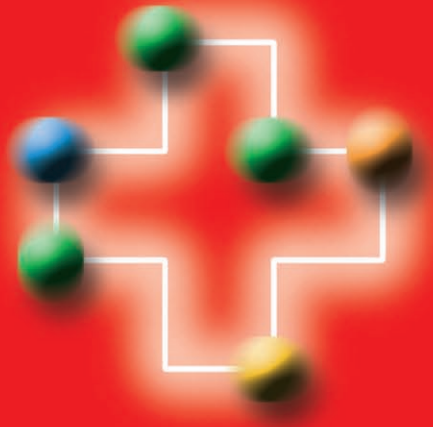Hoffmann - Rockstroh - Kamps

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Preface 2005

The HIV Medicine textbook has now grown to its full size. As in previous years, all chapters have been thoroughly revised, and most parts of the book were available on the Internet months before they were printed here. That is the way, we firmly believe, that medical textbooks should be handled in the 21st century.

Two years ago, we removed the copyright on HIV Medicine. As a result, our textbook is now available in Spanish, Russian, Portuguese, German, and Romanian (www.hivmedicine.com/textbook/lang.htm). This is clearly a challenge for the future, and the authors of HIV Medicine are ready to take the challenge. As a matter of fact, the 2006 edition is already under way.

The philosophy which governs the publication of HIV Medicine 2005 has recently been published at www.freemedicalinformation.com.

Christian Hoffmann, Jürgen K. Rockstroh, Bernd Sebastian Kamps

Hamburg, Bonn, Paris – July 2005

Preface 2003

Hardly any field of medicine has ever undergone a similar stormy development to that of the therapy of HIV infection. Little more than 10 years passed, between the discovery of the pathogen and the first effective treatment! However, there is also hardly a field that is subjected to so many fast- and short-lived trends. What today seems to be statute, is tomorrow often already surpassed. Nevertheless, therapeutical freedom must not be confused with freedom of choice. This book presents the medical knowledge that is actual today: from December 2002 to January 2003.

Because HIV medicine changes so fast, HIV Medicine 2003 will be updated every year. Additional chapters about opportunistic infections, malignancies and hepatitis are freely available at our Web site www.HIVMedicine.com.

Under certain conditions, the editors and the authors of this book might agree to remove the copyright on HIV Medicine for all languages except English and German. You could therefore translate the content of HIV Medicine 2003 into any language and publish it under your own name – without paying a license fee. For more details, please see http://hivmedicine.com/textbook/cr.htm.

Christian Hoffmann and Bernd Sebastian Kamps

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Content

Part 1

Basics

1. Introduction

Bernd Sebastian Kamps and Christian Hoffmann

The first reports on homosexual patients suffering from previously rare diseases such as pneumocystis pneumonia (PCP) and Kaposi's sarcoma were published in May 1981 (Centers for Disease Control 1981a, 1981b, 1981c). It soon became clear that the new disease affected other population groups as well, when the first cases were reported in injecting drug users. However, it took almost two years until, in 1983, the human immunodeficiency virus type I (HIV-1) was defined as the primary cause of the acquired immunodeficiency syndrome (Barré-Sinoussi 1983, Broder 1984, Gallo 1984).

Almost 25 years have now elapsed. 25 years, in which HIV infection has changed from a fatal condition to a manageable chronic illness. 25 years, in which the development of antiretroviral therapy (ART) has been one of the dramatic advances in the history of medicine. However, for the vast majority of people living with HIV/AIDS, ART is still light years away – largely inaccessible in resource-poor countries where HIV continues to devastate families, communities and societies, especially the poor and the socially marginalized.

In the following 750 pages, we present a comprehensive overview of the treatment of HIV infection and its complications. As in previous years, all chapters have been thoroughly revised, and most parts of the book were available on the Internet (www.HIVMedicine.com) months before they were printed here. The philosophy which governs the publication of HIV Medicine 2005 has recently been published at www.freemedicalinformation.com. That is the way, we firmly believe, that medical textbooks should be handled in the 21st century.

Transmission Routes

There are several ways in which someone can become infected with HIV. These transmission routes are well defined (see also Chapter "Post-Exposure Prophylaxis"). HIV infection can be transmitted through

- unprotected sexual intercourse with an infected partner;
- injection or transfusion of contaminated blood or blood products (infection through artificial insemination, skin grafts and organ transplants is also possible);
- sharing unsterilized injection equipment that has been previously used by someone who is infected;
- maternofetal transmission (during pregnancy, at birth and through breast-feeding).

Occupational infections of healthcare or laboratory workers may occur; however, a 1995 study estimated that although 600,000 to 800,000 needle-stick injuries occurred among healthcare workers every year in the USA, occupational infection was not frequent. The risk of occupational HIV transmission from contaminated needlesticks to healthcare workers was found to be 0.3 % in case series performed prior to the availability of potent ART.

There are sometimes concerns that there may be alternative routes of HIV transmission. It must be explicitly stated that HIV is **NOT** transmitted by mosquitoes, flies, fleas, bees or wasps. HIV is **NOT** transmitted through casual every day contact. No cases of HIV infection have been documented to arise from contact with non-bloody saliva or tears. Since HIV is not transmitted by saliva, it is not possible to contract it through sharing a glass, a fork, a sandwich, or fruit (Friedland 1986, Castro 1988, Friedland 1990). In the opinion of leading experts, exposure of intact skin to HIV-contaminated body fluids (e.g. blood) is not sufficient to transfer the virus.

Sexual intercourse

Unprotected sexual intercourse is the most important transmission route of HIV infection worldwide. Although receptive anal sex is estimated to produce the highest risk of infection, infection after a single insertive contact has also been described. The presence of other sexually transmitted diseases markedly increases the risk of becoming infected with HIV.

The lower the viral load, the less infectious the patient. A prospective study of 415 HIV-discordant couples in Uganda showed that of 90 new infections occurring over a period of up to 30 months, none was from an infected partner with a viral load below 1,500 copies/ml. The risk of infection increased with every log of viral load by a factor of 2.45 (Quinn 2000). It should be noted that the levels of viral load in blood and other body fluids do not always correlate with one another. Thus, individual risk remains difficult to estimate. In addition, HIV-infected patients are not protected from superinfection with new viral strains.

The higher the viral load, the more infectious the patient. This is especially true for patients during acute HIV infection. During acute HIV-1 infection, the virus is replicating extensively in the absence of any detectable adaptive immune response, reaching levels of over 100 million copies of HIV-1 RNA/ml (see Chapter "Acute HIV-1 infection").

Intravenous drug use

Sharing unsterilized injection equipment that has been previously used by someone who is infected is an important HIV transmission route in many countries with a high prevalence of intravenous drug users. In contrast to the accidental needle-stick injury (see also Chapter "Post-Exposure Prophylaxis"), the transmission risk of sharing injection equipment is far higher: the intravenous drug user is controlling the proper position of the needle by aspiration of blood.

Maternofetal

In the absence of any intervention an estimated 15-30 % of mothers with HIV infection will transmit the infection during pregnancy and delivery. In approximately 75 % of these cases, HIV is transmitted during late pregnancy or during delivery. About 10 % of vertical HIV infections occur before the third trimester, and 10-15 % are caused by breastfeeding.

In Western countries, perinatal (vertical) HIV infection has become rare since the introduction of antiretroviral transmission prophylaxis and elective cesarean section. For more details, see Chapter "Pregnancy and HIV".

Injection or transfusion of contaminated blood products

In most Western countries, administration or transfusion of HIV-contaminated blood or blood products has become a rare event. With current testing methods (for details see also Chapter "HIV Testing"), the risk of acquiring HIV from a unit of transfused blood is about 1:1,000,000. However, while Western European countries, the United States, Australia, Canada, and Japan have strict and mandatory screening of donated blood for HIV, not all countries do.

Natural History

The "natural history" described in the following refers to HIV infection in the absence of HAART.

The acute viral syndrome of "primary" HIV infection (which is defined as the time period from initial infection with HIV to the development of an antibody response) shows symptoms which often resemble those of mononucleosis. These appear within days to weeks following exposure to HIV (for details see Chapter "Acute HIV-1 Infection"). However, clinical signs and symptoms may not occur in all patients. During acute HIV infection, there is usually a high plasma viremia and frequently a marked decrease in CD4 cells. The CD4 cell count later increases again, normally to levels inferior to the pre-infection values (see Figure 1).
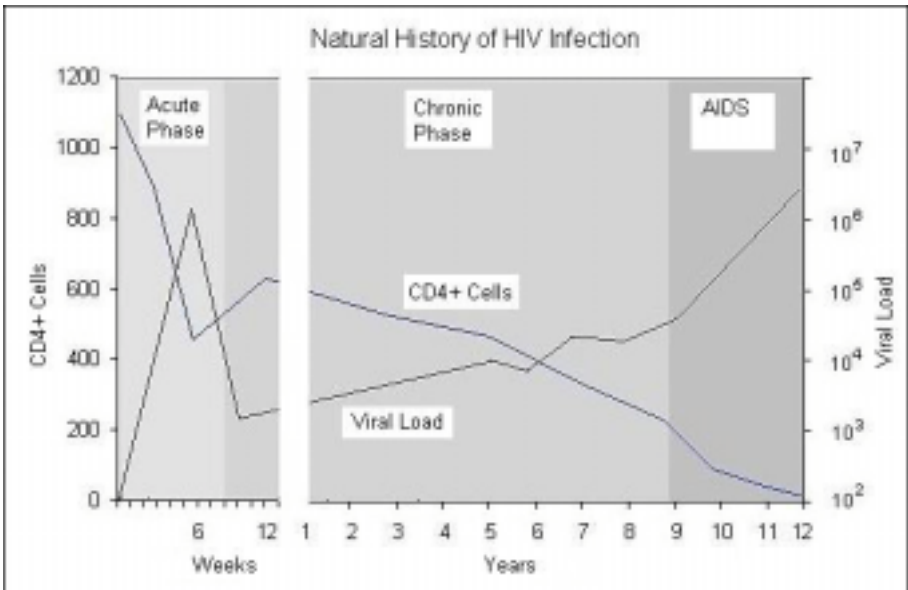
Figure 1: CD4 cell count and viral load during HIV infection.

After the acute infection, an equilibrium between viral replication and the host immune response is usually reached, and many infected individuals may have no clinical manifestations of HIV infection for years. Even in the absence of antiretroviral treatment, this period of clinical latency may last 8-10 years or more. However, the term "latency period" may be misleading, given the incredibly high turnover of the virus and the relentless daily destruction of CD4 T cells.

At the end of the "latency period", a number of symptoms or illnesses may appear which do not fulfill the definition of AIDS. These include slight immunological, dermatological, hematological and neurological signs. Many of them are listed in the Category B of the CDC classification system (see Table 1). Constitutional symptoms, such as fever, weight loss, night sweats, and diarrhea may also develop. In this situation, the level of 200 CD4 cells/µl is an important cut-off, below which the risk of many AIDS-defining illnesses is increasing, among them several opportunistic infections and certain neoplasms (see Table 1). Above 200 CD4 cells/µl, most AIDS-defining illnesses are rare events (see also Chapter "AIDS").

However, the course of infection may vary dramatically, and in some cases, the progression to AIDS may occur rapidly. Host factors mainly determine whether or not an HIV-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors, who represent about 5 % of all infected patients (for details, see "Pathogenesis of HIV-1 Infection").

CDC Classification System

The most widely accepted classification system of HIV infection, initially published by the U.S. Centers for Disease Control and Prevention (CDC) in 1986, is based on certain conditions associated with HIV infection (see Table 1). This classification system was intended for use in conducting public health surveillance and it has been a useful epidemiological tool for many years. In 1993, the CDC classification was revised (CDC 1993b). Since then, the clinical definition of AIDS has been expanded in the USA (not in Europe) to include HIV-infected patients with a CD4 cell count of less than 200 cells/µl or less than 14 % of all lymphocytes, even in the absence of the listed conditions.

Thus, the current CDC classification categorizes persons on the basis of clinical conditions and CD4 T lymphocyte counts. There are three clinical categories (A, B, C – see Table 1) and three CD4 T lymphocyte categories (1, 2, 3 – see Table 2). For example, a patient with oropharyngeal candidiasis and a CD4 cell count of 250/µl would be classified as B2; someone with asymptomatic infection and a CD4 cell count of 550/µl would be in category A1. Categorization of the CD4 cells should be based on the lowest accurate CD4 cell count ("CD4 nadir") and not on the most recent one.

For children less than 13 years of age, there is a modified and revised classification system for HIV infection (see chapter "Antiretroviral Therapy in Children"). It should also be noted that, besides the CDC classification, there exists a staging system for HIV infection published by the World Health Organization (WHO). The WHO classification is an approach for use in resource-limited settings and is widely used in Africa and Asia.

Table 1. Clinical categories of the CDC classification system in HIV-infected persons

Category A

Asymptomatic HIV infection

Acute (primary) HIV infection with accompanying illness or history of acute HIV infection

Persistent generalized lymphadenopathy

Category B

Symptomatic conditions* that are not included among conditions listed in clinical Category C. Examples include, but are not limited to:

Bacillary angiomatosis

Candidiasis, oropharyngeal (thrush)

Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy

Cervical dysplasia (moderate or severe)/cervical carcinoma in situ

Constitutional symptoms, such as fever (38.5° C) or diarrhea lasting longer than 1 month

Hairy leukoplakia, oral

Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome

Idiopathic thrombocytopenic purpura

Listeriosis

Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess

Peripheral neuropathy

Category C - AIDS-defining illnesses**

Candidiasis of bronchi, trachea, or lungs

Candidiasis, esophageal

Cervical cancer, invasive *

Coccidioidomycosis, disseminated or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)

Cytomegalovirus disease (other than liver, spleen, or nodes)

Cytomegalovirus retinitis (with loss of vision)

Encephalopathy, HIV-related

Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis

Histoplasmosis, disseminated or extrapulmonary

Isosporiasis, chronic intestinal (greater than 1 month's duration)

Kaposi's sarcoma

Lymphoma, Burkitt's (or equivalent term)

Lymphoma, immunoblastic (or equivalent)

Lymphoma, primary, of brain

Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary

Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)

Mycobacterium, other species or unidentified species, disseminated or extrapulmonary

Pneumocystis pneumonia

Pneumonia, recurrent*

Progressive multifocal leukoencephalopathy

Salmonella septicemia, recurrent

Toxoplasmosis of brain

Wasting syndrome due to HIV

* These conditions must meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

** Once a Category C condition has occurred, the person will remain in Category C.

Table 2. The CD4 T-lymphocyte categories*
Category 1: >500 CD4 cells/µl
Category 2: 200-499 CD4 cells/µl
Category 3: <200 CD4 cells/µl

*Categorization should be based on the lowest accurate CD4 count, not the most recent one

Epidemiology

This is not the place for a detailed description of the epidemiological situation of the HIV pandemic. The prevalence and incidence of HIV/AIDS vary considerably from continent to continent, from country to country, from region to region. Several countries in sub-Saharan Africa report infection rates of 30 %, especially in urban areas. In other countries, HIV prevalence still remains low. However, low national prevalence rates can be misleading. They often disguise serious epidemics that are initially concentrated in certain localities or among specific population groups and that threaten to spill over into the wider population. By far the best and most comprehensive overview is given by the joint United Nations program on HIV/AIDS (UNAIDS). The annual AIDS epidemic update of UNAIDS reports on the latest developments in the global HIV/AIDS epidemic. With maps and regional summaries, it provides the most recent estimates of the epidemic's scope and explores new trends in the epidemic's evolution. It can be found at the Website http://www.unaids.org/.

Table 1 provides an overview of the devastating situation of the HIV pandemic, according to UNAIDS.

Table 1: The AIDS Epidemic*

Number of people living with HIV/AIDS in 2004		
Total	39.4 million	(35.9 - 44.3 million)
Adults	37.2 million	(33.8 - 41.7 million)
Women	17.6 million	(16.3 - 19.5 million)
Children under 15 years	2.2 million	(2.0 - 2.6 million)
People newly infected with HIV in 2004		
Total	4.9 million	(4.3 - 6.4 million)
Adults	4.3 million	(3.7 - 5.7 million)
Children under 15 years	640,000	(570,000 – 750,000)
AIDS deaths in 2004		
Total	3.1 million	(2.8 - 3.5 million)
Adults	2.6 million	(2.3 - 2.9 million)
Children under 15 years	510,000	(460,000 – 600,000)

* The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information.
Source: UNAIDS,
http://www.unaids.org/wad2004/EPIupdate2004_html_en/epi04_02_en.htm#TopOfPage

Conclusion

HIV can not be transmitted as easily as the influenza virus. Compared to other viral diseases, the prevention of HIV infection is therefore easier. In rich countries, individuals who don't want to be infected with HIV, may protect themselves and will avoid HIV infection. The same people will not be able to avoid the influenza virus of the next pandemia.

HIV infection has become a treatable disease – at least in countries that can afford widespread health coverage. The following chapters describe how patients should be managed in these countries.

Outside these havens of material well-being, things have not changed since the early years of the HIV epidemic 25 years ago. Many people live in a world where no medical progress seems to have been made. This is a shameful situation, and future generations hopefully will do better than we did.

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2. Acute HIV-1 Infection

Marcus Altfeld and Bruce D. Walker

Introduction

Acute HIV-1 infection presents in 40 – 90 % of cases as a transient symptomatic illness, associated with high levels of HIV-1 replication and an expansive virus-specific immune response. With 14,000 new cases per day worldwide, it is an important differential diagnosis in cases of fever of unknown origin, maculopapular rash and lymphadenopathy.

The diagnosis of acute infection is missed in the majority of cases, as other viral illnesses ("flu") are often assumed to be the cause of the symptoms, and there are no HIV-1-specific antibodies detectable at this early stage of infection. The diagnosis therefore requires a high degree of clinical suspicion, based on clinical symptoms and history of exposure, in addition to specific laboratory tests (detection of HIV-1 RNA or p24 antigen and negative HIV-1 antibodies) confirming the diagnosis.

An accurate early diagnosis of acute HIV-1 infection is important, as patients may benefit from therapy at this early stage of infection (see below), and infection of sexual partners can be prevented.

Immunological and virologic events during acute HIV-1 infection

During acute HIV-1 infection, the virus is replicating extensively in the absence of any detectable adaptive immune response, reaching levels of over 100 million copies HIV-1 RNA/ml. It is during this initial cycle of viral replication that important pathogenic processes are thought to occur. These include the seeding of virus to a range of tissue reservoirs and the destruction of HIV-1-specific CD4+ T lymphocytes. The very high levels of HIV-1 viremia are normally short-lived, indicating that the host is able to generate an immune response that controls viral replication. Over the following weeks, viremia declines by several orders of magnitude before reaching a viral setpoint. This set-point following resolution of the acute infection is a strong predictor of long term disease progression rates (Mellors 1995).

Several factors can influence viral replication during acute infection and the establishment of a viral setpoint. These include the fitness of the infecting virus, host genetic factors and host immune responses. While antibodies against HIV-1 with neutralizing capacities are rarely detectable during primary HIV-1 infection, a number of studies have demonstrated a crucial role of HIV-1-specific cellular immune responses for the initial control of viral replication during this stage of infection. A massive, oligoclonal expansion of CD8+ T cell responses has been described during acute HIV-1 infection (Pantaleo 1994), and the appearance of HIV-1-specific CD8+ T cells has been temporally associated with the initial decline of viremia (Koup 1994, Borrow 1994). These CD8+ T cells have the ability to eliminate HIV-1-infected cells directly by MHC class I-restricted cytolysis or indirectly

by producing cytokines, chemokines or other soluble factors, thus curtailing the generation of new viral progeny (Yang 1997). The biological relevance of HIV-1-specific cytotoxic T cells (CTL) in acute HIV-1 infection was highlighted in recent in-vivo studies demonstrating a dramatic rise of SIV viremia and an accelerated clinical disease progress in macaques after the artificial depletion of CD8+ T cells (Schmitz 1999, Jin 1999). Additional evidence for the antiviral pressure of HIV-1-specific CTLs during primary HIV-1 infection has been provided by the rapid selection of viral species with CTL epitope mutations that were detected within a few weeks after HIV-1 and SIV infection in humans and rhesus macaques, respectively (Allen 2000, O'Connor 2002, Price 1997).

During acute HIV-1 infection, the number of CD4+ T cells decline, occasionally to levels that allow the development of opportunistic infections at that time (Gupta 1993, Vento 1993). Even though the CD4+ T cell count rebounds with the resolution of primary infection, it rarely returns to baseline levels in the absence of antiretroviral therapy. In addition to the decline in CD4+ T cell counts, qualitative impairments of CD4+ T cell function are perhaps the most characteristic abnormalities detected in HIV-1 infection. The impairment of HIV-1-specific CD4+ T cell function occurs very early in acute infection (Rosenberg 1997, Altfeld 2001, Lichterfeld 2004), potentially due to the preferential infection of virus-specific CD4+ T cells by the virus (Douek 2002). This is followed by a functional impairment of CD4+ T cell responses to other recall antigens, as well as a reduced responsiveness to novel antigens (Lange 2003). The impairment of HIV-1-specific CD4+ T helper cell function in acute HIV-1 infection subsequently results in a functional impairment of HIV-1-specific CD8+ T cells (Lichterfeld 2004).

In addition to host immune responses, host genetic factors play an important role in both susceptibility and resistance to HIV-1 infection and speed of disease progression following infection. The most important of these is a deletion in the major co-receptor for entry of HIV-1 into CD4+ T cells, a chemokine receptor called CCR5 (Samson 1996). Homozygotes for this 32 base pair deletion (CCR5delta32) do not express the receptor at the cell-surface and can only be infected with HIV strains that are able to use other co-receptors, such as CXCR4. Thus, although CCR5delta32 homozygotic individuals show a significant degree of resistance to HIV-1 infection (Samson 1996), a number of cases of infection with CXCR4-using HIV-1 strains have been described (O'Brien 1997, Biti 1997). Heterozygotes for the deletion exhibit significant lower viral setpoints and slower progression to AIDS. In addition to mutations in the chemokine receptor genes, a number of HLA class I alleles have been described to be associated with both, lower viral setpoints and slower disease progression, including HLA-B27 and -B57 (O'Brien 2001, Kaslow 1996). Recent studies demonstrated that individuals expressing HLA-B57 presented significantly less frequently with symptomatic acute HIV-1 infection and exhibited a better control of viral replication following acute infection (Altfeld 2003). These data demonstrate that host genetic factors can influence the clinical manifestations of acute HIV-1 infection and have an important impact on subsequent viral setpoints and the speed of disease progression.

Signs and symptoms

After an incubation period of a few days to a few weeks after exposure to HIV, most infected individuals present with an acute flu-like illness. Acute HIV-1 infection is a very heterogeneous syndrome and individuals presenting with more severe symptoms during acute infection and a longer duration of the acute infection syndrome tend to progress more rapid to AIDS (Vanhems 1998, Vanhems 2000, Sinicco 1993, Pedersen 1989, Keet 1993, Lindback 1994). The clinical symptoms of acute HIV-1 infection were first described in 1985 as an illness resembling infectious mononucleosis (Cooper 1985). The most common symptoms (see Table 1) are fever, maculopapular rash, oral ulcers, lymphadenopathy, arthralgia, pharyngitis, malaise, weight loss, aseptic meningitis and myalgia (Kahn 1998). In a recently published study by Hecht et al. (Hecht 2002), fever (80 %) and malaise (68 %) had the highest sensitivity for clinical diagnosis of acute HIV-1 infection, whereas loss of weight (86 %) and oral ulcers (85 %) had the highest specificity. In this study, the symptoms of fever and rash (especially in combination), followed by oral ulcers and pharyngitis had the highest positive predictive value for diagnosis of acute HIV-1 infection. In another study by Daar et al. (Daar 2001), fever, rash, myalgia, arthralgia and night sweats were the best predictors for acute HIV-1 infection.

Table 1: Main symptoms of acute HIV-1 infection

Symptom	Frequency	Odds ratio (95% CI)
Fever	80%	5.2 (2.3-11.7)
Rash	51%	4.8 (2.4-9.8)
Oral ulcers	37%	3.1 (1.5-6.6)
Arthralgia	54%	2.6 (1.3-5.1)
Pharyngitis	44%	2.6 (1.3-5.1)
Loss of appetite	54%	2.5 (1.2-4.8)
Weight loss > 2.5 kg	32%	2.8 (1.3-6.0)
Malaise	68%	2.2 (1.1-4.5)
Myalgia	49%	2.1 (1.1-4.2)
Fever and rash	46%	8.3 (3.6-19.3)

From: Hecht FM et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. AIDS 2002, 16: 1119-1129

The symptomatic phase of acute HIV-1 infection lasts between 7 – 10 days, and rarely longer than 14 days. The nonspecific nature of the symptoms poses a great challenge to the clinician and underlines the importance of a detailed history of exposure.

Diagnosis

The diagnosis of acute HIV-1 infection is based on the detection of HIV-1 replication in the absence of HIV-1 antibodies, as these are not yet present at this early stage of infection. Different tests are available for diagnosis of acute HIV-1 infection. The most sensitive tests are based on detection of plasma HIV-1 RNA.

In a recently published study (Hecht 2002), all assays for HIV-1 RNA that were tested (branched chain DNA, PCR and GenProbe) had a sensitivity of 100 %, but occasionally (in 2 – 5 % of cases) led to false positive results. False positive results from these tests are usually below 2,000 copies HIV-1 RNA per ml plasma, and therefore far below the high titers of viral load normally seen during acute HIV-1 infection (in our own studies on average 13 x 10^6 copies HIV-1 RNA/ml with a range of 0.25 – 95.5 x 10^6 copies HIV-1 RNA/ml). Repetition of the assay for HIV-1 RNA from the same sample with the same test led to a negative result in all false positive cases. Measurement of HIV-1 RNA from duplicate samples therefore results in a sensitivity of 100 % with 100 % specificity. In contrast, detection of p24 antigen has a sensitivity of only 79 % with a specificity of 99.5 – 99.96 %. The diagnosis of acute HVI-1 infection must be subsequently confirmed with a positive HIV-1 antibody test (seroconversion) within the following weeks.

During acute HIV-1 infection, there is frequently a marked decrease of CD4+ cell count, which later increases again, but usually does not normalize to the initial levels. In contrast, the CD8+ cell count rises initially, which may result in a CD4+/CD8+ ratio of < 1. Infectious mononucleosis is the most important differential diagnosis. Hepatitis, influenza, toxoplasmosis, syphilis and side effects of medications may also be considered.
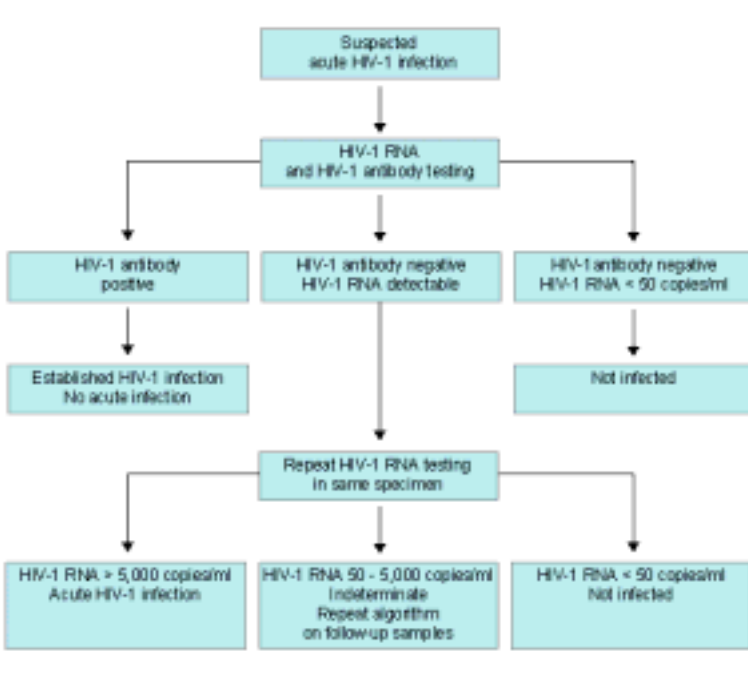
Figure 1: Algorithm for the diagnosis of acute HIV-1 infection

In summary, the most important step in the diagnosis of acute HIV-1 infection is to include it in the differential diagnosis. The clinical suspicion of an acute HIV-1 infection then merely requires performance of an HIV-1 antibody test and possibly

repeated testing of HIV-1 viral load, as shown in the algorithm in Figure 1 (adapted from (Hecht 2002).

Treatment

The goal of antiretroviral therapy during acute HIV-1 infection is to reduce the number of infected cells, preserve HIV-1-specific immune responses and possibly lower the viral set point in the long term. Several studies in recent years have shown that treatment of acute HIV-1 infection allows long-term viral suppression, leads to preservation and even increase of HIV-1-specific T helper cell responses and allows for the conservation of a very homogeneous virus population.

First pilot studies in patients who were treated during acute HIV-1 infection and subsequently went through structured treatment interruptions show that the HIV-1-specific immune response could be boosted in these patients (Rosenberg 2000). Most patients were subsequently able to discontinue therapy and experienced at least temporal control of viral replication, with viral set points remaining below 5,000 copies/ml for more than 3 years in some patients. However, in the majority of individuals in this study (Kaufmann 2004), as well as in other studies assessing viral control following treated primary infection (Markowitz 1999), viral load rebounded during longer follow-up, requiring the initiation of therapy.

The long-term clinical benefit of early initiation of therapy has not been demonstrated yet. It is also not known how long the period between acute infection and initiation of therapy can be without losing immunological, virological and clinical benefit. In view of all these unanswered questions, patients with acute HIV-1 infection should be treated in controlled clinical trials (Yeni 2002). If this is not possible, the option of standard first-line treatment should be offered and discussed. It is important during counseling to clearly indicate the lack of definitive data on clinical benefit of early initiation of antiretroviral therapy and to address the risks of antiretroviral therapy and treatment interruptions, including drug toxicity, development of resistance, acute retroviral syndrome during viral rebound and HIV-1 transmission and superinfection during treatment interruptions.

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3. HIV Testing

Wolfgang Preiser

Awareness of one's HIV infection is the prerequisite for making best use of the latest available therapeutic options. It is therefore recommended to undergo counselling and HIV testing after a potential exposure. In contrast to the past, HIV testing has now gained immense therapeutic relevance: Starting HAART on time may improve the quality of life and indeed prolong life considerably. Consequently, a shift in attitude towards HIV testing has taken place over the past decade: While an HIV test was formerly regarded as primarily a grave encroachment on the civil rights of the individual tested, the carer is now, in the age of HAART, obliged to advise if necessary, emphatically - HIV testing in order to enable the patient to benefit from optimised management of his infection. An HIV test may also be in the interest of a third person; examples being the testing of an index patient after a needlestick injury or the screening of pregnant women.

If a patient suffers from a possibly HIV-related illness, the diagnosis or exclusion of HIV infection offers important clues for further diagnostic and therapeutic management. In most cases this means diagnosing an established HIV infection the patient has had for some time (often years). Special cases are suspected acute primary or vertically acquired infections, as these require particular testing strategies (see below).

Besides individual diagnostic use, HIV tests are used in large numbers in the screeningof blood donors, blood products and transplant organsto guarantee their safety, as well as (often in an anonymous way) for epidemiological surveillance (UNAIDS, 1997a and 2001).

How to test

The diagnosis of an HIV infection is normally made indirectly, i.e. through the demonstration of virus-specific antibodies (Gürtler 1996). These are found in virtually 100% of those infected with HIV and constitute a marker of a humoral immune response against the agent. In contrast to many other viruses, the antibodies do not have an immunoprotective effect leading to immunity. Their presence equals the presence of chronic and active HIV infection. Cases in which individuals persistently fail to have detectable antibodies against HIV despite the presence of HIV infection are exceedingly rare and so far play little or no role in clinical practice (Connick 2005). However, this might change in future (Kassutto 2005).

Besides indirect diagnosis based on detection of antibodies, a direct diagnosis of HIV infection is also possible: either through the demonstration of infectious virus (using cell culture – this is only possible in laboratories of at least biological safety level 3), of viral antigens (p24 antigen ELISA) or of viral nucleic acid (i.e. viral genome); the latter is also termed nucleic acid testing (NAT). Viral genome detection is nowadays most often used, as it does not require a high security laboratory, is more sensitive than antigen detection and allows quantification.

To determine the infection status of a patient, direct virus detection by qualitative tests (providing a "yes/no" answer) is only useful under certain circumstances; such as a suspected primary infection or in the case of babies born to HIV-infected mothers (for details see below). However, quantitative viral genome assays have gained great importance: The determination of the so-called "viral load", i.e. the concentration of viral RNA in plasma, has become an indispensable tool for guiding antiretroviral therapy.

The term "HIV test" (occasionally but inaccurately still referred to as "AIDS test"), however, almost always refers to testing for HIV-specific antibodies as a marker of infection.

HIV antibody diagnosis

Testing for HIV antibodies invariably necessitates the availability of at least two different assays:

1. A screening test and
2. A confirmatory test.

Most screening tests are based on the ELISA principle (enzyme linked immuno sorbent assay) or other, closely related test formats (UNAIDS, 1997b). Screening tests must be extremely sensitive to minimise the chance of yielding a false-negative result. This means that they have to be able to also detect low-avidity antibodies found e.g. early in the course of a primary infection. They also have to be able to detect antibodies directed against all different HIV types (HIV-1, HIV-2) and subtypes (HIV-1-N, HIV-1-O, HIV-1-M) (UNAIDS/WHO, 1992 and 1997).

If the result of such a screening test is positive, this has to be confirmed by at least one confirmatory assay. For this purpose, some countries such as Germany and the United States prescribe the use of a so-called Western blot or immunofluorescence assay (IFT or IFA). In others, such as the United Kingdom, confirmation may be achieved through the use of different tests applied in a defined sequence in the form of an algorithm. This latter approach is by no means inferior to confirmation by Western blot and does in fact have several advantages, such as being cheaper and more objective (Tamashiro 1993).

ELISA screening test

Many commercial ELISA tests are available as 96-well microtitre plates. Although the test may be carried out completely manually, they also allow automatisation and thus the safe and economical testing of large numbers of patient samples. Various other test kits based on similar formats are also available, often performed by large, fully automatic pipetting and analysing machines.

Different ELISA "formats" can be distinguished; they are all based on the principle of a specific antigen-antibody reaction. Initially HIV "whole virus" antigen obtained from cell cultures was used (1st generation tests); nowadays a mixture of recombinant virus proteins or synthetic peptides representing immunodominant epitopes is employed (2nd and further generation tests).

In order to avoid… virus strains, it is important to know how far the antigens used are able to detect antibodies directed against the potentially occurring virus types

(HIV-1, HIV-2) and subtypes (HIV-1-N, HIV-1-O, HIV-1-M). An example are patients who were infected with HIV-2 in West Africa but are only tested for HIV-1 antibodies. However, because of more or less marked cross-reactivity, a reliable serological differentiation between infections with HIV-1 and HIV-2 is only possible using special assays and if necessary will have to be discussed directly with the laboratory.

In most ELISA tests, viral antigen is bound to the so-called solid phase (e.g. on the bottom of the wells in a microtitre plate). Upon addition of patient serum containing antibodies directed specifically against these antigens, antigen-antibody binding will occur. A washing step ensures that all unbound constituents of the serum, including all antibodies not recognising the viral antigen, are removed.

If antibody has bound to the viral antigen, it is then detected through addition of an enzyme-labelled "conjugate". This conjugate may be either a second e.g. goat antibody directed against human antibody molecules ("antiglobulin" assay) or again a viral antigen (often the same coated onto the solid phase: "immunometric" or sandwich assay; 3rd generation tests), coupled with an enzyme molecule. The advantage of "immunometric" assays is that they detect antibodies of all classes (including the "early" IgM antibodies which do not play an important role in HIV infection). Again, a washing step ensures that all unbound conjugate is removed.

Finally a substrate is added. If in the previous step conjugate has been bound, this substrate is converted by the action of the enzyme contained in the conjugate. This causes a change of colour; the intensity ("optical density", O.D.) of this colour reaction is measured and is proportional to the antibody activity in the sample. Positive and negative control specimens are included in each test run and the O.D. values obtained on them are often used to calculate the test's cut-off (i.e. the O.D. value used to distinguish positive from negative values).

A special case are "competitive" assays: Here, enzyme-labelled HIV antibodies are added to the solid phase together with the patient's sample. These antibodies then compete for antigen binding sites with the patient's antibodies. If the patient lacks HIV antibodies, all or most of the enzyme-labelled antibody molecules will bind, causing an intense colour reaction after addition of the substrate. And vice versa: The more specific antibodies are present in the patient's sample, the weaker the colour reaction. Such "competitive" assays are normally highly specific.

The different formats have different advantages and disadvantages; it is therefore important to know which format a particular assay is based on. So-called 4th generation antibody tests combine the detection of HIV antibodies with that of viral p24 antigen, in order to reduce the "diagnostic window" (see below) (Brust 2000).

The accuracy of a test lays in the combination of two factors: the test's sensitivity and its specificity. Sensitivity denotes the test's ability to correctly identify a positive sample as positive, whereas specificity measures its ability to correctly identify a negative sample as such.

Screening tests are extremely sensitive (almost 100 %), which means that even very low HIV antibody activities – e.g. early in the course of a primary infection – are detected. High sensitivity reduces the chance of a "false-negative" test result and thus of an erroneous conclusion: "The patient is not HIV-infected", although he in fact is. Provided a suitable screening test is used, a negative results six or more

months after a potential infection risk means, due to the test's high sensitivity, that the chance of infection is virtually nil (Preiser 2000).

HIV tests sold for the first time after 7 December 2003 are subject to new European Union legislation on in vitro diagnostic devices and have to carry the CE mark. Amongst the conditions to be fulfilled is that 600 HIV-positive samples, including 200 HIV-2-positive ones, obtained at different stages of HIV infection and disease, all have to be identified correctly as positive.

For screening tests, the emphasis has to be placed on the utmost sensitivity; any failure to identify a positive sample correctly could have grave consequences. This high sensitivity, however, causes a somewhat lower specificity. This means that the test result may occasionally be "false-positive". The test result then indicates the presence of antibodies against HIV although in fact some substance present in the sample was erroneously misidentified as HIV antibodies. Such false-positive results may be caused by immune stimulation of some sort (acute virus infections, pregnancy, immunisations, autoimmune diseases). Presently available HIV screening tests have specificity of at least 99.5 %; i.e. among 4,000 HIV-negative samples tested, a maximum of 20 may show a false-reactive test result.

Due to the possibility of non-specific reactivity inherent in any assay, it is preferable to use the term "reactive" – rather than "positive" – screening test result thus avoiding misunderstandings. It is to exclude the risk of false-positive final test reports, that all reactive screening test results must be confirmed by confirmatory testing. Only then should one talk of a "positive HIV test"!

Important: A reactive screening test does not mean HIV infection! Only a positive confirmatory test allows the diagnosis of an HIV infection, and normally only such a result should be communicated to the patient!

Other potential causes for false-positive (or also false-negative) test results are errors occurring in the laboratory or in the pre- or postanalytical phase. Besides mistakes caused by confusing samples or contamination with positive sample material through suboptimal pipetting techniques etc., clerical errors (incorrect labelling of sample tube or request form, incorrect data entry into laboratory or clinical software etc.) may occur. Utmost attention must be paid also to seemingly unimportant steps in order to safeguard the quality of laboratory testing!

Western blot confirmatory assay

The Western blot is a methodology commonly used for confirmatory testing of screening test-reactive samples. HIV is propagated in cell cultures, harvested, purified and denatured (i.e. split into its constituents). Then, the viral proteins are separated according to their molecular weight by electrophoresis and blotted onto a nitrocellulose membrane. The membrane is cut into strips. To perform the test, the membrane is incubated with patient serum. If the serum contains antibodies against the various viral proteins, these will bind to the areas on the strip onto which the respective antigens have been blotted. If an antigen-antibody reaction takes place, it is revealed using an enzyme-labelled secondary antibody and matching substrate, causing the so-called "bands" to appear on the test strip.

HIV proteins and corresponding bands on the Western blot are designated "p" (for protein) or "gp" (for glycoprotein), followed by the relative molecular mass (x

1000). They can be divided (here using the example of HIV-1 Western blot) into three groups: the env or envelope glycoproteins (gp41, gp120, gp160), the gag or nuclear proteins (p18, p24/25, p55) and the pol or endonuclease-polymerase proteins (p34, p40, p52, p68).

The Western blot is a confirmatory assay that is only carried out if the sample was reactive in the screening assay. Both HIV-1 and HIV-2 Western blots are available commercially. The result of a Western blot may be either positive or negative or (in case of an incomplete pattern of visible bands) equivocal which may reflect borderline or non-specific reactivity.

Different organisations have developed different sets of criteria for interpretation of HIV Western blot results. In order for a result to be declared positive, the American Red Cross for instance demands at least three bands, one from each group (i.e. one gag, one pol and one env band). The US-American Food and Drug Administration (FDA) demands the p24, the p34 as well as the gp41 or gp120/160 bands (Centers for Disease Control and Prevention, 1989). According to WHO recommendation, however, a Western blot may be judged positive only if two env bands are found. In Germany, the DIN norm 58969 part 41 applies (Deutsches Institut für Normung, 2000): A serum sample is HIV positive if it reacts with at least one viral glycoprotein and one of the other HIV proteins. All other virus-specific band patterns are regarded as questionable.

Among the disadvantages of Western blot are its relatively high price, the comparatively demanding test procedure and the unavoidable subjectivity when reading and interpreting the result. For these reasons many countries prefer confirmatory tests using suitable testing algorithms, consisting of a combination of different ELISA or rapid tests with well-defined sensitivities and specificities and evaluated in the relevant setting.

In addition to the obligatory safeguarding through confirmatory testing e.g. by Western blot, the serological diagnosis of an HIV infection always requires testing of a second, independently obtained blood sample from the patient. If at all possible, the patient should only then be informed about the diagnosis.

Rapid / Simple Test Devices

Nowadays, a number of rapid HIV tests are available; these are also referred to as "point-of-care", "bedside" tests or "rapid/simple test devices". These tests are based on one of four immunodiagnostic principles: particle agglutination, immunodot (dipstick), immunofiltration or immune chromatography (Giles 1999, Branson 2000). In most cases test results are available within fifteen to thirty minutes; often, whole blood or capillary blood (obtained from the tip of a finger or the lobe of the ear) can be used, thus sparing the centrifugation of a venous blood sample obtained through venepuncture.

Many of these rapid tests contain an "inbuilt" internal control, e.g. as a control band indicating whether the sample material and, if applicable, the reagents were added correctly. If this "inbuilt" control fails, the test result must not be accepted (important to avoid false-negative results, when e.g. the sample was not added or insufficient time allowed until reading the result).

Such rapid tests may be useful if the result is needed quickly, for instance in emergency rooms, before emergency operations, after needlestick injuries and to minimise the rate of "unclaimed" test results (if the result is only available after a few days, some of those tested will not return to receive it). Rapid tests, which are easy to perform and require little in terms of equipment, are also useful in developing countries (Branson 2003, WHO 2004). Nevertheless such tests should fulfill the same basic requirements as ELISA screening tests (WHO/UNAIDS 1998). In developed countries, a rapid test should ideally only be used as first guidance, and the patient retested as soon as possible in a regular routine laboratory. Problems commonly encountered with rapid tests – besides the need for adequate training of personnel – are the necessity to counsel the patient before testing and to obtain his consent. Any HIV test which can be performed by lay persons always carries the potential of misuse (such as compulsory testing of prisoners etc.).

In the meantime several HIV rapid tests have been licensed by FDA: OraQuick™ (OraSure Technologies, Pennsylvania, USA), Reveal™ (MedMira Laboratories, Halifax, Nova Scotia), Uni-Gold Recombigen™ HIV Test (Trinity Biotech, Ireland) and Murex single use diagnostic system (SUDS). After worrying experiences (at least five HIV-infected individuals were found to have been informed that their reactive rapid test result had been false-positive, i.e. that they were HIV-negative!) the Centers for Disease Control and Prevention (CDC) recently emphasised the need for adequate confirmatory testing and, if necessary, follow-up testing after four weeks (CDC 2004).

Sample types

In most cases, serum, EDTA plasma, and also occasionally whole blood are used for HIV antibody testing. If sample processing is delayed, it may be preferable to remove the plasma or serum from the corpuscular constituents of blood, as haemolysis may lead to problems with certain tests.

Immunoglobulins may even be eluted from blood spots that were added onto filter paper and dried. Testing of such eluates for HIV antibodies is used for the (anonymous and unlinked) screening of pregnant women, using Guthrie test cards with routinely obtained blood spots from newborn babies (whose antibody prevalence mirrors that of their mothers). In developing countries with insufficient facilities for cold storage and transport, dried blood spots may offer a useful and inexpensive tool for sample storage and transport. Once completely dry, blood even from HIV-infected patients does not constitute an infection risk.

Alternatively, urine or oral fluid (oral transsudate, often incorrectly referred to as "saliva") may also be employed for some assays (Tamashiro 1994, King 2000). The FDA licensed a rapid test using oral fluid for the diagnosis of HIV infection in March 2004; the same assay, marketed by OraSure Technologies, has been licensed since November 2002 as a rapid test for the detection of HIV antibodies in whole blood (see above). According to available information this assay allows the detection of antibodies against HIV-1 or HIV-2 with a sensitivity of 99.3 % and a specificity of 99.9 %.

Under certain conditions, only such non-blood specimen types make testing possible, as they allow non-invasive sampling. However, their sensitivities and specificities are mostly considerably lower. Therefore, blood remains the preferred type of

specimen. Whatever type of sample is used, a reactive test result of course requires confirmatory testing.

Test performance

HIV antibody tests are among the best commercially available immunological assays. Sensitivity (high sensitivity → few false-negative results) and specificity (high specificity → few false-positive results) are the two most important parametres; they have to be calculated for each assay individually. However, in practice it is not so much the sensitivity and specificity of a test that is of interest but rather its predictive value. This is due to one's lack of knowledge of the real HIV status of the patient tested and the need to deduce his/her status from the test's result. The positive predictive value (PPV) is the probability with which a patient with a positive test result is indeed infected; and vice versa, the negative predictive value (NPV) is the likelihood of a patient who tested negative being truly not infected.

TABLE 1: Two-by-two table.

		Test result: positive	negative
True patient status (e.g. as determined by reference test):	positive	true-positive	false-negative
	negative	false-positive	true-negative

Table 1 explains the connection between the parameters

Sensitivity
= number true-positive / (number true-positive + number false-negative)
= probability of a positive test result if the patient is infected

Specificity
= number true-negative / (number true-negative + number false-positive)
= probability of a negative test result if the patient is not infected

Positive predictive value (PPV)
= number true-positive / (number true-positive + number false-positive)
= probability that a patient tested positive is indeed infected

Negative predictive value (NPV)
= number true-negative / (number true-negative + number false-negative)
= probability that a patient tested negative is indeed not infected

Although this may initially not seem plausible, the predictive value of a test does not only depend on its sensitivity and specificity but also on the HIV prevalence (i.e. the pre-test-probability to be positive or negative, respectively) in the population tested. Figure 1 illustrates this relation, using fictitious populations with HIV seroprevalence rates between 0.02 % (e.g. European blood donors) and 20 % (e.g. sexually active groups in highly endemic countries). It can be seen that in the former, the vast majority of positive (or more aptly, reactive) test results are indeed false-positive: only 4.8 % of those who test positive are truly infected! In contrast,

98 % of the positive test results in the high-risk group with a seroprevalence of 20 % are "true" (which is why, according to WHO, confirmatory testing may exceptionally be omitted here). These examples stress the importance of adequate confirmatory testing strategies for all positive screening test results!

Unfortunately, this statistical phenomenon is frequently, for propaganda purposes, misused: Inevitably, in blood donors e.g. in Germany with a low HIV prevalence, indeed only a small proportion of those with a reactive screening test result are truly infected. However, because any screening test reactivity must be followed up further by confirmatory testing even before the individual concerned is informed, this phenomenon should not have major consequences: For if the Western blot does not confirm the reactive ELISA result, the patient or blood donor is simply not HIV-"positive"! Nevertheless, it is unfortunately often used to "prove" the alleged uselessness of HIV tests.
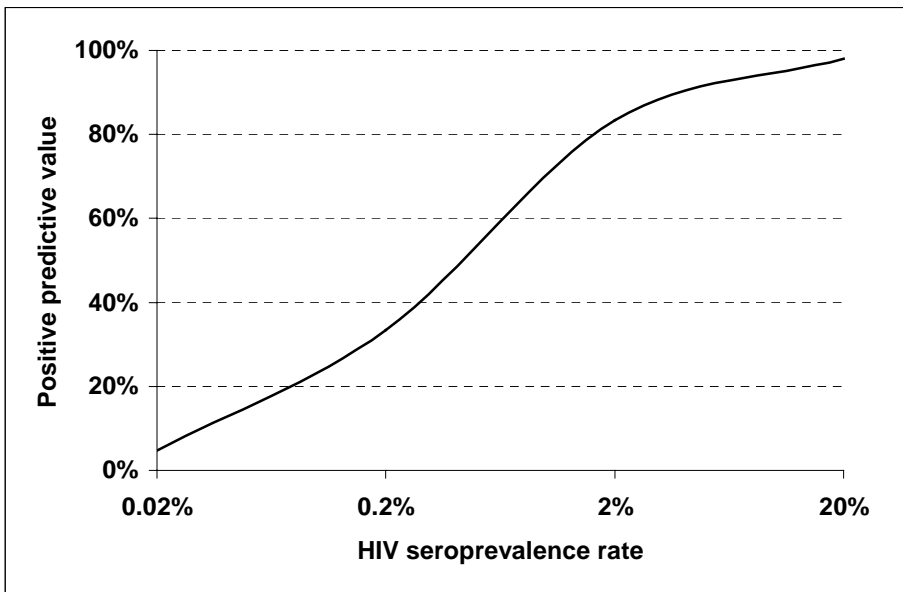
FIGURE 1: Illustration of the dependence of the positive predictive value (PPV) on the seroprevalence rate in the population tested, using an antibody test with a constant specificity of 99.6 % (i.e. 4 false-positive results per 1,000 samples tested).

When to test

After an infection, it normally takes between three to twelve weeks before the antibodies produced through the immune response of the infected individual become detectable. An HIV test should therefore not be performed too early after a potential risk contact, even though, understandably, concerned patients may be anxious and press for it. It is important, however, after an occupational exposure, to test immediately in order to confirm initial seronegativity in the needlestick recipient! In around 5 % of newly infected individuals it will take more than two months until antibodies are formed. Another test may therefore be indicated later on.

The chance to have acquired HIV infection is increased if one of the following questions can be answered positively:

- Have you had sexual intercourse without condom with someone who is HIV-infected?
- Have you had sexually transmissible infections such as chlamydia or gonorrhoea lately?
- Have you used the same syringes or cannulas as other intravenous drug addicts (needle sharing)?
- Have you received a blood transfusion or blood clotting factors between 1978 and 1985?
- Have you ever had sex with someone who would answer one of the above questions with Yes?

Increasingly, it is argued that HIV testing "should no longer be accorded any special status" (Manavi 2005, Beckwith 2005). It has been found that, with the epidemiological shift into groups not formerly considered as "high-risk", HIV infections may be missed and that the burden of adequate pre-test counselling may discourage carers to suggest patients to be tested.

Problem: The "diagnostic window"

One important problem of HIV antibody testing is the so-called "diagnostic window". This is the time period that elapses between the time of acquisition of HIV infection until detectable levels of antibodies are present (Busch 1997). The switch from antibody-negative to antibody-positive is called "seroconversion". The screening tests currently used are able to recognise an HIV infection six weeks after primary infection in about 80 % and after the 12th week in almost 100 % of cases; only in very rare cases an infection is recognised only after three or even six months. 4th generation screening assays attempt to shorten the duration of the "diagnostic window" by detecting HIV antibodies and HIV p24 antigen simultaneously (Gürtler 1998, Ly 2001). These 4th generation tests have their own problems, however: Although they turn positive earlier, due to methodological reasons (Meier 2001), there may occur a second "diagnostic window" phase later on during which the tests may again turn to be negative ,

Early during seroconversion the screening test will be only borderline or weakly reactive. The Western blot carried out for confirmation may at this stage not show any bands at all or an incomplete band pattern, with the p24 band often the first to become visible. The results obtained in such cases are often indistinguishable from those found in uninfected individuals that display a certain degree of non-specific reactivity; here, too, isolated p24 bands are occasionally seen. This illustrates clearly how important it is to pass important clinical information on to the laboratory carrying out the tests (e.g. "suspected primary infection", "routine screening" etc.)!

Such cases often have to remain unclear for the time being, but are resolved by follow-up testing within a short time. If one is indeed dealing with an early seroconversion, seroreactivity will have increased significantly only a few days later, and within a few weeks a complete band pattern will be found on Western blot. It de-

pends on the individual circumstances whether direct virus detection e.g. by means of PCR is advisable at the outset. Attention: Antiretroviral post-exposure prophylaxis may make direct virus detection more difficult and potentially delay seroconversion.

The gradual increase of seroreactivity in the course of seroconversion may be utilised diagnostically: So-called "desensitised" or "detuned" testing strategies can be used to measure HIV incidence (i.e. the rate of new infections – in contrast to standard antibody testing that measures HIV prevalence, i.e. established infections): By deliberately combining highly sensitive with less sensitive antibody tests, these strategies are able to estimate which proportion of positive samples have only recently undergone primary infection (Parekh 2001, Constantine 2003).

Direct detection of HIV

An HIV infection may also be diagnosed through the detection of virus, rather than indirectly through the detection of antibodies. Virus detection is only necessary in certain situations and, because of its higher cost, should only be undertaken if indicated.

Virus isolation in cell cultures is reserved for special cases, as it is demanding, carries a certain risk and therefore requires the use of a high-security laboratory.

Alternatively, assays for the detection of HIV-1 p24 antigen are available. Although the p24 antigen ELISA has generally been replaced by the more sensitive nucleic acid detection assays, 4th generation antibody screening tests incorporate p24 antigen detection in addition to HIV antibody detection, to shorten the "diagnostic window" period (see above).

The detection of viral nucleic acid (i.e. of virus genome) may be achieved by different laboratory techniques. These methods may be used to detect either proviral cDNA in leucocytes (which requires EDTA whole blood samples) or viral RNA in the cell-free compartment (which requires EDTA plasma or EDTA whole blood).

Qualitative testing for viral genome serves as a marker of infection. It supplements or substitutes antibody testing for the diagnosis of HIV infection in special situations (such as suspected fresh primary infection: absence of antibodies during the diagnostic window; newborn of infected mother: presence of maternal antibodies – also see below).

The quantitative detection of HIV RNA in plasma is used as a prognostic marker, to monitor therapy and to estimate infectiousness (Berger 2002). The most sensitive tests can detect as little as approximately 50 copies/ml.

Various commercial and "in house" methods are available for quantitative nucleic acid testing. These may be based on different technologies: polymerase chain reaction (PCR), branched DNA (b-DNA), nucleic acid sequence-based amplification (NASBA) or ligase chain reaction (LCR). So-called "viral load" testing has now become an indispensable clinical tool, both as a prognostic and as a therapeutic marker.

Test results

False-positive results by Western blot are very rare. A positive Western blot result therefore confirms the presence of HIV-specific antibodies and thus, HIV infection.

A positive test result (i.e. screening and confirmatory tests positive and mistaken sample identity excluded by testing of a second sample) means that the individual tested

- is infected with HIV (i.e. carries the virus that causes AIDS) – except in young children (see below);
- may infect others with HIV unless precautions are taken

A positive test result does NOT mean that the person tested

- has AIDS;
- will necessary develop AIDS.

A negative test result means:

- HIV antibodies were not detected in the blood of the individual at the point in time when he or she was tested.

A negative test result does NOT mean that:

- the individual is not infected with HIV (the test could have been performed during the "diagnostic window" period);
- the person tested is immune or resistant to HIV;
- the person tested can have sexual intercourse without taking "safe sex" precautions.

Beyond the "diagnostic window", meaning later than six months after a possible exposure to HIV, an HIV screening test is rarely "false-negative". Thus, a negative test means that the person is not infected with HIV – always assuming of course that in the meantime no renewed exposure has taken place.

A rare "equivocal" result in the confirmatory assay means:

- The test has not given an unequivocal result. As a consequence, follow-up testing after a short while is required. Particularly in case of clinical symptoms such as fever, lymph node enlargement, a rash or neurological symptoms there may be the suspicion of an acute HIV infection in which seroconversion has only just begun. First antibody reactivities are found, however the full pattern of Western blot bands is not yet present. Seroconversion tends to follow certain patterns; in Western blot, some bands are positive early on (such as p24 or gp120), others appear later.
- In case of an unequivocal Western blot and if an acute primary infection is suspected for clinical and/or anamnestic reasons, direct detection of virus should be attempted by means of PCR. The aim of this is to detect and possibly treat an acute HIV infection in time (also see chapter "Acute HIV infection"). The earlier, the better!

Caution: If in the case of a suspected fresh primary infection a quantitative HIV RNA assay is used for virus detection in plasma (because it is often more easily available than PCRs for the detection of proviral DNA in leucocytes), one has to keep in mind that such tests may occasionally lead to false-positive results (Rich

1999). Such false-positive results – that may be seen typically – indicate low levels of HIV RNA (normally not more than 2,000 copies/ml) that are very unlikely to be found in true acute infection (which normally presents with high "viral load" values). Nevertheless, this problem has sometimes caused confusion and misdiagnoses.

This phenomenon may probably occur with any of the available viral load assays. If it is not recognised, the patient will be given an erroneous diagnosis of "infected" with all its possibly deleterious consequences. To avoid this problem (assuming error-free running of the assay and sufficient quality control practices in the laboratory), a test for proviral cDNA in the leucocyte fraction of the blood should be used; however, this is offered by relatively few laboratories.

Special case: Babies born to HIV-infected mothers

Fortunately, the risk of mother-to-child transmission of HIV (MTCT) (see chapter "HIV and pregnancy") has been extremely reduced in industrialised countries and may be as low as 1 %. Nevertheless HIV diagnosis is essential in all exposed newborns!

In babies born to HIV-infected mothers, HIV antibodies are normally detectable up to around 12 to 15 months of age. These are passively acquired maternal antibodies transferred transplacentally into the unborn child from around the 30th week of pregnancy onwards. These maternal IgG antibodies confer some physiological immune protection against many infections but in the case of HIV are without protective efficacy. This means, however, that all children of HIV-positive mothers, including those not themselves infected (the majority in any setting), will initially have positive HIV antibody test results, albeit with decreasing reactivities over time, until they become negative after complete elimination of maternal antibodies.

Therefore, previously one had to wait – normally for nine months or longer – for a significant fall in the child's antibody level; only testing of repeat blood samples taken at regular intervals could exclude HIV infection of the child with certainty (Newell 1995). If HIV antibodies persist in a vertically exposed child beyond the age of 15 months, the child is HIV-infected.

Today PCR allows a more rapid diagnosis. HIV infection of the child should be diagnosed or, hopefully, excluded directly through detection of the virus. So far it is unclear whether the detection of proviral (intracellular) HIV cDNA (from leucocytes) or of (extracellular) HIV RNA (from blood plasma) is more sensitive. In any case, all positive test results must be confirmed immediately on a second sample.

Important: Many methods for the detection of HIV nucleic acid may fail in case of "exotic" (i.e. non-subtype B) HIV-1 subtypes (and with HIV-2) and yield false-negative results (Haas 1996). To exclude this, a maternal sample should also be tested if necessary (e.g. if the mother or her source of infection are from outside Europe) to ensure the test's ability to detect the viral strain in question. If the mother tests PCR-positive with the same assay, a negative test result on the child may be used; otherwise a suitable method must be chosen in a specialised laboratory or one has to resort to antibody testing alone with its limitations (see above). As far as quantitative RNA detection methods are concerned, the problem of falsely low-positive results needs to be recognised (see above)!

In exposed babies, at least two negative HIV PCR results are required in order to exclude HIV infection: the first one between the 1st and the 4th month of life, the second after the 4th month, as only then it reaches its full significance for exclusion (Rossi 1992). In addition, PCR should be performed already during the first month of life (however not within the first days after delivery, as contamination with maternal virus may occur), as the earliest possible diagnosis of a neonatal infection is important to allow Pneumocystis prophylaxis and early antiretroviral therapy in the first months of life. If already this first sample tests positive (and is confirmed), this points to an intrauterine infection (less frequent); in case of perinatal transmission during birth (most common scenario), virus will only be detectable in the samples obtained later. Attention: Breastfeeding carries a significant risk of transmission; what stated above is only valid if postnatal acquisition of infection is excluded!

Also with negative HIV PCR results, the complete elimination of maternal antibodies should be documented at least once in HIV-exposed children.

Special case: Needlestick injury or other occupational HIV exposure

Here, two aspects need to be considered: testing of the index patient (the "donor") from whom the potential risk of infection arose) and testing of the exposed (the "recipient"). The national and local regulations pertaining to this must of course be followed, for legal and other reasons.

If the index patient is known, he should be tested – after relevant counselling and consent; ideally the injured individual's superior should be called in immediately – for HIV antibodies, HBsAg (do not forget immunisation against hepatitis B virus if necessary), and HCV antibodies. According to the circumstances (e.g. weekend), the use of a rapid assay should be considered (see above). Often a first, preliminary decision must be made even before the test result of the index patient is available; for any delay in instituting HIV post-exposure prophylaxis (HIV PEP) reduces its chances of success (CDC 2001). Therefore: If there is any doubt, the first one or two doses of HIV PEP (that should be readily available day and night in the form of a so-called "starter pack") should be taken and later discontinued once a negative test result becomes available! It would be a mistake to start HIV PEP only once a positive result has been obtained as this will normally mean delaying the first dose beyond the time period during which its chances of preventing infection are at its highest!

If the index patient is seronegative, the chances of him/her – in the absence of any clinical evidence suggesting an acute retroviral syndrome – currently being in the "diagnostic window" phase are remote. It is therefore normally not advisable to employ a method for direct detection of virus (to exclude a fresh primary infection prior to seroconversion)! In case of an unknown index patient the epidemiological situation needs to be taken into account. Important: Used injection needles etc. should not normally be tested for HIV antibodies or HIV genome; effort, cost and particularly the remaining uncertainty (because of the questionable validity of the result) are out of proportion compared to the extremely remote risk of infection with an agent that fortunately has a low stability and tenacity.

If the index patient is HIV-positive, all available information (including the current "viral load", results of resistance assays etc.) must be considered in the decision on the type of HIV PEP (see the relevant chapter).

In case of an HIV-positive index patient, the injured individual should be at once tested for HIV antibodies by means of a routine screening assay . Demonstration of initial seronegativity is legally important in order to claim compensation and insurance cover in case of occupational transmission! Further follow-up testing is recommended 6 weeks, 3 months and again 6 months after exposure (Ciesielski 1997). If the index patient is HIV-infected, a further follow-up test of the injured recipient is recommended after 12 months; otherwise this is optional (Ridzon 1997). In addition, an HIV test (and possibly also a test for direct detection of virus) should be done immediately if anytime after the incident the recipient develops illness compatible with an acute retroviral syndrome.

What is relevant in practice?

With each and every HIV test, different important aspects need to be taken into account. Unfortunately and regrettably, careless and negligent actions still sometimes occur.

It has to be realised:

Despite all therapeutic progress, a positive test result still has massive psychological consequences for the person concerned! The meaning of a positive test result can hardly be overrated.

Every patient therefore must be informed that he/she is to be tested for HIV – in advance! A "routine pre-operative" check, as it is still sometimes carried out, can, particularly if the result is positive, carry not only unpleasant but often considerable legal consequences for the medical staff in charge. Although it does not have to be obtained in writing, the patient's consent has to be documented in the patient notes. With children or patients unable to give legally valid consent, parents or legal carers have to be informed.

On the other hand, while obtaining valid consent is important, this does not always require in-depth discussions about risk factors, consequences etc. Instead, pre-test counselling should be adequate for the individual's situation. One should avoid causing unnecessary anxiety and psychological distress.

HIV test results should only be communicated by doctors who are either themselves knowledgeable about HIV and AIDS or who know where to refer patients with a newly diagnosed HIV infection without delay. Individuals confronted with this diagnosis for the first time are in need of intensive support, and they need this immediately! Sometimes patients are still provided with outdated information, and it may then take them weeks, sometimes months, until they first get into contact with a competent medical person.

A positive HIV test result should never be communicated to the patient over the telephone. Firstly, this does not allow sufficient post-test counselling, and secondly it makes it impossible to judge the patient's reaction – which may even be suicidal Occasionally the reaction is very irrational and emotional, necessitating an extended counselling session. This individual reaction cannot be anticipated. If at all possible,

a repeat appointment should be made at the time of drawing the sample. In case of a negative test result, one can then still telephone the patient....

For the reasons mentioned, a rapid test for self-testing is extremely problematic. So-called "point-of-care" or "bedside" tests may be very useful in certain circumstances, e.g. in emergency rooms, but also harbour the problem of unprofessional utilisation without adequate counselling and care of the patient.

A reactive screening test result on its own must never, under any circumstances, be communicated to the patient ! As there are numerous factors that may cause a screening test to become false-positive, the result of a confirmatory assay always has to be awaited. If the band pattern in Western blot is incomplete, this may represent ongoing seroconversion (i.e. acute infection) or non-specificity. Such tests should always be discussed with the laboratory and with an experienced HIV carer – before the patient is informed. We have seen cases in which the patient was left in the belief to be HIV-infected for days or even weeks – only because of a cross-reactive ELISA and failure to await the result of confirmatory testing.

But even with HIV seropositivity confirmed by Western blot, the following statement should be added to each first positive result: "The demonstration of HIV-specific antibodies does not mean that the patient is suffering from AIDS. Every positive result must be confirmed on a second, independently obtained blood sample, and the patient should only then be informed!"

With each sample sent for HIV testing, one should be aware of the reason behind its request . AIDS phobia poses a difficult problem and is not so rare – i.e. people who are as firmly as erroneously convinced that they are HIV-infected, almost always without any appreciable risk. Often they want to be tested at short intervals and by different carers, sometimes also requesting expensive PCR tests. Such individuals (who often also suffer from the delusion that positive test results are withheld from them) need psychological and perhaps psychiatric help rather than repeatedly HIV testing.

Useful Internet sources relating to HIV testing

- World Health Organization (WHO), Department of Essential Health Technologies:
  http://www.who.int/bct/Main_areas_of_work/BTS/HIV_Diagnostics/HIV_Diagnostics.htm
  with the following web pages:
  Overview of HIV Diagnostic Technologies:
  http://www.who.int/bct/Main_areas_of_work/BTS/HIV_Diagnostics/Overview_of_HIV_Diagnostic_Tech.htm
  HIV Test Kit Evaluation:
  http://www.who.int/bct/Main_areas_of_work/BTS/HIV_Diagnostics/HIV_Test_Kit_Evaluation.htm
  with downloadable reports containing the evaluation results of different commercially available HIV tests and the "WHO HIV Test Kit Bulk Procurement Scheme"
- UNAIDS: HIV diagnostic tests:
  http://www.unaids.org/en/in+focus/topic+areas/hiv+diagnostic+tests.asp

from which one can reach "Sources and prices of selected drugs and diagnostics for people living with HIV/AIDS" in its current version

- The 3 by 5 Initiative, AIDS Medicines and Diagnostics Service (AMDS), HIV/AIDS Diagnostics: http://www.who.int/3by5/amds/diagnostics/en/
- Centers for Disease Control and Prevention (CDC), USA, Division of HIV/AIDS Prevention:
  http://www.cdc.gov/hiv/testing.htm, http://www.cdc.gov/hiv/rapid_testing/
- U. S. Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER): Licensed / Approved HIV, HTLV and Hepatitis Tests: http://www.fda.gov/cber/products/testkits.htm
- The European Commission, Enterprise & Industry, Medical Devices:
  http://europa.eu.int/comm/enterprise/medical_devices/index.htm
  In Vitro Diagnostic Directive (IVDD)

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4. Pathogenesis of HIV-1 Infection

Andrea Rubbert and Mario Ostrowski

Since the initial description of the human immunodeficiency virus type I (HIV-1) in 1983 (1, 2) and HIV-2 in 1986 (3), these two viruses have been identified for almost 20 years as the primary cause of the acquired immunodeficiency syndrome (AIDS). As HIV-1 is the major cause of AIDS in the world today, our discussion will be primarily limited to HIV-1 infection. Worldwide, the number of HIV-1 infected persons exceeds 40 million, the majority of whom live in the developing countries of Sub-Saharan Africa, Asia and South America.

The introduction of protease inhibitors and non-nucleotide reverse transcriptase inhibitors (NNRTI) to antiretroviral treatment regimens in 1995 began the era of highly active antiretroviral therapy (HAART), and resulted in dramatic improvements in the mortality and morbidity of HIV disease, as determined by a decreased incidence of opportunistic infections, tumors, and deaths. Despite all the therapeutic advantages achieved during the last decade, including the development of HAART, once an individual has become infected, eradication of the virus still remains impossible.

In addition, new problems relating to the short- and long-term toxicity of drug treatments and the occurrence of resistance mutations in both circulating and transmitted viruses are emerging. In most countries in South East Asia and Africa, the incidence and prevalence of HIV-1 infection continues to increase and surpass that of Europe and North America. However, due to the high costs of drug regimens and the lack of a healthcare infrastructure in these developing countries, the widespread use of HAART is currently still difficult. The further course of the HIV-1 pandemic, therefore, mainly depends on how and to what degree the developing countries with a high HIV-1 prevalence are able to take advantage of the medical progress achieved in Europe and North America, and whether an effective prophylactic vaccine becomes available in the near future.

An understanding of the immunopathogenesis of HIV-1 infection is a major prerequisite for rationally improving therapeutic strategies, developing immunotherapeutics and prophylactic vaccines. As in other virus infections, the individual course of HIV-1 infection depends on both host and viral factors.

The course of infection with HIV-1 in HIV-infected humans may vary dramatically, even if the primary infections arose from the same source (4). In some individuals, with a long-term non-progressive HIV-1 infection (i.e., lack of decline in CD4 counts, or chronic infection for at least 7 years without the development of AIDS), a defective virion was identified (5). Thus, infection with a defective virus, or one which has a poor capacity to replicate, may prolong the clinical course of HIV-1 infection. However, in most individuals, HIV-1 infection is characterized by a replication-competent virus with a high daily turnover of virions.

Host factors may also determine whether or not an HIV-1-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors, who represent about 5% of all infected patients. The identification and characterization of host factors contributing to the

course of HIV infection, including immunological defense mechanisms and genetic factors, will be crucial for our understanding of the immunopathogenesis of HIV infection and for the development of immunotherapeutic and prophylactic strategies.

1. The structure of HIV-1

HIV-1 is a retrovirus and belongs to the family of lentiviruses. Infections with lentiviruses typically show a chronic course of disease, a long period of clinical latency, persistent viral replication and involvement of the central nervous system. Visna infections in sheep, simian immunodeficiency virus infections (SIV) in monkeys, or feline immunodeficiency virus infections (FIV) in cats are typical examples of lentivirus infections.

Using electron microscopy, HIV-1 and HIV-2 resemble each other strikingly. However, they differ with regard to the molecular weight of their proteins, as well as having differences in their accessory genes. HIV-2 is genetically more closely related to the SIV found in sootey mangabeys (SIV_{sm}) rather than HIV-1 and it is likely that it was introduced into the human population by monkeys. Both HIV-1 and HIV-2 replicate in CD4 T cells and are regarded as pathogenic in infected persons, although the actual immune deficiency may be less severe in HIV-2-infected individuals.

1.1. The morphologic structure of HIV-1

HIV-1 viral particles have a diameter of 100 nm and are surrounded by a lipoprotein membrane. Each viral particle contains 72 glycoprotein complexes, which are integrated into this lipid membrane, and are each composed of trimers of an external glycoprotein gp120 and a transmembrane spanning protein gp41. The bonding between gp120 and gp41 is only loose and therefore gp120 may be shed spontaneously within the local environment. Glycoprotein gp120 may also be detected in the serum (6) as well as within the lymphatic tissue of HIV-infected patients (7). During the process of budding, the virus may also incorporate different host proteins from the membrane of the host cell into its lipoprotein layer, such as HLA class I and II proteins, or adhesion proteins such as ICAM-1 that may facilitate adhesion to other target cells. The matrix protein p17 is anchored to the inside of the viral lipoprotein membrane. The p24 core antigen contains two copies of HIV-1 RNA. The HIV-1 RNA is part of a protein-nucleic acid complex, which is composed of the nucleoprotein p7 and the reverse transcriptase p66 (RT). The viral particle contains all the enzymatic equipment that is necessary for replication: a reverse transcriptase (RT), an integrase p32 and a protease p11 (overview in: 8) (Fig. 1).

1.2. The organization of the viral genome

Most replication competent retroviruses depend on three genes: *gag*, *pol* and *env*: **gag** means "**g**roup-**a**nti**g**en", **pol** represents "**pol**ymerase" and **env** is for "**env**elope" (overview in: 9) (Fig. 2). The "classical" structural scheme of a retroviral genome is: 5'LTR-gag-pol-env-LTR 3'. The LTR ("**l**ong **t**erminal **r**epeat") regions represent the two end parts of the viral genome, that are connected to the cellular DNA of the host cell after integration and do not encode for any viral proteins. The *gag* and *env*

genes code for the nucleocapsid and the glycoproteins of the viral membrane; the *pol* gene codes for the reverse transcriptase and other enzymes. In addition, HIV-1 contains six genes (*vif, vpu, vpr, tat, rev* and *nef*) in its 9kB RNA, that contribute to its genetic complexity. *Nef, vif, vpr* and *vpu* were classified as accessory genes in the past, as they are not absolutely required for replication in vitro. However, the regulation and function of these accessory genes and their proteins have been studied and characterized in more detail in the past few years. The accessory genes, *nef, tat* and *rev,* are all produced early in the viral replication cycle.

Tat and *rev* are regulatory proteins that accumulate within the nucleus and bind to defined regions of the viral RNA: TAR (transactivation-response elements), found in the LTR; and RRE (rev response elements), found in the *env* gene, respectively. The *tat* protein is a potent transcriptional activator of the LTR promoter region and is essential for viral replication in almost all in vitro culture systems. Cyclin T1 is a necessary cellular cofactor for *tat* (10). *Tat* and *rev* stimulate the transcription of proviral HIV-1 DNA into RNA, promote RNA elongation, enhance the transportation of HIV RNA from the nucleus to the cytoplasm and are essential for translation. *Rev* is also a nuclear export factor that is important for switching from the early expression of regulatory proteins to the structural proteins that are synthesized later.
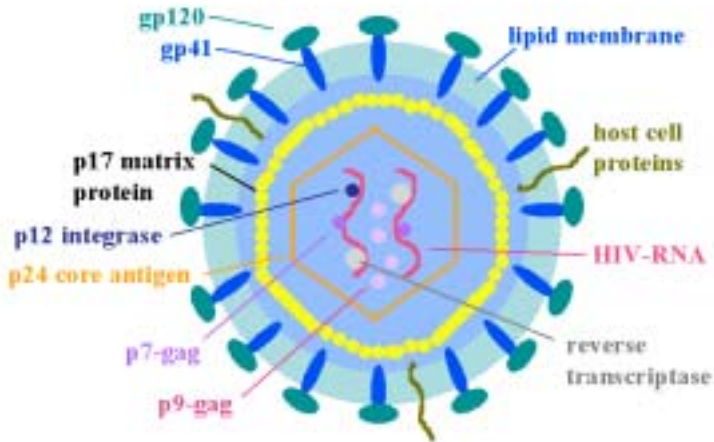
Figure 1: Structure of an HIV virion particle. For detailed explanations see text.
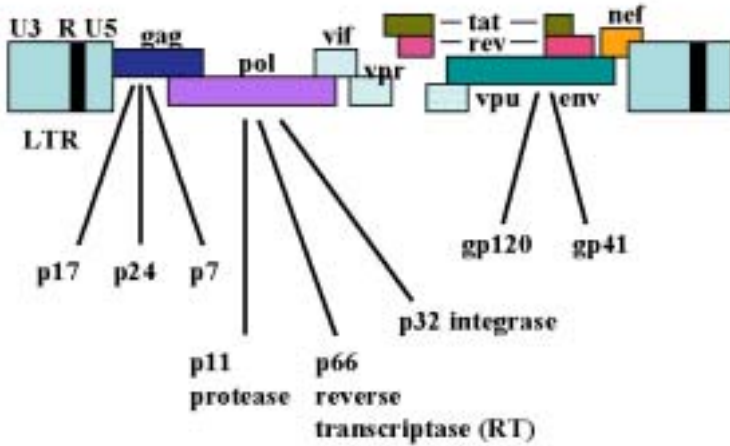
Figure 2: HIV and its genes. For detailed explanations see text.

Nef has been shown to have a number of functions. *Nef* may induce downregulation of CD4 (11) and HLA class I molecules (12) from the surface of HIV-1-infected cells, which may represent an important escape mechanism for the virus to evade an attack mediated by cytotoxic CD8$^+$ T cells and to avoid recognition by CD4 T cells. *Nef* may also interfere with T cell activation by binding to various proteins that are involved in intracellular signal transduction pathways. (Overview in: 13).

In SIV-infected rhesus macaques, an intact *nef* gene was essential for a high rate of virus production and the progression of disease. HIV-1, with deletions in *nef,* was identified in a cohort of Australian long-term non-progressors (5). However, more recent reports indicate that some of these patients are now developing signs of disease progression together with a decline of CD4 T cells. Thus, although, deletions of the *nef* gene may slow viral replication, they cannot always prevent the development of AIDS.

Vpr seems to be essential for viral replication in non-dividing cells such as macrophages. Vpr may stimulate the HIV-LTR in addition to a variety of cellular and viral promoters. More recently, *vpr* was shown to be important for the transport of the viral pre-integration complex to the nucleus (Overview in: 14) and may arrest cells in the G2 phase of the cell cycle.

Vpu is important for the virus "budding" process, because mutations in *vpu* are associated with persistence of the viral particles at the host cell surface. *Vpu* is also involved when CD4-gp160 complexes are degraded within the endoplasmic reticulum and therefore allows recycling of gp160 for the formation of new virions (15).

Some recent publications have highlighted a new and important role for vif in supporting viral replication (16). *Vif*-deficient HIV-1 isolates do not replicate in CD4 T cells, some T cell lines ("non-permissive cells") or in macrophages. *Vif*-deficient isolates are able to enter a target cell and initiate reverse transcription, but synthesis of proviral DNA remains incomplete. In vitro fusion of "permissive" and "non-permissive" cells leads to a "non-permissive" phenotype, suggesting that the repli-

cation of HIV depends on the presence or absence of a cellular inhibitor. This endogenous inhibitory factor was recently identified as APOBEC3G (17). APOBEC3G ("apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G") belongs to a family of intracellular enzymes that specifically de-aminate cytosine to uracil in mRNA or DNA resulting in an accumulation of G-to-A mutations that lead to degradation of viral DNA. By forming a complex with APOBEC3G, vif blocks the inhibitory activity of APOBEC3G (Fig. 3a).
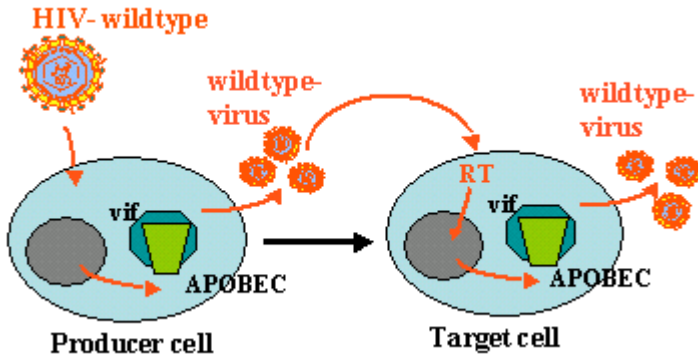
3a
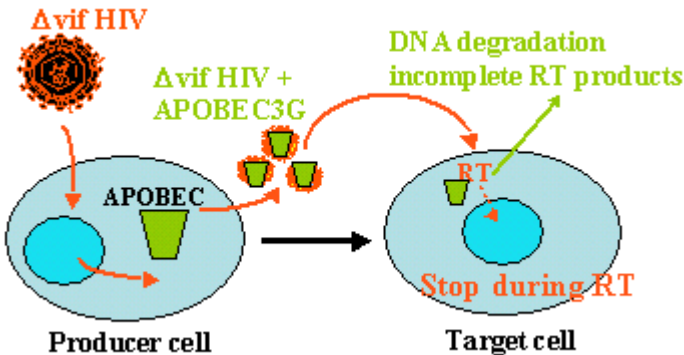
3b

Figure 3: HIV wild-type infection: vif interacts with APOBEC3G, binds to APOBEC3G and prevents its incorporation in newly formed viruses (Fig 3a). Vif-deleted HIV isolates fail to inhibit intracellular APOBEC3G, which is then incorporated into new viruses and interferes with reverse transcription in the target cell.

Of interest, the antiviral activity of APOBEC3G is highly conserved among various species, whereas the blockade of APOBEC3G by *vif* is highly specific for HIV. HIV-1 *vif* does not complex to murine or rhesus APOBEC3G. In the absence of *vif*, APOBEC3G is incorporated into newly formed viral particles and in subsequently infected target cells, synthesis of proviral DNA is blocked (Fig 3b). In contrast, in

the presence of *vif*, APOBEC3G is complexed, degraded and not incorporated in newly formed virions. APOBEC3G is expressed in lymphocytes and macrophages representing the primary target cells of HIV infection.

Currently, there are still a lot of open questions regarding the regulation of intracellular APOBEC3G: for example, whether there is a critical amount of intracellular APOBEC3G that restricts HIV infection in the presence of *vif,* or whether genetic polymorphisms of APOBEC3G exist that may potentially affect the course of disease. Meanwhile, the epitopes by which vif and APOBEC3G interact with each other have been characterized and the pathway of intracellular degradation of the APOBEC3G-vif complex explored. Of note, specific inhibitors that block the interaction of vif and APOBEC3G or that interfere with the intracellular degradation of APOBEC3G could represent promising future treatments. In principle, blockade of cellular structures will likely be associated with a minimal risk that the development of resistance might compromise the efficacy of an antiviral agent. Therefore, targeting *vif* and APOBEC3G represents an interesting therapeutic approach.

In summary, these data explain not only why *vif* is essential for HIV replication but also give one reason why HIV replication is species-specific. Another cellular factor (see below) has also been discovered which explains species specificity of HIV replication.

The crucial role for APOBEC3G or other cytidine deaminases might not be restricted to HIV-1. An accumulation of G-to-A mutations was also demonstrated in various HBV isolates. In vitro, the accumulation of HBV-DNA is dramatically reduced in the presence of APOBEC3G but co-transfection with *vif* can revert this inhibition (18).

2. The HIV replication cycle

2.1. HIV entry

CD4 as a primary receptor for HIV

CD4 is a 58 kDa monomeric glycoprotein that can be detected on the cell surface of about 60% of T-lymphocytes, on T cell precursors within the bone marrow and thymus, and on monocytes and macrophages, eosinophils, dendritic cells and microglial cells of the central nervous system. The extracellular domain of the CD4 on T cells is composed of 370 amino acids; the hydrophobic transmembrane domain and the cytoplasmic part of CD4 on T cells consist of 25 and 38 amino acids, respectively. Within the extracellular part of CD4, four regions D1-D4 have been characterized that represent immunoglobulin-like domains. Residues within the V2 region of CD4 (amino acids 40-55) are important for the bonding of gp120 to CD4 and this region overlaps the part of the CD4 where its natural ligands, HLA class II molecules, bind.

The identification of the gp120 binding site on the CD4 of CD4 T cells stimulated attempts to use soluble CD4 (sCD4) to neutralize the circulating virus in patients, the aim being the inhibition of viral spread. However it became evident, that even

though laboratory viral isolates were easily neutralized by sCD4, neutralization of primary patient-derived isolates had not been achieved.

In contrast, sCD4 was able to induce conformational changes within the viral envelope that promoted the infection of target cells (19).

CD4 attaches to the T cell receptor complex (TCR) on CD4 T cells and binds to HLA class II molecules on antigen-presenting cells. The binding of gp120 to CD4 is not only a crucial step for viral entry, but also interferes with intracellular signal transduction pathways and promotes apoptosis in CD4 T cells (20). In the past couple of years, the idea of blocking CD4 as the primary cellular receptor of HIV has regained interest. PRO542 represents a genetically engineered tetravalent CD4-IgG2 fusion protein that not only inhibited viral replication in vitro, but also showed an impressive antiviral efficacy in patients with high viral load that were included in initial clinical trials (21).

CD4, as a primary and necessary receptor for HIV-1, HIV-2 and SIV, was already characterized in 1984 (22, 23). However, experiments, using non-human cell lines transfected with human CD4, showed that expression of human CD4 on the cell surface of a non-human cell line was not sufficient to allow entry of HIV. Therefore the existence of additional human co-receptors necessary for viral entry was postulated. On the other hand, some laboratory HIV-1 isolates, as well as some HIV-2 and SIV isolates are able to infect human cells independently from CD4. Interestingly, monoclonal antibodies against CD4 induced conformational (CD4I) epitopes to bind to the gp120 of CD4-independent viruses. This observation suggests that the gp120 of CD4-independent viruses already exposes the regions that are necessary for co-receptor recognition and binding and therefore binding to CD4 is not a prerequisite of entry for these viruses. CD4-independent viruses are easy to neutralize using the serum of HIV-infected patients, suggesting that the immune response selects against CD4-independent viruses (24).

Chemokine receptors as co-receptors for HIV entry

A milestone for the characterization of the early events leading to HIV-1 entry was an observation by Cocchi and his co-workers in 1995. CD8^{+} T cells from HIV-infected patients are able to suppress viral replication in co-cultures with HIV-infected autologous or allogenic CD4 T cells, and this is independent from their cytotoxic activity (25). Cocchi identified the chemokines MIP-1α, MIP-1ß and Rantes in supernatants from CD8^{+} T cells derived from HIV-infected patients, and was able to show that these chemokines were able to suppress replication in a dose-dependent manner of some, but not all, viral isolates tested (26). MIP-1α, MIP-1ß and Rantes are ligands for the chemokine receptor CCR5, and a few months later several groups were able to show that CCR5 is a necessary co-receptor for mono-cytotropic (M-tropic) HIV-1 isolates (27,28,29). A few weeks earlier, the chemokine receptor CXCR4 (fusin) was described as being the co-receptor used by T cell-tropic (T-tropic) HIV isolates (30). Monocytotropic (M-tropic) HIV-1 isolates are classically those viruses that are most easily propagated in macrophage cultures, are unable to infect T cell lines (i.e., immortalized T cells), but are able to easily infect primary T cells from peripheral blood samples. Conversely, T cell-tropic HIV-1 isolates have classically been identified as being those that are easily propagated in T cell lines, and grow poorly in macrophages, but are also able to easily infect pri-

mary T cells from peripheral blood samples. Thus, it should be noted that both M-tropic and T-tropic HIV-1 variants can easily infect primary human non-immortalized T cells in vitro.

Chemokines ("**Chemo**tactic cyto**kines**") and their receptors have been previously characterized with regard to their role in promoting the migration ("chemotaxis") of leukocytes and their pro-inflammatory activity. They are proteins of 68-120 amino acids which depend on the structure of their common cysteine motif, and which may be subdivided into C-X-C (α-chemokines), C-C (ß-chemokines) and C-chemokines. Chemokines typically show a high degree of structural homology to each other and may share the receptors they bind to. Chemokine receptors belong to the group of receptors with seven transmembranic regions ("7-transmembrane receptors"), which are intracellularly linked to G-proteins.

SDF-1 ("stromal cell-derived factor 1") was identified as the natural ligand of CXCR4 and is able to inhibit the entry of T-tropic HIV-1 isolates into activated CD4 T cells. Rantes ("regulated upon activation T cell expressed and secreted"), MIP-1α ("macrophage inhibitory protein") and MIP-1ß represent the natural ligands of CCR5 and are able to inhibit the entry of M-tropic HIV-1 isolates into T cells. A schematic model is depicted in Fig. 4: T-tropic HIV-1 isolates mainly infect activated peripheral blood CD4 T cells and cell lines and use CXCR4 for entry into the $CD4^+$-positive target cell. M-tropic isolates are able to infect CD4 T cells, monocytes and macrophages, and depend on the use of CCR5 and CD4 for viral entry.

The interaction of gp120 and the cellular receptors is now understood in more detail. Gp120 primarily binds to certain epitopes of CD4. Binding to CD4 induces conformational changes in gp120 that promote a more efficient interaction of the V3 loop of gp120 with its respective co-receptor. Membrane fusion is dependent on gp120 co-receptor binding. Gp41, as the transmembrane part of the envelope glycoprotein gp160, is crucial for the fusion of the viral and the host cell membrane. Similar to influenza hemagglutinin, it was postulated that consequent to the binding of gp120 to CD4, a conformational change is induced in gp41 that allows gp41 to insert its hydrophobic NH_2 terminal into the target cell membrane. Gp41 has been compared to a "mouse trap" and a crystallographic analysis of the ectodomanic structure of gp41 seems to confirm that hypothesis (31). The identification of crucial amino acid sequences for this process was used to synthesize peptides that bind to gp41 within the domains, are critical for the induction of conformational changes, and that may inhibit membrane fusion.

T20 is the first of several peptides that bind to gp41 and has been tested in clinical trials for suppressing viral replication (32). Currently, T20 is available as a therapeutic option for selected patients. One disadvantage of T20 is that it must be taken intramuscularly rather than as a pill.

Using transfected cell lines, besides CCR5 and CXCR4, other chemokine receptors, such as CCR3, CCR2, CCR8, CCR9, STRL33 ("Bonzo"), Gpr 15 ("Bob"),Gpr 1, APJ and ChemR23, were identified and shown to be used for entry by certain HIV isolates (33, 34). APJ may represent a relevant co-receptor within the central nervous system. Despite this broad spectrum of potentially available co-receptors, CCR5 and CXCR4 seem to represent the most relevant co-receptors for HIV-1 in vivo.
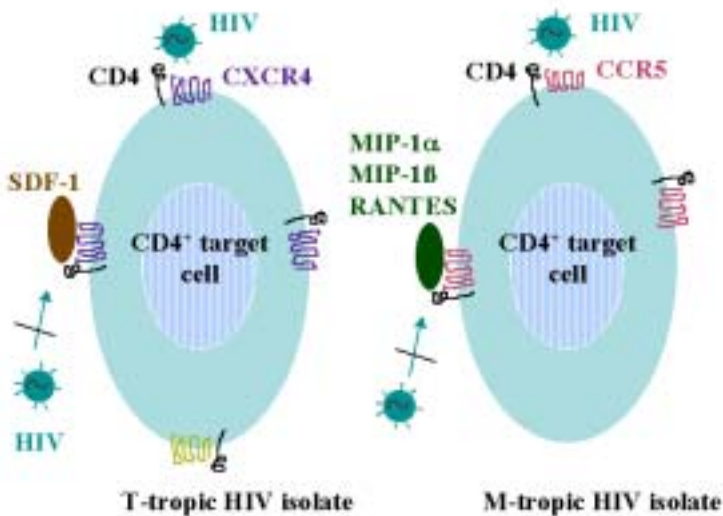
Figure 4: Inhibition of virus entry of CCR5-utilizing (monocytotropic) and CXCR4-utilizing (T-cell tropic) HIV isolates by the natural ligands of the chemokine co-receptors CCR5 and CXCR4.

The importance of CCR5 as the predominant co-receptor for M-tropic HIV isolates is underscored by another observation. The majority of individuals with a genetic defect of CCR5 are resistant to infection with HIV-1 (35). In vitro experiments show that lymphocytes derived from these individuals are resistant to HIV-1 infection using M-tropic isolates but not to infection with T-tropic isolates. Lymphocytes from these individuals do not express CCR5 on their cell surface and genetically have a 32 base pair deletion of the CCR5 gene. Worldwide, a few patients have been identified that have acquired HIV-1 infection despite a homozygous deletion of the CCR5. As expected, all of them were infected with CXCR4-using HIV-1 isolates (36). In epidemiological studies, the allelic frequency of the CCR5 gene deletion is 10-20% among Caucasians, particularly amongst those of Northern European descent. The frequency of a homozygous individual is about 1% in Caucasians (37). Studies conducted on African or Asian populations, however, do not find this 32 base pair deletion of the CCR5, suggesting that this mutation arose after the separation of these populations in evolutionary history.

Individuals that are heterozygous for the 32 bp deletion of the CCR5 show a decreased expression of CCR5 on the cell surface and are more frequently encountered within cohorts of long-term non-progressors compared to patients who have a rapid progression of disease (37). In addition, HIV-infected individuals who are heterozygous for the 32 bp deletion of the CCR5, have a slower progression to AIDS, a better treatment response to HAART and lymphoma incidence is decreased. These data demonstrate that the density of CCR5 on the cell surface is not only a limiting factor for replication of HIV in vitro but also in vivo.

In addition to the 32bp deletion of the CCR5, other genetic polymorphisms, with regard to the chemokine receptors (CCR2) or their promoters (CCR5), have been described. Based on the occurrence of these polymorphisms within defined patient

cohorts, they were associated with a more rapid or a more favorable course of disease, depending on the particular polymorphism (38, 39).

In patients who have a rapid progression of disease (rapid drop in CD4 T cell count), virus isolates that use CXCR4 as a predominant co-receptor tend to be frequently isolated from their cells, in comparison to patients with a stable CD4 T cell count.

The expression of co-receptors on CD4$^+$ lymphocytes depends on their activation level.

CXCR4 is mainly expressed on naive T cells, whereas CCR5 is present on activated and effector/memory T cells. During the early course of HIV-1 infection, predominantly M-tropic HIV-1 isolates are detected. Interestingly, M-tropic HIV-1 isolates are preferentially transmitted regardless of whether or not the "donor" predominantly harbors T-tropic isolates. At present, it remains unclear whether this "in vivo" preference of M-tropic HIV-1 isolates is determined by selected transportation of M-tropic isolates by sub-mucosally located dendritic cells or whether the local cytokine/chemokine milieu favors the replication of M-tropic viruses. Recent intriguing studies by Cheng Meyer et. al. suggest that M-tropic HIV-1 viruses are able to 'hide' more easily from the immune system by replicating in macrophages, in comparison to T-tropic viruses, thus giving them a survival advantage in the infected individual.

The blockade of CCR5, therefore, seems to represent a promising target for therapeutic intervention. In vitro, monoclonal antibodies to CCR5 (2D7 and others) are able to block the entry of CCR5-using HIV isolates into CD4 T cells and macrophages. Small molecule inhibitors of CCR5 have been designed and are currently being tested in clinical trials. In vitro studies, as well as experiments using SCID mice, however, suggest that blockade of CCR5-using isolates may alter their tropism towards increased usage of CXCR4.

Small molecule inhibitors such as T22, ALX40-4C or AMD3100 are able to inhibit CXCR4 (40, 41) and are also subject to preclinical and clinical trials.

Strategies are currently being developed to modulate expression of chemokine receptors. Intrakines are chemokines that stay within the cytoplasm and are able to capture and bind to their corresponding receptor on its way to the cell surface (42). "Short interfering RNA" (siRNA) represents a new molecular tool that is able to selectively inactivate target genes. Double-stranded RNA is split by the enzyme dicer-1 into short pieces ("21-23mers"). These oligomers may complementary bind to longer RNA sequences that are subsequently degraded. This strategy is currently employed in plants and used for its antiviral activity. The use of siRNA against CCR5 can prevent the expression of CCR5 in vitro.

Although the therapeutic use of chemokine receptor blockers seems promising, a lot of questions still remain unanswered. Using knockout mice it was demonstrated that the absence of CXCR4 or SDF-1 is associated with severe defects in hematopoiesis and in cerebellar development (43). Currently, it remains unclear whether the blockade of CXCR4 in postnatal or adult individuals may also affect other organ systems.

2.2. Postfusion events

Following membrane fusion the virus core "uncoats" into the cytoplasm of the target cell. These "early events" have recently been studied in more detail. HIV can enter into rhesus lymphocytes but replication is stopped before or during early reverse transcription. This intracellular blockade is mediated by a cellular factor, TRIM5α, which is a component of cytoplasmic bodies and whose primary function is yet known. TRIM5α from various species exhibits differential inhibition on various retroviruses. For example, TRIM5α from rhesus macaques, TRIM5$\alpha_{rh,}$ more profoundly inhibits HIV replication than human TRIM5α , whereas SIV (simian immunodeficiency virus) which naturally infects Old World monkeys, is less susceptible to either form of TRIM5α, thus explaining in part the species specificity of HIV for human cells (44). TRIM5α from human cells or non-human primates is able to inhibit replication of other lentiviruses and represents a novel cellular resistance factor whose definitive biological significance has yet to be fully characterized. It is unclear how exactly TRIM5α blocks reverse transcription and it has been hypothesized that TRIM5α interferes with the incoming virus capsid protein targeting it for ubiquitination and proteolytic degradation.

