver using enzymes that limit or promote drug metabolism.

Cytokines chemical messenger proteins released by certain white blood cells, including macrophages, monocytes, or lymphocytes. An intercellular chemical messenger protein released by white blood cells. Cytokines facilitate communication among immune system cells and between immune system cells and the rest of the body.

Cytotherapy the use of liquid nitrogen to freeze and destroy an abnormal lesion; sometimes used to create scar formation in order to prevent further spread of a condition (e.g., retinitis).

Desensitization gradually increasing the dose of a medication in order to overcome severe allergic reactions. Desensitization procedures became popular when administering Bactrim for the first time.

Diagnosis confirmation of illness based on an evaluation of a patient's medical history, symptoms, and laboratory tests.

Directly Observed Therapy (DOT) a patient takes a medication while under direct observation by another individual. Usually used in antituberculosis treatment.

Dose-Escalating describes a preliminary clinical trial in which the amount of a drug is either periodically increased or decreased with each new trial arm that is added. Used to determine how well a drug is tolerated in people and what its optimum dose might be, given the observed balance between activity and side effects.

Dose-Response Relationship the relationship between the dose of a vaccine and an immune or physiologic response. In vaccine research, a dose-response effect means that as the dose of the vaccine increases, so does the level of the immune response (antibodies and CTL activity).

Double-Blinded denotes a clinical trial in which neither the participants nor the doctors know who is receiving the experimental drug and who is receiving the

placebo or standard comparison treatments. This method is believed to achieve the most accurate, generalizable results because neither the doctor nor the patients can affect the observed results with their psychological biases.

Drug–Drug Interaction the effects that occur when two or more drugs are used together. Such effects include changes of absorption in the digestive tract, changes in the rate of the drugs' breakdown in the liver, new or enhanced side effects, and changes in the drugs' activity.

Efficacy strength, effectiveness. The ability of a drug to control or cure an illness. Efficacy should be distinguished from activity, which is limited to a drug's immediate effects on the microbe triggering the disease.

Endogenous relating to or produced by the body.

Endoscopy endoscopy is a diagnostic procedure in which an instrument is passed through the mouth or rectum to examine an internal organ or to obtain a biopsy. In people with HIV infection, the most common types of endoscopy are bronchoscopy to examine the lungs and endoscopies to examine the digestive system. Upper endoscopy of the intestine involves passing an endoscope through the mouth to examine the esophagus, stomach, or upper small intestine. Lower endoscopy of the intestine involves passing an endoscope through the rectum to examine the large intestine or colon.

Endpoint a category of data used to compare the outcome in different arms of a clinical trial. Common endpoints are severe toxicity disease progression or fall in such surrogate markers as CD4 count, but sometimes death is used as an endpoint. Usually when an endpoint reaches a certain set magnitude of change from baseline, a trial participant is removed from the trial and receives an open-label therapy (either a standard treatment or experimental one being tested).

Enteric pertaining to the intestines.

Enteritis inflammation of the intestine.

Enzyme a cellular protein the shape of which allows it to hold together several other molecules in close proximity to each other. Enzymes are able in this way to induce chemical reactions in other substance with little expenditure of energy and without being changed themselves. A protein that can cause chemical changes in other substances without being changed itself.

Enzyme linked immunosorbent assay (ELISA) the blood test most often used to screen for HIV infection. ELISA detects HIV antibodies, not HIV itself. Because ELISA is sensitive it has a high false-positive rate and is therefore confirmed by a more specific test.

Eradication the complete elimination of HIV from the body, including the blood and tissues such as the lymph nodes.

Exogenous developed or originating outside the body.

Expanded Access refers to any of the FDA procedures (compassionate use, parallel track, and treatment IND) that distributes experimental drugs to patients who are failing on currently available treatments for their condition and also are unable to participate in ongoing clinical trials.

Experimental Drug a drug that has not been approved for use as a treatment for a particular condition.

First-Line Treatment the optimal starting therapy for a treatment-naive patient. Because of the potential for the development of cross-resistance by HIV and other microbes, the choice of first-line medication(s) will affect the efficacy of succeeding (second-line) therapies.

Fusin a protein necessary for HIV binding with a host cell.

Gastrostomy Tube a tube inserted into the stomach via a surgically created artificial opening.

Gene Therapy any number of experimental treatments in which cell genes are altered. Some gene therapies attempt to provoke new immune activity; some try to render cells resistant to infection; some involve the development of enzymes that destroy viral or cancerous genetic material cells.

gp41 a glycoprotein from HIV's outside envelopes that complexes with gp120 to form the mechanism enabling HIV to latch onto and enter cells.

gp120 a glycoprotein from HIV's envelope that binds to CD4 molecules on a cell's outside membrane. Free gp120 in the body may be toxic to cells on its own, causing CD4 depletion in the immune system through apoptosis and neurological damage leading to AIDS dementia complex.

Growth Factor one of many intercellular regulatory molecules that affects cell proliferation and maturation in various tissues.

Guidelines clinical practice recommendations made by agreement of experts or based on a literature review by a panel of experts and consumers. Purpose is to educate health care providers, improve the care provided to individuals with specified conditions, and, when possible, enhance the cost-effectiveness of health care.

HAART (Highly Active Antiretroviral Therapy) aggressive anti-HIV treatment usually including a combination of protease and reverse transcriptase inhibitors the purpose of which is to reduce viral load to undetectable levels.

Half-Life the amount of time required for half of a given substance (such as a drug) or half the current population of a given type cell to be eliminated from the body.

Heptavax a vaccine for hepatitis B.

Herbal Treatments small amounts of plants, including roots, bark, leaves, or juices used for therapeutic purposes.

Hickman Catheter people who need long periods of treatment with specific drugs given by vein will often have a tubing called a Hickman catheter. The catheter is inserted by a specialist, usually a surgeon, through the skin of the chest, and then tunneled under the skin to a vein in the chest. The end of the catheter comes out the chest wall above the breast. Drugs can be injected into the catheter as necessary. The advantage of a Hickman catheter is that it permits access to the vein without repeated needlesticks.

HIV Set Point the rate of virus replication that stabilizes and remains at a particular level in each individual after the period of primary infection.

Holistic comprehensive care; as in physical, social, mental, and emotional health taken together. Also, various systems of health protection and restoration, both traditional and modern, that are reputedly based on the body's natural healing powers, the various ways the different tissues affect one another, and the influence of the external environment.

Holistic (Wholistic) Medicine various systems of health protection and restoration, both traditional and modem, that are reputedly based on the body's natural healing powers, the various ways the different tissues affect one another, and the influence of the external environment.

Home Care medical care and related services that are given at home by family members, nurses, or health care providers, or a combination thereof.

Hospice a facility in which medical and mental health care are provided to a terminally ill patient (usually within 6 months of death). The hospice philosophy emphasizes alleviating the patient's discomfort and supporting the family in the grieving process.

Human Immunodeficiency Virus (HIV) the AIDS virus; a retrovirus of the lentivirus class; formerly called LAV or HTLV-III. HIV type 1 (HIV-1) is the common cause of HIV disease in North America; HIV type 2 (HIV-2) is prevalent in some parts of Africa and occasionally occurs in North America and Europe.

Humoral Immunity responses against disease rendered by lymphocytes where antibodies are produced and circulate in the bloodstream to act against antigens.

Hypercin an experimental treatment for hepatitis B and CMV infection.

Hypersensitivity an allergic reaction; the body reacts with an exaggerated immune response to drugs or other substances.

Iatrogenic refers to an unfavorable response to medical or surgical treatment; symptoms attributable to a medical therapy, e.g., peripheral neuropathy caused by an antiviral drug.

Idiopathic refers to a disease or condition of unknown cause or origin.

IL-1 (Interleukin-1) a cytokine that is released early in an immune system response by monocytes and macrophages. It stimulates T-cell proliferation and protein synthesis. Another effect on IL-1 is that it causes fever.

IL-2 (Interleukin-2) a cytokine secreted by Th1 CD4 cells to stimulate CD8 cytotic T lymphocytes. IL-2 also increases the proliferation and maturation of the CD4 cells themselves. During HIV infection, IL-2 production gradually declines. Use of IL-2 therapy is under study as a way to raise CD4 cell counts and restore immune function.

IL-4 (Interleukin-4) a cytokine secreted by the Th2 CD4 cells that promotes antibody production by stimulating B-cells to proliferate and mature.

IL-6 (Interleukin-6) a cytokine whose production affects many different cells in the immune system.