HIV-1 entry into quiescent T cells is comparable to HIV-1 entry into activated T cells, but synthesis of HIV-1 DNA remains incomplete in quiescent cells (45). The conversion of viral RNA into proviral DNA, mediated by the viral enzyme reverse transcriptase (RT), occurs in the cytoplasm of the target cell and is a crucial step within the viral replication cycle. Blockade of the RT by the nucleoside inhibitor zidovudine was the first attempt to inhibit viral replication in HIV-1 infected patients. Today, numerous nucleoside, nucleotide and non-nucleoside RT inhibitors are available for clinical use and have broadened the therapeutic arsenal substantially since the mid eighties.

Reverse transcription occurs in multiple steps. After binding of the tRNA primers, synthesis of proviral DNA occurs as a minus-strand polymerization starting at the PBS ("primer binding site") and extending up to the 5' repeat region as a short R/U5 DNA. The next step includes degradation of RNA above the PBS by the viral enzyme RNAase H and a "template switch" of the R/U5 DNA with hybridization of the R sequence at the 3' RNA end. Now the full length polymerization of proviral DNA with degradation of the tRNA is completed. Reverse transcription results in double-stranded HIV DNA with LTR regions ("long terminal repeats") at each end.

HIV-1 enters into quiescent T cells and reverse transcription may result in the accumulation of proviral, non-integrating HIV-DNA. However, cellular activation is necessary for integration of the proviral HIV DNA into the host cell genome after transportation of the pre-integration complex into the nucleus. Cellular activation may occur in vitro after stimulation with antigens or mitogens, in vivo activation of the immune system is observed after antigen contact or vaccination or during an opportunistic infection. In addition, evidence is emerging that HIV-1 gp120 itself may activate the infecting cell to enhance integration. Besides monocytes, macrophages and microglial cells, latently infected quiescent CD4^{+} T cells that contain non-integrated proviral HIV DNA represent important long-living cellular reservoirs of HIV (46). Since natural HIV-1 infection is characterized by continuing cycles of viral replication in activated CD4^{+} T cells, viral latency in these resting

CD4$^+$ T cells likely represents an accidental phenomenon and is not likely to be important in the pathogenesis of this disease. This small reservoir of latent provirus in quiescent CD4$^+$ T cells gains importance, however, in individuals who are treated with HAART, since the antivirals are unable to affect non-replicating proviruses and thus the virus will persist in those cells and be replication competent to supply new rounds of infection, if the drugs are stopped. Thus, the existence of this latent reservoir has prevented HAART from entirely eradicating the virus from infected individuals.

Until recently it was not clear, why HIV replicates poorly in quiescent CD4 T cells. The cellular protein Murr1 that plays a role in copper metabolism is able to inhibit HIV replication in unstimulated CD4 T cells. Murr1 was detected in primary resting CD4 T cells and interferes with activation of the transcription factor NFκB by inhibiting the degradation of IκBα. IκBα prevents NFκB from migrating to the nucleus, especially after cytokine stimulation (e.g., TNFα). Because the HIV LTR region has multiple sites for NFκB, preventing NFκB migration to the nucleus should inhibit HIV replication. Inhibition of murr-1 by siRNA is associated with HIV replication in quiescent CD4 T cells (47). Persistence of HIV in quiescent CD4 T cells and other cellular reservoirs seems one of the main reasons why eradication of HIV is not feasible. If it is ever possible to achieve, a more detailed knowledge of how and when cellular reservoirs of HIV are established and how they may be targeted is of crucial importance for the development of strategies aiming at HIV eradication.

Cellular transcription factors such as NF-kB may also bind to the LTR regions. After stimulation with mitogens or cytokines, NF-kB is translocated into the nucleus where it binds to the HIV-LTR region, thereby initiating transcription of HIV genes. Transcription initially results in the early synthesis of regulatory HIV-1 proteins such as *tat* or *rev*. *Tat* binds to the TAR site ("transactivation response element") at the beginning of the HIV-1 RNA in the nucleus and stimulates transcription and the formation of longer RNA transcripts. *Rev* activates the expression of structural and enzymatic genes and inhibits the production of regulatory proteins, therefore promoting the formation of mature viral particles. The proteins coded for by *pol* and *gag* form the nucleus of the maturing HIV particle; the gene products coded for by *env* form the gp120 "spikes" of the viral envelope. The gp120 spikes of the envelope are synthesized as large gp160 precursor molecules and are cleaved by the HIV-1 protease into gp120 and gp41. The *gag* proteins are also derived from a large 53 kD precursor molecule, from which the HIV-protease cleaves the p24, p17, p9 and p7 *gag* proteins. Cleavage of the precursor molecules by the HIV-1 protease is necessary for the generation of infectious viral particles, and therefore the viral protease represents another interesting target for therapeutic blockade (48). The formation of new viral particles is a stepwise process: a new virus core is formed by HIV-1 RNA, *gag* proteins and various *pol* enzymes and moves towards the cell surface. The large precursor molecules are cleaved by the HIV-1 protease, which results in the infectious viral particles budding through the host cell membrane. During the budding process, the virus lipid membranes may incorporate various host cell proteins and become enriched with certain phospholipids and cholesterol. In contrast to T cells, where budding occurs at the cell surface and viri-

ons are released into the extracellular space, the budding process in monocytes and macrophages results in the accumulation of virions within cellular vacuoles.

The replication of retroviruses is prone to error and is characterized by a high spontaneous mutation rate. On average, reverse transcription results in 1-10 errors per genome and per round of replication. Mutations can lead to the formation of replication-incompetent viral species. But, mutations causing drug resistance may also accumulate, which, provided that there is selection pressure under certain antiretroviral drugs and incomplete suppression of viral replication, may become dominant.

In addition, viral replication is dynamic and turns over quickly in infected individuals at an average rate of 10^9 new virus particles being produced and subsequently cleared per day. Thus, within any individual, because of the extensive virus replication and mutation rates, there exists an accumulation of many closely related virus variants within the 'population' of viruses, referred to as a viral "quasispecies". The selection pressure on mostly the pre-existing mutations may not only be exerted by certain drugs, but also by components of the immune system, such as neutralizing antibodies or cytotoxic T cells (CTL).

3. HIV and the immune system

3.1. The role of antigen-presenting cells

Dendritic cells as prototypes of antigen-presenting cells

Dendritic cells, macrophages and B cells represent the main antigen-presenting cells of the immune system. Dendritic cells (DC) are the most potent inducers of specific immune responses and are considered essential for the initiation of primary antigen-specific immune reactions. DC precursors migrate from the bone marrow towards the primary lymphatic organs and into the submucosal tissue of the gut, the genitourinary system and the respiratory tracts. They are able to pick up and process soluble antigens and migrate to the secondary lymphatic organs, where they activate antigen-specific T cells.

DC represent a heterogeneous family of cells with different functional capacities and expression of phenotypic markers, depending on the local microenvironment and the stage of maturation. Immature DC have the capacity to pick up and process foreign antigens, but do not have great T cell stimulatory capacities. However, mature DC show a predominant immunostimulatory ability. DC in tissues and Langerhans' cells, which are specialized DC in the skin and mucosal areas, represent a more immature phenotype and may take up antigen. Once these DC have taken up the antigen, they migrate to the lymphoid tissues where they develop a mature phenotype.

The stimulation of $CD8^+$ T lymphocytes and the formation of antigen-specific cytotoxic T cells (CTL) depend on the presentation of a peptide together with MHC class I antigens. DC may become infected with viruses, for instance influenza. Viral proteins are then produced within the cytoplasm of the cell, similar to cellular pro-

teins, then degraded to viral peptides and translocated from the cytosol into the endoplasmic reticulum, where they are bound to MHC class I antigens. These peptide-MHC class I complexes migrate to the DC surface. The number of specific antigen-MHC class I complexes is usually limited and must eventually be recognized by rare T cell clones, up to a ratio of 1:100.000 or less. The T cell receptor (TCR) may display only a low binding affinity (1mM or less). The high density of co-stimulatory molecules on the DC surface, however, enhances the TCR-MHC: peptide interaction allowing efficient signaling to occur through the T cell and resulting in proliferation (clonal expansion) of the T cell. Virus-infected cells or tumor cells often do not express co-stimulatory molecules, and thus may not be able to induce a clonal expansion of effector cells. This underscores the importance of having a highly specialized system of antigen-presenting cells, i.e., DC, in operation to prime T cells to expand and proliferate initially.

The interaction of dendritic cells and B/T cells

B and T lymphocytes may be regarded as the principle effector cells of antigen-specific immune responses. However, their function is under the control of dendritic cells. DC are able to pick up antigens in the periphery. These antigens are processed and expressed on the cell surface, together with co-stimulatory molecules that initiate T cell activation. B cells may recognize antigen after binding to the B cell receptor. Recognition of antigen by T cells requires previous processing and presentation of antigenic peptides by DC. T cells express different T cell receptors (TCR), that may bind to the peptide:MHC class I on the surface of dendritic cells to allow activation of $CD8^+$ T cells, or to the peptide:MHC class II molecules, to activate CD4 T cells. The ability of DC to activate T cells also depends on the secretion of stimulatory cytokines such as IL-12, which is a key cytokine for the generation and activation of T_H1 and natural killer (NK) cells.

Only a few DC and small amounts of antigen are sufficient to induce a potent antigen-specific T cell response, thus demonstrating the immunostimulatory potency of DC. The expression of adhesion molecules and lectins, such as DC-SIGN, support the aggregation of DC and T cells and promote the engagement of the T cell receptor (TCR). DC-SIGN is a type C lectin that has also been shown to bind to lentiviruses, such as SIV and HIV-1 and -2 by interaction of gp120 with carbohydrates (49). In vivo, immunohistochemical studies show expression of DC-SIGN on sub-mucosal and intradermal DC, suggesting an implication of DC-SIGN in vertical and mucosal transmission of HIV. The expression of DC-SIGN was shown to enhance the transmission of HIV to T cells and allows utilization of co-receptors if their expression is limited. Thus DC-SIGN may be a mechanism whereby HIV-1 is taken up by DC in the mucosal tissues. It is then transported by the DC to the lymphoid tissues, where HIV-1 can then infect all the residing CD4 T cells.

3.2. Lymphatic tissue as the site of viral replication

Viral replication within the lymphatic tissue is already extensive in the early stages of the disease (50,51). During the initial phase of HIV-1 infection, there is a burst of virus into the plasma, followed by a relative decline in viremia. During this time, a strong HIV-1 specific cytotoxic T cell response is generated, which coincides with the early suppression of plasma viremia in most patients. Virions are trapped by the

follicular dendritic cell (FDC) network within the lymphoid tissue. Macrophages, and activated and quiescent CD4 T cells are the main targets of infection. During the whole course of infection with HIV-1, the lymphoid tissue represents the principle site of HIV-1 replication. The frequency of cells containing proviral DNA is 5-10x higher in lymphoid tissue than in circulating peripheral mononuclear cells in the blood, and the difference in viral replication in lymphoid tissue exceeds that in the peripheral blood by about 10-100x. Thus, the virus mainly accumulates in the lymph nodes.

After entry of HIV-1 into a quiescent CD4 T cell and after completion of reverse transcription, the viral genome is represented by proviral unintegrated HIV DNA. The activation of CD4 T cells is necessary for the integration of the HIV DNA into the host cell genome and is therefore a prerequisite for the synthesis of new virions. In this regard, the micromilieu of the lymphoid tissue represents the optimal environment for viral replication. The close cell-cell contact between $CD4^+$ T cells and antigen-presenting cells, the presence of infectious virions on the surface of the FDC, and an abundant production of pro-inflammatory cytokines such as IL-1, IL-6 or $TNF\alpha$, promotes the induction of viral replication in infected cells and augments viral replication in cells already producing the virus. It should be noted that both IL-1 and $TNF\alpha$ induce $NF-\kappa\beta$ which binds to the HIV-1 LTR to promote proviral transcription. The importance of an antigen-induced activation of CD4 T cells is underlined by several in vivo and in vitro studies that demonstrate an increase in HIV-1 replication in association with a tetanus or influenza vaccination or an infection with Mycobacterium tuberculosis (52). Even though the clinical benefit of vaccination against common pathogens (e.g. influenza and tetanus) in HIV-1-infected patients outweighs the potential risk of a temporary increase in viral load, these studies indicate that in every situation where the immune system is activated, enhanced viral replication can also occur.

Patients undergoing HAART demonstrate a dramatic decrease in the number of productively infected CD4 T cells within the lymphoid tissue (53). However, in all patients examined so far, there persists a pool of latently infected quiescent T cells despite successful suppression of plasma viremia (46). It is these latently infected cells which may give rise to further rounds of viral replication, if the antiviral drugs are stopped.

During the natural course of HIV-1 disease, the number of CD4 T cells slowly decreases while plasma viremia rises in most patients. If sequential analysis of the lymphoid tissue is performed, progression of the disease is reflected by destruction of the lymphoid tissue architecture and a decreased viral trapping. Various immunohistological studies indicate that the paracortex of the lymph nodes represents the primary site where HIV replication is initiated (50, 51). Infection of the surrounding CD4 T cells, as well as the initiation of T cell activation by DC, contributes to the spreading of HIV-1 within the lymphoid environment.

Similarly to SIV infection in rhesus macaques, HIV infection, at all stages of disease, is associated with preferential replication and CD4 T cell destruction in the gut lamina propria and submucosa than in lymph nodes (54, 55, 56). This is likely because the gut is predominantly populated by CCR5-expressing effector memory CD4 T cells, which are ideal targets for HIV replication compared to the mixed populations of CD4 T cells found within the lymph nodes. It remains to be estab-

lished, however, whether this severe CD4 T cell depletion within the gut, even early in infection, plays a direct role in the abnormal CD4 T cell homeostasis seen throughout the course of disease.

Recent studies have also examined the effect of HIV infection on the thymus gland and its role in CD4 T cell depletion and homeostasis. Recent work has suggested that thymic output of CD4 T cells is decreased during HIV infection, particularly with older age, and that this defect is due to abnormalities of intra-thymic proliferation of T cells, whose mechanism is still undefined, as thymocytes do not express CCR5 and should not necessarily be targets of HIV (57, 58).

3.3. The HLA system and the immune response to HIV

CD8 T cells recognize "their" antigen (peptide) in context with HLA class I molecules on antigen-presenting cells, whereas CD4 T cells require the presentation of antigenic peptides in context with HLA class II molecules. The generation of an HIV-specific immune response is therefore dependent on the individual HLA pattern.

Antigen-presenting cells may bind HIV peptides in different ways within "grooves" on the HLA class I molecules. Therefore, CD8 T cells can be activated in an optimal or suboptimal way or may not be activated at all. Using large cohorts of HIV-1 infected patients, in whom the natural course of disease (fast versus slow progression) is known, HLA patterns were identified that were associated with a slow versus fast disease progression. These studies suggest that the HLA type could be responsible for the benign course of disease in about 40% of patients with a long-term non-progressive course of disease. Homozygosity for HLA Bw4 is regarded as being protective. Patients who display heterozygosity at the HLA class I loci characteristically show a slower progression of immunodeficiency than patients with homozygosity at these loci (59). An initial study by Kaslow in 1996 demonstrated that HLA B14, 27, B51, B57 and C8 are associated with a slow disease progression, however, the presence of HLA A23, B37 and B49 were associated with the rapid development of immunodeficiency (60). All patients with HLA B35 had developed symptoms of AIDS after 8 years of infection. More recent studies suggest that discordant couples with a "mismatch" at the HLA class I have a protective effect towards heterosexual transmission (61).

In vitro studies in HLA B57-positive patients demonstrate that these patients display HLA B57-restricted CTL directed against HIV-1 peptides. However, it is possible that the identification of protective HLA alleles or HLA-restricted peptides in HIV-1-infected patients with a benign course of disease does not necessarily indicate that the same alleles or peptides are crucial for the design of a protective vaccine. Kaul and co-workers were able to show that CD8 T cells from HIV-1-exposed but uninfected African women recognize different epitopes than CD8 T cells from HIV-1-infected African women (62). This suggests that the epitopes, that the immune system is directed against during a natural infection, might be different from those that are protective against infection.

HLA class II antigens are crucial for the development of an HIV-1-specific CD4 T cell response. Rosenberg (1997) was the first to show that HIV-1-infected patients with a long-term non-progressive course of disease had HIV-1-specific CD4 T cells that could proliferate against HIV-1 antigens (63). The identification of protective

or unfavorable HLA class II alleles is less well elaborated than the knowledge about protective HLA class I alleles. Cohorts of vertically infected children and HIV-infected adults demonstrate a protective effect of HLA DR13 (64).

KIR receptors ("Killer cell immunoglobulin like receptors") represent ligands that bind to HLA class I antigens and by functioning as either activating or inhibiting receptors they regulate the activation status of NK cells. Polymorphisms of KIR genes were shown to correlate with slow or rapid progression of HIV disease, especially when the analysis includes known HLA class I polymorphisms (65).

In summary, various genetic polymorphisms have been identified that have an impact on the course of HIV disease. However, there is currently no rationale to recommend routine testing of individual patients or to base therapeutic decisions on genetic testing.

3.4. The HIV-specific cellular immune response

Cytotoxic T cells (CTL) are able to recognize and eliminate virus-infected cells. A number of studies clearly demonstrate that CTL are crucial for the control of HIV replication and have a substantial impact on disease progression once infection is established. However, there is little evidence to assume that CTL play a major role in primary protection.

In comparison to HIV-1-infected patients with a rapid decline in CD4 T cell numbers, patients with a long-term non-progressive course of disease ("LTNP" = long-term non-progressors) have high quantities of HIV-1-specific CTL precursors with a broad specificity towards various HIV-1 proteins. The different capacities of certain HLA alleles to present viral particles more or less efficiently and to induce a generally potent immune response may explain why certain HLA alleles are associated with a more rapid or a slowly progressive course of disease (see above).

Individuals have been described, who developed CTL "escape" mutants after years of stable disease and the presence of a strong CTL response. The evolution of CTL escape mutants was associated with a rapid decline in CD4 T cells in these patients, indicating the protective role of CTL (66).

HIV-specific CTL responses have been detected in individuals exposed to, but not infected by HIV-1. Nef-specific CTL have been identified in HIV-1-negative heterosexual partners of HIV-infected patients and env-specific CTL have been found in seronegative healthcare workers after exposure to HIV-1-containing material (needle stick injuries) (67). Unfortunately patients with a broad and strong CTL response do not seem to be protected from superinfection by a different, but closely related HIV isolate (68).

The presence of a CTL response is not correlated just with the suppression of plasma viremia during the initial phase of HIV infection. Patients who underwent structured therapy interruptions, especially when HAART was initiated early following infection, demonstrated the appearance of HIV-specific CTL during the pauses.

However, it is still unclear in most patients who exhibit a potent temporary CTL response, why this CTL response diminishes later on. The appearance of viral "escape" mutants might explain why previously recognized epitopes are no longer immunodominant.

The nef protein may downregulate HLA class I antigens and therefore counteract the recognition of infected cells by CTL. In addition, the majority of infected individuals show detectable CTL responses. It is unclear why they are unable to control the virus. Interestingly, CTL from HIV-infected patients shows a lack of perforin and an immature phenotype in comparison to anti-CMV-directed effector cells (69), even though the ability to secrete chemokines and cytokines is not impaired. Another recent study provided evidence that the killing capacities of HIV-specific CTL was associated with the ability to simultaneously produce interferon-γ and TNFα (70).

CD8 T cells may also become infected with HIV (71), although this was not demonstrated for HIV-specific CD8 T cells. It is unclear, whether CD8 T cells temporarily express CD4 and which chemokine co-receptors mediate infection of these CD8 T cells.

Proliferation and activation of CTL is dependent on antigen-specific T cell help. Rosenberg and his group were able to demonstrate that initiation of HAART during primary HIV infection was associated with persistence of an HIV-specific CD4 T cell response that was not detected in patients analyzed during the chronic stage of disease (63). HIV preferentially infects pre-activated CD4 T cells and as HIV-specific CD4 T cells are among the first cells to be activated during HIV infection, their preferential infection was demonstrated by Douek and his group (72). Therefore it is currently unclear whether the loss of HIV-specific CTL activity during the course of disease reflects an instrinsic defect of CTL or develops secondary to a loss of specific CD4 T cell help.

Various therapeutic vaccine strategies have been developed during the last few years and mostly tested in SIV-infected rhesus macaques aiming at inducing an SIV-specific CTL response that may alter the natural course of disease. Recently, a promising approach was published by Lu and his group who reported on a vaccine trial using autologous dendritic cells in SIV-infected rhesus macaques that were pulsed with inactivated SIV (73). In contrast to the unvaccinated control group, monkeys that were vaccinated showed a dramatic decrease in the viral load, and the development of anti-SIV-directed humoral and cellular immune responses. Meanwhile, a pilot trial has been initiated in a cohort of 18 HIV-infected antiretroviral-naive patients with stable viral load. The patients were vaccinated with autologous monocyte-derived dendritic cells that were pulsed with inactivated autologous virus. During the following 112 days, a median decrease of 80% of the viral load was observed and maintained for more than one year in 8 patients. In parallel, gag-specific CD8 T cells and HIV-specific CD4 T cells producing IFNγ and/or interleukin-2 were detected (74). Therapeutic vaccination using autologous dendritic cells appears to become a potential immunotherapeutic, but more controlled clinical studies are definitely needed.

In addition to the cytotoxic activities directed against HIV-infected cells, CD8 T cells from HIV-1 infected patients exhibit a remarkable, soluble HIV-1 inhibitory activity that inhibits HIV-1 replication in autologous and allogeneic cell cultures (75). Despite multiple efforts, the identity of this inhibitory activity ("CAF") has not been clarified, although chemokines, such as MIP-1α, MIP-1ß, RANTES (26), IL-16 (76), the chemokine MDC (77), and defensins (78), may account for at least some of the inhibition.

3.5. The T$_H$1/T$_H$2 immune response

Depending on the secretion pattern of cytokines, CD4 T cells may be differentiated into T$_H$1 and T$_H$2 cells. T$_H$1 CD4 T cells primarily produce interleukin-2 (IL-2) and IFNγ, which represent the cytokines that support the effector functions of the immune system (CTL, NK-cells, macrophages). T$_H$2 cells predominantly produce IL-4, IL-10, IL-5 and IL-6, which represent the cytokines that favor the development of a humoral immune response. Since T$_H$1 cytokines are critical for the generation of CTLs, an HIV-1-specific T$_H$1 response is regarded as being a protective immune response. Studies on HIV-exposed but non-infected individuals have shown, that following in vitro stimulation with HIV-1 env antigens (gp120/gp160) and peptides, T cells from these individuals secrete IL-2 in contrast to non-exposed control persons (79). Similar studies were undertaken in healthcare workers after needle-stick injuries and in newborns from HIV-infected mothers. Although these observations may indicate that a T$_H$1-type immune response is potentially protective, it should be considered, that similar immune responses might also have been generated after contact with non-infectious viral particles and therefore do not necessarily imply a means of protection against a replication-competent virus.

3.6. HIV-1 specific humoral immune responses

The association between an HIV-1-specific humoral immune response and the course of disease is less well characterized.

In a SIV model, injection of an antibody cocktail consisting of various neutralizing antibodies is able to prevent SIV infection after a mucosal virus challenge (80), indicating that primary protection is mainly dependent on a broad humoral immune response. In contrast, B cell depletion by a monoclonal antibody directed against B cells in monkeys with already established SIV infection, does not affect the course of plasma viremia (81).

A slow progression of immunodeficiency was observed in patients with high titers of anti-p24 antibodies (82), persistence of neutralizing antibodies against primary and autologous viruses (83), and lack of antibodies against certain gp120 epitopes (84).

Long-term non-progressors with HIV tend to have a broad neutralizing activity towards a range of primary isolates and show persistence of neutralizing antibodies against autologous virus. At present, it is unclear whether the presence of neutralizing antibodies in LTNP represents part of the protection or whether it merely reflects the integrity of a relatively intact immune system. Individuals that have a substantial risk for HIV-1 infection, but are considered "exposed, non-infected", by definition represent individuals with a lack of a detectable antibody response to HIV-1. This definition implies that a systemic humoral immune response may not represent a crucial protective mechanism. It has been shown that these individuals may demonstrate a local (mucosal) IgA response against HIV-1 proteins that are not detected by the usual antibody testing methods (85). Thus, local IgA, rather than systemic IgG, may be associated with protection against HIV-1 infection. There is also some evidence that some anti-HIV-1 antibodies can enhance the infection of CD4 T cells.

A number of old and recent studies have shown that neutralizing antibodies do exist in HIV-1-infected individuals, however, there is a time lag in their appearance. That is, individuals will develop neutralizing antibodies to their own viruses with time, however, by the time these antibodies develop, the new viruses circulating in the individual's plasma will become resistant to neutralization, even though the older ones are now sensitive to the current antibodies in the patient's serum. Thus, the antibody response appears to be hitting a 'moving' target, allowing viruses to escape continuously. Further knowledge gained on understanding the mechanisms of humoral escape will likely lead to potential new therapies.

Improved knowledge and understanding of the pathophysiological mechanisms during the course of HIV-1 infection have not only contributed to the development of antiretroviral treatment strategies, but have given rise to new therapeutic approaches, such as cytokine therapies, e.g., IL-2 and therapeutic vaccination. However, the most important challenge and thus, the demand for a better understanding of the immunopathogenesis of HIV-1 infection, remains the development of a protective vaccine, which is urgently needed to interrupt the epidemic especially in countries of the Sub-Sahara and Southeast Asia.

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Part 2

HAART

5. ART 2005

1. Perspective

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. Few other areas have been subject to such fast- and short-lived trends. Those who have experienced the rapid developments of the last few years have been through many ups and downs:

The early years, from 1987-1990, brought great hope and the first modest advances using monotherapy (Volberding 1990, Fischl 1990). But, by the time the results of the Concorde Study had arrived (Hamilton 1992, Concorde 1994), both patients and clinicians had plunged into a depression that was to last for several years. Zidovudine was first tested on humans in 1985, and introduced as a treatment in March 1987 with great expectations. Initially, at least, it did not seem to be very effective. The same was true for the nucleoside analogs zalcitabine, didanosine and stavudine, introduced between 1991 and 1994. The lack of substantial treatment options led to a debate that lasted for several years about which nucleoside analogs should be used, when, and at what dose. One such question was: Should the alarm clock be set to go off during the night for a sixth dose of zidovudine?

Many patients, who were infected during the early and mid-80s, began to die. Hospices were established, as well as more and more support groups and ambulatory nursing services. One became accustomed to AIDS and its resulting death toll. There was, however, definite progress in the field of opportunistic infections (OI) – cotrimoxazole, pentamidine, ganciclovir, foscarnet and fluconazole saved many patients' lives, at least in the short-term. Some clinicians started to dream of a kind of "mega-prophylaxis". But the general picture was still tainted by an overall lack of hope. Many remember the somber, almost depressed mood of the IXth World AIDS Conference in Berlin, in June 1993. Between 1989 and 1994, morbidity and mortality rates were hardly affected.

Then, in September 1995, the preliminary results of the European-Australian DELTA Study (Delta 1995) and the American ACTG 175 Study (Hammer 1996) attracted attention. It became apparent that combination therapy with two nucleoside analogs was more effective than monotherapy. Indeed, the differences made on the clinical endpoints (AIDS, death) were highly significant. Both studies demonstrated that it was potentially of great importance to immediately start treatment with two nucleoside analogs, as opposed to using the drugs "sequentially".

This was by no means the final breakthrough. By this time, the first studies with protease inhibitors (PIs), a completely new drug class, had been ongoing for several months. PIs had been designed in the lab using the knowledge of the molecular structure of HIV and protease – their clinical value was initially uncertain. Preliminary data, and many rumors, were already in circulation. In the fall of 1995, a fierce competition started up between three companies: Abbott, Roche and MSD. The licensing studies for the three PIs, ritonavir, saquinavir and indinavir, were pursued with a great amount of effort, clearly with the goal of bringing the first PI onto the market. The monitors of these studies in the different companies "lived" for weeks

at the participating clinical sites. Deep into the night, case report files had to be perfected and thousands of queries answered. All these efforts led to a fast track approval, between December 1995 and March 1996, for all three PIs – first saquinavir, followed by ritonavir and indinavir – for the treatment of HIV.

Many clinicians (including the author) were not really aware at the time of what was happening during these months. AIDS remained ever present. Patients were still dying, as only a relatively small number were participating in the PI trials – and very few were actually adequately treated by current standards. Doubts remained. Hopes had already been raised too many times in the previous years by alleged miracle cures. Early in January 1996, other topics were more important: palliative medicine, treatment of CMV, MAC and AIDS wasting syndrome, pain management, ambulatory infusion therapies, even euthanasia.

In February 1996, during the 3rd Conference on Retroviruses and Opportunistic Infections (CROI) in Washington, many caught their breath as Bill Cameron reported the first data from the ABT-247 Study during the latebreaker session. The auditorium was absolutely silent. Riveted, listeners heard that the mere addition of ritonavir oral solution decreases the frequency of death and AIDS from 38 % to 22 % (Cameron 1998). These were sensational results in comparison to everything else that had been previously published!

But for many, the combination therapies that became widely used from 1996 onwards, still came too late. Some severely ill patients with AIDS managed to recover during these months, but, even in 1996, many still died. Although the AIDS rate in large centers had been cut in half between 1992 and 1996 (Brodt 1997), in smaller centers roughly every fifth patient died in this year.

However, the potential of the new drugs was slowly becoming apparent, and the World AIDS Conference in Vancouver a few months later, in June 1996, was like a big PI party. Even regular news channels reported in great depth on the new "AIDS cocktails". The strangely unscientific expression "highly active antiretroviral therapy" (HAART) began to spread irreversibly. Clinicians were only too happy to become infected by this enthusiasm.

By this time, David Ho, Time magazine's "Man of the Year" in 1996, had shed light on the hitherto completely misunderstood kinetics of HIV with his breakthrough research (Ho 1995, Perelson 1996). A year earlier, Ho had already initiated the slogan "hit hard and early", and almost all clinicians were now taking him by his word. With the new knowledge of the incredibly high turnover of the virus and the relentless daily destruction of CD4+ T cells, there was no longer any consideration of a "latent phase" – and no life without antiretroviral therapy. In many centers almost every patient was treated with HAART. Within only three years, from 1994-1997, the proportion of untreated patients in Europe decreased from 37 % to barely 9 %, whilst the proportion of HAART patients rose from 2 % to 64 % (Kirk 1998).

Things were looking good. By June 1996, the first non-nucleoside reverse transcriptase inhibitor, nevirapine, was licensed, and a third drug class introduced. Nelfinavir, another PI, had also arrived. Most patients seemed to tolerate the drugs well. 30 pills a day? No problem, if it helps. And how it helped! The number of AIDS cases was drastically reduced. Within only four years, between 1994 and 1998, the incidence of AIDS in Europe was reduced from 30.7 to 2.5 per 100 patient years – i.e. to less than a tenth. The reduction in the incidence of several feared

OIs, particularly CMV and MAC, was even more dramatic. HIV ophthalmologists had to look for new areas of work. The large OI trials, planned only a few months before, faltered due to a lack of patients. Hospices, which had been receiving substantial donations, had to shut down or reorientate themselves. The first patients began to leave the hospices, and went back to work; ambulatory nursing services shut down. AIDS wards were occupied by other patients.

In 1996 and 1997 some patients began to complain of an increasingly fat stomach, but was this not a good sign after the years of wasting and supplementary nutrition? Not only did the PIs contained lactose and gelatin, but the lower viremia was thought to use up far less energy. It was assumed that, because patients were less depressed and generally healthier, they would eat more. At most, it was slightly disturbing that the patients retained thin faces. However, more and more patients also began to complain about the high pill burden.

In June 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs (Ault 1997). In February 1998, the CROI in Chicago finally brought home the realization among clinicians that protease inhibitors were perhaps not as selective as had long been believed. One poster after the next, indeed whole walls of pictures showed fat abdomens, buffalo humps, thin legs and faces. A new term was introduced at the beginning of 1998, which would influence the antiretroviral therapy of the years to come: lipodystrophy. And so the old medical wisdom was shown to hold true even for HAART: all effective drugs have side effects. The actual cause of lipodystrophy remained completely unclear. Then, in early 1999, a new hypothesis emerged from the Netherlands: "mitochondrial toxicity". It has become a ubiquitous term in HIV medicine today.

The dream of eradication (and a cure), still widely hoped for in the beginning, eventually had to be abandoned, too. Mathematical models are evidently not suitable for predicting what will really happen. In 1997, it was still estimated that viral suppression, with a maximum duration of three years, was necessary; after this period, it was predicted that all infected cells would presumably have died. Eradication was the magic word. At every conference since then, the duration of three years has been adjusted upwards. Nature is not so easy to predict, and newer studies came to the sobering conclusion that HIV remains detectable in latent infected cells, even after long-term suppression. To date, nobody knows how long these latent infected cells survive, and whether even a small number of them would be sufficient for the infection to flare up again as soon as treatment is interrupted. Finally, during the Barcelona World AIDS Conference, experts in the field admitted to bleak prospects for eradication. The most recent estimates for eradication of these cells were approximately 50-70 years. One thing is certain: HIV will not be curable for at least the next 10 years.

Instead of eradication, it has become more realistic to consider the lifelong management of HIV infection as a chronic disease in the future, similar to diabetes mellitus. This means, however, that drugs have to be administered over many years, which demands an enormous degree of discipline from patients. Those who are familiar with the management of diabetes understand the challenges that patients and clinicians have to face and how important it will be to develop better combinations in the coming years. Hardly anyone will have the discipline and ability, both mentally and physically, to take the currently available pills several times daily at

fixed times for the next ten, twenty or even thirty years. But, presumably, this will not be necessary. There will be new and improved treatment regimens. Once-daily regimens are coming; maybe even twice-weekly.

At the same time, the knowledge of the risks of antiretroviral therapy has changed the approach of many clinicians towards treatment over the last three years. By the year 2000, many strict recommendations from previous years were already being revised. "Hit HIV hard, but only when necessary" is now heard more than "hit hard and early" (Harrington and Carpenter 2000). The simple question of "when to start?" is now being addressed at long symposia. It is often a question that requires great sensitivity.

Despite all the skepticism, it is important not to forget what HAART can do. HAART can often achieve miracles! Cryptosporidiosis and Kaposi's sarcoma simply disappear; PML may even be cured completely; secondary prophylaxis for CMV can be stopped; and above all: patients feel significantly better, even if some activists and AIDS counselors still do not want to admit this.

This also means, however, that many younger clinicians in Western countries who entered into HIV medicine at the end of the 90s often no longer know what AIDS really means. AIDS for them is an accident, whose damage can be fixed. They did not experience the "stone age" of AIDS.

HIV clinicians are well advised, perhaps more than other clinicians, to remember the "stone age", whilst still keeping an open mind for new approaches. Those, who are strictly opposed to the interruption of treatment, and insistent on particular schemata of treatment, are not only overlooking the realities of treatment, but also losing touch. Those, who do not make an effort to broaden their knowledge several times a year at different conferences, will not be able to provide adequate treatment for their patients in a field that changes direction at least every two to three years. Those, who adhere strictly to evidence-based HIV medicine, and only treat according to guidelines, quickly become outdated. HIV medicine is ever changing. Treatment guidelines remain just guidelines. They are often out of date by the time of publication. There are no laws set in stone. However, those, who confuse therapeutic freedom with random choices and assume that data and results coming from basic research can be ignored, are also missing the point. Individualized treatment is not random treatment. In addition, it cannot be stressed enough, that clinicians are also responsible for the problem of bad compliance. Even if many experienced clinicians have come to disregard this: every patient has the right to know why he is taking which therapy or, indeed, why it has been omitted.

HIV remains a dangerous and cunning opponent. Patients and clinicians must tackle it together. The following describes how this can be done.

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2. Overview of Antiretroviral Agents

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Table 2.1: Antiretroviral agents

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)			
Trade name	Abbrev.	Drug	Manufacturer
Combivir™	CBV	AZT+3TC	GSK
Emtriva™	FTC	Emtricitabine	Gilead
Epivir™	3TC	3TC, lamivudine	GSK
Hivid™	ddC	ddC, zalcitabine	Roche
Kivexa™		3TC+ABC	
Retrovir™	AZT	AZT, zidovudine	GSK
Trizivir™	TZV	AZT+3TC+ABC	GSK
Truvada™		FTC+TDF	Gilead
Videx™	ddI	ddI, didanosine	BMS
Viread™	TDF	Tenofovir	Gilead
Zerit™	d4T	D4T, stavudine	BMS
Ziagen™	ABC	Abacavir	GSK
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)			
Rescriptor™	DLV	Delavirdine	Pfizer
Sustiva™	EFV	Efavirenz	BMS
Viramune™	NVP	Nevirapine	Boehringer Ingelheim
Protease Inhibitors (Pis)			
Agenerase™	APV	Amprenavir	GSK
Crixivan™	IDV	Indinavir	MSD
Fortovase™	SQV-FTV	Saquinavir soft gel	Roche
Invirase™	SQV-INV	Saquinavir hard gel	Roche
Kaletra™	LPV	Lopinavir/ritonavir	Abbott
Lexiva™/Telzir™	FPV	Fosamprenavir	GSK
Norvir™	RTV	Ritonavir	Abbott
Reyataz™	ATV	Atazanavir	BMS
Viracept™	NFV	Nelfinavir	Roche
Fusion inhibitors			
Fuzeon™	T-20	Enfuvirtide	Roche

Four classes of antiretroviral agents are currently available for the treatment of HIV infection: nucleoside and nucleotide analogs (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors with T-20 as the prototype. Over 20 drug products have now been licensed, including formulations of both individual and combined antiretroviral agents. A number of other drugs and new classes of drugs are in the pipeline and expected to be licensed in the next few years. Research is also focusing on immunomodulatory approaches with vaccines or cytokines (interferons, interleukins).

The following overview will deal mainly with individual antiretroviral agents and their specific features and problems. Common combinations are described in the chapter on "Which HAART to start with".

Nucleoside Analogs ("nukes", NRTIs)

Mechanism of action

Nucleoside analogs ("nukes") are also referred to as nucleoside reverse transcriptase inhibitors. Their target is the HIV enzyme reverse transcriptase. Acting as alternative substrates or "false building blocks", they compete with physiological nucleosides, differing from them only by a minor modification in the ribose molecule. The incorporation of nucleoside analogs aborts DNA synthesis, as phosphodiester bridges can no longer be built to stabilize the double strand.

Nucleoside analogs are converted to the active metabolite only after endocytosis, whereby they are phosphorylated to triphosphate derivatives. AZT and d4T are thymidine analogs, while ddC, FTC and 3TC are cytidine analogs. Combinations containing AZT plus d4T, ddC plus 3TC or FTC plus 3TC are therefore pointless, since both drugs would compete for the same bases. ddI is an inosine analog, which is converted to dideoxyadenosine; abacavir is a guanosine analog. There is a high degree of cross-resistance between nucleoside analogs (see also "Resistance" chapter).

Nucleoside analogs are easy to take, and once-daily dosing is sufficient for most of these drugs. Overall tolerability is fairly good. Frequent complaints during the first weeks are fatigue, headache and gastrointestinal problems, which range from mild abdominal discomfort to nausea, vomiting and diarrhea. The gastrointestinal complaints are easily treated symptomatically.

However, nucleoside analogs can cause a wide variety of long-term side effects, including myelotoxicity, lactate acidosis, polyneuropathy and pancreatitis. Although lipodystrophy was initially linked exclusively to treatment with protease inhibitors, many disorders of lipid metabolism (especially lipoatrophy) are now also attributed to nucleoside analogs (Galli 2002). Long-term side effects that are probably related to mitochondrial toxicity were first described in 1999 (Brinkmann 1999). Mitochondrial function requires nucleosides. The metabolism of these important organelles is disrupted by the incorporation of false nucleosides, leading to mitochondrial degeneration. More recent clinical and scientific data indicates that there are probably considerable differences between individual drugs with regard to mitochondrial toxicity: d4T, for example, is more toxic than abacavir. See further details in the chapter "Mitochondrial toxicity".

Nucleoside analogs are eliminated mainly by renal excretion and do not interact with drugs that are metabolized by hepatic enzymes. There is therefore little potential for interaction. However, substances such as ribavirin, which is also activated by intracellular phosphorylation, may interact with nucleoside analogs of AZT, d4T and ddI (Piscitelli 2001).

Individual agents: Special features and problems

Abacavir (Ziagen™) is a guanosine analog with good CNS penetration. Earlier studies have shown that this drug can lower viral load by approximately 1.4 logs within 4 weeks, but that resistance develops relatively rapidly (Harrigan 2000).

Abacavir is phosphorylated intracellularly to carbovir triphosphate, which has a long half-life (Harris 2002). In October 2004, abacavir was licensed for once-daily therapy (Gazzard 2003, Clumeck 2004).

Abacavir is also a component of Trizivir™, together with AZT+3TC, and numerous studies have therefore tested abacavir in this combination (see Triple Nuke). In the 5095 Study, the combination proved virologically less effective than efavirenz plus AZT+3TC (Gulick 2004). The randomized, double blind CNA3005 Study had also shown lower efficacy in comparison to indinavir, particularly with higher viral load (Staszewski 2001). However, abacavir was more effective than indinavir in the randomized, open label CNA3014 Study, due to better compliance (Vibhagool 2004). In another study, efficacy was comparable to nelfinavir (Matheron 2003). Abacavir, in addition to 3TC, is also a component of Kivexa™. The nucleoside backbone of abacavir+3TC is about as effective as AZT+3TC (DeJesus 2004) and d4T+3TC (Podzamczer 2004), although it causes less lipodystrophy than the latter.

Several studies, such as CNA3002 and CNA3009, have shown that abacavir can also be used to intensify a regimen that is failing virologically if it is added early enough, before the viral load is too high (Katlama 2000, Rozenbaum 2001). Abacavir is frequently used to replace a PI or NNRTI in order to simplify HAART. Several studies such as TRIZAL, NEFA, CNA30017 and SimplifyHAART have demonstrated that patients on a successful PI- or NNRTI-containing HAART regimen can switch relatively safely to abacavir plus two other nucleoside analogs (Katlama 2003, Montaner 2000, Martinez 2003, Bonjoch 2004). However, there is a certain degree of risk associated with this strategy, particularly in extensively pre-treated patients who may then experience virological failure (Opravil 2002, Martinez 2003).

With respect to mitochondrial toxicity, abacavir seems to compare favorably to d4T. However, switching from d4T to abacavir led to moderate changes at best and sometimes only subclinical effects in cases with existing lipodystrophy (Carr 2002, Thompson 2003, John 2003). Most in vitro data confirms that improvement of lipoatrophy is associated with an increase in mitochondrial DNA (Hoy 2004, Martin 2004, McComsey 2004+2005).

One drawback to the use of abacavir is the risk of a hypersensitivity reaction (HSR). HSR occurs in approximately 4-6 % of patients, almost always (93 %) within the first six weeks of treatment. Every treating physician should be familiar with this syndrome. In acutely infected HIV patients, the risk seems significantly higher (up to 18 %), and abacavir should be avoided in these cases (Stekler 2004). HSR can be fatal after rechallenge in individual cases. Cases of severe HSR have been reported after only a single abacavir tablet (De la Rosa 2004) or even after treatment interruption despite prior tolerability (El-Sahly 2004). The combination of strongly worded warnings contained in the package insert and the often unspecific symptoms of the HSR poses a constant challenge to the treating physician. Several reports have now suggested that patients with HLA type B5701 may be genetically predisposed and therefore at a higher risk than others (Mallal 2002, Hetherington 2002).

AZT – Zidovudine (Retrovir™) was the first antiretroviral agent to be put on the market, in 1987. Even very early studies still testing AZT monotherapy were able to

show a significant survival benefit – at least in significantly immunocompromised patients (Fischl 1987). In contrast, two other early, very large studies, ACTG 016 and ACTG 019, were not able to demonstrate significant survival benefit (in asymptomatic patients), although the risk for progression was significantly reduced in both (Fischl 1990b, Volberding 1990). Even at that time, it started to become apparent that success of AZT monotherapy was likely to be limited. The Concorde Study actually brought a certain degree of disrepute for AZT. It showed that there was no long-term benefit of AZT treatment. In addition, the higher doses that were given in these first few years led to considerable myelotoxicity (Fischl 1990a).

Even with the standard doses given today, monitoring of blood count is obligatory. Long-term treatment almost always increases MCV, and there is also a limited use for monitoring adherence to AZT. Initial gastrointestinal complaints may present a short-term problem. AZT-related myopathy or even cardiomyopathy are quite rare. AZT seems to have a more favorable profile with regard to long-term toxicity. Lack of neurotoxicity and good CNS penetration are important advantages of this drug, which has remained the cornerstone of many HAART regimens and transmission prophylaxis.

AZT is also a component of both Combivir™ and Trizivir™, at a slightly higher dose (300 mg instead of 250 mg). This may occasionally lead to higher myelotoxicity and therefore anemia. It is also of note that the patent of AZT is expiring in 2005, and the drug price is subsequently expected to drop at least by half. GSK, the manufacturer, is now conducting studies almost exclusively with the abacavir+3TC combination.

ddC - Zalcitabine (Hivid™) was the third nucleoside analog to reach the market in 1992. Studies such as Delta-1, ACTG 175 and CPCRA007 showed a significant survival benefit of the AZT+ddC combination compared to AZT monotherapy in treatment-naive patients (Hammer 1996, Delta 1996, Saravolatz 1996). In AZT-pretreated patients, however, addition of ddC showed hardly any benefit (Fischl 1995, Delta 1996, Saravolatz 1996). AZT+ddI is more effective than AZT+ddC (HCTG 1999). The drug has become marginalized in the last years due to cross-resistance with ddI and 3TC (Craig 1997), problems with peripheral neuropathy, painful stomatitis, the three times daily dosing requirement, and lack of data in the HAART era. For these reasons, ddC is by far the least used nucleoside analog at the present time. Although twice daily dosing does seem possible (Moyle 1998), there is now no rationale for the use of ddC. It therefore seems likely that this drug will disappear from antiretroviral therapy altogether.

ddI – Didanosine (Videx™) is a nucleoside analog with proven efficacy in numerous randomized studies. The introduction of acid-resistant tablets in 2000, replacing the chewable tablets used for many years, has done much to improve tolerability. ddI remains a component of many HAART regimens. Randomized studies such as Delta 1, ACTG 175 and CPCRA007 showed significant improvement in survival rates of treatment-naive patients with AZT+ddI compared to AZT monotherapy. As with ddC, this effect was less marked in AZT-pretreated patients. Therefore, the addition of ddI in Delta 2 led to significant survival benefit, although this was not the case in CPCRA007 (Saravolatz 1996). In ACTG 175, monotherapy with ddI

was more potent than AZT, even with regard to disease progression (Hammer 1996). However, this advantage for ddI could not be shown in other studies (Dolin 1995, Floridia 1997). Following failure with AZT, ddI is probably more effective than d4T (Havlir 2000).

Gastrointestinal complaints and polyneuropathy are the main side effects. Pancreatitis is a specific side effect occurring in up to 10 % of cases, and can be fatal in individual cases. This toxicity is probably dose-dependent (Jablonowski 1995). The cause for this is unclear, but could possibly be related to ddI-specific disorders of purine metabolism (Moyle 2004). Special caution should be given to combinations with d4T, hydroxyurea or tenofovir (Havlir 2001, Martinez 2004). Patients with a history of pancreatitis or even chronic pancreatitis should not be treated with ddI. In patients weighing less than 60 kg, the dose should be reduced from 400 mg to 300 mg, and a dose reduction to 250 mg is necessary when administered in combination with tenofovir (Kearney 2003). However, combination with tenofovir seems to be unfavorable for various reasons (see below).

One advantage of using ddI is simple once-daily dosing, which is possible due to the long intracellular half-life; it is counterbalanced by the need to take the drug under fasting conditions. In addition, most other nucleoside analogs are now also licensed for once-daily dosing.

d4T – Stavudine (Zerit™) was the second thymidine analog to be introduced after AZT. It is often initially better tolerated than AZT, producing less gastrointestinal side effects and limited myelotoxicity. It is definitely just as effective (Spruance 1997, Squires 2000) and used to be one of the most frequently prescribed antiretroviral agents of all. However, several randomized studies have recently discredited the drug. In the Gilead 903 Study, d4T was tested in a double blind design against tenofovir (both combined with 3TC+efavirenz) in treatment-naive patients. Both drugs showed comparable virological efficacy, but tenofovir was tolerated significantly better than d4T, particularly with respect to mitochondrial toxicity and lipid changes (Gallant 2004). In fact, the FTC-301 Study, in which d4T was again tested in a randomized, double blind design against FTC (both combined with ddI+efavirenz) had to be prematurely terminated, because d4T was not only more toxic, but also showed significantly lower virological efficacy (Saag 2004).

It is now beyond a doubt that lipoatrophy occurs more frequently with d4T than with other nucleoside analogs. The data is depressing: not only laboratory studies (Thompson 2003, Van der Valk 2003, Martin 2004, McComsey 2004), but also clinical observations confirm the mitochondrial toxicity of d4T. A small prospective study showed that d4T was the most important factor contributing to loss of fat tissue on arms and legs (Mallon 2003). In a German cohort, the risk of lipoatrophy on d4T doubled in one year (Mauss 2002); in a Swiss cohort it tripled in two years (Bernasconi 2002). Other data, with one exception (Bogner 2001), points in the same direction (Mallal 2000, Chene 2002, Saves 2002). Numerous studies have now been published in which substitution of d4T with other nucleoside analogs, particularly abacavir or tenofovir, had positive effects on lipoatrophy and other metabolic disorders (Carr 2003, John 2003, Moyle 2003, Martin 2004, McComsey 2004, Suleiman 2004). However, the effect on increases in subcutaneous fat tissue was usually not detectable clinically, only on dexa scan. Thus, it may take years for

lipoatrophy to visibly improve following discontinuation of d4T. Therefore, based on current data, there is only one option for patients with lipoatrophy: d4T should be replaced ideally with abacavir or tenofovir, if the resistance profile permits. There is, however, no assurance for resolution of lipoatrophy, and, above all, great patience is required.

Mitochondrial toxicity of d4T also causes problems beyond lipodystrophy. It is a risk factor for lactic acidosis, hyperlactacidemia and Guillain-Barré-like syndromes, particularly in combination with ddI or 3TC, (Gerard 2000, John 2001, Miller 2000, Mokrzycki 2000, Marcus 2002, Shah 2003). Whether these problems will be lessened by the introduction of the new d4T PRC capsules (see New Drugs) is questionable.

FTC- Emtricitabine (Emtriva™) is a new cytidine analog, which was originally developed under the name Coviracil. It is biochemically very similar to 3TC, but has a longer half-life. Once-daily dosing with 200 mg is possible, and the drug also has HBV efficacy. Tolerability is good, although hyperpigmentation occurred in one study. FTC is more effective than 3TC in vitro (Van der Horst 2001), which was recently demonstrated in a small in vivo study (Rousseau 2003). However, as with 3TC, efficacy is limited by the M184V point mutation. Subsequent to data from the FTC-301 Study (Saag 2004), which was prematurely discontinued, the drug was swiftly licensed in 2003. This randomized, double blind trial showed that FTC was clearly more effective and tolerable than d4T (both in combination wit ddI and efavirenz). The combination of tenofovir+FTC was superior to AZT+3TC in the 24-week analysis of another study, as there was better tolerability (Gazzard 2004). AZT+FTC are as effective as AZT+3TC (Benson 2004). FTC seems to have a low affinity for the mitochondrial polymerase, so the risk of mitochondrial toxicity is likely to be relatively low. The ALIZE study has since confirmed the good long-term tolerability and efficacy of a once-daily combination of FTC+ddI+efavirenz (Molina 2003). FTC is already an important HAART component, particularly of once-daily regimens. In 2005, a fixed-dose combination of FTC and tenofovir (Truvada™) was licensed in Europe.

3TC – Lamivudine (Epivir™) is a well tolerated nucleoside analog. Its main disadvantage is rapid development of resistance, and a single point mutation (M184V) is sufficient for loss of effectiveness. As a result, 3TC is weaker than other nucleoside analogs for monotherapy, since resistance is likely to develop after only a few weeks (Eron 1995). The full effect of 3TC only emerges in combination with other nucleoside analogs. Indeed, several large studies such as NUCB 3002 or CAESAR showed significant impact on disease progression and survival when 3TC was added to nucleoside therapy (Staszewski 1997). As a component of Combivir™ and Trizivir™, 3TC is the most frequently used antiretroviral drug. The M184V point mutation even has advantages: not only does it improve the susceptibility of certain AZT-resistant viruses in some patients (Boucher 1993), but it also impairs viral fitness (Miller 2002). Keeping 3TC as part of a combination despite proven resistance is therefore sensible to conserve the M184V mutation and thus reduce the replicative capacity of HIV. This has now been demonstrated in a study of monotherapy in treatment-experienced patients with the M184V mutation: maintaining

3TC monotherapy was associated with a lower increase in viral load and fall in CD4 cell levels than completely stopping HAART (Castagna 2004, see "Salvage" chapter).

In the Atlantic Study, 3TC in combination with d4T+ddI proved significantly weaker virologically than indinavir or nevirapine (Van Leeuwen 2003). Combination with abacavir and tenofovir is also not good, as recently published data from the ESS30009 Study has shown (Gallant 2003, see also the section "Triple Nuke").

Once-daily dosing is now possible and has been licensed (Sension 2002, DeJesus 2004). 3TC is therefore likely to continue to play an important role in many once-daily combinations. A pleasant effect of 3TC is also its good efficacy against hepatitis B viruses, although this is again limited by the relatively rapid development of resistance (Dienstag 1999, Dore 1999).

Tenofovir (Viread™) acts as a false building block similar to nucleoside analogs, targeting the enzyme reverse transcriptase. However, in addition to the pentose and nucleic base, it is monophosphorylated and therefore referred to as a nucleotide analog. The accurate description of the substance is tenofovir DF (disoproxil fumarate), referring to the phosphonate form from which the phosphonate component is only removed by a serum esterase, and which is activated intracellularly in two phosphorylation steps (Robbins 1998).

In the 902 and 907 studies, in which tenofovir was added to existing HAART, tenofovir decreased viral load by approximately 0.62 logs after 48 weeks (Schooley 2002, Squires 2003). Side effects in these studies were comparable to the placebo arms. The 903 Study was a double blind study in which treatment-naive patients were given tenofovir or d4T (with a backbone regimen of 3TC+efavirenz). Results showed at least equivalent potency (Gallant 2004). However, tolerability was better in the tenofovir group, especially with regard to polyneuropathy and lipid changes. This is consistent with in vitro data, showing that phosphorylated tenofovir has a low affinity for mitochondrial polymerases (Suo 1998). As a result of this convincing clinical data and its licensing in 2001, the drug is now very widely used in antiretroviral therapies.

This extensive use has revealed a few problems. There seem to be significant interactions: tenofovir reduces the breakdown of ddI via inhibition of the purine nucleotide phosphorylase. Therefore, dose reduction of ddI to 250 mg is absolutely necessary (Kearney 2002). More recent data on efficacy (Clotet 2004, Negredo 2004, Podzamczer 2004, Moyle 2004) shows that combination with ddI should be avoided. Several cases of pancreatitis have occurred despite the reduced dosage of ddI, so caution is really required (Blanchard 2003, Martinez 2004). A case of fatal lactic acidosis has also been published, which developed when tenofovir was added to a d4T+ddI combination (Rivas 2003). In contrast, atazanavir levels drop when it is combined with tenofovir, so this PI should be boosted with ritonavir (Taburet 2003). Several cases of renal failure on tenofovir have also been reported, partly in the context of a Fanconi syndrome, a defect of proximal tubular transport (Karras 2003, Schaaf 2003, Peyriere 2004). Patients with renal disease should either not be treated with tenofovir at all, or at least receive a lower dose. In addition, newer data reports poor results with triple nuke therapy (see also "Triple Nuke" chapter), for which tenofovir currently does not seem to be a good candidate. If virological

treatment failure occurs, the K65R mutation, a problematic nucleoside analog resistance mutation, frequently appears.

The choice of nuke backbones

Until now, all classical HAART regimens have contained two nucleoside analogs as the "backbone" of treatment. This has mainly historical reasons: nucleoside analogs were the first available drugs for HIV therapy, and when protease inhibitors appeared on the scene, treatment with two nucleoside analogs was standard. As knowledge has grown about the mitochondrial toxicity of nucleoside analogs, this concept is now being questioned by an increasing number of experts. However, data on combinations without nucleoside analogs (see "Nuke Sparing") is still relatively sparse, so that there are currently no recommendations for such strategies. In comparison, nucleoside analogs and their combinations have been well investigated – countless studies over the years, especially before the introduction of PIs and NNRTIs, concentrated on figuring out the optimal combination of two nucleoside analogs.

AZT+3TC

In many international guidelines, AZT+3TC is still regarded as the standard backbone for first-line therapy. There is more experience with this combination than with any other. The resistance profile is favorable: the M184V mutation that frequently develops during 3TC treatment probably increases sensitivity to AZT. To start with, AZT+3TC are usually given as Combivir™. Although the licensing study for Combivir™ showed no differences in toxicity (Eron 2000), in our experience the 300 mg AZT dose in Combivir™ is too high for some patients and leads to anemia. In such cases, it is worth trying AZT+3TC as individual formulations, and thereby lowering the AZT dose to 250 mg.

AZT+3TC has comparable efficacy to the other frequently used combinations d4T+ddI and d4T+3TC, or AZT+FTC (Foudraine 1998, Carr 2000, Eron 2000, French 2002, Gathe 2002, Squires 2000, Benson 2004). The ACTG 384 Study even showed superiority for AZT+3TC over d4T+ddI (Robbins 2003, Shafer 2003), and several other studies also found lower toxicity, particularly in relation to lipoatrophy (Molina 1999, Chene 2002). However, AZT+3TC will soon lose ground for two main reasons: firstly – bid dosing is required, disqualifying AZT+3TC from once-daily regimens; secondly – mitochondrial toxicity is likely even on AZT+3TC. In the ACTG 384 Study, the development of lipoatrophy occurred only slightly later than with d4T+ddI (Robbins 2003, Shafer 2003).

Modern nuke backbones without AZT or d4T

The typical nuke backbone up until now contained one thymidine analog, i.e. AZT or d4T. The toxicity of both drugs, as well as the problematic resistance patterns with the failure of such a therapy (see "Resistance" chapter) have led to increased questioning of this concept. There are now several effective therapies that have completely excluded thymidine analogs. Large studies have shown that several of these are equivalent to AZT+3TC. This is true for TDF+3TC, TDF+FTC and, to a lesser extent, for ABC+3TC. These combinations also have the advantage that they can be included in once-daily regimens. Daily doses of TDF+FTC and ABC+3TC will each be available in a single tablet from 2005.

TDF+3TC/FTC

In the Gilead 934 Study, using 509 treatment-naive patients, the TDF+FTC (Truvada™) combination was tested against AZT+3TC (Combivir™) in an open design, with all patients also receiving efavirenz. At 24 weeks, a larger proportion of patients in the TDF+FTC arm reached less than 50 copies/ml (73 % versus 65 % in the ITT analysis, p=0.04). This was even true for patients with a higher baseline viral load. The differences in the ITT analysis were primarily related to the poorer tolerability of Combivir™. The rate of treatment discontinuation was 21 % for Combivir™, compared to 10 % in the TDF+FTC arm. Virological failure and resistance mutations were approximately equal in both arms and infrequent. It will be interesting to see if these differences are maintained even after 48 weeks.

In combination with PIs, there is good data available for TDF+FTC with once or twice daily lopinavir/r (Molina 2004). In the Gilead 903 Study, the combination of TDF+3TC was not only as virologically effective as d4T+3TC, but also significantly more tolerable (Gallant 2004). The data available from this study so far shows that these differences remained beyond 144 weeks.

Abacavir+3TC

Another alternative to AZT+3TC is ABC+3TC, which will be licensed in 2005 as Kivexa™, a fixed-dose once-daily combination tablet. The double blind, randomized CNA30024 Study showed comparable efficacy for AZT+3TC and ABC+3TC, both combined with efavirenz (DeJesus 2004). ABC+3TC even led to a significantly higher rise in CD4 T cells, although there was also a higher rate of allergies at 9 % versus 3 % (DeJesus 2004). Studies such as CLASS or ZODIAC also demonstrated good potency for ABC+3TC and efavirenz (Bartlett 2002, Gazzard 2003). In the ABCDE Study, ABC+3TC had the same efficacy as d4T+3TC (Podzamczer 2004), but were also less toxic. It is important to note that ABC+3TC have significantly shorter half-lives than TDF+FTC. This could mean that ABC+3TC is less forgiving if tablets are taken irregularly, and resistance may be more likely to occur. On the other hand, an advantage to TDF+FTC could be that L74V, usually occurring alongside the M184V mutation, is associated with less cross-resistance than the tenofovir-associated K65R mutation.

There is one clear disadvantage in combination with NNRTIs: the higher risk of occurrence of allergies under both abacavir and NNRTIs makes it difficult to distinguish between an NNRTI rash and the abacavir HSR. We therefore do not recommend using these at the same time, as treatment options may be unnecessarily eliminated.

It should be noted that the studies cited here were primarily investigating first-line therapy. In treatment-experienced patients, numerous other individually tailored backbones may become necessary as a result of resistance and intolerability. However, the combinations discussed below should be avoided if possible.

Poor and non-recommended backbones

Newer guidelines from England and Germany explicitly recommend avoiding the previously popular d4T+ddI combination. Mitochondrial toxicity is too high, and it performed more poorly than AZT+3TC in the ACTG 384 Study (Robbins 2003). In cases of treatment failure, thymidine analog mutations (TAMs) are usually present,

which can limit future treatment options. In view of the wide selection of nucleoside analogs available today, ddI+d4T is no longer justified for first-line therapy.

d4T+3TC is another combination recommended only in certain situations for first-line therapy. Although it is very well tolerated initially, d4T leads to problems with long-term toxicity. We would still use this combination today in cases of AZT-induced myelotoxicity or if tenofovir is contraindicated due to renal problems. Studies such as ABCDE or 903 have shown that d4T+3TC clearly causes more lipoatrophy than ABC+3TC or TDF+3TC in the long run (Podzamczer 2004, Gallant 2004). d4T should therefore be replaced as soon as possible.

AZT+ddI is not very favorable as it can have more gastrointestinal side effects. In addition, ddI has to be taken on an empty stomach, while AZT is tolerated better when taken with a meal.

In general, all ddC-containing combinations should be avoided (HTCT 1999, Bartlett 1996). The combinations AZT+d4T and FTC+3TC should not be used, as each have antagonistic effects. The combination of TDF+ddI should be given with caution, as at least two studies have shown lower efficacy in significantly immuno-compromised patients and in patients with high viral load (Podzamczer 2004, Moyle 2004), in addition to poor immunological effects (Clotet 2004, Negredo 2004). TDF+ABC are likely to be problematic due to rapid development of resistance. Even alternating backbones, i.e. changing regularly from one backbone to another, can currently not be recommended, although initial studies are indicating that this strategy is at least not harmful (Molina 1999, Martinez-Picado 2003).

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Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Mechanism of action and efficacy

As with the nucleoside analogs, the target enzyme of NNRTIs is reverse transcriptase. NNRTIs were first described in 1990. In contrast to the NRTIs, they are not "false" building blocks, but rather bind directly and non-competitively to the enzyme, at a position in close proximity to the substrate binding site for nucleosides. The resulting complex blocks the catalyst-activated binding site of the reverse transcriptase, which can thus bind fewer nucleosides, slowing polymerization down significantly. In contrast to NRTIs, NNRTIs do not require activation within the cell.

The three currently available NNRTIs – nevirapine, delavirdine and efavirenz – were introduced between 1996 and 1998. Although studies such as the INCAS Trial or Protocol 0021II had already clearly demonstrated the superiority of triple therapy with nevirapine or delavirdine compared to double nuke therapy (Gallant 1998, Raboud 1999, Conway 2000), the "rise" of the NNRTIs was rather hesitant, and did not receive the media attention given to the PIs.

This was due to the early observation that functional monotherapy with NNRTIs, i.e. the mere addition of an NNRTI to a failing regimen, showed practically no effect (Mayers 1998, D'Aquila 1996). There were also initial difficulties in dealing

with the problematic resistance profile of NNRTIs. The risk of cross-resistance is very high, and it can develop very rapidly; one point mutation at position 103 (K103N) of the hydrophobic binding site is enough to eliminate the entire drug class! Resistance has now even been described in mothers taking a single dose of nevirapine at birth for maternal transmission prophylaxis (Eshleman 2002). This phenomenon is not rare. In two large studies, the frequency of NNRTI mutations following perinatal nevirapine prophylaxis was between 14 and 32 % (Cunningham 2002, Jourdain 2004). Real time PCR has recently been shown to detect mutations in 89 % of samples.

It is therefore important to always remember that NNRTI-containing regimens are very vulnerable – waiting too long to switch with insufficient suppression of viral load is almost certain to lead to complete resistance to this class of drugs. Subsequent withdrawal of the NNRTI does not induce any immunological or virological changes (Picketty 2004). This is because NNRTI mutations do not reduce the replicative capacity of HIV to the extent seen with PI or NRTI mutations.

Both randomized and large cohort studies have now demonstrated that NNRTIs are extremely effective in combination with nucleoside analogs. The immunological and virological potency of NNRTIs in treatment-naive patients is at least equivalent, if not superior, to that of PIs (Staszewski 1999, Friedl 2001, Torre 2001, Podzamczer 2002, Robbins 2003, Squires 2003). In contrast to PIs, however, the clinical effect has not yet been proven, as the studies that led to the licensing of NNRTIs all used surrogate markers. The efficacy of NNRTIs in treatment-experienced patients is probably weaker in comparison to PIs (Yazdanpanah 2004).

Nevertheless, the simple dosing and the overall good tolerability have enabled nevirapine and efavirenz to become important components of HAART regimens, which are often even ranked above those containing PIs. Many randomized studies have been able to demonstrate over the last years that it is possible to switch from a PI to a NNRTI if good virological suppression has already been achieved. Virological control was sometimes even better on NNRTIs than on the continued PI regimen; see also the chapter "When to change".

While delavirdine has lost relevance for several reasons (see below), nevirapine and efavirenz can be considered equivalent. So far, no study has provided definitive evidence that one NNRTI is more potent than another. Cohort studies from the last few years suggest a slight superiority of efavirenz (Phillips 2001, Cozzi-Lepri 2002); however these studies have only limited value as they included very heterogeneous patient groups. Overall, differences are likely to be small, particularly in treatment-naive patients. A randomized pilot study from Spain (SENC Study) at least showed no significant differences between nevirapine and efavirenz in this group of patients (Nunez 2002).

In the 2NN Study ("The Double Non-Nucleoside Study"), both NNRTIs were compared for the first time in a large-scale randomized study (Van Leth 2004). A total of 1216 patients received a nuke backbone of d4T+3TC with either nevirapine 1 x 400 mg, nevirapine 2 x 200 mg, efavirenz 1 x 600 mg or efavirenz 1 x 800 mg plus nevirapine 1 x 400 mg. The proportion of patients with a viral load below 50 copies/ml after 48 weeks was 56 %, 56 %, 62 % and 47 %, respectively. The only significant virological difference was an advantage of the efavirenz arm over the double NNRTI arm, mainly due to higher toxicity in the latter. In the nevirapine

arm with 1 x 400 mg, severe hepatic side effects occurred more frequently than in the efavirenz arm; on the other hand, lipids were more favorably influenced in the nevirapine group. The 2NN Study and numerous other switch studies (Fisac 2002, Martinez 2003) demonstrate that the choice of treatment regimen should be based mainly on the different side effect profiles of nevirapine and efavirenz (see below).

Nevirapine and efavirenz are both metabolized by cytochrome P450 enzymes (Miller 1997). Nevirapine is an inductor, whereas efavirenz is both an inductor and an inhibitor of the cytochrome P450 isoenzyme. The combination of efavirenz with saquinavir or lopinavir leads to strong interactions that require dose adjustments of the PI.

Individual agents: Special features and problems

Nevirapine (Viramune™) was the first licensed NNRTI. Nevirapine with AZT+ddI is probably the oldest HAART combination of all. It has been investigated since 1993, starting with the ACTG 193A Study, and proved superior to monotherapy and dual therapy in severely immunocompromised patients. This was true for both survival and progression – although the difference in survival was not significant (Henry 1998). The AZT+ddI+nevirapine combination has been well investigated since the INCAS and ACTG 241 Studies (Raboud 1999, D'Aquila 1996). INCAS demonstrated a suppression of the viral load to below 20 copies/ml after one year with AZT+ddI+nevirapine in 51 % of patients – compared to 12 % of those on AZT+ddI and 0 % on AZT+nevirapine. Clinical progression rates were at 12 %, compared to 25 % and 23 %, which was not a significant difference due to the small sample size (p=0.08). In pretreated patients in ACTG 241 (AZT+ddI plus nevirapine or placebo), however, no trend could be shown in favor of this combination.

Nevirapine has also been tested against protease inhibitors in randomized studies. In the Atlantic Study, combination with d4T+ddI was comparable to combination with indinavir (van Leeuwen 2003). Given with AZT+3TC in the Combine Study, there was at least a trend towards higher virological efficacy in comparison to nelfinavir (Podzamczer 2002).

Nevirapine causes elevation of liver enzymes in up to 16 % of patients, which may be severe in rare cases. Lead-in dosing is always required. A recently published study showing that lead-in dosing is not required if efavirenz was previously administered (Winston 2004) still requires confirmation. During the first eight weeks on nevirapine, biweekly monitoring of transaminases is recommended. A rash develops in 15-20 % of cases and leads to discontinuation in up to 7 % of patients (Miller 1997). In the case of an isolated rash or isolated elevation of transaminases (up to five times the upper limit of normal), treatment may usually be continued. Prophylactic administration of antihistamines or steroids does not prevent the rash (GESIDA26/02 2004, Launay 2004). However, it is recommended to stop treatment if a rash occurs together with even slight elevation of transaminases (>2-fold of norm). Patients with chronic hepatitis are at a higher risk (Sulkowski 2000); in addition, there seems to be a correlation to drug plasma levels (Gonzalez 2002). However, other studies have not been able to confirm this (Almond 2004, Dailly 2004). An increased risk has also been reported for patients with good immune status. Women with CD4 cell counts above 250/µl have a 12-fold elevated risk (11 % ver-

sus 0.9 %); the US FDA even issued a warning relating to this in 2004. It is important to note that hepatic toxicity may occur even after several months (Sulkowski 2002). Permanent and significant γ−GT elevations are very common, which may subject patients to false suspicions of excess alcohol consumption.

Nevirapine has a good lipid profile. In studies such as Atlantic or 2NN, patients receiving nevirapine had favorable lipid changes for cholesterol and triglycerides, increasing HDL (Van der Valk 2001, Van Leth 2004). The Spanish Nefa Study demonstrated this too, as well with efavirenz, albeit to a lesser extent (Fisac 2002). Whether these positive effects will have clinical relevance over time and really help to prevent cardiovascular events remains to be seen.

The pharmacokinetics of nevirapine seem to allow once-daily dosing (Van Heeswijk 2000). Various studies such as 2NN, SCAN, VIRGO or Atlantic have already successfully used 400 mg once daily (Garcia 2000, Raffi 2000, van Leeuwen 2003, Van Leth 2004).

Efavirenz (Sustiva™, Stocrin™**)** was the third NNRTI to be approved, and the first for which it could be shown that NNRTIs were at least as effective and probably even better than PIs in untreated or only slightly treatment-experienced patients. In particular, the 006 Study is now seen as a milestone in HIV therapy – it demonstrated that efavirenz was superior to indinavir in combination with AZT+3TC (Staszewski 1999). Since then, efavirenz has been compared to other drugs in many large randomized studies. Efavirenz usually did well – in the CLASS Study, efavirenz in combination with ABC+3TC was significantly more effective than d4T or boosted amprenavir (Bartlett 2002). In ACTG 5095, efavirenz in combination with AZT+3TC was better than abacavir (Gulick 2004); in ACTG 384 it was better than nelfinavir (Robbins 2003, Shafter 2003); and in AI424-034 it was at least as effective as atazanavir (Squires 2004).

Efavirenz may cause mild CNS side effects and should therefore be taken in the evening. Patients should be warned about these possible side effects, which usually include dizziness and somnolence. Nightmares also occur frequently. In addition, patients should be warned about potentially hazardous tasks such as driving or operating machinery. The side effects probably correlate with high plasma levels (Marzolini 2001). Newer studies show that efavirenz disrupts the architecture of sleep (Gallego 2004). In one study, after four weeks of treatment with efavirenz, 66 % of patients complained of dizziness, 48 % of abnormal dreams, 37 % of somnolence and 35 % of insomnia (Fumaz 2002). Although these symptoms seem to resolve during the course of further treatment, they may persist in about one fifth of patients (Lochet 2003). In such cases, efavirenz should be replaced if possible.

Liver problems occur less frequently than with nevirapine, and lead-in dosing is not necessary. Once-daily dosing is safe due to the long half-life. However, lipids are by far not as favorably affected as with nevirapine. Gynecomastia is also typical for efavirenz, which is not only a psychological burden, but may be painful (Rahim 2004). In such cases, efavirenz should be replaced with nevirapine if possible. Efavirenz is contraindicated in pregnancy.

Table 2.2. Frequencies of the most important side effects of nevirapine and efavirenz (numbers are based on various studies referenced in this chapter)

	Nevirapine	Efavirenz
CNS side effects	Rare	58-66 %
Severe CNS side effects	Very rare	5-7 %
Hepatotoxicity	17 %	8 %
Dyslipidemia	No	Frequent
Gynecomastia	No	Rare
Rash	15 %	5 %

Delavirdine (Rescriptor™) was the second NNRTI that was licensed by the FDA in April 1997. Due to a high pill burden and the required three times daily dosing, delavirdine is currently rarely prescribed. The need for prescription should be carefully considered. In 1999, an application for licensure in Europe was rejected due to insufficient efficacy data. Nevertheless, delavirdine is likely to be as virologically effective as the other NNRTIs (Wood 1999, Conway 2000). In the DLV 21 Study, using 369 mostly treatment-naive patients, delavirdine was investigated together with AZT+3TC and compared with AZT+3TC and AZT+delavirdine. After one year, 68 % had a viral load below 50 copies/ml in the triple combination arm compared to less than 10 % in the other two arms (Para 1999). Rashes are probably even more frequent than with the other two NNRTIs. In DLV 21, the rate was 30 %, which was also confirmed in other studies (Sagest 1998). Delavirdine increases plasma levels of various PIs, including ritonavir, nelfinavir and saquinavir (Fletcher 2000, Harris 2002). However, use of this characteristic as a boosting strategy has not yet been widely accepted.

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Protease Inhibitors (PIs)

Mechanism of action and efficacy

The HIV protease cuts the viral gag-pol polyprotein into its functional subunits. Inhibition of the protease, preventing proteolytic splicing and maturation, leads to the release of virus particles that are unable to infect new cells. With knowledge of the molecular structure of the protease encoded by the virus, the first protease inhibitors were designed in the early nineties; these substances were modified in such a way that they fit exactly into the enzyme active site of the HIV protease (reviews: Deeks 1997, Sommadossi 1999, Eron 2001).

Since 1995, protease inhibitors have revolutionized the treatment of HIV infection. At least three large studies with clinical endpoints proved the efficacy of indinavir, ritonavir and saquinavir (Hammer 1997, Cameron 1998, Stellbrink 2000). Although PIs have been criticized in recent years due to their high pill burden and side effects (see below), they remain an essential component of HAART, especially for treatment-experienced patients. With growing knowledge of the mitochondrial toxicity of nucleoside analogs and the introduction of easy-to-take PIs, this class of drugs is currently experiencing something of a renaissance – now even PI-only regimens are being investigated.

As with the NNRTIs, there has been competition among pharmaceutical companies to establish which PI has superior efficacy. However, there have been few comparative randomized studies, which is not just the fault of the pharmaceutical industry, but also the result of restrictive regulations in many countries preventing the conduct of such studies, or at least making them very difficult.

But even in the case of PIs, the differences are not so significant as to completely compromise individual members of this class. Two exceptions have to be mentioned: the hard gel capsule saquinavir-HGC and ritonavir on its own. Boosted PI regimens are presumably more effective (see below for more details).

Apart from gastrointestinal side effects and high pill burden, all PIs used in long-term therapy can be implicated in lipodystrophy and dyslipidemia (review in Nolan 2003). Smaller randomized studies have shown that elevation of lipid levels is more pronounced in ritonavir-containing regimens (full, not booster dose) than with saquinavir or nelfinavir (Roge 2001, Wensing 2001). In addition, there may be significant drug interactions on ritonavir and with boosted regimens. Sexual dysfunction has also been attributed to PIs (Schrooten 2001), although data is inconclusive (Lallemand 2002).

There is a high degree of cross-resistance between protease inhibitors, which was described even before PIs were put on the market (Condra 1995). All PIs are in-

hibitors of the CYP3A4 system and interact with numerous other drugs (see "Drug Interactions" chapter). Ritonavir is by far the strongest inhibitor, saquinavir probably the weakest.

Individual agents: Special features and problems

Amprenavir (Agenerase™) was the fifth PI to enter the European market, in June 2000, and is to date only licensed for treatment-experienced patients. This drug is weak when not boosted (Goodgame 2000, Fetter 2000), and not acceptable due to the high pill burden (8 pills bid). Boosting with ritonavir improves efficacy (Nadler 2002), although it remains inferior to the NNRTI efavirenz (Bartlett 2002). Important side effects include gastrointestinal disorders and, in contrast to other PIs, rashes in up to 30 %, which may be severe in rare cases. Whether the incidence of lipodystrophy and dyslipidemia under boosted amprenavir is reduced in comparison to other Pis – in line with theoretical suggestions (Furfine 2000) and some laboratory studies (Lenhard 2000) – remains to be clearly proven (Noble 2000). The resistance profile of the drug is particularly interesting, as it only partially overlaps with that of other PIs (Schmidt 2000). It has shown fairly good results in salvage settings (Eron 2001, Lastere 2003, Corbett 2004). It is possible that Agenerase™ will be removed from the market after licensing of the follow-on drug fosamprenavir (Telzir™, see below). Patients should be switched to Telzir™ (Rodriguez 2004).

Atazanavir (Reyataz ™) was the first once-daily PI to be licensed in 2004. Two Phase II studies, AI424-007 (Sanne 2003) and AI424-008 (Murphy 2003), demonstrated better tolerability in comparison to nelfinavir. In contrast to other PIs, atazanavir does not have a negative influence on lipid levels (Robinson 2000, Piliero 2002, Sanne 2003), which is its main advantage besides the once-daily dosing; it also does not induce insulin resistance (Noor 2004). Whether this will be reflected clinically (with less lipodystrophy), as suggested in some clinical case reports (Haerter 2004), remains to be confirmed. One problem with atazanavir is that more than half the treated patients experience elevated bilirubin levels, which can reach grade 3-4 in approximately one third of all cases (Squires 2004). Some patients even develop jaundice. The mechanism for this resembles that of Gilbert's syndrome (and the increased levels with indinavir – do not combine these two drugs!); there is reduced conjugation in the liver. Although this effect is harmless according to the manufacturer and only few cases of serious hepatic disorders have been described to date (Eholie 2004), liver function should be monitored and treatment discontinued in cases of significantly elevated bilirubin (>5-6 times the upper limit of normal).

In the early Phase II studies, the antiretroviral potency of atazanavir, in combination with d4T+3TC, was comparable to nelfinavir (Murphy 2003, Sanne 2003). In a large Phase III study (AI424-034), atazanavir (with a nuke backbone of AZT+3TC) showed comparable virological efficacy to efavirenz (Squires 2004). Lipid levels were clearly better in the atazanavir arm than in the efavirenz arm. Data from other studies is now available showing that lipids improve when nelfinavir or other PIs are replaced by atazanavir (Nieto-Cisneros 2003, Wood 2004). Boosting of atazanavir with ritonavir does not seem to have negative effects on lipid levels and is now generally recommended, particularly for combinations with NNRTIs or teno-

fovir, which significantly lower atazanavir levels (Preston 2002, Taburet 2004). Unfavorable interactions occur particularly in combination with proton pump inhibitors (see "Drug Interactions" chapter).

Atazanavir is slightly less effective than lopinavir in treatment-experienced patients, at least when it is not boosted (Nieto-Cisneros 2003). This does not seem to be the case if ritonavir is added (DeJesus 2004). The primary resistance mutation for this drug is I50L, which does not impair sensitivity to other PIs (including amprenavir), and possibly even increases it (Colonno 2003). On the other hand, there are a number of cross-resistance mutations, and susceptibility to many virus isolates with moderate PI resistance is reduced (Schnell 2003). Currently, atazanavir is only licensed for treatment-experienced patients – but this is likely to change in 2005.

Fosamprenavir (Telzir™, Lexiva™) is a calcium phosphate ester of amprenavir. Fosamprenavir has better solubility and absorption than the parent compound. This means that a significantly lower number of pills have to be taken. Fosamprenavir was licensed for treatment-naive and –experienced patients in 2004. The recommended doses are either a) 1400 mg bid (2 pills bid), b) 700 mg bid plus 100 mg ritonavir bid (2 pills bid) or c) 1400 mg plus 200 mg ritonavir once daily (4 pills qd). Once-daily dosing is not recommended for treatment-experienced patients. One advantage of the drug is that there are no restrictions with respect to food intake, and it can be taken on an empty stomach or with a meal.

Three pivotal studies have investigated fosamprenavir: NEAT, SOLO and CONTEXT. In the NEAT Study, unboosted fosamprenavir was slightly more effective virologically and had better tolerability than nelfinavir in treatment-naive patients (Rodriguez-French 2004). However, this study was limited by a relatively heterogeneous study population and high dropout rates in both arms. In the SOLO licensing study, boosted once-daily fosamprenavir was about as effective as nelfinavir (Gathe 2004). No resistance was found on boosted fosamprenavir even after 48 weeks (MacManus 2004). In the CONTEXT Study, fosamprenavir was almost as effective as lopinavir/r in PI-experienced patients; the difference was not significant (Elston 2004). As a potent inductor of amprenavir metabolism, efavirenz can significantly (probably with clinical relevance) lower plasma levels, as can nevirapine. This does not occur when fosamprenavir is boosted with ritonavir (Wire 2002, DeJesus 2004). Beware of the combination with lopinavir – plasma levels (AUC, Cmin) of both drugs are lowered! This seems to eliminate what would otherwise have been an interesting salvage option (Kashuba 2003).

Indinavir (Crixivan™) is one of the oldest and now most extensively tested PIs. In large, widely received studies in treatment-naive and –experienced patients, it was initially very successful (Gulick 1997, Hammer 1997). Later, indinavir had mixed success, at least in the unboosted form. In the Atlantic Study, indinavir was about as effective as nevirapine (Van Leeuwen 2003), but in the 006 Study it was clearly weaker than efavirenz (Staszewski 1999). In the double blind, randomized CNAAB3005 Study, indinavir was more effective than abacavir, particularly with high viral load (Staszewski 2001). In the CHEESE Study and MaxCmin1 studies, efficacy was comparable to saquinavir-SGC (Cohen-Stuart 1999, Dragstedt 2003). The large amount of available data is currently probably the most important argu-

ment in favor of this drug. Low protein binding (60 %) seems to allow better CNS penetration than with other PIs (Martin 1999). Whether this is clinically significant remains to be seen.

There are, however, a number of problems associated with indinavir. Firstly, it causes nephrolithiasis in approximately 5-25 % of patients (Meraviglia 2002), and thus requires good hydration (at least 1.5 liters daily). Unboosted indinavir must be taken three times daily on an empty stomach (Hass 2000), a form of dosing that is unacceptable today. For this reason, boosting with ritonavir is recommendable, although this can increase the rate of side effects (Harley 2001, Arnaiz 2004). In the MaxCmin1 Trial, the dropout rate in the indinavir group was clearly higher than among patients receiving saquinavir (Dragstedt 2003). Beyond PI-specific side effects such as lipodystrophy and dyslipidemia, other problems that are relatively specific to indinavir include mucocutaneous side effects reminiscent of retinoid therapy, with alopecia, dry skin and lips, and ingrown nails. Many patients may also develop asymptomatic hyperbilirubinemia. Although it seems that the dose and thus toxicity can be reduced in most patients by boosting and monitoring plasma levels, indinavir has come to play a lesser role for all of these reasons.

Lopinavir/r (Kaletra™) was licensed in April 2001 as the first PI to contain a fixed booster dose of ritonavir. This increases concentrations of lopinavir by more than 100 fold (Sham 1998). Lopinavir levels can possibly be boosted even further by increasing the ritonavir dose, which may be useful in salvage therapy (Flexner 2003).

In treatment-naive patients in a randomized double-blind study, lopinavir/r was significantly superior to an unboosted regimen with nelfinavir. The proportion of patients with less than 50 copies/ml was 67 % versus 52 % after 48 weeks (Walmsley 2002). Lopinavir/r also showed slightly better results than boosted saquinavir in the open-label randomized MaxCmin2 Trial on a heterogeneous population of treatment-experienced patients. This was particularly true for tolerability, but also with respect to treatment failure (Youle 2003). However, patients treated in the MaxCmin2 Study still received the poorly tolerated Fortovase™ formulation of saquinavir; in addition, more patients in the Fortovase™ arm interrupted treatment for personal reasons. In the on-treatment analysis, at least the efficacies of saquinavir/r and lopinavir/r were comparable.

In the M97-720 Study, in which patients received 3TC+d4T plus different doses of lopinavir/r, a long-term effect can be seen even after several years (Kessler 2003). In the US, lopinavir/r is therefore now recommended as a component of first-line therapy, although it is still unclear which PIs could be used when such regimens fail. Development of resistance with lopinavir/r first-line therapy has hardly been described, but is theoretically possible (Walmsley 2002, Kagan 2003, Stevens 2003, Conradie 2004, Fried 2004). However, lopinavir/r has a high genetic barrier to resistance, and it is likely that at least 6-8 cumulative PI resistance mutations will be necessary for treatment failure (Kempf 2002). The drug has very good efficacy in salvage therapy (Benson 2002), and is one of the most important drugs in this setting (see "Salvage Therapy" chapter). However, in two large studies in PI-experienced patients, virological efficacy of lopinavir/r was not significantly higher than that of boosted atazanavir (DeJesus 2004) or fosamprenavir (DeJesus 2003).

A significant problem, in addition to gastrointestinal side effects (diarrhea, nausea), is the often considerable dyslipidemia, which is probably more marked than with most other PIs (Walmsley 2002, Calza 2003). As for all PIs, lopinavir/r causes lipo-dystrophy syndrome – in one long-term study, the prevalence was 15 % after five years (Hicks 2003). A number of interactions should also be considered. The dose must be increased in combination with efavirenz and nevirapine, probably also with concurrent administration of amprenavir. Newer studies show that once-daily lopi-navir/r (800/200) is possible, although diarrhea will occur slightly more often (Molina 2004).

Nelfinavir (Viracept™) was the fourth PI to be put on the market and was for a long time one of the most frequently used PIs. The dose of 5 capsules twice daily is just as effective as 3 capsules three times daily. Boosting with ritonavir does not lead to significant improvement in plasma levels (Kurowski 2002).

In the pivotal 511 study (with AZT+3TC), 61 % of patients had below 50 copies/ml at 48 weeks (Saag 2001). In the open-label, randomized CNAF3007 Study, the decrease in viral load was comparable to abacavir (Matheron 2003). In comparison to NNRTIs or other PIs, nelfinavir is probably slightly less potent, and the data is not so favorable overall. In the Combine Study, nelfinavir was weaker (not significantly) than nevirapine (Podzamczer 2002). In ACTG 384 and 364, nelfinavir showed lower efficacy than efavirenz in both treatment-naive and nuke-experienced patients (Albrecht 2001, Robbins 2003, Shafer 2003). In the Crown Study, nelfinavir did slightly less well than indinavir, but was tolerated better (Mendo 2003). Finally, in the double blind, randomized M98-863 Study, the efficacy of nelfinavir was significantly poorer than that of lopinavir/r – after one year, 52 % versus 67 % of patients reached a viral load below 50 copies/ml (Walmsley 2002).

The most important side effect of nelfinavir is diarrhea, which may be considerable. The drug is otherwise very well tolerated. Another positive aspect is the good resistance profile. The D30N primary mutation for nelfinavir reduces viral fitness (Martinez-Picado 1999) and does not influence the efficacy of other PIs. Unfortunately, however, other mutations that can jeopardize the success of later regimens also frequently occur (Hertogs 2000).

Nelfinavir is only rarely effective if a PI-containing regimen has failed (Lawrence 1999, Gulick 2000, Chavanet 2001, Hammer 2002). In several studies, such as SPICE and TIDBID, nelfinavir was combined with saquinavir, which then significantly elevated plasma levels (Cohen 1999, Moyle 2000). This led to increased efficacy, at least in patients with prior nucleoside analog therapy. However, such a combination has a very high pill burden and is associated with even more diarrhea – it is only accepted by few patients today. A new formulation enabling a reduction to two capsules bid is being developed; this may reverse the recent downward trend of this drug.

Ritonavir (Norvir™) was the first PI for which efficacy was proven in a study with clinical endpoints (Cameron 1998). However, it is now obsolete as a single PI, since tolerability is too poor (Katzenstein 2000). In particular, gastrointestinal complaints and perioral paresthesias can be very disturbing. Ritonavir is therefore now

only given at a low dose for boosting. The so-called "baby dose" used for this purpose (100 mg bid) is tolerated significantly better. Ritonavir inhibits its own metabolism via the cytochrome P450 pathway. The potent enzyme induction results in a high potential for interactions; thus, many drugs are contraindicated for concomitant administration with ritonavir. Metabolic disorders probably occur more frequently than with other PIs. Caution should generally be exercised in patients with impaired liver function. It is important to inform patients that ritonavir capsules must be stored at cool temperatures, which can become a problem when travelling.

Saquinavir (Invirase™, Fortovase™) was the first PI to be licensed in December 1995 for HIV therapy and is currently the only PI that is available in different formulations. The soft gel capsules (Fortovase™ or saquinavir-SGC) were an improvement of the originally licensed hard gel capsules (Invirase™ or saquinavir-HGC). More recently, film-coated tablets (Invirase 500™) have been approved in both the US and the EU.

Invirase 500™ tablets have an improved oral bioavailability, allowing reduction of the pill count to two tablets twice a day. Invirase 500™ is now the preferred formulation of saquinavir. It should be given with 100 mg of ritonavir.

The MaxCmin1 and MaxCmin2 studies, which involved treatment-naïve and pretreated patients, were head-to-head trials to compare ritonavir-boosted PI regimens. In MaxCmin1, saquinavir-SGC/r demonstrated comparable antiretroviral effects to indinavir/r. However, more treatment-limiting adverse events were observed in the indinavir/r arm. Probably because of a better toxicity profile, more patients on saquinavir/r remained virologically suppressed (Dragstedt 2003). InMaxCmin2, boosted saquinavir-SGC compared slightly less favorably to lopinavir/r (Youle 2003). However, this was only true in the ITT, and not in the on-treatment analysis – significantly more patients stopped saquinavir-SGC therapy for personal reasons. Moreover, some patients in the saquinavir/r arm had previous exposure to saquinavir, whereas no patient had previous exposure to lopinavir/r.

Saquinavir is well tolerated except for moderate gastrointestinal problems. With no serious short-term problems, Saquinavir is an attractive PI for patients who need a boosted PI-regimen.

Why "boosting" PIs?

Ritonavir is a very potent inhibitor of the isoenzyme 3A4, a subunit of the cytochrome P450 hepatic enzyme system. Inhibition of these gastrointestinal and hepatic enzymes with small doses of ritonavir allows boosting of the most important pharmacokinetic parameters of almost all PIs (Kempf 1997): maximum concentration (Cmax), trough levels (Ctrough) and half-life. This useful interaction between ritonavir and the other PIs simplifies daily regimens by reducing the frequency and number of pills to be taken every day, in many cases independent of food intake. Some PIs can now be used in twice-daily regimens. Current trials are investigating the possibility of once-daily dosing. Boosting of indinavir or amprenavir, for example, even seems to be effective against resistant viral strains as a result of the elevated drug plasma levels (Condra 2000). Boosting is usually indicated by addition of "/r" after the drug name.

Indeed, nelfinavir is the only PI for which boosting with ritonavir is not recommended as plasma levels do not rise significantly (Kurowski 2002). In addition to boosting with ritonavir, boosting with a combination of saquinavir and nelfinavir is a possibility (Moyle 2000, Stellbrink 2002). In our experience, it works very well, but is no longer practical today due to the large number of pills.

There is a high degree of variability in ritonavir-boosted plasma levels among individuals. Therapeutic drug monitoring is therefore recommended. In addition to achieving elevated trough levels of the boosted drug, which prevents plasma levels from dropping below the minimal inhibitory concentration, ritonavir also increases peak levels, which may lead to more side effects.

Saquinavir/r is the most-studied boosted combination. Due to the low oral bio-availability of saquinavir, this combination was tested very early on (detailed review: Plosker 2003). Plasma levels of saquinavir can be increased 20 fold by ritonavir. Studies have shown that the boosted combination 400/400 (= 400 mg saquinavir plus 400 mg ritonavir, both twice daily) is virologically the most effective (Cameron 1999). In patients already taking saquinavir, boosting may have only moderate effects (Smith 2001). Boosting of saquinavir in the better tolerated 1000/100 combination has now been licensed. When boosting saquinavir, Invirase™ is now used more commonly than Fortovase™. Boosted levels of saquinavir are probably even higher for Invirase™ (Kurowski 2002), which also has less adverse effects with respect to gastrointestinal complaints. Fortovase™ is likely to disappear from the market soon.

The combination of **indinavir/r** has also been well investigated. Good pharmacokinetic data exists on the 800/100 mg bid dose (Van Heeswijk 1999). In a smaller pilot study with this combination, however, results showed nephrolithiasis in 19 of 57 patients (Voigt 2002). The 400/400 mg dose possibly induces less renal side effects. The boosted combination of indinavir/r seems to exemplify the increased risk of side effects that may be seen with boosting. Thus, in studies such as BEST or NICE, switching from indinavir to indinavir/r was associated with a slightly higher rate of side effects and drop-outs (Harley 2001, Shulman 2002, Arnaiz 2003). Newer studies suggest that boosting of indinavir results in doses that are too high in many patients (Ghosn 2003). The German MIDAS protocol is attempting to gradually reduce indinavir doses. It seems likely that a dose of 400/100 mg bid will be possible in most patients.

Lopinavir/r is to date the only fixed-dose boosted combination therapy available in one capsule (see above). Data is also available on **amprenavir/r**, especially for salvage therapy (Condra 2000, Duval 2002). **Fosamprenavir** and **atazanavir** are two new PIs, available since last year, that allow once-daily dosing when boosted. Plasma levels seem to decrease with increasing duration of treatment, even for well-boosted PIs – after 10 months, saquinavir levels in six patients had dropped by 40 % (Gisolf 2000). If there is any doubt (lack of efficacy, increased side effects), it is therefore advisable to measure plasma levels of all boosted combinations, particularly with severe liver disease, as the extent of interactions cannot always be predicted. It is not rare that dose adjustments may be required. All boosted combinations except atazanavir seem to increase lipid levels (Van der Valk 2003).

Which boosted combination is best?

There is relatively little clinical data available yet from direct comparisons between boosted PI regimens. So far, no major differences have become apparent: in the randomized MaxCmin1 Trial, the efficacy of saquinavir/r and indinavir/r was comparable. The drop-out rate in the indinavir/r group was significantly higher, probably due to side effects (Dragstedt 2003). In the MaxCmin2 Study, both treatment-naive and treatment-experienced patients were randomized to receive either saquinavir/r (soft gel) or lopinavir/r. At first glance, saquinavir/r did slightly less well in the ITT analysis (Youle 2003). After 48 weeks, the proportion of patients with less than 50 copies/ml was 65 % versus 57 % in favor of lopinavir/r. However, this significant difference was not detectable in the on-treatment analysis (70 % versus 75 %). A possible explanation is that a relatively large number of patients in this open-label study discontinued saquinavir/r therapy "of their own accord" (possibly because of the high number of pills). There was therefore no conclusive proof of the higher virological efficacy of lopinavir/r in this study. This was also true for the AI424-045 Study, in which lopinavir/r was no better than boosted atazanavir/r in treatment-experienced patients (DeJesus 2004). In the CONTEXT Study, there was only a trend in favor of lopinavir/r in treatment-experienced patients compared to fosamprenavir/r, at least with the twice-daily dose. The once-daily dose of fosamprenavir/r is likely to be weaker (Elston 2004).