IL-12 (Interleukin-12) a cytokine released by macrophage in response to infection that promotes the activation of cell-mediated immunity. Specifically, IL-12 triggers the maturation of Th1 CD4 cells, specific cytotoxic T-lymphocyte responses and an increase in the activity of NK cells. IL-12 is under study as an immunotherapy in HIV infection.

Immune Deficiency a breakdown or inability of certain parts of the immune system to function; increases susceptibility to certain diseases.

Immune Reconstitution the natural or therapy-induced revival of immune function in a body damaged by HIV infection, particularly after initiation of a highly potent antiviral therapy.

Immune Suppression a state in which the immune system is damaged and does not perform its normal functions; can be induced by drugs or result from diseases.

Immune-Based Therapy (IBT) anti-HIV treatment that aims to modulate, supplement, or extend the body's immune responses against HIV infection or other diseases. Also called immunotherapies. Examples of experimental immunotherapies for HIV include passive immunotherapy therapy (PIT), IL-2 and therapeutic vaccines.

Immunity natural or acquired resistance to a specific disease. Immunity may be partial or complete, long-lasting or temporary.

Immunization the process of protecting an individual against communicable diseases by injecting weakened or killed infectious organisms into the body to cause the immune system to produce antibodies and activate T cells against the organism without causing the full-blown disease.

Immunocompetent refers to an immune system capable of enveloping a normal protective response when confronted with invading microbes or cancer.

Immunocompromised refers to an immune system in which the response to infections and tumors is subnormal.

Immunodeficiency a breakdown or an inability of certain parts of the immune system to function that renders a person susceptible to certain diseases that he or she ordinarily would not develop.

Immunoglobulin (Ig) a general term for antibodies, which bind onto invading organisms, leading to their destruction. There are five classes: IgA, IgD, IgM, IgE, IgG.

Immunoglobulin A (IgA) an immunoglobulin found in bodily fluids such as tears and saliva and in the respiratory, reproductive, urinary, and gastrointestinal tracts. IgA protects the body's mucosal surfaces from infection.

Immunoglobulin G (IgG) the prominent type of immunoglobulin existing in the blood. Also called gamma globulin.

Immunomodulator A substance capable of modifying one or more functions of the immune system.

Immunotherapy treatment aimed at reconstituting an impaired immune system. Examples of experimental immunotherapies for AIDS include passive hyperimmune therapy (PHT), IL-2 and therapeutic vaccines.

Inclusion/Exclusion Criteria the medical or other reasons why a person may or may not be allowed to enter a trial. For example, some trials do not allow pregnant or nursing women to join, others do not allow people taking certain drugs, and others exclude people with certain illnesses.

Indication purpose for which a drug is prescribed. The FDA-approved indications appear on a printed insert included with the manufacturer's drug packaging.

Incidence the rate of occurrence of some event, such as the number of individuals who get a disease divided by a total given population per unit of time.

Induction Therapy the initial, concentrated phase of a particular treatment.

Informed Consent the ability of people receiving services (i.e., HIV antibody test, certain medical procedures (like an operation), participation in a clinical trial, to make competent decisions about their medical care. Before taking the test, undergoing the procedure, or participating in the trial, the person or the person's representative must sign an informed consent form stating that he or she has been informed about the purpose, benefits, risks, and alternatives to the test, procedure, or trial, and that he or she consents to it. In the case of participation in a clinical trial, the informed consent form explains the purpose of the trial, what will be done, the risks of participation, the benefits of participation, what other treatments are available, and the right of the participant to leave the trial at any time.

Infusion the process of giving a substance to an individual by injecting it into a vein. This procedure can be a one-time event or can be continued over many hours, days, or even months.

Inoculum Size a term used in the field of infectious diseases to describe the number of microbes necessary to cause an infection. In HIV infection, for example, a certain number of viruses is required before infection takes place. The specific number is not known. What is known is that the probability of transmitting HIV with the transfusion of one unit (or 500 milliliters) of infected blood is 80% to 90%. The probability of transmitting HIV with a needlestick injury, which injects only a fraction of a milliliter of blood, is 0.4%. This difference in the probabilities of transmission is most likely due to differences in inoculum size.

Institutional Review Board (IRB) a regulating committee composed of internal staff, hospital affiliates, and community members which reviews and approves all human trials conducted within a particular hospital or research center. The IRB ensures that a trial is conducted in an ethical manner, with proper protection of human subjects.

Integrase the HIV enzyme that inserts HIV's genes into a cell's normal DNA. Integrase operates after reverse transcriptase has created a DNA version of RNA form of HIV genes present in virus particles.

Intent-to-Treat a method of analysis of medical trials that groups each participant according to the treatment arm to which they were initially assigned (e.g., experimental drug, standard therapy, placebo), regardless of whether they remained in that arm for the duration of the study.

Interferons proteins originally defined by their activity against viral infections; alpha, beta, and gamma interferons have been investigated as therapy for some opportunistic diseases.

Intolerance the inability of the body to appropriately metabolize an agent or drug.

Invasive disease in which organisms or cancer cells are spreading throughout the body; a medical procedure in which a device is inserted into the body.

Investigational New Drug status given an experimental drug after the FDA approves an application for testing it in people.

In Vitro testing and experiments conducted in a laboratory setting (i.e., test tube or culture plate).

In Vivo testing and experiments conducted in animals or humans, in a living, natural environment.

Karnofsky Performance Score a measure given by a physician to a patient's ability to perform certain ordinary tasks: 100—normal, no complaints; 70—unable to carry on normal activity; 50—requires considerable assistance; 30 — hospitalization recommended.

Kaplan–Meier Curve a common mechanism for graphically analyzing a therapy's efficacy. The Kaplan–Meier curve displays a statistical estimate of the percentage of people receiving a given therapeutic regimen who at each observation point after entering a trial, continue to do acceptably well on their assigned therapy. Plotting the curves for a trial's different treatment arms on the same chart yields a comparison of the various regimens. The chart allows researchers to compare people who enter a study at different times.

Lavage the washing out of an organ or cavity, e.g., to obtain a sample for diagnosis.

Limit of Detection (Limit of Quantification) refers to the sensitivity of a quantitative diagnostic test, such as the viral load assay. The limit of detection is the level below which the test can no longer accurately measure the amount of a substance, such as HIV RNA. If a person has an "undetectable" viral load, it does not mean that HIV is no longer present, but rather, that the test is not sensitive enough to measure the amount. For viral load assays, "limit of quantification" is becoming the preferred term.

Lipase Level enzymes in the digestive system that break down fat.

Live-Vector Vaccine a vaccine that uses a non-disease-causing organism (virus or bacterium) to transport HIV or other foreign genes into the body, thereby stimulating an effective immune response to the foreign products. This type of vaccine is important because it is particularly capable of inducing CTL ac-

tivity. Examples of organisms used as live vectors in HIV vaccines are canarypox and vaccinia.

Log (Logarithm) formally, the number of times ten must be multiplied with itself to equal a certain number. For example 100,000 is log 5 because it is equal to 10 x 10 x 10 x 10 x 10. Logs are used to measure changes in viral load. For example, a reduction in viral load from 100,000 to 1000 copies/ml is a two log (or 99%) reduction. Note that half/log change is not a fivefold difference but a change of 3.16-fold (the square root of ten).

Long Terminal Repeat (LTR) the genetic material at each end of the HIV genome. When the HIV genes are integrated into a cell's own genome, the LTR interacts with cellular and viral factors to initiate the transcription of the HIV DNA into an RNA for that is packaged in new virus particles. Activation of the LTR is a major step in triggering HIV replication.

Maintenance Therapy extended drug therapy, usually at a diminished dose, administered after a disease has been brought under control. Maintenance therapy is utilized when a complete cure is not possible, and a disease is likely to recur if therapy is halted.

Megadosing medical treatment with very large doses of a nontoxic substance, usually a vitamin.

Metabolite any substance produced by metabolism or by a metabolic process.

Microbicide an agent that inactivates, kills, or destroys microbes.

Mutation a change in the charger of a gene that is perpetuated in subsequent cell divisions.

Myelotoxic destructive to the bone marrow.

Naïve usually used when talking about a specific treatment (i.e., "AZT naïve"). It means a person has not taken this drug before.

Naive T Cell a T cell arising from the immune system's production of fresh cells in the bone marrow. Naive T cells respond to newly encountered pathogens containing antigens the immune system has not processed before. The naive T cells' activation and proliferation create an acquired immune response to the newly encountered pathogenic agent. After the disease is eradicated, a portion of the T-cell population engendered by the activated naive T cell constitutes a reservoir of memory cells, which proliferate and respond very quickly to any recurrence of the disease.