Table 2.3: Well investigated boosted PI regimens

	Dose in mg	Pills/day	Comment
Saquinavir/r	1000/100 bid	2 x 6	Officially licensed for boosting
Saquinavir/ r	400/400 bid	2 x 6	Good efficacy, but problematic due to increased rate of side effects
Indinavir/r	800/100 bid	2 x 3	Higher rate of nephrolithiasis (?)
Indinavir/r	400/400 bid	2 x 5	Good pharmacokinetic data
Lopinavir/r	400/100 bid	2 x 3	Only fixed-dose combination in one capsule
Amprenavir/r	600/100 bid	2 x 5	No longer advisable since licensing of fos-amprenavir
Fosamprenavir/r	700/100 bid	2 x 2	Licensed in 2004
Fosamprenavir/r	1400/200 qd	1 x 4	Only approved for PI-naive patients. Once daily
Atazanavir/r	300/100 qd	1 x 3	Fewest pills for PI-ART, once daily
Saquinavir/ Nelfinavir	600/750 tid	3 x 6	Only well documented boosted combination without ritonavir, but too many pills three times a day

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Entry inhibitors

There are three crucial steps for entry of HIV into the CD4 T cell:

1. binding of HIV to the CD4 receptor ("attachment" – target of attachment in-hibitors),
2. binding to coreceptors (target of coreceptor antagonists), and finally
3. fusion of virus and cell (target of fusion inhibitors).

Every step of HIV entry can theoretically be inhibited. All three drug classes, namely attachment inhibitors, coreceptor antagonists and fusion inhibitors are currently summarized as entry inhibitors. In 2003, T-20 – the first drug of this class – was licensed in Europe and the US. Numerous other drugs are in the pipeline, but will not be available within the next two years. These are discussed in the HAART 2005/2006 chapter.

T-20 (**Enfurvitide, Fuzeon™**) is the prototype of the fusion inhibitors. It is a relatively large peptide comprised of 36 amino acids, and therefore, like insulin, needs to be administered by subcutaneous injection. It binds to an intermediate structure of the HIV gp41-protein, which appears during fusion of HIV with the target cell. T-20 was licensed in Europe and the US in 2003 for the treatment of HIV-1 infection in antiretroviral-experienced adults and children over 6 years of age. It is still preferable to treat patients within clinical studies, so that clinical experience with this new drug can be collected.

In one of the first studies, HIV patients were given T-20 monotherapy intravenously. Antiviral activity was dose-dependent, and at the higher dose of 100 mg bid, median viral load was reduced by almost 2 log (Kilby 1998). The first study on 78 highly treatment-experienced patients who received subcutaneous application of T-20 in addition to stable HAART – either via an insulin pump or twice daily subcutaneously – also showed positive dose-dependent effects (Kilby 2002). However, maximal suppression was lower at 1.6 logs. In the T20-205 Study, 70 patients, mostly PI-experienced, received 2 x 50 mg T-20 subcutaneously daily for 48 weeks (Lalezari 2000). After 48 weeks, an effect on viral load was still evident in one third of patients, but it became apparent that T-20 was of more benefit to patients who received other additional new drugs for their HAART regimen. The first Phase II study (T20-206) finally showed that the simple addition of T-20 as "monotherapy" would not be very beneficial (Lalezari 2002). Approximately two thirds of the T-20 patients in this study had local reactions (mostly mild) at the injection site. Otherwise, T-20 was generally well tolerated.

Two Phase III studies finally led to licensing of T-20. TORO 1 ("T-20 versus Optimized Regimen Only") enrolled 491 extensively pretreated patients in North America and Brazil, most with multiresistant viruses. In TORO 2, 504 patients in Europe and Australia were enrolled. Patients in both studies, on an optimized HAART regimen, either received 90 mg T-20 bid subcutaneously or none at all (Lalezari 2003, Lazzarin 2003). In TORO-1, the reduction in viral load was

0.94 logs better with T-20; in TORO-2 this difference was 0.78 logs. The impact on viral load was still apparent after 96 weeks (Arasteh 2004).

The success of T-20 therapy should be monitored early on, particularly in view of the cost. Patients without a decrease in viral load of at least one log after 8-12 weeks will not experience further benefit on T-20, and can be spared the required twice-daily injections. It is also not recommended to inject twice the dose of T-20 once a day: although 180 mg qd is bioequivalent (as measured by AUC) to the standard 90 mg bid dose, a recent study showed a trend towards a lesser decrease in viral load with the 180 mg dose that was clearly associated with lower trough levels (Thompson 2004).

A new occurrence in the TORO studies was the increased frequency of lymphade-nopathy and bacterial pneumonia (4.9/100 PY versus 0.6/100 PY) under T-20 (Lal-ezari 2003). There was also more septicemia on T-20, but the difference was not significant. The reason for the increased rate of infections has remained unclear, but binding of T-20 to granulocytes has been suspected.

Resistance mutations develop relatively rapidly on T-20, but seem to reduce viral fitness (Lu 2002). Receptor tropism of the virus seems to be less significant than initially thought. In the TORO studies, a short sequence on the gp41 gene was re-sponsible for reduced susceptibility to T-20; this requires only simple point muta-tions. In contrast, viruses resistant to conventional HAART (NRTIs, NNRTIs, PIs) are susceptible (Greenberg 2003). As T-20 is a relatively large peptide, it induces antibody production. However, this does not seem to impair efficacy (Walmsley 2003).

In summary: patients with a well-controlled viral load or who still have options with "classical" HAART do not require T-20. For salvage therapy, however, the drug seems to be very valuable. Although there is still no data from studies with clinical endpoints, patients will likely benefit clinically from this drug. Mathemati-cal analyses of the TORO studies have shown survival gains of 1.5 years compared to optimized HAART (Hornberger 2003). The price remains an important aspect of T-20, and HAART costs twice as much with the addition of T-20. The company claims that it is one of the most complicated drugs it has ever manufactured. This is unlikely to change even if an improved formulation becomes available – the com-pany is currently working on pegylation of T-20, which would allow weekly dos-ing.

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3. ART 2005/2006: The Horizon and Beyond

Christian Hoffmann, Fiona Mulcahy

Although more than two dozen different products are now available for treatment of HIV infection, there is a growing need for new drugs. This is not just true for patients with multiresistant viruses awaiting new treatment options. Significant problems related to long-term toxicity and adherence are anticipated with therapies that will presumably need to span whole decades, as eradication of HIV is currently not possible. As a result, there is an urgent need for new drugs that are easier to take, with high genetic barriers to the development of resistance and above all less toxic. To eventually reach the goal of eradication, new drugs need to be more potent than those available today. The following overview of substances that could make it to the clinic based on current data (December 2004) does not claim to be complete.

Refurbished old drugs

Several currently available drugs are under further development, the most important goals being the reduction of pill burden, easier dosing and less side effects. New formulations as well as combination products are being developed; licensing applications for some of these are already in progress.

Zerit PRC™ (PRC = "prolonged release capsule", in the US: XR = "extended release") is a capsulated once-daily formulation of d4T. The formulation is stable, does not accumulate and seems to cause less polyneuropathy, possibly due to lower peak levels. In the BMS AI455-099 Study, 100 mg d4T XR was tested in a double-blind, randomized study in almost 800 patients against the standard dose of 2 x 40 mg d4T daily (in combination with 3TC and efavirenz). At 48 weeks, there were no differences in efficacy (CD4 cell count, viral load) and safety, but also no differences in rates of polyneuropathy (Baril 2002). d4T XR was approved by the FDA in December 2002. However, it is still (in December 2004) not available and there is no expanded access program. It is anticipated that d4T treatment will be manufactured in 37.5 mg, 50 mg, 75 mg and 100 mg capsules. Patients weighing more than 60 kg should be given 100 mg, patients weighing less than 60 kg, 75 mg. There are currently other attempts to improve d4T through minor modifications to its molecular structure. In vitro data indicates there seem to be d4T-like substances that are less toxic and presumably more effective (Haraguchi 2003, Dutschman 2004).

Nelfinavir 625 mg – this new formulation was approved in the US in April 2003. It reduces the nelfinavir dose to 2 tablets bid. One study has shown that this formulation is better tolerated, particularly with respect to gastrointestinal side effects – despite the fact that plasma levels are around 30 % higher than with the previous nelfinavir formulation (Johnson 2003, Kaeser 2003). If these observations are confirmed, nelfinavir is likely to gain importance, particularly as its tolerability profile is otherwise good.

Kaletra™ tablets – although no data is available yet, the manufacturer Abbott expects to have a new tablet available towards the end of 2005 to replace the current

soft capsules. This will allow pill reduction to 2 tablets bid and also eliminate the need for refrigeration.

Combination products

In August 2004, the US FDA licensed two new combination drugs: Truvada™ and Kivexa™. These drugs will certainly create new options for antiretroviral therapy: both products will significantly reduce the pill burden of many regimens, as each is given daily as a single tablet. In 2004, Gilead, BMS and Merck together announced a new combination pill of FTC, tenofovir and efavirenz. However, it will take another one to two years for this to happen. Experience from Africa and Thailand has shown that combination products are not so difficult to manufacture. There have already been very encouraging results for many regimens (Laurent 2004).

Kivexa™ (in the US: Epzicom[TM]) is a product from GlaxoSmithKline, made up of 600 mg abacavir (Ziagen™) and 300 mg 3TC (Epivir™). GSK seems to be exploring new options in view of the expiring patent protection for AZT in 2005; it recently conducted unusually large studies focusing on the abacavir+3TC combination. Several of these studies were able to show that the nucleoside backbone of abacavir and 3TC is at least as effective as Combivir™ (AZT+3TC). In the ZODIAC Study, it was demonstrated that abacavir could be given once-daily (Gazzard 2003). The CNA30024 Study showed that abacavir+3TC were not inferior to Combivir™ (De Jesus 2004). The ABCD Study was able to show comparable antiviral efficacy for the ABC+3TC and the d4T+3TC combinations, while finding less lipodystrophic side effects with ABC+3TC (Podzamczer 2004). The main advantage of Kivexa™ is the once-daily dosing. When prescribing this product, it is important not to forget the abacavir component of Kivexa™, which comes with the risk of hypersensitivity syndrome (HSR). Patients should be counseled accordingly. It is also problematic to administer Kivexa™ with an NNRTI (nevirapine or efavirenz). If an allergy occurs, differential diagnosis between an NNRTI rash and the abacavir HSR is often difficult, and may result in unnecessary elimination of treatment options.

Truvada™ is a product from Gilead, containing 300 mg tenofovir (Viread™) and 200 mg FTC (Emtriva™). The FDA gave the go-ahead in August 2004, probably based on the preliminary results of the 934 Study. This study, which was conducted in treatment-naive patients in Europe and the US, tested FTC and tenofovir against AZT+3TC (as a fixed combination in Combivir™) in an open-label design. All patients received efavirenz as the third drug. Of the 509 patients evaluated, 73 % reached a viral load below 50 copies/ml in the ITT analysis, compared to 65 % in the Combivir™ arm (Gazzard 2004). This difference was significant (p=0.038), although this was largely due to poorer tolerability of Combivir™. Only 3 % of patients on FTC+tenofovir had to stop treatment due to side effects, compared to 9 % in the Combivir™ arm. In particular, anemia (no less than 14 severe cases) and gastrointestinal problems led to treatment discontinuation in the Combivir™ arm.

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New nucleoside analogs

Since the development of the guanosine analog DAPD came to a halt, hopes are now focused mainly on cytidine analogs. The most promising substances are currently elvucitabine, reverset and SPD-754. Mitochondrial toxicity seems to be low, and most are effective against hepatitis B. One problem with cytidine analogs could be the combination with the cytidine analog 3TC, where a loss of efficacy seems possible.

ACH-126,433 (Elvucitabine) is a nucleoside analog developed by Achillion Pharmaceuticals. It is an enantiomer of DPC 817, with the chemical name beta-L-d4FC, and is effective against HIV and HBV. In vitro studies show potency even in the presence of numerous nuke resistance mutations (Fabrycki 2003). It is also of interest as it seems to have low mitochondrial toxicity, and because of its very long half-life (Dunkle 2001). Phase II studies are underway in HIV-infected patients and in patients with hepatitis B. A small, double-blind study showed a reduction in viral load between 0.7 and 0.8 logs after 28 days in patients with the M184V mutation.

However, this study had to be prematurely terminated, as 6/56 patients developed leukopenia on a dose of 100 mg elvucitabine (Dunkle 2003). Several patients also developed rashes. It is currently being deliberated which dose would retain sufficient activity while at the same time being less toxic – this may require only once-weekly dosing (Stypinski 2004).

Reverset (previously DPC 817) is a new oral cytidine analog (chemical name D-D4FC) with a long half-life that is expected to have very good activity in cases of AZT/3TC resistance (Shinazi 2002). Following early studies by Dupont and BMS (under the name DPC 817), this drug is now being developed further by Pharmasset (Murphy 2003). Initial studies on humans seem quite successful (Stuyver 2004). In 24 treatment-naïve patients, once-daily doses of 50, 100 and 200 mg as monotherapy induced a drop in viral load of approximately 1.7 logs after 10 days. 87.5 % of patients even reached < 400 copies/ml (Murphy 2004). Reverset, if added to a failing regimen, significantly lowered the viral load even in patients with viral resistance. In a total of 8 patients, this decrease was around 0.8 logs after 10 days, although it was significantly less in patients with several TAMs (Murphy 2004). This substance is currently being investigated in Phase II studies.

SPD-754 (previously BCH-10652) is a heterocyclic cytidine analog from Shire Biochem. Initially, the racemate of SPD-754 was developed by Biochem Pharma under the name BCH-10652 (dOTC). The substance has a chemical resemblance to 3TC (Taylor 2000, Bethell 2002). SPD-754 has in vitro activity against a broad spectrum of TAMs. Up to 5 nucleoside mutations do not significantly impair activity. SPD-754 is therefore an important hope for patients with multiple nucleoside resistance mutations. A first placebo-controlled study in a total of 63 HIV-infected patients treated with SPD-754 monotherapy showed decreases in viral load between 1.18 and 1.65 logs after 10 days depending on the dose – which is exceptional potency for a nucleoside analog (Cahn 2003). The drug has been well tolerated and has very good oral bioavailability (Francis 2003).

What about long-term toxicity? In monkeys, there were minor skin problems, usually hyperpigmentation, after 52 weeks of exposure. SPD-754 was thus significantly less toxic than its racemate BCH-10652, which caused severe degenerative dermatopathy in all exposed monkeys. Nevertheless, these results give cause for concern (Locas 2004). Other disadvantages are becoming apparent: 3TC and FTC significantly lower intracellular levels of SPD-754 – probably competitively. Combination with cytidine analogs such as 3TC and FTC could therefore pose a problem (Bethell 2004). Further drugs that are in the pipeline at Shire Biochem include SPD-756 (BCH-13520) and SPD-761. However, these are not as far developed and might disappear completely, as not much has been heard about these recently.

Phosphazide (Nicavir) is a nucleoside that was developed mainly in Russia, and is very similar to AZT. After 12 weeks of phosphazide monotherapy (400 mg), viral load in a small group of patients dropped by a median 0.7 logs. Since phosphazide is a prodrug of AZT, it requires an additional activation step. The D67N mutation seems to reduce efficacy (Machado 1999). A small study has shown potency in combination with ddI and nevirapine (Kravtchenko 2000), another with ddI and saquinavir (Sitdykova 2003). It is still hard to see the advantage over AZT – although better tolerability had been presumed, this has not been proven, and further studies are required for approval in the US and Europe.

Racivir is another cytidine analog which like reverset is being developed by Pharmasset (Otto 2003). It is very similar to FTC, and is a mixture of FTC and its enantiomer. It has shown good antiviral activity in combination with d4T and efavirenz after two weeks. Whether racivir will make it to the clinic after this Phase I/II study, and what the main advantage is over FTC remains to be seen.

MIV-310 (Alovudine, FLT) is a thymidine analog, initially tested in the 80s by Lederle but abandoned at the time, mainly due to myelotoxicity. Now, having been bought by the Swedish company Medivir and then passed on to Boehringer Ingelheim in 2003, MIV-310 could be celebrating a comeback, as it seems to have excellent efficacy against nucleoside resistant viruses (Kim 2001). Once-daily dosing also seems possible. In 15 patients with a median of 6 nucleoside resistance mutations, addition of alovudine to the existing regimen lowered viral load considerably – by 1.88 logs after 4 weeks in the 11 patients not taking d4T (Katlama 2004). The original dose of 20 mg was associated with a high rate of side effects, but these seem to be acceptably reduced at the lower dose of 7.5 mg. A dose-finding study is currently underway in patients with multi-nucleoside resistance.

Stampidine is a nucleoside analog developed by the American Parker Hughes Institute. It resembles d4T and is apparently 100 times more potent than AZT in vitro (Uckun 2002). It also has activity against HIV mutants with up to 5 TAMs. Considerable efficacy was demonstrated in FIV (feline immunodeficiency virus) infected cats. This attracted much attention on the internet, but whether these positive results can be replicated in humans remains to be seen (Uckun 2003). In recent months, it has been discussed more as a potential microbicide (D'Cruz 2004).

DAPD (Amdoxovir) is a guanosine analog that is converted in vivo to the highly potent DXG. DAPD has good activity against AZT/3TC-resistant viruses and HBV (Corbett 2001). After clinical observations of possible lens anomalies in patients on DAPD (Thompson 2003), things came to an end for this product in early 2004: the company terminated the licensing contract with two US universities. However, DAPD may yet reappear, as other universities may want to continue the research…

GS 7340 is a nucleotide analog and a prodrug of tenofovir. It is being developed by Gilead with the goal of improving the low cellular levels of tenofovir (Lee 2002). Animal studies have shown very high drug concentrations in the lymph nodes, and so the company is hoping to see higher antiviral potency. Dose-finding studies are currently being performed in humans. Little data is available to date.

Out of sight, out of mind: the following drugs are currently not being pursued:

- Adefovir dipivoxil (bis-POM PMEA) from Gilead, low activity against HIV, nephrotoxicity
- FddA (Beta-fluoro-ddA, Lodenosine™) from US Bioscience, development stopped in 1999 due to severe liver and kidney damage
- dOTC from Biochem Pharma, toxicity in monkeys
- Lobucavir from BMS, carcinogenicity

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New NNRTIs

More than with any other drug class, "me-too" drugs are not needed here. Various drugs have already been abandoned (see below); the road to approval is especially long and hard for NNRTIs, even though they are relatively cheap to develop. Since efavirenz was licensed in 1998, no NNRTI has made it onto the market – despite the urgent need for new substances in this class in view of increasing NNRTI resistance.

Etravirine (TMC 125) has possibly the best chance. Etravirine is a diarylpyrimidine (DAPY) analog and a second-generation NNRTI with good activity against the wild-type and resistant mutants, particularly with classical NNRTI mutations such as K103N and Y181C. In a Phase I/II study, etravirine lowered viral load by an average of 2.0 logs in treatment-naïve patients after only one week (Gruzdev 2003). In a Phase IIB study, 16 patients on stable ART, mostly harboring several NNRTI mutations, were treated with 900 mg etravirine bid for 7 days. Viral load decreased by a median of 0.9 logs, and in some cases even up to 1.7 logs (Gazzard 2003, Sankatsing 2003). Even after this time point, viral load continued to decrease. TMC 125 was well tolerated. The half-life is long, and the drug is metabolized in the liver. Although the first pharmacokinetic data indicates unfavorable interactions with PIs (especially indinavir and saquinavir), etravirine appears to be developing into a promising drug, with a high genetic barrier to resistance. This seems to stem from the fact that, as a DAPY analog, etravirine has a very flexible conformation for binding to the reverse transcriptase (RT) of HIV-1. Mutations at the binding site of RT can therefore hardly influence the binding and activity of this NNRTI (Das 2004). Let us hope for the best. However, the number of treated patients remains small, and the duration of treatment was usually less than two weeks – therefore statements on possible side effects seem speculative at this stage. Nevertheless, etravirine is expected to have the usual problems associated with efavirenz and NNRTIs in general (dizziness, rash).

Capravirine (AG1549, previously S-1153) is a relatively well-advanced NNRTI, initially developed by Shionogi Pharmaceuticals (Fujiwara 1998) and subsequently sold to Pfizer/Agouron. Capravirine is effective in vivo against viruses with the K103N mutation (Wolfe 2001, Gewurz 2004), and is therefore a hopeful candidate in the battle against NNRTI-resistant viruses. After animal studies in dogs showed

an unusually high rate of vasculitis at higher doses, Agouron stopped all Phase II/III clinical trials in 2001. Safety evaluations have now shown that capravirine does not cause such side effects in humans (Hawley 2002), and development will continue. The dose will probably be set at 2 x 700 mg/day. Capravirine is metabolized via CYP3A4 like the protease inhibitors – and significant interactions can occur, which are currently being extensively investigated. An increase in the dose of lopinavir/r will probably be necessary (Bu 2004). The activity of capravirine is presumably short-lived. In a study in 36 patients with NNRTI resistance, capravirine lowered viral load to below 400 copies/ml, but only 16 patients remained below 400 copies/ml after 28-34 months (Hammond 2003). Of the 20 patients in whom this was not the case, 6 patients developed virological failure and 5 discontinued capravirine because of side effects.

Calanolide A is an NNRTI that has been in development by Sarawak MediChem Pharmaceuticals since 1997. The drug has an unusual natural origin – it was extracted from plants growing in the Malaysian rain forest. Calanolide A mainly seems to be active against isolates with classical NNRTI resistance mutations, i.e. Y181C, but also K103N (Quan 1999). The drug has been well tolerated in healthy volunteers (Creagh 2001). In HIV-infected patients, one double-blind, randomized, placebo-controlled study found a 0.81 log reduction in viral load after 14 days (Sherer 2000). According to the company website, Phase II/III studies are planned for 2004/2005, but no data is available yet. In view of the slow development, it is becoming doubtful whether this substance will really make it.

GW5634 is a second-generation benzophenone NNRTI, resulting from prior studies of GW8248 and GW8635, which both had poor oral bioavailability (Burnette 2003, Schaller 2003). GW5634 is the prodrug of GW8248, which had good in vitro activity against NNRTI resistant viruses (Freeman 2003, Romines 2003, Hazen 2003). However, individual resistance mutations have been detected (V106I, P236L, E138KL), indicating that GW8248 or GW5634 will not be invincible. GW 5634 is currently being tested in Phase I studies.

The following NNRTIs are no longer being developed:

- Atevirdine from Upjohn, the company prioritized development of delavirdine (the right decision?)
- DPC 083 (BMS-561390) – development stopped in May 2003 due to unsatisfactory PK and safety data
- DPC 961 – suicide thoughts in healthy volunteers; the sister drug DPC 963 has an uncertain future
- Emivirine (EMV, MKC-442, Coactinon) – quite far developed by Triangle, but still too weak; development stopped in 2002
- GW420867X – to much cross-resistance, no fewer side effects, classical me-too drug without any advantage
- GW8248 – from GSK, poor bioavailability
- HBY-097 from Hoechst-Bayer, unfavorable side effects
- Loviride from Janssen Pharmaceuticals, too weak in (relatively advanced) clinical trials (CAESAR Study)

- MIV-150 from Medivir/Chiron, poor bioavailability, being developed further as a microbicide
- PNU142721 from Pharmacia & Upjohn, similar resistance profile to efavirenz
- TMC120 (dapivirine) from Tibotec, poor oral bioavailability, TMC 125 seems better

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New protease inhibitors (PIs)

Progress with new PIs is modest overall, despite the fact that there is a big fanfare anytime one of the involved companies has any in vitro data suggesting activity against PI-resistant viruses. Many substances have been lost along the way. Besides tipranavir and perhaps TMC 114, there is not much to look forward to in the mid-term.

Tipranavir (Aptivus™) is the first non-peptidic protease inhibitor. It was initially a product from Pharmacia Upjohn, and has now been developed for some time by Boehringer. It has been licensed in the US. Tipranavir has good efficacy against PI-resistant viruses (Larder 2000, Schwartz 2002), and is currently one of the biggest hopes for salvage patients. Tipranavir shows considerable efficacy even in the presence of so-called UPAMs (universal protease inhibitor-associated mutations = L33I/V/F, V82A/F/L/T, I84V and L90M), i.e. mutations conferring resistance against all currently available PIs. However, even the activity of tipranavir is not unlimited, and susceptibility to tipranavir begins to decrease significantly in the presence of three or more UPAMs. In the BI 1182.52 Study, patients with more than 1.000 copies/ml and at least two previous treatment regimens replaced their PI with tipranavir. After two weeks, the decrease in viral load in patients with two PI mutations was still 1.4 logs, although it was only 0.3 logs for those with three or more mutations (Cooper 2003). Other observations suggest that sensitivity might be reduced more quickly than initially hoped (Hall 2003).

It remains unclear so far whether tipranavir is clinically effective after lopinavir failure – there is only in vitro data on this so far. The modest oral bioavailability of tipranavir requires ritonavir boosting (McCallister 2002). Ritonavir increases the Cmax at least 4-fold, and Cmin by 20-fold or more. Plasma levels can be increased even further by a high-fat meal. The usual dose is therefore 500 mg tipranavir plus 200 mg ritonavir orally twice a day with food.

Unfortunately, there are a number of unfavorable interactions (Roszko 2003, Walmsley 2004). Combination with delavirdine is contraindicated, and ddI should only be administered after an interval of several hours. Plasma levels of lopinavir, saquinavir and amprenavir drop significantly, so that double-PI regimens with tipranavir should currently not be attempted.

On a better note, data from the RESIST-1 Study, first presented in October 2004, is very encouraging (Hicks 2004). This study enrolled patients from North America and Australia with a treatment history of both nucleoside analogs as well as NNRTIs and PIs, including at least two PI-containing regimens. These patients had a viral load of at least 1,000 copies/ml and a minimum of one primary PI mutation (but not more than 2 mutations at codons 30, 82, 84 and 90). A total of 620 patients were randomized to treatment with an optimized, boosted PI regimen (with lopinavir/r in 61 %) or tipranavir/r. In both arms, addition of T-20 was possible. Response was defined as a decrease in viral load of at least one log. After 24 weeks, significantly more patients in the tipranavir arm achieved this, at a rate of 42 %, compared

to 22 % in the other arm. In addition, 25 % (versus 10 %) of patients on tipranavir even achieved a viral load below 50 copies/ml. Tolerability was good.

This data shows that tipranavir maintains good efficacy in heavily treatment-experienced patients. It also demonstrated, yet again, that every salvage drug should be given together with another active substance if possible.

TMC 114 is a nonpeptidic PI, originally developed by the Belgian company Virco/Tibotec (now bought by Johnson & Johnson). The drug has good activity against PI-resistant viruses (Koh 2003). An explanation for this favorable characteristic is now being proposed – the binding affinity for resistant viral mutants is apparently less reduced for TMC 114 than for other PIs (King 2004). Encouraging first data is now available from a Phase II study (Arasteh 2003): 50 patients with treatment failure after multiple PIs were randomized to different doses of this promising PI (all boosted with 100 mg ritonavir). Although there was an average of 6-8 primary PI mutations present, the viral load decreased by 1-1.5 logs after 14 days. TMC 114 has been well tolerated, except for gastrointestinal side effects. Boosting with ritonavir is likely to be necessary.

GW640385X (VX-385) is a PI resulting from a collaboration between Vertex and Glaxo, similarly to amprenavir and fosamprenavir. VX-385 has already been successfully tested in a first Phase I study. It was investigated in a double-blind and placebo-controlled design as a single dose, at increasing dose levels, with and without ritonavir (Reddy 2003). Doses up to 800 mg were well tolerated. Although it is chemically very similar to amprenavir, in vitro data suggests that there will hardly be any cross-resistance (Florance 2004). However, activity of VX-385 is reduced in the presence of the I54L/M+I84V mutation, and with A28S (Yates 2004).

AG-001859 – Pfizer has also now started development of a new PI. AG-001859 is an allophenylnorstatin-containing PI, currently being investigated in Phase I studies. In vitro data shows that this substance has antiviral activity even in the presence of multiple primary and secondary PI mutations (Hammond 2004).

SM-309515 is a new PI from Sumitomo Pharmaceuticals, and has apparently entered Phase I studies. Earlier versions failed due to the short half-life, and attempts are now being made to improve this (Mimoto 2003). PK data in dogs seemed comparable to atazanavir. The drug remained effective against mutations such as S37N, I47V, R57K, and I84V. Conversely, sensitivity to all other tested PIs remained despite resistance against SM-309515. The drug is being tested in humans with ritonavir boosting.

Out of sight, out of mind – development of the following PIs has been stopped:

- DPC 684 – cardiotoxic, apparently with a narrow therapeutic range
- DPC 681 – bought by BMS, which does not seem interested in further development
- GS 9005 (previously GS 4338) – from Gilead
- JE-2147 (AG1776, KNI-764) – from Pfizer, apparently stopped (nothing new since 1999)
- KNI-272 (Kynostatin), poor PK data
- Mozenavir (DMP-450) – development stopped by Gilead in 2002 as there were no advantages to other PIs

- RO033-4649 – from Roche, probably too similar to saquinavir
- SC-52151 and SC-55389A – poor bioavailability
- TMC 126 – the company is concentrating on TMC 114

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Entry inhibitors

There are three crucial steps for entry of HIV into the CD4 T cell:

1. binding of HIV via the gp120 envelope protein to the CD4 receptor ("attachment" – target of attachment inhibitors),

2. binding to coreceptors (target of coreceptor antagonists) via conformational changes to gp120, and finally

3. fusion of virus and cell (target of fusion inhibitors).

Drugs which interfere with these steps are currently summarized as entry inhibitors. Even if the antiviral effects of most drugs now being tested are not overwhelming, the concept is intriguing and the availability of new drugs with different mechanisms of action could open up completely new and currently unpredictable possibilities for the treatment of HIV infection. On the other hand, a lot of the data does not go beyond basic science at this stage, and many of the drugs discussed below may eventually disappear.
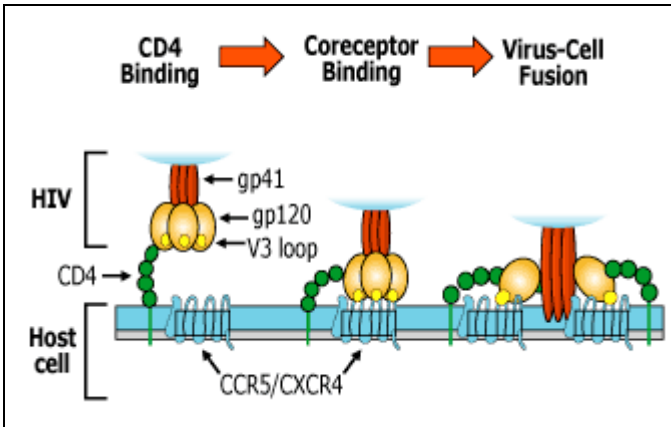
Figure 1: The three main steps of HIV entry into the cell (from: Moore JP, Doms RW. The entry of entry inhibitors: a fusion of science and medicine. PNAS 2003, 100:10598-602).

Attachment inhibitors

This group is very heterogeneous, so it is not possible to speak of a single drug class. Since the beginning of the nineties, there has been a number of investigations into soluble CD4 molecules that prevent the attachment of HIV to the CD4 cell (Daar 1990, Schooley 1990). But, after attaining disappointing results, this approach was forgotten for several years. With the growing knowledge of the mechanism of HIV entry into the cell, as well as following the success of T-20 as the first entry inhibitor, the development of attachment inhibitors has been reinvigorated. However, most drugs are not yet far advanced, often have problematic PK data and are therefore still in the proof-of-concept stage. Most attachment inhibitors act on the interaction between the viral protein gp120 and the CD4 receptor. In contrast to coreceptor antagonists (see below), the activity of attachment inhibitors seems to be independent of coreceptor tropism (Trkola 1998).

Pro-542 (or recombinant CD4-IgG2) is a soluble antibody-like tetravalent fusion protein developed by Progenics, which prevents attachment of HIV to CD4 T-lymphocytes by binding to gp120. Phase I studies have shown good tolerability, and viral load decreased even after a single infusion at 10 mg/kg – although only marginally (Jacobson 2000). In a more recent study, Pro-542 was given at a higher dose of 25 mg/kg as an infusion in 12 HIV-infected patients (Jacobson 2004). The average decrease in viral load was 0.5 logs, and this effect was maintained over 4-6 weeks. Surprisingly, activity was greater in more advanced HIV infection. X4-tropic viruses (see below) were just as susceptible as R5-tropic strains. This substance was well tolerated after a single infusion. Pro-542 has also been tested in children (Shearer 2000). In the SCID mouse model, Pro-542 has shown remarkable efficacy (Franti 2002). However, the impractical route of administration (infusion) is a major disadvantage.

BMS-488,043 is an early attachment inhibitor from BMS, which binds very specifically and reversibly to HIV gp120 and thereby prevents attachment of HIV to the CD4 cell. It has now replaced BMS-806. In early 2004, the first results in HIV-infected patients were published (Hanna 2004). Patients received either 800 mg or 1800 mg, both twice daily, or placebo. Viral load after 7 days of monotherapy dropped in both dose groups by a median 0.72 or 0.96 logs. In 7/12 patients in the 800 mg group, viral load was reduced by more than one log; in the 1800 mg dose group this proportion was 8/12 patients. The substance was well tolerated in this study. However, pill burden is still very high – the formulation urgently requires further improvement.

TNX 355 (previously "Hu5A8") is a monoclonal antibody that binds to the CD4 receptor and thereby prevents the entry of HIV. It is currently being developed by Tanox Biosystem (Houston, Texas). The mechanism of action has not been clearly explained. In contrast to other attachment inhibitors, TNX355 does not seem to prevent binding of gp120 to CD4, but rather binding of gp120 to CCR5 and CXCR4. Some experts therefore describe it as a coreceptor antagonist. It can only be administered intravenously. A first Phase Ia study has been completed, in which treatment-experienced patients received different single doses of TNX 355. 10/12 patients experienced a decrease in viral load of more than one log (Kuritzkes 2004). At the highest dose of 25 mg/kg, the median drop in viral load was 1.1 logs; the maximum antiviral activity was seen after three weeks. Resistance seems to develop rapidly (Jacobson 2004). In the US, placebo-controlled studies are currently underway, in which extensively pretreated patients receive TNX 355 as an infusion every two weeks for a year. The study is still recruiting, and data is not expected before the end of 2005.

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Coreceptor antagonists

In addition to the CD4 receptor, HIV requires coreceptors for entry into the target cell. The two most important ones are CXCR4 and CCR5. HIV variants mainly using CCR5 are referred to as R5 viruses; those using CXCR4 are referred to as X4 viruses. In one analysis of two large cohorts, around 80 % of all viruses exhibited CCR5 tropism, i.e. are R5 viruses. Receptor tropism correlates with the stage of infection. R5 viruses are more likely to occur at higher CD4 cell counts and lower viral loads (Moyle 2004). X4 viruses appear almost only in advanced stages of disease: at above 500 CD4 cells/µl, only 6 % exhibit CXCR4-tropism, compared to over 50 % at CD4 cell counts below 25/µl (Harrigan 2004). X4 viruses usually occur only in dual tropic X4/R5 populations; populations consisting exclusively of X4 viruses are very rare. One study found significantly more viruses with CXCR4 tropism in treatment-experienced patients (Demarest 2004).

Based on coreceptor specificity, substances are classified as CCR5 or CXCR4 antagonists. A number of very promising substances, particularly among the CCR5 antagonists, are now fairly advanced in development. The competition between the companies involved (Schering-Plough, Pfizer and GSK) is somewhat reminiscent of that occurring in 1995 between the PI companies (Roche, MSD and Abbott) – each wants to be the first, and huge pressure is pushing development ahead.

Despite the euphoria surrounding this class of drugs, several questions arise: which patients would be ideal candidates for CCR5 antagonists? Initially it would seem that only patients with R5-tropic viruses would qualify. Although past studies have unanimously demonstrated that the proportion of X4-tropic viruses is fairly small, at around 20 % overall, it seems that particularly patients with advanced HIV infection and extensive prior therapy would benefit least from CCR5 antagonists. This also means that CCR5 antagonists will have to be given earlier on. The second question is: will the expected shift to X4 viruses induced by CCR5 antagonists harm patients? There is much data to support the association of X4 viruses with rapid CD4 cell decline and disease progression (Connor 2997, Scarkatti 1997, Xiao

1998). Although complex phylogenetic studies have demonstrated that X4-tropic viruses emerging under treatment with CCR5 antagonists are probably selected from pre-existing pools and do not develop as a result of a switch in receptor usage (Lewis 2004), the risk associated with possible X4 selection remains uncertain. Finally, an important problem is how to test for viral tropism. ViroLogic is currently the only laboratory conducting this complex test, which requires living cells. Nobody knows how accurate this test really is and what the presence of dual tropic viral populations comprised of both R5 and X4 strains signifies.

Vicriviroc (SCH-D, **Sch-417690)** is a CCR5 antagonist from Schering-Plough with oral bioavailability. It is already in Phase II studies. In the Phase I studies, presented in February 2004, the highest dose of 50 mg daily induced an average drop in the viral load of 1.62 logs (Schürmann 2004). The substance has so far been well tolerated. Arrhythmia (QT elongation), which occurred under the earlier version SCH-C, was not observed. In addition to Phase II studies in treatment-naïve patients, studies in treatment-experienced patients and in patients with HCV coinfection are also being conducted.

Maraviroc (UK 427,857) is a CCR5 receptor antagonist from Pfizer that is about as advanced in development as SCH-D – and probably just as promising. Data from the first Phase Ib study were published in September 2003 (Pozniak 2003). 24 asymptomatic patients with R5-tropic viruses, more than 250 CD4 cells/µl and a viral load above 5,000 copies/ml were distributed between three arms in a double-blind design. They received 10 days of treatment with UK-427,857: 25 mg once-daily, 100 mg twice-daily, or placebo. In the 100 mg group, the median decrease in viral load was 1.42 logs after 10 days. The drug has been well tolerated in all studies so far. This is also true for a study in 54 healthy volunteers, who received four weeks of 100 or 300 mg UK-427,857 twice-daily (Russell 2003). UK427,857 has no activity against X4 viruses. Several Phase II studies are underway.

Aplaviroc (873,140) is a new CCR5 antagonist from GSK, for which clinical data was first presented in October 2004. Results do not seem to differ significantly from those of the competitors Schering and Pfizer (Lalezari 2004). 40 patients were allocated in a randomized double-blind procedure to receive different doses of 873,140. At the highest dose of 600 mg, viral load dropped by 1.66 logs after 10 days, and the drug was well tolerated.

TAK-220 is a CCR5 receptor antagonist from the Japanese company Takeda. After the predecessor TAK-779, which required parenteral administration, had to be abandoned due to irritation at the injection site (Este 2001), efforts are focusing on TAK-220 (Iizawa 2003), which can be given orally. In rats and monkeys, oral bioavailability was adequate. It seems that Phase I studies are now starting.

Pro-140 is a CCR5 antagonist from Progenics, which acts as a monoclonal antibody (Trkola 2001). In animal studies (SCID mouse model), single doses of the drug achieved significant and dose-dependent reductions in viral load without evidence of rebound under treatment (Franti 2002). In vitro data suggests good tolerability, as the normal function of CCR5 receptors is apparently not disturbed, at least not at the doses that are required for inhibition of HIV replication (Gardner 2003). Clinical data is still lacking, and there is no information on tolerability.

AMD 070 is a CXCR4 receptor antagonist like its predecessor AMD-3100. This receptor is mainly used by R4-tropic SI strains – HIV isolates found at later stages

of infection that are associated with a rapid decline in T helper cells (van Rij 2002). AMD 070 is not effective against R5-tropic viruses. After AMD-3100 had to be abandoned due to severe side effects (arrhythmia), development is continuing with AMD 070 – the drug apparently has good oral bioavailability, and initial studies in humans are underway (Schols 2003). Healthy volunteers tolerated AMD 070 well, but developed leukocytosis. Plasma levels were higher than the EC90 of HIV, as determined in vitro (Stone 2004) – activity after oral dosing is therefore likely. The strategy for double entry inhibition, i.e. the combination with a CCR5 antagonist, will certainly be intriguing. The first in vitro data testing this hypothesis is now available (Schols 2004).

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Fusion inhibitors

(For T-20, see the summary in the Drug chapter)

Although the fusion inhibitor T-20 was the first entry inhibitor, there has been little development in this field. T-1249 was initially intended to follow T-20, but development was stopped in early 2004, although the substance was both well tolerated and effective against T-20-resistant virus isolates. The official reason from the company was that the manufacturing process was too complicated. The real reason was probably different. The success of T-20 has been too modest so far, and T-1249 would have required daily subcutaneous injection. This is unappealing for many patients and clinicians – expectations in the HAART era are high. It therefore now seems unlikely that another drug will make it to licensing in the next years. It still needs to be demonstrated whether small molecular fusion inhibitors, a new group of fusion inhibitors with oral bioavailability, are effective (Jiang 2004).

T-649 is a T-1249 analog that binds to the HR2-region of gp41, like T-20. However, the binding site seems to overlap only partially with that of T-20 (Derdeyn 2001). Combination of T-20 and T-649 can possibly prevent or delay development of resistance. However, mechanisms for T-649 resistance have since been discovered (Heil 2002).

FP-21399 is being developed by Lexigen (previously Fuji ImmunoPharmaceutical) as a fusion inhibitor. A single dose shows good tolerability. The most frequent side effects were discoloration of skin and urine. However, the initial viral load data was not convincing – out of 13 patients, only 2 had a decrease in viral load of at least 1 log after 4 weeks (Dezube 2000). Since then, not much has been heard. Whether FP-21399 will be developed further is uncertain.

Out of sight, out of mind: entry inhibitors whose development has been stopped:

- AMD 3100 (CXCR4A) from AnorMed, due to cardiotoxicity
- BMS 806 (attachment inhibitor) from BMS, replaced with BMS 488,043
- T-1249 (fusion inhibitor) from Roche/Trimeris, little prospect of success
- SCH-C (CCR5A) from Schering-Plough, due to arrhythmia

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Integrase inhibitors

Integrase is one of the three key enzymes encoded by the HIV *pol* gene. This enzyme is involved in integration of viral DNA into the host genome (Nair 2002). Integrase inhibitors differ from entry inhibitors, as they do not prevent entry of the virus into the cell. The development of new and effective drugs in this class is proving difficult, and progress is slow (Debyser 2002). A good number of drugs have appeared over the last years, only to disappear again just as quickly. This is true for S-1360, an integrase inhibitor that was developed by Shionogi/GSK and discussed here last year as showing promising initial data (Fujiwara 2002, Yoshinaga 2002). Antiviral activity in humans was probably too weak. The newest product at GSK is now S-1368.

Merck has also been working tirelessly on integrase inhibitors for some time. After some difficulties, the first prototypes are now ready for testing in clinical trials (Hazuda 2002). A new class, the naphthyridine-7-carboxamides, shows good oral bioavailability. **L-870812** and **L-870810** are currently the most promising drugs in this class. In an animal model in SIV-infected monkeys, the viral load decreased in 4 of 6 animals by more than one log. Phase I trials were started based on this data.

The pyranodipyrimidine integrase inhibitors are completely new; of these, a substance called **V-165** seems to be the most potent (Debyser 2003, Fikkert 2003).

In view of past experience, it seems unrealistic to expect significant progress or drugs that actually make it to the clinic in the area of integrase inhibitors within the next few years – even if the companies involved are very hopeful. We'll wait and see.

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Immunotherapy and its relevance in clinical practice

In recent years, in addition to "conventional" ART, immunomodulatory treatment strategies have been investigated to an increasing extent (reviews in: Mitsuyasu 2002, Sereti et Lane 2001). All of these therapies still lack proof of clinical benefit. Some important approaches are nevertheless addressed briefly below.

Interleukin-2 (Proleukin™)

Interleukin-2 (IL-2, aldesleukin, Proleukin™) is a cytokine that is produced by activated T cells and which induces proliferation and cytokine production in T cells, B

cells and NK cells (review in: Paredes 2002). It has been employed in oncology for years. IL-2 was already investigated in the early nineties, either intravenously or as a continuous infusion in HIV-infected patients (Wood 1993, Carr 1998). It is now usually administered subcutaneously. There are a few reports of the use of IL-2 in acute infection (Dybul 2002), but most studies have been in chronically infected patients.

The most important effect of IL-2 in HIV medicine is the increase in CD4 and CD8 T cells, which may be quite impressive in individual cases (Kovacs 1996). Several randomized studies have consistently demonstrated significant increases in CD4 T cells with varying subcutaneous regimens. After administration of IL-2, CD45RO memory cells initially increase, followed by naive CD45RA T cells (Chun 1999, Carcelain 2003). The life span of CD4 and CD8 T cells may also be lengthened.

IL-2 is usually given at doses of 2 x 4.5 million I.E. subcutaneously over 5 days, in cycles 6-8 weeks apart (Davey 2000, Losso 2000, Abrams 2002, Lelezari 2000, Hengge 1998). Daily low-dose treatment has also been investigated (review in: Smith 2001). Viral load was usually unaffected by IL-2. The main results of several large, randomized studies are summarized in the following table.

Table 3.1: Larger, randomized IL-2 studies. VL = viral load, MIU = Million International Units

Study	n	Patients (Median CD4 at baseline)	Doses of Interleukin-2 (MIU)	Main results (In each case comparing IL-2 arm to arm without IL-2)
ANRS 079 Levy 2001	118	PI-naïve (CD4 200-550)	2 x 5 for 5 days 10 cycles	Median CD4 increase (865 versus 240 after 74 weeks) No difference in VL
ACTG 328 Mitsuyasu 2001	174	HAART (CD4 264)	1 x 7.5 for 5 days every 8 weeks	Median CD4 increase (614 versus 396 after 84 weeks)
CPCRA 059 Abrams 2002	511	HAART (> 300 CD4)	2 x 1.5-7.5 for 5 days every 8 weeks	CD4 increase in the IL-2 arms higher by 251 at month 12, no difference in viral load
Lalezari 2002	115	HAART (< 300 CD4)	1 x 1.2 daily	No significant difference in CD4, but in NK and naive CD4 at 6 months
ANRS 082 Katlama 2002	72	HAART (< 200 CD4)	2 x 4.5 for 5 days every 6 weeks	Median CD4 increase (51 versus 11 after 24 weeks)
Davey 2000	82	HAART (CD4 2-500)	2 x 7.5 for 5 days every 6 weeks	Median CD4 increase (384 versus 64 after 52 weeks) VL -0.28 versus 0.09 logs (p = 0.03).

In all larger studies, the combination of IL-2 with HAART has so far proven to be relatively safe. Nevertheless: the drug has considerable side effects – fever, chills and flu-like symptoms with myalgia that may be severe and are usually dose-limiting. The side effects are the result of the IL-2-induced release of cytokines and invariably resolve 2-3 days after the last dose. Paracetamol, rest and intake of electrolyte-rich solutions may be helpful. The side effects, which are more severe than with interferon, cannot be suppressed completely. Pegylated interleukin-2 is presumably weaker and does not have a better tolerability overall (Carr 1998). Combination with prednisone does not have any advantages (Tavel 2003).

Unfortunately, the activation of T cells has no influence on viral reservoirs. Although it was initially hoped that IL-2 could be used to purge virus in the reservoirs and thereby "wash out" latently infected cells from the body (Chun 1999), it is now clear that this does not occur. In the German COSMIC Study, 56 patients with more than 350 CD4 T cells/µl on HAART were randomized to receive IL-2 or placebo. Although IL-2 led to a normalization of CD4 cell count in significantly more patients, IL-2 did not influence viral replication, proviral DNA or latently infected cells (Stellbrink 1998 + 2002).

Most studies have now shown that CD4 T cell nadir is predictive for CD4 cell increases under IL-2 (Markowitz 2003). In other words: the greater the impairment of the immune system, the less likely it is to benefit from IL-2 therapy. The source of the CD4 cell increases under IL-2 is also a subject of some discussion. Some authors suspect that the increase is more due to peripheral expansion than to increased thymus output (Lu 2003), others have assigned greater importance to the thymus (Carcelain 2003).

One question remains unanswered: are the CD4 T cells generated by IL-2 of the same quality as "normal" CD4 T lymphocytes? The immune response to specific antigens such as tetanus, gp120, hepatitis A or B seem to remain unaffected by IL-2 (Valdez 2003). The most important question remains unanswered today – do the increases in CD4 count really prevent AIDS? Do patients really benefit clinically from these difficult IL-2 treatments? Little is also known about the long-term use of IL-2 – the longest study performed to date lasted three years (Gougeon 2001).

Answers to these questions on long-term side effects and above all on clinical benefit were expected from ESPRIT and SILCAAT, the two ongoing multinational studies. But, due to the very low number of clinical events (death, AIDS), it is unlikely that either of these studies will provide definitive answers.

ESPRIT (http://www.espritstudy.org) is a randomized study in which around 4,000 patients with at least 300 CD4 T cells/µl are being treated with IL-2 or not in addition to antiretroviral therapy (Emery 2002). In the summer of 2003, the first preliminary data was published (Weiss 2003). By this time, 1,929 patients had been randomized. The interim analysis included 1,394 patients: after three cycles, 64 % of patients in the IL-2 arm experienced treatment success, defined as CD4 T cell increases of at least 200/µl. A higher CD4 T cell nadir, higher CD4 T cells at baseline and younger age were associated with treatment success, as expected. Enrolment has now been completed.

SILCAAT had a similar concept, but enrolled patients with 50-299 CD4 T cells/µl and a viral load of < 10,000 copies/ml. Patients received a total of 6 cycles of 2 x 4.5 MIU IL-2 subcutaneously over 5 days every 8 weeks. After enrolment of

1,957 patients in 137 centers in 11 countries, the study was stopped in October 2002, as it was simply too expensive for the manufacturer – costs were estimated at around $130 million. After major protests, SILCAAT is now continuing with a simplified design. First results have recently been published (Levy 2003): in 449 patients who have now been followed for one year, the median CD4 increase was 123 cells/µl – which is definitely a considerable gain for this group of immunocompromised patients. This gain was again greater in patients with better CD4 cells at baseline, as in ESPRIT. Data from the SILCAAT therefore also seems to indicate that even IL-2 has limited effects for reconstituting the immune system once it has been destroyed.

Summary: despite SILCAAT and ESPRIT, IL-2 therapy must continue to be viewed skeptically based on available data. In our view, there are only a few patients who should potentially be considered for therapy with IL-2. These are patients with no immunological response, patients whose CD4 counts remain below 100/µl despite good viral suppression over longer periods of time.

Hydroxyurea (Litalir™, Droxia™)

Hydroxyurea is an old chemotherapeutic agent with relatively low toxicity which is still being used today in hematology (mostly in chronic myelogenous leukemia). It inhibits DNA synthesis via the ribonucleotide reductase, and leads to an intracellular shortage of deoxynucleotide triphosphates. A synergistic effect on HIV replication in combination with ddI was demonstrated in 1994 (Lori 1994).

A randomized, double-blind study from Switzerland attracted attention in 1998 (Rutschmann 1998). The investigators treated 144 patients with hydroxyurea or placebo in addition to d4T+ddI. After 12 weeks, 54 % of hydroxyurea-treated patients demonstrated a viral load below 200 copies/ml compared to 28 % in the placebo group. Was this the discovery of a new cheaper option for HIV treatment? In the light of these seemingly exciting results, the fact that the CD4 T cell increase in the hydroxyurea group was only 28 versus 107 cells/µl in the placebo group had to be tolerated. Hydroxyurea was even more in fashion after publication of the "Berlin Patient": a patient, who had been treated with hydroxyurea in addition to indinavir and ddI during acute infection, had stopped all therapy after a few months and subsequently showed no detectable plasma viremia (Lisziewicz 1999). Was this unexpected outcome due to hydroxyurea? Several smaller studies from the US and Argentina seemed to confirm these positive results, seen primarily in combination with ddI (Hellinger 2000, Lori 1999, Rodriguez 2000). Many treating physicians added the drug to ART, and even children received hydroxyurea. Many already dreamed of a cheap combination of ddI+HU for Africa.

These initial hopes subsided quite rapidly. Although hydroxyurea is usually well tolerated, the combination with ddI and d4T in particular seemed problematic. Data from early 2000 reported an additive effect, with a frequency of polyneuropathy of almost 30/100 patient years (Moore 2000).

The ACTG 5025 Study (Havlir 2001), in which hydroxyurea was evaluated as a "stabilizer" of successful therapy (stable undetectable viral load), led to the temporary demise of this drug in HIV therapy. Three deaths on the combination of ddI+d4T (+IDV) due to pancreatitis, all in the hydroxyurea group, were reported. There was also a higher rate of treatment failure in patients receiving hydroxyurea,

probably due to toxicity rather than to virological failure. The risk of pancreatitis on ddI seems to be four times higher in combination with hydroxyurea (Moore 2001). Randomized studies also failed to show an effect in primary infection: obviously, further Berlin patients cannot simply be "reproduced", at least not for hydroxyurea (Zala 2002).

In 1999, BMS received a warning from the FDA for having too enthusiastically promoted hydroxyurea for HIV therapy (http://www.hiv.net/link.php?id=164).

Newer data is possibly showing an effect after all. In 69 patients – with treatment failure under a PI and naïve for efavirenz/ABC – the combination of d4T+ddI+ABC+efavirenz in a randomized study from France had astonishing results. After one year, 55 % on hydroxyurea versus 21 % were below 50 copies/ml (Lafeuillade 2002). But should such data be considered after all that has happened with this drug in the past? In 2004, at least two further randomized studies were published, showing toxicity but no positive effects (Blanckenberg 2004, Stebbing 2004). In our opinion: hydroxyurea should not be used anymore for antiretroviral therapy outside of clinical studies, and such studies should have relevant objectives.

Interferon

The antiretroviral effect of interferon has been known for years (Milvan 1996). The effect of 3 million I.E. daily s.c. is about 0.5-1 logs (Haas 2000). Higher dosing may increase this effect further (Hatzakis 2001). An in-depth investigation of the antiviral activity of interferon was initially not conducted because of the subcutaneous delivery route and its side effects. However, there have recently been indications that the drug may be useful for salvage therapy. Pegylated interferons now allow for weekly administration, and improved efficacy with the pegylated drug is anticipated, in analogy to the studies in the setting of hepatitis C infection. Studies on this are underway. Schering-Plough in particular is currently involved in trying to license the product. However, there have been setbacks, as with IL-2, and a pivotal multinational study in highly treatment-experienced patients was aborted in October 2002 due to insufficient recruitment.

Other immunotherapies

The prototype of therapeutic vaccination already suffered disaster years ago. Remune™, developed by a team headed by Jonas Salk, is a therapeutic vaccine comprised of an envelope-depleted (gp120) virus which, although indeed immunogenic, does not seem to provide any clinical benefit (i.e., prolongation of life and delay of disease progression). A large trial was interrupted prematurely in May 1999 as no benefit had been demonstrated for study participants. More than 2,500 patients had taken part for a mean of 89 weeks in this multinational study, which was designed to evaluate the addition of Remune™ to HAART. As well as the lack of clinical benefit, not even advantages with respect to CD4 cell count or viral load could be shown (Kahn 2000). The product is now probably obsolete, even though there have been dubious reports, mainly from Thailand, claiming that some effect exists.

G-CSF and **GM-CSF** – the cytokines G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) have frequently been used in HIV patients. G-CSF is available as filgastrim, pegfilgastrim and lenogastrim; GM-CSF is available as sargramostim or molgramostin.

G-CSF is licensed for treatment of prolonged neutropenia in patients with advanced HIV infection to reduce the risk of bacterial infections. Treatment with G-CSF can be particularly useful in patients on chemotherapy or myelosuppressive drugs such as ganciclovir or AZT. G-CSF significantly reduces bacterial infections in neutropenic HIV patients. In a large randomized study, 258 neutropenic HIV patients (neutrophils 750-1,000/μl) with CD4 T cell levels below 200/μl were either treated for 24 weeks with G-CSF (3 times/week) or not. The rate of severe neutropenia was only 1.7 %, versus 22 % in the control group (Kuritzkes 1998). The incidence of bacterial infections was reduced by 31 %, and the number of inpatient days was reduced by 45 %. There was no effect on viral load. In patients TCH CMV retinitis, G-CSF was also shown to have significant survival benefit, although the mechanisms remained unclear (Davidson 2002).

GM-CSF showed a slight effect on viral load in three double-blind, randomized studies (Angel 2000, Skowron 1999, Brites 2000); however, in one study in patients with uncontrolled infection there was a slight increase (Jacobsen 2003). No effect was observed under G-CSF (Aladdin 2000). GM-CSF seems to prevent significant loss of CD4 cells during longer treatment interruptions (Fagard 2003). However, such approaches cannot be recommended outside of clinical studies. The side effects and significant cost of G-CSF and GM-CSF should also be considered. Whether any clinical benefit exists remains unclear.

Cyclosporin A (Sandimmune™) – Immune activation may lead to increased HIV replication, and an attractive treatment hypothesis has been to suppress the immune system in an attempt to slow down viral replication. This is the rationale behind studies investigating the use of cyclosporin A (Calabrese 2002, Rizzardi 2002). The drug is normally used for prophylaxis of transplant rejection after allogenic organ transplantation. In the largest study to date, 28 HIV patients were recruited to receive cyclosporin A 4 mg/kg or placebo daily for 12 weeks, with or without antiretroviral therapy (two nucleoside analogs; Calabrese 2002). The results are easily summarized: cyclosporin A had no effect on CD4 or CD8 count, nor on expression of activation markers such as CD38 or HLA-DR. Cyclosporin A therefore probably has no future in the therapy of chronically infected HIV patients. Whether, and how, cyclosporin A might improve treatment of acute HIV infection needs to be clarified in further studies. Use of both immunosuppressants (CsA) and immunostimulants (IL-2) in this setting shows the clear discrepancy between scientific knowledge and hope.

Mycophenol (Cellcept™) follows a concept similar to that of hydroxyurea and cyclosporin A. Mycophenol inhibits the inosine monophosphate (IMP) dehydrogenase and is normally used for prophylaxis of acute transplant rejection in patients with allogenic kidney, heart or liver transplantations, as well as for some autoimmune diseases. Inhibition of lymphocyte proliferation and reduction of target cells should theoretically inhibit replication of HIV. First reports from small cohorts of patients seem to demonstrate an effect on viral load in some cases (Margolis 2002, Press 2002). Whether this will be confirmed by randomized trials seems uncertain. An initial randomized study suggests that this is unlikely (Sankatsing 2004).

Cannabinoids have no effect. A controlled, prospective, randomized study, in which patients could either smoke marijuana or receive TCH (dronabinol, Marinol™) or placebo in addition to HAART, showed no effects on lymphocyte sub-

populations or lymphocyte function after three weeks (Bredt 2002). THC, which is metabolized via the cytochrome P450 system, also had no detrimental effects on viral load or plasma levels of protease inhibitors (Abrams 2003).

Corticosteroids have been and continue to be used and propagated by some HIV clinicians again and again. However, such treatment does not stand the test of controlled studies. In a placebo-controlled study with 0.5 mg prednisone/kg over 8 weeks, there were no effects on CD4 T cells or viral load (McComsey 2001). In ACTG 349, 24 patients were treated with 40 mg prednisone daily or not in a double-blind randomized design (Wallis 2003). After 8 weeks, there was a trend towards higher levels of CD4 cells in the prednisone arm (> 40 %, p = 0.08), but there were no effects on activation markers or apoptosis. Two patients on prednisone developed asymptomatic necrosis of the femoral head. This study should advise caution before the use of steroids for "immunological" reasons is considered.

Interleukin-12 – IL-12 stimulates T lymphocytes and NK cells to generate a Th1-type immune response. In a randomized Phase I study with rhIL-12 100 ng/kg 2 x/week, the drug was well tolerated but had no effect on lymphocyte subpopulations, antigen-specific immune response or viral load (Jacobson 2002). Further development is therefore uncertain. The same would appear to be true for interleukin-10 (Angel 2000). In the age of highly effective antiretroviral therapies, such experimental therapies have to meet ever-increasing standards.

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4. Goals and Principles of Therapy

Christian Hoffmann and Fiona Mulcahy

In the flood of monthly evaluations – including CD4 count, viral load, routine laboratory, genotypic and phenotypic resistance testing, and drug plasma levels – the ultimate goal of antiretroviral therapy should always be borne in mind:

To prolong the patient's life,
while maintaining the best possible quality
of health and life.

This paradigm suggests that it is equally important to not only prevent opportunistic infections and malignancies, but also to minimize the side effects of therapy. Ideally, antiretroviral treatment should have little or no influence on daily life. Even if a high CD4 count and a low viral load are useful therapeutic goals, the patient's condition is at least as significant as the laboratory results! Patients, too, often lose focus on what really matters. The response to the doctor's query: "How are you?" is often accompanied by a glance toward the CD4 count result on the chart: "That's what I'd like you to tell me!". It may therefore be useful to reflect upon what one realistically aims to achieve. Treatment aimed only at improving laboratory values with little emphasis on the physical and mental well being of the patient cannot be successful.

Success and Failure of Treatment

Both success and failure of treatment can be evaluated using different criteria – virological, immunological or clinical. Of these, the earliest indicator is **virological** success or failure (decrease or increase in viral load). This is followed, often a little later, by **immunological** treatment success or failure (rise or fall in CD4 cell count). **Clinical** treatment failure usually only becomes apparent much later – first the lab values deteriorate, then the patient! On the other hand, success of treatment may be seen much earlier; many patients suffering from constitutional symptoms rapidly improve on HAART. In the Swiss Cohort, the incidence of opportunistic infections after only three months on HAART was reduced from 15.1 to 7.7 per 100 patient years (Ledergerber 1999). For clinical treatment success, in particular for prevention of AIDS, immunological success is probably at least as important as virological success (Grabar 2000, Piketty 2001).

Virological treatment success and failure

Virological treatment success is usually understood as being the suppression of viral load to below the level of detection of 50 copies/ml. This is based on the understanding that, the more rapid and complete the decrease in viral load, the longer the therapeutic effect (Kempf 1998, Powderly 1999, Raboud 1998).

In the INCAS Trial, the relative risk of treatment failure (defined here as an increase to above 5,000 copies/ml) in patients who had reached a viral load be-

low 20 copies/ml was 20 times lower than in those who had never reached a level under 400 copies/ml (Raboud 1998).

On HAART, viral load declines in two phases (see also the chapter "Monitoring"); there is an initial very rapid decrease in the first weeks, followed by a slower phase, in which plasma viremia declines only slowly. A decrease to below the level of detection may take up to 3-4 months; in cases of very high baseline viral load it may take 4 or 5 months. However, a viral load above the level of detection after 6 months of treatment is almost always seen as failure. The same is true if a rebound in viral load is confirmed by a second determination after a short interval. In such cases, improvements in therapy (e.g. adherence, change of regimen) should soon be considered.

Virological treatment failure can be recognized quite early – therefore, early monitoring even after only four weeks is useful not only to the patient for psychological reasons ("less viruses, more helper cells"). But it is also an important indication for the treating physician of the further success of treatment. If the viral load is not below 5,000 copies after four weeks of HAART, later treatment failure is likely (Maggiolo 2000).

The cut-off point of 50 copies/ml is arbitrary. It is based on the currently available assays for measurement of viral load. Whether 60 copies/ml are indeed worse than 30 copies/ml and indicate a lesser success of treatment has still not been proven. At these low levels, methodological inaccuracies must also be taken into account. A single viral load rebound ("blip") to low levels (up to 1000 copies/ml) is often irrelevant (see below).

A viral load "below the level of detection" of 50 copies/ml means just that – no more, no less. Numerous studies indicate that replication and therefore development of resistance can continue even with an undetectable virus load. 50 viral copies/ml indicate that 5 liters of blood contain 250,000 viruses; in addition, even more actively replicating viruses are present in the lymphatic organs. Thus, theoretically, measurable viremia, even at very low levels, may possibly translate to a higher risk of resistance in the long-term. Perhaps there is indeed a relevant difference between 100 and 10 copies/ml with regard to the risk of developing resistance. But we just don't know yet.

The good news is that morbidity and mortality may be lowered significantly even if the viral load is not decreased below the level of detection (Mezzaroma 1999, Deeks 2000, Grabar 2000). This should be borne in mind when treating patients who have only a limited number of treatment options. In such cases, it may be more sensible to abandon viral load as a measure of success (see "Salvage Therapy" chapter). In patients with multiresistant viruses, virological success in the strict sense may not be possible; here, stabilizing the CD4 count should be of top priority. Patients often remain immunologically stable for relatively long periods of time, even with insufficient viral suppression.

A large cohort study has shown that CD4 T cells do not drop as long as the viral load remains below 10,000 copies/ml or at least 1.5 logs below the individual set point (Lederberger 2004). The most important risk factors for virological treatment failure are extensive pre-treatment with antiretroviral drugs (pre-existing resistance mutations) and nonadherence (review: Deeks 2000). Whether viral load and CD4 count at the time of treatment initiation really play a role, has not yet been conclu-

sively proven; in several cohorts no influence was detected (Cozzi-Lepri 2001, Phillips 2001, Le Moing 2002; see also discussion in the chapter "When to Start HAART").

How long does virological treatment success last?

Little is known about how long treatments remain effective. The rumor that treatment success is limited to only a few years is still widespread. It originates from the early years of HAART. However, many patients at the time were still inadequately treated or had been pre-treated with mono- or dual therapy, and had thus developed extensive resistance. In such patients, the effect of treatment may be more short-lived, as even a single point mutation is often enough to topple a whole regimen.

Following the eight to nine years during which HAART has been employed, a surprisingly high number of patients still have viral loads below the level of detection, even after this considerable period of time. This is particularly true for patients who were adequately treated from the start, as judged by today's standards (starting with triple therapy and/or rapid switching of several drugs). One of the few trials with a longer follow-up period studied 336 antiretroviral-naïve patients who had reached a viral load below 50 copies/ml within 24 weeks (Phillips 2001). After 3.3 years, the risk of viral rebound seemed at first glance to be relatively high at 25.3 %. More detailed analysis showed that a large proportion of the patients experiencing viral rebound had actually interrupted HAART. True virological failure was only seen in 14 patients, which corresponds to a risk of 5.2 % after 3.3 years. Most importantly, the risk of virological failure decreased significantly with time.

In the Phase II M97-720 Study, in which 100 patients were originally treated with d4T+3TC+lopinavir/r, 62 % still had less than 50 copies/ml after six years in the ITT analysis (Gulick 2004). Despite the fact that several patients had interrupted treatment for different reasons, real virological failure was very rare. An impressive 98 % were below the level of detection after six years in the on-treatment analysis. In the Merck 035 subanalysis, patients on AZT+3TC+indinavir were also followed for six years. In the last ITT analysis, 58 % were still below the level of detection, despite the fact that these patients had been pre-treated with nucleoside analogs (Gulick 2003).

These studies clearly show that, providing treatment is not interrupted, viral load may remain below the level of detection for many years, perhaps even decades.

"Blips" – Do they mean virological failure?

Blips are transient increases in viral load. They occur in 20-40 % of patients and have been associated with a higher level of viral replication. There is no association with any particular HAART regimens, but rather with the time of treatment initiation – the earlier treatment was started, the less likely the occurrence of blips (Di Mascio 2004).

Blips often worry both patients and clinicians. Strictly speaking, if one defines virological success as having less than 50 copies/ml, blips signify treatment failure. However, increasing data indicates that blips seem to have no consequences in the medium-term, and do not necessarily indicate virological, immunological or even clinical treatment failure (Havlir 2001, Moore 2002, Sklar 2002, Mira 2003). This is true both for patients on first-line therapy and for highly treatment-experienced pa-

tients. In one analysis of 18 months, therapy failure was approximately doubled (Greub 2002).

However, longer follow-up is still required to clarify if patients experiencing occasional blips are at a higher risk of developing resistance. Based on available data, however, blips should not necessitate an immediate change of HAART, as they are more likely to be the result of immunological mechanisms (Di Mascio 2003, Miller 2004). Considerable variability between viral load assays should also be noted.

Blips should nevertheless raise the opportunity for discussion with the patient on the subject of adherence. Does the patient take his or her drugs regularly, or are doses occasionally missed? Are the dosing directions (on an empty stomach or with a meal) followed correctly? Measurement of plasma drug levels may be indicated.

It should be noted that other factors can also be responsible for intermittent viremia. In one large, retrospective analysis, 26 % were caused by intercurrent infections (Easterbrook 2002). For example, syphilis can cause a significant increase in viral load and reduction of CD4 cells (Buchacz 2004). Viral load can also increase temporarily after immunizations (Kolber 2002).

All these points should be considered before changing therapy prematurely and a repeat viral load test within a short interval is advisable.

Immunological treatment failure and success

Immunological treatment success is generally defined as an increase in the CD4 cell count. A more precise definition for immunological treatment success does not currently exist. Depending on the study, increases *by* 50, 100 or 200 CD4 T cells/µl or increases *to* above 200 or 500 CD4 T cells/µl are defined as success. Failure is usually described as the absence of an increase or as a decrease in the CD4 T cell count in patients receiving HAART.

It is difficult to predict the rise in CD4 count in patients on HAART, as there is significant individual variation. As with the decrease in viral load, the increase in CD4 count occurs in two phases. After a first, usually rapid increase over the first three to four months, further increases are considerably less pronounced. In a prospective study involving some 1,000 patients, the CD4 count increased during the first three months by a median of 21.2 CD4 T cells/µl per month; in the following months the increase was only 5.5 CD4 T cells/µl (Le Moing 2002). It is still under debate whether the immune system is restored continuously after a long period of viral load suppression or whether a plateau is possibly reached after three to four years, beyond which there is no further improvement (Smith 2004, Viard 2004).

The lower the CD4 count at baseline, the less likely it is to normalize completely (Valdez 2002, Kaufmann 2003). The immune system often does not recover completely. In the Swiss Cohort, only 39 % of 2,235 patients who had begun HAART in 1996-97 reached a CD4 count above 500/µl (Kaufmann 2003).

Immunological treatment success is not necessarily linked to maximal viral suppression; even partial suppression can result in improved CD4 T cell count (Kaufmann 1998, Mezzaroma 1999, Ledergerber 2004). The initial level of viral load is also not significant; what seems to be decisive is that the viral load remains lower than before treatment (Deeks 2002, Ledergerber 2004).

Recent reports have identified some antiretroviral regimens which may have unfavorable effects on immune reconstitution. Significant drops in CD4 count were observed in patients with a suppressed viremia who switched to a simplified regimen of ddI and tenofovir plus nevirapine (Clotet 2004, Negredo 2004). The reason for this is still not understood, but seems to be related to negative interactions between ddI and tenofovir. Alternatives should be considered in patients failing immunologically on this regimen. In another study, the CD4 increase on abacavir+3TC was significantly better than on AZT+3TC (both combined with efavirenz), despite comparable virological success. This may be related to the myelotoxicity of AZT (DeJesus 2004).

Once CD4 cells have normalized and plasma viremia remains undetectable, it is unlikely that they will reduce significantly (Phillips 2002). In such cases, immunological treatment success does not necessitate frequent continued monitoring!

Discordant response

Failure to achieve every one of the therapeutic goals – clinical, immunological and virological – is referred to as a discordant response.

Some patients may have virological treatment success without immunological improvement, continuing to have a very low CD4 T cell count despite undetectable viral load (Piketty 1998, Renaud 1999, Gabrar 2000, Piketty 2001). In addition to age, the risk factors for a lack of immunological treatment response, despite good viral suppression, include low CD4 counts at baseline, as well as having a low viral load at the start of treatment (Florence 2003). In older patients, immunological response is often only moderate in comparison to virological response. Various studies have demonstrated that the probability of not achieving a rise in CD4 count increases with patient age and with progressive decrease in thymus size as detected by CT (Goetz 2001, Marimoutou 2001, Piketty 2001, Teixera 2001, Viard 2001). Patients who are intravenous drug users also have relatively poor increases in CD4 cells compared to other patients (Dragstedt 2004).

Other possible causes for a lack of immunological response despite good viral suppression may be immuno- or myelosuppressive concomitant therapies.

Conversely, HAART may be extremely effective immunologically and induce significant increases in the CD4 count, while viral load remains detectable. This can sometimes be observed in children and adolescents (see "Pediatrics" chapter). The frequencies of such discordant responses in adults are outlined in the table below.

Table 4.1: Prospective cohort studies, treatment response*

Response to HAART	Piketty 2001 n = 42	Grabar 2000 n = 2236
Virological and immunological response	60 %	48 %
Discordant: only immunological response	19 %	19 %
Discordant: only virological response	9 %	17 %
No treatment response	12 %	16 %

* Immunological response: rise in CD4 T cells > 100/µl after 30 months (Piketty 2001) or > 50/µl after 6 months (Grabar 2000). Virological response: continually at least 1 log below baseline or < 500 copies/ml (Piketty 2001) or < 1,000 copies/ml (Grabar 2000).

Practical considerations in dealing with viral load and CD4 count

- Viral load is the most important parameter in treatment monitoring.
- If possible, use only one type of assay (in the same lab) – bear in mind that there is considerable methodological variability (up to half a log)!
- Virological success should be monitored one month after initiation or modification of HAART.
- Viral load should be below 50 copies/ml after 3-4 months (with high initial viral load, after 6 months at the latest) – if it is not, look for a cause!
- The greater the decrease in viral load, the more durable the response to treatment.
- Transient, low-level increases in viral load (blips) are usually insignificant – but VL should be monitored at short intervals (e.g. 2-4 weeks after such blips).
- The older the patient, the likelier a discordant response (low viral load with no significant increase in CD4 count).
- In contrast to viral load, increase in CD4 T cells, i.e. immunological success, is difficult to influence. CD4 T cells are probably more predictive of the individual risk for AIDS.
- Once CD4 count is good, it requires less frequent monitoring. Remember that with higher CD4 counts, values may vary considerably from one measurement to the next (which may mislead the patient to either a false sense of euphoria or unnecessary concern).

Clinical treatment success and failure

Clinical treatment success is dependent on virological and immunological therapeutic success. In individual patients, clinical response is not always easy to assess. After all, there is no way to show what might have occurred if treatment had not been started. As an asymptomatic patient cannot feel any better, it may be difficult to find good arguments to continue treatment in the presence of side effects, which, at least temporarily, may affect the quality of life.

Clinical success is almost always evaluated via clinical endpoints (AIDS-defining illnesses, death), although the improvement on HAART in a patient with considerable constitutional symptoms should also be seen as clinical success. With regard to risk of disease progression, the immunological response is at least as important as the virological response (Table 4.2).

However, the extent of virological success is of great significance: in the Swiss Cohort, out of those with a constantly undetectable viral load, the proportion of patients developing AIDS or dying was 6.6 % after 30 months. In contrast, this proportion was 9.0 % in patients with viral rebound and even 20.1 % if the viral load was never suppressed to undetectable levels (Ledergerber 1999). The importance of complete and sustained virological treatment success for clinical benefit has also been reported from other cohorts (Salzberger 1999, Thiebaud 2000).

Table 4.2: Risk of progression, as defined by immunological and virological treatment response. See previous table caption for definitions. 95 % confidence interval in parentheses.

	Grabar 2000 n=2236	Piketty 2001 n = 42
CD4 T cells at baseline (median)	150	73
	Relative risk	Relative risk
Virological and immunological response	1	1
Immunological response only	1.6 (1.0-2.5)	6.5 (1.2-35.8)
Virological response only	2.0 (1.3-3.1)	9.7 (1.6-58.4)
No treatment response	3.4 (2.3-5.0)	51.0 (11.3-229.8)

Clinical failure is usually defined as the development of an AIDS-associated condition or even death. However, illness is not always indicative of clinical treatment failure. This is particularly true for the immune reconstitution syndrome, where a pre-existing, subclinical infection becomes apparent during the first weeks following initiation of antiretroviral therapy (see "AIDS" chapter). The manifestation of an OI with rising CD4 cells does not indicate failure, but rather, to put it simply, that the immune system is starting up again.

On the other hand, if a patient develops serious side effects or even dies, this should clearly be regarded as treatment failure. Luckily, this is rare. It should be noted that there may also be other causes. Many severe, life-threatening events that affect HIV patients on HAART today are associated neither with HAART nor AIDS (Reisler 2003).

What can be achieved today?

Every HIV clinician sees the remarkable strides made possible by HAART reflected in his or her own patients (see example below). In many areas, the incidence of AIDS has been reduced to less than a tenth (Mocroft 2000). Some illnesses that occur only with severe immunodeficiencies are rarely seen today. CMV retinitis or MAC disease have become unusual. AIDS cases occur mainly in patients who are not being treated with antiretroviral therapy – usually because they are unaware of their infection or do not want to acknowledge it. In our outpatient clinic, more than half of the patients who have developed AIDS-defining illnesses since 2000 were diagnosed with HIV infection only when they presented with AIDS. In patients followed in specialized centers, AIDS has become a rare occurrence. This is not surprising: less than 15 % of patients in our outpatient clinic now have CD4 T cells below 200/µl.

The mortality rate has continued to decline over time (Mocroft 2002). In the Euro-SIDA Cohort, the risk of suffering or dying from AIDS in the years 1998-2002 was half that of 1996-1997 (Mocroft 2003).

Data from prospective, controlled studies on this dramatic change is still limited, as there have been few randomized trials with clinical endpoints (Hammer 1997, Cameron 1998, Stellbrink 2000). The results seen in these studies, due to their design, led to licensing of the PIs. In a multi-center trial, 1,090 clinically advanced patients received ritonavir liquid formulation or placebo in addition to their ongoing treatment. The probability of AIDS and death with a follow-up of 29 weeks was

21.9 % in the ritonavir arm and nearly double (37.5 %) in the placebo arm (Cameron 1998). In the SV14604 Study, the largest study of its kind to date, involving 3,485 patients, the frequency of AIDS and death was reduced by about 50 % in the group receiving AZT+ddC+saquinavir hard gel, compared to the groups on dual therapy (Stellbrink 2000).

Table 4.3: Patient case (female, 41 years) demonstrating advances in treatment due to HAART*

		CD4 T cells	Viral load
Feb 95	AZT+ddC	23 (4 %)	NA
Nov 96	AIDS: Toxoplasmosis, MAC, Candida esophagitis	12 (1 %)	815,000
Feb 97	d4T+3TC+SQV	35 (8 %)	500
June 97	stopped HAART due to polyneuropathy		
July 97	AZT+3TC+IDV	17 (4 %)	141,000
Mar 98		147 (22 %)	< 50
Mar 99	AZT+3TC+IDV/r+NVP	558 (24 %)	100
Mar 00		942 (31 %)	< 50
Sep 04		854 (30 %)	< 50

*Excellent immune reconstitution despite initial severe immunodeficiency and several AIDS-defining illnesses. Primary/secondary prophylaxis (MAC, Toxoplasmosis, PCP) has now been discontinued.

Studies of mono- or dual therapy are no longer ethically justifiable and the number of clinical endpoints that occur is fortunately now extremely low. As a result, the duration of any contemporary study to prove clinical benefit of one combination over another would have to be extended over long periods. Unrealistically large study populations would also now be required given the extremely low probability of progression – only rarely will such investigations be undertaken in the future (Raffi 2001).

Table 4.4: Decline in morbidity and mortality in large cohorts

	Where? (n)	Patients (Period)	Mortality (/100 py)	Morbidity (/100 py)
Palella 1998	USA (1255)	< 100 CD4 T cells/µl (1/94-6/97)	29.4 → 8.8	21.9 → 3.7*
Ledergerber 1999	Switzerland (2410)	6 months *before* versus 3 months *after* HAART (9/95-12/97)	NA	15.1 → 7.7
Mocroft 2000	Europe (7331)	All (94-98)	NA	30.7 → 2.5
Mocroft 2002	Europe (8556)	All (94-01)	15.6 → 2.7	NA

* MAC, PCP, CMV. Mortality/Morbidity each per 100 py = patient years

This is why data from large cohorts such as Euro-SIDA, the Swiss Cohort and American HOPS Cohort is usually used (see Table 4.4).

With regard to opportunistic infections and malignancies, the effect of HAART is equally as apparent on their clinical course as it is on their incidence. Illnesses such as cryptosporidiosis or PML can be cured, while Kaposi's sarcoma can resolve completely without specific therapy. Prophylaxis of pneumocystis pneumonia, toxoplasmic encephalitis, CMV or MAC infection can usually be safely withdrawn. These effects are discussed in more detail in the corresponding chapters.

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Eradication – Is it Feasible?

At this point in time, eradication of HIV in the sense of a cure is still unrealistic. Although as late as 1997, many still dreamt of eradication, leading researchers are now inclined to be pessimistic. The main problem lies in the pool of latently HIV-infected cells, which probably comprise a lifelong reservoir (review: Saksena 2003).

Even after years of sufficient viral suppression to below 20-50 copies/ml, cellular viral transcription still takes place (Dornadula 1999, Furtado 1999, Zhang 1999, Sharkey 2000). This is particularly true for blood cells, but also applies to lymph nodes and sperm (Lafeuillade 2001, Nunnari 2002). Different methods have been used in the last few years to attempt to flush out these latent reservoirs (IL-2, hydroxyurea, OKT), but all have failed (Kulkosky 2002, Pomerantz 2002).

In a more recent study, a half-life of 44.2 months was calculated for the latently infected reservoir in 62 patients, whose viral load had been successfully suppressed on HAART for seven years (Siciliano 2003). The calculated time to eradication of these reservoirs was 73.4 years. Even in a highly selected group of patients, without even a single viral blip measured during a minimum of three years of stable HAART and with an overall trend for a slightly more rapid decrease in infected cells, the time to eradication was 51.2 years.

Newer studies demonstrate that latently infected reservoirs consist of very heterogeneous cell populations, the stability of which is probably even independent of residual viral replication. Therefore, even complete inhibition of viral replication would be insufficient to eradicate HIV (Strain 2004).

Other Important Aspects of HAART

Besides the goals described above – virological, immunological and clinical treatment success – several other aspects need to be considered. Cost reduction, prevention, and improving compliance remain a constant challenge for every HIV clinician.

Reduction of costs

It is important for clinicians to be informed about the price of drugs which they prescribe and to rationalize in any way that would be cost beneficial to patients and health services.

Antiretroviral therapies are expensive. Individual drugs cost between $200 and $2,000 per month, depending on the drug and the country in which it is prescribed. Even within drug classes, astonishing differences exist. In some countries, Crixivan™ is relatively cheap, while Reyataz™ is the most expensive PI (even more expensive when boosted). A combination regimen with Trizivir™ and Kaletra™ adds up to at least $2,000 per month. As a health care provider, it is therefore important to have an idea of costs and to question the pricing policy of some pharmaceutical companies. For example, in some countries Combivir™ costs slightly less than the individual drugs AZT and 3TC, but Trizivir™ costs significantly more than AZT and 3TC or Combivir™ plus abacavir. When the AZT patent expires in September 2005, these differences will be even greater.

In 2004, Abbott's decision to drastically increase the price of ritonavir in the US (the price for the booster dose went up to $8.60 from $1.70 daily) led to massive protests. However, the complaints from activists were unsuccessful and Abbott won its case in a US court – this is after all a free market economy…

Despite all criticism, the positive effect of HAART remains unquestioned and should not be forgotten despite the discussion of its cost. Reliable estimates assume an expenditure of between $13,000 and $23,000 per additional QUALY (quality-adjusted year of life; Freedberg 2001) – relatively cheap in comparison to many other therapies. HAART reduces the cost of expensive treatment of opportunistic infections, inpatient and outpatient care. In one German study, between 1997 and 2001, total annual outgoings per patient decreased from €35,865 to €24,482 (Stoll 2002). Many patients are able to work again, resulting in an overall economic gain for society (Sendi 1999). This should also be considered when confronting insurance companies.

Prevention

The lower the viral load, the less infectious the patient. A prospective study of 415 HIV-discordant couples in Uganda showed that of 90 new infections over a period of up to 30 months, none occurred from an infected partner with a viral load below 1,500 copies/ml. The risk of infection increased with every log of viral load by a factor of 2.45 (Quinn 2000). In a study from Thailand on 493 patients, this factor was 1.81 – and here no case of infection was recorded below 1,094 copies/ml (Tovanabutra 2002). In the San Francisco Cohort, infectiousness in the HAART era dropped by 60 %, based on the probability of transmission per couple (Porco 2004). HAART is thus an important component of prevention (Hosseinipur 2002).

Most patients are interested in knowing: "Do I still need to use a condom?" The answer is: "Yes!" Studies have shown that the decrease of viral load in plasma and seminal fluid is roughly parallel and that a decrease of several logs in plasma after several months may also be seen in semen (Liuzzi 1999). Although the same seems to be true for the vaginal and anorectal mucosa, individual risk remains difficult to estimate (Cu-Uvin 2000). Furthermore, viral load levels in blood and other body fluids do not always correlate with one another. In addition, HIV-infected patients are not protected from superinfection with new viral strains. Dual infections with several subtypes are often associated with accelerated disease progression (Gottlieb 2004).

There has also been concern that the preventive effects of HAART lead to an increase in risk behavior. Calculations have shown that an increase in risk behavior of only 10 % would offset the effects of HAART (Blower 2001, Law 2001). However, a recently published meta-analysis concluded that HAART does not increase risk behavior of patients, even if viral load is undetectable (Crepaz 2004).

However, in the French PRIMO Cohort, so-called risk contacts of patients increased from 5 % to 21 % between 1998 and 2001 (Desquilbet 2002). Small syphilis endemics among HIV-infected individuals are now being reported in every major city in the USA and Europe. Of equal concern is the increasing data on transmission of multiresistant viruses. In some countries, condom sales have declined – in Germany, sales dropped by 4.4 % in 2001 for the first time since 1998. Blind faith in the preventive effects of HAART is therefore not justified.

Adherence as a goal of therapy

Adherence is the Achilles heel of antiretroviral therapy. Nonadherence is a main, if not the most important, factor in treatment failure (review: Turner 2002). Insufficient plasma drug levels and partial suppression of viral load are the conditions under which resistance can develop. There is no question that HAART has to be taken regularly. All or nothing: a recent study proved that, with regard to resistance, it is still better not to take any drugs at all. Taking more than 90 % or less than 69 % of drugs were both associated with a lower risk for resistance (Sethi 2003). Compliance is defined as consent and acceptance of a treatment regimen by the patient. In the mid-90s a newer, more politically correct term was adopted – "adherence". This term describes both clinician and patient working together to achieve a treatment concept acceptable for both, and emphasizes, quite correctly, that not only the patient may be responsible for treatment failure. Adherence includes all factors that influence staying on a regimen, in terms of "acceptability". Whichever term is used, two facts remain:

1. If 5 % of pills are not taken, treatment success becomes precarious.
2. Clinicians usually overestimate the compliance of their patients.

"Risk patients" for noncompliance include individuals with substance or alcohol abuse or those experiencing side effects. Many studies have, however, also identified both patients with depression or younger age as being particularly at risk (Murri 2001, Frank 2002). Positive factors are physician experience, confidence of the patient in the positive effects of HAART, and social support. Race, sex or stage of disease do not seem to be relevant. The individual's view of disease and health, acceptance of modern medicine and fear of side effects are further considerations. However, all of these factors vary greatly, and in the end, compliance is difficult to predict in individual cases (Lerner 1998).

The importance of taking drugs regularly has been demonstrated in numerous studies in recent years. In one study of 99 patients, in which compliance was evaluated by way of an electronic monitoring system, the rate of treatment failure was only 22 % in patients with a level of compliance of at least 95 % (95 % of doses taken). Failure rates in patients with 80-94 % or < 80 % compliance were 61 % and 80 %, respectively (Paterson 2000). However, it must be taken into consideration that this much cited study is now relatively old. Newer drugs with longer half-lives, higher resistance barriers and better overall pharmacokinetics may be more forgiving of noncompliance. In the aforementioned study, 41 % of patients were misjudged by their treating clinicians with regard to compliance. Nurses seemed to have a better understanding of their patients, judging incorrectly in only 30 % of cases (Paterson 2000). The importance of compliance is also demonstrated by the successes reported in patients with directly observed therapy (DOT). A DOT study performed in one of Florida's correctional facilities showed 100 % of subjects with a viral load below 400 copies/ml at 48 weeks, compared with 81 % in an unmonitored control group in the general population (Fischl 2001).

Poor adherence not only leads to virological failure. It also has immunological consequences. In an analysis of two prospective studies, patients with a compliance of 100 %, 80-99 % and 0-79 % experienced reductions in viral load by 2.77, 2.33 and 0.67 logs after one year. At the same time, the CD4 cell count rose by 179, 159 and 53 cell/μl, respectively (Mannheimer 2002).

Furthermore, noncompliance also has clinical effects beyond the surrogate markers. In a Spanish study, patients who did not take more than 10 % of their drugs had a four-fold increase in mortality risk (Garcia 2002). This data has been confirmed in other studies (Maher 1999, Hogg 2000, Wood 2004). Hospital stays are also less frequent in patients with high compliance (Paterson 2000). In addition, it should be considered that noncompliant patients increase the risk of transmission of resistant viruses.

The basic mechanisms for development of resistance should be explained to patients. One must emphasize that, in contrast with other chronic illnesses, resistance mutations do not disappear once they have developed. Diabetes and hypertension make effective examples: whereas these diseases may "tolerate" forgetting the occasional tablet (insulin or blood pressure levels can easily be lowered again the next day), HIV is different – here even short-term lapses can have irreversible consequences. And every new occurrence of resistance makes therapy more complicated and more difficult. Patients have to be made aware of this unusual feature of HIV disease. These conversations should be repeated from time to time and become a standard component of routine care. Cooperation with special treatment discussion groups offered by various support organizations can be useful. The table below provides additional suggestions.

If compliance remains low

Despite all our efforts, some patients will not be able to improve their compliance. Physicians and other health care providers are advised not to take this personally or to feel offended should a patient not want to participate in the advances of medicine. Even if it may be difficult to accept others' views on life, disease and treatment, tolerance and acceptance should remain fundamental to the interactions of all health care providers with their patients. Some providers, especially those who treat selective patient populations in university settings, sometimes forget the reality of routine medical practice. Rigidly upholding the principles of modern medicine usually doesn't help here, and putting patients under pressure achieves even less. It is important to clearly outline and explain one's own position.

The question of whether noncompliant patients should continue to be treated with antiretroviral therapy is not always easy to address. On the one hand, there are patients who benefit even from suboptimal therapy; on the other hand, drugs are expensive and should not be prescribed too readily. When resources are limited, available drugs should be used prudently.

Twelve tips to improve adherence

1. Every patient should receive a written (legible!) treatment plan, which should be reviewed at the end of the visit. It should include a telephone number to call in case of problems or questions.

2. Patient and clinician should agree on the treatment plan. The patient's concerns or critical questions should be discussed.

3. The patient should have the impression that the treatment regimen was not randomly chosen, but tailored to his/her individual needs.

4. The explanation of a new or modified treatment plan takes time, and should not be rushed – all questions should be answered.

5. The reasons why adherence is so important should be explained. It makes sense to repeat such conversations – they should not only take place when initiating or modifying treatment, but should be part of routine care.

6. Possible side effects should be explained, as well as what can be done to alleviate them.

7. Support groups and other types of assistance should be utilized and offered.

8. It is important to tell the patient to come back if any problems are encountered with HAART – it is better to solve them together than have the patient try to deal with them alone at home.

9. The patient should know that the treatment regimen must be taken in its entirety ("Last month I left out the big tablets").

10. Prescriptions should be documented, in order to get a rough idea of adherence. Irregularities should be addressed openly.

11. During the early phases of therapy, the patient should be informed of treatment success as seen by reduction of viral load and rise in CD4 count.

12. Ensure clinical vigilance to detect the early signs of depression and treat appropriately.

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5. When to Start HAART

Christian Hoffmann, Fiona Mulcahy

"It's the most important question in HIV therapy" (A. Fauci)

The indication for antiretroviral therapy is based on the clinical assessment, CD4 cell count, and viral load. These three important factors determine whether therapy should be started or if it can still be deferred. At first glance, it appears straightforward: the lower the CD4 count and the higher the viral load, the higher the risk of AIDS (Mellors 1997, Lyles 2000), and the more urgent the indication for treatment. In older patients, the risk of progression seems generally to be higher.

But, how high is the individual risk really? The following table lists the (selected) risks of developing AIDS within six months, as identified in the impressive CASCADE analysis of 3,326 patients from the pre-HAART era (Phillips 2004). The range of individual risks of progression vary widely – from 0 to almost 50 %. For a 55 year-old patient with a CD4 cell count of 50/µl and a viral load of 300,000 copies/ml, the risk of progressing to AIDS within the next 6 months was 44.8 %. In a 25 year-old patient with 500 CD4 cells/µl and a viral load of 3,000 copies/ml, the risk was only 0.3 %. This demonstrates the importance of these parameters for estimating the individual risk and indication for treatment (some other examples of possible constellations and their respective risks are shown in Table 5.1).

Table 5.1: Predicted six-month percentage risk of developing AIDS, according to age, viral load and CD4 count (data from the pre-HAART era)

	100 CD4/µl	200 CD4/µl	350 CD4/µl
35 years			
VL 10,000	5.3	2.0	1.1
VL 100,000	10.6	4.1	2.3
55 years			
VL 10,000	10.7	4.6	1.8
VL 100,000	20.5	9.2	3.6

VL = Viral load. (From: Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004, 18:51-8. http://amedeo.com/lit.php?id=15090829)

Nevertheless, the best time for initiation of therapy remains the subject of controversial debate. The risk of AIDS must be weighed against the risks of long-term toxicity and viral resistance. These risks and the realization that eradication cannot be achieved in the foreseeable future have led to less rigid guidelines in many countries in recent years. Most health care providers have distanced themselves from the initial "hit hard and early" dogma of 1996, which recommended therapy from the earliest stages of infection. Similarly, it is now no longer common practice to treat every patient with a viral load above 10,000 copies/ml, independent of the

CD4 cell count, as was still generally recommended in the 1997 US guidelines (Carpenter 1997).

Table 5.2: Recommendations from various guidelines on when to initiate therapy

Clinical	CD4 cells/µl	Initiation of HAART is...
CDC B+C	All values	"recommended" (DHHS, GA, GB, EACS)
CDC A	< 200	"recommended" (DHHS, GA, GB, EACS)
CDC A	200-350	"recommended by most experts independent of viral load, although controversial " (DHHS)
		"generally advisable, independent of viral load" (GA)
		"recommended, but the exact timing should depend on individual factors"* (GB)
		"recommended independent of viral load" (EACS)
CDC A	350-500	"most experts recommend deferring with VL > 100,000, some clinicians will treat; defer with VL < 100,000" (DHHS)
		"recommended by some experts with VL 50,000–100,000; most were hesitant to treat with VL of 50,000" (GA)
		"to be deferred" (GB)
		"recommended with VL > 100,000, to be considered with VL 50,000-100,000, to be deferred only with VL < 50,000" (EACS)
CDC A	> 500	"deferral recommended by most experienced clinicians and treatment recommended only by some for VL > 100,000; defer with VL < 100,000"** (DHHS)
		"to be deferred"** (GB)
		„most experts hesitant to treat" (GA)
		"recommended with VL > 100,000, otherwise to be deferred" (EACS)

VL = viral load. *The individual factors include symptoms, patient wishes, expected adherence, potential toxicity, decline in CD4 cells, level of viral load and age **No distinction is made between 350-500 and > 500 CD4 cells

DHHS: Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, Department of Health and Human Services (DHHS), 29 October 2004. http://aidsinfo.nih.gov/guidelines/adult/archive/AA_102904.html

GA: German-Austrian Guidelines on Antiretroviral Therapy of HIV Infection (May 2004).

GB: British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy, July 2003. http://www.bhiva.org/guidelines/2003/hiv/index.html

EACS: European guidelines for the clinical management and treatment of HIV-infected adults in Europe; AIDS 2003; 17:S3-S26, June 2003

The critical question now is how to practically apply the new, more appealing motto of "hit hard but only when necessary" (Harrington 2000). At least all international guidelines agree that all symptomatic patients as well as patients with less than 200 CD4 cells/µl should be treated. However, for patients with more than 200 CD4 cells/µl, the situation becomes more confusing. Lack of randomized studies forces all guidelines to rely on cohort studies, meta-analyses and evaluation of

larger databases. Such data is problematic, however, as important aspects such as compliance or prior treatment regimens are not captured, and very heterogeneous patient populations are included. As a result, a wide range of interpretations is possible, which partly explains the significant differences seen, as shown in Table 5.2. This summarizes the current guidelines from the USA, Europe, Britain and Germany/Austria on starting therapy.

Guidelines merely provide points of reference and are not set in stone. Decisions must be made on a case-by-case basis, even if some health insurance providers tend to ignore this and use such guidelines to their advantage. In some situations, therapy may be started earlier than recommended in the guidelines; in other cases, therapy might (or even should) be deferred. The following chapter discusses relevant studies on initiation of therapy in chronic HIV infection (the special case of acute HIV infection is discussed in a separate chapter).