Naked DNA Vaccine purified DNA used as a vaccine to insert into cells'genes that produce specific proteins.

Natural History Study study of the natural development of something (such as an organism or a disease) over a period of time.

Neucleoside Analog a type of antiviral drug, such as AZT, ddl, ddC, or D4T, in which the makeup constitutes a defective version of a natural neucleoside. Neucleoside analogs may take the place of the natural nucleosides, blocking the completion of a viral DNA chain during infection of a new cell by HIV

The HIV enzyme reverse transcriptase is more likely to incorporate nucleoside analogs into the DNA's construction than is the DNA polymerase normally used for DNA creation in cell nuclei. A drug that mimics part of HIV's genetic material and stops the virus from reproducing.

Neutropenia abnormal drop in the number of a type of white cells called neutrophils.

NNRTI (Nonnucleoside Reverse Transcriptase Inhibitor) a member of a class of compounds, including delavirdine and nevirapine, that acts to directly combine with and block the action of HIV's reverse transcriptase. In contrast, nucleoside analogs block reverse transcriptase by capping the unfinished DNA chain that the enzyme is constructing. NNRTIS have suffered from HIV's ability to rapidly mutate and become resistant to their effects.

Nystatin (Mycostatin) a drug used to control fungal infections.

Nucleoside a building block DNA or RNA, the genetic material found in living organisms. Before being added to a DNA or RNA sequence, nucleosides must have a phosphate group added.

Nucleotide nucleic acid chains are composed of subunits called nucleotides. Nucleosides are related to nucleotides, the subunits of nucleic acids; however, nucleosides do not carry the phosphate groups of the nucleotides.

Off-Label a drug prescribed for conditions other than those approved by the FDA.

Open-Label Trial a study in which both researchers and participants know what drug a person is taking and at what dose.

Orphan Drug a status granted by the FDA to unpatentable medications developed for rare diseases. Orphan drug status gives the drug's manufacturer a 7-year right to exclusively market the compound. This protection of unpatentable orphan drugs encourages their development by greatly increasing their profitability.

p24 one of the several proteins (the protein with a molecular weight of 24,000) that make up HIV (specifically the core). It can be measured in blood and other body fluids.

p24 Antigen Test although less accurate, the p24 antigen test is, like the PCR test and a culture for HIV, a test that detects the presence of HIV in the blood. The test has been used to monitor viral activity. An antigen is anything that causes the immune system to identify it as foreign and to manufacture antibodies against it. A p24 antigen test detects p24 and therefore HIV Unlike PCR and HIV cultures, however, the p24 antigen test is not especially sensitive, and most people with HIV infection have tests for the p24 antigen that are negative. Levels of p24 are highest both early and late in the disease; the numbers of HIV are likewise highest at the same times.

Palliative offering relief of symptoms or comfort without ameliorating the underlying disease process. Offering comfort or relief of symptoms without making the underlying disease process any less or better. It is the type of care offered in a hospice.

Parallel Track Program a system of distributing certain experimental drugs to individuals who are unable to participate in ongoing clinical trials ofthat drug.

Parenteral intravenous or intramuscular administration of substances such as therapeutic drugs or nutritive solutions.

Parenterally infusion by injection.

Passive Immunotherapy a process in which individuals with advanced disease (who have low levels of HIV antibody production) are infused with plasma rich in HIV antibodies or an immunoglobulin concentrate (HIVIG) from such plasma. The plasma is obtained from asymptomatic HIV-positive individuals with high levels of HIV antibodies.

PCR (Polymerase Chain Reaction) a highly sensitive test that measure the presence or amount of RNA or DNA of a specific organism or virus (for example, HIV or CMV) in the blood or tissue. Unlike the standard blood test for HIV infection, which detects antibodies to HIV, the PCR detects HIV itself. PCR tests are being used to gauge HIV disease progression and the effect of particular treatments on HIV infection.

Pentamidine used for prevention or treatment of PCP.

Pharmacokinetics the behavior of drugs in the body, including how a drug is absorbed, metabolized, and eliminated. The extent the body is able to absorb, distribute, and eliminate a drug over time.

Phase I Clinical Trial the earliest stage clinical trial for studying an experimental drug in humans. Phase I trials are generally comparatively small, typically involving 20 to 100 patients and lasting several months. They provide an initial evaluation of a drug's safety and pharmacokinetics—how the drug is absorbed, what tissues it reaches, and how long it takes to leave the body. Such studies also usually test various doses of the drug (dose ranging) to obtain an indication of the appropriate dose to use in later studies. Approximately 70% of drugs successfully complete phase I.

Phase II Clinical Trial a more advanced state clinical trial that follows the Phase I trials. A phase II trial gathers preliminary information on whether an experimental drug works. The major purposes are to continue to determine the short-term safety and effectiveness. Data are often based on laboratory tests that provide quick but indirect measurements of a drug's effect on disease. Phase II trials often involve up to several hundred people who are randomly assigned to take either the experimental drug or a "control" (the standard treatment for the disease or no treatment at all). Usually the trial is double-blinded, which means no one (not the patient, doctor, nurse, or researcher) knows who is getting the drug until the trial is completed and the results are analyzed. Approximately 33% of drugs successfully complete phase II.

Phase III Clinical Trial an advanced stage clinical trial that should conclusively show how well a drug works as compared to other treatments. Typically involves from several hundred to several thousand patients, takes place at multiple sites, and may last from 1 to 4 years. They should measure whether a

new drug extends survival or otherwise improves the health of patients on treatment (clinical improvement) rather than just provide surrogate marker data. Approximately 25% to 30% of drugs successfully complete phase 111.

Phase IV a trial designed to evaluate the long-term safety and efficacy of a drug for a given indication, usually carried out as a postmarketing study after a drug has been approved by the FDA.

PICC Line (Peripherally Inserted Central Catheter) a catheter inserted into an arm vein and used for periods of up to 3 months. This catheter does not need to be surgically implanted and can be inserted at home by a trained nurse.

Pilot Trial a feasibility study intended to gain preliminary information about efficacy, safety, or a particular research hypothesis. Pilot trials are used to work out the details of further clinical trials.

Placebo an inactive substance that is used in some clinical trials. Often one group is given a placebo and another group is given a real drug, and the results in the groups are compared.

Placebo-Controlled Study a method of investigation of drugs in which an inactive substance or the standard therapy (the placebo) is given to one group of patients while the drug being tested is given to another group. The results obtained in the two groups are then compared.

Polyvalent Vaccine a vaccine that is active against multiple viral strains.

Postexposure Prophylaxis (PEP) administering drug treatment to prevent disease in an individual after exposure to an infectious organism. For example, guidelines have been established for postexposure prophylaxis of health care providers who have been exposed to HIV through needlesticks.

Prednisone an approved steroid used to reduce inflammation.

Prevalence the number of individuals with a condition in a specific population.

Preventive HIV vaccine a vaccine designed to prevent HIV infection.

Prime-Boost in HIV vaccine research, administration of one type of vaccine, such as a live-vector vaccine, followed by or together with a second type of vaccine, such as a recombinant subunit vaccine. The intent of this combination regimen is to induce different types of immune responses and enhance the overall immune response, a result that may not occur if only one type of vaccine were given for all doses.

Primary Care Setting a place where comprehensive care is delivered (e.g., a physician's office, community health clinic, preventive nursing service).

Principal Investigator the head researcher responsible for organizing and overseeing a clinical trial.

Prodome a symptom that indicates the onset of a disease.

Prophylactic vaccines only work as a preventive and must be given before infection.

Prophylaxis prevention; a treatment intended to preserve health.

Prospective Study refers to studies designed to follow the progress of a cohort forward in time, rather than analyzing data from previous research.

Protease an enzyme that triggers the breakdown of proteins. HIV's protease enzyme breaks apart long strands of viral protein into separate proteins constituting the viral core and the enzymes it contains. HIV protease acts as new virus particles are budding off a cell membrane.

Protease Inhibitors a drug that binds to and blocks HIV protease from working, thus preventing the production of new functional viral particles.

Protease inhibitors compounds that block the ability of HIV to produce the enzyme protease, an essential enzyme for the HIV replication process.

Protocol a detailed plan for a clinical trial that states the trial's rationale, purpose, drug or vaccine dosages, length of study, route of administration, and who may participate.