Experiences from Daily Practice

Even if the indication for HAART seems obvious, a conversation with the patient should clarify whether he or she is indeed prepared to start treatment. The problem is not the initiation of HAART, but its continuity, day after day, month after month. The decision to initiate treatment is often made prematurely. In some cases, patients put themselves under pressure unnecessarily, or let others do so. A single lower CD4 count value, a prolonged case of flu seeming to indicate a weakened immune system ("I never had anything like that before"), springtime lethargy, new study results, a promising new drug in the newspaper ("I've heard so much about X"), a partner who has started therapy – none of these are indications for initiation of treatment.

As a rule, as much time as is needed should be taken for the decision to start therapy. This is usually possible. A well-informed patient complies better with treatment and adherence! We recommend that patients come for several consultations to prepare for treatment. There are two exceptions: patients with an acute HIV infection, and those with severe immunodeficiency or AIDS. However, even in the presence of most AIDS-defining conditions, the acute disease should often be treated first before initiating antiretroviral therapy, as the potential for complications with PCP, toxoplasmosis or CMV therapies unnecessarily jeopardize treatment options. Not a single study to date has shown a benefit of commencing HAART simultaneously with OI therapy.

 If a long vacation is planned, it is better to delay therapy so that treatment response and side effects can be adequately monitored. On the other hand, patients may sometimes find one reason after another (stress at work, exams, change of job, etc.) to delay initiation of treatment. Many patients are afraid of AIDS, but often just as afraid of HAART ("the pills are the beginning of the end!"). They may have irrational or simply false expectations of HAART and its consequences – starting therapy does not mean that one will be subjected to daily infusions and no longer able to work!

Therapy should be explained to every patient from the outset. It is also useful to define individual threshold values for the commencement of therapy with patients early on, so that therapy is started only when these levels are reached. In our experience, patients are more motivated by this approach.

We also tend to start HAART earlier in older patients (above 50 years). The regenerative capacity of the immune system in older patients is significantly reduced (Ledermann 2002, Grabar 2004). More importantly, the risk of developing opportunistic infections not only depends on viral load and CD4 count, but also on age (Phillips 2004). Another example from the CASCADE Study cited above (Table 5.1) exemplifies this: a 25 year-old with 100 CD4 cells/µl and a viral load of 100,000 copies/ml has a risk of approximately 10 % for developing AIDS within six months – for a 55 year-old, this level of risk is reached at 150 CD4 cells/µl and a viral load of 30,000 copies/ml!

Symptomatic Patients

There is currently consensus that every symptomatic patient should receive antiretroviral therapy. This is, of course, mainly true for patients in WHO Stage C (with AIDS), but also for all patients in Stage B. Although this should be correct in most cases, it may be advisable to consider the situation more closely in individual cases. To avoid misunderstanding: all opportunistic infections indicative of severe immunodeficiency, such as CMV, MAC, toxoplasmosis or PCP, and also AIDS malignancies (including the non-AIDS-defining Hodgkin's Disease), should therefore prompt rapid initiation of therapy, especially if there is no specific treatment available, as in the case of PML. In such cases, rapid initiation of maximally suppressive HAART is the only treatment option available.

However: Herpes zoster (Stage B) may occur even with a slight immune defect and does not necessarily indicate immunological deterioration. Thrombocytopenia or constitutional symptoms may also have other causes. A further example: tuberculosis, which is an AIDS-defining illness and therefore implies an "urgent" indication for therapy, is a facultative opportunistic infection. It may occur without or with only moderate immunodeficiency. In our experience, one is justified in waiting with HAART in a TB patient with good CD4 T cells. The British treatment guidelines (http://www.bhiva.org) specifically mention pulmonary tuberculosis as being a possible exception in which treatment may be deferred. A relevant case study is outlined in Table 5.3.

Table 5.3: Case study, in which HIV treatment, if it had been given in accordance to the guidelines, could have led to almost ten years of over-treatment. NA = not available

		CD4 (%)	Viral load
May 95	Pulmonary tuberculosis (= AIDS)	330 (27)	NA
Feb 96	End of tuberculosis treatment	437 (29)	NA
	Patient refuses (urgently recommended) HAART		
Oct 97	Patient refuses (urgently recommended) HAART	402 (33)	29,500
Oct 98	Patient refuses (urgently recommended) HAART	440 (30)	13,000
Oct 99	Patient refuses (urgently recommended) HAART	393 (29)	13,500
Oct 00	Patient refuses (recommended) HAART	520 (30)	12,500
Jun 02	Doctor does not want to start HAART	521 (29)	7,440
Oct 04	HAART is rarely discussed…	391 (26)	15,300

On the other hand, typical illnesses that may be relatively harmless in comparison, such as oral candida or oral hairy leukoplakia, are also unerring indications of an impaired immune system. They may often precede far more serious illnesses. In such cases, it is advisable to offer the patient therapy, even if the CD4 count is relatively stable.

Asymptomatic Patients – below 200 CD4 cells/µl

There is general consensus that the available data provides clear evidence for initiation of therapy in these patients. 200 CD4 cells/µl is the cut-off, and one should not wait for values to drop below this level, as the risk for severe complications increases significantly with increasing duration of immunosuppression (Mellors 1997, Egger 2002). For patients with CD4 cells of 200/µl and a high viral load, the six-month risk for AIDS is sometimes greater than 10 % (Phillips 2004). It is therefore advisable not to let this happen, as the first manifestation of AIDS may include OIs, eg. PML, CMV, and toxoplasmic encephalitis, which are often associated with permanent sequelae.

However, such considerations are redundant for many of the patients presenting for the first time in outpatient clinics and private practices today. At least one third of these patients have a CD4 cell count below 200 cells/µl. Nevertheless, even here the point is not to start therapy within a matter of days, but rather to prepare patients for initiation of HAART. We have now made it our practice to start PCP prophylaxis in such patients. The first two weeks are used for diagnostic procedures to provide informative counseling and to identify patients with psychosocial issues. Requirements with respect to pill burden and dosing schedules need to be raised. HAART is started only when these issues have been addressed.

The risk of AIDS remains elevated in these patients even after initiation of HAART. This is logical – severe immunodeficiency requires a longer time to reconstitute, and patients therefore remain at risk during the initial months of treatment. However, this risk is relatively low: in an analysis of treatment-naïve patients with less than 200 CD4 cells/µl at the beginning of therapy, 8.3 new AIDS-defining illnesses per 100 patient years were observed - in patients with at least 350 CD4 cells/µl this value was 1.8/100 patient years. Similarly, mortality was slightly elevated at 2.9 versus 0.7/100 patient years (Phillips 2001).

Asymptomatic Patients – 200-350 CD4 cells/µl

Even in these patients, most guidelines more or less urgently recommend starting treatment, although the immediate risk of developing AIDS is still low. In the MACS Cohort, frozen blood samples obtained in the years 1985-1988 were analyzed and correlated with the clinical course of disease in these patients (Phair 2002). Results showed that not a single patient with more than 200 CD4 cells/µl and a viral load below 20,000 copies/ml developed AIDS within the following year. The authors concluded that it is possible to wait in cases of low viral load in such patients. It is nevertheless advisable to consider individual factors in this CD4 cell category. Is the patient willing and able to take therapy? If there are doubts, it is better to wait. How rapid is the CD4 cell decline? If there is no clear trend, it may also be appropriate to wait. See below for results of cohort studies.

Asymptomatic Patients – above 350 CD4 cells/µl

The cut-off level of 350 CD4 cells/µl is important in many guidelines. Above 350 CD4 cells/µl, it is usually recommended to defer therapy. In the MACS Cohort, not a single patient with more than 350 CD4 cells/µl and a viral load below 60,000 copies/ml developed an AIDS illness within a year (Phair 2002).

For patients with more than 350 CD4 cells/µl, the 2004 recommendations from the US and Germany have been slightly revised. At a viral load below 50,000 copies/ml, both guidelines recommend deferring treatment – but it should be considered with a high viral load, although it is no longer strongly recommended. Only the British guidelines are more conservative and generally recommend deferring initiation of treatment.

It is now more widely recognized that only two studies have been able to show the advantage of beginning with HAART at these CD4 cell counts; all others have not found any such advantage for the patient. Proponents of early initiation of therapy often cite a matched-pair analysis from Switzerland, which indicated a small, though statistically significant clinical benefit if HAART was started with CD4 cells above this level (Opravil 2002). 283 patients, who were started on HAART with a count above 350 CD4 cells/µl, were matched by age, sex, CD4 count, viral load and risk group for HIV infection with control patients who had been untreated for at least 12 months. At follow up around three years later, the AIDS risk was more than twice as high in the untreated group. However, besides considerable methodological problems due to the design of this study, one challenging question remains when looking more closely at the 52 CDC Category B illnesses (including 10 AIDS cases) which occurred additionally in the untreated group: are OHL (8 cases), oral thrush (10), herpes zoster (9), thrombocytopenia (9), and a few cases of tuberculosis, pneumonia and Candida esophagitis worse than the side effects of antiretroviral therapy? Over one third (35 %) of treated patients discontinued HAART, 51 due to gastrointestinal complaints, 25 due to CNS, renal problems, or lipodystrophy. Is there really clinical benefit in starting treatment early? If one takes into account the toxicity of the drugs and the associated reduction in the quality of life, this benefit seems to come at quite a high price.

Another analysis has similarly concluded that there is a survival benefit if antiretroviral therapy is started in patients with more than 350 CD4 cells/µl (Palella 2003). In this highly complicated analysis based on data from the American HOPS Cohort, patients were assigned to groups based on the first (baseline) CD4 cell count. Patients of the same group, who had either started ART immediately or waited until they had "dropped" into a lower group, were compared. This simple but effective design eliminated a problem encountered in most cohort studies, in that a patient's risk is usually only determined at the time when therapy is started. In the HOPS Study, the clock was theoretically started at the same time point for all patients. However, even this study raises many new questions when analyzed more closely. For example, the overall analysis also included patients that had started treatment with ART (i.e. mono or dual therapy). The first patients included in the analysis were from 1994! Therefore it is possible to argue that no difference would have been seen with the highly effective combinations available today. Adherence (see below) was not considered in this analysis. Patients who started therapy later were more frequently black, substance abusers with no health insurance. Nevertheless,

the risk of mortality was low in the end. In the group of patients that actually started HAART at levels above 350 CD4 cells/µl, the mortality risk was 6.9/1,000 patient years, compared to 10.0/1,000 patient years in patients with 200-350 CD4 cells/µl at the beginning of treatment.

According to expert commentaries, this data cannot be used to swing the pendulum back in favor of starting treatment early (Mocroft 2004).

Why has no randomized study been performed to address this question? An editorial on the cohort described above provided some calculations (Lane 2003): in order to design a randomized study with 80 % power on starting treatment above or below 250 CD4 cells/µl, about 650 events would be required to detect a 20 % difference in mortality. With an estimated probability for progression of 1 % per patient year, around 65,000 patients would have to be followed for one year, or 6,500 patients for 10 years – an impossible venture.

In summary: as many different cohorts have not shown any difference between groups of patients with 200-350 and above 350 CD4 cells/µl (see tables below), the available data is unconvincing.

Consequences for the Further Course of Disease

In addition to the risk of death and disease progression, the controversy over the optimal time for starting therapy also raises other questions. Based on large cohorts, there have been repeated attempts to prove that the time point when therapy is started influences virological or immunological treatment success. The problems with such arguments are discussed below.

Is virological response less durable with a low CD4 cell count and a high viral load?

At first glance, many cohort studies have clearly demonstrated that virological response is poorer if the CD4 cell count at initiation of treatment was low and the viral load high (Casado 1998, Mocroft 1998 and 2000, Miller 1999, Wit 1999, Deeks 1999, Chaisson 2000, Grabar 2000, Le Moing 2002, Yamashita 2001, Palella 2003). In a meta-analysis of 30 prospective studies, baseline CD4 cell count was important for viral load decline on treatment (Skowron 2001). It might appear straightforward: the higher the viral load and the lower the CD4 count, the less the virological success of HAART. Defenders of an early initiation of HAART often cite this data. They forget three important points:

First, this is not true for the two large cohorts in which only treatment-naive patients were studied (Cozzi-Lepri 2001, Phillips 2001). These confirm our observations that even a treatment-naive patient with a high viral load and a low CD4 cell count has good chances of sufficient and long-term suppression of viral load. Under these circumstances, the initial lab values are less important – if the patient is compliant! Even in the French APROCO Cohort, in which greater differentiation existed between treatment-naive and treatment-experienced patients (Le Moing 2002), treatment-naive patients with a high viral load at baseline showed at most an insignificant negative trend. That viral load and CD4 cell count have predictive values in all cohort studies in which most (up to 91 %) patients included were usually pre-treated with NRTIs, indicates one thing above all: virological success of HAART may be compromised in patients with prolonged mono or dual

therapy. Previous nucleoside analog therapy has been a risk factor for virological treatment failure in many cohorts (Casado 1998, Deeks 1999, Chaisson 2000, Grabar 2000, Le Moing 2002). In the HOPS Cohort, lack of prior therapy was decisive particularly for long-term treatment success (Holmberg 2003). As there are fortunately now very few patients on mono or dual therapy who have to change to HAART, it is justified to concentrate exclusively on treatment-naive patients.

Secondly, the relative risk of virological failure was often only increased in patients with substantial immunosuppression (below 50-100 CD4 cells/µl) or very high viral load (above 100,000 copies/ml). At levels above 200 CD4 cells/µl or a viral load of less than 100,000 copies/ml, differences could generally not be detected (see below).

Thirdly, hardly any of these studies considered compliance. A patient who starts HAART under emergency conditions at 30 CD4 cells/µl (and who presumably went to the physician only shortly before or even after clinical manifestation of AIDS) may have a different view on sickness and health and may be less compliant than someone who seeks medical advice with a good CD4 count and begins HAART after thorough reflection. It seems clear that the benefit of HAART will be different for such patients. Adherence was an important and even decisive predictor in the few studies in which it has been investigated (Le Moing 2002, Wood 2003+2004).

If these aspects are considered, the issue of whether virological response is really poorer with less favorable baseline values becomes less clear cut. Even a patient with high viral load and a very low CD4 cell count can potentially control infection quite successfully! The prerequisite for this is that the drugs are taken regularly – and the regimen administered must be a potent one: data from prospective studies such as SOLO or M98-863, in which nelfinavir (a relatively weak PI) was tested against lopinavir or fosamprenavir showed poorer responses in highly viremic patients on nelfinavir.

Is immunological response less durable with a low CD4 cell count and a high viral load?

Multiple factors influence the increase in CD4 cells: duration of immunosuppression, age, thymus size or extent of thymus degeneration (see chapter "Goals and Principles of Therapy"). Do these include baseline values at initiation of therapy? Astonishingly, several cohorts found no association. (Yamashita 2001, Pezzotto 2001, Cozzi-Lepri 2001). However, these studies all showed that the rise in CD4 cells is similar, although levels remained lower if the CD4 count was initially low. In addition, it is our experience that immune reconstitution is rarely complete if values were initially low; the more damaged the immune system, the less likely a complete recovery in the long run (Garcia 2004). In the Swiss Cohort, having a low CD4 cell count at baseline was a clear risk factor for not attaining 500 CD4 cells/µl after four years (Kaufmann 2002). There is also concern over the 10-15 % of patients with a discordant response where HAART is virologically extremely successful, but CD4 cell count remains low (Piketty 1998, Renaud 1999).

Another consequence of starting therapy later can be that antigen-specific immune reconstitution remains impaired, both against HIV and other pathogens. Numerous studies suggest that qualitative immune reconstitution does not initially occur at the

same pace as quantitative reconstitution (Gochorov 1998, Tortatjada 2000, Lederman 2001, Lange 2002). One can make the analogy with a patch of desert where weeds will grow before flowers. So, what are the clinical consequences of these lab data? Why does the risk of AIDS decrease so impressively and rapidly with a rising CD4 cell count? Why can even severely immunodeficient patients discontinue their anti-infectious prophylaxis quite safely, once their CD4 cell count has risen to above 200/µl? These clinical observations – at least in the short term – seem to contradict our knowledge of the currently observed immune reconstitution.

Does the risk of clinical progression remain high even after starting HAART with a low CD4 cell count and a high viral load?

Almost all studies demonstrate a clear correlation between CD4 cell count at initiation of HAART and rates of both AIDS and death (Hogg 2000, Grabar 2000, Cozzi-Lepri 2001, Kaplan 2001, Phillips 2001, Egger 2002, Kaplan 2003, Palella 2003, Sterling 2003). Patients with a CD4 count below 50/µl when starting therapy continue to have a particularly high risk for developing AIDS (Hogg 2003). In other cohorts, the risk remained elevated even below a CD4 count of 200 cells/µl (Phillips 2001, Sterling 2001, Kaplan 2003). An Italian cohort showed that increased risk of clinical progression was associated with a CD4 count that did not rise and remained below 50 CD4 cells/µl despite HAART (Cozzi-Lepri 2001).

The largest study to date on this topic was published in 2002 by the ART Cohort Collaboration. Here, several cohorts were pooled and almost 13,000 patients on HAART were analyzed. The data seems clear-cut (Egger 2002). Baseline CD4 cell count correlated highly with the probability of AIDS or death (see Table 5.4).

Table 5.4: Risk of progression in the ART Cohort Collaboration (Egger 2002)

Baseline CD4 cells/µl	Relative risk
50-99 versus < 50	0.74 (0.62-0.89)
100-199 versus < 50	0.52 (0.44-0.63)
200-349 versus < 50	0.24 (0.20-0.30)
> 350 versus < 50	0.18 (0.14-0.22)

One should note the moderate difference between the groups above 200 CD4 cells/µl. Viral load at baseline was only relevant if it was at a very high level, i.e. above 100,000 copies/µl.

All cohorts showed very low rates of morbidity and mortality. However, the follow-up periods were usually short and lasted less than three years. More significant differences may emerge in the long term.

Above 200 CD4 cells/µl the situation becomes more complicated. Most studies have not yet been able to provide evidence for the benefit of starting therapy early (above 350 CD4 cells/µl). Table 5.5 summarizes studies on this topic.

Table 5.5: Studies on the influence of baseline CD4 count on treatment success in patients with > 350 CD4 cells/µl and in patients with 200-350 CD4 cells/µl at initiation of HAART.

	Less AIDS, fewer deaths?	More pronounced increase in CD4 cells?	Improved virological response?
Canadian Cohort (Chaisson 2000, n=553)	NA	NA	**No** (trend)
Italian Cohort (Cozzi-Lepri 2001, n=1.421)	**No**	**No**	**No**
CDC database, USA (Kaplan 2001, n=10.885)	**No**	NA	NA
Baltimore Cohort (Sterling 2003, n=333)	**No**	NA	**No**
Swiss, Frankfurt, EuroSIDA Cohorts (Phillips 2001, n=3226)	**No**	NA	**No**
Swiss Cohort (matched pair analysis subgroup) (Opravil 2002, n=2x283)	**Yes**	NA	NA
HOPS Cohort (Palella 2003, n=1464)	**Yes**	NA	**Yes**
Barcelona Cohort, single-center (Garcia 2004, n = 861)	**No**	**No** (trend)	**NA**

NA = not available

In a meta-analysis of the three large European cohorts cited above, the difference was minimal (Egger 2002). The AIDS rate was 2.3 versus 1.8, the mortality rate 1.0 versus 0.7 per 100 patient years. This means one more case of AIDS in 200 patient years! Vast randomized studies would probably be necessary to detect a difference between the two patient groups.

Another major problem is that cohort studies do not consider the success of HAART on the individual level. This problem was recently addressed: in a complex analysis, in which data from almost 10,000 treatment-naïve patients from different cohorts was combined, CD4 cell counts and viral load after six months were considered in addition to the baseline values (Chene 2003). Result: the success of HAART is key for the further risk of suffering AIDS and/or dying. Baseline values were irrelevant. In other words – if HAART is successful, the initial status does not matter.

All in all, the available results, despite their limitations, do support the current trend of deferring initiation of therapy at levels above 200 CD4 cells/µl. This risk assessment will change again as soon as better combinations with better long-term tolerability become available. Some experts feel this is already the case and are proponents of starting earlier (Holmberg 2004, Schechter 2004). However, better treatment options could also mean that it would actually be possible to start later. The evaluation of the indication for treatment must therefore continually be re-examined in the light of new developments.

Practical tips for starting therapy in asymptomatic patients

▪ Below 200 CD4 cells/µl treatment should be started as soon as possible. However, even here, one should take the time to get acquainted with the patient, give proper counseling on OI prophylaxis and diagnostic procedures – it's not usually a question of having to start within a few days!

▪ Above 200 CD4 cells/µl, there is more time – the individual history of the patient and course of CD4 cell count over time has to be taken into account.

▪ A decrease of more than 80-100 CD4 cells/µl per year is too much! Don't delay too long in such patients!

▪ There is considerable variability in laboratory values. Therefore, a single CD4 count (especially when in the range of 200-350/µl) should always be repeated before starting treatment.

▪ Above 350 CD4 cells/µl: wait! Continue to monitor at least every three months.

▪ The higher the viral load, the more frequent checks of CD4 count are necessary: at a viral load > 100,000 copies/ml, testing should be performed at least every two months.

▪ Initiation of treatment may be justified at levels above 350 CD4 cells/µl – if viral load is very high, CD4 count is decreasing rapidly or the patient requests it (after careful counseling).

▪ Check ahead of time whether a patient may be suitable for enrolment in a clinical trial.

Arguments for and against an <u>EARLY</u> start

- "The lower the CD4 cell count, the longer the patient will remain at risk later."

(Counter: This statement applies mainly to patients with substantial immunosuppression in whom initiation of therapy should not be debated. The earlier one starts, the more long-term toxicities will occur!)

- "A lower CD4 count often implies that only moderate immunological-virological treatment success is possible – at some stage, the destruction of the immune system is irreversible."

(Counter: This is mainly true for patients with substantial immunosuppression. However, the virological response does not seem to be reduced in treatment-naive patients.)

- "The longer one waits, the fitter the virus becomes via generation of quasi-species and immune escape variants, and the more difficult it is to treat."

(Counter: Interesting laboratory hypothesis. But, where's the relevant clinical data?)

- "The worse the condition of the patient, the worse the tolerability of HAART."

(Counter: Ancient, proven medical wisdom. But, does it apply here, where we are referring to asymptomatic patients?)

- "HIV should be treated as early as possible, as should any other infectious disease."

(Counter: HIV is not akin to any other infectious disease. HIV cannot be cured like many bacterial infections. Herpes viruses, for which there is no cure, are also treated only as needed.)

- "It has been proven that patients are less infectious on treatment."

(Counter: And may be more prone to risk behavior. In addition, the risk of transmission of primary resistance mutations increases.)

Arguments for and against a <u>LATE</u> start

- "The earlier one starts, the sooner and more certain the side effects."

(Counter: This may be true. The question is: does one more year without therapy, but with an increasing risk of AIDS, really make a difference?)

- "The earlier one starts, the higher the risk for resistance in the long term."

(Counter: OK, but... compliant patients, who have sufficient suppression of viral load, have good chances of not developing resistance, even over many years.)

- "Even a bad immune system can regenerate; after all, prophylaxis can be safely stopped after a rise in CD4 count."

(Counter: This may be true for some patients, but not for all. There are indications that the qualitative response remains impaired.)

- "It is never too late to start therapy at 200 CD4 cells."

(Counter: Who can be so sure? Some AIDS defining diseases may rarely occur even in this scenario; there is no certainty that PML or lymphoma might not develop – and if should they, good advice is hard to find.)

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6. How to Start with HAART

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Once the decision has been made that HAART is necessary, the next question is: what to start with? More than two dozen drugs are now available, and the number of possible combinations is almost infinite. Of course, it is preferable that every treatment-naïve patient participates in a clinical study. This is the only way that differences between the various combinations can be established in the future, which will ultimately further improve the quality of treatment. In the past year, several combinations turned out to be suboptimal, which would never have emerged without the conduction of controlled studies. However, in practice it is not always possible to treat patients in clinical trials. For information regarding the treatment of these patients, the following summarizes the data available to date.

Recommended Initial Regimens at a Glance

Combinations that we recommend for first-line therapy (December 2004) are shown in the table below.

Table 6.1: Combinations suitable for initial therapy of HIV infection (not in order of preference!)

NRTIs		NNRTI/PI
AZT + 3TC		Lopinavir/ritonavir
*TDF + 3TC	plus either	Efavirenz
TDF + FTC		Nevirapine
Alternatives		Alternatives
AZT + FTC		Fosamprenavir/ritonavir
**ABC + 3TC		Saquinavir/ritonavir
***d4T + 3TC		Atazanavir/ritonavir****
***AZT + 3TC + ABC		

NRTI combinations recommended for initial regimens (left upper column) may also be combined with alternative NNRTIs/PIs (right lower column) and vice versa.
* Convincing data is only available for combination with efavirenz.
** May be problematic with nevirapine due to possible allergies, therefore combine only with PIs if possible.
*** Now only recommended in special cases (poor compliance, problems with interactions, low viral load with AZT+3TC+ABC)
**** In some countries, atazanavir is not approved for initial therapy

It should be noted that many other combinations are possible. These may be acceptable in individual cases or in investigational studies, but general recommendations for their use cannot be given.

First-line therapies that are currently completely unacceptable include full dosage ritonavir (because of side effects) or unboosted saquinavir (high pill burden). There

is also insufficient data on boosted amprenavir as an initial therapy. It is therefore not licensed for first-line therapy, likewise delavirdine, T-20 and, in some countries, atazanavir. The same is true for the old formulation of nelfinavir and indinavir/ritonavir due to the high number of pills and relatively poor tolerability. Similarly, the nuke backbones of d4T+ddI and TDF+ddI are not recommended for first-line therapy. Unboosted indinavir requires three times daily dosing and is therefore also no longer suitable. Other problematic combinations are listed at the end of this chapter.

A Practical Approach to the First Regimen – Important Rules

Common initial regimens consist of two nucleoside analogs, combined with either a (possibly boosted) PI, an NNRTI or a third nucleoside analog. No single combination has clearly been shown to be superior to another, and in a 2001 meta-analysis (and also a good review) of 23 clinical studies in 3,257 patients, virological and immunological effects were comparable for most regimens. An important factor was simply the number of pills – the fewer pills, the better. Pill burden is therefore an important consideration when choosing a treatment regimen (Bartlett 2001). However, the simplest therapy may not necessarily be the best. In fact, some differences in efficacy have recently started to emerge. These are considered later in the text.

The choice of the initial regimen should always be adapted to the individual situation with respect to compliance, concurrent illnesses and concomitant medications, and the needs of the patient. The following are important points to consider for the initial regimen.

Practical tips for first-line therapy:

- The first regimen offers the patient the best chance of long-term success; this regimen should therefore be potent and endurable.
- The pros and cons of different combinations should be discussed with the patient – there is usually enough time for this.
- The initial regimen ideally should be dosed at no more then twice daily. Once-daily combinations should be considered.
- First-line therapy should not consist of all three drug classes, in order to keep further options open for later.
- Care should be taken to avoid overlapping toxicities.
- Don't insist on theoretically superior combinations if reality requires a different choice.
- Each patient should receive the ART he is able to take!
- All drugs should be started on the same day – no lead-in mono- or dual therapy!
- Be sure to check whether the patient would be eligible for a clinical study! All patients, especially if treatment-naïve, should be encouraged to participate in clinical trials!

What Should Be Clarified Beforehand?

Dosing issues

Can the patient really take drugs several times a day? Is this realistic with regard to the individual, professional or social situation? If in doubt, a simpler regimen is preferable to one that is presumed to be more effective. Intravenous drug users, for example, may be unable to comply with a complicated or high pill burden regimen. In this situation, once-daily regimens for i.v. drug users (Proenca 2000, Staszewski 2001, Conway 2002), which are also suitable for DOT (Directly Observed Therapy) have already been described.

For many patients, the numbers of pills or requirements for food intake are important. The range of licensed and recommended initial regimens varies from 2 to 16 pills per day. Some find it unacceptable to have to take pills at certain times during the day, on an empty stomach, or with fatty foods. Patients today are also more demanding than a few years ago – justifiably so! There are now alternatives! Even the size of tablets can be a problem for some patients. Such issues must be discussed *before* initiating therapy.

Concurrent illnesses

Every patient must be thoroughly questioned and examined with regard to possible concurrent illnesses before starting treatment. These must be considered when choosing a regimen. ddI is contraindicated in patients with pancreatitis. Similarly, pre-existing polyneuropathy requires that any d-drugs (ddI, ddC, d4T) be avoided. Non-insulin-dependent diabetes can become insulin-dependent on PI treatment. In such cases, the use of PIs for first-line therapy should be carefully considered.

Liver disease and chronic hepatitis must also be taken into account, because the risk of developing severe hepatotoxicity on nevirapine or ritonavir is highest in these patients (Den Brinker 2000, Martinez 2001, Saves 1999, Sulkowski 2000+2002). However, a recently published study conducted in over 1,000 patients found no difference between lopinavir/ritonavir and nelfinavir in patients with hepatitis C (Sulkowski 2004). 3TC or FTC and preferably also tenofovir should be incorporated into the first regimen in patients with hepatitis B. Other illnesses such as renal disease must also be considered (see Table 6.2).

Interactions with medications and drugs

Interactions are important in the choice of combination regimens. Whereas interactions between antiretroviral drugs are well known, interactions with other concomitant medications are often less well characterized. The urgent need for more research was recently demonstrated in a study investigating the interactions between HAART and statins. In healthy volunteers, the measurement of plasma levels showed that levels of simvastatin were elevated by 3,059 % after concurrent dosing with ritonavir or saquinavir (Fichtenbaum 2002). One case of fatal rhabdomyolysis on simvastatin and nelfinavir has been described (Hare 2002).

Many drugs should be avoided in combination with particular antiretroviral drugs, as incalculable interactions may occur. These include certain contraceptives. Even drugs that seem unproblematic at first glance can have unfavorable effects: one study that received a lot of attention showed that plasma levels of saquinavir were

reduced by half due to concurrent administration of garlic capsules (Piscitelli 2002). Even a seemingly harmless substance such as vitamin C can influence plasma levels. A small study in healthy volunteers showed that one gram of vitamin C can significantly lower unboosted indinavir levels (14 %) (Slain 2003).

Table 6.2: Concurrent illnesses requiring caution with specific drugs. These recommendations are not absolute contraindications.

Illness	Caution with
Active hepatitis B	Nevirapine, boosted PIs
	(In contrast: 3TC, FTC, tenofovir are beneficial!)
Active hepatitis C	Nevirapine, boosted PIs
Active substance abuse, substitution	NNRTIs, ritonavir
Anemia	AZT, possibly also 3TC
Arterial hypertension	Indinavir
Chronic diarrhea, intestinal diseases	Nelfinavir, lopinavir, other PIs
Diabetes mellitus	PIs (especially if a NIDDM is at risk of becoming an IDDM!)
Myocardial infarction	PIs (potentially beneficial: nevirapine)
Kidney disease	Indinavir, tenofovir
Pancreatitis	ddI
Polyneuropathy	d4T, ddC, ddI
Psychoses, other CNS illnesses	Efavirenz

Coumarin-derivative anticoagulants such as warfarin can also be a problem – ritonavir can significantly lower plasma levels (Llibre 2002). Further typical "problem drugs" include migraine remedies, prokinetic drugs and sedatives. One fatal case has been described with ergotamine and ritonavir (Pardo 2003).

Drugs or alcohol can also interact with HAART. For those in substitution programs, the methadone requirement may be significantly increased by certain antiretroviral drugs such as nevirapine and efavirenz (Clarke S 2001). To a lesser extent, this is also true for ritonavir and nelfinavir. There is inconsistent data on lopinavir, but it may also require dose adjustments (McCance-Katz 2003, Stevens 2003). Tenofovir does not seem to have significant interactions with methadone (Smith 2004).

Other combinations may lead to even more dangerous effects. Several deaths have been reported after simultaneous dosing with ritonavir and amphetamines or ecstasy, or the popular narcotic gamma hydroxybutyric acid (GHB, Samsonit™ or "liquid ecstasy"; Hales 2000, Harrington 1999). Ritonavir in particular can inhibit the metabolism of various drugs such as amphetamine, ketamine or LSD (excellent review in: Antoniou 2002). Clinician and patient are well advised to have an open conversation about drug use before starting therapy. Marijuana and THC appear to have a low potential for interactions (Kosel 2002). Amphetamines seem to be particularly dangerous and neurotoxic in HIV patients (Langford 2003).

Not every substance can be discussed here. Many are described in the respective drug chapters and in the chapter on interactions. It is always recommended to check

the package insert. Initiation of HAART provides a good opportunity to re-evaluate existing prescribed medications.

Cumulative toxicities

Several potential cumulative toxicities should be considered in the choice of therapy.

If other myelotoxic drugs (valganciclovir!) are necessary, caution is required with AZT. The same is true for interferon, hydroxyurea, dapsone and ribavirin.

Patients taking acyclovir have renal problems significantly more frequently on indinavir (Herman 2001). Tenofovir should also be avoided with renal problems or potentially nephrotoxic drugs.

Which Drug Classes Should Be Used?

All combinations currently used as initial regimens consist of two nucleoside analogs plus either a PI, an NNRTI or a third nucleoside analog. Any other combinations are experimental or hardly justified for use outside the framework of clinical studies. Advantages and problems of these three strategies are outlined in the table below. There are few studies comparing all three strategies. The pharmaceutical industry has a limited interest in such large projects. Indeed, why determine, with huge financial commitments, that one's own drug may be weaker? Such studies are therefore usually performed independently of industry, but also take longer.

In the Atlantic Study, 298 patients were randomized open-label to receive d4T+ddI+3TC versus d4T+ddI+nevirapine versus d4T+ddI+indinavir (Van Leeuwen 2003). After 48 weeks, 49 %, 49 % and 40 % of patients, respectively, attained a viral load of less than 50 copies/ml in the intent-to-treat analysis (ITT). These differences were not significant. However, several subanalyses (96 weeks, patients with high viral load) did show differences: although indinavir and nevirapine were both quite comparable, they were significantly better than 3TC. This study provided the first arguments against triple-nuke therapy. However, the combinations tested in the Atlantic Study are now fairly outdated.

In the CLASS Trial, the following three classes are being tested with an ABC+3TC backbone: amprenavir/ritonavir as a boosted PI regimen, efavirenz as an NNRTI option and d4T as a third nucleoside analog. 48-week data from 297 patients is available (Bartlett 2002). As in the Atlantic Study, differences in the various arms were not significant based on the normal viral load assay with a detection limit of 400 copies/ml. Differences only became apparent with the ultrasensitive assay, where only the NNRTI arm had an advantage so far. This was also true for a subgroup of patients with a high viral load of above 100,000 copies/ml. Interestingly, there was no difference between the other two arms (boosted PI regimen versus triple nuke!), although it does seem like the virological failure rate in the triple nuke arm was relatively high.

The different strategies are discussed here in more detail. Options that will play a more important role in the future will also be considered, such as nuke sparing, once-daily combinations and so-called induction therapies. These are effective and promising according to current, preliminary data, but cannot yet be generally rec-

ommended. Combinations that are problematic and better avoided will also be mentioned.

Table 6.3: Combining drug classes: Advantages (↑) and disadvantages (↓)

2 Nukes + PI	2 Nukes + NNRTI	2 Nukes + 3rd Nuke
↑ a lot of data, with clinical endpoints and in significantly immuno-compromised patients	↑ equivalent, perhaps even better suppression of viral load than with PIs	↑ very low pill burden, easy dosing
↑ long-term data avail-able	↑ low pill burden! once-daily may be possible	↑ leaves many options
↑ high genetic barrier for resistance (several resistance mutations necessary)	↑ leaves PI options	↑ few interactions
↓ high pill burden (for some older PIs), partly strict dosing require-ments	↓ clinical effect not proven (only surrogate marker studies)	↓ less potent, espe-cially with higher viral load, bad data on teno-fovir-containing triple nuke combinations
↓ frequent drug interac-tions	↓ no data in severely immunocompromised patients	↓ no clinical endpoints, no long-term data
↓ some PIs with cross-resistance, leaves lim-ited options	↓ rapidly occurring complete cross-resistance	
↓ long-term toxicity, lipodystrophy, dyslipi-demia with most PIs	↓ strict monitoring re-quired initially (esp. nevirapine), allergies frequent	

Two Nucleoside Analogs Plus a PI

The combination of two nukes plus one protease inhibitor is the only HAART to date that is supported by efficacy data from randomized studies with clinical end-points (Hammer 1997, Cameron 1998, Stellbrink 2000). Most importantly, data is available over longer periods than for other combinations. Some studies have been ongoing for over five or six years (Gulick 2003, Hicks 2003). Many experts still like to use these combinations today, particularly in patients with AIDS or high viral load, as another advantage is the relatively robust efficacy with respect to viral resistance. These regimens, however, often involve a considerable pill burden and relatively frequent side effects, which makes compliance difficult. The following briefly describes the most common combinations:

Two nukes plus lopinavir/r

These combinations are now among those most frequently used for initial therapy, and categorized in many guidelines as preferred regimens. Long-term efficacy seems to be good (Hicks 2003). No resistance has been described for such therapy

to date. The combination of d4T+3TC+lopinavir/r seemed to show better efficacy than d4T+3TC+nelfinavir in the only comparative study described to date. At week 48, 67 % versus 52 % of patients had a viral load below 50 copies/ml (Walmsley 2002). Whether this drug is really more effective for initial therapy than other boosted PIs remains uncertain at the moment. It is also not clear what treatment would be effective if lopinavir/r fails. The most frequently used nuke backbone has been d4T+3TC. There is also positive data on TDF+FTC (Molina 2004).

Two nukes plus saquinavir/r

The combination of AZT+ddC+saquinavir-HGC was the first PI-combination for which survival benefit was shown in a randomized study; in fact this was the largest randomized HIV study ever (Stellbrink 2000). Today, however, saquinavir is generally given in its boosted form (saquinavir/r) and with other NRTIs. Pill burden would be too high without the addition of ritonavir, as the bioavailability of saquinavir is too low. Tolerability is probably better than for indinavir/r, which is no longer recommended for first-line therapy (Dragstedt 2003). The boosted combination of 1,000 mg saquinavir with 100 mg ritonavir, both twice daily, has been licensed. Saquinavir is now available as 500 mg tablets.

ABC+3TC plus fosamprenavir

With the end of the patent protection of AZT looming ahead, GSK has started a number of studies in recent years testing its other two nukes ABC+3TC as a backbone. The fixed combination tablet Kivexa™ is now providing a new once-daily option. In the NEAT and SOLO studies, ABC+3TC showed good efficacy in combination with fosamprenavir (Gathe 2004, Rodriguez-French 2004). There is only little data on other PI combinations. We would therefore recommend fosamprenavir as the best option for combination with the ABC+3TC backbone. Despite relatively good data on efavirenz (Gazzard 2003, DeJesus 2004, Podzamczer 2004), we do not recommend the combination of ABC+3TC plus an NNRTI for first-line therapy, due to the potentially problematic occurrence of allergy (abacavir? NNRTI?), which can unnecessarily jeopardize future treatment options.

Two nukes plus nelfinavir

Nelfinavir combinations have long been among the most frequently used ART regimens. The licensing studies tested nelfinavir mainly with AZT+3TC (Saag 2001, Gartland 2001). In the Combine Study, nelfinavir seemed slightly weaker than nevirapine (Podczamzer 2002). In CPCRA042, nelfinavir was as effective as ritonavir, but with significantly better tolerability (Perez 2002). However, nelfinavir is less potent when compared directly to other PIs such as fosamprenavir (boosted or not) or lopinavir/r (Walmsley 2002, Gathe 2004, Rodriguez-French 2004).

Nelfinavir-containing combinations have a high pill burden and are associated with unpleasant diarrhea, so that we generally no longer recommend it for first-line therapy.

Two Nucleoside Analogs Plus an NNRTI

NNRTIs have an equal, if not presumably even superior effect on surrogate markers as PI combinations. NNRTIs have done well in numerous randomized studies: efa-

virenz-based regimens in studies such as 006, ACTG 384, ACTG 5095 or CLASS were superior to indinavir, nelfinavir, amprenavir/r or triple nukes (Staszewski 1999, Robbins 2003, Gulick 2004, Bartlett 2002). The nevirapine-containing regimens in Combine or Atlantic were at least equivalent to nelfinavir and indinavir, and better than triple nukes (Podzamczer 2002, van Leeuwen 2003). A direct comparison in the 2NN Study showed no major differences between efavirenz and nevirapine (van Leth 2004).

Advantages of NNRTI-regimens include the low pill burden and good tolerability. In contrast to PIs, however, data with clinical endpoints is unavailable. Neither is there any long-term data or studies on severely immunocompromised patients. A disadvantage of NNRTI combinations is the rapid development of cross-resistance.

AZT+3TC plus nevirapine or efavirenz

These regimens are among those most frequently used in the last few years (006, Combine, ACTG 384, 5095). Patients must be made aware of side effects that may occur during the first weeks. There may be nausea initially, and allergies to NNRTIs are not rare. Dose escalation of nevirapine after 2 weeks is essential due to auto-induction of its own metabolism, as is monitoring for the possible CNS side effects of efavirenz. Once the first weeks have passed without complications, a combination such as AZT+3TC plus nevirapine or efavirenz can often be continued for many years without major problems.

Some clinicians still use ddI instead of 3TC. We do not recommend this, since ddI needs to be taken on an empty stomach and AZT is tolerated better when taken with a meal. Still: AZT+ddI+nevirapine is probably the oldest HAART combination and should therefore at least be mentioned. It was already tested between 1993 and 1996, in the ACTG 193A Study. Here it proved superior to dual therapies in immunologically advanced patients with regard to both survival and disease progression, although not significantly for the latter (Henry 1998). AZT+ddI+nevirapine was also well investigated in the INCAS Trial and ACTG 241 (Raboud 1999, D'Aquila 1996).

TDF+3TC/FTC plus efavirenz (or nevirapine)

This seems to be a good combination. In the double-blind Gilead 903 Study, virological efficacy was equivalent to d4T+3TC (plus efavirenz), and tolerability was significantly better (Gallant 2004). Toxicity was reduced, and polyneuropathy, lipodystrophy and even lipid level changes were significantly less frequent in the tenofovir arm.

In the Gilead 934 Study, TDF+FTC plus efavirenz were more effective than AZT+3TC after 24 weeks, because of tolerability (Gazzard 2004). There is no reliable data on nevirapine in combination with TDF+3TC/FTC yet. However, it is not expected to be significantly different.

d4T+3TC plus efavirenz or nevirapine

D4T+3TC is useful if there are problems with hematopoiesis (anemia or thrombocytopenia). This applies to patients receiving chemotherapy, ganciclovir, or ribavirin. In the 2NN Study, d4T+3TC+efavirenz and d4T+3TC+nevirapine were about comparable (Van Leth 2004); in the Australian OzCombo2 Study, d4T+3TC in

combination with nevirapine was as effective as d4T+ddI or AZT+3TC (French 2002).

Three Nucleos(t)ide Analogs – Triple Nuke

Triple nuke therapies, i.e. combinations of three nucleoside or nucleotide analogs, have several advantages: few pills, few interactions, no side effects typical of PIs or NNRTIs, and the fact that two entire drug classes can be spared for later. A big disadvantage of triple nuke therapies is that they appear to be less potent than other combinations.

AZT+3TC+ABC

The combination of AZT+3TC+ABC in a single tablet (Trizivir™) is the classic triple nuke combination and one of the simplest HAART regimen with respect to the number of pills. Only two pills daily comprise a triple combination. Not only patients with compliance problems, but also those taking co-medications with a high potential for drug interactions (tuberculosis and MAC therapy, warfarin), are well suited to this regimen. The combination is usually well tolerated, although careful counseling on the hypersensitivity reaction to abacavir is necessary. With respect to the AZT dose, the same applies for Trizivir™ as for Combivir™ in that it may be too high for some patients.

Trizivir™ does not seem to be as effective as some "divergent" combinations comprised of several drug classes. Although this combination fared quite well in studies such as CNA3007 and ESS40002 with nelfinavir (combined with AZT+3TC or d4T+3TC, Kumar 2002, Matheron 2003), there was evidence of inferiority when compared to indinavir in the CNA3005 Study: approximately the same number of patients had a viral load of less than 400 copies/ml after one year; however, there was an important difference in patients with more than 100,000 copies/ml at baseline, and only 31 % (Trizivir) versus 45 % (AZT+3TC+Indinavir) reached a viral load below 50 copies/ml (Staszewski 2001). However, this was a double-blind, randomized study – and all patients had to take a total of 16 tablets daily distributed over three doses, which eliminated any possible positive effect in favor of adherence to Trizivir™. The open-label, randomized CN3014 Study showed no significant difference between AZT+3TC+abacavir and AZT+3TC+indinavir either – but this study also had methodological problems (Vibhagool 2004).

ACTG 5095 tested AZT+3TC+ABC against NNRTI-containing regimens for the first time (Gulick 2004). In this double-blind, randomized study, 1,147 treatment-naïve patients received either AZT+3TC+ABC, AZT+3TC plus efavirenz, or AZT+3TC+ABC plus efavirenz. The endpoint was virological failure, defined as a viral load above 200 copies/ml after 16 weeks or later. After an average 32 study weeks, 21 % of patients in the Trizivir™ arm had a viral load above 200 copies/ml – in a combined evaluation of the efavirenz arms this proportion was only 11 %. This difference was significant, and the triple nuke arm was discontinued as a result. At week 48, 74 % vs. 89 % had a viral load below 200 copies/ml.

TDF-containing triple nuke therapy (and quadruple nuke)

In 2003, several studies showed that the combination of tenofovir plus two nucleoside analogs is unfavorable. After an initial pilot study in 19 patients reported poor

responses on ABC+3TC+tenofovir (Farthing 2003), the ESS3009 Study finally heralded the end of TDF-triple nuke therapies (Gallant 2003). The study investigated a fixed once-daily combination of ABC+3TC plus tenofovir against ABC+3TC plus efavirenz. After evaluation of the first 194 of a total of 345 treatment-naïve patients, the study was discontinued – 49 % of patients in the tenofovir arm experienced virological treatment failure, compared to only around 5 % in the efavirenz arm. First genotypical resistance analyses found the M184V mutation in a large number of patients with treatment failure in the tenofovir arm, combined with the TDF-resistance mutation K65R in the majority of cases. The low genetic resistance barrier is probably the reason for this poor result, which was also observed in treatment-experienced patients who wanted to simplify HAART (Hoogewerf 2003).

The combination of ddI+3TC+tenofovir also seems to be poor (Jemsek 2004). However, we have had fairly good experience with AZT+3TC+tenofovir in a multicenter study. The thymidine analog seems to be protective against tenofovir-associated mutations (Mauss 2005). At least two prospective studies have reported good responses on quadruple nuke therapy with AZT+3TC+abacavir plus tenofovir (DeJesus 2004, Moyle 2004). The long-term toxicity and efficacy of these combinations is still unknown.

Other triple nuke therapies

Besides those involving Trizivir™ and tenofovir, a number of other studies have investigated triple nukes. As expected, the results are heterogeneous. In the open-label, randomized CLASS Study, d4T+3TC+ABC were just as effective as ABC+3TC plus boosted amprenavir/r, but less effective than ABC+3TC plus efavirenz. After 48 weeks, 62 % of patients had a viral load below 50 copies/ml, compared to 59 % and 76 % in the other two arms (Bartlett 2002).

Poorer results came from Denmark in 2003 on the d4T+ddI+ABC combination (Gerstoft 2003). In this open-label randomized study, only 43 % of patients had a viral load below 20 copies/ml after 48 weeks. This result was significantly worse than in the two other arms (69 % for AZT+3TC plus nelfinavir+nevirapine, 62 % for AZT+3TC plus saquinavir+ritonavir).

In the Atlantic Study, d4T+ddI+3TC were virologically significantly weaker than d4T+ddI plus indinavir or nevirapine (Van Leeuwen 2003). After 96 weeks, the proportion of patients with less than 50 copies/ml in the triple nuke arm was just 28 %, compared to 44 % and 55 % in the two divergent arms.

But data is also available on AZT+ddI+3TC (Lafeuillade 1997), as well as on the d4T+FTC+ABC combination, with which 63 % of 188 patients reached a viral load below 400 copies/ml after 48 weeks (Sanne 2003). Most experts agree that, based on the negative experience with tenofovir combinations as described above, combinations without thymidine analogs should generally not be used for triple nuke regimens.

Summary on triple nukes for initial therapy

It is difficult to continue to promote triple nukes, at least as an initial regimen. Even when disregarding the dismal results from tenofovir-containing therapies, this strategy is a bit poorer in comparison to divergent regimens. On the other hand, it would be wrong to dismiss triple nuke therapy entirely, because the strategy has some ad-

vantages, particularly for patients with compliance problems as well as those with numerous co-medications with the potential for interactions. One may also wonder whether triple nukes are not just as good as divergent combinations in the long term despite the higher one-year rate for treatment failure, since subsequent regimens might work better. Triple nuke therapy also remains under consideration for maintenance therapy (see following chapter).

Future Combinations

Future combinations need to be more effective, simple and tolerable. However, there is not always time to wait for new drugs to be developed! As a result, there are three approaches being closely investigated with the currently available drugs: combinations without any nucleoside analogs (nuke sparing); combinations that require only once-daily dosing; and so-called induction therapies, comprised of intensive combinations using more than three active drugs or drugs from three different classes.

Nuke sparing

All classical HAART regimens have to date included a "backbone" consisting of two nucleoside or nucleotide analogs. This mainly has historical reasons: nucleoside analogs were the first available drugs against HIV, and by the time NNRTIs and PIs were under development, treatment with two nucleoside analogs was standard. With growing knowledge of the mitochondrial toxicity of nucleoside analogs, experts have increasingly questioned this concept. Nuke sparing, i.e. complete omission of nucleoside analogs, is a slogan that is being discussed more and more. PI-only combinations are already being used frequently today in salvage therapy (see corresponding chapter). But for initial therapy? Since the combination of indinavir+efavirenz fared quite badly in the 006 Study (Staszewski 1999), nuke sparing initially seemed to be a thing of the past. But nucleoside analogs are increasingly under fire. Long-term observations from an initial long-term study, in which 65 PI-naïve patients intensified their saquinavir/r combination with nucleoside analogs or not, were clear (Cohen 2002). Lipoatrophy was significantly less frequent after five years in those 28 patients, who had not received additional nucleoside analogs. This confirms that, as suspected, nucleoside analogs are likely to be the main cause of lipoatrophy. Table 6.4 shows the first results on this hypothesis.

There is only a single randomized study to date. The EASIER Study treated patients with indinavir/r and efavirenz with or without addition of d4T. The 48-week analysis showed comparable effects with respect to the surrogate markers – and d4T did not have any additional effect. However, this study was compromised by the relatively high dropout rate, reflected in the poor results of the ITT analysis (Stek 2003). It is also unclear whether mitochondrial toxicity and side effects improve with nuke sparing. A substudy of HIVNAT009 reported that lipoatrophy resolved, and that visceral fat and subcutaneous limb fat increased (Boyd 2003b).

Table 6.4: Nuke sparing in treatment-naive patients and patients with little prior treatment experience, prospective studies, with results of intent-to-treat analyses

	n (naïve)	Combination	Proportion < 50 copies/ml
Staszewski 1999	148 (126)*	EFV+IDV (006 Study)	47 % after 48 weeks 35 % after 144 weeks
Boyd 2003a	61 (0)*	EFV+IDV/r (HIVNAT 009)	87 % after 48 weeks
Stek 2003	47 (na)*	EFV+IDV/r (EASIER)	53 % after 48 weeks
Raffi 2004	86 (65)	EFV+LPV/r (BIKS)	73 % after 48 weeks (< 400)
Lopez-Cortes 2003	42 (0)**	EFV+SQV/r	71 % after 52 weeks
Hellinger 2003	20 (4)*	SQV+LPV/r	76 % after 48 weeks

*Patients all PI-naïve. **22/42 with less than 50 copies/ml at the time of switch. Number of completely treatment-naïve patients in parentheses. na = not available.

Despite this data, it seems premature to be able to really recommend nuke sparing as an equal alternative in its own right. Innovative study concepts such as LORAN should prove interesting, testing atazanavir+lopinavir/r against AZT+3TC+lopinavir/r in a randomized design. In the US, ACTG 5142 is a similar study, in which the nuke-sparing arm is efavirenz-lopinavir/r. Results are not expected before the end of 2005.

Once-daily

By the end of 2004, ten drugs had been licensed in Europe for once-daily dosing: ddI, abacavir, FTC, 3TC, d4T-PRC (d4T XR), efavirenz, tenofovir, atazanavir and fosamprenavir. Further drugs that are up for approval include nevirapine and lopinavir/r. As a result, multiple new once-daily options for initial therapy have emerged in the last months. Initial studies in treatment-naïve patients, usually not controlled, have shown fairly good results (see next table).

It should be noted, however, that most data obtained so far is from very small studies.

How good are once-daily regimens compared to those taken twice daily? Only a few studies have tested once-daily combinations for initial therapy against classic regimens in a randomized design. In a small Italian study, ddI+3TC+efavirenz was significantly better than Combivir™+efavirenz and Combivir™+nelfinavir (Maggiolo 2003). In the FTC-301 Trial, ddI+FTC+efavirenz was better than ddI+d4T+efavirenz, and this study was even stopped prematurely after a median follow up of 42 weeks due to the clear advantage (efficacy, tolerability) of the once-daily arm (Saag 2004). In ZODIAC, once-daily abacavir was not inferior to abacavir administered twice daily (both in combination with 3TC+efavirenz; Gazzard 2003).

Table 6.5: Relevant once-daily studies in treatment-naïve patients.

Study	n	Combination	Proportion < 50 copies/ml
DeJesus 2004	123	AZT+3TC+ABC+TDF	71 % after 24 weeks (ITT)
Gazzard 2003	385	ABC+3TC+EFV	66 % after 48 weeks (ITT)
Jayaweera 2004	70	d4T-PRC+3TC+EFV	71 % after 48 weeks (ITT)
Maggiolo 2001	75	ddI+3TC+EFV	77 % after 48 weeks (ITT)
Molina 2001	40	ddI+EFV+FTC	90 % after 64 weeks (< 400, ITT)
Gathe 2004	115	TDF+FTC+LPV/r	70 % after 48 weeks (ITT)
Saag 2004	286	ddI+FTC+EFV	76 % after 60 weeks (ITT)
Staszewski 2000	70*	ddI+3TC+NVP	70 % after 24 weeks (OT)

ITT = intent-to-treat, OT = on treatment, *68 % were treatment-naïve.

Several studies are currently investigating switching to such once-daily regimens. Initial data on ddI+TDF+nevirapine, ddI+FTC+efavirenz or d4T-PRC+3TC+efavirenz indicate that this also seems to work (Negredo 2004, Brett-Smith 2003, Molina 2003).

Arguments against once-daily regimens

Despite the studies above, some experts fear that once-daily dosing may be unfavorable with respect to the development of resistance. If one dose is forgotten, a whole day of treatment is lost at once. These regimens may therefore be "less forgiving", particularly if there are problems with compliance (and this is exactly the patient group in which these therapies are being used).

The higher peak levels may also reduce tolerability, as suggested by several studies. In the 2NN Study, the once-daily arm with nevirapine had a higher incidence of hepatotoxicity (Van Leth 2004); in the 418 Study, once-daily lopinavir led to significantly more diarrhea than twice-daily doses (Molina 2004). Trough levels are also lower with once-daily regimens. In the CONTEXT Study, this became relevant as trough levels for fosamprenavir in treatment-experienced patients were too low (Elston 2004). For this reason, fosamprenavir is not recommended for once-daily use in treatment-experienced patients. Trough levels for once-daily lopinavir are sometimes also too low, and often cannot be increased to sufficient levels even with additional pills (Burger 2004).

In addition: it has yet to be shown that once-daily regimens really improve compliance. In our experience, it is a larger jump to change from three to two doses a day than from two to one. A recently published meta-analysis showed that compliance is better for once-daily than three or four times daily dosing. However, the difference to twice-daily dosing was not significant (Claxton 2001).

Another study also showed that once-daily and bid dosing were no different, if the bid regimens were simple and had good tolerability (Stone 2004). Patients request once-daily treatment, but only if there are no restrictions regarding food intake and the number of pills is low (Moyle 2003). The higher number of pills associated with once-daily PI combinations such as saquinavir/r, indinavir/r and lopinavir/r will therefore limit the popularity of such regimens despite the fairly good data available

(Hugen 2000, Kilby 2000, Cardiello 2002+2003, Eron 2004, Molina 2004). 6-9 pills are too many.

It is advisable to discuss the pros and cons of once-daily therapy with the patient. It is certainly not required that all patients are treated with these regimens, even if the drug companies like to claim otherwise. Well-investigated combinations should be given priority (see table), as some once-daily regimens have been shown to be sub-optimal. These include not only tenofovir-containing triple nuke combinations (see above), but also combinations such as ddI+tenofovir plus efavirenz (Moyle 2004, Podzamczer 2004).

Induction with 4 or 5 drugs

There is widespread consensus for the use of triple combinations in first-line therapy. A meta-analysis (Jordan 2002) of 58 randomized clinical studies found that the relative risk of disease progression with triple therapy was approximately 0.6 compared to dual therapy.

However, increasing numbers of clinicians are speculating whether more intensive approaches are necessary in some patients. Rapid development of resistance, which is theoretically more likely in patients with a high viral load, is a growing concern. A number of physicians have already started to give initial treatment with four or even five drugs, and then to simplify the regimen to a triple combination after several months, once the viral load has dropped below the level of detection. This mainly theoretical concept has not yet been validated, and is only based on theoretical hypotheses or smaller proof-of-concept studies (Ramratnam 2004).

Quadruple therapy or more than 3 drugs

Current data does not support the approach of using more individual drugs. Giving two instead of one PI or NNRTI in studies such as SPICE, Danish PI or 2NN hardly showed any benefit and sometimes even produced negative results (Moyle 2000, Katzenstein 2000, van Leth 2004). There is also little evidence at the moment in favor of giving three instead of two nucleoside analogs (usually Trizivir™ instead of Combivir™). Although the TETRA pilot study showed relatively good response rates on AZT+3TC+ABC+efavirenz in patients with a high viral load, it seems questionable whether this could not also have been achieved with less nukes (Easterbrook 2003).

In the randomized QUAD Study, in which 53 patients with a viral load of > 100,000 copies/ml were enrolled, AZT+3TC+ABC+efavirenz were neither virologically nor immunologically more effective than AZT+3TC+efavirenz (Orkin 2004). Instead, 9 (versus 3) patients in the quadruple arm interrupted therapy due to intolerability.

In another small, randomized study (unfortunately also called QUAD), there was no difference between AZT+3TC (Combivir™) and AZT+3TC+ABC (Trizivir™), both combined with saquinavir/r, in patients with a high viral load (Staszewski 2003).

The final results from the ACTG 5095 Study are still pending, but preliminary analyses seem to show no major differences between Combivir™+efavirenz and Trizivir™+efavirenz (Gulick 2004).

More drug classes

The data on whether to use three or two drug classes is by no means consistent. The main studies that have investigated this question are outlined briefly below.

ACTG 388: in this open-label study, 517 treatment- or PI-naïve patients with relatively advanced HIV infection (less than 200 CD4 cells/µl or a high viral load above 80,000 copies/ml) were randomized to three different regimens (on a regular AZT+3TC nuke backbone): indinavir versus indinavir+efavirenz versus the double PI combination indinavir+nelfinavir (Fischl 2003). After a follow up of two years, virological failure in the indinavir+efavirenz arm was significantly lower than in the other two arms. Surprisingly, the poorest results came from the indinavir+nelfinavir arm, which also showed a trend towards more frequent development of serious adverse events. Therefore, ACTG 388 showed an advantage of triple-class therapy over conventional regimens; it must be noted, however, that some patients in this study were treatment-experienced and around 10 % already had resistance mutations at baseline.

ACTG 384: this trial intended to address several relevant issues: is a quadruple regimen better than a triple regimen? Are PI-containing regimens superior to NNRTI-containing regimens? Are there differences between d4T+ddI and AZT+3TC as nuke backbones? A total of 980 patients were randomized to six treatment arms (Robbins 2003, Shafer 2003): either AZT+3TC or d4T+ddI combined with efavirenz, nelfinavir or efavirenz+nelfinavir. The nucleoside analog component was blinded; the other drugs were given open-label. Preliminary data after an average follow-up of 28 months (with a relatively high number of dropouts) is just as interesting as it is confusing. AZT+3TC was more effective than d4T+ddI, but only in combination with efavirenz, not with nelfinavir. Conversely, efavirenz was superior to nelfinavir, but only with AZT+3TC as a backbone. The quadruple regimen was better than all triple regimens combined, but not in comparison to the single most effective regimen of AZT+3TC+efavirenz. The latter, however, had a relatively high number of patients dropping out. The toxicity of d4T+ddI was higher than that of AZT+3TC.

INITIO is a multinational trial with approximately 900 patients, investigating various approaches in an open-label randomized design. The main arms are d4T+ddI plus either efavirenz, nelfinavir or efavirenz+nelfinavir. Second-line regimens are also pre-determined. The main disadvantage of this long-term study is that the treatment regimens being studied have become somewhat outdated, and dropout rates could be high as a result (More information can be found at the website http://hiv.net/link.php?id=165).

ANRS 081 tested a triple-class regimen consisting of d4T+nevirapine+indinavir compared to a conventional d4T+3TC+indinavir regimen in 145 patients who were either treatment-naïve or with only little prior treatment experience. Here the triple-class regimen fared significantly worse: at week 72, 52 % in the nevirapine arm versus 79 % had a viral load below 20 copies/ml. 43 % of patients discontinued their nevirapine therapy (Launay 2002).

FORTE tested triple-class therapy with two nucleoside analogs, one PI and one NNRTI against standard therapy with two nucleoside analogs plus an NNRTI. Different individual drugs were used (Williams 2004). Triple-class therapy was administered for 24-36 weeks, and then switched to a simpler regimen. In the ITT

analysis, more patients in the standard therapy arm had developed virological failure after 32 weeks (43 % versus 18 %, p = 0.002), and there was a 0.86 logs higher decrease in viral load in the triple-class arm. After 48 weeks, 81 % versus 65 % of patients had less than 50 copies/ml. There were no significant differences in toxicity.

In summary: these studies currently indicate that any supposed improved efficacy of these regimens is counterbalanced by more side effects. Indeed, there is the risk of scaring patients away with the higher number of pills and side effects. It is still unclear whether such intensification of therapy is useful.

Other experimental strategies: PI monotherapy, alternating therapy

Several studies introduced a very avant-garde concept in the summer of 2003: monotherapy with boosted PIs. Although the negative experience with mono or dual therapies during the first years of antiretroviral therapy seems to prohibit such approaches, the high resistance barrier and good efficacy profile of lopinavir/r have prompted a few clinicians to dare to explore the proof-of-principle. The data is astonishing: in a study from Texas on 30 treatment-naïve patients, lopinavir/r monotherapy showed sustained good efficacy lasting beyond 48 weeks – 18 of 20 patients had a viral load below 50 copies/ml at this time point (Gathe 2004). Monotherapies are now also being tested in so-called maintenance therapies (see Chapter 8, "How to Change HAART?").

Another new approach is alternating therapy, which involves changing treatment every few weeks. In the SWATCH Study (Martinez-Picado 2003), a total of 161 patients were randomized to a regimen of d4T+ddI+efavirenz or AZT+3TC+nelfinavir. A third arm changed between the two regimens every three months, as soon as the viral load was below the level of detection. After 48 weeks, virological failure in the alternating arm was significantly reduced. There was no difference for all other parameters (CD4 cells, side effects, adherence, quality of life). It is interesting to see whether this experimental approach will hold up to further investigation.

Problems with Initial Therapies

Combinations generally considered to be suboptimal include all forms of mono- and dual therapy, especially two nucleoside analogs. Even one nucleoside analog plus one NNRTI is not good, as shown by the INCAS Trial (Montaner 1998). In addition, there are several typical mistakes that should be avoided if possible. When using nucleoside analogs, it is important to make sure that they are not competing for the same bases. Therefore, combination of thymidine analogs (AZT and d4T) or cytidine analogs (FTC, 3TC, ddC) makes no sense. The thymidine analogs AZT and d4T are even antagonistic (Havlir 2000, Pollard 2002). Other suboptimal combinations are addressed in more detail below.

Problem: Combination of "d-drugs"

The nukes ddI+ddC and d4T+ddC should not be combined because of the increased rate of side effects (polyneuropathy). This is due to mitochondrial toxicity, and now also applies to the commonly used d4T+ddI combination. There will possibly still be a future for d4T+ddI when the new d4T formulation (d4T-PRC) becomes avail-

able. In addition to being less toxic, d4T-PRC+ddI could be suitable for once-daily combinations.

Problem: Unsuitable individual drugs

The unboosted, old HGC formulation of saquinavir (Invirase™) is now unsuitable, as plasma levels attained are too low. The Euro-SIDA Study demonstrated that patients on saquinavir-HGC had a significantly higher risk of progression to AIDS (RR 1.30) compared to indinavir (Kirk 2001). Similarly, the randomized Master-1 Study showed saquinavir-HGC to be significantly weaker than indinavir (Carosi 2001). However, the SV14604 Study with saquinavir-HGC is to date the largest HAART study worldwide with clinical endpoints. It demonstrated an approximate 50 % reduction of AIDS with AZT+ddC+SQV-HGC compared to AZT+ddC (Stellbrink 2000). ddC is generally no longer recommended due to its weak efficacy.

Ritonavir is also unsuitable as an individual drug, as it is so badly tolerated at its full dose. Around 47 % of patients in the CPCRA042 Study discontinued their ritonavir therapy (Perez 2002). The same is true for saquinavir-SGC, since the pill burden is too high; no patient today can be expected to take 3 x 6 capsules daily.

Amprenavir should be replaced with fosamprenavir. Atazanavir, T-20 and delavirdine should be excluded from first-line regimens, as they have not been licensed for this purpose.

Problem: Starting abacavir plus NNRTIs simultaneously

A new abacavir-containing combination should not include a new NNRTI. Both can cause allergies, which are hardly distinguishable from one another. In the case of abacavir, even a suspected allergy rules out re-exposure, and this important drug may be "lost" unnecessarily for all future combinations. In the CNA30024 Study, a notable 9 % of patients developed a hypersensitivity reaction on ABC+3TC+efavirenz (DeJesus 2004). Thus, if abacavir and NNRTIs are to be taken together in a new combination, initiation of treatment with each of the two drugs should be spaced at least 4-6 weeks apart.

Problem: Combination of NNRTIs

NNRTIs act non-competitively at the same site, and furthermore all can cause a rash, making differential diagnosis difficult. Efavirenz levels seem to be lowered considerably in combination with nevirapine (Veldkamp 2001). This is probably also true for delavirdine (Harris 2000). In the wake of the 2NN Study, it finally seems clear that the combination of efavirenz and nevirapine should be avoided. The study arm with this combination fared significantly worse than the other arms, mainly due to toxicity (Van Leth 2004).

Problem: Starting gradually

All drugs should be started simultaneously. A number of studies have investigated whether the number of drugs should be slowly increased. At least since 1996 – the end of the era of mono- and dual therapy – such strategies should be obsolete. In the Merck 035 Study, highly significant differences were shown between patients who had received three drugs immediately and those who were started on only two drugs (Gulick 1998). The CNA3003 Study (Ait-Khaled 2002) provides a further example:

173 treatment-naïve patients were randomized double-blind to a combination of AZT+3TC+ABC versus AZT+3TC. At week 16, patients from the dual therapy arm could switch open-label to AZT+3TC+ABC or add further antiretroviral drugs if the viral load was above 400 copies/ml. At week 16, the viral load was above 400 copies/ml in 10 % in the triple therapy arm versus 62 % in the dual therapy arm. More importantly, 37 (versus 3) patients in the dual therapy arm had developed the M184V mutation. Although abacavir remained effective in most cases where it was added and TAMs were the exception, this example shows how quickly resistance can develop. This is significant in the long-term: a large cohort study showed that the risk of virological treatment failure was doubled even after years if dual therapy had been given for as short as a few weeks (Phillips 2002).

Thus, initiating triple therapy only gradually, as is sometimes practiced due to concern over too many side effects, is wrong and dangerous.

Problem: Tenofovir plus certain nukes (ddI!)

Tenofovir should not be administered as part of a triple nuke regimen. Too many studies have reported poor response rates, particularly in combination with abacavir+3TC (Farthing 2003, Gallant 2003, Hoogewerf 2003, Jemsek 2004), see chapter "Triple Nuke". Another combination that is not advised based on newer data is tenofovir and ddI with an NNRTI. Reports on this have shown higher toxicity, in particular pancreatitis (Martinez 2004), and efficacy does not seem to be good. At least two studies testing the combination of tenofovir+ddI plus efavirenz were discontinued prematurely (Podzamczer 2004, Moyle 2004). In both studies, particularly patients with a significant immunodeficiency and high viral load tended to develop virological failure even during the first few weeks. After this (and other unpublished) data, BMS sent out a warning letter about tenofovir+ddI. There are now even reports that CD4 cells drop on this combination (Clotet 2004, Negredo 2004).

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7. When to Change HAART

Christian Hoffmann, Fiona Mulcahy

HAART is changed for three main reasons:

1. Acute side effects
2. Long-term toxicity (or concern regarding this)
3. Virological treatment failure

Changes in antiretroviral therapy are very common, especially within the first or second year. Treatment modification is required in approximately 50 % of patients within the first year. In an English cohort, 44 % of patients had had their regimen modified by 14 months (Mocroft 2001); in a German study, 53 % of patients had changed drugs after one year, mostly because of adverse drug events (Fätkenheuer 2001).

Change Due to Acute Side Effects

Not every acute side effect requires immediate modification of the treatment regimen. A bit of nausea or diarrhea in the beginning can and should be tolerated. One should always remember that the number of available drugs is limited. Gastrointestinal side effects that occur during the first weeks are not dangerous and often improve spontaneously or can be treated symptomatically. The same is true for some allergic reactions and for relatively mild CNS disorders with efavirenz (mild allergies). However, certain adverse drug events almost always require discontinuation or changing of HAART. These include:

- Severe diarrhea, which persists despite loperamide even after several weeks (usually due to nelfinavir, lopinavir, saquinavir)
- Severe nausea, which persists despite metoclopramide, requires continuous treatment or leads to significant weight loss (usually AZT, ddI)
- Polyneuropathy (d4T, ddC, ddI, possibly also 3TC) – often resolves only very slowly, therefore change treatment quickly!)
- Severe anemia (AZT)
- Severe, progressive muscular weakness (d4T, ddI)
- Pancreatitis (ddI, ddI+TDF!, d4T+ddI+HU! In rare cases lopinavir/r)
- Lactic acidosis (most often d4T+ddI, but also all other NRTIs)
- Severe allergies with involvement of mucous membranes, fever (typically abacavir, NNRTIs, more rarely amprenavir, fosamprenavir)
- Renal failure (tenofovir, indinavir)
- Nephrolithiasis or recurring renal colic (indinavir)
- Hepatotoxicity with transaminases > 5 x normal values (nevirapine, ritonavir)
- Jaundice (nevirapine, atazanavir, indinavir)
- Psychosis (efavirenz, possibly also AZT)

Change Due to Concern over Long-term Toxicity

In the last few years, many clinicians have started to change virologically success-
ful combinations out of concern for cumulative long-term toxicities. In particular
PI- and d4T-containing combinations are sometimes replaced with NNRTIs and
other nucleoside analogs. A large number of so-called switch studies have appeared
in the last few years on this topic. The most important randomized studies are dis-
cussed below. It should be noted that a considerable number of these studies are not
yet peer-reviewed and have only been presented as conference abstracts.

Table 7.1: Randomized studies on switching from PIs to other drugs

Source	n	Wk	VLS	Effect of switch
PI → NVP				
Barreiro 2000	138	24	Advantage	L unchanged, LD better
Ruiz 2001	106	48	n.s.	L possibly better, LD un-changed
PI → EFV				
Katlama 2000	134	48	n.s.	L unchanged, LD n.a.
Martinez 2001	93	48	Disadvantage (trend)	L mostly unchanged, LD bet-ter, LA worse
Becker 2001	346	48	Advantage	L unchanged, LD n.a.
PI → ABC				
Clumeck 2001	211	24	Advantage	L better, LD subjectively better
Pulvirenti 2001	87	24	n.s.	L better, LD n.a.
Keiser 2002	104	24	Disadvantage (trend)	L better
Opravil 2002	163	84	Disadvantage (trend)	L better, LD unchanged
Katlama 2003 * Lafeuillade 2003 *	209	48	n.s.	L better, LD better
PI → EFV v NVP				
Patterson 2001	76	24	n.s.	L only better on NVP (triglyc-erides), LD unchanged
Negredo 2002	77	48	n.s.	L only better on NVP (TG, chol), LD unchanged
PI → EFV v NVP v ABC				
Martinez 2003 *Fumero 2002*	460	48	Trend against ABC	L only better on ABC. LD probably unchanged

Note: In all studies (except Martinez 2003), randomization was against continuing PIs. All had
an open-label design and all patients had been on PIs for several months at the time of the
switch, with undetectable viral load. In all studies, quality of life improved in the switch arms (if
it was evaluated). Studies in italics have only been available as conference abstracts. VLS =
viral load suppression in the switch arm versus the continuing arm. Wk = weeks, LD = lipodys-
trophy, LA = lipoatrophy, L = lipids, n.a. = not available, n.s. = not significant, TG = triglycerides

*Here only 62 % of patients were taking a PI, the rest were on NNRTIs or triple nuke.

PI replacement

One main conclusion can be drawn from the studies on PI-switch: switching from PI-containing to NNRTI-containing regimens for reasons of existing or possible long-term toxicity is virologically safe, if the viral load is well suppressed (see Table 7.1).

However, a recently published meta-analysis has indicated that switching to an NNRTI may have some immunological disadvantages, as CD4 cells possibly increase slightly less on non-PI regimens (Owen 2004).

Lipid levels are most likely to improve after switching to abacavir, and least likely to do so on efavirenz. Whether lipodystrophy really improves after stopping a PI is still unclear. There seem to be subjective improvements, but these are difficult to quantify.

Switching from a PI to abacavir poses an increased risk of virological failure, particularly with prior nucleoside analog treatment and the associated resistance mutations. Potential side effects also need to be considered with every switch: a rash or hepatotoxicity can be expected with nevirapine, and efavirenz may be associated with adverse CNS events. There is the risk of a hypersensitivity reaction with abacavir, the frequency of which reached a considerable 10 % in the TRIZAL Study (Katlama 2003).

Quality of life improved significantly in the switch arms of most studies, probably due to the reduced pill burden.

D4T replacement

The thymidine analog d4T is also frequently replaced with other nucleoside analogs. Such switch studies have however been smaller, and often inconsistent – sometimes PIs were replaced at the same time (see Table 7.2). Nevertheless, these studies show that lipoatrophy improves when d4T is replaced (usually) by abacavir (McComsey 2004, Martin 2004). Subcutaneous limb fat increased on dexa scanning, although such changes were often not clinically apparent (Martin 2004).

Table 7.2: Randomized studies on switching from d4T to other drugs

Source	n	Switch	Wk	Effect of switch
Carr 2002 Martin 2004	106	ABC instead of d4T or AZT	104	LA better, lipids unchanged
McComsey 2004	118	AZT or ABC instead of d4T	48	LA better, lactate better
John 2003	37	AZT instead of d4T and ABC instead of PI	48	LA of limbs slightly better, lipids and abdominal fat unchanged
Moyle 2003	30	ABC instead of d4T or PI/NNRTI, or AZT+ABC instead of d4T+PI	48	LA better (when replacing d4T) Lipids better (when replacing PI)

No study showed any difference with respect to virological failure. Wk = weeks, LA = lipoatrophy. In McComsey: only patients with LA were investigated, and the study was also not randomized.

These studies confirm laboratory studies on the mitochondrial toxicity of d4T and various cohort studies (see under d4T).

However, the abacavir-HSR remains a problem, as mentioned above. In the Mitox Study, it occurred in 10 % of patients (Carr 2002). Another study at 24 weeks has recently shown that there is no improvement in the mitochondrial DNA after switching from d4T to abacavir (Hoy 2004). This is in contrast to earlier findings (McComsey 2004). The value of such measurements remains controversial, as the methods have not been completely validated (see chapter on mitochondrial toxicity).

Switching to tenofovir

There are no randomized studies yet on switching to tenofovir. Tenofovir is less toxic, and in the 903 Study it was tolerated significantly better than d4T (Staszewski 2003). First attempts to switch to tenofovir have been fairly positive (Haberl 2003). In the 903 Study, lipids improved in patients that were switched from d4T to tenofovir (Suleiman 2004). Another retrospective study has shown that switching from d4T to tenofovir improved both lipids and liver enzymes (Schewe 2003). However, in view of the problematic data on triple nuke therapy with tenofovir (see corresponding section), one should be cautious when making such a switch.

In practice, regimens are also switched for reasons other than stopping PIs or d4T out of concern over long-term toxicity. Such switching (e.g. abacavir or tenofovir instead of ddI or AZT) is based on laboratory studies showing a certain hierarchy with respect to mitochondrial toxicity (Kakuda 2000, see also chapter on mitochondrial toxicity). Therefore, it is currently advisable to wait for the results of clinical studies.

Virological Treatment Failure

Every change in treatment due to virological failure requires experience and a certain degree of finesse. But also decisiveness! There are many possibilities for mistakes here. It is important to explain the reasons for change to the often skeptical patient ("Shouldn't I save other drugs for later?").

HAART should be rapidly changed in the case of insufficient viral suppression and/or after an increase in plasma viremia, as suboptimal therapy always carries the risk of new resistance mutations, which may eliminate future treatment options via cross-resistance. First-line therapy with AZT+3TC+indinavir is a good example. If this regimen fails but continues to be taken, the virus may generate typical mutations such as 41L, 67N, 210W, 215F, 184V, 82T, 84V, 46L, 90M – and this eliminates all currently available drugs with the exception of NNRTIs, ddI (and T-20). If an NNRTI is added, it is easy to have no options left at all. Even individual mutations may create significant problems: K65R, which very frequently occurs on failing tenofovir-containing triple nuke therapies, leads to considerable loss of efficacy for abacavir, 3TC (most likely also FTC) and probably ddI. Viral replication in the presence of insufficient plasma levels is ideal for the development of resistance mutations.

In the case of clear virological failure, action must be taken without delay – the longer one waits, the more difficult things become! Insufficient viral suppression means a viral load above the level of detection of 50 copies/ml. Some clinicians,

however, tolerate values up to 500 or even 1,000 copies/ml. In patients with good options for subsequent regimens and good compliance, we consider this unwise (with the few exceptions described below). The patient's frequent argument "But I'm fine!" makes no difference here!

In cases of clinical treatment failure (disease progression) or immunological failure (stagnation or decrease in the level of CD4 T lymphocytes), in which the viral load is below 50 copies/ml, the value of a change in therapy is uncertain. However in the case of tenofovir plus ddI, which may be more unfavorable for immunological reconstitution (Negredo 2004); change could be considered.

Several questions need to be addressed when considering the needs of the individual patient:

a) What are the reasons for the (increased or still increased) measurable viral load?

A viral load above 50 copies/ml does not necessarily mean that resistance mutations have developed. It may also indicate insufficient plasma levels (measure these if possible!). This may be due to: drug malabsorption, drug interactions or simply insufficient dosing (e.g. in very big, heavy patients). Compliance is also critical. Any possible difficulties associated with the regimen should be openly addressed: Is it the number of pills? Do restrictions in food intake cause problems? Would once-daily treatment be better? Are there other reasons, such as depression? The risks of resistance developing as a result of non-compliance should be reiterated. If plasma levels are sufficient and viral load remains detectable (monitor blips at short intervals – within a few weeks!), treatment should definitely be changed as soon as possible.

b) How vulnerable is the present combination?

NNRTI regimens are extremely sensitive, as cross-resistance can develop particularly rapidly for the whole class. Therefore, a prompt change in therapy is even more vital than with the other drug classes. Delaying this by even a few days or weeks may be too long! Rapid development of resistance can also be expected with 3TC (and probably FTC). A PI-containing regimen without an NNRTI may allow a little more time, but the credo still applies: the higher the viral load at the time of modification, the lower the chances of success. One should not wait too long.

c) What options does the patient have, and what are the consequences of the change in therapy?

The more options that remain available, the sooner they should be utilized. Therapy can often be intensified quite easily (e.g. adding abacavir plus an NNRTI). In such cases, the decision to change or intensify a regimen is less difficult.

Intensification of therapy may not be feasible in all cases. A patient on triple-class therapy as well as extensive pre-treatment usually has few options left. These are often reduced even further by side effects. In such cases, the goal of achieving a viral load below the level of detection may have to be abandoned (see also "Salvage Therapy" chapter).

References

See at the end of the next chapter.

8. How to Change HAART

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The approach to changing a treatment regimen that is successful but intolerable due to side effects is usually straightforward. The suspected drug is replaced with another drug of the same class. However, difficulties can arise if alternate drugs are contraindicated because of potential toxicity or if resistance mutations against these drugs are suspected. In such cases, changes have to be individualized according to the situation of the patient.

This chapter discusses two other important reasons for switching, where certain principles should apply: changing due to virological failure, and changing HAART to simplify the regimen. Switching out of concern for lipodystrophy has been discussed in previous chapters.

Change due to virological failure

The same principles apply as when initiating therapy: compliance, dosing issues, concurrent diseases, comedications and drug interactions. It is also essential to consider treatment history and possible existing resistance mutations. Although desirable before any change in treatment, resistance tests are not always practical. It is therefore useful to become familiar with the most important resistance mutations, particularly for nucleoside analogs (see Table 8.1). The basic principles for changing therapy in cases of virological failure apply: the faster the change, the better; the virus should be given as little time as possible to generate more resistance mutations. In addition: the more drugs that are changed, the higher the likelihood of success for the new regimen.

Table 8.1: Expected resistance mutations with different nuke backbones

Failing nuke backbone	Mutations
AZT/d4T+3TC AZT+3TC+ABC	M184V and then successive TAMs, the longer one waits
TDF+3TC/FTC	K65R and/or M184V
ABC+3TC	L74V > K65R and/or M184V
AZT/d4T+ddI	TAMs, Q151M, T69ins
TDF+ABC/ddI	K65R

The situation with NNRTIs is more straightforward: there is usually complete cross-resistance. Continuation in the presence of these resistance mutations is of no use, as they have no impact on the replicative fitness of the virus.

There are also relevant cross-resistance mutations for PIs. Resistance testing is therefore recommended here. However, we have started to treat with lopinavir/r after failure of the first PI. This is now the area of salvage, discussed in more detail in the next chapter.

Table 8.2 provides a rough guide on how to proceed without knowledge of resistance mutations.

Table 8.2: Changing first-line therapy without knowledge of resistance mutations*

Failing initial therapy	Potentially successful change	
3 Nukes	2 new nukes plus NNRTI or PI	possibly also:
	2 new nukes plus NNRTI plus PI	(with high viral load)
2 Nukes + 1 NNRTI	2 new nukes plus PI	
PI + NNRTI	2 nukes + boosted PI	
2 Nukes + 1 PI	2 new nukes plus NNRTI plus possibly new boosted PI	
	or boost present PI	

* Note: there is insufficient data available on all these changes. In individual cases, other modifications or simply waiting may be advisable.

If the increase in viral load is minimal, treatment success may be achieved even with simple changes – if one acts quickly. In the case of two nukes plus an NNRTI, for example, treatment may possibly be intensified simply by the addition of abacavir (Degen 2000, Katlama 2001 Rozenbaum 2001). In a placebo-controlled study, 41 % of patients on stable ART with a viral load between 400 and 5,000 copies/ml achieved a viral load below 400 copies/ml at 48 weeks after addition of abacavir alone (Katlama 2001). Such results could possibly be even better with more rigorous entry levels (for example, not waiting to change therapy until 5,000 copies/ml are reached, but acting already at 500 copies/ml).

Addition of tenofovir – one extra tablet a day – also seems possible in certain cases. Tenofovir reduced the viral load under stable HAART by 0.62 logs (Schooley 2002). Our experience with this approach has been good in cases with minimal increases in the viral load (up to 500 copies/ml) and in the absence of TAMs.

In patients who have been treated exclusively with NRTIs (in particular after prolonged treatment), this strategy is not promising. Extensive resistance mutations usually exist, so that a complete change of HAART is necessary. At least two randomized studies (some blinded) have shown that most benefit is achieved by switching to an NNRTI plus a PI plus at least one new nucleoside analog. This has been shown for both nelfinavir plus efavirenz and indinavir plus efavirenz (Albrecht 2001, Haas 2001). In patients previously treated with NRTIs or NNRTIs, a PI must be used.

Change to simplify the regimen – do maintenance therapies work?

Can HIV infection be treated in a similar fashion to some hematological diseases or tuberculosis, with a sequence of intense induction therapy followed by less toxic (and less expensive) maintenance therapy? The idea is appealing, and has circulated almost since the existence of HAART. Between 1998 and 2003, the answer was clearly that maintenance therapies do not work. By 1998, three randomized studies (Trilège, ADAM, ACTG 343) had already destroyed all hope that HAART might be reduced to two or even one drug.

In the French Trilège Trial, 279 patients adequately treated with HAART were randomized to three arms of different intensity (Pialoux 1998, Flander 2002). At 18 months, the viral load had increased to above 500 copies/ml in 83 patients – 10 on AZT+3TC+indinavir, but 46 on AZT+3TC and 27 on AZT+indinavir. However, temporary dual therapy had no negative effect, and resistance did not develop (Descamps 2000). In the ADAM Trial (Reijers 1998), patients who had been treated

with d4T+3TC plus saquinavir+nelfinavir for several months either stopped or continued their nucleoside analogs. The study was already doomed at interim analysis: 9/14 (64 %) patients simplifying therapy already had a detectable viral load at 12 weeks, versus 1/11 (9 %) of those continuing on the previous regimen. The third study, finally led to the end of the notion of maintenance therapy was ACTG 343. 316 patients, with a viral load below 200 copies/ml for at least two years, either continued to receive AZT+3TC+indinavir or took a simplified regimen of AZT+3TC or indinavir. The rate of treatment failure (viral load above 200 copies/ml) was 23 % in the two maintenance arms compared to only 4 % in patients on continued therapy (Havlir 1998).

In the last few years, several newer, better drugs have been licensed. In particular, lopinavir has considerable antiviral potency and a high resistance barrier, and this potentially casts a different light on the negative image of maintenance therapies.

In at least three pilot studies, patients with good viral load suppression were able to successfully simplify therapy with lopinavir monotherapy (Arribas 2004, Pierone 2004, Ruane 2004). However, patient numbers were low and observation periods short. In the OK Study, 21 patients were randomized to groups taking either lopinavir/r alone, or in combination with two nucleoside analogs. Prior to randomization in this study, the viral load had to be undetectable for at least six months. In the monotherapy maintenance arm, there were three (slight) increases in viral load to above 400 copies/ml by week 24, versus no increase in the triple therapy arm (Arribas 2004). Another drug that might be suitable for such mono-maintenance therapy is fosamprenavir/r, which, like lopinavir/r, also seems to have a relatively high genetic barrier. In the SOLO Study, no resistance was observed on boosted fosamprenavir even after 48 weeks (MacManus 2004). However, there is no data available yet on fosamprenavir maintenance therapy.

In contrast, there is now data from a pilot study on indinavir monotherapy (Kahlert 2004). 12 patients have so far changed from stable HAART to maintenance with indinavir/r; viral load has not increased above 400 copies/ml in any of these. There is also data on boosted saquinavir/r: in the Prometheus Study, PI- and d4T-naive (some completely treatment-naive) patients were randomized to a regimen of saquinavir/r plus/minus d4T. After 48 weeks, 88 % versus 91 % of patients in the on-treatment analysis were below 400 copies/ml. However, particularly patients with high viral loads were not stable on this PI treatment strategy (Gisolf 2000).

The approach taken in the French COOL Study (B4493) seems promising. 140 patients were randomized to TDF+3TC+efavirenz or TDF+efavirenz for 48 weeks. Inclusion criteria included HAART with a viral load below 50 copies/ml for at least three months; patients with prior treatment failure were excluded. There were no restrictions on CD4 cell count. An interim analysis of 45 patients who had been followed for 24 weeks was presented at the World AIDS Conference in Bangkok: not a single case of virological failure had been seen (Girard 2004).

Triple nuke therapy, though now fairly obsolete for first-line therapy, seems to also be justifiable for maintenance therapy (Bonjoch 2004, Markowitz 2004, van Raalte 2004): In the ESS40013 Study, a total of 448 patients were treated with AZT+3TC+ABC plus efavirenz. After 36 or 44 weeks, 282 patients with undetectable viral load at this time were randomized to continue with the same therapy or to stop efavirenz. After 96 weeks, 79 % versus 77 % of patients were still below

50 copies/ml, proving that triple nuke treatment was not inferior (Markowitz 2004). In a Spanish study, 134 patients with an undetectable viral load for at least 24 weeks were randomized to receive either Trizivir™ or Combivir™ plus nevirapine (Bonjoch 2004). After 48 weeks, the number of patients with an undetectable viral load was comparable across both arms (71 % versus 73 % in the ITT analysis).

Despite these interesting results, maintenance therapies apart from triple nuke regimens are not yet justifiable for treatment outside of well-designed clinical studies. HIV infection cannot yet be compared to tuberculosis.

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9. Salvage Therapy

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Background

The term "salvage therapy" is not clearly defined. It is currently used confusingly in both HIV medicine and oncology to refer to varying situations. Some clinicians speak of salvage only if all drug classes have failed, whereas others employ the term from second-line therapy onward. As yet, no consensus on the definition of salvage has been reached. Here, we define salvage as the therapeutic approach when at least one PI-containing regimen has failed.

The investigation of new salvage strategies is problematic, as it is difficult to find homogeneous and sufficiently large patient study populations. Although patients with multiresistant viruses are no longer hard to find, each patient has an individual pre-treatment history, different resistance mutations and thus different prerequisites for a salvage regimen. In any one of the larger clinical centers, more than 40 to 50 different combinations are in use. As a result, few randomized studies have been conducted, and larger trials have only recently been initiated.

The OPTIMA Study (OPTions In Management with Antiretrovirals) is currently investigating different strategies, such as mega-HAART or three-month treatment interruption, before initiation of a new HAART regimen. By June 2004, almost 300 patients had been randomized. The results will not be available for a while, and until then, one must rely on data from smaller, mostly uncontrolled studies, which usually describe between 20 and 100 salvage patients.

At least two important conclusions have been established by these studies: firstly, the higher the viral load on the failing PI regimen, the worse the chances of success for the subsequent combination (Chavanet 2001, Deeks 1999, Hall 1999, Paredes 1999, Mocroft 2001). The more time the virus has to develop resistance and gain fitness, the more intractable it becomes! Secondly, various studies have shown that usually only 30 to 50 % of patients who fail PI regimens are able to achieve a viral load below the level of detection on a boosted combination such as saquinavir/r (Deeks 1998, Fätkenheuer 1999, Hall 1999, Paredes 1999, Gulick 2002). The response to saquinavir/r may be slightly improved if the initial regimen contained nelfinavir (Tebas 1999): this is probably due to the D30N mutation specific to nelfinavir. However, this has recently become the subject of much controversy (Ghani 2003).

The ACTG 398 Study confirmed earlier observations, and is to date the largest randomized salvage study. 481 patients with a viral load above 1,000 copies/ml and extensive pre-treatment (1-3 PIs) were randomized to either receive an additional, second PI in the salvage arm (depending on previous treatment) or to continue the previous regimen (Hammer 2002). Only 31 % of patients achieved a viral load below 200 copies/ml after 24 weeks. In the group receiving two PIs, the rate was significantly higher (35 % versus 23 %). On the whole, however, the response to the

salvage regimen was – until the introduction of lopinavir/r – rather modest (review in Battegay 1999).

Several new salvage strategies have emerged that may be more promising, and possibly even used in combination. These have been extensively investigated in recent years and are discussed here:

- Salvage with lopinavir/r
- Salvage with double PIs
- Salvage through recycling of older drugs
- Mega- and giga-HAART, treatment interruptions
- New salvage drugs
- Utilizing NNRTI hypersusceptibility
- Just waiting, and even simplifying ART

Salvage with Lopinavir/r

The introduction of lopinavir/r (Kaletra™) has significantly improved salvage therapy. Despite the disturbing occurrence of dyslipidemia, the drug remains almost irreplaceable for salvage. The resistance barrier is high (Kempf 2001), and even patients with extensive prior treatment may benefit from it. Lopinavir/r-containing combinations should therefore be considered after failure of the first PI. Response is often surprisingly good, and the higher the drug plasma levels, the better (Boffito 2002). At least 5-7, if not 8 PI mutations are necessary for failure of lopinavir/r (Kempf 2001, Masquelier 2002). In 70 patients on a failing PI regimen, the decrease in viral load was an impressive 1.4 logs at two weeks after simple substitution of the PI with lopinavir/r (Benson 2002). A realistic example of the efficacy of lopinavir/r in a heavily treatment-experienced patient is shown in Table 9.1.

Table 9.1: Patient example of the success of lopinavir/r in salvage therapy

Date	(HA)ART	CD4 T cells	Viral load
Mar 93	AZT	320	N/A
Jan 95	AZT+ddC	190	N/A
May 96	AZT+3TC+SQV	97	N/A
Feb 97	d4T+3TC+IDV	198	126,500
Aug 97	d4T+3TC+NFV	165	39,500
Mar 98	d4T+ddI+SQV+RTV+HU	262	166,000
Sep 98		238	44,000
July 00	AZT+3TC+NVP+LPV/r	210	186,000
Oct 00		385	< 50
Oct 04		569	< 50

This example illustrates several phenomena: insufficient responses to new regimens after failure of the first PI; insufficient viral suppression over two years with surprisingly stable CD4 T cell levels; and finally a durable response to lopinavir/r – after more than four years of suboptimal PI-treatment! NNRTI hypersusceptibility may also have possibly been present in this case (see below). At the time of switch to lopinavir/r, genotypic and phenotypic resistance to various nucleoside analogs (and PIs) had developed.

However, newer studies show that there will soon be competition even for lopinavir. Boosted atazanavir has almost comparable efficacy in patients previously treated with at least two combinations. BMS AI424-045 enrolled patients who had failed at least two HAART regimens, including at least one PI regimen. In addition, all patients received a new nucleoside analog as well as tenofovir. After 48 weeks, virological efficacy was comparable, and so it could be shown that atazanavir was not inferior in this patient population (DeJesus 2004). In the Context Study, boosted fosamprenavir was only slightly weaker (Elston 2004). TMC114 and particularly tipranavir (see the respective sections) are also developing as new PI options, although there is still a lack of long-term experience. Nevertheless, it is clear that any new substances will have to at least measure up to lopinavir.

Salvage with Double PIs

A further attractive approach for salvage therapy is to use low doses of ritonavir (as contained in Kaletra™) to boost not only lopinavir but also other PIs. The following provides an overview of data on this strategy. Such double PI combinations are not only attractive for salvage, but will also be investigated further for first-line nuke-free therapies in treatment-naïve patients. The Loran Study, in which lopinavir and atazanavir are tested in treatment-naïve patients, is a primary example.

Lopinavir/r + saquinavir/r: in vitro data indicate that there is synergy between these two drugs (Molla 2002). The ritonavir dose in Kaletra™ (at the normal dose of 4 capsules bid) seems to suffice for 1,000 mg bid saquinavir, as shown in the LopSaq Study (Stephan 2004). There do not seem to be any unfavorable interactions between saquinavir and lopinavir/r (Ribera 2004), as has been described for amprenavir and lopinavir/r (see below). A small observational study showed better responses with the lopinavir/r + saquinavir combination than with lopinavir/r + amprenavir (Zala 2002).

The efficacy of lopinavir/r + saquinavir was more closely examined in the LopSaq Study (Hellinger 2002, Staszewski 2004). The largest study of its kind, it enrolled 163 heavily treatment-experienced patients for different reasons (resistance, toxicity) to be treated with a nuke-free combination consisting of lopinavir/r (400/100 mg bid) plus saquinavir (1,000 mg bid). 88 patients interrupted therapy prior to starting this regimen. At the last follow up, 115 patients were evaluated by week 48. 77 patients (61 %), a considerable proportion, showed good virological response to this therapy, and 50 patients even reached a viral load below 50 copies/ml. However, patients with numerous PI resistance mutations and low CD4 cell counts responded poorly (Staszewski 2004).

Atazanavir/r + saquinavir/r: saquinavir does not seem to influence atazanavir levels, and the levels of both PIs can be improved by addition of ritonavir. A pilot study on 18 HIV-infected patients investigated a once-daily combination with 300 mg atazanavir, 100 mg ritonavir and 1,600 mg saquinavir. Surprisingly, PK parameters for saquinavir were significantly improved by atazanavir, and trough levels of saquinavir increased by over 110 % (Boffito 2004). The reason for this interaction between saquinavir and atazanavir is still unclear, but could be related to gastrointestinal transport mechanisms. It is interesting to note that intracellular levels of saquinavir are also significantly elevated (Ford 2004). The regimen was well

tolerated, although hyperbilirubinemia frequently occurred. Indirect bilirubin was increased 5-fold on average.