Pseudovirion a virus-like particle that resembles a virus but does not contain its genetic information and cannot replicate. In some viral diseases pseudovirions can interfere with infection by the real infectious virus.

Psychotrophic Drugs drugs that affect an individual's behavior or mental functions.

Qualitative Assay a test that determines the presence or absence of a substance.

Quality of Life expression used in speaking of issues relating to normalizing the life of a chronically ill individual. In defining quality of life, health care providers must consider not only the physical responses to medical therapy, but also the psychological implications of illness for both the patient and the family. The overriding goal of care should be to relieve suffering and increase patient well-being.

Quantitative Assay a test that measures the amount of a substance in a specified sample size.

Quinolone a class of synthetic antibiotic drugs with broad-spectrum antibacterial activity; examples include ciprofloxcin, ofloxacin, and sparfloxacin.

Reagent any chemical used in a laboratory test or experiment.

Recombinant refers to compounds produced by laboratory or industrial cultures of genetically engineered living cells. The cell's genes have been altered to give them the capability of producing large quantities of the desired compound for use as a medical treatment. Recombinant compounds often are versions of naturally occurring substances.

Refractory refers to disease that is resistant to treatment.

Regimen a formalized schedule for administering drugs, including how much of a drug to take, how often to take it, and whether to take it with food or other drugs.

Remission a period when the signs of a disease have been eliminated through treatment or the immune response. A disease may be in remission without a complete cure having been effected.

Resistance (to a drug) the ability of an organism, a microorganism, or a virus to lose its sensitivity to a drug. For example, after long-term use of AZT, HIV can develop strains of virus in the body that are no longer suppressed

by the drug, and therefore are said to be resistant to AZT. Resistance is thought to result from a genetic mutation. In HIV, such mutations can change the structure of viral enzymes and proteins so that an antiviral drug can no longer bind with them as well as it used to. Resistance detected by searching a pathogen's genetic makeup for mutations thought to confer lower susceptibility is called *genotypic resistance.* Resistance found by successfully growing laboratory cultures of the pathogen in the presence of a drug is called *phenotypic resistance.* High-level resistance reduces a drug's virus-suppressing activity hundreds of times. Low-level resistance represents only a few fold reduction in drug effectiveness. Depending on the toxicity of the drug, low-level resistance may be overcome by using higher doses of the drug in question.

Retrospective Study a study that tries to answer a new medical question by reviewing data gathered in the past. A retrospective study cannot be rigorously designed and risks attributing effects to the wrong causes.

Reverse Transcriptase (RT) a viral enzyme that transcribes viral RNA into DNA so that genetic material of the virus can be integrated into genetic material of the T-cell helper and other host cells. Many antivirals inhibit the action of this enzyme, including AZT, ddI, and ddC.

Ribonucleic Acid (RNA) a complex nucleic acid responsible for translating genetic information from DNA and transferring it to the cells' protein-making machinery.

Ryan White CARE (Comprehensive AIDS Resources Emergency) Act passed in 1990 to provide services for persons with HIV infection, this act seeks "to improve the quality and availability of care for individuals and families with HIV disease." It directs financial assistance to metropolitan areas with the largest numbers of reported cases of AIDS for emergency services and to all states for improved care and support services and early intervention services.

Salvage Therapy urgent treatment for a disease or illness that has not responded to standard therapy.

Scid mice scid mice are used in studies as models of humans with immune diseases such as AIDS.

Secondary Care Setting a place where patients are referred for special care (e.g., a community or general hospital).

Sensitivity the ability of a drug to have an effect on an organism. For example, a strain of HIV is sensitive to AZT if the drug can stop the virus from replicating.

Side Effect an unintended action or effect of a drug. Undesired drug side effects may include nausea, diarrhea, skin rash, peripheral neuropathy, and liver damage.

Stem Cell cell from which all blood cells derive. Bone marrow is rich in stem

cells. Clones of stem cells may become any one of the repertoires of immune cells depending on what cytokines and hormones they are exposed to.

Surrogate Markers a laboratory measurement of biological activity in the body that indirectly indicates the effect of treatment on disease state. CD4 cell counts and viral load are examples of surrogate markers in HIV infection.

Synergy (adj.: Synergistic) the interaction of two or more treatments such that their combined effect is greater than the sum of the individual effects observed when each treatment is administered alone.

Specificity the ability of a test to correctly identify an individual who is not infected.

Standard Therapy a therapy that is FDA approved and widely used as first-line treatment.

Systemic affecting the whole body; not localized.

Tat inhibitors Experimental agents that block HIV's tat gene; for possible use in combination therapies.

Teratogenicity the ability to cause defects in a developing fetus. This is distinct from mutagenicity, which causes genetic mutations in sperms, eggs, or other cells. Teratogenicity is a potential side effect of many drugs, such as thalidomide.

TH Naïve aT cell that is not yet directed to produce either a cell-mediated (TH-1) or humoral (TH-2) response.

TH1 Response an acquired immune response in which the most prominent feature is high cytotoxic T-lymphocyte activity relative to the amount of antibody production. The Th 1 response is promoted by CD4 "Th1"T-helper cells.

TH2 Response an acquired immune response the most prominent feature of which is high antibody production relative to the amount of cytotoxic T-lymphocyte activity. The Th2 response is promoted by CD4 "Th2"T-helper cells.

Therapeutic HIV vaccine a vaccine designed to boost the immune response to HIV in a person already infected with the virus. Also referred to as an immunotherapeutic vaccine.

Therapeutic Index the ratio between the toxic concentration of a drug and an effective one. To be a useful therapy, the therapeutic index has to be high. For example, cyanide will kill all the HIV in a patient, but only at levels high enough to kill the patient, too—its therapeutic index is too low.

Therapeutic Vaccines used to treat disease after infection occurs.

t.i.d. a term used on prescriptions to mean "take three times a day"; from the Latin phrase ter in die.

Titer the concentration or activity of a given dissolved substance, such as a drug, antibody, or antigen, as measured by the solution's chemical reactivity in a "titration assay." In particular, the extent to which an antibody-plasma ex-

tract can be diluted before losing its ability to protect against the corresponding antigen.

Topical Solvents a liquid substance having dissolving properties when placed on the skin and/or mucous membranes.

TPN (Total Parenteral Nutrition) a liquid food substitute infused directly into the blood and designed to meet a person's entire nutritional needs. TPN provides an alternate route in cases of severe gastrointestinal distress in which nutrient absorption is poor. It strengthens the body and relieves the digestive tract while therapy for the underlying condition progresses. TPN's high cost precludes its use as a long-term therapy.

Toxicity state of being poisonous or harmful. The harmful effects of a given drug that occur during therapy. The term is similar to side effect and adverse reaction.

Toxin a harmful or poisonous agent.

Transfusion putting whole blood, platelets, or plasma into the bloodstream.

Treatment-Naive refers to patients with no history of previous treatment for a particular condition.

Treatment Vaccine designed to produce new or renewed therapeutic immune response in a person already infected.

Trough Level the minimum concentration of a drug in blood plasma, occurring before the next time that drug is administered. Sometimes abbreviated as Cmin, Achieving an adequate trough level that retains sufficient antimicrobial activity is important in avoiding the rise of drug-resistant microbes.

Undetectable an HIV viral load result that is below the specificity of test.

Vaccination immunization with antigens administered for the prevention of infectious diseases.

Vaccine a vaccine is a drug, given by mouth or by injection that stimulates the immune system to form antibodies to some microbe. The polio vaccine, for instance, stimulates the immune system to form antibodies against the poliovirus. These newly formed antibodies now protect the person against any subsequent exposure to that microbe. Some vaccines work less well than others; with the polio vaccine, protection is nearly 100%; with the influenza vaccine, protection is about 70%. Vaccines for HIV infection are being tested in people with and without HIV infection.

Viral Load the amount of HIV RNA per unit of blood plasma. An indicator of virus concentration and reproduction rate, HIV viral load is increasingly employed as a predictor of disease progression. It is measured by PCR and bDNA tests and is expressed in numbers of copies of or equivalents to the HIV RNA genome per milliliter of plasma. (Note that there are two RNA copies per HIV virion.)

Viremia the presence of virus in the blood or blood plasma. Plasma viremia is a quantitative measurement of HIV levels similar to viral load but is accom-

plished by seeing how much of a patient's plasma is required to start an HIV infection in a laboratory cell culture.

Virulence the power of a microorganism to cause grave disease.

Wild-Type the most common form of HIV before mutation takes place.

Window Period time from infection with HIV until detectable seroconversion.

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