With the ATSAQ Study, the first data on the efficacy of atazanavir/r + saquinavir was published (Rottmann 2004): 40 heavily treatment-experienced patients were treated with a nuke-free combination of 300 mg atazanavir, 100 mg ritonavir and 2 x 1,000 mg saquinavir. After a median 32 weeks, 85 % of patients had reached a viral load below 400 copies/ml.

Three further studies are currently underway, testing different doses of this combination. Despite the fact that saquinavir levels are elevated by atazanavir, this combination is probably not useful without ritonavir. In the BMS A1424-045 Study, saquinavir and atazanavir did less well than boosted atazanavir or lopinavir (DeJesus 2004). In the AI424-009 Study, the unboosted combination was also relatively weak (Haas 2003). It should therefore not be used.

Saquinavir/r + fosamprenavir: the combination of saquinavir and amprenavir was tested early on (Eron 2001). However, saquinavir levels seemed to be lowered by amprenavir, probably necessitating a higher ritonavir dose (Corbett 2002). Newer studies have focused more on the combination of saquinavir with fosamprenavir. As with amprenavir, saquinavir levels dropped significantly in 18 patients treated with a combination of 1,000 mg saquinavir, 100 mg ritonavir and 700 mg fosamprenavir (all bid). This negative interaction could be well compensated by increasing the ritonavir dose to 200 mg bid (Boffito 2004). Since the resistance profiles of these two drugs only partially overlap, use of this combination might be interesting, particularly with the new 500 mg saquinavir capsules, which significantly reduce the pill burden.

Lopinavir/r + indinavir: in vitro data shows synergistic activity for lopinavir and indinavir. This combination has been tested with different doses of indinavir. In the Crix-Lop Study from Frankfurt, 28 highly treatment-experienced patients have now been enrolled (Staszewski 2003), and 17 of these remained on treatment even after 46 weeks (2 x 800 mg indinavir/400 mg lopinavir). It was shown once again that the low ritonavir dose is sufficient to boost both PIs (von Hentig 2003, Isaac 2004), however the data is not completely clear-cut, and case numbers are fairly low. An additional ritonavir dose is possibly necessary, and TDM is recommended. Indinavir and lopinavir do not usually seem to require dose adjustment.

Lopinavir/r + fosamprenavir: the resistance profile is very promising, and the lopinavir + (fos)amprenavir combination is probably the most extensively investigated double PI strategy. Unfortunately, the unfavorable PK data that is emerging is likely to prevent widespread use of this combination. A complex interaction has already been described between lopinavir and amprenavir, which causes levels of both drugs to drop significantly (Khanlou 2002, Mauss 2002, DeLuca 2004, Raguin 2004). Increasing the ritonavir boosting dose is not beneficial (Mauss 2004, Taburet 2004). Similar unfavorable interactions seem to apply also to fosamprenavir (Kashuba 2003, Wire 2004). Taking the two PIs at different intervals to each other does not prevent low fosamprenavir levels (Corbett 2004).

As a result, this combination cannot be recommended until further data becomes available. If treatment with lopinavir/r and fosamprenavir is nevertheless attempted based on the individual resistance profile, significant dose adjustment will be required – based on TDM.

Other double PI combinations: the double PI combination of atazanavir and indi-navir should be avoided as both drugs cause hyperbilirubinemia. Severe diarrhea is to be expected when combining lopinavir/r and nelfinavir, and a pilot study found further decreased lopinavir levels (Klein 2003). Indinavir and nelfinavir seem to have relatively weak activity in combination (Schranz 2000, Riddler 2003).

The new PI tipranavir seems to have negative interactions with several other PIs. In one study, levels of lopinavir, saquinavir and amprenavir all dropped significantly, which is why a double PI regimen with tipranavir is currently not advisable. In contrast, interactions between tipranavir and indinavir may not be as relevant (Leen 2004).

Interestingly, an initial pilot study showed favorable interactions between atazana-vir and fosamprenavir (Khanlou 2004).

It should be noted that double PI combinations should only be considered in salvage patients experiencing NRTI side effects (mitochondrial toxicity), and should be administered by experienced clinicians with access to therapeutic drug monitoring, so that dose adjustment is possible if required.

Table 9.2: Double PI combinations with sufficient supporting data

Combination	Dose/comment	Source
More favorable		
Lopinavir/r + saquinavir	400/100/1,000 bid	Staszewski 2004
Atazanavir/r + saquinavir	300/100/1,000 bid	Boffito 2004
Saquinavir/r + fosamprenavir	1,000/200/700 bid	Boffito 2004
Lopinavir/r + indinavir	400/100/800 bid	Staszewski 2003
Less favorable		
Lopinavir/r + (fos)amprenavir	Poor PK data	Kashuba 2003
Atazanavir + saquinavir	Poor activity	DeJesus 2004
Tipranavir + LPV/APV/SQV	Poor PK data	Walmsley 2004
Lopinavir/r + nelfinavir	Poor PK data, diarrhea	Klein 2003
Atazanavir + indinavir	Elevated bilirubin	
Indinavir + nelfinavir	Relatively poor activity	Riddler 2002

Salvage Through Recycling of Older Drugs

One can occasionally also make use of drugs that have already been used in the past, as in the Jaguar Study, for example (Molina 2003). 168 patients with more than 1,000 copies/ml and a median 4 NRTI mutations on stable HAART received either ddI or placebo in addition. Viral load was reduced by 0.60 logs after 4 weeks. 68 % of patients had previously received ddI, and even in these patients, viral load was still reduced by 0.48 logs.

Mega- and Giga-HAART, Treatment Interruptions

Following the slogan "the more, the better", several studies have shown that differ-ent intensified treatment combinations – often described as "mega"- or "giga"-

HAART – may indeed be effective. The success of these mostly uncontrolled studies is debatable. On five- or six-drug regimens, sufficient suppression of viral load was achieved only in a variable percentage of patients (22-52 %; Grossman 1999, Miller 2000, Montaner 2001, Piketty 2002, Youle 2002). First and foremost, these studies indicate that there are some patients who are capable of tolerating such intensive combinations. But a lot remains to be criticized: only well-informed and highly motivated patients can be considered for mega-HAART regimens, and such approaches are often unrealistic in clinical practice. It is important to consider that potential drug interactions are difficult to predict for such combinations, and therefore plasma levels should be measured whenever possible. However, most PIs can be combined quite well without causing significant interactions or toxicity (van Heeswijk 2001, Eron 2001).

So, do structured treatment interruptions (STI) before initiation of such intensified regimens provide additional benefit? Possibly.

In the GIGHAART Study (Katlama 2002 + 2004), heavily treatment-experienced patients with advanced HIV infection (less than 200 CD4 cells/µl, viral load above 50,000 copies/ml) were randomly allocated to eight weeks of treatment interruption or not. All 68 patients were subsequently switched to a combination of 7-8 drugs: 3-4 NRTIs, hydroxyurea, 1 NNRTI and 3 PIs (usually amprenavir/r or lopinavir/r plus indinavir, saquinavir or nelfinavir). In the group that underwent treatment interruption, efficacy after 24 weeks was significantly better, and viral load dropped by 1.08 versus 0.29 logs. There was also a significantly greater increase of 51 versus 7 CD4 cells/µl. These effects were still visible after 48 weeks, although less marked. In the multivariate analysis, the following factors were associated with virological response (decrease of > 1 log): STI (ratio 3.2), STI plus reversion to wild-type (12.4), adequate plasma trough levels (5.6) and use of lopinavir (6.0).

However, results from the GIGHAART Study have not remained unquestioned. In the CPRC064 Study, in which patients interrupted treatment for four months prior to the salvage regimen, no differences were found between those patients on STI and those who were not (Lawrence 2003). However, it was disconcerting to see that patients who interrupted treatment not only had worse CD4 counts, but also a significantly higher frequency of severe clinical events during the follow-up period (22/138 versus 12/132). The study was even stopped prematurely as a result. Two other randomized studies (CCTG 578 and Retrogene) did not find any virological benefit in interrupting treatment prior to starting an intensified salvage regimen (Haubrich 2003, Ruiz 2003).

Despite all the discussions concerning mega- or giga-HAART, the primary treatment goal of achieving an undetectable viral load must be abandoned in some patients. This is particularly true if, despite the best compliance, significant side effects are the only result of treatment, due to cumulative toxicity and drug interactions. Here, more is clearly not always better. Quality of life is important to keep in mind. In such cases, it could be wiser to lower the bar and wait for new options (see below). Such patients should be monitored in larger centers where new options become available sooner and where clinicians have experience with intensified regimens. Using up a single new drug at a time should be avoided; if possible, two or more effective drugs should be used!

New Salvage Drugs (Tipranavir, T-20)

T-20 was the first entry inhibitor to be licensed in 2003, and has impressive efficacy even in patients that have been extensively treated with conventional HAART regimens. This has been impressively demonstrated in two large, randomized Phase III studies (Lalezari 2003, Lazzarin 2003); the drug reduced viral load by approximately one log in this population. T-20 should therefore be considered as a possible component of salvage regimens in all salvage patients. Further details can be found in the chapter "Drug Classes and Overview of Antiretroviral Agents".

TMC-114 and tipranavir are two PIs that are currently quite advanced in development, and showing fairly good activity against multiresistant viruses (see chapter "ART 2005/2006"). New NNRTIs such as TMC 125 are also fairly advanced in development. Some of these drugs will become available within the next one to two years in expanded access programs, or when they are tested in Phase III studies. Salvage patients should be treated within such studies if possible.

One should also remember to take the time to encourage patients with long treatment careers who feel that they have no remaining therapeutic options. It is important that no patient loses hope. There is no such thing as having exhausted all treatment options; this is even truer in HIV medicine than in other medical specialties. There is always new progress, and the pharmaceutical industry is now very aware of the fact that new drugs will only be successful if efficacy can be shown against multiresistant viruses. Luckily, the very experienced patients with 10, 15 or 20 years of treatment history are often not very nervous at all (and usually much less so than young HIV clinicians). They have learned that something new is almost always likely to develop…

Utilizing NNRTI Hypersusceptibility

NNRTI-naïve patients (no prior nevirapine or efavirenz) often still respond surprisingly well to NNRTI-containing salvage regimens. In a small, randomized study on 56 NNRTI-naïve patients, the proportion of patients with less than 200 copies/ml after 36 weeks increased from 22 to 52 %, if nevirapine was given in addition to two new nucleoside analogs and nelfinavir (Jensen-Fangel 2001). In ACTG 359, addition of delavirdine to a new PI regimen increased the virological response rate from 18 to 40 % (Gulick 2002).

NNRTI hypersusceptibility may have been responsible for this. Viral strains are considered hypersusceptible to certain drugs if the IC50 (50 % inhibitory concentration) for the drug is lower than that of the wild-type in phenotypic resistance tests. This phenomenon, for which the biochemical correlate is still the subject of debate, generally occurs very rarely with nucleoside analogs, but quite frequently with NNRTIs, and mostly in viruses that have developed resistance mutations against nucleoside analogs.

NNRTI hypersusceptibility was first described in January 2000 (Whitcomb 2000). Several prospective studies have since described this phenomenon more closely (Albrecht 2001, Haubrich 2002, Katzenstein 2002, Mellors 2002). In a recently published analysis of more than 17,000 blood samples, the prevalence of hypersusceptibility to delavirdine, efavirenz and nevirapine in NRTI-naïve patients was 5 %, 9 % and 11 %, respectively. In NRTI-experienced patients, prevalence was notably

29 %, 26 % and 21 % (Whitcomb 2002). There seems to be some evidence that patients with NNRTI hypersusceptibility have better virological responses. Of 177 highly treatment-experienced (but NNRTI-naïve) patients, 29 % exhibited this type of lowered IC50 for one or several NNRTIs (Haubrich 2002). Of the 109 patients who received a new NNRTI-containing regimen, those with NNRTI hypersusceptibility achieved better results. Viral load was significantly lower even after 12 months (-1.2 versus -0.8 logs), and the CD4 cell count was also higher.

Recent studies have demonstrated that NRTI mutations, predominantly at codons 215, 208 and 118, are independently associated with NNRTI hypersusceptibility (Shulman 2004). In another study, mutations were mainly at codons 41, 184, 210, 215. Even if the real significance and molecular correlate for NNRTI hypersusceptibility remain uncertain, the consequence is clear: patients with NRTI mutations and without NNRTI resistance should always receive an NNRTI in their new regimen if at all possible.

Watch and Wait or Even Simplifying ART

Sometimes even the most intensified salvage protocol is not effective. Viral load cannot be suppressed to undetectable levels, despite the use of T-20 and lopinavir plus a second PI and other antiretroviral drugs. What should be done with such patients? The answer is: keep going, as long as the patient tolerates therapy! Multiresistant viruses are typically slightly less aggressive than wild-type viruses, at least for a certain period of time. Therefore, HAART should not be stopped in very immunocompromised patients who are then at risk of developing opportunistic infections. In fact, all efforts should be made particularly in such cases to at least partially control the virus. Just waiting even on a suboptimal regimen is therefore a strategy that can be used to gain valuable time until new drugs become available. In such cases, HAART is not being taken in vain: suboptimal HAART is better than none at all, and some suppression of viral load still better than none. Patients benefit even with only a slight reduction in viral load (Deeks 2000). In a large cohort study, CD4 cell counts did not drop as long as the viral load remained below 10,000 copies/ml, or at least 1.5 logs below the individual set point (Lederberger 2004).

The critical question relates to how intensively treatment should be continued: Some drugs can certainly be discontinued. NNRTIs such as nevirapine or efavirenz can be stopped if resistance mutations have been found, since NNRTI mutations do not influence replicative fitness (Piketty 2004). What about PIs? First data from a small pilot study on this issue gained some attention in February 2003. The results showed that it might even be possible to simplify a failing regimen if no other options are available (Deeks 2003). 15 patients failing therapy and without further treatment options stopped only their protease inhibitors, and continued with nucleoside analogs. Only 2 of the 15 patients had a viral load increase of more than half a log by week 24. Results from one of our own patients (we now have several) where this approach has now been successful for many months are shown in Table 9.3. Resistance testing after more than one year showed, as in the Deeks cohort, that there were no changes in the MDR virus. The approach of "watch and wait" on a simple nucleoside regimen thus seems feasible in some patients for a certain period of time. The reasons for this phenomenon, however, are still not well understood.

Table 9.3: Patient example showing several months of successful "wait and watch"-strategy

Date	(HA)ART	CD4 cells	Viral load
until 1997	AZT, AZT+ddC, AZT+ddI	40 (nadir)	107,000
Mar 97	AZT+3TC+SQV-HGC	84	259,000
Oct 97	d4T+3TC+SQV+NFV	211	67,000
Jun 98	D4T+3TC+NVP+IDV/r	406	1,200
Jan 00	AZT+3TC+ABC+NVP+IDV/r	370	1,030
Sep 00		387	900
Mar 02	AZT+3TC+ABC+TDF+NVP+IDV/r	429	3,350
Sep 02	d4T+ddI+3TC+NVP+LPV/r	283	5,000
Nov 02*		348	7,600
Jan 03		315	16,400
Feb 03	AZT+3TC+ABC	379	6,640
May 03		241	2,400
Nov 04		304	9,100

*Resistance testing showed a total of 20 mutations, with genotypic resistance against all drugs tested. Compliance of the patient is very good, and plasma levels were always adequate.

An Italian study took another innovative approach, enrolling 50 patients with a viral load of at least 1,000 copies/ml on a 3TC-containing regimen, with evidence of the M184V mutation and at least 500 CD4 cells/µl (Castagna 2004). Patients were randomized to completely interrupt treatment or to continue with 3TC 300 mg alone. The rationale: the M184V mutation reduces the replicative fitness of HIV. And indeed – patients on 3TC had a significantly lower increase in viral load (0.6 versus 1.2 logs) and lost significantly less CD4 cells (73 versus 153 CD4 cells/µl). The M184V mutation was maintained in all patients on 3TC, and no other mutations accumulated. In contrast, a shift to wild-type was observed in all patients without 3TC.

As patient numbers are still very small in the data presented to date, many observers understandably remain very skeptical about such strategies. The main question is how long such strategies could remain successful. It is thus advisable to monitor CD4 cells at short intervals. Nevertheless, if such approaches could be confirmed in larger studies, they would be very attractive.

In addition to better tolerability and simpler dosing, the approach with nucleoside analog therapy would have the advantage of not exerting selective pressure to generate further PI or NNRTI mutations. Drugs such as tipranavir or TMC 114, which do not have unlimited efficacy for salvage, would not be compromised. At the same token, it is essential to discontinue NNRTIs immediately, as replicative fitness is not influenced by NNRTI mutations. Otherwise, there is risk of eliminating future NNRTI options such as TMC 125.

Practical Tips for Salvage Therapy

1. First question: what previous treatment has the patient received, with what level of success and for how long – if this in unclear, a resistance test should be performed (no resistance test during treatment interruption!).

2. After addressing point 1, use as many new (active) drugs as possible when changing therapy, but remember to consider potential side effects!

3. Don't wait too long to switch, thus giving the virus the opportunity to develop further resistance mutations – the higher the viral load at the time of switch, the worse the chances for success.

4. Use lopinavir/r! Also consider double boosting and T-20!

5. Has the patient ever taken NNRTIs? If not, it's high time! If so, and if there is NNRTI-resistance: stop NNRTIs!

6. Consider a treatment interruption prior to starting the salvage regimen, if the CD4 cell count and history allow.

7. Don't demand too much from the patient! Not every patient is well suited for mega- or giga-HAART.

8. Encourage the patient! TMC-114, tipranavir or TMC-125 will become available soon, and there is no such thing as having no more therapeutic options. It is usually possible to just wait, and keep things as they are while waiting for new options.

9. Don't immediately exploit a single new drug (especially T-20!) – if the patient's condition and his or her CD4 T cell count allow it, at least wait for a second new drug.

10. Don't allow reversion to wild-type virus – even a "failing" regimen should be continued in the absence of further options, possibly even in a simplified form.

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10. When to Stop HAART

A current review of treatment interruption

Christian Hoffmann, Fiona Mulcahy

Hardly a topic in the field of HIV medicine has evoked more heated discussion in the last years than treatment interruption. However, in the discussion over possible risks or advantages, many issues are often confused, without a distinction being drawn between:

- Structured treatment interruption (STI)
- Structured intermittent treatment (SIT)
- Drug holidays
- Irregular taking of drugs
- Permanent discontinuation of therapy

The reasons and goals for treatment interruption differ greatly. When discussing rationale or risks, it should be clear why treatment is being interrupted:

- At the patient's request
- To improve compliance and patient psyche ("life sentence" removed)
- To reduce long-term toxicity
- For immunological reasons
- As a salvage strategy

One should not fail to realize that most treatment interruptions presumably occur without the clinician's knowledge. For this reason alone, treatment interruptions are an important aspect of antiretroviral therapy, whether, as a clinician, one approves of them or not. To categorically oppose treatment interruption means to disregard the realities of treatment. The following summarizes the findings of recent years. This chapter is limited to patients with chronic HIV infection; (for recommendations on acutely infected patients see the chapter on "Acute HIV Infection").

What Happens to Viral Load and CD4 T-Lymphocyte Levels during Treatment Interruptions?

Almost all patients who stop treatment experience a rebound in viral load within a few weeks, even patients with previously undetectable HIV levels for several years (Davey 1999, Chun 2000). Viral load usually rebounds above the level of detection within 10-20 days (Davey 1999, Harrigan 1999, Garcia 1999). The doubling time of plasma viral load is around 1.6 – 2.0 days. The viral load in compartments such as the CNS changes in parallel to that in the plasma (Garcia 1999, Neumann 1999), and this probably also applies to semen and vaginal fluid; patients must therefore be informed about the higher risk of transmitting HIV.

Occasionally, an initial overshooting viral load rebound is observed (De Jong 1997, Birk 2001). Only after a few weeks does the viral load settle to its initial, pre-

treatment level (Hatano 2000). The rebounding virus evidently does not originate from latent reservoirs; other populations must exist, from which these new viruses can emerge within such a short period of time (Chun 2000, Ho 2000, Imamichi 2001).

Treatment interruptions can have serious immunological consequences. CD4 cell counts often drop within a short time to pre-treatment levels. In a study of 68 patients, the calculated time point at which the initial pre-HAART CD4 cell count was reached again was only 25 weeks (Phillips 2001). CD4 T cell losses vary greatly between patients but may reach 200 or 300/µl within a few weeks. The higher and faster the CD4 T cells increased on HAART, the more rapid their decline (Sabin 2001, Tebas 2002). CD4 nadir is also important. The lower it was, the more rapidly the cell count drops again (Maggiolo 2004). Age also seems to play a role – the older the patient, the more extensive the immunological deterioration is likely to be. The loss of CD4 T cells during interruptions may not be regained as quickly. In a prospective, controlled study, we saw a clear disadvantage for patients undergoing treatment interruptions. After a follow up of 18 months, CD4 T cells were more than 120/µl less in these patients than in matched patients who had not interrupted treatment (Jaeger 2002).

The Risks: Resistance, Clinical Problems, AIDS

Viral resistance has to be anticipated whenever there is viral replication in the presence of suboptimal drug levels, and when resistant mutants have a selective advantage over the wild-type virus. As a result, there are concerns that resistance may develop particularly during the washout phase of medication (increasing viral replication with insufficient plasma levels) and on re-initiation of treatment (continued replication despite sufficient plasma levels).

However, in the case of single treatment interruptions, the probability of development of resistance in individual patients may not be particularly high, as shown in 1999 by the French COMET Study, one of the first studies on treatment interruption. In ten patients, no resistance developed during treatment interruptions, and after re-initiation of therapy, viral load was suppressed again without a problem (Neumann 1999). But, there is currently no certainty as to whether such interruptions might not eventually lead to development of resistant isolates, which merely require more time until they are able to dominate the wild-type. Mathematical models show that this risk – at least theoretically – is not low, especially if viral load rises to high levels (Dorman 2000, Bonhoeffer 2000).

Repeated treatment interruptions probably bear a higher risk than a single interruption. In several studies, these have led particularly to NNRTI- or 3TC-resistance (Metzner 2000, Martinez-Picado 2002, Schweighardt 2002). The risk of resistance seems particularly high for strategies involving stopping and starting of HAART at fixed intervals (Ananworanich 2003, Dybul 2003, Yerli 2003; see also section on SIT below).

The following table describes the example of a patient who was clinically well and who interrupted treatment for several weeks. It was probably the repeated stopping and starting of HAART that ultimately led to resistance in this case.

Table 10.1: Example of the development of resistance due to repeated treatment interruptions*

Date	HAART/comments	CD4 T cells	Viral load
Jun 97	AZT+3TC+SQV	288	67,000
Oct 99	HAART stopped, patient feeling well	540	< 50
Dec 99	Diagnosis of autoimmune hyperthyroidism	400	63,000
Jan 00	AZT+3TC+NVP (+ carbimazole)	260	74,000
Feb 00	Diagnosis of anemia (Hb 7.3 g/dl)	347	1,500
	HAART stopped again		
Mar 00	d4T+3TC+NVP (+ carbimazole)		
Apr 00	Resistance mutations K103N, M184V	360	2,400

*During the first treatment interruption the patient developed autoimmune hyperthyroidism, the treatment of which led to severe anemia after re-initiation of HAART, so that HAART had to be interrupted again. As a result, resistance developed against NNRTIs and 3TC. Autoimmune phenomena in the context of treatment interruption as seen in this patient have not previously been described.

The sharp increase in viral load that may often occur can present as a retroviral syndrome. The symptoms are similar to acute HIV infection, with lymphadenopathy, fever, asthenia and malaise (Colven 2000, Kilby 2000, Zeller 2001). Thrombocytopenia has also been described during interruptions (Ananworanich 2003).

The risk of AIDS seems to be low for single interruptions provided the immune defect is only moderate. In the Swiss Cohort, the risk of progression was not increased (Taffe 2002). In 127 patients who interrupted treatment, we observed no increased risk of AIDS after 18 months, compared to 252 matched controls (Jaeger 2002). However, almost all these patients were immunologically stable. The risk is probably higher in patients with severe immunodeficiency. In a smaller study in significantly immunocompromised patients, several AIDS-defining illnesses occurred (Deeks 2001). CPRC064 came to a similar troubling conclusion: 270 patients with multiresistant viruses and mostly significant immunodeficiency (median 144 CD4 cells/µl) participated in this randomized study (Lawrence 2003). One group of patients underwent a four-month treatment interruption before starting the salvage regimen, while the control group continued treatment. During the observation period of almost 12 months, a significantly higher number of AIDS illnesses (17 versus 5) occurred in the group interrupting therapy compared to the control group. This study was stopped early. In a multivariate analysis, two factors were predictive for death or progression: treatment interruption (relative risk 2.74; 95 % confidence interval: 1.25-5.98) and CD4 cell count at the time of interruption – here, the risk increased by 1.38 (1.11-1.72) with every drop of 50 CD4 cells. More than half of all clinical events (mostly Candida esophagitis and Pneumocystis pneumonia) occurred in patients with less than 50 CD4 cells/µl. This study clearly demonstrated that severely immunocompromised patients are particularly at risk of developing AIDS during long treatment interruptions of several months. Treatment interruptions should be avoided in such patients.

STI at the Patient's Wish, for Reduction of Toxicity

Interruption of therapy can have psychological advantages (Tuldra 2001). Quality of life improves (Moreno 2003), and many patients are relieved of the burden of continuous, lifelong therapy. Clinicians should take the wish for treatment interruption seriously. Presumably most patients expressing such a wish will interrupt sooner or later anyway; so the interruption may as well be structured!

What about side effects? Increased lipid levels (cholesterol, triglycerides) drop quite rapidly after stopping treatment (Hatano 2000, Jaeger 2002). However, the reduction of drug exposure during interruptions is unlikely to be so significant as to affect the cardiovascular risk profile.

Lactate and elevated liver function tests (γGT) may also decrease fairly rapidly (Jaeger 2002). In many patients, symptoms such as fatigue or asthenia quickly disappear. One study clearly showed that mitochondrial DNA actually regenerates during treatment interruptions (Cote 2002). Whether or not lipodystrophy improves, remains to be proven. Short treatment interruptions have not had any effect on morphological changes (Hatano 2000). Resolution of lipodystrophy even after longer interruptions is by no means certain; we have a patient who was treated during seroconversion and developed a buffalo hump after one and a half years, which has not resolved even after what has now been over four years of treatment interruption.

STI – for Immunological Reasons

Hardly any patient has become as famous as the acutely infected homosexual man treated in a Berlin private practice a few years ago who, with a viral load of approximately 80,000 copies/ml, began a HAART regimen consisting of didanosine, indinavir and hydroxyurea. The virus rapidly became undetectable. After several problems – and two short treatment interruptions – HAART was finally stopped after 176 days. Surprisingly, even without drugs, plasma viremia has remained below the level of detection for more than five years. Although virus was still detectable in lymph nodes, thus excluding eradication, the immune system in this case – referred to as "The Berlin Patient" among experts in the field (Lisziewicz 1999) – was obviously capable of durable control of infection. But why? Was it the early initiation of therapy, the hydroxyurea, or the treatment interruptions? To be honest, it must be admitted that no one knows the answer, even today. There may be a completely different explanation: it is possible that certain host factors in this patients that have not yet been investigated could influence the course of disease – completely independently of HAART, STI or hydroxyurea. Nevertheless, STI has been extensively investigated in acutely infected patients (see chapter "Acute HIV infection").

Attempts to improve HIV-specific immune responses with treatment interruptions in chronically infected patients have been unsuccessful. The theory of endogenous vaccination seems plausible: transient increases in viral load could strengthen HIV-specific immune responses, which decline with increasing viral suppression on HAART.

In several pilot studies from 2000/2001, successive interruptions seemed to indeed prolong the time to viral rebound or decrease the rate of rebound, and, in parallel, there were measurable improvements in HIV-specific CD4 or CD8 T cell immune

responses (Haslett 2000, Garcia 2001, Lori 2000, Ortiz 1999, Papasavvas 2000, Ruiz 2003). However, almost none of these studies included more than 2-6 patients, and a control group was usually missing. Was this wishful thinking?

STI was finally "put to the test" in the Spanish-Swiss SSITT Study (Oxenius 2002, Fagard 2003): 133 patients were monitored throughout four ten-week treatment cycles, each consisting of eight weeks HAART and two weeks of treatment interruption. After this, HAART was permanently interrupted. Treatment success – defined as a viral load below 5,000 copies/ml without HAART after week 52 – occurred in 21/99 patients. However, 5/21 patients had a low viral load even before the initiation of HAART. Most importantly, none of the 32 patients with a pre-HAART viral load above 60,000 copies/ml achieved a viral load of less than 5,000 copies/ml. This first large study on chronic infection clearly demonstrated that repeated STIs may lower the viral load set point in only a few patients, usually those with low initial viral load. In contrast to acute infection, improvement of HIV-specific immune response seems unlikely in the setting of chronic HIV infection. SSIT finally proved: treatment interruptions on immunological grounds alone are not justified and are dangerous.

STI – in Multidrug Resistance

In most patients with multidrug resistance, treatment interruption leads to a gradual shift back to the wild-type virus and a loss of resistance. For this reason, resistance testing during treatment interruption is often of little use since mutations disappear from the blood as early as two weeks after treatment interruption (Devereux 1999).

This shift is particularly pronounced in modestly immunosuppressed patients. The time to shift is increased in more advanced stages of disease and with a longer duration of treatment (Miller 2000, Izopet 2000). PI mutations are the first to disappear, while NNRTI mutations are the most protracted; NNRTIs probably impair viral fitness less than other antiretroviral drugs (Deeks 2001, Birk 2001). It is assumed that the wild-type merely dominates the resistant mutants. Special PCR methods are still able to detect low quantities of resistant viruses during STI (Izopet 2000), and after treatment is restarted, resistance mutations rapidly dominate again (Delaugerre 2001). Only a few cases have been described in which resistance mutations were apparently flushed out completely. One such patient, from Erlangen, Germany, has been described (Walter 2002), who was not able to attain sufficient viral suppression despite intensified HAART, and who then interrupted treatment. During the following seven months of treatment interruption, there was a gradual reversion to the wild-type virus, and after re-starting HAART (which, according to previous resistance testing, should have had no effect), the viral load has now been successfully suppressed for several years.

At least two studies to date have shown that the shift resulting from treatment interruptions can be beneficial for salvage strategies. In the Frankfurt Cohort, a shift was associated with improved response to the salvage regimen (Miller 2000). In the GIGHAART Study, there was still evidence of antiviral efficacy after one year in patients who had interrupted treatment before starting a salvage regimen (Katlama 2004). However, this data is in contrast to that of two other studies in which an increased risk of AIDS was seen during treatment interruptions (Lawrence 2003, Ruiz 2003, see above).

Structured Intermittent Treatment (SIT) at Fixed Intervals

In the initial phase following treatment interruption, the viral load usually continues to be very low. Plasma viremia only reaches pre-treatment levels after about four, sometimes even six weeks. The risk of developing resistance is presumably small at lower levels of viral replication (Bonhoeffer 2000). Does this indicate that ultra-short treatment interruptions could be utilized to reduce drugs, costs and long-term toxicity?

In an NIH pilot study on SIT (structured intermittent treatment), 10 chronically infected patients with more than 300 CD4 cells/µl and a viral load below 50 copies/ml were switched to a combination of d4T, 3TC, ritonavir and indinavir. This combination was administered as seven days of treatment and seven days interruption ("7-on-7-off") for a period of at least 44 weeks. The result: neither the viral load nor the proviral DNA increased. CD4 cells and HIV-specific immune responses remained unchanged, suggesting that the immune system is probably unaffected by such ultra-short breaks in treatment. A significant reduction in lipid levels did, however, occur (Dybul 2001). Some patients experienced several blips (temporary increases in viral load) to above 100 copies/ml. The same group has recently reported successful use of the same strategy in eight patients using ddI, 3TC and efavirenz. Seven of eight patients have now been followed for more than 60-84 weeks (Dybul 2004). Nevertheless: at this time, it is impossible to predict whether this treatment strategy might result in a higher risk of resistance in the long term. There are still no larger studies. In addition, patients in the NIH pilot studies were carefully selected, with good immune status and many years of viral suppression. This appealing strategy is therefore probably only applicable to a few patients. A three-armed study from Thailand has already gathered more negative experience with the 7-on-7-off approach (Ananworanich 2003). In this study, 19 of 36 patients experienced virological treatment failure within a short period of time, and this treatment arm was consequently stopped prematurely. According to the authors, the main reason for these poor results was the fact that the majority of patients were NRTI-experienced. This means: if nucleoside analogs are unstable, such on-off strategies are problematic.

The FOTO Study ("Five On, Two Off") took a slightly different approach, in which patients took HAART only from Monday to Friday and stopped at the weekends (i.e. sparing 28 % of ART). This study enrolled patients with an undetectable viral load for at least three months on a PI- or efavirenz-containing HAART regimen. Preliminary results at 24 weeks show that none of the 17 efavirenz-treated patients had an increase in viral load, although 2 of 9 PI-treated patients did (Cohen 2004). The authors speculate that the long half-life of efavirenz could be the reason for this difference.

Longer interruptions with fixed intermittent treatment definitely seem to be unfavorable. Results from a randomized NIH study with fixed intervals (one to two months each of interruption and treatment) were disconcerting (Dybul 2003). The SIT arm contained significantly more patients with virological treatment failure. Resistance mutations developed particularly against NNRTIs and 3TC. The study was even stopped early. The Spanish-Swiss SSITT Study also showed some 3TC resistance (Yerli 2003). Once again, this demonstrated that rigid regimens are worse

than those that are individually tailored. Fighting a tricky virus such as HIV requires flexibility!

Structured Intermittent Treatment (SIT), CD4-driven

While fixed intervals seem to work in only few patients, another approach is more promising: it involves individualized treatment interruptions, usually based on CD4 cell count. In other words, in patients with a good CD4 count, HAART is interrupted until CD4 count drops below an immunological cut-off. Numerous studies have shown that this allows for a considerable reduction in drug exposure. Although mostly patients with very good immune status have been enrolled, there were some differences with respect to the eligibility criteria and the definition of the cut-off. An overview of several prospective studies is shown in Table 10.2.

Which patients have to restart HAART? In the BASTA Study, these were mainly patients with a low nadir prior to HAART (Maggiolo 2004). According to the authors, this provides the rationale for starting HAART earlier, as this is possibly better for preserving HIV-specific immune responses, thus allowing HAART to be stopped later. A Spanish Study had similar results (Ruiz 2004), and the probability of remaining off therapy was greater with higher CD4 cells and a lower viral load before HAART. Critics claim that these studies merely demonstrate that those starting HAART too early can stop again sooner and for longer.

Table 10.2: Prospective studies in which HAART was interrupted based on CD4 cell count (usually compared to one control arm, in which HAART is taken continuously).

Source	n	CD4 count at baseline	CD4 cut-off to restart	Results in STI arm
Marchou 2003 (Window)	390	> 450 > 6 Mo	< 300	48 weeks FU in 80 patients: no patient had to restart therapy
Ruiz 2004	201	> 500 > 6 Mo	< 350 or VL > 100,000	Median duration of STI 44 weeks, 6 % ARS, 70 % restarted due to high VL
Maggiolo 2004 (BASTA)	69	> 800	< 400	Drop in CD4 cells strongly dependent on nadir before HAART
Boschi 2004	71	> 500	< 200	69 % restarted therapy after 60 weeks of STI, 71 % reduction of HAART exposure, no resistance so far
Mussini 2004	140	> 500	< 350	54 % still on STI, now for a median 105 months
Moreno 2003	52	> 600 > 6 Mo	< 350	23/25 without HAART after 48 weeks

ARS = acute retroviral syndrome; FU = follow up; Mo = months

Results from the largest study on this topic will not be available for a while yet. 6,000 patients are to be randomized in SMART (http://hiv.net/link.php?id=167). The eligibility criteria are not as strict as in the other studies, and restarting of therapy is planned relatively late: HAART will only be restarted when the CD4 cells have dropped to less than 250/µl. The first patients were enrolled into this highly ambitious project in January 2002; by July 2004, almost 1,800 patients had been recruited. In view of its large patient numbers, the first results will take a while to

process. Success in this study would, however, fundamentally change the current approach of lifelong HAART.

Beyond this, there have been approaches to increase the duration of STIs with immunomodulating drugs such as hydroxyurea (Foli 2004) or mycophenolic acid (Garcia 2004). These approaches are still experimental and not yet justifiable outside of clinical studies, and their benefit is questionable.

Special Case: Permanent Interruption

Can patients who were started too early on HAART (according to present guidelines) stop treatment again for the time being? The answer is clearly: yes.

Not only the CD4 cell-driven STI studies (see above), but also other data have shown that this is possible in many patients. In an observational study on 101 patients at the John Hopkins University, 67 % have remained without HAART for a mean period of 74 weeks. The higher the CD4 T cell level at initiation of therapy, the longer the possible interruption of HAART (Parish 2002). In another study, age and the CD4 cell increase on HAART correlated to the decrease during STI (Tebas 2002). The following table shows an example of permanent interruption.

Table 10.3: Example of permanent interruption after early initiation, numerous interruptions, so far without significant deterioration of CD4 cells *

Date	HAART/Comment	CD4 cells	Viral load
03/96	d4T+3TC (many interruptions)	330	15,000
03/97	d4T+3TC+SQV (some interruptions)	300	< 500
08/99	Long interruption (9 weeks)	380	< 50
11/99	ddI+3TC+NVP	491	110
09/00	Discontinuation	438	< 50
02/01	Still no HAART	390	250
07/02	Still no HAART	397	1,900
10/02	Still no HAART	268	800

*The low viral load set point during the last years is surprising – did the patient benefit from treatment interruptions? (Note: viral load was measured with several methods to exclude error. The relative CD4 values were between 13-15 % for the whole period.)

Practical Tips for Treatment Interruptions

- Don't try to convince patients to interrupt therapy – a clear risk/benefit analysis is currently not yet possible!

- Those who have no problems with HAART should not interrupt therapy – STIs for immunological reasons are not meaningful in chronically infected patients.

- The patient's wish should be respected – information should be provided on clinical (retroviral syndrome), immunological (loss of CD4 cells) and virological (resistance) consequences.

- Patients must be aware that the risk of infection is increased – even after long and complete viral suppression, viral load returns to initial levels after 4-6 weeks without HAART.

- CD4 cells and viral load should be monitored monthly during interruptions.

- Risk of resistance is possibly higher with NNRTIs (choose robust regimens and stop NNRTIs several days earlier if possible – consider the half-life of the drugs).

- Patients who started HAART "too early" according to current standards can probably interrupt quite safely.

- Interruptions in severely immunocompromised patients should occur only within clinical studies – benefits in salvage has not yet been proven.

- Avoid resistance testing during treatment interruptions – it usually only measures the wild-type.

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11. Monitoring

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Which parameters should be included in routine laboratory monitoring of HIV patients? What can be expected from the results? This section deals with viral load, CD4 cells, routine checks, and plasma levels. Resistance tests are the subject of a separate chapter ("HIV Resistance Testing"). For the tests to be performed on initial presentation, see the appropriate chapter.

Viral Load

Viral load is the amount of viral copies in the blood. Alongside the CD4 cell count, viral load has become the most important surrogate marker for HIV infection (Hughes 1997, Mellors 1997, Lyles 2000, Ghani 2001, Phillips 2004). It provides both valuable information on the level of risk of disease progression and whether antiretroviral therapy is indicated; it is the critical value in determining the success of therapy. Other surrogate markers used frequently in the past, such as p24, neopterin or β_2-microglobulin, are now obsolete. Viral load assays measure the amount of HIV RNA (viral genetic material), which correlates directly with the number of viruses. The units are viral copies/ml (or genome equivalents). A change of one or more logs refers to the change in viral load by one or more decimal powers.

Number of copies	Log_{10}
10	1.0
50	1.7
100	2.0
500	2.7
1,000	3.0
10,000	4.0
50,000	4.7
100,000	5.0
1,000,000	6.0

Assessment

The higher the viral load, the higher the risk of a decrease in CD4 cells, with subsequent disease progression or occurrence of AIDS-related illnesses (Mellors 1997, Lyles 2000, Phillips 2004). A viral load above 100,000 copies/ml, i.e. 5.0 logs (sometimes even above 50,000 copies/ml), is generally considered to be high; a value below 10,000 copies/ml, low. These thresholds are not absolute and can only provide points of reference.

The effects of plasma viremia on immune status can vary greatly between individuals. There are some patients whose CD4 cells remain stable for relatively long periods despite having a high viral load, while others experience a rapid drop, although the viral load is relatively low. Viral load is probably generally lower in women than in men. In a meta-analysis, the difference was 41 % or 0.23 logs (95 % confi-

dence interval 0.16-0.31 logs) (Napravnik 2002). The reason for this is unclear. Whether this phenomenon has an impact on the indication for treatment, is still the subject of discussion.

Methods

Three methods or assays are currently used to measure viral load: Reverse Transcription Polymerase Chain Reaction (RT-PCR); branched-chain DNA (B-DNA); and, less frequently, Nucleic Acid Sequence-Based Amplification (NASBA). These three methods differ both in levels of detection and in the linear range within which measurement is reliable or reproducible (see Table 11.1 below). In all methods, the minute amount of viral RNA must first be amplified to enable measurement. In the case of PCR and NASBA, the viral RNA is transformed in several enzymatic steps and then amplified to measurable amounts. B-DNA does not require this enzymatic step; signal amplification occurs via binding of branched DNA fragments to viral RNA.

Although intra-assay variability is fairly good for all three methods and one can expect reproducible values, methodological variations must be taken into account when interpreting the results. Differences of less than 0.5 logs are not considered significant. A decrease from 4.3 to 3.9 logs, for example (corresponding to a decrease from approximately 20,000 to 8,000 viral copies/ml), does not necessarily signify a drop in viral load. The same holds for increases in viral load. Changes of up to threefold can therefore be irrelevant! Patients who, after hearing mere numbers, frequently worry unnecessarily or become falsely optimistic should be made aware of this.

Considerable differences exist between the three methods (Coste 1996), and to change from one method to another is therefore generally not advisable. The results obtained by b-DNA are usually lower than the PCR by a factor of 2. Different subtypes are also detected with varying success according to the method employed (Parekh 1999); one should be particularly cautious in patients from Africa and Asia with non-B subtypes, for example, in whom the viral load at first presentation can be unexpectedly low. In such cases, use of a different assay may actually be indicated. However, newer versions with improved primers are probably superior in measuring even unusual HIV subtypes with adequate sensitivity. All assays have a linear dynamic range, outside of which precise numbers are not so reliable. There are two tests for PCR, the standard and the ultrasensitive assay. The linear range of the ultrasensitive assay ends at 75,000 copies/ml, and thus this test should only be used if low viral loads are expected.

The following rule applies: one method, one laboratory! The laboratory should be experienced and routinely perform a sufficiently large number of tests. Measurement should take place as soon as possible after blood withdrawal, and correct collection and shipping of centrifuged plasma is also important (contact the laboratory ahead of time on these issues).

Table 11.1: Methods of measurement, including test version, linear range and level of detection should be clearly indicated for the clinician on every test result

Company	Roche/Abbott	Bayer/Chiron	Organon
Method	RT-PCR	b-DNA	NucliSens HIV-1 QT
Linear range of assay	400 – 750,000 ultrasensitive: 50 – 75,000	100 – 500,000	40 – 10,000,000
Comparability	Values ca. 2 x higher than B-DNA (version 2.0 and 3.0)	Values ca. 50 % of PCR (version 2.0 and 3.0)	Values approx. like PCR
Advantages	Less false positive results than B-DNA	Equally good for all subtypes (A-G), technically relatively simple	Equally good for all subtypes (A-G), large linear range

Influencing factors

Apart from methodological variability, a host of other factors may influence levels of viral load, including vaccinations and concurrent infections. During active opportunistic infections, viral load is often particularly high. One study showed a 5- to 160-fold elevated viral load during active tuberculosis (Goletti 1996). Viral load can also increase significantly during syphilis (Buchacz 2004). In these situations, determining the viral load does not make much sense. Following immunizations, for instance for influenza (O'Brien 1995) or pneumococcus (Farber 1996), the viral load may be transiently elevated (Kolber 2002). As the peak in viral load occurs one to three weeks after immunization, routine measurements of viral load should be avoided within four weeks of immunization.

It should be noted that not every increase in viral load is indicative of virological treatment failure and resistance. Slight transient increases in viral load, called blips, are usually of no consequence, as numerous studies in the last few years have shown (see chapter on "Goals and Principles of Therapy"). The possibility of mixed up samples always has to be considered – people make mistakes.

Viral kinetics on HAART

The introduction of viral load measurement in 1996-1997 fundamentally changed HIV therapy. The breakthrough studies by David Ho and his group showed that HIV infection has significant in vivo dynamics (Ho 1995, Perelson 1996). The changes in viral load on antiretroviral therapy clearly reflect the dynamics of the process of viral production and elimination. The concentration of HIV-1 in plasma is usually reduced by 99 % as early as two weeks after the initiation of HAART (Perelson 1997). In one large cohort, the viral load in 84 % of patients was already below 1,000 copies/ml after four weeks. The decrease in viral load follows biphasic kinetics. In the first phase, i.e. within the first three to six weeks, an extremely rapid drop occurs, followed by a longer phase during which the viral load only gradually decreases further (Wu 1999).

The higher the viral load at initiation of therapy, the longer it takes to drop below the level of detection. In one study, the range was between 15 days with a baseline viral load of 1,000 and 113 days with a baseline of 1 million viral copies/ml (Rizzardi 2000). The following figure shows the typical biphasic decrease in viral load after initial high levels (in this case almost 4 million copies/ml).
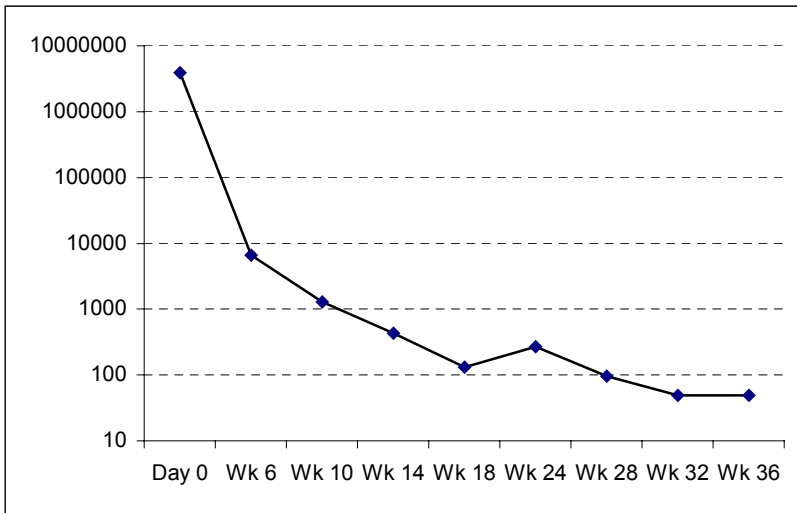
Figure 1: Typical biphasic decrease in viral load on HAART. Viral load was initially very high, and reached a level below 50 copies/ml only at week 32. Note the temporary increase at week 24, which is possibly due to methodological variability. HAART was not changed.

Numerous studies have focused on whether durable treatment success can be predicted early in treatment (Demeter 2001, Kitchen 2001, Lepri 2001, Thiabaut 2000). In a study on 124 patients, a decrease of less than 0.72 logs after one week was predictive of virological treatment failure in more than 99 % of patients (Polis 2001). However, this has little clinical relevance, and in our opinion, it is pointless to start measurement of viral load only one or two weeks after initiation of therapy.

In the first few months, we typically measure viral load every four weeks until it has dropped below the level of detection – the most important goal! After this, viral load can be measured every three months. In case of rebound, closer monitoring becomes necessary.

Following initiation of therapy, viral load should be below 5,000 copies/ml after one month. Higher values are predictive of failure to reach levels below detection (Maggiolo 2000).

Viral load can also be measured fairly reliably in body fluids other than blood or plasma (for example cerebrospinal, vaginal or seminal fluid). However, such tests are usually performed for scientific purposes and are not routine.

Practical tips for dealing with viral load (see also chapter "Goals and Principles of Therapy")

- Use only one assay, if possible.
- Use only one experienced laboratory, if possible, no home-brewed assays.
- Watch for assay variability (up to half a log) and explain this to the patient!
- Monitor viral load every four weeks with new HAART, until the viral load is below the level of detection (50 copies/ml).
- Then measure viral load at greater intervals – on successful HAART every three months is sufficient.
- Without HAART, measurement every three months is sufficient.
- Don't measure shortly after vaccinations or with concurrent infections.
- Implausible results should be rechecked after 2-4 weeks. Remember differences between subtypes (in some cases it may be useful to use another method).

CD4 Cells

CD4 cells are T lymphocytes that express the CD4 receptor on their surface. This lymphocyte subpopulation is also referred to as T helper cells. Alongside viral load, measurement of the CD4 cell level is the most important parameter or surrogate marker in HIV medicine. It allows for a reliable estimation of the individual risk of developing AIDS. Every HIV patient should have had a CD4 cell measurement within the last six months! Two reference values are generally accepted: above 400-500 CD4 cells/µl, severe AIDS-related diseases are very rare; below 200 CD4 cells/µl, the risk of AIDS-related morbidity increases significantly with increased duration of immunosuppression. However, most AIDS-related illnesses only occur below 100 CD4 cells/µl.

Several points should be considered when measuring CD4 cells (usually by flow cytometry). Blood samples should be processed within 18 hours. The lower normal values are between 400 and 500 cells/µl, depending on the laboratory. Samples should always be sent to only one (experienced) laboratory. The higher the level of CD4 cells, the greater the variability. Differences of 50-100 cells/µl are not unusual. In one study, the 95 % confidence intervals with a real value of 500/µl were between 297 and 841/µl. At 200 CD4 cells/µl, the 95 % confidence interval was between 118 and 337/µl (Hoover 1993).

Measurement of CD4 cells should only be repeated in the case of highly implausible values. As long as the viral load remains below the level of detection, there is no need to be concerned, even with greater decreases in CD4 cells. In such cases, the relative values (CD4 percentages) and the CD4/CD8 ratio (ratio of CD4 cells to CD8 cells) should be referred to; these are usually more robust and less prone to fluctuation. As a general point of reference: with values above 500 CD4 cells/µl, more than 29 % is to be expected, with less than 200 CD4 cells/µl less than 14 %. The normal ranges for the relative values and the ratio may be defined differently by individual laboratories.
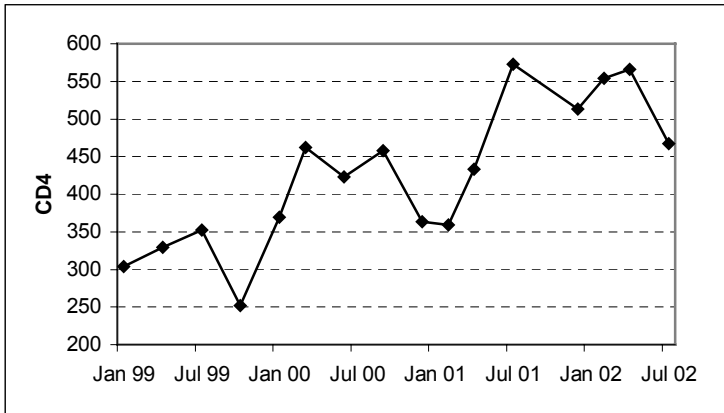
Figure 2. Patient example for variations in absolute CD4 cells/µl over a period of four years. The viral load was continuously below 50 copies/ml; HAART remained unchanged.

If there are considerable discrepancies between absolute and relative CD4 cells, any decisions involving treatment should be carefully considered – if in doubt, it is better to check the values one more time! The remaining differential blood count should also be scrutinized carefully: is leukopenia or leukocytosis present?

Clinicians sometimes forget that the result of the CD4 cell count is of existential importance for the patient. To go to the doctor and discuss the test results involves a great deal of stress for many patients ("worse than getting grades"). Insensitively informing the patient of a supposedly bad result can lead to reactive depression. From the start, patients must be informed about the possible physiological and method-related variability of laboratory tests. In the case of unexpectedly good results, every effort should be made to contain premature euphoria. In the long run, this saves time and discussions, and the patient is spared unnecessary ups and downs. We do not consider it advisable for non-physician personnel (without extensive HIV experience) to inform patients of results.

Once CD4 cell counts within the normal range are reached in addition to adequate viral suppression, half-yearly measurements suffice, in our opinion. The probability of CD4 cells dropping to values below 350/µl is extremely low in such cases (Phillips 2003). Patients, who might sometimes insist on more frequent monitoring of immune status, can be assured that there are usually no detrimental changes in the CD4 cell count as long as HIV remains suppressed.

Influencing factors

Several other factors influence CD4 cell counts apart from laboratory-related variables. These include concurrent infections, leukopenia of varying etiology, and steroids or other immunosuppressive therapies. Extreme exertion (marathons!), surgical procedures or pregnancy can also lead to lower values. Even diurnal variation occurs; CD4 cells are lower at noon, and highest in the evening around 8 p.m. (Malone 1990). Psychological stress seems to play a negligible role, even though patients often assume the contrary.

Kinetics of CD4 cells on HAART

Similarly to viral load, a biphasic increase in CD4 cells occurs following the initiation of HAART (Renaud 1999, Le Moing 2002), with a rapid increase within the first three to four months and a much slower rise thereafter. In a study of almost 1,000 patients, the CD4 cell count increased by 21/µl per month during the first three months. In the following 21 months, this rate was only 5.5 CD4 cells/µl per month (Le Moing 2002). The initial rapid increase in CD4 cells is probably due to redistribution, which is followed by the new production of naïve T cells (Pakker 1998). Diminished apoptosis may also play a role (Roger 2002).

It is still being debated whether the immune system steadily continues its recovery even after a long period of viral load suppression, or whether a plateau is reached after three to four years, beyond which there is no further improvement (Smith 2004, Viard 2004).

Several factors can influence the extent of immune reconstitution during HAART. The degree of viral suppression is crucial – the lower the viral load, the more pronounced the effect (Le Moing 2002). The absolute increase is higher if initial CD4 cell counts were high (Kaufmann 2000). Naïve T cells still present at initiation of therapy are a particularly important factor for long-term immune reconstitution (Notermans 1999). Age is also important (Grabar 2004). The larger the thymus and the more active the process of thymopoiesis, the more significant the rise in CD4 cells is likely to be (Kolte 2002); due to age-related degeneration of the thymus, CD4 cells in older patients do not increase as much as those in younger ones (Viard 2001). However, we have seen both 20 year-old patients with very poor CD4 count recovery and 60 year-old patients with very good, above average increases in CD4 cells. The regenerative capacity of the human immune system seems to vary considerably, and no method to date has been capable of reliably predicting this capacity.

It is possible that some antiretroviral therapies such as the ddI+tenofovir combination are associated with less immune reconstitution than others. Immunosuppressive concurrent medications should also be considered (see chapter "Goals and Principles of Therapy").

Beyond the measurement of the CD4 cell count and lymphocyte subpopulations, a number of other assays allow detailed testing of the qualitative or functional capacity of the immune system, for example in response to specific antigens (Gorochov 1998, Lederman 2001, Lange 2002, review in Telenti 2002). These, often cumbersome, methods are not currently necessary for routine diagnostics, and their use remains questionable. However, they could one day help to better describe individual immune status and, for example, identify those (few) patients, who are at risk of developing opportunistic infections despite good CD4 cell counts.

Practical tips for dealing with CD4 cells

▪ As with viral load: use only one (experienced) laboratory.

▪ The higher the values, the greater the variability (consider numerous factors) – compare the relative (percentage) values and CD4/CD8 ratio with previous results!

▪ Do not disconcert the patient when there are apparent decreases – if viral suppression is sufficient, the drop is usually not HIV-related! Only highly implausible results should be repeated.

▪ If the viral load is below the level of detection, three-monthly measurements of CD4 cells are sufficient.

▪ In the presence of good viral suppression and normal CD4 cells, CD4 cells (not viral load!) may also be checked less frequently.

▪ CD4 count and viral load should always be discussed by the physician.

Other Routine Checks – What Should Be Monitored?

Besides the CD4 cell count and viral load, several other parameters should be monitored in the HIV patient. The following recommendations apply to clinically asymptomatic patients with normal results on routine laboratory evaluation, who have been on stable treatment for several months, or who are not taking antiretroviral therapy. Of course, if treatment is started or changed, or if the patient develops complaints, more frequent monitoring is required. Depending on the problem, additional tests may be necessary. A complete physical examination should be performed regularly, and this often leads to the discovery of important findings such as Kaposi lesions or mycoses (thrush!). The lower the CD4 cells, the more frequently patients should be examined.

Table 11.2: Minimal evaluations per year in stable asymptomatic patients

	Patient on ART per year	Untreated per year
Blood count, LDH, ALT, AST, creatinine, bilirubin, alk. phosphatase, lipase, γGT, glucose	4-6 x	2-4 x
Viral load	4 x	2-4 x
CD4 cells	2-4 x	2-4 x
Lipids	1-2 x	1 x
Physical examination	2-4 x	1-2 x
Gynecological examination	1 x	1 x
Fundoscopy if CD4 cells < 200/µl	2-4 x	4 x

In patients with less than 200 CD4 cells/µl, we usually perform fundoscopies every three to six months to exclude CMV retinitis. Close cooperation with an HIV-experienced ophthalmologist is important. The better the CD4 cells, the less often fundoscopies are necessary. When CD4 counts have normalized, these can be

stopped completely. Regular gynecological examinations with PAP smears are also recommended (see also the European guidelines: http://hiv.net/link.php?id=185).

Rectal examination (including proctoscopy) is now recommended by many experts for early detection of precancerous lesions and anal cancer, as the incidence of these seems to be increasing in the HAART era.

However, such guidelines or recommendations are interpreted very differently. In our experience, in cases of good immune status, unless there is a specific suspicion, routine X-rays, ultrasound examinations (exception: patients with chronic hepatitis, as hepatocellular carcinoma is not rare in such cases!), multiple serologies or lactate measurements are not necessary.

An annual ECG is only indicated in our view in patients with a specific risk profile (see also the chapter "HIV and Cardiac Disease"). The tuberculin test (the Mendel-Mantoux skin test with 5 IE once a year) should only be repeated if it is negative initially.

Therapeutic Drug Monitoring (TDM) – When Should Plasma Levels Be Measured?

Individual plasma levels of many antiretroviral drugs may vary quite considerably for differing reasons (e.g. compliance, metabolism, absorption). But, sufficient plasma levels are essential for success of virological treatment (Acosta 2000). In the VIRADAPT Study, adequate PI-concentrations were even more crucial than knowledge of resistance mutations (Durant 2000). The importance of sufficient plasma levels has also been shown for NNRTIs (Marzolini 2001, Veldkamp 2001).

On the other hand, very high plasma levels correlate with a higher rate of side effects. Reported renal problems with indinavir (Dielemann 1999), gastrointestinal disturbances with ritonavir (Gatti 1999), hepatotoxicity with nevirapine (Gonzalez 2002), or CNS problems with efavirenz (Marzolini 2001) were all associated with high plasma levels.

The measurement of drug concentrations in serum or plasma (therapeutic drug monitoring, TDM) has therefore become an important tool for monitoring therapy. The best reviews are to be found in Back 2002, Burger 2002, and Clevenbergh 2004. Due to the increasing complexities of antiretroviral combinations, TDM of protease inhibitors and NNRTIs will probably become more important in the future.

Several problems associated with TDM are limiting its broader use. The measurement of nucleoside analogs, for example, is senseless since they are converted to the active metabolites only intracellularly. Intracellular measurements are difficult and will not be available in routine clinical practice.

Measuring NNRTIs or PIs may therefore currently determine levels of only one component of a (failing) combination. Further problems include not only viral strains with different levels of resistance, different inhibitory concentrations, variable protein binding, and time-dependent variability of plasma levels, but also methodological problems with the assays, as well as the lack of clearly defined limits. Many uncertainties thus remain in the assessment of therapeutic drug plasma levels. Until data from randomized studies is available, proving the clinical value of TDM, both the measurement and interpretation of the results should be left to specialized centers.

Measurement of plasma levels is currently recommended (German-Austrian guide-lines from May 2004) in the following situations:

- Complex drug combinations and concomitant medications that could lead to interactions or reduced efficacy,
- Suspected absorption problems, and
- Pregnancy.

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6. Management of Side Effects

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Patients on HAART commonly suffer from side effects. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity. About 25 % of patients stop therapy within the first year on HAART because of side effects (d'Arminio Monforte 2000). About the same number of patients do not take the recommended dosages of their medication due to concerns regarding the side effects (Eron 2000, Chesney 2000). Patients who report significant side effects, are more often non-adherent to therapy (Ammassari 2001).

The patient should be counselled in detail on the potential side effects, so that he or she is in a position to recognize them and to consult his physician in time. This can save lives, for example in the case of the abacavir hypersensitivity reaction, and the irreversible damage of side effects, such as polyneuropathy, can be prevented through early diagnosis. Being prepared for the occurrence of possible problems and providing potential solutions improves both the acceptance of treatment and the adherence. However, patients should not be frightened by all this information – the extensive package inserts are often ominous enough. It may be difficult to distinguish between symptoms related to HIV infection and those caused by antiretroviral therapy. An accurate history, including any co-medication (not forgetting over-the-counter products!) is paramount. It is important to consider the intensity, variation and reproducibility of complaints, as other possible causes should be excluded before symptoms are judged as being side effects of treatment.

It must be stressed that the majority of patients are able to tolerate HAART well, even over years. Nevertheless, the monitoring of treatment by an HIV clinician, even in asymptomatic patients, is recommended in at least three-monthly intervals, and even more often at the beginning of a new HAART, when it should be weekly or fortnightly. Standard evaluations include a thorough history (allergies?, other side effects?), physical examination and measurement of vital signs and body weight. Routine investigations include a full blood count, liver, pancreas and renal function tests, electrolytes (plus phosphate in patients on tenofovir) as well as fasting cholesterol, triglycerides and glucose levels.

For lipodystrophy see chapter on "Lipodystrophy Syndrome".

Gastrointestinal side effects

Gastrointestinal side effects are the most common side effects of almost all antiretroviral drugs - nucleoside analogs, NNRTIs and particularly protease inhibitors - and occur especially during the early stages of therapy. Typical symptoms include abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting. Heartburn, abdominal pain, meteorism and constipation may also occur. Nausea is a common symptom with zidovudine-containing regimens; diarrhea occurs frequently with zidovudine, didanosine and all PIs, particularly nelfinavir, as well as with saquinavir and lopinavir/r, atazanavir and ritonavir. Treatment with zidovudine rarely leads

to a severe form of gastritic pain, nausea and vomiting in the early phase of therapy, in which case it should be discontinued.

In addition to the often considerable impact on everyday life, gastrointestinal side effects can lead to dehydration, malnutrition with weight loss, and low plasma drug levels with the risk of development of resistant viral strains.

In most cases, symptoms occur at the beginning of therapy. Patients should be informed that these side effects usually resolve after four to six weeks of treatment. If gastrointestinal side effects occur for the first time after longer periods on HAART, other causes such as gastritis and infectious diarrhea are likely.

Nausea and vomiting

If administration on an empty stomach leads to nausea and vomiting, most drugs can also be taken together with meals. When a drug (e.g. didanosine, indinavir, rifampin) has to be administered on an empty stomach, small quantities of low-fat salty crackers may lessen the nausea. Ginger, peppermint or chamomile teas or sweets may also be helpful, as well as frequent small meals. Care should be taken with fatty foods and dairy products. Coffee, smoking, alcohol, aspirin and very spicy foods should be avoided if possible.

If symptomatic treatment is necessary, metoclopramide has been proven to be useful. Dimenhydrinate, cimetidine, ranitidine or ondansetron can also be taken. Antiemetic drugs should not only be administered if the patient is already feeling sick, but rather taken regularly, ideally 30 to 45 minutes before HAART. If taken on a regular basis, attention should be paid to side effects such as dyskinesia. After a few weeks, doses can generally be slowly reduced. If nausea persists for more than two months, a change of treatment should be considered – otherwise adherence problems will certainly occur.

Emend™ (aprepitant) is a substance P/neurokinin 1 (NK1) receptor antagonist. It is used since 2004 to prevent and control nausea and vomiting caused by cancer chemotherapy. Hitherto, no data exist regarding the use in HIV drug-associated nausea. However, due to the potential interaction with many HIV drugs (cytochrome P450 3A4 system) it should not be used.

Diarrhea

In patients with massive diarrhea, the priority is to treat dehydration and loss of electrolytes. Other causes such as gastrointestinal infections or lactose intolerance should be excluded. Difficult to digest foodstuffs (particularly those rich in fats or glucose) should be avoided and those that are easy to digest (e.g. potatoes, rice, noodles), eaten instead. It makes sense to remember approved homespun remedies (see table 1).

If significant dehydration and loss of electrolytes occur, coke and salty crackers, sports drinks, herbal teas or electrolyte solutions may be taken (see reviews in: Highleyman 2002, Schwarze 2002, Sherman 2000). Oral rehydration solution can be easily made from the juice of 5 oranges, 800 ml of boiled water or tea (cooled to room temperature), one teaspoon of iodized salt and two tablespoons of sugar.

Oat bran tablets have been proven to be useful and cheap for PI-associated diarrhea. They are taken together with antiretroviral therapy (daily dose 1500 mg). Pancreli-

pase, a synthetic pancreatic enzyme, has also been shown to be effective for PI-associated diarrhea.

Nelfinavir-associated diarrhea is alleviated by calcium (Turner 2004), taken as calcium carbonate, at a dosage of 500 mg BID. However, as calcium binds many other substances, it should be taken 2 hours apart from HIV medication.

According to a Brazilian pilot study, oral supplements of glutamine or alanyl–glutamine alleviate diarrhea and can also boost the levels of antiretroviral drugs in the blood (Bushen 2004). Patients received 30 g glutamine plus 15 g glycine, or 4 g alanyl-glutamine plus 42 g glycine, or 44 g alanyl-glutamine daily. The best results were seen in the high-dose alanyl-glutamine group. A former study showed effectiveness of L-glutamine, starting at a dose of 10 g/day increasing to a maximum of 30 g/day (Heiser 2002).

The probiotics, Saccharomyces boulardii and Lactobacillus acidophilus, are used in infectious diarrhea and to prevent antibiotic-associated diarrhea. They can sometimes ameliorate medication-associated diarrhea. Alternatively, psyllium may be effective. It should not be taken together with loperamide or opium tincture, or at the same time as HIV medication.

The cornerstone of symptomatic treatment is loperamide which inhibits bowel movement (initially 2 – 4 mg, followed by 2 mg, up to a maximum of 16 mg daily). If loperamide is not effective, opium tincture is an alternative (initially 5 drops, maximum 15 to 20 drops), attention should be paid to the risk of intestinal obstruction, especially if overdosed. In some cases, a combination of different antidiarrheal drugs may be appropriate.

Table 1: "Approved" homespun remedies

Pectin

in apples (raw with paring), bananas (purée), carrots (purée, cooked, soup), St. John's bread (oatmeal gruel or rice gruel with St. John's flour). Pectin is a dietary fiber, which is not digested, it binds water and toxic substances and lessens the diarrhea.

Gruel

Soups made of oatmeal or rice gruel

Tanning agents

Black or green tea, dried blueberries (tea, powder), dark chocolate

CNS disorders

Efavirenz

In up to 40 % of patients, treatment with efavirenz leads to CNS side effects such as dizziness, insomnia, nightmares; even mood fluctuations, depression, depersonalization, paranoid delusions, confusion and suicidal ideation may occur (Lochet 2003). These side effects are observed mainly during the first days and weeks of treatment. Discontinuation of therapy becomes necessary in only 3 % of patients. There is an association between high plasma levels of efavirenz and the occurrence of CNS symptoms (Marzolini 2001).

On the one hand, high efavirenz plasma levels can be caused by medication inter-actions, so a thorough drug history should be taken; on the other hand the different perception of drug tolerance of the patients can play an important role. Patients should be informed about the nature of these symptoms, and that they are usually expected to resolve after a short period of time. Driving cars or bicycles or operat-ing machinery can be impaired in the first weeks. If dizziness or drowsiness are experienced, these activities should be avoided. Treatment with efavirenz should not be started before exams or other important events.

If the CNS side effects persist for more than two to four weeks, it is reasonable to prescribe 200 mg pills, so that the dose can be divided into a 400 mg night dose and a 200 mg morning dose. We experienced a reduction in unpleasant CNS side effects in 50% of our patients. The daily dose should not be reduced from 600 mg to 400 mg because of the higher risk of therapy failure and development of drug resistance.

Measurement of drug levels makes sense from the second week of therapy to verify overdosage, but the only consequence is the splitting of the 600 mg dosage (by no means should the dose be reduced to 400 mg). Taking 400 mg/200 mg can reduce the Cmax levels and therefore the toxic potential becomes milder.

Lorazepam can diminish the CNS side effects, and haloperidol can be given for panic attacks and nightmares, but both drugs should be restricted to severe cases, because of their side effects and addictive potency (lorazepam).

CNS side effects are rarely seen with other NNRTIs. If they persist even after split-ting the dosage for more than six weeks, efavirenz should be replaced, for example by nevirapine.

Lamivudine/ Abacavir

Depression, insomnia and even psychosis rarely occur or get worse on lamivudine or abacavir therapy. If the patient complains of CNS-related side effects, lami-vudine or abacavir should be considered as a possible cause (Foster 2004). No data exist for emtricitabine up to date.

Peripheral polyneuropathy

Peripheral polyneuropathy is mainly caused by the NRTIs, zalcitabine, didanosine and stavudine. It usually presents with a distal symmetrical distribution and senso-rimotor paralysis. Patients complain of paresthesia and pain in their hands and feet, and often, with zalcitabine, about perioral dysesthesia. The symptoms often begin gradually after several months of therapy. HIV infection itself can lead to peripheral polyneuropathy, but the drug-induced form becomes apparent much earlier and may develop within a shorter period of time. Patients must be informed that they should consult their treating physician as soon as possible if the typical complaints de-velop. Additional risk factors for polyneuropathy, such as vitamin B12 deficiency, alcohol abuse, diabetes mellitus, malnutrition, or treatment with other neurotoxic drugs, e.g. INH, should be addressed in the appropriate manner. The nucleoside analogs, zalcitabine, didanosine and stavudine, should be avoided in these cases.

Symptoms frequently improve within the first two months following discontinuation of the drugs responsible, but may initially increase in intensity and are not always fully reversible. Because treatment is difficult, and there is no specific therapy, it is extremely important that peripheral polyneuropathy is recognized early by the doctor, resulting in an early change of treatment. The causative agent has to be abandoned.

An easy test, in practice, is to test vibration with a tuning fork. A 64-Hz tuning fork (Rydel-Seiffer) is applied to the appropriate bony surface (e.g., distal hallux, medial malleolus or lateral malleolus) bilaterally. The patient is asked to report the perception of both the start of the vibration sensation and the cessation of vibration on dampening. As the intensity of the vibration starts to diminish the two triangles move closer together again. The intensity at which the patient no longer detects the vibration is read as the number adjacent to the intersection. It can thus be quantified and compared to the results of other tests. Through this simple method first signs of polyneuropathy can be recognized easily and early.

Apart from symptomatic treatment with metamizole, acetaminophen (paracetamol), carbamazepine, amitriptyline, gabapentine and opioids, methods such as acupuncture or transcutaneous nerve stimulation have been tried with variable success. Vitamin B supplementation can help to improve peripheral polyneuropathy faster. Tight shoes or long periods of standing or walking should be avoided; cold showers may relieve pain before going to bed. Uridintriphosphate (Keltican™) is approved for diabetic polyneuropathy, but data about its effectiveness are scant. Indeed, no data or evidence are available to date on its use in HIV neuropathy.

Renal problems

Indinavir

Renal problems occur particularly on indinavir treatment, and are caused by indinavir crystals, which may be found in the urine of up to 20 % of patients. Approximately 10 % of patients develop nephrolithiasis, which is not visible on X-ray, accompanied by renal colic. Nephrolithiasis is primarily caused by high indinavir levels in relation to a low body mass index (Meraviglia 2002), drug interactions and individual fluctuations of the drug plasma level. In one study, the intake of indinavir/ritonavir 800/100 mg with a light meal reduced the indinavir nephrotoxic maximum plasma concentration, probably reflecting a food-induced delay in the absorption of indinavir (Aarnoutse 2003). More than 20 % of patients have persistent asymptomatic leukocyturia associated with a gradual loss of renal function without urological symptoms (Dielemann 2003). However, renal failure is rare (Kopp 2002).

Symptoms of acute colic include back pain and flank pain as well as lower abdominal pain, which may radiate to the groin or testes. Hematuria may also occur. Evaluations should include a physical examination, urine and renal function tests. Ultrasound evaluation can exclude urinary obstruction but does not detect small indinavir stones.

For acute therapy, intravenous analgesia (e.g. metamizole, 1 to 2.5 g) or diclofenac (e.g. 100-150 mg) may be given in combination with spasmolytic drugs (e.g. butyl-scopolamine, 20 mg). This usually relieves the symptoms quite rapidly, and may be repeated after a few minutes if symptoms persist. If this is unsuccessful, pethidine 50-100 mg by i.v. or i.m. injection can be administered. Fluids should be given in moderation during colics.

As prophylaxis, a daily intake of 1.5 l of fluids is recommended, which should be increased during hot weather and on consumption of alcohol. Interruption of therapy, following a single incidence of colic, is not usually necessary. Indinavir plasma levels should be measured and, if high, the dose adjusted. Renal function and urine should be monitored in all patients, at least every 3 months during indinavir treatment, even in the absence of urological symptoms. With recurring colics, however, indinavir should be discontinued. Non-steroidal anti-inflammatory drugs, quinolones, ampicillin, foscarnet, aciclovir, sulfonamides (cotrimoxazole, sulfadiazine) and allopurinol can also cause nephrolithiasis, and should therefore be used with caution in combination with indinavir (Boubaker 1998).

Tenofovir

Tenofovir has been approved since 2001 and is, like the two nephrotoxic drugs, adefovir and cidofovir, a nucleotide analog. Animal studies showed a dose-related nephrotoxicity, but although several case reports have suggested its occurrence, severe renal toxicity was not observed in the major clinical trials with tenofovir (Antoniou 2003, Gallant 2004, Schooley 2002). Acute renal failure and proximal tubulopathy with Fanconi's syndrome and nephrogenic diabetes insipidus have been reported (Callens 2003, Coca 2002, Creput 2003, Earle 2004, Karras 2003, Peyrière 2004, Rollot 2003, Saumoy 2004, Schaaf 2003). Two studies showed that the use of tenofovir is also associated with a modest decline in creatinine clearance in comparison to patients never treated with tenofovir (Gallant 2005, Mauss 2005).

Proximal tubular damage manifests as proximal tubular acidosis, normoglycemic glycosuria, hypophosphatemia, hypouricemia, hypokalemia, generalized aminoaciduria, and proteinuria. Renal toxicity occurs after some months, rarely at the beginning of therapy (Hansen 2004, Izzedine 2004, Rifkin 2004). Risk factors include a relatively high tenofovir exposure, pre-existing renal impairment, low body weight, co-administration of nephrotoxic drugs, or lopinavir/ritonavir treatment. Protease inhibitors can interact with the renal transport of organic anions, leading to proximal tubular intracellular accumulation of tenofovir. This may lead to Fanconi's syndrome-type tubulopathy and systemic accumulation of didanosine (Izzedine 2004, Rollot 2003). Furthermore, extensive pre-treatment with nucleoside reverse transcriptase inhibitors seems to be another risk factor (Peyrière 2004, Saumoy 2004). However, even in patients without any predisposing factors, nephrotoxicity may occur (Barrios 2004).

In case of renal dysfunction, especially in patients with low body weight and on lopinavir treatment, tenofovir should be avoided if possible, or the dosing interval should be adjusted. The manufacturer recommends administering tenofovir every 48h in patients with a creatinine clearance between 30 and 49 ml/min and twice a week between 10 and 29 ml/min. Normal creatinine levels may be misleading especially in subjects with low body weight, which is why creatinine clearance should

be measured before initiating tenofovir treatment. Renal function tests including creatinine, urea, creatinine clearance, proteinuria, glycosuria, blood and urine phosphate should be monitored every other week.

Tenofovir is not recommended for use in patients with pre-existing renal insufficiency. It should also be avoided with concomitant or recent use of nephrotoxic agents such as aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2. Usually the abnormalities resolve after discontinuation of the drug (Izzedine 2004, Rifkin 2004).

Hepatotoxicity

Elevated liver function tests are common with HAART, and severe hepatotoxicity occurs in up to 6 % of patients (Becker 2004). Their occurrence depends on the drug classes or agents used as well as on pre-existing liver dysfunction. The level of liver toxicity ranges from mild and fully reversible liver enzyme elevation to rare but rapidly occurring, occasionally fatal, liver failure. Severe hepatotoxicity and hepatic failure have been observed during treatment with nevirapine and ritonavir (De Maat 2003, Law 2003). Case reports also exist about liver failure occurring with indinavir, atazanavir, efavirenz, nelfinavir and different nucleoside analogs (Abrescia 2002, Carr 2001, Clark 2002). Patients with pre-existing liver disease should receive these drugs only under strict monitoring (Sulkowski 2002, 2004).

Hepatotoxic reactions occur at different time points for different drug classes: nucleoside analogs lead to hepatic steatosis, which is probably caused by mitochondrial toxicity and usually occurs after more than 6 months on treatment (Montessori 2003). NNRTIs often cause a hypersensitivity reaction within the first 12 weeks. In one study, severe hepatotoxicity was observed in 15.6 % of patients on nevirapine and in 8 % of those on efavirenz. Those patients who were concurrently taking PIs and were co-infected with hepatitis B virus and/or hepatitis C virus had the highest risk (Sulkowski 2002). The exact cause remains unclear, but higher PI drug levels due to decreased metabolism may play a crucial role. PIs can lead to hepatotoxicity at any stage during the course of treatment – once again, patients with chronic viral hepatitis are particularly at risk. One possible cause is an immune reconstitution syndrome on HAART, with increased cytolytic activity against the hepatitis viruses. Among the PIs, toxic hepatitis is seen most frequently in patients on ritonavir, while boosted protease inhibitors do not show an increased risk of hepatotoxicity (Sulkowski 2004).

Nevirapine

Liver toxicity occurs more commonly on nevirapine than on other antiretroviral drugs. Clinically asymptomatic and symptomatic liver toxicity, including rapidly occurring fatal liver failure have been observed. Serious and fatal liver toxicity has been reported during post-exposure prophylaxis (MMWR 2001), but not after single doses of nevirapine. Females and patients with higher CD4 cell counts are at increased risk of liver toxicity with nevirapine. The risk of symptomatic hepatotoxicity for females is more than three-fold that of males, and in females with CD4 cell counts > 250 cells/µl, the risk is 12-fold in comparison to females with CD4+ cell counts < 250 (11 % vs. 0.9 %). Males with CD4+ cell counts > 400 cells/µl have a

five-fold increased risk of symptomatic liver toxicity than males with CD4+ cell counts < 400 (6.3 % vs. 1.2 %). The Indications and Usage section of the Viramune label now advises against starting nevirapine treatment in women with CD4+ cell counts greater than 250 cells/mm³ unless benefits clearly outweigh risks (http://www.fda.gov/cder/drug/advisory/nevirapine.htm).

Liver toxicity occurs usually early during therapy (within 18 weeks of starting). If liver enzymes increase to > 5x upper limit of normal (ULN) during treatment, nevirapine should be stopped immediately. If liver enzymes return to baseline values and if the patient has had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, it may, on a case-by-case basis, be possible to reintroduce nevirapine. However, frequent monitoring is mandatory in such cases. If liver function abnormalities recur, nevirapine should be permanently discontinued. If clinical hepatitis (anorexia, nausea, jaundice, etc.) occurs, nevirapine must be stopped immediately and never readministered.

Atazanavir and Indinavir

Atazanavir and indinavir inhibit the hepatic enzyme UDP-glucuronosyltransferase, increasing the level of bilirubin in up to 47 % of the patients. It is not usually associated with signs or symptoms of hepatocellular injury, and clinically resembles Gilbert's syndrome. Fewer than 2 % of patients discontinue atazanavir therapy because of this adverse effect (Busti 2004). The levels of bilirubin return to normal following discontinuation of the drugs. If bilirubin is only mildly elevated (< 3 times ULN) and the serum liver enzyme levels are normal, treatment change is not mandatory. If the bilirubin is constantly markedly elevated, medication should be discontinued: nobody knows about the long-term consequences of hyperbilirubinemia (Sulkowsky 2004).

Besides serological tests for viral hepatitis, an abdominal ultrasound should be performed to recognize structural liver dysfunction early, e.g. non-alcoholic steatohepatitis or liver cirrhosis, before initiating HAART. Liver function should be monitored biweekly at the start of treatment with nevirapine and PIs and even more frequently in patients with pre-existing liver disease. Monthly tests are generally sufficient for all other drugs. If liver enzymes (ALT, AST) are moderately elevated (< 3.5 times ULN) in the absence of clinical symptoms, treatment can be continued under close monitoring. If liver enzymes are elevated to more than 3.5 times ULN, additional diagnostic tests should be performed, including an abdominal ultrasound. In cases of co-infection with hepatitis B or C, treatment of these conditions should be considered. With other pre-existing liver conditions, it may be useful to determine drug plasma levels. Discontinuation of treatment may not be necessary (exception: nevirapine).

If liver enzymes are elevated in a later phase of therapy (after more than 6 months), a thorough investigation including serology for viral hepatitis, CMV, and EBV, as well as an abdominal ultrasound, should be performed. Lactic acidosis, hypersensitivity reactions to abacavir and other hepatotoxic drugs should also be considered. Furthermore, analysis of blood gases including pH, base excess and bicarbonate concentration, lactate levels and a thorough drug history can help. Liver biopsy reveals macro- and microvesicular steatosis and mitochondrial alterations in NRTI-

induced steatosis and is therefore helpful to identify a nucleoside-induced hepatopathy and to distinguish it from other causes of liver injury.

In patients with HCV co-infection, hepatitis C should, if possible, be treated before the initiation of HAART, to reduce the frequency of severe hepatotoxicity (see Chapter "Hepatitis C"). In HBV co-infection, the HAART regimen should include lamivudine and/or tenofovir. Patients with pre-existing liver dysfunction should undergo drug plasma level monitoring, especially during treatment with PIs. Doses can be adjusted according to the plasma levels so that a precocious discontinuation of therapy can be avoided. However, no relationship has been found between hepatic injury and plasma levels of nevirapine (Dailly 2004).

Finally, drug interactions and hepatotoxicity related to other drugs (e.g. ACE inhibitors), taken concomitantly, should not be overlooked.

Changes in blood count

Anemia

Some of the antiretroviral drugs (especially zidovudine) are myelosuppressive, especially with respect to the red cells, and therefore lead to anemia (de Jesus 2004). Most commonly affected are patients with advanced HIV infection and pre-existing myelosuppression, on chemotherapy or co-medication with other myelotoxic drugs such as cotrimoxazole, pyrimethamine, amphothericin B, ribavirin, and interferon, or with other antiretroviral drugs.

5 to 10% of patients taking zidovudine develop anemia – usually during the first 3 months of therapy, but sometimes even after years on treatment (Carr 2001). Zidovudine should be discontinued in severe cases, and a blood transfusion may be necessary. MCV is always elevated, even in patients on zidovudine without anemia, and is therefore a good proof of adherence. It sometimes makes sense to change from Combivir™ to the single drugs Retrovir™ and Epivir™ in anemic patients, because of the lower zidovudine dose in Retrovir™ (250 mg) compared to Combivir™ (300 mg). In patients with advanced HIV infection and multiple viral resistance, and therefore no options to change to less myelotoxic drugs, erythropoetin is an option, but should be avoided as a long-term option if possible, due to the associated high costs.

Leukopenia

HIV infection itself may cause pancytopenia. A very low CD4 cell count may therefore be rarely due to a severe leukopenia. In this case, the percentage of the CD4 cells and the CD4/CD8 ratio is normal.

Due to drug-induced neutropenia, it is possible that besides viral suppression the CD4 cells remain low after an initial rise. In these cases treatment should be changed to less myelotoxic antiretroviral drugs such as stavudine, lamivudine, most of the PI and all NNRTIs. Zidovudine should be avoided. Leukopenia may also occur on indinavir, abacavir or tenofovir.

Negredo (2004) showed that in patients with good virological control, on tenofovir and didanosine as the nuke backbone, the CD4 cell count rose as expected until

around 6 months, when it gradually decreased again. It was seen especially in patients with a daily dose of 400 mg didanosine, but also in patients on the lower dose (250 mg/day). The probable cause is the synergistic myelotoxic potential and an increased mitochondrial toxicity of the two drugs, which has a negative effect on the T-cells in particular.

Allergic Reactions

Allergic reactions are frequent during HIV therapy (Pirmohamed 2001). They occur with all NNRTIs, as well as with the nucleoside analog, abacavir (see below) and the PI, amprenavir. Because amprenavir is a sulfonamide, it should be given with caution to patients with sulfonamide allergies.

NNRTIs

Nevirapine and delavirdine may cause a slight rash in 15 to 20 % of patients, 5 to 10 % of which discontinue treatment. The rash is seen less frequently on efavirenz therapy, where only 2 % of the patients discontinue the drug (Carr 2001).

The NNRTI allergy is a reversible, systemic reaction and typically presents as an erythematous, maculopapular, pruritic and confluent rash, distributed mainly over the trunk and arms. Fever may precede the rash. Further symptoms include myalgia (sometimes severe), fatigue and mucosal ulceration. The allergy usually begins in the second or third week of treatment. Women are more often and more severely affected (Bersoff-Matcha 2001). If symptoms occur later than 8 weeks after initiation of therapy, other drugs should be suspected. Severe reactions such as the Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) or anicteric hepatitis are rare (Rotunda 2003).

Treatment should be discontinued immediately in cases with mucous membrane involvement, blisters, exfoliation, hepatic dysfunction (transaminases > 5 times the upper limit of normal) or fever > 39°C.

If patients present with a suspected nevirapine-associated rash, additional hepatotoxicity and liver failure should be considered and liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from nevirapine.

Approximately 50 % of NNRTI allergies resolve despite continuation of therapy. Antihistamines may be helpful. Prophylactic treatment with glucocorticosteroids or antihistamines has been shown to be of no benefit for the prevention of nevirapine allergy; in fact, rashes were even more common in some studies (Knobel 2001, Montaner 2003, Launay 2004, The Grupo Estudio 2004). Following a severe allergic reaction, the drug responsible for the reaction should never be given again.

Abacavir hypersensitivity

Abacavir causes a hypersensitivity reaction (HSR), which may be life-threatening if not recognized in time. It occurs in approximately 5-8 % of patients (Chirouze 2005, Clay 2002, reviews in Hewitt 2002). A higher rate is noted in patients on a once-daily regime (James 2005). The HSR occurs after a median of 8 days, and

within the first 6 weeks in 93 % of cases. Studies have found a correlation between the HLA type (particularly HLA-B 57) and the occurrence of HSR (Hetherington 2002, Mallal 2002, Martin 2004). Possibly pre-prescription routine HLA typing may be reasonable and cost-effective in the future (Hughes 2004).

The rash associated with the abacavir hypersensitivity reaction is often discrete, in contrast to the skin reactions caused by nevirapine and efavirenz; in 30 % of patients it may not occur at all. 80 % of patients have fever. In addition to general malaise (which gets worse from day to day!), other frequent symptoms include gastrointestinal side effects such as nausea, vomiting, diarrhea and abdominal pain. Respiratory symptoms, such as dyspnea, cough and sore throat, are rare. Changes in the blood count, elevation of liver transaminases, alkaline phosphatase, creatinine and LDH may accompany the HSR. There is usually no eosinophilia. One case of Stevens-Johnson syndrome has been described (Bossi 2002).

The synchronous start of therapy with abacavir and NNRTIs is unfavorable because of the difficulties of differentiating between allergic reactions to NNRTIs and HSR. If abacavir is part of the initial therapy and flu-like symptoms occur, it is difficult to distinguish between immune reconstitution syndrome (ISR) and HSR; hence HIV therapy should be carried out by HIV-experienced doctors. The HSR is diagnosed clinically. The differential diagnosis from an intercurrent infection is often difficult. Criteria in favor of HSR include the development of symptoms within the first 6 weeks of treatment, deterioration with each dose taken and the presence of gastrointestinal side effects. If abacavir is discontinued in time, the HSR is completely reversible within a few days. HSR may be fatal if not diagnosed. Following discontinuation of abacavir, further supportive treatment includes intravenous hydration and possibly steroids.

If the suspicion of HSR is only vague, and abacavir is not stopped, the patient should be seen or spoken to (by telephone) daily, to be able to react immediately in case of clinical worsening. Once the diagnosis of HSR has been established, rechallenge with abacavir can be fatal and is strictly contraindicated. If there was only a vague suspicion of HSR, rechallenge under in-patient conditions is possible. Whenever treatment has been interrupted, it should be noted that the HSR can occur for the first time after restarting treatment, even without a prior HSR.

Treatment with abacavir requires detailed counseling (and documentation!) on the possible occurrence and symptoms of the HSR. Patients should know whom to contact in cases of suspected HSR, preferably also at night and at weekends. It is important, however, not to frighten patients to the extent that they themselves discontinue treatment too early.

Lactic acidosis

In comparison to asymptomatic hyperlactacidemia, which occurs in approximately 15% of NRTI-treated patients (Carr 2001, Hocqueloux 2003), lactic acidosis is a rare but life-threatening complication. NRTIs are thought to cause mitochondrial toxicity via inhibition of the mitochondrial DNA polymerase. The incidence is approximately 3.9/1000 NRTI patient years (John 2001) (see also chapter on Mitochondrial Toxicity of Nucleoside Analogs).

It occurs most frequently on treatment with stavudine and didanosine, less in patients on zidovudine, abacavir and lamivudine. Risk factors are obesity, female sex, pregnancy and therapy with ribavirin or hydroxyurea, a diminished creatinine clearance and a low CD4 cell nadir (Bonnet 2003, Butt 2003, Carr 2003, Fleischer 2004). In case treatment with ribavirin is necessary, didanosine has to replaced.

The clinical symptoms, including fatigue, nausea and vomiting, abdominal pain, weight loss and dyspnea, are non-specific and may develop acutely or more gradually. Blood results show elevated lactate levels with or without metabolic acidosis (blood should be taken in a cooled fluoride oxalate tube, with transport on ice and the lactate measured within 4 hours). CPK, LDH, lipase, amylase, γGT and the anion gap may be increased; serum bicarbonate may be decreased. Hepatic steatosis can be seen on ultrasound or CT.

One study showed that serum lactate levels rise significantly after initiation of NRTI therapy, and then remain stable at between 1.5 and 3 mmol/l (John 2001). 8 to 21 % of the patients with at least one NRTI have elevated serum lactate levels (< 4 mmol/l), with no or only mild symptoms. Cases of severe lactic acidosis can occur without prior symptomatic hyperlactacidemia. Lactate levels should therefore not be monitored routinely, as increases are not predictive and may lead to unnecessary changes in treatment (Brinkman 2000, Vrouenraets 2002). In contrast, lactate levels should be tested immediately in symptomatic patients complaining of fatigue, sudden weight loss, abdominal disturbances, nausea, vomiting or sudden dyspnea, in pregnant women on NRTI treatment and in patients, who receive NRTIs again after having suffered a lactic acidosis (Carr 2003).

For lactate levels between 2 and 5 mmol/l, "watchful waiting" with regular monitoring is recommended (see Brinkman 2001). If the resistance profile allows, NRTI treatment may be modified, e.g. switch from stavudine/didanosine to abacavir, zidovudine or tenofovir. At levels above 5 mmol/l, NRTI treatment should be stopped immediately and supportive treatment initiated; for example, correction of the acidosis. The mortality of patients with lactate levels above 10 mmol/l is approximately 80 % (Carr 2001, Carr 2003, Falco 2002, Vrouenraets 2002).

Different drugs have been used to treat lactic acidosis with limited success, including vitamin B complex, coenzyme Q10, vitamin C and L-carnitine. These treatment approaches are based on case reports, not studies. In one small study, 6 patients were successfully treated with intravenous vitamin B-complex (100 mg thiamine, 20 mg riboflavin, 200 mg nicotinamide, 20 mg pyridoxine, 20 mg dexapanthenol) plus L-carnitine (1000 mg) twice daily (Brinkman 2000). This treatment is given intravenously until lactate levels fall below 3 mmol/l, and is then continued orally. Normalization of lactate takes an average of 8 weeks following the discontinuation of therapy. The supplementation of uridine is a new, but promising treatment approach (Walker 2003, Walker 2004) (see chapter on Mitochondrial Toxicity of Nucleoside Analogs).

Pancreatitis

Up to 7 % of patients treated with didanosine suffer from pancreatitis. Occasionally, stavudine, lamivudine and zalcitabine cause pancreatitis too. The combinations of didanosine plus stavudine or didanosine plus tenofovir carry a particularly high risk for pancreatitis. Alcohol consumption and treatment with pentamidine are further risk factors.

The mechanism by which didanosine triggers pancreatitis is not known but may be influenced by its metabolism through the purine pathway (Moyle 2004). A significant interaction between didanosine and tenofovir leads to a 40% rise in didanosine plasma concentration. Cases of severe, sometimes fatal, pancreatitis on concurrent didanosine and tenofovir therapy, have been reported. Didanosine and tenofovir should therefore not be co-administered in patients weighing less than 60 kg, who have renal dysfunction or who take lopinavir/r (see Lopinavir) (Blanchard 2003, Martinez 2004).

Antiretroviral drug-induced pancreatitis is not distinguishable from pancreatitis of any other etiology, either clinically or in laboratory tests. Antiretroviral therapy should be stopped immediately. Treatment is the same as for pancreatitis of other etiologies. The symptoms and laboratory changes usually resolve rapidly (Carr 2001). Drugs that have induced pancreatitis once, must never be given again. If patients have a history of pancreatitis of any origin, didanosine is contraindicated.

Avascular necrosis

Avascular necrosis occurs in approximately 0.4 % of HIV patients, and is therefore significantly more frequent than in the general population (Cheonis 2002). The postulated association with PIs could not be confirmed (Miller 2002, Loiseau-Peres 2002). Risk factors for avascular necrosis are alcohol abuse, hyperlipidemia, steroid treatment, hypercoagulability, hemoglobinopathy, trauma, nicotine abuse and chronic pancreatitis. Virological (viral load) parameters are not associated with a risk of developing avascular necrosis (Miller 2002, Mondy 2003).

The most common site of the necrosis is the femoral head and, less frequently, the head of the humerus. Initially, patients complain of pain when bearing weight on the affected joint, with symptoms worsening over days and weeks. The initial stages may be asymptomatic, but are followed by severe bone pain and reduced mobility. Necrosis of the femoral head produces pain in the hip or groin, which may radiate to the knee.

All patients on HAART, especially those with additional risk factors (steroids!) should be monitored closely if hip pain occurs for the first time. Even in subjects with moderate bone or joint pain, an MRI should be performed early on, as this is more sensitive than conventional radiography. Early diagnosis and treatment can spare patients pain, loss of mobility and surgical intervention.

If the diagnosis is confirmed, patients should be referred to an orthopedic surgeon as soon as possible. Different treatment strategies are available for reducing bone and joint damage as well as pain, depending on the stage of disease, localization and grade of severity. In the early stages, reduced weight bearing with crutches is

often sufficient. Surgical core decompression is an option: several holes are drilled in the femoral neck or head, causing new blood vessels to develop and thereby reducing the pressure within the bone. In the more advanced stages, the chances of success decrease with the size of the necrosis. The alternative – osteotomy – has the disadvantage of reducing the mobility of patients over long periods of time. In severe cases, a total endoprosthesis (TEP) is usually necessary.

Further risk factors need to be identified and eliminated. If possible, steroids should be discontinued. Sufficient data are missing as to whether treatment modification on non–PI therapy is successful (Mondy 2003). Physiotherapy is recommended. Non-steroidal anti-inflammatory drugs (e.g. ibuprofen) are the treatment of choice for analgesia (Cheonis 2002).

Osteopenia/Osteoporosis

HIV-infected individuals have a lower bone density than uninfected individuals (Loiseau-Peres 2002). Bone density is determined by the measurement of X-ray absorption (e.g. DEXA scan) or ultrasound waves. Results are given as the number of standard deviations (the T-score) from the mean value in young, healthy individuals. Values between -1 and -2.5 standard deviations (SD) are referred to as osteopenia, values above -2.5 SD as osteoporosis.

In addition to HIV infection, other factors such as malnutrition, diminished fat tissues, steroid treatment, hypogonadism, immobilization and treatment with PIs and NRTIs, seem to play a role in the pathogenesis of this disorder. Osteopenia and osteoporosis are often asymptomatic. Osteoporosis occurs mainly in the vertebrae, lower arms and hips.

The following tests should be performed on all patients with AIDS: a lumbar spine X-ray in the standard anteroposterior and lateral views, bone density measurement (DEXA scan) of the lumbar spine and hip; and laboratory blood tests, including calcium, phosphate and alkaline phosphatase. Osteopenia should be treated with 1000 I.E. vitamin D daily and a calcium-rich diet or calcium tablets with a dose of 1200 mg/day. Patients should be advised to exercise and give up alcohol and nicotine. In cases with osteoporosis, aminobiphosphonates should be added. Because testosterone suppresses osteoclasts, hypogonadism should be treated (Cheonis 2002, Cheonis 2000, Mondy 2003, Tebas 2000).

Increased bleeding episodes in hemophiliacs

HIV patients with hemophilia A or B, after some weeks of treatment with protease inhibitors, may have increased episodes of spontaneous bleeding into joints and soft tissues. Rarely, intracranial and gastrointestinal bleeding has occurred. The etiology is unclear (Review: Wilde 2000).

Specific side effects

Enfuvirtide (T-20)

The typical side effect of enfuvirtide is an injection site reaction (ISR) with erythema, induration, nodules, pruritus, ecchymosis, pain and discomfort. Almost every patient is affected, most of them, however, only mildly. ISR, therefore, rarely limits treatment, and only 3 to 7 % of patients discontinue therapy (Arasteh 2004, Lazzarin 2003). The practitioner and the patient have to get used to the injection technique and the management of ISR. Good injection technique (including aseptic conditions) in conjunction with rotating injection sites (see Table 1), may be most effective in minimizing the incidence and severity, as well as the incidence of associated events, including infections. The appropriate management of ISR can lessen the reaction (see Table 1, Clotet 2004, Buhk 2004).

Table 1: Suggestions for prevention and management of injection site reactions (ISR) and other injection-related adverse events (Clotet 2004)

Good injection technique

- Ensure solution is at room temperature
- Avoid muscle by bevelling needle at 45–90 degrees, depending on body habitus
- Inject slowly
- Maintain sterile technique (wash hands, use gloves, clean injection area and vial caps with alcohol swabs, never touch needle)
- Feel for hard, subcutaneous bumps, avoid injecting into sites of previous ISR
- Avoid indurated or erythematous areas
- Avoid injections on the belt line
- Rotate sites (abdomen, thighs, arms) and never inject two consecutive doses into the same place
- Gentle manual massage after every injection

Interventions for ISR

1. Injection pain
- Topical anaesthetic (e.g. lidocaine gel)
- Oral analgesics pre-injection (e.g. ibuprofen or metamizole)
- Numb area with ice or a cool pack before injecting

2. Management of pruritus
- Oral antihistamines
- Emollient creams or lotions (non-alcohol based and fragrance-free)

Another side effect, observed after 48 weeks in the TORO study, was a higher rate of bacterial pneumonia (gram+/ gram-) in patients taking enfuvirtide. The cause is unclear. Thus, patients undergoing enfuvirtide therapy should be monitored for pneumonia (Clotet 2004, Tashima 2003).

Patients taking enfuvirtide and travelling to foreign countries should be prepared for questions about the injection material. Taking along a medical certificate stating

that the patient is on subcutaneous injection therapy can help to avoid unpleasant situations.

Indinavir

Paronychia of the toes or fingers and ingrown toenails are typical side effects of indinavir, occurring in 4 to 9% of patients. Furthermore, approximately 30% of patients receiving indinavir show two or more mucocutaneous changes, such as cutaneous xerosis, cheilitis, hair loss or alopecia, resembling retinoid-like side effects. Indinavir is the only antiretroviral drug that induces retinoid-like effects, as it probably interferes with the retinoid metabolism. There is no relation to sex, age or immune status, but to indinavir plasma levels. In these patients, measurement of the plasma level makes sense, adjusting the dose if necessary.

These adverse effects are usually mild, so that there is often no need to discontinue therapy. Paronychia, however, can cause massive pain; in which case, stopping indinavir can save the patient from surgical intervention, because it then resolves without recurrence (Garcia-Silva 2002).

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7. Lipodystrophy Syndrome

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Background

The HIV lipodystrophy syndrome, which includes metabolic complications and altered fat distribution, is of major importance in HIV therapy. The metabolic abnormalities may harbor a significant risk of developing cardiovascular disease, with as yet unknown consequences. In addition, several studies report a reduced quality of life in patients with body habitus changes leading to reduced treatment adherence. Despite the impact of lipodystrophy syndrome on HIV management, little is known about the pathogenesis, its prevention, diagnosis and treatment. Current data indicate a rather multifactorial pathogenesis where HIV infection, its therapy, and patient-related factors are major contributors. The lack of a clear and easy definition reflects the clinical heterogeneity, limits a clear diagnosis and impairs the comparison of results among clinical studies. Therapeutic and prevention strategies have so far been of only limited clinical success. Thus, general recommendations include dietary changes and life style modifications, altering antiretroviral drug therapy (replacement of protease inhibitors with NNRTI or replacement of stavudine and zidovudine with e.g. abacavir or tenofovir), and finally, the use of metabolically active drugs. Here we summarize the pathogenesis, diagnosis and treatment options of the HIV lipodystrophy syndrome.

Clinical manifestation

Lipodystrophy was originally described as a condition characterized by regional or generalized loss of subcutaneous fat. The non-HIV-associated forms, such as congenital or familial partial lipodystrophy, have a very low prevalence. Generally, these forms are associated with complex metabolic abnormalities and are difficult to treat. The term "lipodystrophy syndrome" in association with HIV, was introduced to describe a complex medical condition including the apparent abnormal fat redistribution and metabolic disturbances seen in HIV-patients receiving protease inhibitor therapy (Carr 1998). Since then, other conditions, such as osteopenia and hyperlactemia, have been summarized under the diagnosis of the lipodystrophy syndrome. But, even years after its first description, there is still no consensus on a case definition for lipodystrophy syndrome in HIV patients. Thus, the diagnosis of lipodystrophy in clinical practice often relies on a more individual interpretation than on an evaluated classification. Finally, changes in the fat distribution have to be considered as being rather dynamic processes. In most cases, lipoatrophy is clinically diagnosed when significant fat loss has already occurred.

HIV-associated lipodystrophy includes both clinical and metabolic alterations. The most prominent clinical sign is a loss of subcutaneous fat (lipoatrophy) in the face (periorbital, temporal), limbs, and buttocks. Prospective studies have demonstrated an initial increase in limb fat during the first months of therapy, followed by a pro-

gressive decline over the ensuing years (Mallon 2003). Peripheral fat loss can be accompanied by an accumulation of visceral fat which can cause mild gastrointestinal symptoms. Truncal fat increases initially after therapy and then remains stable (Mallon 2003). Visceral obesity, as a singular feature of abnormal fat redistribution, appears to occur in only a minority of patients. Fat accumulation may also be found as dorsocervical fat pads ("buffalo hump") within the muscle and the liver. Female HIV patients sometimes complain about painful breast enlargement which has been attributed to the lipodystrophy syndrome. Whether gynecomastia in male patients is a component of the syndrome remains unclear. There is now accumulating evidence that the major clinical components – lipoatrophy, central adiposity and the combination of both – result from different pathogenetic developmental processes.

The prevalence of lipodystrophy syndrome has been estimated to be between 30 and 50% based on cross-sectional studies. A prospective study over an 18-month period after initiation of therapy revealed a prevalence of 17 % (Martinez 2001). Lipodystrophy, and in particular lipoatrophy, has been observed most frequently in patients receiving a combination regimen of nucleoside analogues and protease inhibitors, although almost all antiretroviral drug combinations can be associated with fat redistribution. The risk of the syndrome increases with the duration of treatment, the age of the patient and the level of immunodeficiency. Lipodystrophy has been observed during the therapy of both the acute and chronic states of HIV infection and even following post-exposure prophylaxis. Children can be affected, like adults, with clinical fat redistribution shortly after initiation or change of antiretroviral therapy. The evolution of the individual clinical components of the lipodystrophy syndrome is variable. Subcutaneous fat loss has been observed during exclusive therapy with NRTIs but develops faster under a combination of NRTIs and protease inhibitors. The nucleoside analogue linked most strongly to lipoatrophy is stavudine, particularly when used in combination with didanosine. Tenofovir combined with lamivudine and efavirenz is associated with less loss of limb fat than stavudine in a similar combination in therapy-naïve HIV patients (Gallant 2004). Single case reports even describe body habitus changes compatible with the lipodystrophy phenotype in antiretroviral therapy-naïve patients.

Frequently, complex metabolic alterations are associated with the described body shape alterations. These include peripheral and hepatic insulin resistance, impaired glucose tolerance, type 2 diabetes, hypertriglyceridemia, hypercholesterolemia, increased free fatty acids (FFA), and decreased high density lipoprotein (HDL). Often these metabolic abnormalities appear or deteriorate before the manifestation of fat redistribution. The prevalence of insulin resistance and glucose intolerance has been reported in the literature at 20 to 50% depending on the study design and measurement methods. Frank diabetes is less frequent with a prevalence of between 1 and 6 %. Lipodystrophic patients present with the highest rates of metabolic disturbances.

Hyperlipidemias are a frequently observed side effect of antiretroviral therapy, especially in combinations that include protease inhibitors. Given that many HIV patients present with already decreased HDL levels, these are not further reduced by antiretroviral drugs. Hypertriglceridemias, especially in patients with evidence of body-fat abnormalities, are the leading lipid abnormality either alone or in combination with hypercholesterinemia. Several weeks after initiation or change of HIV

therapy, lipid levels usually reach a plateau and remain stable. All protease inhibitors can potentially lead to hyperlipidemia, although to different extents. For example, atazanavir (Reyataz™) appears to be less frequently associated with dyslipidemia and insulin resistance. In contrast, ritonavir (Norvir™) often leads to hypertriglyceridemia correlating to the drug levels.

The therapy-induced dyslipidemias are characterized by increased low density lipoproteins (LDL) and triglyceride-rich very low density lipoproteins (VLDL). Detailed characterization revealed an increase of apoplipoprotein B, CIII and E. Raised levels of lipoprotein(a) have been described in protease inhibitor recipients. Mild hypercholesterolemia can occur during therapy with efavirenz (Sustiva™) but is not typical under therapy with nevirapine (Viramune™). Stavudine-based, antiretroviral therapy is associated with early and statistically significant increases in total triglycerides and cholesterol or NRTIs. It is important to note that HIV infection itself is associated with disturbed lipid metabolism. During disease progression, the total cholesterol, LDL, and HDL levels decline and the total triglyceride level rises. The latter is presumably caused by increased cytokine concentrations (TNFα, IFNγ) and an enhanced lipogenesis in addition to impaired postprandial triglyceride clearance.

Recently, more signs and symptoms have been described in association with the lipodystrophy syndrome. Their pathogenetic relationship to fat redistribution and metabolic changes have not yet been fully evaluated. Thus, future studies need to assess whether conditions such as dry skin, ingrown toenails, aseptic hip necrosis, osteopenia and osteoporosis are linked to the lipodystrophy syndrome or are caused by independent drug or disease-related effects.

HAART, lipodystrophy syndrome and cardiovascular risk

The fat redistribution and disturbances in glucose and fat metabolism resemble a clinical situation that is known as the "metabolic syndrome" in HIV-negative patients. This condition includes symptoms such as central adipositas, insulin resistance and hyperinsulinemia, hyperlipidemia (high LDL, Lp(a) hypertriglyceridemia and low HDL) and hypercoagulopathy. Given the well-established cardiovascular risk resulting from this metabolic syndrome, there is growing concern about a potential therapy-related increased risk of myocardial infarction in HIV patients. These fears are further sustained by reports of arterial hypertension on HAART (Seaberg 2005), a high rate of smoking among HIV patients and increased levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) in patients with lipodystrophy. Although many of the, mainly retrospective, studies dealing with this issue are inconclusive, data from a large international study (D:A:D study) provide evidence of a 27 % increased relative risk of myocardial infarction during the first 7 years of HAART (Friis-Møller 2003). It is, however, of note that older age, male gender, smoking, diabetes mellitus, and pre-existing coronary artery disease were still associated with a higher risk of sustaining cardiovascular events than HAART in this study. Although the CHD risk profile in D:A:D patients worsened over time, the risk of myocardial infarction decreased over time after controlling for these changes (Sabin 2005). Several other studies used ultraso-

nography to measure the thickness of the carotid intima media or endothelial function to predict the cardiovascular risk. Some of these investigations found abnormal test results (e.g. reduced flow-mediated dilation) that correlated either with the use of protease inhibitors or the presence of dyslipidemia (Currier 2003). Long-term follow-up results will be necessary to substantiate these preliminary observations. While there is some indication of an increased rate of coronary artery disease during HAART, the benefit of suppressed viral replication and improved immune function resulting in reduced morbidity and mortality, clearly argues for the use of antiretroviral drugs according to current international guidelines. It seems obvious however, that pre-existing cardiovascular risk factors in individual patients need to be considered more carefully before starting or switching HAART.

Recommendations such as the National Cholesterol Education Program (NECP) have been proposed for non-HIV-infected patients with similar risk constellations. These guidelines are being proposed by some authors for HIV patients as well (Dube 2000, Schambelan 2002, Grinspoon 2005). According to these recommendations, the overall cardiovascular risk in HIV-infected patients can be determined from specific risk factors by using the Framingham equation. Prediction of coronary heart disease using this equation, however, may have some limitations. A 10-year CHD risk estimation at any time point is determined by the individual's past and expected future lipid levels (best assessed as area under the curve). Hyperlipidemia in many treated HIV patients, however, does not follow the 10-year time course seen in the "normal population" due to frequent therapy changes that may lower total cholesterol, increase HDL, and improve atherogenic risk. Thus, the validity of this calculation for the long-term cardiovascular risk assessment in young patients with changing lipid levels and medication regimens requires further studies.

Clearly, more clinical studies are necessary to assess whether these recommendations are also applicable in the presence of HIV and to determine the clinical value of lipid lowering drug therapy in these patients. Most importantly, the information about drug interactions of lipid lowering and antiretroviral drugs is still incomplete. The accumulation of pre-existing and drug-related risk factors will get more clinical attention, because, by improving the HIV-associated morbidity and mortality, HAART consequently increases an additional relevant cardiovascular risk factor: the age of patients who are effectively treated with antiretroviral drugs.

Pathogenesis

For a better understanding of the pathogenesis of the complex metabolic abnormalities, it is useful to separate individual aspects of the lipodystrophy syndrome: adipocytes/fat redistribution, lipid metabolism, and carbohydrate metabolism. This is because it is very likely that the lipodystrophy syndrome is not a stereotypic syndrome but rather an amalgam of miscellaneous clinical features, with perhaps multifactorial causes. Studies published during recent years provide evidence for two fundamental assumptions: firstly, lipoatrophy and lipoaccumulation result from divergent or only partially overlapping pathogenetic reasons. Secondly, NRTIs, NNRTIs, PIs, and even drugs within each class contribute to the lipodystrophy syndrome and its individual features by different, probably overlapping and certainly synergistic mechanisms.

NRTI and lipodystrophy

The patterns of fat redistribution in patients who are exclusively receiving NRTIs are unlike those observed in patients during PI therapy. Peripheral fat loss is the major symptom observed in NRTI therapy (particularly using stavudine and didanosine combinations), although a few clinical studies have described a minimal intra-abdominal fat increase in these patients, which is clearly less than under PIs. Given that, commonly, only a mild increase in triglycerides has been observed, exclusive NRTI therapy seems to be of minor impact on lipid metabolism. Postprandially elevated FFA in patients with lipodystrophy, together with in vitro experiments, have led to the hypothesis that NRTIs could impair fatty acid binding proteins (FABP) which are responsible for cellular fat uptake and intracellular fat transport. In contrast, addition of stavudine (Zerit™) to a dual PI regimen does not result in a further increase in the total cholesterol or triglyceride levels.

It is well established that long-term NRTI therapy can cause mitochondrial toxicity. The clinical manifestation of this side effect presents in symptoms such as hepatic steatosis, severe hyperlactatemia, and polyneuropathy. As an explanation for these symptoms, the "pol-γ hypothesis" has been proposed, which was later extended to reveal the lipoatrophy observed under NRTIs (Brinkmann 1999). To maintain an adequate bioenergetic level for accurate cell function, all metabolically active cells depend on a persistent polymerase γ-mediated mitochondrial (mt) DNA synthesis. Mitochondria require a constant supply of nucleosides for this process. The mitochondrial DNA polymerase γ retains both DNA- as well as RNA-dependent DNA polymerase activity. The latter is perhaps responsible for the HIV reverse transcriptase activity and therefore its susceptibility for interactions with NRTIs. Experimental data revealed that for NRTI uptake into mitochondria, the subsequent phosphorylation and then incorporation into the DNA, certain pharmacodynamic requirements need to be fulfilled. These requirements, which include thymidine kinase activity and deoxynucleotide transport specificity of the mitochondrial membrane, are apparently different for zidovudine (Retrovir) and stavudine (Zerit™), which partially explains the prevailing association between lipoatrophy and stavudine therapy. The postulated mechanisms of NRTI-induced mitochondrial dysfunction consist of competitive inhibition, incorporation into the mtDNA resulting in mtDNA depletion, impairment of mitochondrial enzymes, uncoupling of oxidative phosphorylation and induction of apoptosis. Depletion of mtDNA and structural changes in the mitochondria, resulting in increased rates of apoptosis in subcutaneous adipocytes, have been confirmed by some studies. Despite the experimental link between mitochondrial toxicity and fat tissue as one potential target organ, the degree to which mitochondrial damage contributes to fat distribution abnormalities and its specificity remains unknown. In contrast, mitochondrial damage is widely believed to be responsible for other NRTI-related side effects, such as myopathy, hyperlactatemia, microvesicular steatosis, and steatohepatitis with lactic acidosis (Nolan & Mallal 2004).

Protease inhibitors and lipodystrophy

PIs account for the majority of metabolic abnormalities associated with lipodystrophy syndrome. Numerous studies report increases in the levels of total triglycerides and triglyceride-rich lipoproteins (VLDL) accompanied by raised LDL levels after

initiation of PI therapy (Walli 1998). Conversely, these parameters improved substantially in most studies after discontinuation of the PI or on switching to abacavir (Ziagen™) or nevirapine (Viramune™). The hyperlipidemic changes are frequently associated with hyperinsulinemia and/or insulin resistance.

It has been proposed, based on in vitro experiments, that PIs such as saquinavir (Invirase™/Fortovase™), indinavir (Crixivan™), and ritonavir (Norvir™) are able to inhibit proteasomal degradation of apolipoprotein B leading to intracellular stockpiling of this lipoprotein and excessive release in response to FFA (Liang 2001). Using stable isotopes in vivo, other authors demonstrate a dramatic increase in FFA turnover together with increased lipolysis and decreased clearance of triglyceride-rich VLDL and chylomicrons (Shekar 2002). These conditions point towards an impaired postprandial insulin-mediated lipid metabolism, since insulin, on the one hand, normally inhibits lipolysis and, on the other hand, increases uptake of FFA, triglyceride synthesis, and fat oxidation in favor of glucose oxidation.

So far, it remains unclear whether impaired insulin action eventually leads to dyslipidemia, or whether hyperlipidemia is responsible for reduced insulin function and insulin resistance in the periphery. Presumably, both mechanisms are important given that some PIs (e.g. indinavir) have been shown to induce insulin resistance without changes occurring in lipid metabolism after short-term administration (Noor 2001, Noor 2002), whereas other PIs (e.g. ritonavir) have been demonstrated to cause mainly hypertriglyceridemia due to increased hepatic synthesis without major changes occurring in glucose metabolism (Purnell 2000). However, comparative clinical studies on the association of different PIs with insulin resistance, are still lacking.

It is reasonable to speculate that lipid abnormalities and, in particular increased FFA levels, contribute substantially to the peripheral and central insulin resistance of skeletal muscles and the liver, presumably due to the increased storage of lipids in these organs (Gan 2002). Given this hypothesis, the visceral adiposity could reflect the adaptation of the body in response to raised FFA concentrations and an attempt to minimize the lipotoxic damage to other organs.

Several in vitro experiments have indicated that almost all PIs can potentially lead to insulin resistance in adipocytes. Short-term administration of indinavir caused an acute and reversible state of peripheral insulin resistance in healthy volunteers, which was determined in an euglycemic-hyperinsulinemic clamp. These effects are most likely caused by the inhibition of glucose transport mediated by GLUT-4, the predominant transporter involved in insulin-stimulated cellular glucose uptake in humans (Murata 2002). A common structural component found in most PIs has been proposed to cause GLUT-4 inhibition (Hertel 2004). In some patients with lipodystrophy, additional impairment of glucose phosphorylation may contribute to insulin resistance (Behrens 2002). This is presumably due to an impaired insulin-mediated suppression of lipolysis and subsequently increased FFA levels (Behrens 2002, van der Valk 2001) and accumulation of intramyocellular lipids. Peripheral insulin resistance may also account for an increase in the resting energy expenditure in HIV lipodystrophy and a blunted insulin-mediated thermogenesis.

Indinavir may also induce insulin resistance by inhibiting the translocation, processing or phosphorylation of the sterol regulatory element-binding protein 1c (SREBP-1c) (Caron 2001, Bastard 2002). Either directly or via the peroxisome

proliferator activated receptor γ (PPARγ), SREBP-1 regulates FFA uptake and synthesis, adipocyte differentiation and maturation, and glucose uptake by adipocytes. Similarly, the function of these factors have been proposed to be disturbed in inherited forms of lipodystrophies. Finally, hypoadiponectinemia, as found in patients with abnormal fat distribution, may contribute to insulin resistance (Addy 2003).

Diagnosis

Both the lack of a formal definition and uncertainty about the pathogenesis and possible long-term consequences, leads to a continuing discussion about appropriate guidelines for the assessment and management of HIV lipodystrophy syndrome and its metabolic abnormalities. Outside clinical studies, the diagnosis relies principally on the occurrence of apparent clinical signs and the patient reporting them. A standardized data collection form may assist in diagnosis (Grinspoon 2005). This appears sufficient for the routine clinical assessment, especially when the body habitus changes develop rather rapidly and severely. For clinical investigations however, especially in epidemiological and interventional studies, more reliable measurements are required. But so far, no technique has demonstrated sufficient sensitivity, specificity or predictive value to definitively diagnose the HIV lipodystrophy syndrome by comparison with results obtained from a "normal" population. A recent multicentre study to develop an objective and broadly applicable case definition proposes a model including age, sex, duration of HIV infection, HIV disease stage, waist-to-hip ratio, anion gap, serum HDL cholesterol, trunk to peripheral fat ratio, percentage leg fat, and intra-abdominal to extra-abdominal fat ratio. Using these parameters, the diagnosis of lipodystrophy had a 79 % sensitivity and 80 % specificity.

Although this model is largely for research and contains detailed body composition data, alternative models and scoring systems, incorporating only clinical and metabolic data, also gave reasonable results (for more information, see http://www.med.unsw.edu.au/nchecr).

Despite individual limitations, several techniques are suitable for measuring regional fat distribution. These include dual energy x-ray absorptiometry (DEXA), computer tomography (CT), magnetic resonance imaging (MRI) and sonography. Anthropometric measurements are safe, portable, cheap and much easier to perform than imaging techniques. Waist circumference alone, as well as sagittal diameter, are more sensitive and specific measures than waist-to-hip ratio. Repeated measurements of skin fold thickness can be useful for individual long-term monitoring but need to be performed by an experienced person.

The main imaging techniques (MRI, CT, DEXA) differentiate tissues on the basis of density. Single-slice measurements of the abdomen and extremities (subcutaneous adipose tissue = SAT, visceral adipose tissue = VAT) and more complex three-dimensional reconstructions have been used to calculate regional or total body fat. Limitations of these methods include most notably their expense, availability and radiation exposure (CT). Consequently, CT and MRI should only be considered in routine clinical practice for selected patients (e.g. extended dorso-cervical fat pads, differential diagnosis of non-benign processes and infections).

Table 1. HIV Lipodystrophy: Case definition and scoring system

Parameter		OR	95% CI	p value	Score*
Demographic					
Gender	male	1.0			0
	female	9.33	3.86-22.52	< 0.001	22
Age	≤40 years	1.0			0
	>40 years	2.02	1.20-3.4	0.008	7
Duration of HIV infection	≤ 4 years	1.0			0
	> 4 years	3.11	1.69-5.71	< 0.001	11
CDC Category	A	1.0			0
	B	1.32	0.73-2.39	0.361	3
	C	1.92	1.02-3.61	0.043	7
Clinic					
Waist : hip ratio	0.1	1.34	1.06-1.69	0.014	multiply by 29
Metabolic					
HDL cholesterol	0.1 mM	0.87	0.81-0.94	<0.001	multiply by –14
Anion gap	1 mM	1.10	1.04-1.166	0.001	multiply by 1
Body composition					
VAT:SAT	≤ 0.45	1.0			0
	0.45-0.83	0.82	0.38-1.76	0.613	-2
	0.83-1.59	1.40	0.62-3.18	0.416	3
	> 1.59	3.70	1.44-9.55	0.007	13
Trunk: limb fat ratio	1.0	1.72	1.12-2.66	0.014	multiply by 5
leg fat ratio	> 21.4	1.0			-16
	14.5-21.4	1.27	0.57-2.87	0.559	-14
	8.8-14.5	2.32	1.00-5.40	0.051	-8
	≤ 8.8	5.04	1.90-13.35	0.001	0

According to Carr & Law (2003). This model has a sensitivity of 79% (95% CI, 70-85 %) and a specificity of 80% (95 % CI, 71-87 %).

* The final lipodystrophy score is obtained by adding individual scores for every variable and subtraction of 43 (constant). A final score of ≥ 0 for a patient indicates the diagnosis of lipodystrophy, a score of < 0 means no lipodystrophy. CDC, U.S. Centers for Disease Control and Prevention; HDL, high-density lipoprotein; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

Table 2. Proposed grading scale for lipodystrophy based on lipodystrophy case definition cores relative to the subjective physician assessment-derived total lipodystrophy severity score (according to Carr & Law 2003).

Grading scale	Lipodystrophy-score
0	< 0
1	0-9.9
2	10-14.9
3	15-22.9
4	≥ 23

DEXA is appropriate for examining appendicular fat, which is comprised almost entirely of SAT, and has been successfully employed in epidemiological studies. However, SAT and VAT cannot be distinguished by DEXA, which therefore limits the evaluation of changes in truncal fat. Application of sonography to measure specific adipose compartments, including those in the face, requires experienced investigators and has been minimally applied in HIV infection so far. Bioelectrical impedance analysis estimates the whole body composition and cannot be recommended for measurement of abnormal fat distribution.

Patients should routinely be questioned and examined for cardiovascular risk factors, such as smoking, hypertension, adiposity, type 2 diabetes, and family history. For an accurate assessment of blood lipid levels, it is recommended to obtain blood after a fasting of at least 8 hours. Total cholesterol and triglycerides together with LDL and HDL cholesterol should be obtained prior to the initiation of, or switch to, a new potent antiretroviral therapy and repeated 3 to 6 months later. Fasting glucose should be assessed with at least a similar frequency. The oral glucose tolerance test (OGTT) is a reliable and accurate instrument for evaluating insulin resistance and glucose intolerance. An OGTT may be indicated in patients with suspected insulin resistance such as those with adipositas (BMI > 27 kg/m^2), a history of gestational diabetes and a fasting glucose level of 110 to 126 mg/dl (impaired fasting glucose). An intravenous glucose tolerance test or hyperinsulinemic-euglycemic clamp appears only feasible in clinical studies. The diagnosis of diabetes is based on fasting glucose levels > 126 mg/dl, glucose levels of > 200 mg/dl independent of fasting status, or a 2-hour OGTT glucose level above 200 mg/dl. Additional factors that could lead to or assist in the development of hyperlipidemia and/or insulin resistance always need to be considered (e.g. alcohol consumption, thyroid dysfunction, liver and kidney disease, hypogonadism, concurrent medication such as steroids, β-receptor blockers, thiazides, etc.).

Therapy

So far, most attempts to improve or even reverse the abnormal fat distribution by modification of the antiretroviral treatment have shown only modest clinical success. In particular, peripheral fat loss appears to be resistant to most therapeutic interventions. The metabolic components of the syndrome may be easier to improve (Table 3).

Lifestyle changes

Dietary interventions are commonly accepted as the first therapeutic option for hyperlipidemia, especially hypertriglyceridemia. Use of NCEP guidelines may reduce total cholesterol and triglycerides by 11 or 21 %, respectively. Whenever possible, dietary restriction of the total fat intake to 25-35 % of the total caloric intake should be a part of the treatment in conjunction with lipid-lowering drugs. Consultation with professional and experienced dieticians should be considered for HIV-infected patients and their partners. Patients with excessive hypertriglyceridemia (>1000 mg/dl) may benefit from a very low fat diet and alcohol abstinence to reduce the risk of pancreatitis, especially if there is a positive family history or concurrent medications that may harbor a risk of developing pancreatitis. Regular exercise may have beneficial effects, not only on triglycerides and insulin resistance, but probably also on fat redistribution (reduction in truncal fat and intramyocellular fat) and should be considered in all HIV-infected patients (Driscoll 2004). All patients should be advised and supported to cease smoking in order to reduce the cardiovascular risk. Cessation of smoking is more likely to reduce cardiovascular risk than any choice or change of antiretroviral therapy or use of any lipid-lowering drug.

Table 3. Therapeutic options for HIV-associated lipodystrophy and related metabolic complications

Lifestyle changes (reduce saturated fat and cholesterol intake, increase physical activity, cease smoking)
Change antiretroviral therapy [replacement of PI, replacement of stavudine (Zerit™) or zidovudine (Retrovir™)]
Statins [e.g. Atorvastatin (Sortis™), Pravastatin (Pravasin™), Fluvastatin (Lescol™)]
Fibrates [e.g. Gemfibrozil (Gevilon™) or Bezafibrat (Cedur™)]
Metformin (e.g. Glucophage™)
Thiazolidinediones [rosiglitazone (Avandia™), pioglitazone (Actos™)]
Recombinant human growth hormones (e.g. Serostim™)
Surgical intervention

Specific interventions

Given the extensive indications that PIs are the culprits substantially contributing to the metabolic side effects, numerous attempts have tried to substitute the PI component of a regimen with nevirapine, efavirenz, or abacavir. Similarly, given the close association of stavudine-based therapy with lipoatrophy, replacement of this thymidine nucleoside analogue by, for example, abacavir or tenofovir has been evaluated in several studies. Indeed, these "switch studies" have demonstrated substantial improvement, although not normalization, of serum lipids (total and LDL cholesterol, triglycerides) and/or insulin resistance in many patients. Protease inhibitor cessation has not been shown to improve lipoatrophy. However, stopping administration of the thymidine nucleoside analogue stavudine or zidovudine usually leads to a slow recovery (over months and years) measured by DEXA and moderate clinical increase in limb fat (Moyle 2005). Under restricted inclusion criteria and study conditions, most patients maintained complete viral suppression after changes

to the HAART regimen, but not all of these studies included control groups with unchanged antiretroviral therapy. The most advantageous changes of metabolic parameters have been observed after replacement of the PI by nevirapine or abacavir. This option is, however, not always suitable, and the clinical benefit of effective viral suppression and improved immune function needs to be considered in view of the drug history, current viral load, and resistance mutations (Martinez 2003). When options are limited, antiretroviral drugs that may lead to elevation of lipid levels should not be withheld for fear of further exacerbating lipid disorders.

Table 4.   Preliminary treatment recommendations and LDL cholesterol goals for HAART-associated hyperlipidemias

Risk Category	Recommendations		
	"aimed for" LDL	diet if LDL	Lipid-lowering drugs if LDL
CHD or risk equivalent ≥ 2 RF and 10-years risk ≤ 20%	< 100 mg/dl	≥ 100 mg/dl	≥ 130 mg/dl
10-year risk 10-20%	< 130 mg/dl	≥ 130 mg/dl	≥ 130 mg/dl
10-year risk <10%	< 130 mg/dl	≥ 130 mg/dl	≥ 160 mg/dl
0-1 risk factors	< 160 mg/dl	≥ 160 mg/dl	≥ 160 mg/dl

Coronary heart disease (CHD) includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia. CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease, diabetes, and >2 risk factors with 10-year risk for hard CHD >20%. Risk factors (RF) include: age (male ≥ 45 years, female ≥ 55 years or premature menopause without hormone replacement), positive family history for premature CHD (in first-degree relatives < 55 years and first-degree female relatives < 65 years), cigarette smoking, hypertension (blood pressure ≥ 140/90 mmHg or taking antihypertension drugs), HDL < 40 mg/dl (1.0 mmol/l). If HDL cholesterol is over > 60 mg/dl (1.6 mmol/l), subtract one risk factor from the total (adapted from Dubé 2000 and Schambelan 2002).

Lipid lowering agents should be considered for the treatment of severe hypertriglyceridemia, elevated LDL or a combination of both. The clinical benefit, however, of lipid lowering or insulin-sensitizing therapy in HIV patients with lipodystrophy remains to be demonstrated. In light of the potentially increased cardiovascular risk to recipients of antiretroviral therapy, an American AIDS clinical trial group (ACTG) published recommendations based on the National Cholesterol Education Program (NCEP) for primary and secondary prevention of coronary artery disease in seronegative patients (Table 4). In addition, more detailed recommendations by an International AIDS Society-USA Panel have been published to provide guidelines for physicians actively involved in HIV care. However, these recommendations should be considered as being rather preliminary, given the so far limited numbers, sizes and durations of the clinical studies they are based on.It appears reasonable to measure fasting lipid levels annually before and 3-6 months after antiretroviral therapy is initiated or changed. Whenever possible, the antiretroviral therapy least likely to worsen lipid levels should be selected for patients with dyslipidemia. Decision on lipid lowering therapy can be based on estimating the 10-

year risk for myocardial infarction according to the Framingham equation (http://hin.nhlbi.nih.gov/atpiii/calculator.asp). It remains to be shown, however, whether this long-term risk calculation is applicable for HIV-infected patients given the changing lipid levels and medication regimens during HIV therapy.

HMG-CoA reductase inhibitors have been successfully used in combination with dietary changes in HIV patients with increased total and LDL cholesterol. These drugs may decrease total and LDL cholesterol by about 25% (Grinspoon 2005). Many of the statins (as well as itraconazol, erythromycin, diltiazem, etc.) share common metabolization pathways with PIs via the cytochrome P450 3A4 system, thereby potentially leading to additional side effects due to increased plasma levels of statins which can then cause liver and muscle toxicity. Based on limited pharmacokinetic and clinical studies, atorvastatin (Sortis™), fluvastatin (Lescol™), and pravastatin (Pravasin™), carefully administered at increasing doses, are the preferred agents for a carefully monitored therapy in HIV-infected patients on HAART. Lovastatin (Mevinacor™) and simvastatin (Zocor™) should be avoided due to their potential interaction with PIs.

Fibric acid analogues such as gemfibrozil or fenofibrate are particularly effective in reducing the triglyceride levels by up to 50 % (Rao 2004, Badoui 2004, Miller 2002, Calza 2003) and should be considered in patients with severe hypertriglyceridemia (>1000 mg/dl). Fibric acid analogues retain a supportive effect on lipoprotein lipase activity and can thereby lower LDL levels. Despite their potentially synergistic effect, co-administration of fibric acid analogues and statins in patients on HAART should only be used carefully in selected individuals, since both can cause rhabdomyolysis. Niacinic acid has been shown to only minimally improve the hyperlipidemia induced by HAART. It does, however, increase the peripheral insulin resistance and is therefore currently not recommended for HIV patients receiving HAART (Gerber 2004). Finally, it should be stressed that the long-term effects of lipid-lowering agents and their impact on cardiovascular outcomes, especially in HIV patients with moderate or severe hypertriglyceridemia, are unknown.

Metformin has been evaluated for the treatment of lipodystrophy syndrome. Some studies have revealed a positive effect on the parameters of insulin resistance and the potential reduction of intra-abdominal (but also subcutaneous) fat, although not clinically obvious. Metformin, like all biguanides, can theoretically precipitate lactic acidosis but this adverse interaction has not been described. Use of metformin should be avoided in patients with creatinine levels above 1.5 mg/dl, increased aminotransferase levels, or hyperlactatemia. Thiazolidinediones, such as rosiglitazone (Avandia™) or pioglitazone (Actos™), exhibit the potency to improve insulin sensitivity via stimulation of the PPAR γ and other mechanisms. Rosiglitazone has been successfully used to treat abnormal fat distribution in genetic lipodystrophies. Three published studies on HIV patients, however, revealed no or only a minimal improvement in the abnormal fat distribution. But, insulin sensitivity was increased at the expense of increased total cholesterol and triglycerides (Carr 2004, Hadigan 2004, Sutinen 2003). Thus, rosiglitazone cannot be recommended for general treatment of lipoatrophy in HIV patients at this time (Grinspoon 2005).

Recombinant growth hormone (e.g. Serostim™) at doses of 4-6 mg/d sc over a time course of 8-12 weeks has been demonstrated in some small studies to be a successful intervention for reducing visceral fat accumulation, but it also reduces subcuta-

neous fat (Kotler 2004). Unfortunately, these improvements have been shown to consistently reverse after the discontinuation of growth hormone therapy. Studies with lower maintenance doses have not been performed yet. The possible side effects associated with growth hormone therapy include arthralgia, peripheral edema, insulin resistance and hyperglycemia.

Surgical intervention (liposuction) for the treatment of local fat hypertrophy has been successfully performed, but appears to be associated with an increased risk of secondary infection, and recurrence of the fat accumulation is possible. For the treatment of facial lipoatrophy, repeated subcutaneous injection of poly-L-lactic acid (Sculptra™, New-Fill™), a resorbable molecule that promotes collagen formation, has been effectively used in HIV-patients (Valantin 2003, Lafaurie 2003). In 2004, Sculptra™ was approved by the Food and Drug Administration as an injectable filler to correct facial fat loss in people with human immunodeficiency virus. We recommend consultation with experienced specialists for surgical treatments and injection therapy. Further evaluation in long-term follow-up studies is necessary to fully assess the value of these methods.

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8. Mitochondrial Toxicity of Nucleoside Analogs

Ulrich A. Walker and Grace A. McComsey

Introduction

Two years after the introduction of protease inhibitors into the armamentarium of antiviral therapy, reports of HIV-infected individuals experiencing clinically relevant changes in body metabolism began to surface. These „metabolic" symptoms were initially summarized under the term „lipodystrophy" (Carr 1998). Today, nine years after the introduction of highly active antiretroviral therapy (HAART), this lipodystrophy syndrome is increasingly understood as the result of overlapping, but distinct effects of the different drug components within the HAART antiretroviral cocktail. The main pathogenetic mechanism through which nucleoside analogues are thought to contribute to the metabolic changes and organ toxicities is mitochondrial toxicity (Brinkman 1999).

Pathogenesis of mitochondrial toxicity

NRTIs are prodrugs (Kakuda 2000) because they have to be activated in the cell through phosphorylation before they are able to inhibit their target, e.g. HIV reverse transcriptase. In addition to impairing the HIV replication machinery, the NRTI-triphosphates also inhibit a human polymerase called "gamma-polymerase" which is responsible for the replication of mitochondrial DNA (mtDNA). Thus, the inhibition of gamma-polymerase by NRTIs leads to a decline (depletion) of mtDNA, a small circular molecule normally present in multiple copies in each mitochondrion and in hundreds of copies in most human cells. The only biological task of mtDNA is to encode for enzyme subunits of the respiratory chain, which is located in the inner mitochondrial membrane. Therefore, NRTI by causing mtDNA-depletion also lead to a defect in respiratory chain function.

An intact respiratory chain is the prerequisite for numerous metabolic pathways. The main task of the respiratory chain is to oxidatively synthesize ATP, our chemical currency of energy. In addition, the respiratory chain consumes NADH and FADH as end products of fatty acid oxidation. This fact explains the micro- or macrovesicular accumulation of intracellular triglycerides, which often accompanies mitochondrial toxicity. Last but not least, a normal respiratory function is also essential for the synthesis of DNA, because the de novo synthesis of pyrimidine nucleosides depends on an enzyme located in the inner mitochondrial membrane. This enzyme is called dihydroorotate dehydrogenase (DHODH) (Löffler 1997). The clinical implications of this fact are detailed below.

The onset of mitochondrial toxicity follows certain principles (Walker 2002b):

1. Mitochondrial toxicity is concentration dependent. High NRTI-concentrations cause a more pronounced mtDNA-depletion compared to low concentrations. The

clinical dosing of some nucleoside analogs is close to the limit of tolerance with respect to mitochondrial toxicity.

2. The onset of mitochondrial toxicity requires prolonged time. Changes in mito-chondrial metabolism are observed only if the amount of mtDNA-depletion exceeds a certain threshold, an effect observed solely with prolonged NRTI-exposure. As a consequence of this effect, the onset of mitochondrial toxicity is typically not ob-served in the first few months of HAART. Furthermore, long-term NRTI exposure may also lead to mitochondrial effects despite relatively low NRTI concentrations.

3. There are significant differences in the relative potencies of nucleoside and nu-cleotide analogs in their ability to interact with gamma-polymerase. The hierarchy of gamma-polymerase inhibition for the active NRTI metabolites has been deter-mined as follows: zalzitabine (HIVID[TM]) > didanosine (Videx[TM]) > stavudine (Zerit[TM]) > lamivudine (Epivir[TM]) > abacavir (Ziagen[TM]) = tenofovir (Viread[TM]).

4. Zidovudine may be peculiar because its active triphosphate is only a weak in-hibitor of gamma-polymerase. Nevertheless this NRTI is a mitochondrial toxin by other mechanisms. Interestingly, it has been demonstrated recently, that zidovudine can be non-enzymatically converted into stavudine within the body, at least within some cells (Becher 2003, Bonora 2004). This effect may account for the fact that mtDNA-depletion has also been described under treatment with zidovudine by some investigators.

5. Mitochondrial toxicity is tissue specific. Tissue specificity is explained by the fact that the uptake of the NRTI-prodrugs into cells and their mitochondria, as well as activation by phosphorylation may be different among individual cell types.

6. There may be additive or synergistic mitochondrial toxicities if two or more NRTIs are used in combination.

Clinical manifestations

MtDNA-depletion may manifest clinically in one or several main target tissues (Fig. 1).

In the *liver* mitochondrial toxicity is associated with increased lipid deposits, resulting in micro or macrovesicular steatosis. Steatosis may be accompanied by elevated transaminases. Such steatohepatitis may progress to liver failure and lactic acidosis, a potentially fatal, but fortunately rare complication. Although steatohepatitis and lactic acidosis were already described in the early 90s in patients receiving didanosine monotherapy (Lambert 1990), mitochondrial liver toxicity is now observed under treatment with all NRTIs that have a relatively strong potential to inhibit gamma-polymerase, especially with the so called „D-drugs" didanosine (Videx[TM]), stavudine (Zerit[TM]) and zalzitabine (HIVID[TM]). However, liver complications were also described with zidovudine (Retrovir[TM]). It has been demonstrated in the hepatic tissue of HIV-patients, that each of the D-drugs leads to a time dependent mtDNA-depletion. On electron microscopy, morphologically abnormal mitochondria were observed.
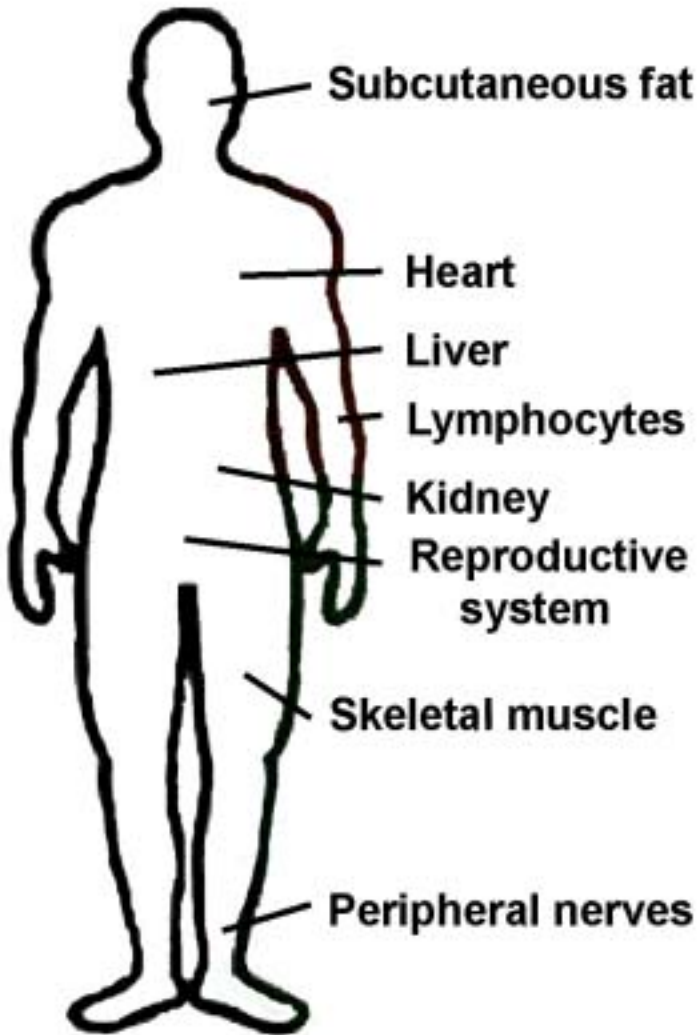
Figure 1: Organ manifestations of mitochondrial toxicity.

A typical complication of mitochondrial toxicity is an *elevation in serum lactate*. Such hyperlactatemia was more frequently described with prolonged stavudine treatment (Saint-Marc 1999, Carr 2000), especially when combined with didanosine. The toxicity of didanosine is also increased through the interactions with ribavirin and hydroxyurea. The significance of asymptomatic hyperlactatemia is unclear. When elevated lactate levels are associated with symptoms, these are often non specific such as nausea, right upper quadrant abdominal tenderness or myal-

gias. In the majority of cases, levels of bicarbonate and anion gap (Na^+ - [$HCO3^-$ + Cl^-]) are normal, although liver transaminases are mildly increased in the majority of cases (Lonergan 2000a). Therefore, the diagnosis relies on the logistically more cumbersome direct determination of serum lactate. In order to avoid artifacts, venous blood must be drawn without the use of a tourniquet from resting patients. The blood needs to be collected in fluoride tubes and transported to the laboratory on ice for immediate analysis. Non-mitochondrial causes must also be considered in the differential diagnosis of lactic acidosis (Table 1) and underlying organ toxicities should be looked for.

Table 1. Causes of hyperlactatemia/ lactic acidosis

Type A lactic acidosis	Type B lactic acidosis
(*Tissue hypoxia*)	(*Other mechanisms*)
Shock	Thiamine deficiency
Carbon monoxide poisoning	Alkalosis (pH>7.6)
Heart failure	Epilepsy
	Adrenalin (iatrogenic, endogenous)
	Liver failure
	Neoplasm (lymphoma, solid tumors)
	Intoxication (nitroprusside, methanol, methylen glykol, salicylates)
	Fructose
	Rare enzyme deficiencies
	mtDNA-mutations
	mtDNA-depletion

A *mitochondrial myopathy* in antiretrovirally treated HIV-patients was first described with high dose zidovudine therapy (Arnaudo 1991). Skeletal muscle weakness may manifest under dynamic or static exercise. The serum CK is often normal or only minimally elevated. Muscle histology helps to distinguish this form of NRTI toxicity from HIV-myopathy which may also occur simultaneously. On histochemical examination, the muscle fibers of the former are frequently negative for cytochrome c-oxidase and carry ultrastructurally abnormal mitochondria, whereas those of the latter are typically infiltrated by CD8-positive T-lymphocytes. Exercise testing may detect a low lactate threshold and a reduced lactate clearance but in clinical practice these changes are difficult to distinguish from lack of aerobic exercise (detraining).

Prolonged treatment with D-drugs may also frequently lead to a predominantly symmetrical, sensory and distal *polyneuropathy* of the lower extremities (Simpson 1995, Moyle 1998). An elevated serum lactate level may help to distinguish this axonal neuropathy from its HIV-associated phenocopy. The differential diagnosis may also take into account the fact that the mitochondrial polyneuropathy mostly occurs weeks or months after initiation of D-drugs. In contrast, the HIV-associated polyneuropathy generally does not worsen and may indeed improve with prolonged antiretroviral treatment.

In its more narrow sense, the term „lipodystrophy" denotes a change in the distribution of body fat. Some subjects affected with lipodystrophy may experience ab-

normal fat accumulation in certain body areas (most commonly abdomen or dorso-cervical region), whereas others may develop fat wasting (Bichat's fat pad in the cheeks, temporal fat, or subcutaneous fat of the extremities). Both fat accumulation and fat loss may at times occur simultaneously in the same individuals. Fat wasting (also called *lipoatrophy*) is partially reversible and generally observed not earlier than one year after the initiation of antiretroviral therapy. In the affected subcutaneous tissue, ultrastructural abnormalities of mitochondria and reduced mtDNA-levels have been identified, in particular in subjects treated with stavudine (Walker 2002a). In vitro and in vivo analyses of fat cells have also demonstrated diminished intracellular lipids, reduced expression of adipogenic transcription factors (PPAR-gamma and SREBP-1), and increased apoptotic indices. NRTI-treatment may also impair some endocrine functions of adipocytes. For example, they may impair the secretion of adiponectin and through this mechanism may promote insulin resistance. Stavudine has been identified as a particular risk factor, but other NRTIs such as zidovudine may also be contributing. When stavudine is replaced by another NRTI, mtDNA-levels and apoptotic indices improve, along with an objectively measurable, albeit small increase of subcutaneous adipose tissue (McComsey 2004a). In contrast, switching away from protease inhibitors did not ameliorate lipoatrophy or adipocyte apoptosis. Taken together, the available data are consistent with a predominant effect of mitochondrial toxicity in the pathogenesis of lipoatrophy.

Some studies have suggested an effect of NRTIs on the mtDNA-levels in blood (Coté 2003, Miro 2003). The functional consequences of such mitochondrial toxicity on *lymphocytes* is yet unknown. In this context, it is important to note that a delayed loss of CD4 and CD8-lymphocytes was observed, when didanosine plasma levels were increased by comedication with tenofovir or by low body weight (Negredo 2004). Recent in vitro investigations with exposure of mitotically stimulated T-lymphocytes to slightly supratherapeutic concentrations of didanosine also detected a substantial mtDNA-depletion with a subsequent late-onset decline of lymphocyte proliferation and increased apoptosis (Setzer 2005a, Setzer 2005b). Thus, mitochondrial toxicity is the most likely explanation for the late onset decline of lymphocytes observed with didanosine. The data suggest that the mitochondrial toxicity of NRTIs on lymphocytes has immunosuppressive properties.

Asymptomatic elevations in *serum lipase* are not uncommon under HAART, but of no value in predicting the onset of pancreatitis (Maxson 1992). The overall frequency of pancreatitis has been calculated as 0.8 cases/ 100 years of NRTI-containing HAART. Clinical pancreatitis is associated with the use of didanosine in particular. Didanosine reexposure may trigger a relapse and should be avoided. A mitochondrial mechanism has been cited to explain the onset of pancreatitis, but this assumption remains unproven.

New studies have also raised the question, whether or not zidovudine can be used safely to reduce the risk of HIV vertical transmission. Pregnant monkeys were treated with zidovudine plus lamivudine for a period of 10 weeks prior to delivery and zidovudine was found to be incorporated into mtDNA. The NRTI combination was also associated with mtDNA-depletion in skeletal muscle, heart and brain (Gerschenson 2004).

Mitochondrial symptoms were found at increased frequency in *infants* perinatally exposed to NRTIs (Blanche 1999). Hyperlactatemia is not infrequently observed and may persist for several months after delivery (Noguera 2003). Very low mtDNA-levels were measured in the placenta, as well as in the peripheral cord blood of neonates (Shiramizu 2003). Other clinical trials in contrast did not detect an increased perinatal risk in association with perinatal zidovudine-prophylaxis although key parameters of mitochondrial dysfunction were not assessed. Long-term follow-up data are urgently needed. The present information however does not justify deviating from the currently recommended strategy to use zidovudine to prevent vertical HIV-transmission.

The existence of mitochondrial damage to the *kidney* is controversial. Supratherapeutic doses of the nucleotide analog reverse transcriptase inhibitor tenofovir (Viread^TM) induced a Fanconi-syndrome with tubular phosphate loss and consecutive osteomalacia in animals (Tenofovir review team 2001). Tenofovir is taken up into the renal tubules by means of a special anion transporter and it cannot be ruled out that excessively high intracellular drug concentration may lead to a clinically relevant gamma-polymerase inhibition and mtDNA-depletion, despite the fact that tenofovir has only a low potency to impair the replication of mtDNA. Although several cases of renal phosphate loss were reported under tenofovir treatment, it should be noted that neither the trials leading to drug approval, nor the subsequent field data were able to provide proof of the mitochondrial toxicity of tenofovir to renal tubules.

Monitoring and diagnosis

There is currently no method to reliably predict the mitochondrial risk of an individual patient. Routine screening of asymptomatic NRTI-treated subjects with lactate levels is not warranted, since elevated lactate levels in asymptomatic subjects are not predictive of mitochondrial toxicity (McComsey 2004b). In contrast, there should be a low threshold to promptly check lactate levels in subjects who experience symptoms consistent with mitochondrial toxicity. The determination of mtDNA-levels in PBMCs is subject to systematic errors and high variability; the method is not internationally standardized. Quantifying mtDNA within affected tissues is likely to be more sensitive; however this form of monitoring is invasive and not prospectively evaluated with regard to clinical endpoints.

Once symptoms are established, histological examination of a biopsy may contribute to the correct diagnosis. The following findings in tissue biopsies point towards a mitochondrial etiology: ultrastructural abnormalities of mitochondria, diminished histochemical activities of cytochrome c-oxidase, increased activity of succinate dehydrogenase, the detection of intracellular and more specifically microvesicular steatosis, and the so called ragged-red fibers.

Treatment and prophylaxis of mitochondrial toxicity

Drug interactions may precipitate mitochondrial symptoms and must be taken into account. The mitochondrial toxicity of didanosine (Videx™) for example is augmented through drug interactions with ribavirin, hydroxyurea and allopurinol (Ray 2004). When didanosine is combined with tenofovir (Viread™), the didanosine dose must be reduced to 250 mg QD. An impairment of mitochondrial metabolism may also result from comedication with ibuprofen, valproic acid and acetyl salicylic acid – these substances inhibit the mitochondrial utilization of fatty acids. Numerous cases have been described, in which a life-threatening lactic acidosis was triggered by valproic acid, both in HIV infected patients and in patients with inherited mutations of mtDNA. Acetyl salicylic acid may damage mitochondria and such damage to liver organelles may result in Reye's syndrome. Amiodarone and tamoxifen also inhibit the mitochondrial synthesis of ATP. Acetaminophen and other drugs impair the antioxidative defense (glutathione) of mitochondria, allowing for their radical mediated damage. Aminoglycoside antibiotics and chloramphenicol not only inhibit the protein synthesis of bacteria, but under certain circumstances may also impair the peptide transcription of mitochondria as our bacteria-like endosymbionts. Adefovir and cidofovir are also inhibitors of gamma-polymerase. Alcohol as a mitochondrial toxin is advised against.

The most important clinical intervention is likely the discontinuation of the NRTI(s) responsible for mitochondrial toxicity. Randomized studies have demonstrated that switching stavudine (Zerit™) to a less toxic alternative led to an objective and progressive improvement in lipoatrophy (Martin 2004). In contrast, a switch from protease inhibitors to NNRTIs was not associated with an improvement of lipoatrophy. These findings stress the importance of mitochondrial toxicity in the pathogenesis of this syndrome of fat distribution.

The supplementation of uridine is a new, but promising strategy. As outlined above, any respiratory chain impairment also results in the inhibition of DHODH, an essential enzyme for the synthesis of uridine and its derived pyrimidines (Fig 2). This decrease in intracellular pyrimidine pools leads to a relative excess of the exogenous pyrimidine nucleoside analogs, with which they compete at gamma-polymerase. A vicious circle is closed and contributes to mtDNA-depletion. By supplementing uridine either prophylactically or therapeutically, this vicious circle may be interrupted, resulting in increased mtDNA-levels. Indeed, uridine abolished in hepatocytes all the effects of mtDNA-depletion and normalized lactate production, cell proliferation, the rate of cell death and intracellular steatosis. (Walker 2003). In contrast, vitamin cocktails were not beneficial in this model. New data indicate that uridine is able to also prevent the loss of mtDNA, lipids and mitochondrial functions in adipocytes exposed to stavudine (Walker 2004a). Adipocyte apoptosis was also prevented.
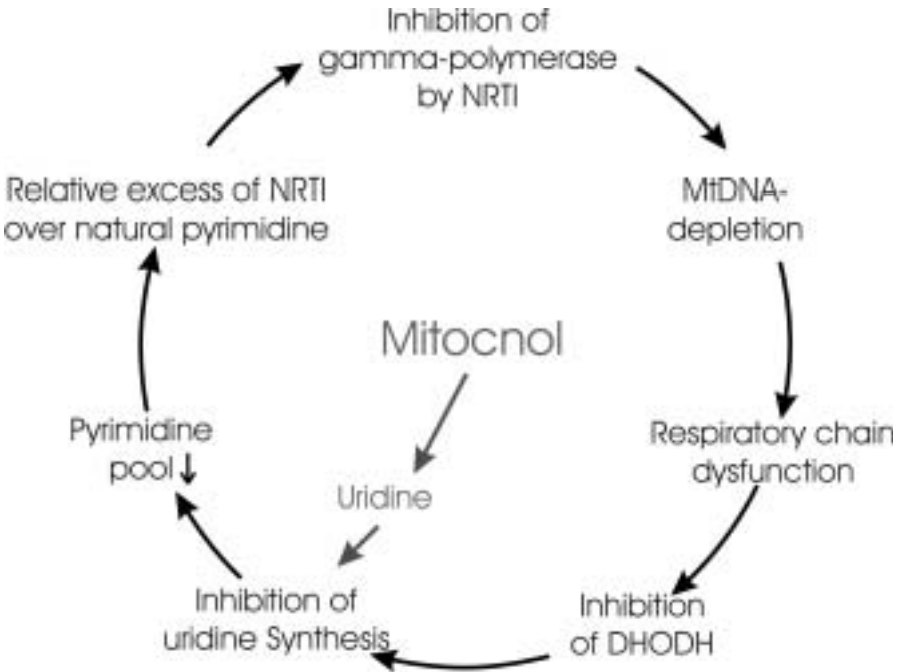
Figure 2: Suggested mechanism of Mitocnol (NucleomaxX[TM]) in the prevention and treatment of mitochondrial toxicity.

The oral substitution of uridine as a pyrimidine precursor is well tolerated by humans, even at high doses (van Groeningen 1986, Kelsen 1997). There are no known negative interactions with the efficacy of the antiretroviral treatment (Sommadossi 1988, Koch 2003). A food supplement called Mitocnol was shown to increase human serum uridine concentrations to levels which are protective in vitro (Venhoff 2004) Clinical data of Mitocnol (also known as NucleomaxX[TM]) have recently become available and are encouraging (Walker 2004b). More information is available at www.mitocnol.com and www.nucleomaxX.com.

 In asymptomatic hyperlactatemia > 5 mmol/l, symptomatic hyperlactatemia and of course in lactic acidosis, all NRTIs should be immediately discontinued (Brinkman 2000). The supplementation of vitamin cocktails has been recommended, but there are no data that demonstrate the efficacy of this intervention with respect to mtDNA-depletion (Walker 1995, Venhoff 2002). Spontaneous normalization of lactate may require several weeks. More mitochondrial friendly NRTIs may then be reintroduced but patients should be monitored closely (Lonergan 2003). The proposed supportive treatment of hyperlactatemia and lactic acidosis is summarized in Table 2.

Table 2. Supportive treatment of lactate elevation in HIV-infected patients (non-pregnant adults)

Lactate 2-5 mmol/L + symptoms	Lactate > 5 mmol/L or lactic acidosis
Discontinue mitochondrial toxins	Discontinue mitochondrial toxins
Consider vitamins and	Intensive care
NucleomaxX (36g TID on 3 consecutive days/ month)	Maintain hemoglobin > 100 g/L
	Avoid vasoconstrictive agents
	Oxygen
	Correct hypoglycemia
	Bicarbonate controversial – 50-100 mmol if pH<7.1
	Coenzyme Q_{10} (100 mg TID)
	Vitamin C (1 g TID)
	Thiamine (Vit. B_1, 100 mg TID)
	Riboflavin (Vit. B_2, 100 mg QD)
	Pyridoxine (Vit. B_6, 60 mg QD)
	L-acetyl carnitine (1 g TID)
	NucleomaxX (36 g TID until lactate <5 mmol/L)

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9. HIV Resistance Testing

Eva Wolf

The development of resistant viral strains is one of the main reasons for failure of antiretroviral therapy. If there is resistance to several drug classes, the number of alternative treatment regimens is limited and the virological success of subsequent therapies, or so-called salvage regimens, may be only short-lived.

The rapid development of resistant variants is due to the high turnover of HIV – approximately 10 million new viral particles are produced every day (Perelson 1996) – and the exceptionally high error rate of HIV reverse transcriptase. This leads to a high mutation rate and constant production of new viral strains, even in the absence of treatment. In the presence of antiretroviral drugs, resistant strains are selected for as the dominant species (Drake 1993).

Assays for resistance testing

There are two established assays for measuring resistance or sensitivity of HIV to specific antiretroviral drugs – the genotypic and the phenotypic resistance tests (Wilson 2003). Both assays are commercially available (examples of genotypic resistance tests are: HIV-1 TrueGene™, *Bayer Healthcare Diagnostics;* ViroSeq™, *Celera Diagnostics/Abbott Laboratories;* virco™Type HIV-1, *Virco*; GenoSure (Plus), *LabCorp;* and GeneSeq, *Virologic*. Phenotypic resistance tests include: Antivirogram™, *Virco*; PhenoSense™, *ViroLogic;* and Phenoscript™, *Viralliance*).

The cost of genotyping ranges from 350 to 500 Euro, depending on the assay and laboratory used. It is approximately twice as high for phenotyping.

The drawback with both methods is that a minimum amount of virus is necessary in order to perform the test. A viral load below 500-1000 copies/ml often does not allow any detection of resistance.

Phenotyping

Phenotypic resistance tests involve direct quantification of drug sensitivity. Viral replication is measured in cell cultures under the selective pressure of increasing concentrations of antiretroviral drugs and is compared to viral replication of wild-type virus.

Drug concentrations are expressed as IC_{50} values (50% inhibitory concentration). The IC_{50} is the concentration of drug required to inhibit viral replication by 50%. The sensitivity of the virus is expressed as the IC_{50} compared to the so-called cut-off value. The cut-off value indicates by which factor the IC_{50} of an HIV isolate can be increased in comparison to that of the wild-type, whilst still being classified as sensitive. The determination of the cut-off is crucial for the interpretation of the results!

Three different cut-offs are currently being used. The *technical cut-off* is a measure of the methodological variability of the assay and is approximately 2.5 fold more than the IC_{50}. The *biological cut-off*, for example the comparative value on an antivirogram, involves the inter-individual variability of virus isolates from ART-naive

HIV patients and is slightly higher than the technical cut-off. The biological cut-off does not, however, allow prediction of the clinical response to a drug. The *clinical cut-off* indicates up to which levels of IC_{50} virological success can still be expected.

For protease inhibitors (PIs), one has to take into account whether or not the respective clinical cut-off values are derived from clinical studies using unboosted or boosted PIs. Through boosting with ritonavir, drug levels may overcome certain levels of resistance.

Disadvantages of phenotypic testing include the lengthy procedure and high expense of the assay.

Genotyping

Genotypic assays are based on the analysis of mutations associated with resistance. These are determined by the direct sequencing of the amplified HIV genome or by specific hybridization techniques with wild-type or mutant oligonucleotides. Genotype tests only detect viral mutants comprising at least 20 to 30% of the total population and provide an indirect measurement of drug resistance. Mutations that are associated with reduced sensitivity have been well-described for most HIV drugs, but the high number of different resistance patterns, which may also contain compensatory mutations, make the determination of the degree of resistance to particular drugs difficult.

The analysis of genotypic resistance patterns is based on the correlation between the geno- and the phenotype. There is data available from *in vitro* studies, clinical observations and duplicate testing, in which genotypically localized mutations were investigated for phenotypic resistance.

One approach to predict phenotype from genotype is the so-called "virtual" phenotype (e.g. VirtualPhenotype™): a genotypic mutation pattern is interpreted with the aid of a large database of samples of paired genotypic and phenotypic data. Genotypes matching the patient's virus are identified through a database search. The IC_{50}'s of these matching viruses are averaged, thus producing the likely phenotype of the patient's virus.

Rule-based interpretation systems are commonly available to aid the interpretation of genotypic mutation patterns. Expert panels (e.g. the French ANRS (National Agency for AIDS Research) AC11 Resistance group) have developed algorithms based on literature and clinical outcomes.

In addition, machine learning approaches such as decision trees and support vector machines (as implemented by the geno2pheno system) can be applied to predict phenotypic drug resistance (Beerenwinkel 2003).

Some of the most important databases for resistance profiles and interpretational systems are available free of charge on the following websites:

Stanford-Database: http://hiv.net/link.php?id=24

Los Alamos-Database: http://hiv.net/link.php?id=25

geno2pheno: http://hiv.net/link.php?id=26

HIV Genotypic Drug Resistance Interpretation – ANRS AC11:

http://hiv.net/link.php?id=138

Commercial suppliers of resistance tests also provide interpretation guidelines for their systems (e.g. VirtualPhenotype™ and virco™Type HIV-1, *Virco*; TruGene™, *Bayer Healthcare Diagnostics*; Retrogram™, *Virology Networks*).

The discussion about genotypic resistance in this chapter focuses on the sequencing of the reverse transcriptase, the protease and the env (gp41) gene and on the respective resistance patterns that emerge with treatment.

Most data are derived from patients with subtype B viruses (representing only 12% of the worldwide HIV-infected population). However, by now, non-subtype B viruses have also been investigated for the development of resistance (van de Vijver 2004). Resistance pathways and patterns may differ in the various subtypes.

Background

Within the nucleotide sequences of the HIV genome, a group of three nucleotides, called a codon, defines a particular amino acid in the protein sequence. Resistance mutations are described using a number, which shows the position of the relevant codon, and two letters: the letter preceding the number corresponds to the amino acid specified by the codon at this position in the wild-type virus; the letter after the number describes the amino acid that is produced from the mutated codon.

Mechanisms of resistance

Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are prodrugs that only become effective after being converted to triphosphates. Nucleotide analogs require only two instead of three phosphorylation steps. Phosphorylated NRTIs compete with naturally occurring dNTPs (deoxynucleotide triphosphates). The incorporation of a phosphorylated NRTI into the proviral DNA blocks further elongation of the proviral DNA and leads to interruption of the chain.

There are two main biochemical mechanisms that lead to NRTI resistance (De Mendoza 2002). *Sterical inhibition* is caused by mutations enabling the reverse transcriptase to recognize structural differences between NRTIs and dNTPs. Incorporation of NRTIs is then prevented in favor of dNTPs (e.g. in the presence of the mutations M184V, Q151M, L74V, or K65R; Naeger 2001, Clavel 2004). *Phosphorylysis* via ATP (adenosine triphosphate) or pyrophosphate leads to the removal of the NRTIs already incorporated in the growing DNA chain. This is the case with the following mutations: M41L, D67N, K70R, L210W, T215Y and K219Q (Meyer 2000). Phosphorylysis leads to cross-resistance between NRTIs, the degree of which may differ between substances (AZT, d4T > ABC > ddC, ddI > 3TC).

Non-nucleoside RT inhibitors (NNRTIs) also inhibit the viral enzyme reverse transcriptase (RT). NNRTIs are small molecules that bind to the hydrophobic pocket close to the catalytic domain of the RT. Mutations at the binding site reduce the affinity of the NNRTI to the RT and thus lead to treatment failure.

Protease inhibitors (PIs) hinder the cleavage of viral precursor gal-pol-polyprotein by the enzyme protease, thereby producing immature, non-infectious viral particles. PI resistance usually develops slowly, as several mutations must first accumulate. This is also referred to as the genetic barrier. For PIs, a distinction is made between *major* (or *primary)* and *minor* (or *secondary) mutations*. *Major mutations* are those,

which are selected for early in the process of resistance to one drug and which are located within the active site of the target enzyme, the HIV protease. They reduce the ability of the protease inhibitor to bind to the enzyme. Major or primary mutations may also lead to reduced activity of the protease. *Minor or secondary mutations* are located outside the active site and usually occur after primary mutations. They compensate for the reduction in viral fitness caused by primary mutations (Johnson 2004). However, the differentiation of primary and secondary mutations can only provide an approximate estimation of the degree of resistance.

Fusion inhibitors differ from NRTIs, NNRTIs and PIs, which block the replication of HIV in the infected cell. Instead, fusion inhibitors prevent HIV from entering its target cells. The first step in cell entry occurs when the HIV envelope glycoprotein, gp120, binds to the CD4-receptor and the chemokine co-receptors, CCR5 or CXCR4, of the target cell. Once gp120 binds to the CD4/chemokine complex, a conformational change in the transmembrane glycoprotein subunit, gp41, enables fusion of the viral and cellular membranes and thereby the entry of HIV into the host cell.

The fusion inhibitor T-20 (enfuvirtide) is a synthetic peptide that inhibits the conformational change of gp41 necessary for fusion of virions to host cells. A single amino acid substitution in gp41 can reduce the efficacy of T-20.

Transmission of resistant HIV strains

The prevalence of mutations already present in treatment-naïve patients differs among demographic regions. In a European multi-centric study with more than 1,600 newly diagnosed HIV-infected patients, the prevalence of primary resistance mutations in 1996 – 2002 was about 10 %. Resistance was primarily observed in recent infections with subtype B (Wensing 2003). Out of 371 isolates of treatment-naïve patients in 40 cities in the U. S., 14% had at least one resistance mutation (Ross 2004). In San Francisco and in a Spanish study, the prevalence of resistance among patients with acute or recent infection was even higher, at 26 % and 19 % respectively (Grant 2003, de Mendoza 2003).

The clinical relevance of primary resistance mutations at the initiation of treatment is apparent. Transmitted resistance mutations can limit further treatment options. However, primary treatment outcomes in ART-naïve patients are not necessarily affected by pre-existing mutations (Hicks 2003, Little 2002, Hanna 2001, Balotta 1999). Under careful consideration of any pre-existing resistance, primary treatment success is often possible. A retrospective study with 202 patients showed that, when initiating treatment without the knowledge of resistance, patients with pre-existing mutations had a slower treatment response and a higher risk of treatment failure (Little 2002).

Clinical studies

The clinical importance of performing resistance testing before making changes to the therapy, has been demonstrated in several prospective, controlled studies, both for genotypic (Durant 1999, Baxter 1999, Tural 2001) and phenotypic resistance testing (Cohen 2000). Patients whose physicians had access to information about any existing mutations before the therapy was changed, usually had more signifi-

cant decreases in the viral load than patients in whom treatment was changed without knowledge of the resistance profile.

Interpretation of genotypic resistance profiles

NRTIs

For several NRTIs, such as lamivudine, and for NNRTIs, a high degree of resistance can develop following only a single mutation (Havlir 1996, Schuurman 1995). For this reason, such drugs should only be used in highly effective regimens. However, the lamivudine-specific mutation, M184V, also reduces viral replication capacity (often referred to as reduced viral fitness) by 40 – 60 % (Sharma 1999, Miller 2003). After 52 weeks with lamivudine monotherapy, the viral load remained 0.5 log below the initial levels despite early development of the M184V mutation (Eron 1995). When compared to treatment interruptions, continuous monotherapy with 3TC delays virological and immunological deterioration (Castagna 2004).

FTC (emtricitabine), an NRTI approved in 2003, has the same resistance pattern as 3TC. Treatment failure is associated with the M184V mutation (van der Horst 2003).

Thymidine analog mutations, mostly referred to as "TAMs", include the mutations M41L, D67N, K70R, L210W, T215Y and K219Q, which were initially observed with zidovudine therapy (Larder 1989). It is now known that these mutations can also be selected for by stavudine (Loveday 1999). Three or more TAMs are associated with a relevant reduction in the sensitivity to stavudine (Shulman 2001, Calvez 2002, Lafeuillade 2003). The term "NAMs" (nucleoside analog mutations) is also used instead of TAMs, as these mutations are associated with cross-resistance to all other nucleoside analogs, with the exception of lamivudine and emtricitabine.

Viral mutants, isolated from patients in whom treatment on zidovudine, lamivudine or abacavir has failed, usually have a measurable phenotypic resistance. Two TAMs result in a 5.5-fold, three TAMs in a 29-fold and four TAMs or more in a >100-fold reduced sensitivity to zidovudine. The use of abacavir in cases where there is a more than 7-fold reduction in sensitivity no longer promises success. This usually requires at least 3 TAMs in addition to the M184V mutation (Harrigan 2000).

The virological response to didanosine depends on the number of specific TAMs. In the Jaguar study with treatment-experienced patients randomized to didanosine add on (n = 110) or ddI-placebo (n = 58), T215Y/F, M41L and L210W – to a lesser extent also D67N und K219Q – were associated with a reduced efficacy (Molina 2003, Marcelin 2004). The virological response was not dependent on the presence of the mutations M184V and K70R.

The development of a measurable phenotypic resistance to stavudine or didanosine has been observed less frequently, and has been more moderate in character (Larder 2001). The clinical cut-off for stavudine lies below the biological cut-off of 1.8. Presumably, this is also the case for didanosine (Shulman 2004). Since most interpretation systems still use biological cut-offs, phenotypic resistance might be underestimated.

Clinical data indicates that tenofovir is effective even in the presence of NAMs such as D67, K70R, T215Y/F or K219Q/E. However, if three or more NAMs include M41L or L210W, a reduced virological response can be expected (Antinou 2003). The lamivudine-associated mutation, M184V, as well as the L74V mutation, observed on didanosine treatment, and the NNRTI-specific mutations, L100I and Y181C, may have an antagonistic effect on the development of resistance (Vandamme 1999).

M184V induces resensitization to zidovudine and stavudine, providing that there are no more than three other zidovudine- or stavudine-associated mutations present (Shafer 1995, Naeger 2001). In one genotypic and phenotypic resistance study consisting of 9000 samples, a combination of M41L, L210W and T215Y decreased the susceptibility to zidovudine by more than 10-fold in 79 % of cases. If the M184V mutation was also present, only 52 % had a more than 10-fold decreased susceptibility to zidovudine (Larder 1999a). The M184V mutation also increases the sensitivity to tenofovir (Miller 2001). In contrast, the presence of M184V plus multiple NAMs or mutations at positions 65, 74 or 115 increased the resistance to didanosine, zalcitabine and abacavir (Harrigan 2000, Lanier 2001).

So-called multidrug resistance (MDR) to all nucleoside analogs – except lamivudine – is established if one of the following combinations occurs: T69SSX, i.e. the T69S mutation plus an insertion of 2 amino acids (SS, SG or SA) between positions 69 and 70, plus a zidovudine-associated mutation or Q151M, plus a further MDR mutation (V75I, F77L or F116Y; Masquelier 2001).

The MDR mutation, Q151M, alone leads to intermediate resistance to zidovudine, stavudine, didanosine, zalcitabine and abacavir (Shafer 2002a). It is relatively uncommon, with a prevalence of less than 5%. In contrast, Q151M does not lead to the loss of activity of tenofovir. Instead, the T69S insertion induces an approximately 20-fold increase in the resistance to tenofovir (Miller 2001).

The insertion T69SSX together with the mutation M184V, as well as the mutation Q151M together with M184V, leads to a 70% reduction in the viral replication capacity (Miller 2003).

The L74V mutation emerges on didanosine or abacavir and leads to a 2-5 fold increase in the resistance to didanosine or zalcitabine (Winters 1997). The loss of efficacy by a factor of around 2-3 for abacavir is not considered clinically relevant and requires further mutations (Tisdale 1997).

The K65R mutation can emerge while on tenofovir, abacavir, didanosine or zalcitabine and leads to an intermediate resistance to tenofovir, abacavir, didanosine, zalcitabine, lamivudine, emtricitabine, and possibly stavudine (Shafer 2002a, Garcia-Lerma 2003). There is no cross-resistance with zidovudine (Miller 2004). Compared to other mutations, K65R has been observed very rarely. In large clinical trials using tenofovir (TDF) within divergent (PI- or NNRTI-containing) treatment regimens, less than 5 % developed the K65R mutation. However, virological failure of triple-NRTI-combinations such as TDF+3TC+ABC or TDF+3TC+DDI was often associated with the development of K65R (Farthing 2003, Gallant 2003, Landman 2003, Jemsek 2004). The main reason for the high failure rate seems to be the low genetic barrier of these regimens: the emergence of K65R induces a loss of sensitivity to all three drugs.

With combinations containing zidovudine, the incidence of K65R is lower. K65R and TAMs represent two antagonistic resistance pathways. K65R increases the sensitivity to zidovudine and induces a resensitization to zidovudine in the presence of TAMs. Vice versa, TAMs reduce the K65R-associated resistance to TDF, ABC, DDI and DDC (Parikh 2004).

As with M184V, the mutation K65R leads to a 40 – 50 % reduction in the viral replication capacity. If both mutations, K65R and M184V, are present, replication capacity is reduced by 70 % (Miller 2003).

The V75T mutation, which is associated with an approximately 5-fold increase in the resistance to stavudine, didanosine and zalcitabine, is only rarely observed (Lacey 1994).

In large patient cohorts, quantitative measurements of sensitivity have shown that up to 29 % of NRTI-experienced patients have a hypersusceptibility to NNRTIs (i.e. a reduction in the inhibitory concentration by a factor of 0.3 - 0.6). A reduction in the zidovudine or lamivudine sensitivity correlated with an increased NNRTI susceptibility (Whitcomb 2000). However, these results have not influenced treatment strategies so far.

NNRTIs

A single mutation can confer a high degree of resistance to one or more NNRTIs. The relatively frequent K103N mutation leads to a 20 to 30-fold increase in resistance to all available NNRTIs (Petropolus 2000). Further use of NNRTIs in the presence of this mutation is therefore not recommended.

V106A leads to a 30-fold increase in nevirapine resistance and intermediate efavirenz resistance. In contrast to subtype B viruses, the mutation V106M is more frequent in subtype C viruses. V106M is associated with high-level resistance not only to nevirapine but also to efavirenz (Grossman 2004).

A98G (which occurs more frequently in subtype C viruses), K101E and V108 lead to low-grade resistance to all available NNRTIs. Intermediate resistance to efavirenz and delavirdine and low-grade resistance to nevirapine result from the L101I mutation. Y181C/I causes a 30-fold increase in nevirapine resistance, and response to efavirenz is only temporary. G190A is associated with a high degree of nevirapine resistance and an intermediate resistance to efavirenz and delavirdine. G190S and Y188C/L/H are mutations resulting in a high degree of nevirapine and efavirenz resistance (Shafer 2002b, De Mendoza 2002).

PIs

The spectrum of PI mutations is very large. Although there is a high degree of cross-resistance between saquinavir, nelfinavir, indinavir and ritonavir, the primary mutations are relatively specific for the individual drugs. If treatment is changed early on to another PI combination, i.e. before the accumulation of several mutations, the subsequent regimen may still be successful.

Polymorphisms at positions 10, 20, 36, 63, 71, 77 and 93 do not lead to resistance per se, but compensate for the reduced protease activity caused by primary mutations (Nijhuis 1999).

The typical nelfinavir-specific resistance profile, with the D30N primary mutation and further secondary mutations, results in only a low degree of cross-resistance to other PIs (Larder 1999a). Virological failure on nelfinavir can also be associated with the emergence of L90M (Craig 1999). In subtype B viruses, treatment with nelfinavir generally leads to the emergence of D30N or M46I plus N88S. In subtype C, G and AE viruses, however, the mutations L90M and I84V occur more frequently. A reason for these different resistance pathways is the prevalence of natural polymorphisms: whereas the polymorphism M36I is present in only 30 % of subtype B viruses, M36I is present in 70 – 100 % of non-B subtypes (Gomes 2002, Grossman 2004, Sugiura 2002, Hackett 2003).

A comparison between the replicative capacities of a virus with a single protease mutation (D30N or L90M) and that of the wild-type virus, demonstrated a significant loss of viral fitness in the presence of the D30N mutation selected by nelfinavir. In contrast, the L90M mutation only leads to a moderate reduction in the replicative capacity, which can be compensated by the frequently occurring L63P polymorphism. Conversely, the L63P mutation hardly influences the reduced replicative capacity of D30N mutants (Martines 1999).

G48V mainly emerges on saquinavir and leads to a 10-fold decrease in the susceptibility to saquinavir – in combination with L90M it results in a high degree (over 100-fold) decreased susceptibility to saquinavir (Jakobson 1995). Yet generally, any 4 mutations out of L10I/R/V, G48V, I54V/L, A71V/T, V77A, V82A, I84V and L90M, are required to reduce the efficacy of RTV-boosted saquinavir (Valer 2002).

V82A(/T/F/S) occurs mainly with indinavir and/or ritonavir – and, in combination with other mutations, leads to cross-resistance to other PIs (Shafer 2002c).

Mutants that frequently develop with indinavir, harboring M46I/L63P/V82T/I84V or L10R/M46I/L63P/V82T/I84V, are just as fit as the wild-type virus.

The resistance pattern of amprenavir and fosamprenavir is different to that of other PIs. In the course of failing treatment with unboosted amprenavir or fosamprenavir, the following mutations have been selected: I54L/M, I50V or V32I plus I47V – often together with the mutation M46I. In a small study, the corresponding virus isolates showed full susceptibility to saquinavir and lopinavir (Chapman 2004, Ross 2003).

In studies with boosted fosamprenavir as part of a first-line regimen, no specific PI-mutations have been selected to date (DeJesus 2004).

A loss of sensitivity to (fos-) amprenavir and all other approved PIs can be anticipated if the mutation I84V (together with other mutations) is present (Snowden 2000, Schmidt 2000, Kempf 2001, Maguire 2002, MacManus 2003). Researchers on a small study, with 49 PI-experienced patients who were switched to boosted amprenavir, developed an algorithm that also included resistance mutations at positions 35, 41, 63 and 82 (Marcelin 2003).

No specific mutations have been described for lopinavir to date. However, the response to lopinavir in PI-experienced patients correlates with the number of any of the following mutations: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, and L90M (Kempf 2000, Kempf 2001). Five mutations or less result in an increase in the IC_{50} by a median factor of 2.7, with 6-7 mutations this factor is 13.5, and with at least 8 mutations it is 44. The good effi-

cacy, even with several mutations, is due to the high plasma levels of boosted lopinavir, which – for the wild-type virus – are >30-fold above the EC_{50}-concentration during the entire dose interval (Prado 2002).

In studies where boosted lopinavir is part of a first-line regimen, no primary PI-mutations have been observed to date. Very few case reports of primary lopinavir resistance have been published. In one patient, virological failure was associated with the occurrence of V82A followed by the mutations V32I, M46M/I and I47A. Phenotyping resulted in high-grade lopinavir resistance. Susceptibility to other PIs, especially saquinavir, was not affected (Parkin 2004). In a second case, with some pre-existing polymorphisms (M36I, L63P and I93L), the mutations 54V and V82A, followed by L33F, were selected (Conradie 2004).

A more recent algorithm to predict lopinavir resistance also includes mutations at novel amino acid positions. Viruses with any 7 mutations out of L10F/I, K20I/M, M46I/L, G48V, I50V, I54A/M/S/T/V, L63T, V82A/F/S, G16E, V32I, L33F, E34Q, K43T, I47V, G48M/V, Q58E, G73T, T74S, L89I/M display approximately a 10-fold increase in IC_{50}. Mutations at positions 50, 54 and 82 particularly affect the phenotypic resistance (Parkin 2003).

A German team recently reported that even with 5 - 10 PI-mutations, which normally confer broad PI-cross-resistance, resensitization is possible. The mutation L76V which is primarily selected for by lopinavir and rarely by amprenavir, is associated with high-grade resistance to lopinavir and (fos-) amprenavir, but can lead to resensitization to atazanavir and saquinavir (Müller 2004).

The resistance profile of atazanavir, an aza-peptidomimetic PI, partly differs to that of other PIs. In patients, in whom first-line treatment with atazanavir failed, the mutation I50L – often combined with A71V – was primarily observed. On the one hand, I50L leads to a loss of sensitivity to atazanavir; on the other hand, I50L leads to an increased susceptibility to all other currently approved PIs. In PI-experienced patients, the I50L mutation was selected for in only one third of patients failing atazanavir (Colonno 2002, Colonno 2003, Colonno 2004).

In PI-experienced patients, at least partial cross-resistance to atazanavir is probable (Snell 2003). The accumulation of PI-mutations such as L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, L90M, and, in particular, I84V, leads to a loss of sensitivity to atazanavir.

For unboosted atazanavir, the threshold for resistance is generally met if 3-4 PI-mutations are present; for boosted atazanavir, resistance is likely with 6 or more mutations (Colonno 2004, Johnson 2004).

Fusion inhibitors

This section focuses on T20-resistance. A loss of efficacy is generally accompanied by the appearance of mutations at positions 36 to 45 in the HR1 (heptad repeat 1) region of gp41, and most frequently with substitutions at positions 36, 38, 40, 42, 43 and 45 (e.g. G36D/E/S, 38A/M/E, Q40H/K/P/R/T, N42T/D/S, N43D/K, or L45M/L). Further mutations in the gp41 genome, which consists of 351 codons, were found at positions 72, 90 and 113 (Sista 2004, Monachetti 2004, Loutfy 2004). In a small study, 6 of 17 patients with virological failure additionally developed the

mutation S138A in the HR2 region of gp41 – mostly combined with a mutation at position 43 in the HR1-region and a range of HR2 sequence changes at polymorphic sites (Xu 2004).

The replication capacity (RC) in the presence of HR1-mutations is markedly reduced when compared to wild type virus with a relative order of RC wild type > N42T > V38A > N42T, N43K ≈ N42T, N43S > V38A, N42D ≈ V38A, N42T (Lu 2004).

New drugs

The following chapter describes the resistance profiles of several newly developed antiretroviral drugs.

- *TMC125 (Etravirine)*, a second generation NNRTI is effective against both wild-type viruses and viruses with NNRTI-mutations such as L100I, K103N, Y188L and/or G190A/S. In 12 of 16 patients who had failed on previous efavirenz- or nevirapine-based regimens, viral load was reduced by more than 0.5 log after 7 days on TMC125 (Gazzard 2002). *In vitro* attempts showed that drug resistance to TMC125 emerges significantly slower than to nevirapine or efavirenz. High-level resistance to TMC125 emerged after 5 in vitro passages. The dominant virus population contained the RT-mutations V179F (a new variant at this position) and Y181C. Further mutations were E138K, Y188H and M230L (Brillant 2004).

- *Capravirine*, a second generation NNRTI, shows activity even in the presence of the classical NNRTI-mutations such as Y181C, which is associated with loss of sensitivity to nevirapine and delavirdine, or K103N, which confers resistance to all currently available NNRTIs (Dezube 1999, Potts 1999). In June 2005, development of this drug was halted by its manufacturer, Pfizer. Early phase 2 studies failed to demonstrate any statistically significant advantages associated with the use of capravirine in people who had tried and failed other NNRTIs in the past.

- *Tipranavir (TPV)*, the first non-peptidic protease inhibitor, shows good efficacy against viruses with multiple PI-mutations. In phenotypic resistance testing, 90% of isolates with a high degree of resistance to ritonavir, saquinavir, indinavir and nelfinavir were still sensitive to tipranavir (Larder 2000). In a study of 41 patients, pre-treated with at least two PIs, TPV/RTV-treatment remained effective after 48 weeks in 35 patients. A more than 10-fold increase in tipranavir resistance occurred in only one patient. The number and type of PI mutations before initiation of TPV/RTV were not associated with virological response. In four out of six isolates with reduced susceptibility, the point mutations, V82T and L33 (I, F, or V), were observed (Schwartz 2002). Although tipranavir has shown activity against viruses with up to 20-25 PI-mutations, a reduced sensitivity can be anticipated if three or more PRAMs (protease inhibitor-resistance associated mutations) – also referred to as UPAMs (universal PI-associated mutations) – are present (Cooper 2003). PRAMs include the following mutations: L33I/V/F, V82A/F/L/T, I84V and L90M. On the other hand, a sufficient short term viral load reduction of 1.2 log was seen after two weeks on treatment with boosted tipranavir plus an optimized backbone in patients

with at least three PRAMs, compared to only 0.2 – 0.4 log with boosted amprenavir, saquinavir or lopinavir plus an optimized backbone (Mayers 2004). Fourteen percent of patients received T-20 in addition. In a pooled analysis of 291 patients in three phase II-trials, the mutations, V82T, V82F and V82L, but not L90M nor V82A, were associated with tripranavir-resistance. The mutations, D30N, I50V and N88D, were associated with an increased susceptibility for tipranavir (Kohlbrenner 2004).

- TMC114, a further non-peptidic protease inhibitor, shows in vitro and in vivo good activity against a broad spectrum of PI resistant viruses. In vitro, resistance emerged slower against TMC114 than against nelfinavir, amprenavir or lopinavir. Resistance against TMC114 came along with the mutations R41T and K70E, which were also associated with a reduction in replication capacity (de Meyer 2002). A preceding failure on lopinavir was not predictive for virological outcome on TMC114 (Koh 2003, Peters 2004).

Summary

With the aid of HIV resistance tests, antiretroviral treatment strategies can be improved. Pharmaco-economic studies have shown that these tests are also cost-effective (Corzillius 2004).

For several years, national and international HIV treatment guidelines have recommended the use of resistance testing (Arastéh 2004, Hirsch 2003, US Department of Health and Human Services 2004, EuroGuidelines Group for HIV Resistance 2001). With some delay, resistance tests are now covered by public health insurance in several countries.

Currently, both genotypic and phenotypic tests show good intra- and inter-assay reliability. However, the interpretation of genotypic resistance profiles has become very complex and requires constant updating of the guidelines. The determination of the thresholds associated with clinically relevant phenotypic drug resistance is crucial for the effective use of phenotypic testing.

Even if treatment failure requires the consideration of other causal factors, such as compliance of the patient, metabolism of drugs and drug levels, resistance testing is of great importance in antiretroviral therapy.

Finally, it needs to be emphasized that – even with the benefit of well-interpreted resistance tests – only experienced HIV practitioners should start, stop or change antiretroviral therapy with respect to the clinical situation and the psycho-social context of the patient.

Resistance Tables

Table 1: Mutations on the reverse transcriptase-gene leading to NRTI resistance (modified from ANRS – AC 11 Groupe Resistance, Oct. 2004, http://hiv.net/link.php?id=138, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2004))

RTI	Resistance mutations
Zidovudine	T215 Y/F (esp. with other TAMs*)
	≥ 3 of the following mutations: M41L, D67N, K70R, L210W, K219Q/E
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
Stavudine	V75M/S/A/T
	T215Y/F (usually in combination with other TAMs*)
	≥ 3 TAMs*
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
Abacavir	≥ (4-) 5 of the following mutations M41L, D67N, L74V, M184V, L210W T215Y/F
	K65R+L74V+115F+ M184V
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
	K65R (resistance possible)
Lamivudine	M184V/I
	T69SSX (insertion)*
	K65R
Emtricitabine	M184V/I
	T69SSX (insertion)*
	K65R
Didanosine	L74V, esp. with T69D/N or TAMs
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
	K65R (partial resistance, esp. with T69D/N)
	T215Y/F and ≥ of the following mutations: M41L, D67N, K70R, L210W, K219Q/E
Zalcitabine	T69D/N/S
	L74V
	Q151M (esp. with A62V/F77L/F116Y)
	T69SSX (insertion)*
	K65R (partial resistance)
	M184V (partial resistance)
Tenofovir DF	T69SSX (insertion)*
	≥ 3 TAMs with M41L or L210W (in part only partial resistance)
	(≥ 3 -) 6 of the following mutations: M41L, E44D, D67N, T69D/N/S, L74V, L210W, T215Y/F
	K65R (partial resistance)

TAMs = thymidine analog mutations

* T69SSX in combination with T215Y/F and other TAMs leads to a high degree of resistance to all NRTIs and tenofovir

Table 2: Mutations on the reverse transcriptase-gene leading to NNRTI resistance (modified from ANRS – AC 11 Groupe Resistance, Oct. 2004, http://hiv.net/link.php?id=138, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2004))

Mutations associated with a high degree of resistance in **bold font**.

NNRTIs	Resistance mutations
Efavirenz	L100I
	K101E
	K103N(H/S/T)
	V106M
	V108I (with other NNRTI-mutations)
	Y181C(I)
	Y188L(C)
	G190S/A (C/E/Q/T/V)
	P225H (with other NNRTI-mutations)
	M230L
Nevirapine	A98G
	L100I
	K101E
	K103N (H/S/T)
	V106A/M
	V108I
	Y181C/I
	Y188C/L/H
	G190A/S (C/E/Q/T/V)
	M230L
Delavirdine	A98G
	L100I
	K101E
	K103N/T
	V106A/M
	Y181C
	Y188C/L
	M230L
	P236L

Table 3: Mutations on the protease-gene leading to PI resistance (modified from ANRS – AC 11 Groupe Resistance, Sept. 2002, http://hiv.net/link.php?id=138, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2004))

PIs	Relevant resistance mutations and patterns	Further mutations associated with resistance*
Indinavir	M46I/L V82A/F/S/T I84A/V when boosted with rito-navir, several mutations are required for a rele-vant loss of sensitivity	L10I/V/F, K20R/M/I, L24I, V32I, M36I, I54V/L, A71V/T, G73S/A, V77I and L90M
Saquinavir	≥ 4 of the following muta-tions: L10I/ R/V, G48V, I54V/L, A71V/T, V77I, V82A, I84V and L90M	G73S, V82F/S/T
Nelfinavir	D30N I84A/V N88S/D L90M	V82A/F/S/T and at least 2 of the follow-ing mutations: L10I, M36I, M46I/L, I54V/L/M/T, A71V/T, V77I
Fosamprenavir	I50V (esp. with M46I/L) V32I plus I47V I54L/M, I84V	
Fosamprena-vir/Ritonavir (700/100 mg BID) or Amprenavir/ Ritonavir (600/100 mg BID)	≥ 6 of the following muta-tions: L10F/I/V, K20M/R, E35D, R41K, I54V/L/M, L63P, V82A/F/T/S, I84V	G73S
Lopinavir/r	≥ 8 of the following muta-tions: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, G73S, V82A/F/T, I84V, L90M	5-7 of the following mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, G73S, V82A/F/T, I84V, L90M
Atazanavir and Atazavir/Ritonavir (300/100 mg QD)	I50L – frequently in com-bination with A71V – ≥ 3-4 of the following mutations for unboosted atazanavir and ≥ 6 of the following mutations for boosted atazanavir: L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, I84V and L90M	I84V, N88S
Tipranavir	≥ 3 of the following muta-tions: L33I/F/V, V82A/F/S/T, I84V, L90M	L10I/V, K20M/L/T, M46I, I54V, V82A/F/L/T

* *Secondary mutations* at positions 10, 20, 36, 63, 71, 77 and 93, which are outside the active site, can increase resistance in the presence of major/primary mutations.

Table 4: Mutations on the env (gp41)-gene leading to T-20 resistance (modified from ANRS – AC 11 Groupe Resistance, Sept. 2002, http://hiv.net/link.php?id=138, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2004))

Fusion inhibitors	Resistance mutations
T-20	G36A/D/E/S/V
	38A/M/E/K/V
	Q40H/K/P/R/T
	N42T/D/S
	N43D/K/H/S
	N42T+N43S
	L44M
	L45M/L/Q

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10. Pregnancy and HIV

Therapy for mothers and prevention for neonates

Mechthild Vocks-Hauck

Perinatal (vertical) HIV infection has become rare since the introduction of antiretroviral transmission prophylaxis and elective cesarean section. While the vertical HIV transmission rate ranged from 15 to 20 % in the United States and Europe at the beginning of the nineties, it now amounts to only a few percent (Connor 1994, European Collaborative Study 2001, Marcollet 2002, Hollwitz 2004). Postpartum HIV infections are avoidable provided that HIV-infected mothers do not breastfeed.

At the same time as transmission prophylaxis was introduced, the treatment of HIV infection changed too. Nowadays, pregnancy is no longer a contraindication for antiretroviral therapy as long as individual maternal circumstances are taken into consideration (Cooper 2002, CDC 2005).

The following chapter summarizes the recommendations of different guidelines for HIV therapy in pregnancy and perinatal chemoprophylaxis.

Reference is made to the European (Coll 2002), German (DAIG), and Austrian AIDS societies (OEAG) (DAIG 2003) as well as American Guidelines (CDC 2005). In addition, detailed and continuously updated recommendations of the US Guidelines are to be found on the HIVATIS website: http://hiv.net/link.php?id=190.

HIV therapy in pregnancy

Starting HIV therapy during pregnancy

The assessment of indications for therapy and drug selection is similar to that in non-pregnant patients (chapter ART 2005). Since the CD4 T-lymphocyte count decreases physiologically by approximately 10-20 % in pregnant patients, the threshold values should be corrected accordingly before treatment is started. Following the recommendations of the German/Austrian guidelines and the CDC, antiretroviral therapy in symptom-free patients should begin

– when CD4 count is below 200–350 cells/mm^3 and/or

– with a viral load of > 50,000–100,000 copies/ml HIV RNA (by RT-PCR or 3.0 version b-DNA).

Before initiating therapy with one of the common combination regimens, a resistance test should be carried out (see chapter on Resistance).

When setting up a treatment plan, it is important that:

1) AZT (Retrovir™) should be one component of the combination – if the result of the resistance test is favorable; and

2) Efavirenz (Sustiva™, Stocrin™) should be avoided because of possible teratogenic effects in the first trimester, and

3) The combination ddI (Videx™) + d4T (Zerit™) should **not** be used because of possible severe mitochondriopathies (Bristol-Myers 2001).

Even if maximum suppression of viral activity is achieved during pregnancy, this is no guarantee for the prevention of HIV transmission. Therefore, prophylaxis to reduce perinatal HIV transmission is also recommended in sufficiently treated pregnant patients (see below in the section Antiretroviral transmission prophylaxis).

Table 1: Special features of anti-HIV therapy in pregnancy

Explanation of risk: Only AZT is approved for perinatal transmission prophylaxis
HIV resistance testing
No efavirenz (Sustiva™) in the first trimester (teratogenicity)
No hydroxyurea (teratogenicity)
No d4T+ddI (Zerit™+Videx™) because of mitochondriopathies
Nevirapine related hepatotoxicity in women with CD4 counts > 250 cells/mm^3
Raised toxicity through combination therapy, therefore monthly controls of lactate, hepatic transaminase levels, viral load, CD4 count
Therapeutic plasma drug level measurement (TDM) and possible dose adaptation

Continuation of treatment during pregnancy

More and more HIV-infected women in whom pregnancy has been diagnosed, have been pretreated with antiretroviral agents.

As a rule, if pregnancy is diagnosed **after** the first trimester, the antiretroviral therapy (ART) should be continued. Interruption of treatment might give rise to an increase in viral load and a possible deterioration of immune function causing the danger of disease progression and, ultimately, of reduction of the immune status of mother and fetus. AZT should be administered as a component of a combination regimen starting at 32 weeks of gestation at the latest.

Women in whom pregnancy is diagnosed **during** the first trimester should be informed about the benefits and risks of treatment in this period. In cases of reduced immune status, in particular, ART could be continued even in the first trimester under careful laboratory and ultrasonic controls. However, substances which can have a toxic effect on the embryo should not be administered during early pregnancy (Table 1).

In other cases − especially if pregnancy is diagnosed very early − the fear of possible embryotoxic effects may lead to an interruption of ART until the end of the first trimester or 13 weeks of gestation. At present, however, there is not enough data available to give an unambiguous recommendation for each individual case. The clinical, immunological and virological situation of the patient and the known or expected effects on the fetus must be considered before making a decision. A continuously updated summary of the current state of knowledge about antiretroviral drugs in pregnancy can be found on the internet at the web address http://hiv.net/link.php?id=189.

If treatment is interrupted, all drugs (NRTIs and PIs) should be withdrawn and re-administered simultaneously in order to prevent development of resistance. Functional monotherapy after discontinuation regimens with NNRTIs should be avoided.

Pharmacokinetic data demonstrate that detectable drug levels may persist up to three weeks after discontinuation of nevirapine. It is recommended either to continue the dual nucleoside analog components for a period of time after nevirapine discontinuation, or to replace nevirapine by a (boosted) PI, or continue the NNRTI including regimen.

Combination therapy for the duration of pregnancy

The suggestion of offering a combination therapy to pregnant patients with a plasma HIV RNA level > 1,000 copies/ml from the second trimester onward is increasingly the subject of discussion in specialized medical literature. Combination therapy is offered to the patient as a means of "better" prevention, even if it is not indicated on the basis of the immunological and virological situation. This approach is based on the assumption that a decrease in viral load translates into a lowering of the transmission risk.

Furthermore, the possibility that a very low viral load might make vaginal deliveries possible is being discussed. With a viral load of less than 1,000 HIV RNA copies/ml, the advantage of cesarean section compared with vaginal delivery can no longer be verified in women receiving HAART (Shapiro 2004). For this reason, in the USA as well as in some European countries such as France and Switzerland, vaginal delivery is considered an option for women on antiretroviral combination therapy whose HIV status at the time of delivery is less than 1,000 copies/ml and/or undetectable and in whom no obstetric complications are expected.

Interruption of treatment

Women who have to discontinue antiretroviral treatment during pregnancy, e.g. because of hyperemesis, should only restart therapy when drug tolerance can be expected. In this case, as in all others, the rule is: withdraw all drugs simultaneously and re-administer them simultaneously, but avoid functional monotherapy if drugs have a long plasma half-life.

Treatment monitoring

In addition to measuring the hemoglobin concentration to exclude an AZT-associated anemia, transaminases for potential hepatic toxicity, and lactate level to detect lactic acidosis early, the CD4 cell number and viral load should be monitored at monthly intervals. If PIs are part of the treatment, it is of particular importance to monitor the blood glucose level closely (Watts 2004).

The diagnosis and therapy of genital infections are essential. Chlamydia infection, trichomoniasis, and bacterial vaginosis correlate with premature delivery. The latter increases the transmission risk, as do premature rupture of membranes and amnion infection syndrome.

Special aspects of HIV therapy in pregnancy

Because embryotoxicity cannot be excluded and hepatic metabolism is altered in pregnancy, some basic rules must be taken into consideration (CDC 2005) (Table 2). It is important to understand that a detectable plasma viral load always necessitates a resistance test. AZT resistance was verified, for example, in the United

States in approximately 17 % of the women during pregnancy (Palumbo 2001), and infected children seem to have an unfavorable prognosis in these cases (The Italian Register for HIV Infection in Children 1999).

Table 2: Antiretroviral agents in pregnancy

Preferred NRTIs (full placenta transfer)	AZT + 3TC AZT + ddI	AZT is metabolized in the placenta; mitochon-driopathy risk: ddC>ddI>d4T>AZT>3TC>ABC>TDF
Alternative NRTIs (full placenta transfer)	d4T + 3TC	No side-effects for PACTG 332
	Abacavir	Only little published experience
	Tenofovir	No published data in humans
	Emtricitabine	Alternative to 3TC, barely any experience
NNRTIs (full placenta transfer)	Nevirapine	General use in perinatal prophylaxis; Hepatic toxicity ↑ in pregnancy; enzyme induc-tion, resistance mutation rate about 20 % even when administered once/twice
PIs (minimal placenta transfer)	Nelfinavir	Frequent use; often replaced by boosted PIs
	Indinavir	Hyperbilirubinemia, nephrotoxicity
	Ritonavir	Poor tolerance, only as booster
	Lopinavir/r	Some experience
	Saquinavir SGC	Low plasma levels, only boosted
	Amprenavir/	Few data
	Fosamprenavir	No experience
	Atazanavir	No experience; indir. hyperbilirubinemia
Entry Inhibitors	T-20	Only case reports

Antiretroviral agents in pregnancy

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Nucleoside analogs cross the placenta and can cause toxic damage not only to the mother but also to the child. The main problems are anemia and, when using combination therapy, lactate acidosis.

On the basis of pregnancies observed to date, it can be maintained that frequently used nucleoside analogs such as AZT, 3TC and d4T, do not increase teratogenicity by more than twofold (Antiretroviral Pregnancy Registry 2004). Most of our experience is related to AZT administration. Follow-ups of more than 20,000 children who had received AZT prophylaxis did not show any serious side effects. An analysis of the causes of death of 223 children, who died within the first five years of life, ruled out drug-related causes (The Perinatal Safety Review Working Group 2000). In other studies, no damage to mitochondrial DNA could be detected (Vigano 2004).

In contrast to these findings, in a prospective study by Barret et al. (2003) on 2,644 ART-exposed non-infected children, neurological symptoms with persistent mito-chondrial dysfunction were reported in 0.26 %. 24 months after combined nucleo-

side exposure, raised lactate values as well as impairment of hematopoeiesis can still be demonstrated in children (Alimenti 2003, Mofenson 2004).

So far, severe mitochondriopathies have been observed at least twice in pregnant women taking a combination therapy of the nucleoside analogues d4T+ddI plus nelfinavir or nevirapine (Sarner 2002). For this reason, the combination d4T+ddI is advised against in pregnancy (Bristol-Myers 2001). Hepatic toxicity with hyperbilirubinemia was described under AZT+3TC+efavirenz therapy. Following the administration of AZT+3TC+nelfinavir, one pregnant woman died of sudden acute liver failure (Hill 2001). Tenofovir did not show any maternal toxicity in animal experiments, but did cause a fetal growth retardation of 13 % as well as a slight decrease in the bone mineral density (Tarantal 2002).

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

In perinatal prevention, nevirapine was employed successfully, particularly in combination with AZT. Perinatal single and two-dose prophylaxis has resulted in the development of drug resistance (Jackson 2000). Toxic liver injury has been described, particularly in the first 18 weeks of longer treatment regimens, especially if the CD4 cell count is more than $250/mm^3$. Therefore frequent controls of efficacy and potential side effects are vital. If a mother gives birth less than two hours following nevirapine administration, or has not received any prior nevirapine at all, the newborn should receive a dose of nevirapine immediately after birth and a further dose after 48-72 hours (Stringer 2003). Because of embryonic toxicity in the rhesus monkey and also in humans, efavirenz is not used during the first trimester of pregnancy and only after the second in cases without an alternative treatment option and if reliable contraception is practiced after delivery. (CDC 2005).

Protease inhibitors (PIs)

The use of protease inhibitors must be monitored carefully, especially in the later stages of pregnancy, due to a possible diabetogenic effect and hepatic toxicity. Presently, most experience relates to nelfinavir (Bryson 2002). However, in combination therapies, toxic side effects have also been described (see above). Indinavir can lead to hyperbilirubinemia and nephrolithiasis; the plasma levels can be lowered (Kosel 2003). As with indinavir, saquinavir should also be boosted with ritonavir in pregnancy (Acosta 2004). Ritonavir and lopinavir plasma levels are also lowered during pregnancy (Scott 2002, Stek 2004).

A Swiss research group suspected that the use of combination therapy might cause an increase in premature birth rate and a higher rate of malformations. Malformations appear to be rather unlikely due to the minimal placental transfer of PIs (Marzolini 2002) and have not been confirmed by other studies either. With regard to the premature birth rate, the available data is inconsistent (increases were reported by the European Collaborative Study 2003, Thorne 2004, Bekerman 2004; no increases were reported by Mandelbrot 2001 and Tuomala 2002).

The serum levels of HCG and estrogens were not reduced in women on PI-therapy (Einstein 2004).

FDA classification for drugs in pregnancy

The FDA has classified the potential toxicity of drugs in pregnancy into the categories A-D. All HIV virustatic agents belong to the categories B-D, since "harmless-

ness through studies on the human being" (= category A) does not apply to any of these drugs.

FDA category B is defined as follows: "Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women". The FDA category B includes ddI, emtricitabine, tenofovir, atazanavir, saquinavir, ritonavir, nelfinavir and enfuvirtide (T-20).

FDA category C is defined as follows: "Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Use in pregnancy should occur only after careful benefit/risk appraisal." All other drugs, which were not mentioned in category B, fall into the FDA category C. Efavirenz falls into category D because of neural tube defects in humans after first trimester exposure.

FDA category D is defined as follows: "Adequate well-controlled or observational studies in pregnant women have demonstrated a risk for the fetus. Nevertheless, the benefits of therapy may outweigh the potential risk." For example, the drug may be acceptable if it is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.

Prevention of perinatal HIV infection

In approximately 75 % of cases, HIV is transmitted prior to, or during the last weeks prior to birth. About 10 % of vertical HIV infections occur before the third trimester, and 10-15 % are caused by breastfeeding.

The probability of HIV transmission to a neonate correlates with the viral load. This also seems to apply to women who are being treated with antiretroviral drugs (Table 3). If the viral load is undetectable using currently available tests, the probability of transmission is indeed extremely low; however, infections have also been described under such circumstances (Ioannidis 2001). Likewise, premature births and premature rupture of membranes are associated with an increased infection risk for the child.

For this reason, reduction in the level of plasma viremia and improvement in the immune status of pregnant women are vital prophylactic measures. If a mother is treated with antiretrovirals, these drugs should continue to be taken, if possible, during delivery at the usual scheduled intervals in order to achieve the maximum effect and to minimize the risk of developing resistance.

Table 3: Known risk factors for perinatal HIV transmission

High maternal viral load
Low CD4 cell count
AIDS in the mother
Vaginal delivery
Premature rupture of membranes of > 4 h
Pre-term infants (< 37 weeks of gestation)
Breastfeeding

For the general prevention of mother-to-child transmission of HIV, pregnant women should be warned not to use intravenous drugs or to have unprotected sex because of the increased risk of HIV transfer in these cases.

In addition to the indicated or optional antiretroviral therapy of the mother, the following rules should be observed regarding chemoprophylaxis

- Antiretroviral prophylaxis before and during delivery
- Elective cesarean section before onset of labor, because vaginal delivery with a viral load of > 1,000 HIV-RNA copies/ml increases the transmission risk
- Postnatal chemoprophylaxis of the infants (post-exposure prophylaxis)
- No breastfeeding

Antiretroviral transmission prophylaxis

Combination prophylaxis

Standard combination antiretroviral regimens for the treatment of HIV infection should be discussed and offered to all pregnant women with HIV regardless of the viral load. They are clearly recommended if the viral load is > 10,000 copies/ml. Combination prophylaxis should be introduced temporarily from 32+0 weeks gestation until immediately after birth (Table 4).

The combination of AZT+3TC is problematic because of the possible development of resistance in the M184 codon (Mandelbrot 2001). Therefore, HAART prophylaxis is increasingly being used.

Table 4: Combination prophylaxis with combination therapy containing AZT in cases with a viral load > 10,000 RNA copies/ml, but otherwise only standard risk

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After resistance testing starting at 32 + 0 weeks gestation:

2 x 250-300 mg AZT
+ a second NRTI
+ plus NNRTI or (boosted) PI (a third NRTI is rarely used)

During delivery (elective cesarean section from 37+0 weeks gestation to week 37 + 6):
IV infusions of AZT as standard prophylaxis:
2 mg/kg i.v. as a "loading dose" for 1 h to approx. 3 h preoperatively
1 mg/kg i.v. intraoperatively until delivery of the infant

In neonates AZT monoprophylaxis:
2 mg/kg orally every 6 hours *within 6 hours* post partum for 2-4 weeks or
1.5 mg/kg i.v. every 6 hours *within 6 hours* post partum for 10 days

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Prophylaxis in ART-pretreated pregnant women

In pregnant women who have already been pretreated with ART, AZT should be integrated into the combination therapy starting at 32+0 weeks gestation. When using combinations containing d4T, this agent should be substituted by another active component because of AZT antagonism.

Procedure in cases with additional pregnancy risks

The pregnancy risks mentioned in Table 5 require an intensified prophylaxis.

Table 5: Risk adapted prophylaxis in the case of complications during pregnancy and/or delivery

Increased risk	
Multigravidity	Mother: AZT monoprophylaxis, or combination therapy, e.g. AZT + 3TC + nevirapine or AZT + 3TC + nelfinavir/(boosted) PI from 29+0 weeks gestation Children: 4 weeks AZT (Table 7)
Early onset of labor	Mother: combination therapy, e.g. AZT + 3TC + nevirapine or AZT + 3TC + nelfinavir/(boosted) PI
Premature infants from 33+0 to 36+6 weeks of gestation or AZT-prophylaxis of < 4 weeks	Mother: in addition to AZT or a combination therapy: nevirapine* Child: dual combination therapy in the neonate (Table 7)
Highly increased risk	
Premature infants < 33+0 weeks of gestation Premature rupture of membranes > 4 h or Amnion infection syndrome or Rise of the viral load towards the end of pregnancy	Mother: In addition to AZT or a combination therapy: nevirapine Child: triple combination prophylaxis (Table 7)
Incision injury of the child or Ingestion of hemorrhagic amniotic fluid or HIV infection diagnosed only post partum	Child: triple combination prophylaxis (Table 7)

* In the case of preceding nevirapine therapy during pregnancy: reduced plasma half-life, therefore: increase nevirapine dose or alternative extension of therapy; after nevirapine monoprophylaxis 20 % resistant strains in the mother. Thus, combination, where appropriate, with 2 NRTIs over 1-3 weeks (for example ddI, AZT+ddI or d4T+ddI; not 3TC because of rapid resistance development) or combination with (boosted) PI is advised.

Intrapartum prophylaxis without antepartum regimens

If the diagnosis of HIV infection is only established at the time of delivery, mother and newborn receive a dual or triple combination prophylaxis with AZT (plus 3TC and/or nevirapine) in cases highly increased risk (high viral load and/or medical complications during delivery).

Simple prophylaxis

Starting at 32 weeks gestation with a time-limited monoprophylaxis with AZT might be an appropriate option for women with HIV-RNA levels well below 10,000 copies/ml (DAIG 2003), and preferably in those with < 1,000 copies/ml (CDC 2005) who wish to restrict exposure of their fetus to antiretroviral drugs (CDC 2005). This regimen is, however, controversial, not only because AZT-resistant viruses have been increasingly identified, but also because the risk of resistance formation under monotherapy cannot be neglected. The use of AZT alone during pregnancy is mentioned for the sake of completeness; in practice, it is now out-dated and hardly ever used.

Table 6: AZT monoprophylaxis in the case of low virus load (clearly less than 10,000 copies/ml), asymptomatic HIV infection and uncomplicated pregnancy course – out-dated because of the risk of development of resistance

After resistance testing starting at 32 + 0 weeks gestation
2 x 250-300 mg AZT per os
During delivery (elective cesarean section from 37+0 up to 37+6 weeks gestation):
2 mg/kg AZT i.v. as "loading dose" over 1 h to approx. 3 h preoperatively
1 mg/kg AZT i.v. intraoperatively until the delivery of the child
In neonates AZT monoprophylaxis:
2 mg/kg AZT orally every 6 hours *within 6 hours* postpartum for 2-4 weeks or
1.5 mg/kg AZT i.v. every 6 hours *within 6 hours* postpartum for 10 days

Treatment during delivery

Elective cesarean section in cases of uncomplicated course of pregnancy

Cesarean section is carried out swiftly by experienced obstetricians prior to the on-set of labor from 37+0 up to 37+6 weeks of gestation using the Misgav-Ladach technique which reduces bleeding. Blunt preparation and the delivery of the child within the intact amniotic sac are considered ideal (Shepherd 2001). A vaginal delivery in women under HAART with undetectable viral load appears to be possible, because no increased vertical transmission rates are found compared to elective cesarean section in pregnant women with a viral load under 1,000 HIV RNA copies/ml (Shapiro 2004). In some European countries such as France and Switzerland and in the United States, women falling into this category can now deliver a child vaginally. In Europe, the percentage of vaginal births increased from 12 % in 1999 to 24 % in 2002 (Thorne 2004).

High-risk pregnancy

Cesarean section in cases of multigravidity should be carried out using the same technique as for a cesarean section in a single pregnancy. In this context, the skill and experience of the operating surgeon are especially important. Cesarean sections

in cases of premature infants are also important to avoid hypoxia in the neonate; the special aspects of chemoprophylaxis have been described above.

In cases with a premature rupture of membranes of less than four hours duration, a section is expedient for prophylactic reasons, providing the clinical situation at that stage of delivery still permits. If the rupture of membranes has lasted more than four hours, the advantage of cesarean section compared to vaginal delivery is no longer expected. Nevertheless, vaginal delivery should occur as swiftly as possible, since the HIV transmission risk increases by about 2 % per hour. The extension of the prophylactic scheme (Table 5 and 7) is important.

Unknown HIV status in cases of known risk

If, at the time of delivery, the HIV status is unknown and the existence of a risk is known, an HIV test can still be offered to the patient (Bulterys 2004). Although specificity is high, it is still considered inadequate. Thus, the combined use of two rapid tests from different manufacturers is ideal. If one of the two tests is negative, there is probably no infection.

Therapy of neonates

Postnatal standard prophylaxis

The postnatal transmission prophylaxis should begin, if possible, within the first 6 hours following birth with oral or – in the case of gastrointestinal symptoms – intravenous AZT prophylaxis. In Germany, the duration of the oral standard pro-phylaxis has been shortened from six to two (to four) weeks (Vocks-Hauck 2001).

Prophylaxis in cases of increased risk (multiple neonates, premature infants)

In multiple-birth neonates without further risk, AZT prophylaxis of four weeks du-ration is recommended. In addition, premature infants receive nevirapine, which is given either once to the mother before delivery and once to the premature infant, or twice postnatally. If maternal nevirapine administration occurs less than an hour before delivery, then the newborn receives its first dose within the first 48 hours (Stringer 2003). If nevirapine was a part of the combination therapy for the mother, the dose is doubled to 4 mg/kg in newborns because of possible enzyme induction. In addition, newborns receive an extended AZT prophylaxis according to the regi-men proposed for premature infants (see below) for the duration of four to six weeks.

Prophylaxis in cases of highly increased transmission risk

In neonates with additional transmission risks, a combination prophylaxis with AZT+3TC is recommended. A strongly increased risk exists, for example, after premature rupture of membranes, in cases of amnion infection syndrome, high viral load prior to delivery, lacking transmission prophylaxis and incision injury of the child during cesarean section, as well as in cases where the amniotic fluid sucked from the gastrointestinal or respiratory tract of the newborn is hemorrhagic.

Table 7: Postnatal antiretroviral prophylaxis/treatment for infants of HIV-positive mothers

Standard risk	Drug	Side effect
Uncomplicated pregnancy and delivery with complete pre- and intrapartal transmission prophylaxis	AZT, within 6 h after birth: 4 x 2 mg/kg orally for 2-4 weeks or 4 x 1.5 mg/kg i.v. for 10 days	Anemia, neutropenia; gastrointestinal irritation
Increased risk		
Multiple birth	AZT orally or i.v., within 6 h after delivery: (where appropriate, switch to oral administration after 10 days i.v.) 4 x 2 mg/kg orally for 4 weeks	see above
Premature labor Pre-term infants 33+0 up to 36+6 weeks of gestation * Early labor Therapy < 4 weeks in cases of low viral load and without obstetric risks	AZT, within 6 h after birth (see above): 4 x 2 mg/kg orally for 4-6 weeks **plus** Single dose of nevirapine of 2 mg/kg after 48-72 hrs. ** AZT dosage in premature infants < 35 weeks of gestation: AZT 2 x 2 mg/kg orally or 2 x 1.5 mg/kg i.v., from 15th day: 3 x 2 mg/kg orally, in infant < 30 weeks of gestation starting from day 29	AZT: see above, particularly anemia Nevirapine: hepatotoxicity, exanthema
Highly increased risk		
Premature infants < 33 + 0 weeks of gestation** Premature ruptured membranes Amniotic infection Elevated viral load at the end of pregnancy, also if no prophylaxis Incision injury of neonate Ingestion of hemorrhagic amniotic fluid HIV infection diagnosed at birth	AZT (dosage see above) for 4-6 weeks **plus** 3TC* 2 x 2 mg/kg for 4-6 weeks **plus** Nevirapine** 2mg/kg as SD within 2h until 48h. If no prenatal nevirapine or later <2hrs, one additional dose 48-72h pp. If prenatal nevirapine, then only one dose after 48-72hrs.	AZT: As above, in combination with 3TC: gastrointestinal SE, mitochondriopathy (lactate) Nevirapine: hepatotoxicity, exanthema (not to be expected after two doses)

*in premature infants, a triple combination prophylaxis is also possible, but use 3TC cautiously, **Nevirapine: if no prenatal administration was possible, first adm. immediately and second adm. within 48-72 hrs postpartum. Dosage adaptation if possible enzyme induction in case of previous maternal NVP therapy; administration of the 1st dose < 2 hrs prepartal 2nd dose immediately after birth and 3rd dose after 48-72 hrs. AF = amniotic fluid; NN = neonate; pp = postpartum; SE = side effect

Table 8: Studies on antiretroviral prophylaxis in neonates

Drug	Average daily dose	Most frequent Side effects	Study
AZT Zidovudin Retrovir™	8 mg/kg in 4 SD; 4 mg/kg in 2 SD in PI*< 35 GW, from 15th day: 6 mg/kg* in 3 SD, in PI < 30 GW from 29th day	Anemia, neutropenia Mitochondriopathy in combination with 3TC	(P)ACTG's 076, 316, 321, 353, 354, 358; HIVNET 012 III PACTG 331(PI)
3TC Lamivudine Epivir™	4 mg/kg in 2 SD in neonates (< 30 days)	GI SE, vomiting, Mitochondriopathy in combination Incompatibility in premature infants	PACTG 358
DdI Didanosine Videx™	100 mg/m^2 in 2 SD from 14th day	Diarrhea, pancreatitis, mitochondriopathy in combination	PACTG 239, 249; HIV-NAT
D4T Stavudine Zerit™	1 mg/kg in 2 SD from birth to 13 days, 2 mg/kg in 2 SD from 14th day	Mitochondriopathy in combination	PACTG 332, 356; HIV-NAT
ABC Abacavir Ziagen™	Up to 4 mg/kg in 2 SD; > 1 month 16 mg/ kg in 2 SD (Study)	Hypersensitivity reaction (no restart), mitochondriopathy, lactic acidosis	PACTG 321
NVP Nevirapine Viramune™	2-4 mg/kg as SD or 120 mg/m^2 for 14 days, thereafter 7-8 mg/kg or 240 mg/m^2 in 2 SD, maximal 400 mg/m^2	Rash, hepatotoxicity, no restart after symptomatic hepatic event	PACTG 316,356, HIVNET 012
NFV Nelfinavir Viracept™	80 mg/kg in 2 SD (Study) from 1 week and 6 weeks; 110-150 mg/kg in 2 or 3 SD at 2 months	GI SE: particularly diarrhea	PACTG 353, 356 PENTA 7
RTV Ritonavir Norvir™	350 mg/m^2 as SD or 700 mg/m^2 in 2 SD for 4 weeks (Study)	Hyperbilirubinemia, gastrointestinal SE	PACTG 354

I=infant; PI = premature infant; MI = mature born infant; SD = single dose; (P)ACTG = (Pediatric) AIDS Clinical Trial Group; HIV-NAT = HIV-Netherlands Australia Thailand Research Collaboration; NN = neonate; GI SE = Gastrointestinal side effect; GW = gestation week

Reference: Except for AZT in mature born infants, the dosage is taken from the studies. Antiretroviral substances that are not approved, should be used in neonates only in the context of studies, if possible.

Procedure in cases of no pre- and intranatal prophylaxis

Combination prophylaxis of AZT+3TC should start within the first 6 to 12 hours after delivery. In addition, a perinatal nevirapine prophylaxis with two-fold administration is recommended.

If HIV infection is discovered only after birth, a combination prophylaxis, begun within 48 hours, seems to be far more effective than a prophylaxis which is initiated only after 3 days (transmission rates 9.2 % vs. 18.4 %, Wade 1998). However, even then, a certain positive effect of AZT prophylaxis as opposed to no prophylaxis can be still be verified (18.4 % vs. 26.6 %) (Table 7).

Further studies for HIV prevention in neonates

A survey of studies about the pharmacokinetics in neonates is given in Table 8 (Ronkavilit 2001 & 2002 among others).

Studies

In order to continuously improve HIV therapy during pregnancy and the chemoprophylaxis of perinatal HIV infection, a thorough documentation of clinical data is necessary. In the US, the "Antiretroviral Pregnancy Registry" is an extensive therapy register that helps to evaluate the potential teratogenicity of antiretrovirals on the basis of "case reports" on HIV-exposed neonates:

Antiretroviral Pregnancy Registry, Research Park, 1011 Ashes Drive, Wilmington NC 28405; Kontakt: http://www.apregistry.com/contact.htm.

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11. Antiretroviral Therapy in Children

Tim Niehues and Hermione Lyall

Characteristics of HIV infection in childhood

Children are not small adults. The HIV infection in childhood is different from the infection in adults with regard to transmission, the natural course of viral dynamics, maturity of the immune system and clinical manifestations. Several factors have to be considered when giving antiretroviral drugs to children: children may already have been exposed to AZT and other drugs in utero, the pharmacokinetics of the drugs are age-dependent and children require special attention to help with adherence.

More than 95 % of children are infected by perinatal transmission of the virus from the mother to the child (vertical infection). Transmission by transfusion, sexual transmission and drug abuse are much less prevalent. In most cases (75-90 %) HIV is transmitted peri- or intrapartum. Only a small proportion of children are infected in utero (10-25 %). Transmission by breastfeeding is important in resource-poor settings, but plays a minor role in developed countries, where breastfeeding by known HIV-infected mothers is strongly discouraged. The increasing knowledge about how HIV is vertically transmitted has led to a highly effective transmission prophylaxis and significant reduction of the transmission rate to less than 2 %. However, new infections in HIV-exposed children still occur

- if the HIV status of the mother is unknown;
- if transmission prophylaxis is incomplete;
- if the mother doesn't have access to transmission prophylaxis during pregnancy.

Without antiretroviral therapy there is a bimodal natural course of vertical HIV infection: in 10-25 % of the children, rapid progression with AIDS-defining symptoms and lethal complications is observed within the first year of life. In 75-90 % there is a much slower disease course with a mean duration of more than 8 years until AIDS-defining symptoms occur. At present, disease progression is mainly influenced by the efficacy of antiretroviral therapy.

At birth, viral load is usually low (< 10,000 copies/ml) and then slowly rises within the first 2 months of life to values above 100,000 copies/ml and only slowly decreases after the age of 4-5 years. These viral dynamics are significantly different from the rapid increase and decrease of the viral load seen in untreated adults within a few months following the acute HIV infection (figure 1).

In children, the higher viral load is associated with the somatic growth of the lymphatic system and the inability of the immature immune system in children to mount an HIV-specific response. When assessing the immune system in infants and children, it is very important to compare the child's CD4 count with the age-appropriate values (e.g. the mean CD4 count for a 6-month-old baby being 3.0×10^9/l). Lymphocyte counts are very high in infancy and decline to adult levels beyond 6 years of age (table 1).
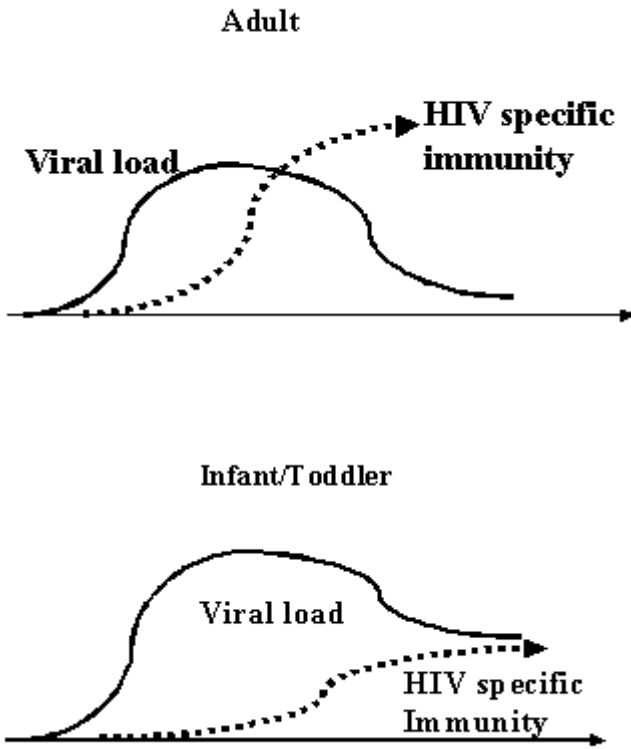
Adult

Infant/Toddler

Figure 1: Differences in the natural course of viral load and anti-HIV immunity between adults and infants/toddlers

The spectrum of clinical manifestations in HIV-infected children is different from that of adults. In adults, typical manifestations of the acute HIV seroconversion illness are: fever, sore throat, lymphadenopathy and a mononucleosis-like disease. HIV seroconversion illness has not been described in perinatally-infected children. Symptomatic disease presenting in childhood has been classified according to severity of symptoms (table 2). In the era of antiretroviral therapy these manifestations have become rare. If antiretroviral therapy in children is effective, opportunistic infections become a rarity. However, in children who newly present with HIV (e.g. if HIV status in the mother is unknown and there was no transmission prophylaxis), opportunistic infections can still be observed.

Table 1. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-Specific CD4 T Cell Count and Percentage [*]

Immune category*	< 12 months		1-5 yrs		6-12 yrs	
	No./mm³	(%)	No./mm³	(%)	No./mm³	(%)
Category 1: No suppression	≥ 1,500	(≥ 25)	≥ 1,000	(≥ 25)	≥ 500	(≥ 25)
Category 2: Moderate suppression	750-1,499	(15-24)	500-999	(15-24)	200-499	(15-24)
Category 3: Severe suppression	< 750	(< 15)	< 500	(< 15)	< 200	(< 15)

[*] Modified from: CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 1994; 43 (No. RR-12): p. 1-10.

Table 2. 1994 Revised HIV Pediatric Classification System: Clinical Categories

Category N: Not Symptomatic

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

Category A: Mildly Symptomatic

Children with **2** or more of the following conditions but none of the conditions listed in categories B and C:
- Lymphadenopathy (> 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

Category B: Moderately Symptomatic

Children who have symptomatic conditions, other than those listed for category A or category C, that are attributed to HIV infection. Examples of conditions in clinical category B include but are not limited to the following:
- Anemia (< 8 gm/dl), neutropenia (< 1,000 cells/mm³), or thrombocytopenia (< 100,000 cells/mm³) persisting > 30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (i.e., thrush) persisting for > 2 months in children aged > 6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before the age of one month
- Diarrhea, recurrent or chronic
- Hepatitis

- Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)
- HSV bronchitis, pneumonitis, or esophagitis with onset before the age of 1 month
- Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Fever lasting > 1 month
- Toxoplasmosis with onset before the age of 1 month
- Varicella, disseminated (i.e., complicated chickenpox)

Category C: Severely Symptomatic

Children who have any condition listed in the 1987 surveillance case definition for acquired immunodeficiency syndrome, with the exception of LIP (which is a category B condition).

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least two culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting > 1 month
- Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements, or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children < 2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for > 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child > 1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain

- Lymphoma, small, non-cleaved cell (Burkitt's), or immunoblastic or large cell
- Lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Pneumocystis carinii pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (non-typhoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at > 1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss > 10 % of baseline, OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child ≥ 1 year of age OR c) < 5th percentile on weight-for-height chart on two consecutive measurements, ≥ 30 days apart PLUS a) chronic diarrhea (i.e., at least two loose stools per day for > 30 days) OR b) documented fever (for ≥ 30 days, intermittent or constant)

[*]Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*, 1994. 43 (No. RR-12): p. 1-10.

Diagnosis of HIV infection < 18 months of age

The detection of anti-HIV antibodies does not prove an infection in infants. High titers of anti-HIV IgG are transferred transplacentally from mother to child. Maternal antibodies can be detected in children up to the age of 18 months. Therefore a direct method of detecting HIV is necessary. Identification by PCR is highly sensitive and specific. Detection of HIV can be achieved within the first 48 hours after birth in 38 % of infected children, and within the first 2 weeks in 93 % of children (Dunn 1995). Once a positive HIV PCR is found, a second independent blood sample should soon be taken for repeat PCR analysis. As diverse subtypes of HIV exist, it is advised to test paired samples from mother and infant by HIV DNA PCR. If the mothers virus is not amplified by the primer set used, then another set or another test can be used to avoid a false negative result in the infant. Cord blood is not useful for the diagnosis because maternal cells may be present and may cause a false positive test result. In general, the disappearance of maternal IgG antibodies to HIV needs to be documented before HIV infection can be definitely excluded in the HIV-exposed child.

Diagnosis of HIV infection > 18 months of age

HIV infection is diagnosed in an analogous way to adults (see chapter "HIV Testing").

When to initiate antiretroviral therapy

Keep the following facts in mind before starting antiretroviral therapy in children:

- Treatment of HIV-infected children is usually not an emergency.
- Take as much time as needed to decide whether to start with HAART or not.

Commencing antiretroviral therapy too early risks possible long-term side effects and early exhaustion of the limited supply of antiretroviral drugs that can be safely used in children. Therefore, many experts defer treatment in asymptomatic children with a low viral load and without immunodeficiency. The indication for treatment is based on CD4 count, viral load and clinical criteria.

Table 3. PENTA recommendations on when to start antiretroviral therapy
http://www.ctu.mrc.ac.uk/penta/guidelines.htm

Infants
1. Clinical
Start all infants with CDC stage B or C (AIDS) disease.
2. Surrogate marker
Start all infants with CD4 % < 25–35 %.
Strongly consider starting with a VL > 1 million copies/ml.
Many experts treat all infants, whether symptomatic or not.
Children aged 1–3 years
1. Clinical
Start all children with stage C disease.
2. Surrogate marker
Start all children with a CD4 % < 20 %.
Strongly consider starting with a VL > 250,000 copies/ml.
Children aged 4–8 years
1. Clinical
Start all children with stage C disease.
2. Surrogate marker data
Start all children with a CD4 % < 15 %.
Strongly consider starting with a VL > 250,000 copies/ml.
Children aged 9–12 years
1. Clinical
Start all children with stage C disease.
2. Surrogate marker data
Start all children with CD4 < 15 %, but with less urgency than in a younger child.
Strongly consider starting with a VL > 250,000 copies/ml.
Adolescents aged 13–17 years
1. Clinical
Start all adolescents with stage C disease.
2. Surrogate marker data
Start all adolescents with an absolute CD4 count between 200 and 350 cells/mm^3.

In a meta analysis of 17 studies (Dunn D; HIV Paediatric Prognostic Markers Collaborative Study Group; HPPMC cohort) with 3,941 children who received no ther-

apy or AZT monotherapy, viral load and CD4 cell counts proved to be independent prognostic markers for the end stage, AIDS or death (Dunn 2003). From this large cohort of children, a computer program has been generated which can be used to give the risk of progression to AIDS or death within 6/12 months according to the age and either CD4 count or viral load in the child ("PENTA Calculator" http://www.ctu.mrc.ac.uk/penta/hppmcs/calcProb.htm). Updated guidelines for treatment from Europe and the United States were published in 2004 (PENTA 2004 http://www.ctu.mrc.ac.uk/penta/; http://aidsinfo.nih.gov/guidelines/). The PENTA guidelines use the HPPMC cohort data to optimize timing of starting treatment at different ages, according to CD4 count / viral load, in order to maintain the 1-year risk of progression to AIDS at < 10 % and death at < 5 %. (tables 3, 4).

Table 4. US Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (http://aidsinfo.nih.gov/guidelines);

A. Indications for Initiation of antiretroviral therapy in children < 12 months of age

Clinical Category	CD4 Cell Percentage	Plasma HIV RNA Copy Number [1]	Recommendation
Symptomatic (Clinical category A, OR B, or C)	< 25 % (Immune category 2 or 3)	Any Value	Treat
Asymptomatic (Clinical category N) AND	≥ 25 % (Immune category 1)	Any Value	Consider Treatment [2]

[1] Plasma HIV RNA levels are higher in HIV-infected infants than older infected children and adults. Because overall HIV RNA levels are high and overlap between infants who have and those who do not have rapid disease progression, HIV RNA levels may be difficult to interpret in infants < 12 months of age.

[2] Because HIV infection progresses more rapidly in infants than older children or adults, some experts would treat all HIV-infected infants < 6 months or < 12 months of age, regardless of clinical, immunologic or virologic parameters.

B. Indications for Initiation of Antiretroviral Therapy in Children ≥ 1 Year of Age

Clinical Category		CD4+ Cell Percentage		Plasma HIV RNA Copy Number	Recommendation
AIDS (C)	OR	< 15 % (Immune Category 3)		Any value	Treat
Mild-Moderate Symptoms (A or B)	OR	15-25 % [1] (Immune Category 2)	OR	≥ 100,000 copies/ml [2]	Consider treatment
Asymptomatic (N)	AND	> 25 % (Immune Category 1)	AND	< 100,000 copies/ml [2]	Many experts would defer therapy and closely monitor clinical, immune, and viral parameters

[1] Many experts would initiate therapy if CD4 cell percentage is between 15 to 20 %, and defer therapy with increased monitoring frequency in children with CD4 cell percentage 21 % to 25 %.

[2] There is controversy among pediatric HIV experts regarding the plasma HIV RNA threshold warranting consideration of therapy in children in the absence of clinical or immune abnormalities; some experts would consider initiation of therapy in asymptomatic children if plasma HIV RNA levels were between 50,000 to 100,000 copies/ml.

General considerations for treatment of HIV-infected children

The treatment of children with antiretroviral drugs is becoming increasingly complex. A successful treatment requires an interdisciplinary approach to the children and their families.
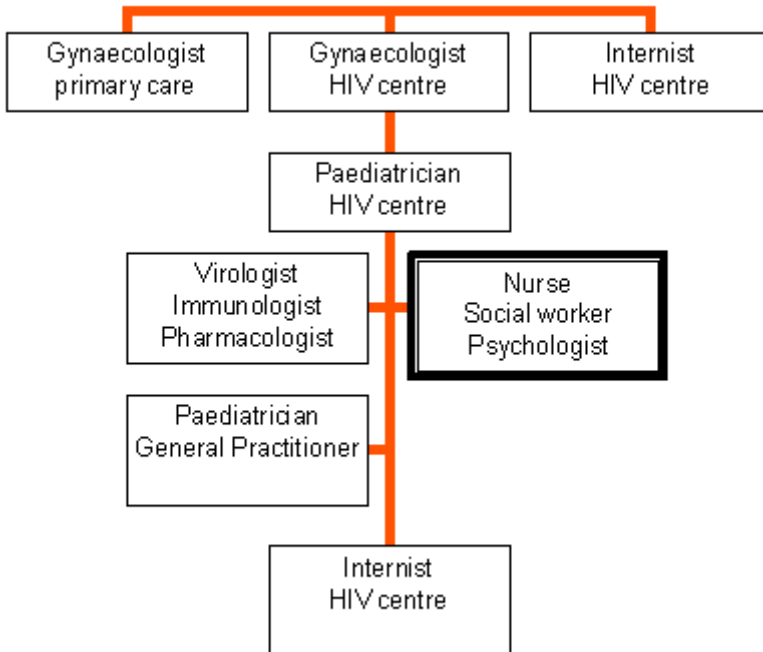

Figure 2: Interdisciplinary care for children and families who are affected by HIV

Antiretroviral therapy cannot be successful without good adherence to treatment. In the prospective PACTG 377, trial adherence was defined as having not missed a single medication dose over the last 3 days. According to this definition, only 70 % of children were found to be adherent (125 children within an observation period of 48 weeks; Van Dyke 2002). These data show that continuous motivation of children and their care providers is of high importance. The modalities of the daily intake of the medication need to be discussed in detail and adjusted to the daily and weekly routines of the family activities. Clear treatment goals need to be set, e.g. 90 % of the prescribed doses. Education of the patient and the family regarding the antiretroviral drugs is necessary. Adherence is particularly problematic in adolescence. In this age group, adherence often needs a close follow up including other health care professions such as psychologists and social workers. Sometimes a brief period of hospitalization at the start of antiretroviral therapy is useful to educate the patient and access the tolerability of the treatment regimen.

Pharmacologic drug monitoring of the antiretroviral drugs allows for assessment of adherence. Moreover, plasma levels can give information about antiretroviral efficacy, the individual pharmacokinetics in the patient and potential toxicity of the drug. There are very little pediatric data on the pharmacokinetics of antiretroviral drugs and children can be included in the current PENTA14 trial (http://www.pentatrials.org). It appears useful to carry out plasma levels to exclude dosage that is too low and to prevent toxicity.

Obviously, regular physical examination and laboratory tests are necessary to monitor antiretroviral therapy in HIV children. Only a physician who is experienced in the care of HIV-infected children and the use of antiretroviral therapy will be able to provide adequate care. Before medication is initiated or changed, the decision should always be based on at least 2 independent blood samples. Infections and vaccinations may influence viral load and CD4 cell count. Therefore, it is not recommended to base decisions on data that have been gathered within 14 days of an infection or vaccination.

Strategy

At present, eradication of HIV cannot be achieved by the existing therapy. In some children, viral load remains below detection level for years and subsequently there are no more HIV-specific antibodies detectable in these children. Even in these children, ultra-sensitive assays can still detect HIV (Persaud 2004). Therefore risks and benefits of antiretroviral therapy have to be balanced in each child. Interruption or incomplete adherence may cause more harm than deferring the therapy. The decision to start antiretroviral therapy has fundamental consequences for the children and families. From this point on, it usually means that children need to take the medication for life. Structured treatment interruptions have not been tested in childhood and adolescence in controlled studies. A retrospective analysis of unplanned treatment interruptions in children demonstrated a significant decline of CD4 percentages by 6.6 % per year (Gibb 2004). PENTA (**P**ediatric **E**uropean **N**etwork for **T**reatment of **A**IDS) is currently offering a pediatric study for CD4-guided treatment interruptions (PENTA11).

Table 5 shows the current treatment concept for choosing antiretroviral drug combinations. In the American PACTG 338-study on 297 children, it has been shown that a PI-containing combination is more effective than a dual combination of 2 NRTI's. It appears useful to start with a combination that includes two substance classes (2NRTI's + PI or 2 NRTI's + NNRTI) in order to spare one or two substance classes for future change of antiretroviral therapy. If there is not full viral suppression on treatment, development of cross-resistance to NNRTIs and PIs is very likely. Therefore, sparing substance classes may be useful for a better long-term efficacy. However, in the recent PACTG 256 study, an aggressive approach with inclusion of 3 substance classes (NRTI + NNRTI + PI) led to a highly effective and long-lasting virus load reduction (72 % of patients over 4 years), especially if therapy was started at an early age (< 3 months) (Luzuriaga 2004). Because of small patient numbers in childhood and adolescence it is highly recommended to include all children who receive antiretroviral therapy in multicenter clinical trials (e. g. PENTA, http://www.pentatrials.org, Tel. Dr. Diana Gibb ++ 44 20 7670 4709; Lynda Harper ++ 44 20 7670 4791). Currently the PENPACT 1 study is pro-

ceeding with participation both of the PENTA and the PACTG group. In this trial one of the questions that will be answered is whether initial therapy in children is more effective with 2 NRTI + PI or with 2 NRTI + NNRTI.

Table 5. Treatment concept in HIV-infected children

Regime	Recommendation
NRTI* 1 + NRTI 2 + PI** or NRTI 1 + NRTI 2 +NNRTI ***	Include children in multicenter clinical trials (e.g. PENPACT 1)

* = Nucleoside Reverse Transcriptase Inhibitor (Zidovudine (AZT), Didanosine (DDI), Lamivudine (3TC), Stavudine (D4T), Abacavir (ABC), Emtricitabine (FTV), Tenofovir).

** = Protease Inhibitor (Nelfinavir (NFV), Lopinavir/r (LPV/RTV), Atazanavir (ATV) Indinavir (IDV), Amprenavir (APV). Ritonavir as booster drug).

*** = Non-nucleoside Reverse Transcriptase Inhibitor (Nevirapine (NVP), Efavirenz (EFV)).

In the placebo-controlled American CNAA3006 study on children who had already received antiretroviral therapy, a triple NRTI therapy was shown to be more effective than a therapy consisting of 2 NRTI's (Saez-Llorens 2001). However, this study was carried out on children who were already on antiretroviral therapy and were not treatment naive. Data in adults suggest that a triple NRTI strategy is less effective than a therapy combination including PI or NNRTI. At present there are no data on triple NRTI therapy as initial therapy for children.

Classes of Antiretrovirals

In the following paragraphs the different antiretroviral classes that are currently used in children are introduced with emphasis on Pediatric issues and in particular daily dosage and side effects. All drugs can lead to nausea, vomiting, fever, headache, diarrhea, rash and anorexia.

Nucleos(t)ide analog reverse transcriptase inhibitors (NRTIs)

NRTIs have been used for over 15 years in the treatment of HIV-infected children. The combination of 2 NRTIs as part of HAART is effective and well tolerated. Severe side effects are rare but potentially life-threatening, such as lactic acidosis and hepatic steatosis. Other side effects are neuromuscular dysfunction, cardiomyopathy, pancytopenia, pancreatitis and neuropathy. All of these effects are probably related to the reduction of mitochondrial toxicity by NRTIs. Due to pharmacologic and antiviral antagonism as well as synergistic neurotoxicity, the following combinations are not recommended: AZT + D4T, DDI +D4T (not first line), DDC + DDI, D4T + DDC and 3TC + DDC. The less mitochondrially toxic NRTI's include 3TC, ABC, FTC and TDF.

Zidovudine (ZDV, AZT, Retrovir™) is available as syrup, capsules, tablets and concentrate for injection or intravenous infusion. Dosage is 180 mg/m² orally every 12 hours. Maximum dosage is 300 mg every 12 hours.

Lamivudine (3TC, Epivir™) is available as oral solution and tablets. Dosage is 4 mg/kg every 12 hours, maximum dosage is 150 mg every 12 hours. In older children and adolescents (> 35 kg body weight) combination with zidovudine (Combivir™) can be used and daily pill burden reduced. In adults, lamivudine shows antiviral activity against hepatitis B virus. Therefore, it is useful to include lamivudine in the HAART regimen for children with chronic hepatitis B. A once-daily regimen in combination with abacavir has been shown to be as effective as twice daily (PENTA 13 Trial).

Stavudine (D4T, Zerit™) is available as oral solution and capsules. Dosage is 1 mg/kg every 12 hours. Maximum dosage is 40 mg every 12 hours. D4T is not recommended for first-line therapy as it has a high risk of causing lipoatrophy (see below).

Didanosine (DDI, Dideoxyinosine, Videx™) is available as oral solution and tablets. Dosage is 200 mg/m^2 once daily. Maximum dosage is 400 mg (body weight $\geq$ 60 kg) or 250 mg (body weight < 60 kg).

Abacavir (ABC, Ziagen™) is available as oral solution and tablets. Dosage is 8 mg/kg every 12 hours, maximum dosage is 300 mg twice daily or 600 mg once daily. In the PENTA 5 trial, ABC-containing regimens showed a better efficacy regarding viral load suppression than combinations containing AZT and 3TC. There is a potential risk of a fatal hypersensitivity reaction. If ABC hypersensitivity occurs and the drug is stopped, it should not be restarted as, rarely, deaths have occurred in adults upon rechallenge.

Emtricitabine (FTC, Emtriva™) is available as capsules. In a phase I study, 6 mg/kg has been suggested as dosage (Wang 2004). The administration of capsules results in a 20 % higher plasma level. Emtricitabine can be given once daily. Maximum dosage is 200 mg once daily.

Tenofovir (TDF, Viread™) is only available as tablets. In 18 children and adolescents between 6 and 16 years of age, a dosage of 200 mg/m² once daily was well tolerated (Hazra 2004). There are no controlled trials regarding the efficacy of tenofovir in children.

Non nucleoside reverse transcriptase inhibitors (NNRTIs)

These drugs have a low genetic barrier to resistance. Within a few weeks suboptimal dosing or adherence can lead to cross-class resistance mutations affecting all available NNRTIs. NNRTIs exist in palatable liquid preparations which are easier for children to tolerate than the liquid PI solutions.

Efavirenz (EFV, Sustiva™) is available as capsules and oral solution. Dosage is 200 mg (body weight 10-15 kg), 250 mg (15-20 kg), 300 mg (20-25 kg), 350 mg (25-33 kg), 400 mg (33-40 kg), 600 mg (> 40 kg) once daily. Maximum dosage is 600 mg once daily. When using the solution, a 20 % higher dosage than for capsules is necessary. Central nervous system symptoms (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) appear to be more common in adults than in children. Skin rash is observed in < 10 % of the patients and is rarely severe, it usually disappears within days despite continuation of efavirenz.

Nevirapine (NVP, Viramune™) is available as tablets and suspension. Dosage is 150 mg/m^2 once daily for 14 days, followed by 150 mg/m^2 every 12 hours, if liver function tests are normal. In a retrospective analysis, once-daily application – 300 mg/m^2 after week 2 – was as effective as twice-daily (Verweel 2003). The most common side effect of nevirapine, in up to 16 % of children during the first weeks of treatment, is a skin rash, which may be quite severe (8 %) and require hospitalization. Life-threatening complications (Steven Johnson Syndrome, toxic epidermal necrolysis) are rare. Hepatotoxicity may also occur, and fatal cases have been reported in adults, but this appears to be less common in children.

Protease inhibitors (PIs)

All protease inhibitors can be used in combination with 2 NRTIs. PIs differ from each other in respect to their tolerability and side effects. As with adults, dyslipidemia is associated with the use of protease inhibitors (Lainka 2002). It includes elevated total cholesterol, triglycerides (TG), and low density lipoprotein cholesterol (LDL-c) and decreases in high density lipoprotein cholesterol (HDL-c) In lipodystrophy, there is a loss of subcutaneous fat (lipoatrophy) and/or a deposition of fat tissue subcutaneously or in visceral stores (lipohypertrophy) including the presence of dorsocervical fat accumulation ("buffalo hump") and increased waist-to-hip ratio. Lipoatrophy is marked by thinning of subcutaneous fat in the face, buttocks, and extremities associated with a prominent appearance of peripheral veins. The body habitus changes usually occur gradually over months to years. The exact prevalence of lipodystrophy in children is unknown and there are no clear diagnostic criteria. Lipodystrophy and dyslipidemia coexist, their interconnection is unclear. Other substance classes such as NRTIs (e.g. stavudine) and NNRTIs (efavirenz, not nevirapine) may also play a role in the pathogenesis of lipodystrophy. Insulin resistance is another side effect which may present with or without fasting hyperglycemia, with new onset diabetes mellitus and exacerbations of pre-existing diabetes. Moreover, PIs may influence bone mineral density and metabolism (Mora 2004). Taken together, the long-term consequences of PI-containing antiretroviral therapy for growth and development of the child are currently not known.

Lopinavir / Ritonavir (LPV/r, Kaletra™) is a co-formulation of lopinavir and ritonavir, in which ritonavir acts as a pharmacokinetic enhancer (booster). It is available as capsules and oral solution. In therapy-naive and -experienced children, the combination of LPV/r and NRTI or NNRTI shows a high efficacy (Saez-Llorens 2003, Fraaij 2004). The dosage is 13 mg/kg lopinavir/3.25 mg/kg ritonavir twice daily (bodyweight 7 - < 15 kg), 11 mg/2.75 mg (15-50 kg), 533 mg/133 mg (> 50 kg). The dosage of LPV/r may need to be increased by up to 30 % when combined with a NNRTI, and therapeutic drug monitoring is useful in this situation.

Nelfinavir (NFV, Viracept™) is available as tablets. It is well tolerated in most children. The dosage is 55 mg/kg every 12 hours, in infants < 3 months, 75 mg/kg every 12 hours. Maximum dosage is 1,250 mg every 12 hours. Some older children require 1,500 mg every 12 hours, more than the adult dose. Therapeutic drug monitoring is useful. In the PENTA 7 trial in newborns and infants below the age of 3 months, combination of nelfinavir with D4T and DDI was poorly absorbed with poor plasma levels and consequently poor viral load suppression (Aboulker 2004). The most common side effect is diarrhea, which rarely causes discontinuation of the

drug. To facilitate the administration of nelfinavir, the tablets can be crushed or readily dissolved in water. In the PENTA 5 study, nelfinavir powder was only poorly tolerated.

Amprenavir (APV, Agenerase™) is not recommended for children < 4 years of age. It is available as capsules and oral solution. Dosage is 20 mg/kg every 12 hours, for the oral solution 22.5 mg/kg every 12 hours. The maximum dosage is 1,200 mg every 12 hours. The dosage of amprenavir needs to be increased by 30 % in case of combination with NNRTI. In 5 children, who were intensively pretreated, amprenavir in combination with delavirdine showed good efficacy (Engelhorn 2004). The most common side effects are nausea, vomiting, diarrhea and headaches. The prodrug of amprenavir is fosamprenavir, which is currently used for antiretroviral therapy in adults at a dosage of 1,400 mg twice daily (without ritonavir) or 1,400 mg + ritonavir 200 mg once daily. There is no pediatric dose. The drug is currently under investigation for use in HIV-infected children.

Ritonavir (RTV, Norvir™) is available as oral solution or capsules. However, most children do not tolerate the taste of the oral solution. The dosage is 350-400 mg/m² every 12 hours, maximum dosage 600 mg every 12 hours. Today, ritonavir is almost exclusively used as a drug to boost other protease inhibitors, and for this purpose, the dosage is 75 mg/m² every 12 hours.

Indinavir (IDV, Crixivan™) is available as capsules. Dosage is 500 mg/m² every 12 hours in combination with ritonavir 750 mg/m² every 12 hours. Side effects include nephrolithiasis, especially at high plasma levels.

Saquinavir (SQV, Invirase™ hard gel capsule or Fortovase™ softgel capsule). Dosage in children is unknown. There is very limited experience with 50 mg/kg every 12 hours. Saquinavir should only be used in combination with ritonavir because of poor bioavailability.

Atazanavir (ATV, Reyataz™) is available as capsules. Atazanavir could be an interesting drug for use in children in the future, because of its once-daily application and lower incidence of dyslipidemia. At present, there is no approved dosage for children. Phase I and II studies are underway. Some patients develop jaundice.

Fusion inhibitors

Fusion inhibitors represent a new antiretroviral class. They inhibit the fusion of the virus with the target cell. In adults, randomized studies have proven an effect of T-20 (the first drug of this substance class) within salvage treatment protocols.

Enfuvirtide (T-20, Fuzeon™) can be used in children older than 6 years of age. The drug is injected subcutaneously at a dosage of 2 mg/kg every 12 hours. A study with 14 children showed no severe side effects, but after a 2-year treatment duration only 6 out of 14 children stayed on this therapy (Church 2004). Reasons for treatment discontinuations were aversion to injections, local injection site reactions, inefficient viral load suppression, thrombocytopenia and edema. There are no controlled studies on the use of T-20 in children.

Drug interaction

There are a great number of interactions, which may complicate antiretroviral therapy when it is co-administered with other drugs. In particular, tuberculosis and atypical mycobacterial treatment may interact with ART, so close monitoring and expert advice should be sought.

Monitoring of therapy efficacy and therapy failure

A good treatment response is documented by a permanent suppression of the viral load below the detection limit. Not all children achieve complete viral suppression, and development of resistance is not uncommon due to the selection pressure of the anti-HIV immune response as well as antiretroviral therapy. There is no commonly used definition of treatment failure in children treated with antiretroviral drugs. Therefore, it is also not certain when to change antiretroviral therapy. In the PENPACT 1 study, this important question is being addressed: children are randomized to change a failing treatment at either low or high viral rebound (> 1,000 or > 30,000 copies/ml) Alternatively, therapy failure can be defined by a decrease in CD4 cell counts, e.g. a decrease by at least 30 % of the absolute CD4 cell number in less than 6 months. In children with relatively low CD4 cell counts of less than 15 %, a decrease by more than 5 % may already be significant for therapy failure. The use of clinical criteria, such as toxicity of the drugs, a progression within the CDC classification, an increased susceptibility to infections, encephalopathy and failure to thrive, may all indicate treatment failure.

The most common cause of treatment failure is insufficient adherence, which can be found in 25-30 % of children. Assessment of adherence may be difficult as questionnaires may not be reliable. Determination of plasma levels and resistance tests (e.g. reoccurrence of wild type) are other options to assess adherence and monitor antiretroviral therapy more effectively.

Change of therapy

There are no systematic data on how and when to change therapy in HIV-infected children. The suppression of viral load that can be reached by a second or third regimen depends on the preceding therapy and the resistance status. The longer and more intensive pretreatment has been, the lower the viral load reduction that can be expected. When a new antiretroviral drug combination is introduced, the age of the child, the availability of appropriate formulations (e.g. solution for infants), side effects and interactions with other drugs are all taken into account. At present, it is unclear whether dyslipidemia and lipodystrophy can be influenced by a change from a PI-containing regimen to an NNRTI-containing HAART (McComsey 2003). In adults, randomized and prospective trials have shown that a change of antiretroviral therapy guided by resistance tests leads to a better treatment response. In children there is a smaller prospective study (Englund 2004).

Usually, the initial treatment regimen contains a double NRTI backbone (e.g. AZT + 3TC). When changing therapy, it appears useful to introduce a backbone with two new NRTI's and one new substance class into the treatment combination. A mega-HAART therapy combining five to six antiretroviral drugs has not been systemati-

cally investigated in children. In single cases, it may be useful to introduce up to five drugs if treatment failure has occurred despite multiple different drug regimens.

Conclusion

In many aspects, HIV infection in children is different from HIV infection in adults. The ongoing growth and development of children, their viral dynamics and immaturity of the immune system result in a different response to HIV in children compared to adults. This has important consequences for diagnosis and treatment of HIV in children. The aim of the therapy is to reach maximum efficacy while avoiding long-term side effects. Sustained success in the treatment of children with HIV infection can be achieved by:

- a multidisciplinary approach;
- standardized treatment protocols;
- participation in multicenter trials;
- development of new drugs and strategies for children.

In developed countries, the clinical picture of HIV infection in children has now changed from an often fatal to a treatable chronic infection. This picture is entirely different in developing countries, where the majority of children do not have access to HAART. According to the WHO, more than 500,000 children died from HIV infection or its sequelae in the year 2004.

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Part 3

AIDS

12.   Opportunistic Infections (OIs)

Christian Hoffmann

OIs in the HAART era

In Western industrialized countries, many OIs have become rare today. This is particularly true for those infections that are associated with severe immunodeficiency, such as CMV and MAC disease. The incidence of these OIs has now been reduced to less than one tenth of their frequency in the pre-HAART era. However, HAART has not only lowered the incidence, but also changed the course of OIs quite considerably. While survival times after the first AIDS illness were previously two to three years at most, many patients now live with AIDS for ten years and longer. Our own study of around 150 patients with cerebral toxoplasmosis demonstrates this: while 5-year survival after the toxoplasmosis episode was at 8 % in the years 1990-1993, it had climbed to 30 % by 1994-1996. This rate has risen to approximately 80 % since 1997.

Most patients who develop AIDS or severe opportunistic infections today are unaware of their HIV infection status. Since the year 2000, around 50 % of patients who presented with AIDS at our outpatient clinic were unaware of their HIV infection at the time. Another 35 % of patients had not been treated with antiretroviral drugs until AIDS was diagnosed. These patients often present late, usually in a very serious condition. AIDS remains life threatening, and a severe PCP does not become less critical because of the overall improvement in long-term survival. The acute danger remains. Therefore, every HIV clinician should be familiar with the diagnosis and therapy of OIs, even today.

Although much has improved in recent years, many problems remain. There is still no adequate treatment available for diseases such as PML or cryptosporidiosis, and resistance will become an increasing problem with other infections. HAART does not always lead to immediate improvement, and may even complicate things because of the atypical course of disease under HAART, as well as with immune reconstitution. For this reason, we have included a separate sub-chapter on the so-called immune reconstitution syndrome. There are still no guidelines for OI prophylaxis in many countries, and the US recommendations cannot always be adopted elsewhere, as seroprevalence rates often differ. In addition, it is becoming clear that nearly every type of prophylaxis or maintenance therapy can be discontinued when a sufficient level of immune reconstitution has been reached.

In many places, diagnostic problems recur again and again for many OIs, perhaps with the exception of larger HIV centers. Those unfamiliar with the pathogens will not recognize them! Therefore, we urgently recommend that after an initial consultation any specimens are sent to specialized reference laboratories. Further advice, if needed, can also be sought from a specialized clinician or a clinical HIV center.

The most important rule remains true even today for nearly all OIs: the poorer the immune status of the patient, the earlier the invasive diagnostic procedures should begin! The primary aim should not be to spare patients extensive diagnostic testing

involving unpleasant procedures. If nothing can be found the first time around, diagnostic tests must be repeated. Treatment should be initiated as rapidly as possible.

The second most important rule: in many cases, a number of OIs can largely be excluded if the immune status and viral load are known. Knowledge of the current status is therefore very important! Table 1 shows cut-offs for CD4 T cells, below which certain infections can be expected. The occurrence of OIs above the respective cut-off values is usually the exception.

Table 1. Important cut-offs for CD4 T cells, above which particular AIDS illnesses are improbable. These CD4 counts are only reference values; exceptions are always possible.

No cut-off	Kaposi's sarcoma, pulmonary tuberculosis, HZV, bacterial pneumonia, lymphoma
< 250/μl	PCP, esophageal candidiasis, PML, HSV
< 100/μl	Cerebral toxoplasmosis, HIV encephalopathy, cryptococcosis, miliary tuberculosis
< 50/μl	CMV retinitis, cryptosporidiosis, atypical mycobacteriosis

The following is intended as a relevant practical overview, and will not include clinical rarities. The literature cited refers to interesting reviews and almost exclusively to controlled and, if possible, randomized studies.

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Pneumocystis Pneumonia (PCP)

PCP is still one of the most frequent OIs. This interstitial pneumonia, from which most patients died in the early years of the HIV epidemic, is caused by pneumocysts. In the last 20 years, there has been significant progress in the knowledge about this organism, especially through DNA analysis (detailed review in: Thomas 2004). Although Pneumocystis was previously classified as a protozoan, it was established in 1988 that it is in fact an unusual type of fungus (Edman 1988). In the 1990s, it was recognized that every host, whether rat, mouse, monkey or human, has its own specific pneumocysts. It also became clear that Pneumocystis carinii, first described in 1910, does not occur in humans at all, but only in rats. The Pneumocystis species that affects humans is referred to as P. jiroveci, not P. carinii - and "carinii" has now been taken out of the name for the pneumonia, although the abbreviation remains the same (Stringer 2002).

The majority of patients diagnosed with PCP are not pre-treated with antiretroviral drugs, even today, and many of these do not know of their HIV infection status (or do not want to). PCP is a life-threatening disease which should be treated by an HIV specialist. It often requires mechanical ventilation and still continues to have a high fatality rate. Older patients have a particularly high mortality risk (Benfield 2001). The relapses that were frequently seen in the past have become rare, thanks to HAART and prophylaxis. Scar tissue formation may result in susceptibility to recurring pneumothoraces. PCP may also rarely occur in relation to an immune reconstitution syndrome (see below).

Signs and symptoms

Every clinician should be familiar with the classic triad of PCP symptoms: dry cough, subfebrile temperatures and gradual onset of dyspnea on exertion (Ask patients specifically! Measure respiratory rate!). This almost always allows differentiation from bacterial pneumonia (Productive cough! High fever! Pain! Dyspnea less likely!). Often there is significant oral thrush. Weight loss of several kilograms in the weeks before is also common. Symptoms may be subtler in cases with suboptimal prophylaxis (rare).

Often, weeks or sometimes even months may go by before the diagnosis of PCP is made. It is important to note that decompensation – as with all interstitial pneumonias – often occurs much more quickly than expected. It is not rare that a patient suddenly requires ventilation after weeks of antibiotic therapy (even broad spectrum antibiotics don't help!) prescribed by the primary health care provider. A patient with significant exertional dyspnea or even resting dyspnea must be sent to hospital immediately!

Diagnosis

If there is clinical suspicion of PCP, physical examination (Respiratory rate? Usually nothing is heard on auscultation, but oral thrush is often a further clinical finding) should be followed without delay by a chest x-ray and, if possible, high resolution computed tomography (HRCT) of the lungs. The chest x-ray often shows relatively characteristic findings with a butterfly-shaped (perihilar) interstitial infiltrate.

In the early stages, the focus is on the mid and lower fields. Cystic changes may also occur (Fätkenheuer 1997). Indistinct, diffuse changes are more easily visible on HRCT than on chest x-ray. A CT scan also allows a fairly certain distinction from other pulmonary infections (Hidalgo 2003).

However, if nothing pathological is visible (experience of radiologist?), which may be the case, rapid initiation of treatment is justified even without a definitive diagnosis – particularly in the presence of the classic triad of symptoms, low CD4 T cell count and no previous prophylaxis. There is almost always partial respiratory insufficiency, which should be confirmed by arterial blood gas analysis. Lactate dehydrogenase (LDH) is often elevated and may have limited use as a parameter for the course of disease. A high LDH is an unfavorable sign and reflects, even if not precisely, the severity of the PCP. In contrast, CRP is usually normal, provided there are no other concurrent infections.

Sputum specimens are generally not useful (review of various methods: Cruciani 2002), so that a bronchoalveolar lavage (BAL) is usually necessary. This can lead to detection of pneumocysts even after several days of treatment; therefore it is not essential to wait for the BAL to start treatment. However, HIV-inexperienced microbiologists may easily overlook Pneumocystis, so that an additional specimen should always be sent to an experienced laboratory. The laboratory should be specifically alerted to the suspicion of PCP. Performing the BAL as soon as possible also allows for the timely diagnosis of co-infections (CMV, pneumococci). It should be noted that respiratory insufficiency can deteriorate with BAL. Full blood count, transaminases and kidney function must be monitored during treatment and and baseline values should be determined at this point.

Newer diagnostic approaches include antibody testing (Bishop 2003) and measurement of S-adenosylmethionine, a substance that pneumocysts require but cannot produce. A recent study demonstrated significantly reduced levels of S-adenosylmethionine in patients with PCP (Skelly 2003). Such tests may spare patients the discomfort of bronchoscopy in the future, but cannot yet be recommended for routine diagnostic testing.

Treatment

General

Treatment should be initiated immediately if there is clinical suspicion. In cases of mild PCP (BGA: $PO_2 > 70\text{-}80$ mm Hg), ambulatory treatment can be attempted; oral medication can even be administered in very mild forms. This may well be possible in cooperation with a competent HIV nursing service. If such monitoring is not possible, if respiratory deterioration occurs, and in every case with resting dyspnea, immediate hospitalization is advised. If ventilation becomes necessary, patients have a poor prognosis, even today. Non-invasive methods (like CPAP) may be beneficial if used from an early stage. This helps particularly in prevention of pneumothoraces (Confalonieri 2002).

In Germany, initiation of HAART is usually postponed in ART-naïve patients until the PCP has resolved. In other countries, treatments are usually administered concurrently. A general recommendation cannot be given at present. A recent retrospective study showed improved survival in patients who began HAART while

hospitalized (Morris 2003). Disadvantages of this approach include possible cumulative toxicities and allergies, which may necessitate discontinuation of both PCP and HIV treatment (Watson 2002).

Drugs

Acute therapy should last for 21 days. The drug of choice is co-trimoxazole. The dose of three 960 mg tablets three times daily is only possible in milder cases. However, these higher oral doses are also associated with poor gastrointestinal tolerability. All severe cases should be treated intravenously in hospital. Due to possible clinical deterioration, which is probably a result of the bursting of pneumocysts in the alveoli, 20-40 mg prednisone bid should always be co-administered initially for 5-10 days. There should be no hesitation to use steroids in this situation. Important: clinical deterioration during the first week of treatment is still not uncommon. Initial treatment should be re-evaluated after one week at the earliest, and only after exclusion of co-infections such as CMV.

The high doses of co-trimoxazole require monitoring of full blood count, electrolytes, renal function parameters and transaminases at least three times weekly. The main problems in addition to myelotoxicity, liver and kidney problems include a rash that usually occurs in the second week of treatment, often accompanied by drug fever. An attempt can be made to interrupt treatment for one or two days, and then continue with half the dose under antihistamines and steroids. Otherwise, co-trimoxazole must be discontinued and replaced with alternative treatments.

All alternatives to co-trimoxazole are less effective. In cases of intolerability or history of sulfonamide allergy, intravenous pentamidine is recommended as the drug of second choice. An induction therapy is administered over the first few days (200-300 mg in 500 ml 5 % glucose or NaCl), and half the dose can then be given from day 6. This treatment is toxic. The main problems include severe decompensation of electrolyte and blood glucose levels (both hyper- and hypoglycemia are possible), pancreatitis, arrhythmia and possible renal failure. Initially, daily monitoring of blood glucose, electrolytes and renal parameters is necessary. In very mild cases, inhalative treatment with daily pentamidine inhalations (300 mg daily for three weeks) can be attempted (Arasteh 1990). Instead of pentamidine, we have had better experience with atovaquone suspension (better than the tablets used in the past!) or with a combination of clindamycin and primaquine. However, data on these regimens is only available for mild to moderately severe cases of PCP (Toma 1998).

Prophylaxis

Patients with less than 200 CD4 T cells/µl are at risk (above this value, the occurrence of PCP is rare) and should therefore receive prophylaxis, ideally with co-trimoxazole. Daily dosing may be slightly more effective than giving the dose three times weekly (El Sadr 1999). Gradual lead-in dosing over 14 days is cumbersome, but effectively prevents allergic reactions (Para 2000).

In cases of mild or moderate allergies, desensitization is a good possibility after several weeks (Leoung 2001), and should definitely be attempted. Although dapsone and pentamidine inhalations are almost equally effective (Bozzette 1995, Bucher 1997), co-trimoxazole prophylaxis is better for preventing bacterial infections

such as enteritis, sinusitis and pneumonia (DiRienzo 2002). More importantly, it simultaneously provides reliable protection for cerebral toxoplasmosis.

Pediatric co-trimoxazole suspension can be used for desensitization, by slowly increasing exposure within six days from 12.5, 25, 37.5, 50 and 75 to 100 % of the dose in the 480 mg tablet. In a study of almost 200 patients, no cases of severe allergy occurred, and there was a reduction of fever and headaches. Approximately three quarters of all patients are thus able to tolerate co-trimoxazole again. However, re-exposure should only be attempted after an interval of eight weeks (Leoung 2001).

Monthly inhalation of pentamidine is a well-tolerated alternative. Coughing may occur, asthma attacks are rare, and pneumothoraces even rarer. A suitable inhalation system should be used, after administration of a beta-sympathomimetic to dilate the bronchi. The loading dose (300 mg tid for the first 5 days) frequently used in the past is no longer a universal standard. In patients with severe pulmonary disease, inhalation is probably less effective.

Treatment/Prophylaxis of PCP
(daily doses, if not specified otherwise)

Acute therapy		Duration: always at least three weeks
Severe to moderately severe PCP	Co-trimoxazole	Co-trimoxazole 5-6 amp. à 480 mg tid **plus**
		prednisolone 2–2–0 tbl. à 20 mg (5-10 days)
Mild PCP	Co-trimoxazole	Co-trimoxazole 3 tbl. à 960 mg tid
Alternatives	Pentamidine	Pentamidine 200-300 mg i.v. for 5 days (4 mg/kg), then halve dose
		In very mild cases: daily inhalations with 300 mg
	Atovaquone	Atovaquone suspension 5-10 ml bid (750–1500 mg bid)
	Clindamycin + Primaquine	Clindamycin 1 amp. à 600 mg i.v. q 6-8 h
		plus primaquine 1 tbl à 30 mg qd
Prophylaxis		Below 200 CD4 cells/µl; after PCP episode
First choice	Co-trimoxazole	Co-trimoxazole 1 tbl. à 480 mg qd or
		co-trimoxazole 1 tbl. à 960 mg 3 x/week
Alternatives	Pentamidine	Pentamidine inhalation 300 mg 1-2 x/month
	Dapsone	Dapsone 2 tbl. à 50 mg qd
	Dapsone + Pyrimethamine	Dapsone 1 tbl. à 50 mg qd **plus** pyrimethamine 2 tbl. à 25 mg/week **plus** leucovorin 2 tbl. à 15 mg/week
	Atovaquone	Atovaquone suspension 5 ml bid (750 mg bid)

Further options are problematic. Dapsone has poor gastrointestinal tolerability, is quite myelotoxic and often leads to elevation of LDH. LDH, an important diagnostic parameter, can therefore not be utilized under treatment with dapsone (Ioannidis 1996). Atovaquone was proven to be of comparable efficacy to co-trimoxazole, dapsone and pentamidine in two multicenter studies (El-Sadr 1998, Chan 1999), and since then, is considered to be a good alternative for PCP prophylaxis. The oral

suspension has better tolerability than the tablet formulation (Rosenberg 2001). A significant disadvantage of atovaquone for long-term prophylaxis is the disproportionately high cost (approximately 1,000 Euro/month!).

PCP prophylaxis regimens can be discontinued fairly safely with sufficient immune reconstitution: more than 200 CD4 T cells/μl for three months (Schneider 1999, Weverling 1999, Lopez 2001, Ledergerber 2001). PCP has only rarely been described in cases with CD4 counts greater than 200 cells/μl after stopping prophylaxis (Degen 2002, Mussini 2003).

Stopping prophylaxis not only reduces side effects and costs, but also avoids other negative developments: the proportion of co-trimoxazole-resistant bacteria is constantly increasing among HIV patients (Martin 1999). The worldwide use of co-trimoxazole has also affected pneumocysts. Resistance analyses were previously difficult, as this organism, even almost 100 years after its discovery, can still not be cultured. However, it is now possible to sequence sections of the genome encoding for dihydropteroate synthetase (DHPS). DHPS is an important enzyme involved in the folate metabolism of many organisms, and is targeted by sulfonamides such as sulfamethoxazole (SMX) and dapsone. The first mutations in the DHPS gene in pneumocysts were discovered in 1997. A recent study showed DHPS mutations in 43 %, while the gene region for dihydrofolate reductase (DHFR), targeted by trimethoprim (TMP), did not show a single relevant mutation. In contrast to SMX, there seems to be no selective pressure associated with TMP – supporting the long-standing suspicion that TMP is not effective against pneumocysts (Ma 1999). Studies in large groups of patients have demonstrated that the frequency of sulfa resistance mutations has significantly increased in recent years. Resistance correlated significantly with the duration of prior prophylaxis and its failure (Helweg-Larsen 1999, Kazanjian 2000, Nahimana 2003).

Current controversy in PCP research

It is presently not clear, whether DHPS mutations should affect decisions on PCP therapy or lead to changes in treatment (Stein 2004). In a Danish study on 144 PCP patients, DHPS mutations correlated with higher mortality rates (Helweg-Larsen 1999). However, a working group in the US found mostly low-level resistance, which could be overcome with high sulfonamide doses (Kazanjian 2000). It should be stressed that resistance testing for pneumocysts is currently still in the experimental stages. Results are often poorly reproducible (Beard 2004).

The sequencing of the Pneumocystis genome has uncovered other possibly relevant findings: it seems highly likely that PCP is caused by a new infection, rather than the reactivation of an existing infection as previously assumed (Stringer 2002, Nahimana 2003, Wakefield 2003). Asymptomatic HIV patients with frequent detection of pneumocysts may be reservoirs (Wakefield 2003), in addition to HIV-negative patients on corticosteroid therapy (Maskell 2003) and of course patients with active PCP. However, other authors doubt patient-to-patient transmission (Wohl 2002), and isolation of PCP patients is still not generally recommended (Thomas 2004).

An Italian working group has repeatedly stressed in recent years that the effect of protease inhibitors on pneumocysts detectable in vitro has clinical relevance – patients with PI-containing HAART apparently have better protection from PCP than

patients on NNRTIs (Atzori 2003). However, these effects have not yet been demonstrated in larger numbers of patients.

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Cerebral toxoplasmosis

Although cerebral toxoplasmosis has become rarer, and the incidence in Europe has been reduced to a quarter as a result of HAART (Abgrall 2001), it remains the most important neurological OI in HIV patients. Today, cerebral toxoplasmosis is typically diagnosed in HIV patients with hitherto unknown HIV infection or in those not under regular routine care. Cerebral toxoplasmosis almost always results from the reactivation of a latent infection with Toxoplasma gondii, an intracellular parasite that infects birds, mammals and humans. Prevalence rates vary considerably worldwide (Porter 1992, Jones 1996). Whereas Toxoplasma gondii is relatively rare in the USA, prevalence rates in central Europe are as high as 90 %. Toxoplasma has an affinity to the CNS. Extracerebral organ manifestations (heart, skeletal muscle, liver, intestine, lung) are extremely rare and often only detected at autopsy.

Cerebral toxoplasmosis is potentially life threatening, and treatment is complicated. In severe cases, there may be residual neurological syndromes with significant disabilities (hemiparesis!). It is not rare to see a remaining lifelong susceptibility to seizures as a result of defective healing. It should be noted that relapses may occur even after long periods of time due to intracerebral persistence.

Signs and symptoms

Clinical symptoms depend on the localization of lesions, with acute or peracute onset within a few days. The major signs include focal neurological deficits such as paresis, speech problems or sensory loss (Porter 1992). A febrile psychosyndrome with confusion is also frequently an early sign. It is not unusual to see an epileptic seizure as the initial presentation, in the absence of other symptoms. Headaches with fever or subfebrile temperatures are always suspicious. Meningitic signs, however, are less typical. Atypical manifestations in patients with immune reconstitution under HAART have been described (Ghosn 2003).

A fairly rare, but important manifestation is Toxoplasma chorioretinitis. It causes impairment of vision, is an important differential diagnosis to CMV retinitis and may occur on its own (Rodgers 1996).

Diagnosis

Cerebral toxoplasmosis is extremely rare above a CD4 T cell count of 100 cells/µl, (Bossi 1998). It should always be expected below 100 CD4 T cells/µl. A CT or MRI scan of the head should be performed promptly (not a week later!) in every case of focal neurological deficit, but also if seizures occur in significantly immunocompromised patients. An MRI is superior to a CT scan and almost always shows more visible lesions. A third of cases have either solitary, several (2-5) or multiple lesions, respectively. In approximately nine out of ten cases, ring enhancement is found around the lesions, often accompanied by edema. Hemorrhage may occasionally occur.

For all radiologically detected lesions, the most likely diagnosis is cerebral toxoplasmosis. In addition, the most important differential diagnosis is an "atypical" cerebral toxoplasmosis. The more lesions there are, the more likely the diagnosis of toxoplasmosis! However, the distinction from a bacterial abscess or cerebral lym-

phoma is not always simple radiologically. Other rare differential diagnoses include PML, infarcts, tuberculomas and cryptococcomas. "HIV-unrelated" diseases such as brain tumors or vascular disease should also be considered.

Before a brain biopsy, suspicion of toxoplasmosis always justifies a treatment attempt. Response to therapy then confirms the diagnosis. The cerebrospinal fluid (CSF), which must not necessarily be analyzed if there are clear radiological findings (several lesions with contrast enhancement), usually shows moderate pleocytosis and slightly elevated total protein. Our experience with Toxoplasma PCR from CSF has not been good. A negative result (frequent!) never excludes toxoplasmosis.

An updated serology should be available for every patient. Up to 97 % of patients with cerebral toxoplasmosis have IgG antibodies, and so a negative result, which should be repeated in another laboratory if there is any doubt, makes toxoplasmosis unlikely. Some clinicians use levels of IgG titers or increased titers as indicators (Derouin 1996), but this approach has not been properly validated. IgM is only rarely positive, and therefore usually does not help. PCR from the blood also has little relevance (review in: Bretagne 2003).

Treatment

Treatment of cerebral toxoplasmosis is not simple. The most frequently used combinations are usually effective (resistance has not yet been convincingly described), but require modification in at least half the patients due to side effects – particularly allergies. Sulfadiazine and clindamycin are presumably equally effective in combination with pyrimethamine (Dannemann 1992). However, one large European study demonstrated a trend, though not significant, in favor of sulfadiazine (Katlama 1996). A loading dose for pyrimethamine during the first few days has been propagated since the first published study (Leport 1988), although sufficient comparative data is not available.

Due to the myelotoxicity of sulfonamides and pyrimethamine, which inhibits transformation of folic acid to folinic acid, it is important to substitute sufficiently with folinic acid (unfortunately expensive!) from the start. Folic acid (cheap!) itself is ineffective, as it cannot be converted in the presence of pyrimethamine (Luft 2000).

We recommend using sulfadiazine and pyrimethamine for an initial attempt as oral treatment. In cases of sulfonamide allergy, sulfadiazine should be substituted with oral or intravenous clindamycin from the beginning. All disoriented patients should receive clindamycin infusions, at least for reasons of compliance. Because of the high rate of allergies under sulfadiazine, however, some clinicians completely oppose this treatment. But clindamycin may also be problematic – consider pseudo-membranous colitis in cases of persistent diarrhea!

If allergies or intolerance to both sulfonamides and clindamycin occur, a combination of atovaquone and pyrimethamine is a possible alternative (Chirgwin 2002). Good results are also reported with intravenous co-trimoxazole, with administration of the same dosages as for PCP (Canessa 1992). A combination of azithromycin plus pyrimethamine could be another alternative (Bosch-Driessen 2002), however there is only very vague data available.

Acute therapy is of four to six weeks duration, possibly longer for the less effective reserve therapies. There is often clinical improvement within a few days. Even in

these cases, a further MRI is recommended after two weeks at the earliest. Significant resolution of lesions is often only visible after four weeks. In cases of increased intracranial pressure or extensive edema, steroids are given (8 mg dexamethasone q 6-8 h). Administration of steroids should be for a limited duration, as there is otherwise a significantly increased risk of aspergillosis. All treatment combinations require initial monitoring of blood count, glucose, transaminases and renal parameters at least three times weekly. Maintenance therapy with the reduced dose should only be initiated if lesions have resolved by at least 75 %.

Prophylaxis

IgG-negative patients can protect themselves from initial infection – they should avoid eating raw or only briefly cooked meat (lamb, beef, pork, game). However, it has not been proven, despite widespread opinion, that HIV patients can infect themselves by mere contact with cats, the definitive host of Toxoplasma gondii. The only study that has seriously investigated this to date could not prove endangerment as a result of proximity to cats (Wallace 1993). Nevertheless, stricter measures of hygiene should be followed (e.g. use gloves for the cat litter box! Details in: Kaplan 2002).

All IgG-positive patients with less than 100 CD4 T cells/µl require primary prophylaxis. The drug of choice is co-trimoxazole. In cases of co-trimoxazole allergy, desensitization may be considered (see PCP). An alternative is dapsone plus pyrimethamine or high-dose dapsone alone. All primary prophylaxes can be discontinued safely if CD4 T cells increase and are above 200/µl for at least three months.

In the absence of immune reconstitution, patients with cerebral toxoplasmosis require lifelong maintenance therapy or secondary prophylaxis, as there are otherwise recurrences in nearly all cases. It usually consists of half the dose of the acute therapy (Podzamczer 2000). However, clindamycin is presumably less suitable, as it cannot cross the intact blood-brain barrier (Luft 2000). Co-trimoxazole seems to be not as effective for secondary prophylaxis, but should be considered because it is simple. However, it definitely requires higher doses than those used to treat PCP (Ribera 1999, Duval 2004). Even secondary prophylaxis can probably be stopped with sufficient immune reconstitution (at least six months above 200 CD4 T cells/µl).

If possible, an updated MRI scan should be available beforehand. If there is enhancement, it may mean that lesions have become active even after years – and there is a risk of a recurrence. We have seen a recurrence even after five years, despite CD4 T cells levels being around 200/µl.

This and other cases (Stout 2002, Ghosn 2003) have shown that quantitative measurement of CD4 T cells on HAART does not always reflect the quality of the Toxoplasma-specific immune response. As a result, there have been increasing efforts in recent years to improve the characterization of this specific immune response via ELISPOT. Studies have shown that the Toxoplasma-specific immune response remains poor in approximately 10-20 % of patients on HAART, despite good CD4 T cell counts (Fournier 2001, Miro 2003). In the future, ELISPOT testing might allow identification of patients who are at risk of recurrence despite good CD4 counts and who should therefore continue with secondary prophylaxis.

Treatment/prophylaxis of cerebral toxoplasmosis
(daily doses, if not specified otherwise)

Acute therapy		Duration: always at least four weeks
First choice	Sulfadiazine+ Pyrimethamine	Sulfadiazine 2-3 tbl. à 500 mg qid **plus**
		pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) **plus** leucovorin 3 x 1 tbl. à 15 mg/week
First choice	Clindamycin + Pyrimethamine	Clindamycin 1 amp. à 600 mg i.v. qid or 1 tbl. à 600 mg qid **plus**
		pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) **plus** leucovorin 3 x 1 tbl. à 15 mg/week
Alternative	Atovaquone + Pyrimethamine	Atovaquone suspension 10 ml bid (1500 mg bid) **plus**
		pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) **plus** leucovorin 3 x 1 tbl. à 15 mg/week
Maintenance therapy		
	As for acute therapy	As for acute therapy, but halve dose
		Discontinue if > 200 CD4 cells/µl for > 6 months (if MRI is normal or without contrast enhancement)
possibly	Co-trimoxazole	Co-trimoxazole 1 tbl. à 960 mg qd
Primary prophylaxis		
Standard	Co-trimoxazole	Co-trimoxazole 1 tbl. à 480 mg qd
Alternative	Dapsone	Dapsone 2 tbl. à 50 mg qd
Alternative	Dapsone + Pyrimethamine	Dapsone 1 tbl. à 50 mg qd **plus** pyrimethamine 2 tbl. à 25 mg/week **plus** leucovorin 2 tbl. à 15 mg/week

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CMV Retinitis

Infections with cytomegalovirus are widespread. In Germany, seroprevalence is around 50-70 %, and above 90 % in homosexual men. In severely immunocompromised individuals, (CD4 count below 50 cells/µl), reactivation of CMV infection can lead to retinitis. In the past, CMV retinitis was a common AIDS-associated illness, leading to blindness in up to 30 % of patients. It occurs mainly in untreated patients, who are often first diagnosed with HIV infection on presentation (Jacobson 2000). An inflammatory CMV retinitis, usually with severe vitritis, is also possible in the course of an immune reconstitution syndrome. If CMV retinitis is not diagnosed and treated promptly, the patient's sight is always at risk. Impairment of vision is almost always associated with lesions, which are no longer reversible even with adequate treatment. This is why CMV retinitis remains a dangerous illness even in the HAART era (Goldberg 2003).

Other manifestations of disseminated CMV infection are rare (ca. 15 %), and can affect every organ. The lung (pneumonia), esophagus (ulcers), colon (colitis) and CNS (encephalitis) are most frequently involved. Sinusitis may also occur (Jutte 2001). The clinical signs of these CMV diseases depend on the organ affected. Diagnosis is often difficult and may only be possible on histology (Goodgame 1993). There is insufficient data on the treatment of these manifestations, so that systemic therapies are usually chosen in analogy to treatment for CMV retinitis (Whitley 1998).

Signs and symptoms

Any visual impairment occurring peracutely or acutely, such as blurred vision or floaters – especially unilaterally – should prompt immediate ophthalmological examination of the patient. Today, not tomorrow! Symptomatic CMV retinitis is an emergency – once there is a black spot in the visual field, it will be permanent. All CMV treatment regimens can only prevent progression of lesions, not reverse them.

Eye pain, burning, increased production of tears and conjunctival irritation are not typical. Many patients suffer from systemic symptoms such as fever and weight loss.

Diagnosis

Diagnosis is made by fundoscopy. Assessment of the usually peripheral, whitish exudates is dependent on the experience of the ophthalmologist. This can frequently be a problem, particularly due to the rare occurrence of the disease today. If the ophthalmologist remains undecided: start with oral ganciclovir if necessary and transport the patient to a larger clinical center with ophthalmologists who are experienced in HIV!

CMV retinitis can almost be excluded at CD4 T cell counts above 100/µl; other viral infections (HSV, VZV) or even neurosyphilis should then be considered. In cases of poor immune status and CD4 count less than 100/µl, toxoplasmic chorioretinitis is the most important differential diagnosis. It is therefore important for the ophthalmologist to review information on the patient's immune status, as there is otherwise a risk of misdiagnosis. CMV lesions may also be confused with cotton

wool spots, which are not rare in HIV patients with high HIV viral load. Multiple small lesions without hemorrhage or exudates are almost always cotton wool spots, and almost never CMV retinitis! Bilateral involvement is usually the exception. Vitritis is rare, except with immune reconstitution syndrome.

CMV serology (IgG almost always positive, IgM variable) is usually not helpful for diagnosis. CMV PCR or a blood test for pp65 antigen to detect antibodies against a CMV-specific phosphoprotein may be more useful. CMV retinitis or a recurrence is unlikely with a negative PCR or pp65 result. The higher the levels of CMV viremia, the higher the risk of CMV disease. Patients with positive CMV PCR have a 3-5-fold elevated risk (Casado 1999, Nokta 2002). Positive CMV PCR is also associated with a poor prognosis for the patient (Deayton 2004).

As with Toxoplasma gondii, there have been recent efforts to determine the antigen-specific immune response more precisely (Jacobsen 2004), although such testing is not yet routine.

Treatment

CMV treatment should always be initiated promptly and strictly monitored by fundoscopy (once a week in the beginning; photodocumentation is advisable). Initially, an intensive induction therapy is administered for two to three weeks, until there is scar formation of the lesions. The HIV clinician and ophthalmologist should work closely together, particularly during the initial phase. Induction therapy is followed by maintenance therapy at a reduced dose.

There have been significant developments for CMV treatment in the past few years. Several new drugs have been licensed. The introduction of oral valganciclovir has led to fundamental changes in treatment. Many treatment approaches investigated in numerous studies, as well as subsequent recommendations developed with great effort only a few years ago, are no longer important.

HAART in particular has dramatically improved the prognosis of patients. All patients should therefore, if this has not already happened, start HAART as soon as possible. This can restore CMV-specific immune responses (Komandouri 1998), so that CMV viremia may disappear even without specific therapy after a few weeks (Deayton 1999, O'Sullivan 1999). However, if retinitis is present, CMV-specific treatment should nevertheless be started, as immune reconstitution may take several months.

Systemic treatment

Valganciclovir, a prodrug of ganciclovir with good oral absorption, has led to a decisive improvement in the treatment of CMV. In a randomized study (Martin 2002) on 160 patients with retinitis, the results were impressive: valganciclovir tablets were just as effective as ganciclovir infusions. As the toxicity profile of both substances – with the exception of slightly more frequent diarrhea on valganciclovir – is comparable, oral treatment requires just as much monitoring of blood counts as the infusion therapy. Our experience with valganciclovir has been good so far. Not only intravenous ganciclovir, but also the other options for systemic treatment have become less important, and are only used in cases of recurrence.

If there is intolerability or resistance to ganciclovir (Drew 1999), foscarnet, which for years has been an important and irreplaceable component in CMV medicine, remains an option. This, however, requires daily infusions. Further problems with this drug include nephrotoxicity, and very painful penile ulcers. Very intensive hydration of the patient is therefore necessary under all circumstances.

There are no direct comparative studies available for cidofovir, used increasingly in recent years due to its long half-life (Berenguer 2000). Although a Phase I study showed a good effect of cidofovir in combination with oral ganciclovir (Jacobson 1999), the benefit of the long half-life (once weekly dosing possible) is outweighed by the considerable renal side effects of the drug (Plosker 1999). We observed creatinine elevations in almost every second patient treated, despite the fact that a strict infusion plan was closely followed (see Drugs section). Oral ganciclovir as monotherapy has become obsolete because of its poor bioavailability.

New drugs in CMV therapy, such as 1263W94 (maribavir), will take a while to come onto the market. CMV retinitis has become rare in the field of HIV infection, and progress is slower in transplantation medicine, where there is currently the greater need for new CMV drugs with improved tolerability.

In one analysis of three large studies, patients with CMV retinitis, who had received additional treatment with G-CSF (filgrastim) in the years 1990-1997, had improved survival rates. In particular, there was a reduction of bacterial infections. However, the reason for this positive effect remains unclear despite extensive analyses. Administration of filgrastim is presently not generally recommended (Davidson 2002).

Local treatment

Several options for local treatment of CMV retinitis have been tested (review in: Smith 1998). Although such treatments can be safely administered by experienced ophthalmologists and are associated with few complications (infections, hemorrhage), disadvantages remain. Weekly intravitreal injections of ganciclovir or foscarnet, or pellet implantation (Vitrasert™, must be replaced every 6-9 months) do not protect from infection of the contralateral eye or from extraocular manifestations (Martin 1999). The same is true for fomivirsen (Vitravene™), an antisense-oligonucleotide for intravitreal injection, which is astonishingly effective even with multiresistant CMV strains (Perry 1999). These local treatments have become less important since HAART and valganciclovir, and some have been taken off the market.

Prophylaxis

Despite the elaborate prospective studies that have been performed, no primary prophylaxis regimen has been convincing. There is no effective vaccine. Therefore, the most important method for prevention in patients with CD4 counts of less than 200 cells/µl is still fundoscopy every three months. With good immune reconstitution, intervals between examinations can be extended. It is important to perform a fundoscopy in severely immunocompromised patients prior to starting HAART. This allows detection of smaller lesions, which may later present with severe inflammation during the course of immune reconstitution.

After at least three weeks of acute therapy, at the earliest with scar formation of lesions, a reduced dose secondary prophylaxis or maintenance therapy should be-

gin. Oral valganciclovir is, again, a good option, as initial data shows that it is also suitable for long-term treatment (Lalezari 2002). However, the drug is not only extremely expensive (three weeks of induction therapy cost around 4,500 Euro – the manufacturer demands a high price for the savings in nursing or hospital care), but also just as myelotoxic as ganciclovir infusions.

Treatment/prophylaxis of CMV retinitis
(daily doses, if not specified otherwise)

Acute therapy		Duration: always at least three weeks
Treatment of choice	Valganciclovir	Valganciclovir (Valcyte®) 2 tbl. à 450 mg bid
Alternative	Ganciclovir	Ganciclovir 5 mg/kg i.v. bid
Alternative	Foscarnet	Foscarnet 90 mg/kg i.v. bid
Alternative	Ganciclovir + Foscarnet	Half of the doses above
Maintenance therapy		Discontinue from > 100-150 CD4 cells/µl > 6 months
Treatment of choice	Valganciclovir	Valganciclovir (Valcyte®) 1 tbl. à 450 mg bid
Alternative	Foscarnet	Foscarnet 120 mg/kg i.v. qd on 5 days/week
Alternative	Cidofovir	Cidofovir 5 mg/kg i.v. qd every 14 days (plus probenecid hydration according to protocol, see Drugs section)
Primary prophylaxis		Not recommended

Discontinuation of secondary prophylaxis is therefore also desirable for this OI (MacDonald 1998, Tural 1998, Jouan 2001), but it also requires strict ophthalmologic monitoring. According to US guidelines, discontinuation should occur at the earliest after six months of maintenance therapy and with an immune reconstitution above 100-150 CD4 cells/µl. However, we have even successfully stopped ganciclovir at lower CD4 cell counts, if both HIV and CMV PCR in blood were below the level of detection. One study showed that stopping after 18 months of HAART/maintenance therapy can be safe above 75 CD4 cells/µl (Jouan 2001).

The previously required life-long daily infusions of ganciclovir or foscarnet via port, pumps and nursing service are luckily now a thing of the past. If there are relapses under oral valganciclovir, we recommend re-induction and maintenance therapy with foscarnet or possibly with cidofovir.

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Candidiasis

Candidiasis is an infection with yeast-forming fungi. Of the 150 Candida species known to date, only approximately 20 cause disease. By far the most frequent species is C. albicans. Other species such as C. tropicalis, C. glabrata and C. krusei are rare, but may respond less readily to treatment with azoles. Although it is commonly assumed that azole resistance is a problem particularly with albicans strains, this has not been the case to date (Sanglard 2002).

Mucocutaneous candidiasis is always a sign of immunodeficiency and should be seen as a reason to consider starting HAART, even with a good immune status. Esophageal candidiasis and even oral thrush often occur following other OIs. Fever, which is not a classic symptom of candidiasis, is a particular indication to be on the alert. If immune status is good, it must be remembered that there are also other reasons for thrush – alcoholism and steroid treatment are only two of many possibilities. In addition to candidiasis of the oropharynx and esophagus, vaginitis is a frequent problem. Candidemia occurs only rarely in HIV-infected patients, even with severe immunodeficiency.

Signs and symptoms

The oropharynx is usually affected, with taste disturbances and a burning sensation on the tongue. White, non-adherent plaques on the buccal mucosa, tonsillar ring and tongue confirm the diagnosis. Involvement of the tongue alone is rare. Occasionally, there may be atrophic candidiasis, which presents only with an erythematous mucosa.

Candida esophagitis usually occurs with oropharyngeal involvement, but in about one third of cases there is no oral thrush. It often presents with dysphagia ("drinking is ok, but food can't go down") and retrosternal pain. Some patients complain of nausea, although vomiting occurs only rarely.

Diagnosis

Diagnosis in the oropharynx can be made based on the clinical appearance. A swab is not primarily required. Characterization by culture or even determination of drug susceptibility is only advised if at least one treatment attempt with fluconazole or itraconazole has failed. Oral candidiasis should not be confused with oral hairy leukoplakia (OHL). The latter are adherent, hairy plaques on the sides of the tongue. OHL is not caused by fungi but by EBV, and is an important disease marker for HIV, even if it is generally harmless and does not require treatment.

Candida esophagitis can also initially be diagnosed clinically. Empiric fluconazole therapy reduces costs (Wilcox 1996)! Upper GI endoscopy is only required if complaints persist. To distinguish fluconazole-resistant esophageal candidiasis from herpes or CMV esophagitis, samples of lesions should be taken. In contrast, determination of serum antibodies or antigen is always unnecessary.

Treatment

With relatively good immune status and presentation for the first time, treatment with topical antimycotics (gargle, rinse mouth and then swallow!) can be attempted. However, systemic treatment is usually necessary. This is more effective and prevents relapses for longer (Pons 1997). Fluconazole is the treatment of choice, and one week of oral treatment is usually sufficient (Sangeorzan 1994). If symptoms persist for more than a week, a swab should be taken and the fluconazole dose may be increased up to 800 mg for the second attempt.

Itraconazole should only be used if the second treatment attempt fails and non-albicans strains have been found. It will be effective in approximately two thirds of cases (Saag 1997). Although itraconazole suspension is as effective as fluconazole (Graybill 1998), we do not primarily use it as plasma levels are unreliable and there are problems with numerous interactions.

Several new and promising antimycotics have been developed in recent years. However, these should only be used in clear cases of fluconazole resistance. Voriconazole is expected to be as effective as fluconazole, but is possibly not tolerated as well (Ruhnke 1997, Ally 2001). Like amphotericin B, it can be used for treatment of multi-azole resistant mycoses. Caspofungin or micafungin, two antimycotics belonging to the new class of echinocandins, also have good efficacy (Keating 2001, Villanueva 2001, Arathoon 2002, de Wet 2004). Both agents, which can only be administered intravenously, showed similar efficacy and tolerability to intravenous fluconazole for treatment of Candida esophagitis in randomized studies (Villaneuva 2001, de Wet 2004).

An adequate HAART regimen should be initiated when such mycoses occur, particularly with multiresistant strains, as these usually disappear with sufficient immune reconstitution (Ruhnke 2000).

Prophylaxis

No survival benefit has been demonstrated for any Candida prophylaxis to date (McKinsey 1999, Rex 2000). It is therefore not advisable, in our opinion, as expensive long-term treatment only leads to resistant mycoses or selection of non-albicans strains (Vasquez 2001). But: check the mouth of every immunocompromised patient at every visit!

Treatment/prophylaxis of candidiasis (daily doses)

Acute therapy		Duration: 5-10 days
In mild cases	Topical	e.g. amphotericin B 1 lozenge qid or
		nystatin suspension 1 ml qid
Treatment of choice	Fluconazole	Fluconazole 1 cap à 100 mg qd for oral candidiasis
		Fluconazole 1 cap à 200 mg qd for esophageal candidiasis
		(twice the dose on the first day in each case)
Alternative	Itraconazole	Itraconazole 1-2 cap. à 100 mg bid or
		Itraconazole suspension 10-20 ml bid (1 ml = 10 mg)
Prophylaxis		Not recommended

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Tuberculosis

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Tuberculosis has a greater impact worldwide on morbidity and mortality in HIV-1-infected individuals than all other opportunistic infections (OI) (Unaids 2003). Approximately 1/3 of the 40 million people infected with HIV-1 are co-infected with *Mycobacterium tuberculosis* (*M. tuberculosis, M. africanum, M. bovis, M. canetti* or *M. microti* – MTB). In sub-Saharan Africa, 2/3 of HIV-infected subjects are co-infected (Colebunders 2002). In fact, the rising incidence of tuberculosis in many regions of the world is closely related to the HIV epidemic (Corbett 2003). In some areas of Africa, more than 60 percent of patients with tuberculosis are infected with HIV-1 (Raviglione 1997). Recently, co-infection of the two pathogens has become more noticeable in Eastern Europe and in Asia (Field 2004, Sonnenberg 2004, Steinbrook 2004, Surendran 2004). In addition, there is increasing concern that HIV-1 will enhance the spread of multidrug resistant MTB in these regions (Kruuner 2001) as MDR-TB is approximately 10 times more prevalent in Eastern Europe than in Africa (Dye 2002, Morozova 2003).

Despite a steadily increasing prevalence of HIV-1 infection in Western Europe and North America in recent years, the incidence of tuberculosis has continuously declined in countries where antiretroviral therapies (ART) against HIV-1 are available (Kirk 2000, Girardi 2000). However, treatment of co-infected patients with ART and antituberculous medications simultaneously is complicated, due to a wide spectrum of pharmacological interactions and side effects.

Interaction of HIV and MTB

The influence of HIV and MTB on immunoregulation by the host is bidirectional. The incidences of post-primary tuberculosis and reactivation tuberculosis are increased in HIV-infected patients in comparison to HIV-seronegative individuals (Havlir 1999, Badri 2001). For example, the incidence of post-primary TB is increased from 5% to 30% in HIV-1 infected subjects. Further, it is likely that tuberculosis enhances immunodeficiency in patients with chronic HIV infection (Toossi 2003). Despite adequate therapy of tuberculosis, the subsequent morbidity and mortality is increased in patients with HIV-infection in comparison to HIV-seronegative patients with tuberculosis (Manas 2004, Whalen 2000). While most opportunistic infections, including all other mycobacterial diseases, occur in the advanced stages of HIV-infection, patients can develop tuberculosis at any stage, regardless of the levels of circulating CD4+ T-cells (Ackah 1995). More than 50 percent of cases with pulmonary tuberculosis occur in patients with CD4+ counts of more than 200 cells/µl in the peripheral blood (Badri 2001). However, the incidence of disseminated tuberculosis is much higher in patients with advanced immunodeficiency (Wood 2000). Recently, it was shown that the risk of developing tuberculosis is already significantly increased in the first year following HIV-antibody seroconversion, (Sonnenberg 2005). The factors which lead to tuberculosis reactivation in HIV-infection have not been determined in detail.

Clinical manifestations

The risk of developing tuberculosis in patients with latent MTB infection (LTBI) is approximately 8 percent per year in HIV-infected patients compared with a lifetime risk of 5 to 10 percent in HIV-seronegative individuals (Unaids 2003). The pathogenesis of tuberculosis is dependent on the stage of immunodeficiency. When LTBI is reactivated in the early stages of HIV-infection, the clinical manifestation resembles tuberculosis in HIV-seronegative individuals with the cardinal clinical features of fever, night sweats and weight loss.

Pulmonary TB

As in HIV-seronegative patients, the typical features of pulmonary tuberculosis in HIV patients with circulating CD4+ counts of more than 200 cells/µl are upper-lobe infiltrates with or without cavities. Acid-fast bacilli (AFBs) can often be detected on examination of the sputum. As immunodeficiency progresses, non-cavernous atypical presentations or tuberculous pleuritis become more prominent. Bronchopulmonary symptoms, such as cough and hemoptysis are often absent when tuberculosis occurs in the advanced stages of HIV infection. The acid fast stain is positive in approximately 5 percent of cases where infiltrates are not visible on standard chest x-ray (Ackah 1995). With progressive immunodeficiency, hematogenous and lymphatic spread of mycobacteria are more common, leading to the clinical picture of miliary (Elliott 1993) or localized extrapulmonary tuberculosis (Mayanja-Kizza 2001). Because CD4+ T-lymphocytes are required for granuloma formation, these features are usually absent on histopathological examination of tissue from these patients (Nambuya 1988).

Extrapulmonary TB

As mentioned earlier, extrapulmonary tuberculosis occurs predominantly in co-infected patients with CD4+ counts of less than 200cells/µl. The most common feature of extrapulmonary tuberculosis is cervical lymphadenopathy. The involved nodes are firm and generally not painful on palpation. The formation of abcesses and draining fistulas, as well as fever and malaise are common.

Tuberculous meningitis often presents with unspecific prodromal symptoms, such as headache, nausea and vomiting followed by elevated temperature and clinical signs of meningeal irritation. The basal meninges are usually involved and cranial palsies of the IIIrd and VIth nerves are common. Mono-, hemi,- or parapareses as well as seizures can occur. In case of doubt, a lumbar puncture should be performed without delay.

In febrile patients with abdominal pain and ascites, peritoneal tuberculosis must be included in the differential diagnosis.

A micronodular pattern is seen on chest x-ray in miliary tuberculosis (lat. milium effusum = millet). On radiological criteria alone, miliary tuberculosis cannot be distinguished from pulmonary cryptococcosis. Miliary dissemination of tuberculosis can also be detected on abdominal ultrasound of the spleen and liver and may involve the adrenals (cave: Addison´s disease) too.

Other extrapulmonary manifestations include pericarditis, osteoarthritis, urogenital or skin tuberculosis. Practically every organ can be involved.

Diagnosis

The diagnostic steps to approach an HIV-infected patient with possible tuberculosis do not differ from those used on the immunocompetent host (Lange 2004). In the differential diagnosis, tuberculosis has to be distinguished primarily from diseases caused by non-tuberculous mycobacteria, from cryptococcosis, histoplasmosis, sarcoidosis, lymphoma, and solid malignant tumors.

The diagnosis is made on clinical, microbiological and radiological grounds. Sputum and other biological materials are evaluated for the presence of acid-fast-staining rods on microscopy. The sensitivity and specificity of sputum-microscopy is poor. Approximately 5,000 – 10,000 mycobacteria/ml are necessary for a routine microscopic diagnosis of acid-fast bacteria in a sample. Approximately 50% of all patients with culture positive pulmonary tuberculosis have no detectable AFBs on examination of three consecutive sputum samples. In addition, discrimination against non-tuberculous mycobacteria is not possible by microscopy.

When AFBs are detected in the sputum or in the bronchoalveolar lavage, the patient should be treated in isolation. There is, however, uncertainty about the duration of isolation. As a rule of thumb, isolation should be kept ongoing until AFBs are undetectable on three sputum samples obtained on different days or until the culture result confirms the presence of non-tuberculous mycobacteria. Patients with MDR tuberculosis should be kept in isolation until sputum cultures turn negative.

When pulmonary tuberculosis is suspected, three sputum samples should be obtained in the morning on different days for microscopy and culture. If patients are unable to cough productively, an attempt to induce sputum by the inhalation of 3 percent hypertonic sodium chloride should be made. Alternatively, early morning gastric aspirate can also be examined for mycobacteria. The acidic gastric aspirate should be buffered in phosphate solution prior to transportation to the laboratory. In patients with advanced stages of HIV infection, the likelihood of smear-positive tuberculosis is decreased. Bronchoscopy is usually indicated if the suspicion of tuberculosis remains high, but no AFBs are found on microscopic examination of sputum. Bronchial secretions or bronchoalveolar lavage is not superior to sputum in the diagnosis of tuberculosis in patients with HIV infection (Conde 2000), but a bronchoscopy may be very helpful in differentiating between tuberculosis and other diseases in the differential diagnosis (Narayanswami 2003), particularly since the coincidence of more than one pulmonary process has been seen in patients with HIV infection. In the case of tuberculosis, histopathological examination of trans-bronchial biopsies may yield typical caseating granulomas and giant cells and may show AFBs. On the day following the bronchoscopy, sputum should again be sampled for analysis, as the diagnostic yield for AFBs is high following the intervention even if no bacteria were detected in the lavage.

For the diagnosis of extrapulmonary tuberculosis, biological samples (heparinized venous blood, CSF, urine, pleural, pericardial, and peritoneal fluid) should be examined. Biopsies from lymph nodes, pleura, peritoneum, synovia, pericardium, etc., are also suitable for the diagnosis of extrapulmonary tuberculosis.

The gold standard in the diagnosis of tuberculosis is the cultural identification of MTB in liquid (2 to 4 weeks) or solid (3 to 5 weeks) media. A culture will be considered "negative" only if no bacteria are identified after 6 to 8 weeks. Non-

tuberculous mycobacteria usually grow much faster than MTB and can be identified in a specialized laboratory often within two weeks. All new clinical isolates of MTB should undergo resistance testing.

For rapid diagnosis, mycobacterial DNA can be detected by PCR in biological specimens.

This is especially helpful in differentiating the species, when acid-fast bacilli are found on microscopic analysis. In this setting, a positive MTB-PCR is more than 95 percent sensitive for the diagnosis of tuberculosis. Unfortunately, the sensitivity of the MTB-PCR is decreased to around 40-77 % in smear-negative sputum samples (Barnes 1997). In extrapulmonary tuberculosis, where acid fast stains often remain negative, or when a rapid diagnosis is needed, for example in TB-meningitis, MTB-PCR should be performed in the initial routine evaluation. For PCR analysis, biopsies should not be fixed in formalin but rather be preserved in "HOPE" (Hepes-glutamic acid buffer-mediated organic solvent protection effect) media (Olert 2001).

Because the use of mycobacterial PCRs in the setting of acid-fast negative stains can lead to false results, these results should always be questioned.

A positive tuberculin skin test can detect an immunological memory to previous or ongoing contact with MTB antigens. However, in HIV-1 infected patients with advanced immunodeficiency and CD4+ counts of less than 200 cells/µl, the tuberculin skin test is usually non-reactive (Fisk 2003). False positive results may be found in patients who were BCG-vaccinated or who had contact to non-tuberculous mycobacteria The test should only be performed intradermally according to the method described by Mendel and Mantoux (until recently the Tine-test was still widely used in some European countries). The standardized dose that is recommended by the WHO and the IUATLD is 2 TU in 0.1ml of PPD RT23/Tween 80. In the United States and some other countries, 5 TU PPD-S, which is thought to be similar in strength, is in use. Following the intradermal occulation of the injection, the diameter of the induration along the short axis of the lower arm is measured by the ball-point technique (Sokal 1975).

In HIV-infected patients, an induration of ≥ 5 mm is positive by definition of the IDSA (Jasmer 2002). The IDSA guidelines for the interpretation of the tuberculin skin test are based on results of clinical studies that were conducted with 5 TU PPD-S in the United States and therefore cannot be directly translated to the situation in other countries, where different antigens are used and where, in certain regions, a large number of individuals have been vaccinated with BCG. In recent years, a new diagnostic approach for the diagnosis of LTBI by an ELISPOT has been developed (Lalvani 2001, Brock 2004, Hill 2004, Mori 2004, Shams 2004). This test detects the secretion of γ-interferon by mononuclear cells that are specific for MTB antigens, such as ESAT-6 and CFP-10, and it seems to be more sensitive and specific than the classical Mendel-Mantoux test. Although this test is able to detect HIV-1-infected patients with LTBI (Chapman 2002), so far it is unclear whether it is superior to the tuberculin skin test in patients with HIV infection and low CD4 counts.

Radiographic changes in tuberculosis are often unspecific and can vary substantially. While tuberculosis can mimic a variety of other pulmonary diseases, pulmonary tuberculosis can be present without obvious changes on the chest x-ray. Classical findings are diffuse upper lobe infiltrations, cavitations and reticulo-nodular infiltrations. Calcifications and scaring may be a sign of previous pulmonary tuberculosis and a clue to reactivated disease. In miliary tuberculosis, the chest x-ray shows a disseminated micronodular pattern. Patients with low CD4 counts often present with tuberculous pleural effusion without pulmonary infiltrates. In case of doubt, a CT scan of the thorax should be made, if possible. When extrapulmonary tuberculosis is diagnosed, pulmonary imaging to detect a lung focus should be performed as well as abdominal sonography to identify abscesses, bowel thickening or ascites.

Therapy

In uncomplicated cases, tuberculosis can be treated successfully with a standard 6-month course. First-line drugs include rifampin, isoniazid, ethambutol, pyrazinamide and streptomycin. Isoniazid and rifampin are the most potent of these drugs. Streptomycin is not orally available and is delivered i.v. or i.m.; it should only be included in the treatment regimen if one of the other four first-line drugs is contraindicated (drug resistance, toxicity, etc.). To avoid the development of drug resistance, active tuberculosis should always be treated initially with a combination of four drugs. Standard therapy is a two-month course of rifampin, isoniazid, ethambutol and pyrazinamide, followed by a four-month course of rifampin and isoniazid. Isoniazid should always be co-administered with pyridoxine (vitamin B6) to prevent the development of peripheral polyneuropathy. Both drugs are available in fixed combinations.

The duration of infectivity of a patient with pulmonary tuberculosis depends on the extent of pulmonary infiltrates and cavitations. Sputum should be regularly (initially every week) evaluated for the presence of AFBs by microscopy and viable mycobacteria by culture until the end of treatment. The infectivity of a patient is low once AFBs are repeatedly absent on smears. However, viable mycobacteria can usually be cultured from sputum for a few weeks following microscopic conversion. Failure of therapy occurs in the presence of drug resistance, non-compliance or insufficient treatment duration (Sonnenberg 2001, Korenromp 2003). If sputum cultures are still positive after two months of treatment, or in cases where the initial treatment regimen was different from quadruple therapy including rifampin and isoniazid, the duration of therapy should be extended to 9 months or more. Despite successful initial therapy, recurrence of tuberculosis occurs more often in HIV-seropositive than HIV-seronegative individuals (Sonnenberg 2001).

Prior to and during therapy with ethambutol, color vision should be examined. Audiometry should be performed when streptomycin is used. Dosages of ethambutol and pyrazinamide need to be adjusted in patients with renal insufficiency. In patients with liver disease (including drug-induced hepatitis), the choice of first-line drugs is limited as rifampin, isoniazid and pyrazinamide can worsen the liver injury. Alternatively, a combination of ethambutol, streptomycin, cycloserine, moxifloxacin and/or linezolid may be tried. Since this therapy is no different to that for multi-drug-resistant tuberculosis, these patients should be treated in specialized centers.

Following the initiation of antituberculous therapy, liver enzymes, serum creatinine and full blood counts should be performed on a regular basis (e.g. initially every week for two months, then every four weeks). Hyperuricemia is common when pyrazinamide is used. A mild, non-gouty polyarthralgia can be treated with allopurinol and non-steroidal antiphlogistics. Arthralgia can also be induced by rifampin and rifabutin.

Drug side effects

The most important side effects of antituberculous drugs are listed in Table 1.

Table 1: Antituberculous drugs

Antituberculous drugs	Recommended daily dose	Common side effects	Drug interactions	Comments
Rifampin (RMP)	10 mg/kg > 50 kg: 600 mg < 50 kg: 450 mg	elevation of liver enzymes, toxic hepatitis, allergy, fever; gastrointestinal disorders: anorexia, nausea, vomiting, abdominal pain; discoloration of urine and other body fluids, thrombocytopenia	many drug interactions: induces cytochrome p450, reduces effectiveness of oral contraceptive pill; for ART drug interactions see table 3	monitor LFTs
Rifabutin (RB)	300 - 450 mg/day	gastrointestinal discomfort, discoloration of urine and other body fluids, uveitis, elevated liver enzymes, arthralgia	weaker inductor of cytochrome p450 than rifampin; for ART drug interactions see table 3	monitor LFTs generally preferred over rifampin in patients treated with ART drugs (see table 3)
Isoniazid (INH)	5 mg/kg maximum 300 mg/day, administer vitamin B6	peripheral neuropathy, elevated liver enzymes, hepatitis; CNS side effects: psychosis, convulsions	avoid DDC, D4T, DDI	avoid alcohol, preexisting liver damage
Ethambutol (EMB)	40-55 kg: 800 mg/day 56-75 kg: 1.2 g/day 76-90 kg: 1.6 g/day	optic neuritis, hyperuricemia, peripheral neuropathy (rare)	antacids may decrease absorption	baseline screening for visual acuity and color perception, repeated at monthly intervals; contraindicated in pts with preexisting lesions of N. opticus

Table 1: Antituberculous drugs

Antituberculous drugs	Recommended daily dose	Common side effects	Drug interactions	Comments
Pyrazinamide (PZA)	ca. 30 mg/kg/day	arthralgia, hyperuricemia, hepatitis, elevated liver enzymes, gastrointestinal discomfort		hyperuricemia: uricosuric agents, monitor LFTs
Streptomycin (SM) i.v./i.m. administration only	0.75 – 1 g maximum cumulative dose 50 g < 50 kg: 0.75 g/day > 50 kg: 1 g/day	auditory and vestibular nerve damage, renal damage, allergies, nausea, skin rash, leukopenia, thrombocytopenia, pancytopenia, hemolytic anemia		audiometry; cumulative dose should not be exceeded; monitor renal function; should not be used in pregnancy
Capreomycin i.v./i.m. administration only	15 – 30 mg/kg/day max. 1 g/day maximum cumulative dose: 50 g > 50 kg: 1 g < 50 kg: 0.75 g	renal damage, Bartter-like syndrome, auditory nerve damage		audiometry, cumulative dose should not be exceeded, monitor renal function, should not be used in pregnancy
Prothionamide	0,75 g - 1 g/day	CNS disorders, liver damage, gastrointestinal discomfort	slowly increase dosage	monitor LFTs
Moxifloxacin (MOX)	400 mg/ day	gastrointestinal discomfort, headache, dizziness, hallucination		Similar bactericidal activity as rifampin, drug resistance is still rare
Ciprofloxacin (CFL)	2 x 500 or 750 mg/day	gastrointestinal discomfort, CNS disorders, tendon rupture (rare)		not approved for treatment in children in adults rather use moxifloxacin
Cycloserine	10 – 15 mg/kg day maximum 1000 mg/day	CNS disorders, anxiety, confusion, dizziness, psychosis, seizures, headache	aggravates CNS side effects of INH and PTH, CNS side effects occur usually within the first 2 weeks	Contraindicated in epileptics
Linezolid	600 mg BID	thrombocytopenia, anemia, CNS disorders		evidence for clinical use relies on case report outcomes, expensive

Patients who exhibit severe side effects should always be treated as inpatients. Re-introduction of the same drug should be avoided if vestibular dysfunction occurs on streptomycin therapy, visual dysfunction occurs on ethambutol therapy or renal failure, shock or thrombocytopenia occur on rifampin therapy. Treatment must then be continued with other antituberculous drugs.

If toxic hepatitis occurs, all drugs should be stopped until the serum bilirubin and transaminases have normalized. In many cases, it is possible to reintroduce the causative drug – usually isoniazid, rifampin or pyrazinamide – in an escalating dosage without further hepatic complications.

When all drugs that could possibly be responsible for a given side effect are stopped and symptoms resolve, drugs can be reintroduced one by one, beginning with the drug that is least likely to cause the adverse effect. As stated above, all drugs should be started at low dosages and dosages should be increased stepwise (Table 2). When no adverse effects occur after 3 days, additional drugs can be added. The drug that is most likely to be responsible for an adverse effect should be the last to be restarted if no alternative is available. If either pyrazinamide, ethambutol or streptomycin seem to be responsible for an adverse effect, therapy should be continued without these drugs. In all cases where second line drugs are used, it is usually necessary to prolong the duration of treatment.

Table 2: Re-Introduction of antituberculous drugs following drug reaction

Drug	Day 1	Day 2	Day 3
INH	50 mg	300 mg	5 mg/kg/d (max 300 mg/d)
Rifampin	75 mg	300 mg	10 mg/kg/d (max 600 mg/d)
Pyrazinamide	250 mg	1g	25 mg/kg/d (max 2.5 g/d)
Ethambutol	100 mg	500 mg	25 mg/kg/d for 2 months & then 15 mg/kg/d
Streptomycin	125 mg	500 mg	15 mg/kg/d i.m., also available i.v.

ART and tuberculosis therapy

Independent of the status of antiretroviral therapy (ART), uncomplicated tuberculosis in HIV-infected persons can be treated using standard therapy over 6 months with a similar success rate to that of HIV-seronegative individuals (Burman 2001, Chaisson 1996, Hung 2003). If the therapeutic response is delayed, for example when sputum cultures still show growth of MTB after 2 months of therapy, the duration of MTB-therapy should be extended to at least 9 months. In practice, parallel treatment with antituberculous drugs and ART can be problematic. Following initiation of antituberculous therapy, patients treated with ART experience paradoxical reactions, with increasing lymphadenopathy, fever or increasing pulmonary infiltrates, five times more often than ART-naïve patients (Narita 1998). In addition, adherence to the large number of drugs and pharmacological interactions of antitu-

berculous and antiviral drugs complicate the synchronous simultaneous treatment of both infections. Both rifampin and protease inhibitors (PI) are metabolized by cytochrome P450 3A. As drug levels are unpredictable, concomittant therapy with PIs and rifampin is generally not recommended (exception: ritonavir ± saquinavir and ritonavir-hyperboosted lopinavir) (Updated Guidelines 2004) (Table 3). Either the combination of 2 nucleoside reverse transcriptase inhibitors (NRTIs) with the non-nucleoside reverse transcriptase inhibitor efavirenz, or the suboptimal combination of 3 NRTIs, are possible therapeutic options for treating HIV infection when tuberculosis is treated with rifampin. As an alternative to rifampin, rifabutin, another rifamycine, is a weaker inductor of cytochrome P450-3A and can also be co-administered with PIs, although dosage adjustments have to be considered (table 4). There are no valid clinical data on the usage of rifamycines and enfurvirtide or tenofovir, but both drugs may be safe to use as they are not metabolized by cytochrome P450-3A.

Table 3: Recommendations for coadministering antiretroviral therapy with Rifampin (Updated Guidelines 2004)

	Antiretroviral dosage adjustment	Rifampin dosage adjustment
Fos-Amprenavir	Should not be used together	
Atazanavir	Should not be used together	
Indinavir	Should not be used together	
Nelfinavir	Should not be used together	
Ritonavir	None	None (600 mg/day)
Saquinavir	Should not be used together	
Lopinavir/Ritonavir	Lopinavir/ ritonavir 3 capsules + 300 mg Ritonavir BID	None (600 mg/day)
Saquinavir/Ritonavir	Saquinavir 400 mg BID, Ritonavir 400 mg BID	None (600 mg/day)
Efavirenz	↑ 800 mg/day	None (600 mg/day)
Nevirapine	200 mg BID	None (600 mg/day)
Delavirdine	Should not be used together	

Treatment of active tuberculosis always has clinical priority over the treatment of HIV.

When tuberculosis occurs in patients with advanced immunodeficiency and less than 100 circulating CD4 cells/μl, the risk of mortality is high, and parallel treatment of both infections is indicated (Dean 2002). Even in this situation, it is recommended that antituberculous therapy be started first and the initiation of ART be delayed for at least two weeks. Providing the antituberculous therapy is tolerated, ART should be introduced. However, patients need to be monitored closely, as the risk of immunereconstitution syndrome is very high.

Table 4: Recommendations for coadministering antiretroviral therapy with rifabutin (Updated Guidelines 2004)

	Antiretroviral dosage adjustment	Rifabutin dosage adjustment
Amprenavir	None	↓ 150 mg/day or 300 mg 3/week
Fos-Amprenavir	None	↓ 150 mg/day or 300 mg 3/week
Atazanavir	None	↓ 150 mg every other day or 150 mg 3/week
Indinavir	↑ 1000 mg TID	↓ 150 mg/day or 300 mg 3/week
Nelfinavir	↑ 1000 mg TID	↓ 150 mg/day or 300 mg 3/week
Ritonavir	None	↓ 150 mg every other day or 150 mg 3/week
Saquinavir	Should not be used together	
Lopinavir/Ritonavir	None	↓ 150 mg every other day or 150 mg 3/week
Ritonavir with Amprenavir, Fos-Amprenavir, Atazanavir, Indinavir or Saquinavir	None	↓ 150 mg every other day or 150 mg 3/week
Efavirenz	None	↑ 450 mg/day or 600 mg 3/week
Nevirapine	None	↑ 300 mg/day or 300 mg 3/week
Delavirdine	Should not be used together	

In patients who develop tuberculosis with CD4 counts of 100 – 200 cells/µl, the initiation of ART can be delayed for at least two months; by this time, the number of antituberculous drugs has been reduced to two for maintenance therapy. When tuberculosis occurs at CD4 counts of above 200 cells/µl, completion of antituberculous treatment prior to the initiation of ART is usually recommended. Patients who are on ART when tuberculosis develops should remain on antiviral treatment, although the therapy may have to be modified depending on the compatibility with antituberculous drugs (Dean 2002).

The most important factor for the success of antituberculous treatment is drug-adherence. In the case of non-compliance, the development of drug resistance and relapses are common. The World Health Organisation recommends that all patients with tuberculosis should therefore be treated with directly observed therapy (DOT).

Therapy of latent tuberculosis

HIV-infected patients with LTBI have a much greater risk of developing active tuberculosis compared to HIV-seronegative controls. The efficacy of prophylactic

isoniazid treatment to prevent tuberculosis in HIV-infected patients with LTBI has been demonstrated in several randomized and controlled studies (Bucher 1999). In particular, ART-naïve patients with a negative tuberculin skin test do not benefit from either primary (Bucher 1999) or secondary prophylaxis of tuberculosis (Churchyard 2003). In addition, chemoprophylaxis with INH has no positive effect on the overall mortality of these patients (Woldehanna 2004). Although ART has a very beneficial effect on the prognosis of patients who developed active tuberculosis and were treated, the effects of ART on patients with LTBI are so far not known. For the treatment of LTBI, a 9-month course of isoniazid and pyridoxine is usually recommended. A recent Cochrane review showed that in comparison to INH monotherapy, short course multi-drug regimens were much more likely to require discontinuation of treatment due to adverse hepatic effects (Woldehanna 2004). Very recently, however, others have found no evidence of liver injury associated with rifampin and pyrazinamide short course treatment in HIV-infected patients (Gordin 2004).

Drug resistant tuberculosis

Despite declining numbers of tuberculosis cases in many industrialized nations in recent years, the proportion of multidrug-resistant tuberculosis (MDR = at least resistance against rifampin and isoniazid) is rising in many countries. In Germany, in 2002, 12.1 % of all MTB isolates were resistant against one of the standard drugs; 2 % of the isolates were MDR-resistant (RKI 2004). In the future, an increase in the number of patients with drug-resistant MTB is expected worldwide. In some areas, such as the Baltic region, the rate of INH-resistant isolates is already greater than 25 % (Morozova 2003). Under these circumstances, selection of the correct drug for treatment of LTBI becomes problematic.

Where possible, patients with MDR tuberculosis should be treated in specialized centers familiar with second-line antituberculous drugs, and should not be discharged before producing repeatedly negative sputum cultures.

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Atypical Mycobacteriosis (MAC)

Atypical mycobacterioses are usually synonymous for infections with Mycobacterium avium complex (MAC). Although MAC is by far the most frequent pathogen, numerous other atypical mycobacterioses exist that cause a similar disease pattern, such as M. celatum, M. kansasii, M. xenopi or M. genavense. MAC bacteria are ubiquitous and can be found in diverse animal species, on land, in water and in food. Exposure prophylaxis is therefore not possible. Isolation of infected patients is also not necessary. While MAC may be detectable in the sputum or stool of asymptomatic patients (colonization), only patients with massive immunodeficiency and less than 50 CD4 T cells/µl develop disease (Horsburgh 1999). This used to include up to 40 % of AIDS patients in the pre-HAART era (Nightingale 1992).

The infection has now become very rare (Karakousis 2004). However, it remains important, as it has developed into a completely new disease in the HAART era. It previously occurred mainly with a chronic, disseminated course of disease, often in patients with wasting syndrome. MAC infections under HAART now occur more frequently in a localized form, almost always related to an immune reconstitution syndrome (see below). The disease now occurs with manifestations that were previously never seen (see below).

Signs and symptoms

The symptoms of *disseminated* MAC infection are usually unspecific. When the CD4 count is less than 100 cells/µl, fever, weight loss and diarrhea should always lead to consideration of atypical mycobacteriosis. Abdominal pain may also occur. As described above, disseminated MAC infection has now become rare.

Localized forms are far more frequent. These include slowly resolving localized lymph node abscesses, which may occur practically everywhere. We have seen abscesses in cervical, inguinal and also abdominal lymph nodes that may develop fistulae and resolve only slowly even after surgical intervention. Any abscess associated with severe immunosuppression and immune reconstitution is highly suspicious of MAC! In addition to skin lesions, localized forms frequently include osteomyelitis, particularly of the vertebrae, and septic arthritis (observed: knee, hand, fingers).

Diagnosis

Diagnosis of the disseminated form is often difficult. Blood cultures (heparinized blood) should always be sent to a reference laboratory. Although atypical mycobacteria usually grow more rapidly than TB bacteria, the culture and final distinction from TB may take weeks. In cases presenting with anemia, bone marrow aspiration is often successful. If atypical mycobacteria are detected in the stool, sputum or even BAL, it is often difficult to distinguish between infection requiring treatment and mere colonization. In such cases, treatment should not be initiated if general symptoms are absent. This is also true for *Mycobacterium kansasii* (Kerbiriou 2003).

Laboratory evaluations usually show elevated alkaline phosphatase, a finding that should always cause suspicion of MAC in severely immunosuppressed patients.

Similarly, MAC infection should be considered in any cases of newly occurring anemia and constitutional symptoms. Cytopenia, particularly anemia, often indicates bone marrow involvement. Ultrasound reveals enlargement of the liver and spleen. Lymph nodes are often enlarged, but become apparent primarily due to their number rather than their size (Gordin 1997). Here, differential diagnoses should always include TB or malignant lymphoma.

Direct specimens should always be obtained for localized forms, as identification of the organism from material drained from the abscess is usually successful.

Treatment

Treatment of MAC infection detected from culture is complex. Similarly to TB, monotherapy does not suffice. Since 1996, many clinicians prefer the combination of a macrolide (clarithromycin or azithromycin) with ethambutol and rifabutin (Shafran 1996). In the past, this treatment was given lifelong; today it is generally considered sufficient to treat for at least six months and until a HAART-induced increase in the CD4 count to above 100 cells/µl has been achieved. After publication of data indicating that rifabutin may be omitted from the regimen (Dunne 2000), the multicenter, randomized ACTG 223 Study demonstrated survival benefit with the triple combination C+R+E compared to C+E and C+R – mortality rates were halved in the triple combination arm (Benson 2003).

Due to the high potential for interactions, however, rifabutin should be discontinued after several weeks when clinical improvement is observed. The clarithromycin dose should not exceed 500 mg bid. In at least two randomized studies, there was a significantly higher number of deaths in treatment arms with a higher clarithromycin dose, for reasons that remain unclear (Chaisson 1994, Cohn 1999). Instead of clarithromycin, azithromycin can also be given, which is cheaper (difference more than 50 Euro/month) and interacts less with cytochrome P450 enzymes. Azithromycin and clarithromycin have comparable efficacy in combination with ethambutol (Ward 1998).

In general, every MAC therapy has a high potential for side effects and drug interactions. All concomitant medications, including HAART, should be carefully examined – dose adjustments are frequently required and there may be contraindications (see Drugs section).

Reserve drugs such as amikacin, quinolones or clofazimine are only required in rare cases today. It is important to perform resistance testing for all atypical mycobacterial infections with species other than M. avium complex.

We have generally stopped treatment of localized MAC infections when the abscess has healed – this usually takes several months. In individual cases, steroids may be helpful temporarily. However, there are no specific guidelines for treatment of local MAC infections.

Prophylaxis

Large placebo-controlled trials in the US have shown that both the macrolides, clarithromycin and azithromycin as well as rifabutin, significantly reduce MAC morbidity and mortality when used for primary prophylaxis in severely immunocompromised patients (Havlir 1996, Nightingale 1992, Pierce 1996, Oldfield 1998).

Prophylaxis also leads to substantial reduction of costs (Sendi 1999). MAC infections are more rare in Europe. As a result, and because of concerns over compliance and development of resistance, few patients in Europe receive primary MAC prophylaxis (Lundgren 1997).

For patients failing currently available HAART regimens and without new treatment options, prophylaxis with a macrolide should be considered at low CD4 cell counts (below 50 cells/µl). Weekly dosing with azithromycin is convenient for patients and has comparable efficacy to daily rifabutin (Havlir 1996).

Primary prophylaxis and maintenance therapies can be discontinued quite safely at CD4 T cell counts above 100/µl (Currier 2000, El Sadr 2000, Shafran 2002, Aberg 2003). It is possible that even partial viral suppression suffices for MAC-specific immune reconstitution (Havlir 2000). Complete recovery as a result of immune reconstitution is possible (Aberg 1998).

Treatment/prophylaxis of MAC (daily doses, if not specified otherwise)

Acute therapy		
Treatment of choice	Clarithromycin + ethambutol + possibly rifabutin	Clarithromycin 1 tbl. à 500 mg bid plus ethambutol 3 tbl. à 400 mg qd plus rifabutin 2 tbl. à 150 mg qd
Alternative	Azithromycin + ethambutol + possibly rifabutin	Azithromycin 1 tbl. à 600 mg qd plus Ethambutol 3 tbl. à 400 mg qd plus rifabutin 2 tbl. à 150 mg qd
Maintenance therapy		As for acute therapy, but without rifabutin Discontinue if > 100 CD4 T cells/µl > 6 months
Primary prophylaxis		Consider for CD4 cells below 50/µl Discontinue if > 100 CD4 T cells /µl > 3 months
Treatment of choice	Azithromycin	Azithromycin 2 tbl. à 600 mg/week
Alternative	Clarithromycin	Clarithromycin 1 tbl. à 500 mg bid

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Herpes simplex

Infections with herpes simplex viruses are a frequent and inconvenient problem for HIV-infected patients (Chang 1995). Two viruses should be distinguished. HSV-1 is transmitted by direct contact with mucosal membranes, as well as by kissing, and causes the typical, itchy perioral herpes blisters on the lips, tongue, gums or buccal mucosa. HSV-2 is sexually transmitted and leads to herpetiform lesions on the penis, vagina, vulva and anus. Herpes lesions have a tendency to spread with decreasing immune status. Chronic disease is frequent, particularly with severe immunodeficiency (below 100 CD4 T cells/µl). In severe cases, other organs may be affected. These include mainly the esophagus (ulcers), CNS (encephalitis), eyes (keratitis, keratoconjunctivitis, uveitis) and respiratory tract (pneumonitis, bronchitis). In such cases and with persistence of lesions for a period of more than four weeks, herpes simplex infection is an AIDS-defining illness.

Signs and symptoms

The typical blisters itch and burn. Oral involvement may impair food intake. In cases of genital or anal herpes (proctitis!), urination and defecation can be very painful. Extensive lesions may occur with severe immunosuppression. Regional lymph nodes are often enlarged. The clinical symptoms of disseminated disease depend on the organs affected.

Diagnosis

Diagnosis of oral, genital or perianal herpes can often be made clinically. If there is doubt, swabs should be taken, placed in viral culture media and rapidly transported to the laboratory. The diagnosis of organ manifestations usually requires histology. Diagnosis is particularly difficult for HSV encephalitis, as cerebrospinal fluid often does not help. Serologies are only useful if they are negative, therefore making HSV infection improbable.

Treatment

For patients with a good immune status and only discrete lesions, topical treatment with acyclovir cream or ointment is adequate. Penciclovir cream is probably as effective as acyclovir (Chen 2000). In general, every treatment, whether topical, oral or systemic, is more effective if started early.

The nucleoside analog acyclovir remains the treatment of choice for systemic treatment. Acyclovir inhibits the DNA polymerase of herpes viruses. Resistance remains rare, even in AIDS patients, despite the fact that this agent has been used since 1977 and numerous generics are now available (Levin 2004). Acyclovir is usually well tolerated and effective against both HSV-1 and HSV-2. In severe cases with mucocutaneous or organ involvement, intravenous treatment should be started immediately. As CNS levels are lower than in plasma, higher doses should be given for encephalitis.

Valacyclovir and famciclovir are equally effective alternatives to acyclovir (Ormrod 2000, Conant 2002), though significantly more expensive (more than

120 €/week!) and not yet licensed for treatment of immunocompromised patients. The main advantage of newer virostatics is their improved oral bioavailability – they require less frequent dosing. Brivudin remains a good alternative for HSV-1 and VZV. However, foscarnet should only be used in exceptional cases due to its significant toxicity. Newer drugs that, unlike acyclovir, do not inhibit DNA polymerase but helicase, another herpes virus enzyme, have been more effective than acyclovir and well tolerated in animal studies – their value for clinical use remains to be shown (Kleymann 2002, 2003).

Prophylaxis

Primary prophylaxis is not recommended. However, a meta-analysis of almost 2,000 patients in 8 randomized studies showed that acyclovir can reduce the risk of both HSV and HZV disease by more than 70 %. Even mortality was reduced by 22 % (Ioannidis 1998). Although this data received much attention in the past, the introduction of HAART has changed its relevance. Nevertheless, it can still make sense, even today, to treat persistent recurring episodes with long-term low dose acyclovir or valacyclovir (DeJesus 2003, Warren 2004).

Treatment/prophylaxis of HSV infection (daily doses)

Acute therapy		Duration: 7-14 days
Treatment of choice	Acyclovir	Acyclovir 1 tbl. à 400 mg 5x/day
Severe cases		Acyclovir ½-1 amp. à 500 mg tid (5-10 mg/kg tid) i.v.
Alternatives	Valacyclovir	Valacyclovir 2 tbl. à 500 mg tid
Alternatives	Famciclovir	Famciclovir 1 tbl. à 250 mg tid
Alternatives	Brivudin	Brivudin 1 tbl. à 125 mg qd
Prophylaxis		Not recommended

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Herpes zoster

Herpes zoster is the reactivation of an earlier infection with varicella virus, which subsequently resides lifelong in the spinal ganglia. Herpes zoster episodes occur even in HIV patients with relatively good immune status, and are also seen during immune reconstitution (Martinez 1998). With more advanced immunodeficiency, herpes zoster tends to become generalized. In addition to involvement of one or more dermatomes, dangerous involvement of the eye (affecting the ophthalmic branch of the trigeminal nerve, "herpes zoster ophthalmicus", with corneal involvement) and ear (herpes zoster oticus) may occur. Most feared is involvement of the retina with necrotizing retinitis. The neurological complications include meningoencephalitis, myelitis and also involvement of other cranial nerves (Brown 2001).

Signs and symptoms

There are often prodromal signs with headache, malaise and photophobia, accompanied only rarely by fever. The affected areas are initially hypersensitive, and then become pruritic and/or painful within hours or days. Pain can precede lesions by several days. Lesions often show segmental (always unilateral!) erythema with herpetiform blisters within one or more dermatomes. Lesions ulcerate, are often hemorrhagic, and gradually dry up. They should be kept dry and clean to avoid bacterial superinfection.

Involvement of several dermatomes often leaves treatment-resistant pain syndromes with zoster neuralgia. Post-herpetic neuralgia can be assumed if pain persists even after more than a month (Gnann 2002).

Diagnosis

Cutaneous involvement usually allows clinical diagnosis of herpes zoster. However, diagnosis may be difficult especially on the extremities and in complicated zoster cases. Typical cases do not require further diagnostic tests. If there is uncertainty, a swab may be taken from a blister and sent to the laboratory in viral culture media. An immunofluorescence assay is presumably more reliable. VZV encephalitis is only detectable through analysis of CSF by PCR. Herpes zoster oticus should be considered in cases of unilateral, peracute hearing loss, which is not always visible from the outside. Either examine the ear yourself or consult an ENT specialist! For visual impairment the same rules apply as for CMV retinitis – refer to the ophthalmologist as quickly as possible!

Treatment

Monosegmental zoster can be treated on an outpatient basis with oral acyclovir. Rapid initiation of treatment is important. Systemic therapy is always necessary, and doses are higher than for HSV. Lesions dry up more rapidly if calamine lotion is used, which also relieves pain. Wear gloves! Lesions are highly infectious initially, and unvaccinated individuals without a history of chickenpox should not come into close contact with a case of herpes zoster.

Analgesics should be given generously. Any complicated, multi-segmental or facial herpes zoster should always be treated with intravenous therapy. This can also be done in ambulatory care with a competent nursing service.

As with HSV, several alternatives for treatment include valacyclovir, famciclovir and brivudin. The unpleasant post-herpetic neuralgia occurs significantly less frequently under these drugs than under acyclovir in HIV-negative patients (Gnann 2002). However, valacyclovir, famciclovir and brivudin have not been tested widely in HIV patients, and are not licensed for treatment of immunocompromised patients. They are also more expensive (up to 120 €/week) than the numerous acyclovir formulations. Acyclovir resistance may occur in the thymidine kinase gene, but is rare (Gershon 2001, Saint-Leger 2001). In these cases, foscarnet can be given.

Pain management of post-herpetic neuralgia is very problematic. Carbamazepine or gabapentin only partially help. Data from immunocompetent individuals indicates that neuralgia is less frequent and resolves more rapidly under valacyclovir than acyclovir. Steroids are generally not advised (Gnann 2002).

Prophylaxis

Varicella vaccination, previously contraindicated in HIV patients, seems to be fairly safe and effective in patients with more than 400 CD4 T cells/µl, as shown in a placebo-controlled study (Gershon 2001). It should at least be considered if VZV serology is negative. In individuals with negative serology and exposure to VZV (highly infectious!), administration of hyperimmunoglobulin (2 mg/kg i.v.) may be attempted in individual cases. Long-term primary prophylaxis is not advised. Some dermatologists, however, do recommend long-term therapy with low doses if there are persistently recurring episodes.

Treatment/prophylaxis of VZV infection (daily doses)

Acute therapy		Duration: at least 7 days
Treatment of choice	Acyclovir	Acyclovir 1 tbl. à 800 mg 5x/day
Severe cases		Acyclovir 1-2 amp. à 500 mg tid (10 mg/kg tid) i.v.
Alternatives	Valacyclovir	Valacyclovir 2 tbl. à 500 mg tid
Alternatives	Famciclovir	Famciclovir 2 tbl. à 250 mg tid
Alternatives	Brivudin	Brivudin 1 tbl. à 125 mg qd
Prophylaxis		Not recommended

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Progressive multifocal Leukoencephalopathy

PML is a severe demyelinating disease of the central nervous system. It is caused by JC virus (JCV), a polyoma virus found worldwide. JCV was named after the initials of the first patient, from which this simple DNA virus was first isolated in 1971 (Major 1992). JC therefore has no connection, as is often wrongly assumed, with Jakob-Creutzfeld syndrome. As seroprevalence is high, at up to 80 %, latent persistent infection is assumed. Only impaired cellular immunity leads to reactivation of JCV and manifestation of disease. It seems certain that JCV reaches the CNS via leukocytes, and affects mainly oligodendrocytes and therefore the cells comprising the myelin sheaths. Destruction of these is macroscopically apparent as multifocal demyelination. The main focus of disease is the white matter of the cerebral hemispheres, but the cerebellum and in some cases the grey matter may also be affected. Severe immunodeficiency is frequently seen, but not obligatory for development of PML. In contrast to CMV or MAC infection, PML does not always indicate the final stages of HIV infection. Although CD4 T cells are usually below 100/µl at manifestation of disease, PML may also occur at above 200 CD4 T cells/µl. The decrease in incidence is not as marked as with other OIs. After cerebral toxoplasmosis, it is now probably the second most common neurological OI (Antinori 2001).

Prognosis was poor in the pre-HAART era. The median interval between the onset of the first symptoms and death was between 3 and 6 months. Patients usually died of secondary complications after being bedridden for many weeks. The prognosis is slightly better at CD4 counts above 200/µl (Berger 1998). Disease progression seems to be much slower under HAART, and even complete remission seems possible (Albrecht 1998). However, these effects are not as impressive as for other OIs: in a Spanish study of 118 PML patients on HAART, 64 % were still alive 2.2 years after diagnosis (Berenguer 2003). Complete remissions are not the rule, even under sufficient HAART. They mainly occur in cases of inflammatory PML, which occurs in the course of an immune reconstitution syndrome (Du Pasquier 2003, Hoffmann 2003).

Signs and symptoms

Although there is a broad spectrum of PML symptoms due to the variety of localized areas of demyelination, the clinical signs and course of disease have several common characteristics. In addition to cognitive disorders, which may range from mild impairment of concentration to dementia, focal neurological deficits are very typical of PML. Mono- and hemiparesis are observed most frequently, as well as speech and even visual deficits. We have seen several blind patients with PML. These deficits may be isolated and initially present as discrete changes in coordination, rapidly leading to considerable disabilities. Epileptic seizures may occur. Loss of sensibility, fever or headache are rare and are usually more typical of cerebral toxoplasmosis.

Diagnosis

Clinical suspicion of PML should be rapidly confirmed radiologically. But beware: a CCT scan is not helpful – it does not clearly reveal the (hypodense) lesions. MRI is much more sensitive for detecting both the number and size of lesions than CCT and usually shows high signal intensity lesions in T2-weighted imaging and in FLAIR sequence, which are hypointense in T1-w and usually show no gadolinium enhancement or mass effect. HAART immune reconstitution may result in inflammatory courses that may involve quite significant enhancement (see Immune reconstitution syndrome). Exclusion of grey matter is typical – since this is a leukoencephalopathy. Also of note: lesions are almost always asymmetrical!

MRI often allows distinction from cerebral toxoplasmosis or lymphoma. However, the huge, extensive lesions covering an entire hemisphere, that are often shown in textbooks, are not always present. Every PML starts small – very discrete, localized, solitary lesions can occur and certainly do not exclude the diagnosis. PML can occur everywhere in the brain, and there are no typically susceptible areas. Lesions are often parieto-occipital or periventricular, but the cerebellum may also be involved. It is important that the images are assessed by a radiologist or clinician familiar with PML. Even then, it is difficult to distinguish PML from HHV-6 infection (Caserta 2004) or HIV leukoencephalopathy (Langford 2002).

Clinicoradiological diagnosis is therefore not definitive. Examination of cerebrospinal fluid is important. Generally, if there is no other co-infection, unspecific inflammatory signs are absent, although the total protein content is usually slightly elevated. Pleocytosis is rarely seen, and more than 100/3 cells make PML unlikely. CSF should always be tested for JCV. Newer PCR methods have a sensitivity of around 80 % and a specificity of over 90 %. A CSF sample should be sent to a JCV-experienced laboratory.

PML is very probable in cases of clinicoradiological suspicion and positive JCV PCR. In such cases, brain biopsies are no longer recommended today. Nevertheless, negative PCR does not exclude the diagnosis. Levels of JCV viral load may vary significantly and do not correlate with the extent of lesions (Eggers 1999, Garcia 2002). Unfortunately, JCV PCR is even less useful in the HAART era – many patients with PML have a low or undetectable JCV CSF viral load under HAART (Di Giambenedetto 2003). Stereotactic brain biopsy may become necessary in individual cases.

Treatment

A specific PML treatment is not available. Numerous strategies such as foscarnet, interferon, immune stimulants and even steroids have been abandoned after only modest successes. Cytosine arabinoside is also no longer recommended following the disappointing results of a randomized study (Hall 1998). Cidofovir and camptothecin are the two new drugs currently being discussed. It is feared that these drugs will have a similar fate in controlled studies. Camptothecin is an alkaloid cytostatic, which inhibits topoisomerase I, a nuclear enzyme that is required for DNA and therefore also JCV replication (O'Reilly 1997). Currently, only data from case studies and a small series of patients exist (Vollmer-Haase 1997, Royal 2003). In the small, usually uncontrolled studies described to date, cidofovir has had positive

effects in some, but not all cases (De Luca 2001, Gasnault 2001, Herrero-Romero 2001, Marra 2002, Wyen 2004). Our own experience has been rather disappointing and, in a retrospective analysis of 35 patients, cidofovir was even associated with a poorer prognosis. However, this chiefly reflects the frustration of patients and clinicians – cidofovir was mainly used in cases of progressive disease (Wyen 2004), and should therefore only be used in exceptions if HAART or optimization is not possible, or patients deteriorate clinically despite sufficient HAART.

In our view, the absolute priority should currently be to optimize ART in cases of PML. In 1998, we were able to show that prognosis significantly improved under HAART (Albrecht 1998). This has been confirmed by several other groups (Clifford 1999, Dworkin 1999, Gasnault 1999, Tantisiriwat 1999). As synergism between HIV and JCV has been demonstrated in vitro, maximal HIV suppression should at least be achieved. Although progression of disease has been described under sufficient antiretroviral therapy, HAART often remains the only real hope for patients today.

Treatment/prophylaxis of PML

Acute therapy		
Treatment of choice	HAART	The most important goal is maximal HIV suppression and immune reconstitution!!!
Experimental	Cidofovir	Cidofovir 5 mg/kg i.v. every 7-14 days (plus probenecid/ hydration per protocol, see Drugs section)
Prophylaxis		Not available

Prophylaxis

There is none. Exposure prophylaxis is also not possible.

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Bacterial pneumonia

Bacterial pneumonia occurs even with relatively good immune status (above 200 CD4 T cells/µl). It is not as closely associated with immunodeficiency, and the decrease in incidence since the HAART era has been more moderate than for other opportunistic infections. Only recurring, radiologically and culturally detected acute pneumonia (more than one episode in the last 12 months) is considered AIDS-defining. As with HIV-negative patients, community-acquired pneumonia should be distinguished from nosocomial pneumonia. Travel history is important, particularly for community-acquired pneumonia.

The bacteria that are most frequently found to cause community-acquired pneumonia in HIV patients are Pneumococcus and Hemophilus influenza. Mycoplasma is important to consider, particularly in younger patients. Klebsiella, Staphylococcus aureus and Pseudomonas aeruginosa are other important pathogens. Legionella are rare. I.v. drug users develop community-acquired pneumonia significantly more often than other patient groups.

Nosocomial pneumonia is often caused by hospital germs (Klebsiella, Staphylococcus, Pseudomonas). In such cases, treatment depends on local resistance patterns and experience (Gant 2000, Vogel 2000).

Signs and symptoms/ Diagnosis

Acute, usually high, fever and productive cough are typical. Breathing may be painful because of accompanying pleuritis, but real dyspnea is rare. Auscultation almost always allows distinction from PCP. If something can be heard, PCP is unlikely! Chest radiography secures the diagnosis. CRP is significantly elevated, LDH usually normal. It is essential to take several blood cultures at body temperatures above 38.5˚C before starting treatment. Sputum culture is a simple method allowing determination of etiology in approximately half of all cases – however, its overall utilization remains controversial (Cordero 2002).

Treatment

General

Treatment of bacterial pneumonia in HIV patients is similar to that in HIV-seronegative patients. Therapy should always begin empirically, without waiting for sputum or blood culture results. The majority of HIV patients can be treated as out-patients. Patients with poor immune status, very high fever (above 39.5 ˚C), poor compliance, signs of organ failure, CNS disorders (confusion) and poor vital signs (tachypnea, tachycardia, hypotonia), as well as older patients (above 65 years), should be hospitalized immediately.

Sufficient hydration is important in all patients. If patients remain in ambulatory care, this means that they must drink a lot (more than 2 l daily). The use of supportive therapy with expectorants or mucolytics such as N-acetylcysteine or antitussives is controversial.

Medication

Different drugs are possible for ambulatory treatment. Even an attempt with penicillin may be justified in some circumstances – depending on local rates of Pneumococcus and Hemophilus influenzae resistance. HIV patients frequently develop allergies.

Aminopenicillins are effective against Hemophilus influenza and various gram negatives. However, when combined with clavulanic acid, which is active against beta-lactamase-producing bacteria, they are associated with more gastrointestinal complaints.

Newer oral cephalosporins have a broader spectrum against gram negatives, while at the same time having good efficacy against Pneumococcus and Hemophilus. They are, however, comparatively expensive.

Macrolides are advantageous for atypical bacteria such as Mycoplasma, Chlamydia and Legionella – but the proportion of macrolide-resistant Pneumococcus is increasing (14 % in Germany).

For quinolones, it should be noted that ciprofloxacin has no or only weak efficacy against many important pathogens. Therefore only newer quinolones should be used.

If patients are hospitalized, intravenous administration is possible initially. In these cases, at least two antibiotics should be combined.

Targeted treatment after isolation of the pathogen, and, in particular, treatment of nosocomial pneumonia, should depend on local resistance patterns and the recommendations of the in-house microbiologist.

Prophylaxis

The Pneumovax™ vaccine provides effective protection. It should be utilized in all HIV patients with adequate immune status (above 200 CD4 cells/µl).

Empiric treatment/prophylaxis of community-acquired bacterial pneumonia (daily doses) - there may be significant differences in price!

Outpatient		Duration: 7-10 days
Mild	Amoxicillin + clavulanic acid	1 tbl. à 875/125 mg tid
Mild	Clarithromycin	1 tbl. à 500 mg bid
Mild	Roxithromycin	1 tbl. à 300 mg qd
Mild	Cefuroxim	1 tbl. à 500 mg bid
Mild	Cefpodoxim	1 tbl. à 200 mg bid
Mild	Moxifloxacin	1 tbl. à 400 mg qd
Inpatient		
Severe	Piperacillin (+ tazobactam)	Tazobac® 1 bottle à 4.5 g i.v. tid **plus**
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd **or** clarithromycin 1 tbl. à 500 mg bid
Severe	Ceftriaxon	Cefriaxon 1 infusion. à 2 g qd i.v. **plus**
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd **or** clarithromycin 1 tbl. à 500 mg bid
Severe	Cefuroxim	Cefuroxim 1 infusion à 1.5 g tid i.v. **plus**
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd **or** clarithryomcin 1 tbl. à 500 mg bid
Prophylaxis	Vaccination (pneumococcal polysaccharide)	Pneumovax 23® pre-filled syringe i.m.

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Cryptosporidiosis

Cryptosporidiosis is a parasitic intestinal disease with fecal-oral transmission. It is mainly caused by the protozoon Cryptosporidium parvum, and may affect both immunocompetent and immunocompromised hosts (very good review in: Chen 2002). First described in 1976, cryptosporidia are among the most important and most frequent causes of diarrhea worldwide. Important sources of infection for this intracellular parasite include animals, contaminated water and food. The incubation period lasts approximately 10 days. While diarrhea almost always resolves within a few days in otherwise healthy hosts or in HIV patients with CD4 counts greater than 200 cells/µl, cryptosporidiosis is often chronic in AIDS patients. Particularly in severely immunocompromised patients (below 50 CD4 T cells/µl), diarrhea may become life threatening due to water and electrolyte losses (Colford 1996). Only chronic, and not acute, cryptosporidiosis is AIDS-defining.

Signs and symptoms

The typical watery diarrhea can be so severe that it leads to death as a result of electrolyte loss and dehydration. 20 bowel movements daily are not uncommon. Tenesmus is frequent, and there is often nausea and vomiting. However, the symptoms are highly variable. Fever is usually absent. The biliary ducts may occasionally be affected, with elevation of biliary enzymes.

Diagnosis

When sending in stool samples, it is important to specifically inform the responsible laboratory of the clinical suspicion. Otherwise cryptosporidia are often overlooked. If the laboratory is experienced and receives the correct tip, just one stool sample is usually sufficient for detection. Antibodies or other diagnostic tests are not helpful. The differential diagnosis should include all diarrhea-causing pathogens.

Treatment

No specific treatment has been established to date. Diarrhea is self-limiting with a good immune status; therefore, poor immune status should always be improved with HAART – and this often leads to resolution (Carr 1998, Miao 2000). To ensure absorption of antiretroviral drugs, generous symptomatic treatment with loperamide and/or opium tincture is advised. If this is unsuccessful, treatment with other anti-diarrheal medications, perhaps even sandostatin, can be attempted. Sufficient hydration is important – this may even require infusions.

We have seen good results in individual cases with the antihelminthic agent nitazoxanide, for which efficacy was shown in a small, randomized study and which is possibly the first drug with real efficacy for treating cryptosporidia (Rossignol 2001). However, a study in African children with cryptosporidiosis showed an effect only in HIV-negative and not in HIV-infected children (Amadi 2002). Unfortunately, the FDA was not satisfied with the data available and as a result, nitazoxanide has only been licensed in the USA for non-immunosuppressed children under 11 years of age. There is no approval for AIDS patients, either in the USA or in Germany, and this is unlikely to change in the near future. There are often problems

with health insurance providers as a result. However, it is possible to obtain nitazoxanide through an expanded access program, by contacting the manufacturer, Romark, directly: http://romark.com.

If immune reconstitution cannot be achieved and the health insurance provider refuses, options become very limited: paromomycin, a nonabsorbed aminoglycoside antibiotic, is available in powder and tablet form, and has been used by many clinicians since a small, uncontrolled study showed a favorable effect on diarrhea (White 2001). In the only double-blind randomized study to date, however, there was no advantage over placebo (Hewitt 2000). There is possibly an effect in combination with azithromycin (Smith 1998).

Treatment/prophylaxis of cryptosporidiosis (daily doses)

Acute therapy		
Symptomatic	Loperamide +	Loperamide 1 cap à 2 mg 2–6 times daily **or**
		loperamide solution 10 ml (10 ml = 2 mg) 2–6 times daily **and/or**
	opium tincture	Opium tincture 1 % = 5–15 drops qid
Symptomatic	Octreotide	Sandostatin solution for injection 1 amp à 50 µg s.c. bid or tid (increase dose slowly)
Curative attempt	Nitazoxanide	Nitazoxanide 1 tbl. à 500 mg bid
Curative attempt	Paromomycin + azithromycin	Paromomycin 1 packet à 1 g tid **plus** azithromycin 1 tbl. à 600 mg qd
Prophylaxis		Exposure prophylaxis: no tap water

Prophylaxis

There is no generally accepted prophylaxis, although retrospective analyses have reported a protective effect of rifabutin and clarithromycin (Holmberg 1998). In our opinion, it is more important that patients, at least in countries with hygiene problems, do not drink tap water. Contact with human and animal feces should be avoided. We have observed that patients mainly become ill during the summer months, often after swimming in rivers. Cryptosporidia are resistant to most disinfectants. In hospital, however, the usual hygiene measures (gloves!) are adequate. Patients need not be isolated, but should not be put in the same room as other significantly immunocompromised patients.

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Cryptococcosis

Infection with the yeast *Cryptococcus neoformans* is feared, even though it is a rare AIDS-defining illness in areas such as Europe. In the USA and Southeast Asia, cryptococcosis is much more frequent and it is one of the most important AIDS-defining illnesses worldwide. *C. neoformans* is probably transmitted via inhalation. Bird droppings are an important reservoir. The pulmonary infection may remain subclinical in immunocompetent patients, but is almost always followed by disseminated disease in HIV patients. Apart from the lungs, the main manifestation after hematogenic spread is in the CNS. CSF examination is therefore obligatory in every suspected case. However, isolated skin manifestations and lymphadenitis also occur. Organ involvement, such as in the urogenital or gastrointestinal tract, is rare.

Cryptococcosis almost always occurs with severe immunodeficiency. In a collection of 114 cases, 87 % had less than 100 CD4 T cells/µl; the median CD4 count was 30 cells/µl (Weitzel 1999). Cryptococcosis is fatal if untreated. Treatment is lengthy, complicated and should be started only on an inpatient basis. Relapses were frequent in the pre-HAART era and occurred in at least 15 % of cases.

Signs and symptoms

The CNS manifestation with encephalitis is the most frequent (ca. 80 %). Patients complain mainly of headache and fever. Clouding of consciousness (confusion) rapidly progresses over a few days. Disorders of gait, hearing or vision as well as paresis, particularly of the cranial nerves, may occur; in such cases intracranial pressure is almost always increased! However, meningeal symptoms are usually absent. In the course of an immune reconstitution syndrome, clinical symptoms are often atypical and characterized by extensive abscesses (Manfredi 1999).

Pulmonary disease leads to symptoms of atypical pneumonia with unproductive cough and chest pain. Skin lesions can initially resemble molluscum contagiosum, and later become confluent in the form of larger, ulcerative lesions.

Diagnosis

Cryptococcosis is life threatening, and the mortality rate in larger studies is between 6 and 25 % (Saag 2000). There is no time to lose during diagnostic testing. Rapid and extensive examination of the lungs and CNS in particular should be initiated in every suspected case (e.g. positive cryptococcal antigen test). The chest x-ray usually does not reveal much; therefore it is important to perform an HRCT scan if pulmonary involvement is suspected. The lesions may present very variably. Diffuse, small lesions similar to tuberculosis may occur, but there can also be sharply defined infiltrates reminiscent of bronchopneumonia. Cavitation and bronchiectasis may also be present. Every attempt should therefore be made to isolate the causative organism by BAL.

An MRI scan of the head should always be performed if there are neurological symptoms. However, in contrast to toxoplasmosis and cerebral lymphoma, it usually does not reveal much, and isolated or multiple mass lesions (cryptococcomas) are very rare. Nevertheless, intracranial pressure is often increased (fundoscopy: papillary edema?).

The most important test for cryptococcosis is lumbar puncture (after fundoscopy and MRI!). Diagnosis can be made via India ink stain in almost all cases. CSF must be examined even in cases with pulmonary or other manifestation to exclude CNS involvement. Cryptococcal antigen in the blood (titer > 1:8) is a good parameter and should always be determined. Blood cultures are also often positive. With cutaneous involvement, the diagnosis is usually made from a biopsy.

Treatment

Meningitis immediately requires a combination of antimycotics during the acute phase of treatment, followed by maintenance therapy with fluconazole (Saag 2000).

Combination prevents resistance and allows reduction of acute therapy to 4-6 weeks. The choice of combination is not clearly defined. In Germany, combination therapy with the three antimycotics amphotericin B, flucytosine and fluconazole is often used for meningitis; this is considered the treatment of choice. It leads to complete remission of meningitis in around 80 % of cases (Weitzel 1999), possibly a slightly higher rate than under dual therapy with amphotericin B and flucytosine as favored in the United States (van der Horst 1997).

However, recent data is raising questions as to the superiority of triple therapy. In one smaller, randomized study of 64 patients in Thailand, the combination of amphotericin B and flucytosine was the most effective treatment, according to measurements of cryptococcal clearance in the CSF (Brouwer 2004). It was even significantly better than triple therapy and also amphotericin B and fluconazole.

Nevertheless, in view of the toxicity of flucytosine (which is now only available for infusion, but not in tablet form), we currently prefer the combination of amphotericin B and fluconazole. In untreated patients, we almost always start HAART during the acute phase of treatment.

In addition to having significantly lower toxicity, liposomal amphotericin B is slightly more effective than conventional amphotericin B (Leenders 1997, Hamill 1999). However, even combinations with liposomal amphotericin B are very toxic. Daily monitoring of kidney and liver enzymes, blood count and electrolytes are highly recommended. Fluconazole should be administered as an infusion, particularly in confused patients.

In cases of isolated pulmonary involvement (CSF negative!) or other extracerebral manifestations, we treat without flucytosine and complete the acute therapy with amphotericin B and fluconazole within two instead of four weeks. If there is a positive cryptococcal antigen test without evidence of CNS, pulmonary or other infection, we treat with fluconazole alone.

Treatment success is monitored based on the clinical course and repeated lumbar punctures. CSF is negative in approximately 60 % of cases after two weeks (Saag 2000). When this is the case, maintenance therapy or secondary prophylaxis can be started, though not sooner than after four weeks of acute therapy. If there is increased intracranial pressure, CSF drainage may become necessary. Steroids are ineffective (Saag 2000).

Prophylaxis

Fluconazole is given as secondary prophylaxis or maintenance therapy. It is significantly more effective than itraconazole – in a very large randomized study, the relapse rate in the fluconazole arm was only 4 % compared to 23 % in the itraconazole arm, resulting in discontinuation of the study before completion (Saag 1999). Fluconazole can probably be discontinued with sufficient immune reconstitution (above 200 CD4 cells/µl, undetectable viral load for three to six months), as demonstrated in several studies (Aberg 2002, Kirk 2002, Vibhagool 2003, Mussini 2004), and after at least six months of maintenance therapy. It is prudent to check for cryptococcal antigen before stopping (Mussini 2004). Positive results require continuation of treatment.

Primary prophylaxis against Cryptococcus neoformans is not recommended, as survival benefit was not demonstrated, even in endemic areas such as Thailand (McKinsey 1999, Chariyalertsak 2002). Exposure can presumably also not be prevented.

Treatment/prophylaxis of cryptococcosis (daily doses, unless specified otherwise), see also Drugs section for further details!

Acute therapy		Duration: always at least six weeks
Treatment of choice	Amphotericin B	Amphotericin B 0.5-0.75 mg/kg qd **or**
		liposomal amphotericin B 3 mg/kg qd (preparation by pharmacy)
		plus
	+ fluconazole	fluconazole 1 bottle à 200 mg i.v. bid **or**
		fluconazole 1 cap. à 200 mg bid
		plus
	+ flucytosine *	flucytosine 1 bottle à 250 ml (2.5 g) i.v. qid
		(= 100-150 mg/kg distributed in four separate doses)
Maintenance therapy		Discontinuation possible from > 200 CD4 cells/µl > 3-6 months
Treatment of choice	Fluconazole	Fluconazole 1-2 cap. à 200 mg qd
Alternative	Itraconazole	Itraconazole 2 cap. à 100 mg bid
Primary prophylaxis		Not recommended

*Note: We have had good experience with amphotericin B and fluconazole dual therapy in some cases, and usually omit flucytosine. Instead, we begin with HAART during the acute therapy phase in these patients, who are almost always HAART naive.

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Salmonella septicemia

Infection with non-typhoid Salmonella, which typically only causes enteritis in healthy individuals, can lead to severe septicemia in immunocompromised patients (Jacobs 1985). In Central Europe, Salmonella septicemia is rare in HIV patients, and accounts for less than 1 % of AIDS cases. In the Swiss cohort of over 9,000 patients, only 22 cases of recurring salmonellosis were documented over a period of nine years (Burkhardt 1999). In Southern Europe or Africa, salmonellosis is much more frequent. The most important reservoir is infected food, particularly poultry. Relapses are frequent. In addition to septicemia, atypical infections with osteomyelitis, empyema, pulmonary abscesses, pyelonephritis or meningitis have been described (Albrecht 1992, Nadelman 1985). Recurring, non-typhoid Salmonella septicemia is considered an AIDS-defining illness.

Signs and symptoms/diagnosis

Patients are often severely ill. Chills and high fever are usually present. If treatment is delayed, there is always a danger of septic shock. Diarrhea may be absent.

Blood cultures mainly lead to isolation of enteritis-causing Salmonella strains such as S. enteritidis and S. typhimurium. The pathogens causing typhoid or paratyphoid fever, S. typhi and S. paratyphi, are rare.

Treatment

Ciprofloxacin is the treatment of choice (Jacobson 1989). Although oral bioavailability is good, we prefer intravenous dosing. Cephalosporins such as cefotaxime or ceftriaxone are also effective. In contrast, resistance to co-trimoxazole or ampicillin has increased. One week of treatment with ciprofloxacin or ceftriaxone is usually enough. Maintenance therapy should continue for 6-8 months and not be stopped too early (Hung 2001). However, lifelong secondary prophylaxis, which was propagated in the past (Nelson 1992), no longer seems necessary.

Prophylaxis

Drug prophylaxis is not recommended. However, HIV patients should generally be told to pay attention to food hygiene.

Treatment/prophylaxis of Salmonella sepsis (daily doses)

Acute therapy		7-14 days
Treatment of choice	Ciprofloxacin	Ciprofloxacin 1 bottle à 200 mg i.v. bid
Alternative	Ceftriaxone	Ceftriaxone 1 bottle à 2 g i.v. qd
Prophylaxis		
	For relapses	Ciprofloxacin 1 tbl. à 500 mg bid (6-8 months)

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Immune reconstitution inflammatory syndrome (IRIS)

For the first time, in mid-1997 and early 1998, two groups described atypical manifestations of CMV retinitis (Jacobsen 1997) and MAC disease with abscess formation (Race 1998) in HIV patients within a few weeks of initiation of HAART. Although the pathogens, pathogenesis and localization were very different, all these illnesses had a distinct inflammatory component and were associated with significant immune reconstitution in these patients. It was therefore suspected early on that these presentations could constitute a syndrome during which a latent infection present at initiation of therapy is fought more effectively by the recovering immune system (DeSimone 2000).

Meanwhile, manifestations of numerous diseases have been attributed to the now established term "immune reconstitution inflammatory syndrome" (IRIS). These usually differ significantly from the courses of diseases seen during the pre-HAART era. One should not be surprised by grotesque, "atypical" clinical or radiological findings. The general rule for IRIS is: anything is possible!

How frequently does IRIS occur? In our experience, a frequency of 5-10 % in patients with less than 200 CD4 cells/µl is realistic. A high viral load before initiation of therapy seems to be an important predictive factor (Hoffmann 1999). However, the prevalence rate of 25 % cited elsewhere seems slightly too high (French 2000).

Mycobacterial IRIS. For MAC, the number of published cases with grotesque, fistular lymphadenitis, cutaneous or muscular abscesses, osteomyelitis, nephritis or meningitis is too large to be cited here. In a total of 83 patients starting HAART with a CD4 count of less than 200 cells/µl, we have seen 6 mycobacterioses, among these 4 MAC infections, within the first weeks of beginning therapy (Hoffmann 1998/1999). Lymph node abscesses usually occur during the first weeks on HAART. Not all cases are avium: an IRIS with Mycobacterium xenopi has recently been described (Chen 2004).

There are now also numerous reports on tuberculosis (John 1998, Chien 1998), which are reminiscent of the "paradox" reactions to TB treatment known since the 1950s. Common to all these patients is the fact that they initially deteriorate drastically under sufficient tuberculostatic treatment and HAART-induced immune reconstitution. Meningitis, as well as marked lymphadenopathy with unspecific histology, can complicate the course of disease, but respond astonishingly rapidly and well to steroids. In one study, four out of five patients, who had clinically developed atypical mycobacterioses after HAART and significant improvements in CD4 T cell levels, showed a significantly increased MAC-specific T cell response in vitro – proving in all likelihood that this phenomenon is indeed caused by the unmasking of subclinical infections (Foudraine 1999).

CMV IRIS. In addition to mycobacteriosis, numerous cases of unusual CMV infections under HAART have been published. Inflammatory CMV retinitis with vitritis, that may lead to visual impairment, papillitis and macular edema, can now be described as a distinct syndrome, differing significantly from the course of CMV retinitis seen in the pre-HAART era (Jacobson 1997, Whitcup 2000). Neovascularization endangers vision even after resolution (Wright 2003). A prospective study

was conducted in 30 patients with CMV retinitis that had reached levels of more than 60 CD4 T cells/μl for at least 2 months on HAART. Of these, 19 patients (63 %!) developed symptomatic vitritis, in some cases with considerable loss of vision (Karavellas 1999). In one small prospective cohort, the proportion reached 12 out of 14 patients (Whitcup 1999). As with MAC disease, in vitro studies have shown that the CMV-specific immune response is improved most significantly in those patients developing vitritis (Mutimer 2002, Stone 2002). Inflammatory CMV manifestations are not limited to the retina and may involve other organs (Gilquin 1997).

PML IRIS. The course of inflammatory PML that occurs during an IRIS is different from the infaust prognosis seen during the pre-HAART era (Cinque 2001, Collazos 1999, Kotecha 1998, Miralles 2001). Clinical symptoms are often more fulminant initially, and on radiology, there is a contrast enhancement which is otherwise atypical for PML, that may resolve over time. Patients have a better prognosis, and PML seems to even resolve completely (Hoffmann 2003, Du Pasquier 2003). We are following four patients with inflammatory PML who have been asymptomatic for years, some of whom live without any residual symptoms. However, fatal cases of inflammatory PML have also been reported (Safdar 2002). In our experience, steroids are ineffective, although there have been accounts of positive results (Nuttall 2004).

Cryptococcal IRIS. Numerous cases with inflammatory courses of disease have been described (Manfredi 1999, Woods 1998, Cinti 2001, Breton 2002, Jenny-Avital 2002, King 2002, Boelaert 2004). In particular, patients who start with HAART after cryptococcal therapy should be watched closely for the first few weeks. In cases of IRIS, the MRI usually shows choriomeningitis with significant enhancement in the choroid plexus. Cryptococcal antigen in the CSF is positive, although culture remains negative (Boelaert 2004).

Other infections. There are now various case studies. These include leishmaniasis (Jiménez-Expósito 1999), pneumocystosis (Barry 2002, Koval 2002), cerebral toxoplasmosis (Tsambiras 2001, Stout 2002, Ghosn 2003) and herpes infections (Fox 1999). Herpes zoster and hepatitis B or C episodes also seem to occur on HAART, particularly during the first weeks (Behrens 2000, Chung 2002, Manegold 2001, Martinez 1998, Domingo 2001). Increasing dermatological problems such as exacerbation of pre-existing folliculitis or skin disease have also been reported (Handa 2001). There are even reports about parvovirus and leprosy (Nolan 2003, Couppie 2004).

Other diseases. Diseases other than opportunistic infections are now recognized to occur under IRIS. These include autoimmune diseases such as Graves' disease, lupus, Sweet's and Reiter's syndromes, Guillain-Barré syndrome, acute porphyria and sarcoidosis, to name but a few (Bevilacqua 1999, Behrens 1998, Fox 1999, Gilquin 1998, Makela 2002, Mirmirani 1999, Neumann 2003, Piliero 2003). Recently, two cases of Peyronie's disease, a fibrosis of the penis, were reported (Rogers 2004)! These reports do lead one to wonder whether all of these manifestations are truly induced by immune reconstitution or perhaps merely chance occurrences. While most publications initially offered little information on the etiology beyond purely hypothetical discussions, it has recently become apparent that changes in the cytokine profile are involved in the pathogenesis of IRIS, together

with an activation of the cellular immune response. However, it seems that the mechanisms differ according to disease and genetic profile (Price 2001).

Consequences

Patients starting HAART with less than 200 CD4 T cells/µl (and particularly those who have a high viral load) require close clinical monitoring during the first weeks. It is important to be alert especially in very immunocompromised patients who have previously declined antiretroviral treatment, but now feel physically "affected" (subfebrile?) and want to start HAART "after thinking about it for a long time". Latent infections are often present in such cases, and these will rapidly become apparent as immune reconstitution occurs. The poorer the immune status, and the longer its duration, the higher the danger of IRIS!

Chest radiography, abdominal ultrasound and fundoscopy should be included in routine investigations of such patients before starting treatment. Clinical examination, often gladly overlooked today, is to be taken seriously! The suggestion by some authors to start MAC prophylaxis even before HAART in severely immunocompromised patients seems problematic. More recent data shows that azithromycin prophylaxis cannot prevent MAC IRIS (Phillips 2002).

Mycobacterioses in particular should be treated generously with steroids. One should always be prepared for atypical localizations, findings and disease courses of opportunistic infections. Things can look very different from what was known in the pre-HAART era! Patients usually have a good prognosis – and IRIS does not indicate failure of HAART.

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Wasting syndrome

Classic wasting syndrome is defined as involuntary weight loss of at least 10 % of original body weight, accompanied by persistent diarrhea (at least two bowel movements daily for more than 30 days) or extreme fatigue and/or fever without apparent infectious etiology. Wasting syndrome is therefore a classical exclusion diagnosis and really more of an epidemiological instrument than a specific disease – with thorough and competent searching, a specific causative agent can usually be found. Although very frequent in the past, classic wasting syndrome has become rare in the HAART era. In a large study conducted in 2000, however, 14 % of patients still indicated having lost more than 10 % of their original body weight (Wanke 2000). Weight loss remains an independent risk factor for mortality, even in the HAART era, and every patient should be weighed regularly! In one large study, mortality risk in patients with a loss greater than 10 % of body weight was more than 4-6-fold above that of patients with stable body weight (Tang 2002). Patients with classic wasting syndrome are often extremely weak. The risk for opportunistic infections is significantly elevated (Dworkin 2003). There is also cognitive impairment in these patients (Dolan 2003).

Diagnosis

The causes of wasting syndrome are complex. First, it is necessary to exclude or treat opportunistic infections (TB, MAC, cryptosporidiosis and microsporidiosis). If there are none to be found, several reasons remain that may contribute, even in combination, to wasting syndrome. These include metabolic disorders, hypogonadism, poor nutrition and malabsorption syndromes (overview: Grinspoon 2003).

Therefore it is important to start with a thorough history. Does the patient have a sensible diet? How are meals distributed throughout the day? Is the patient depressed? Which drugs, which HAART is being taken? Distinction to antiretroviral-related lipodystrophy syndrome is often difficult, particularly in cases of lipoatrophy. Significant weight loss is also typical for HCV therapy with interferon (Garcia-Benayas 2002), but rapidly resolves after finishing treatment. In addition, hypogonadism should be ruled out (measurement of testosterone). There are several simple tests for malabsorption syndromes. It is prudent to start with testing albumin, TSH and cholesterol levels.

Further tests such as D-xylose absorption or biopsies of the small intestine should only be initiated after consulting a gastroenterologist. Other tests to determine body composition (DEXA, densitrometry, bioelectrical impedance analysis) should only be conducted in centers experienced in wasting syndrome in AIDS patients.

Therapy

Wasting syndrome always requires competent diet counseling. Exercise, if possible, is also good. Of course, both only have limited success. Supportive parenteral nutrition only helps if there are problems with absorption (Kotler 1990, Melchior 1996). Effective HAART is important, ideally without drugs that cause lipoatrophy such as d4T or ddI. Severe lipoatrophy may require complete omission of nucleoside analogs (see chapter on Nuke sparing).

Beyond this, many kinds of drug treatment have been attempted. However, these have limited success and are often problematic.

Megestrol acetate, a synthetic gestagenic hormone, shows some benefit as an appetite stimulant in wasting syndrome, as demonstrated in a double-blind, randomized study (Von Roenn 1994). Its main problems are typical steroidal side effects, including hypogonadism (which should really be avoided in cases of wasting syndrome). We therefore do not currently recommend the use of this drug.

What about THC (dronabinol)? Dronabinol, the main active ingredient in marijuana, has been licensed in the US since 1985 as Marinol™, and may be prescribed for pharmacy formulation as drops or hard gel capsules. This drug is certainly attractive for many patients and is sometimes actively demanded. Prescription should be carefully considered, particularly in view of the significant cost (approx. 600 Euros per month for the usual dose of 5 mg tid). The effect on wasting syndrome is moderate at best, if detectable at all (Beal 1995). It is probably even weaker than megestrol acetate (Timpone 1997).

Hypogonadism is a frequent problem in patients with wasting syndrome. It is therefore useful to determine testosterone levels (age-dependent!). If levels are low, testosterone substitution has proven useful, both for weight gain and quality of life (Grinspoon 1998). This effect is sustained, even with long-term use (Grinspoon 1999). If testosterone levels are normal, substitution in cases of wasting syndrome is not indicated. In women, one should generally be very cautious with administration of androgenic hormones. There are other anabolic steroids available in addition to testosterone, such as oxandrolone or nandrolone. However, these are likely to be associated with more side effects, particularly related to the liver (Corcoran 1999). Positive effects have been demonstrated for the anabolic steroid oxymetholone in a small, double-blind, randomized study (Hengge 2003). However, relatively frequent elevation of transaminases may occur, which will limit the broader use of this drug.

Side effects as well as the high cost also limit the use of growth hormones, for which long-term data is still not available (Mulligan 1993, Schambelan 1996).

In our view, testosterone substitution in cases of proven hypogonadism is currently the only relevant therapeutic option for wasting syndrome. Testosterone is administered at a dose of 250 mg i.m. every 3-4 weeks, and a number of relatively affordable generics are available.

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Rare OIs

by Christian Hoffmann and Gerd Fätkenheuer

The following describes several opportunistic infections that rarely occur in central Europe, or have become very rare as a result of HAART. These diseases include aspergillosis, bacillary angiomatosis, histoplasmosis, isosporiasis, coccidioidomycosis (Coccidioides immitis), visceral leishmaniasis, microsporidiosis, Penicillium marneffei mycosis and rhodococcosis. These infections affect HIV patients more frequently than immunocompetent individuals, have more serious courses of disease than in HIV-negative patients and recur more frequently. Despite this, only three, namely histoplasmosis, isosporiasis and coccidioidomycosis, are AIDS-defining according to the current CDC/WHO classification.

Aspergillosis

Aspergillosis occurs almost only in severely immunocompromised patients. However, it is not AIDS defining. In the largest series described worldwide to date with 342 (!) cases of invasive aspergillosis, almost all patients had less than 50 CD4 T cells/µl (Mylonakis 1998). The only way to reach a reliable diagnosis is biopsy. The lung is often primarily affected (pneumonia, tracheobronchitis). The patients, who are usually severely ill, complain of fever, cough, dyspnea and chest pain. Hemoptysis frequently occurs. In addition to the lungs, nearly all other organs can be involved, particularly the CNS (Mylonakis 2000). Initial manifestations can even take the form of rhinosinusitis or abscesses (kidneys, liver) (Hunt 2000).

Aspergillosis particularly occurs in HIV patients on long-term (too long) steroid treatment for another OI. Severe neutropenia (< 1,000 leucocytes) is another risk factor. *Aspergillus fumigatus* is by far the most frequent pathogen. It is found in over 90 % of invasive aspergillosis cases. Therapy with amphotericin B (treatment of choice) and itraconazole has been reported most frequently (Keating 1994, Denning 1990). Even though there have been some new developments in recent years with the introduction of antimycotics such as caspofungin and voriconazole (Herbrecht 2002, Hoang 2001), the prognosis of aspergillosis remains fairly poor. Over 80 % of patients die of this complication. Early invasive diagnostics (CTs, culture, biopsies) are critical.

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Bacillary angiomatosis

Bacillary angiomatosis was first described in the 1980s in HIV patients (detailed, freely accessible review: Maguina 2000, http://hiv.net/link.php?id=11). Bacillary angiomatosis is caused by the rickettsial species *Bartonella henselae* and *Bartonella quintana* ("Rochalimaea" until the beginning of the 1990s).

Bartonella occurs far more frequently in North and South America than in Europe. In one study of 382 febrile HIV patients in San Francisco, Bartonella was found to be the causative organism in 18 % (Koehler 2003). Bacillary angiomatosis remains an important differential diagnosis in all cases with skin lesions of unknown etiology. The pseudoneoplastic, vascular skin proliferation is very often clinically (and histologically) mistaken for Kaposi's sarcoma or hemangioma. Cats are the main host of Bartonella henselae, and the cat flea is the vector. Bartonella quintana frequently affects patients from poor social background, particularly the homeless. Several possible reservoirs have been discussed for such cases (Gasquet 1998).

The vascular nodules or tumors may be isolated, but are usually multiple and reminiscent of fresh Kaposi's sarcoma, with cherry red or purple nodules. One quarter of cases may have bone involvement with painful osteolytic foci (AP elevation!). Here, the skin lesions sometimes resemble dry hyperkeratotic changes such as those seen in psoriasis. Different organs may be affected. In a collection of 21 cases, 19 patients had skin, 5 bone and 4 liver involvement (Plettenberg 2000). Manifestations in lymph nodes, muscle, CNS, eye, gingiva and gastrointestinal tract have also been reported.

The incidence is presumably higher than generally assumed. The gram-negative bacteria are only visible on biopsy samples stained with Warthin Starry silver stain. Those who do not stain with this method will not find bacillary angiomatosis! Pathologists should be informed of the suspected diagnosis, as this stain is not performed routinely. PCR is also possible. Reference laboratories should be contacted for further diagnostic details.

Treatment of bacillary angiomatosis is with erythromycin (at least 4 weeks with 500 mg qid). Relapses are common. Since transmission is mainly via cats, American guidelines recommend not having cats as pets. If there is no way around this, the cat should be healthy and older than one year. Scratches should be avoided.

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Histoplasmosis

Histoplasma capsulatum is a dimorphic mould, found mainly in moist soil and without a capsule despite its name. The South and Midwest of the USA are endemic areas, as are Central America and Africa. Inhalation of microconidia, the spores of H. capsulatum, can cause granulomatous disease in immunocompetent individuals. In HIV patients with impaired immunity (85 % have less than 100 CD4 T cells/µl), infection leads to an acute, life-threatening disease with dry cough, fever, dyspnea and malaise (McKinsey 1998). Miliary TB and PCP are important differential diagnoses. Disseminated courses of disease may also occur, in which the fungus can be detected in bone marrow or by liver biopsy (Albrecht 1994). Skin involvement (ulcerations) may also occur (Calza 2003, Scheinfeld 2003).

Histoplasmosis is AIDS-defining. The pathogen can be detected quite reliably in the blood with an antigen test, similarly to the detection of cryptococcal antigen. Laboratory evaluations often reveal significantly elevated LDH and alkaline phosphatase as well as transaminases. Amphotericin B should be given as initial treatment. Liposomal amphotericin B (3 mg/kg daily for 14 days) is not only less toxic, but possibly also more effective (Johnson 2002). In milder cases, itraconazole (200 mg bid or tid) is effective, and can also be used as a secondary prophylaxis. It is significantly more effective than fluconazole (Wheat 2002), but is associated with a high risk of interactions, particularly with ritonavir (Crommentuyn 2004). With regard to other OIs, secondary prophylaxis for histoplasmosis can be discontinued if immune reconstitution is sufficient (Goldman 2004).

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Isosporiasis

Isospora belli is a ubiquitous intestinal parasite. While it is rare in Europe, it is a great problem is the developing world (especially in the tropics and subtropics). Similar to cryptosporidiosis, this microbe may cause epidemic-type outbreaks in immunocompetent hosts. Patients suffer mild enteritis-like complaints, but sometimes also very severe watery diarrhea, abdominal pain, cramps and nausea. In immunocompromised patients, chronic diarrhea and finally even malnutrition may occur (review in: Goodgame 1996). Chronic isosporiasis with diarrhea lasting for more than four weeks is AIDS-defining. Detection of the relatively large oocysts is possible via normal stool sampling for parasites, as well as in acid-fast stains. Blood tests usually reveal eosinophilia (Certad 2003). Treatment is co-trimoxazole (960 mg daily for one week). Ciprofloxacin is slightly less effective (Verdier 2000).

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Coccidioidomycosis (Coccidioides immitis)

Infection with this mould is endemic in the Southwestern USA (Jones 1995). It should be considered in patients who have been in such regions. Laboratory personnel should be informed even in suspected cases, as there is a high risk of infection. After inhalation of spores, the primary manifestation is in the lung (Pappagianis 1993). Fever, cough, chest pain and general malaise are the most important symptoms. The infection, although often symptomatic, usually resolves in immunocompetent patients without sequelae. Occasionally, there is residual cavitation. Disseminated coccidioidomycosis beyond the lung and hilar lymph nodes (for example chronic meningoencephalitis) occurs practically only in significantly immunocompromised patients with CD4 counts of less than 250 cells/µl (Ampel 2001). It is AIDS-defining. Prognosis was poor in the pre-HAART era. In an analysis of 602 patients with disseminated coccidioidomycosis, mortality after one year was 63 % (Jones 1995).

Amphotericin and azoles are effective (Hernandez 1997). Fluconazole should be given lifelong as maintenance therapy at high doses (400 mg). In the past few years, it seems that the disease has become rarer as a result of HAART, and that maintenance therapy can be discontinued. However, there is still little data available (Woods 2000, best review: Ampel 2001).

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Leishmaniasis (visceral)

Leishmania donovani is a protozoon that is transmitted by sand flies. According to WHO, there are 12 million people infected with leishmania types worldwide. 350 million live in risk areas. Every year, up to 2 million new infections occur, almost two thirds of these in the cutaneous form. In Southern Europe, visceral leishmaniasis (kala azar) is frequent in HIV patients. In Spain, the majority of patients with visceral leishmaniasis are now HIV-infected (Pintado 2001). However, leishmaniasis is not an AIDS-defining illness, although there would be many reasons to include it.

HIV patients with leishmaniasis are significantly immunosuppressed (usually less than 100 CD4 T cells/µl). A few patients had not been in endemic areas for several years (Albrecht 1998). Bone marrow involvement is reflected by the almost obligatory pancytopenia, which may be particularly severe in HIV patients (Pintado 2001). Other symptoms include fever, hepatosplenomegaly and mucocutaneous lesions. The diagnosis is usually made from bone marrow aspirate.

Treatment has proven to be problematic. Although pentavalent antimony compounds have been used for about 60 years (e.g. Pentostam™ and Glucantime™, 20 mg/kg i.v. or i.m. daily for 28 days), these drugs are extremely toxic. In a randomized study, amphotericin B and meglumin antimonate were equivalent, with remission rates of approximately two thirds each – however, in both arms there were severe side effects in almost half the patients, with nephrotoxicity under amphotericin B, and cardiotoxicity and pancreatitis under meglumin antimonate (Laguna 1999). The German Association for Tropical Medicine recommends liposomal amphotericin B as the treatment of choice (2-5 mg/kg daily). Relapses are frequent and occur in almost half of all cases. HAART seems to change this – another argument for inclusion in the AIDS classification (de La Rosa 2002, Fernandez-Cotarelo 2003). A promising new drug is miltefosine, an alkylphosphocholine analog that was initially developed for oncology, but showed no efficacy there. It has good tolerability and efficacy for leishmaniasis, and a good oral bioavailability. It is still unclear how miltefosine inhibits leishmania metabolism, but a Phase III study in India demonstrated it to be highly effective (Sundar 2002). It is administered at a dose of 100 mg daily. We have successfully treated two patients with miltefosine to date.

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Microsporidiosis

Microsporidiosis is an important cause of diarrhea in HIV patients. Microsporidia are obligate intracellular protozoa. At least four genera that are pathogenic in humans have been described. Of these, *Enterocytozoon bieneusi* is probably the most important.

Even in Europe, microsporidia are among the most frequent diarrhea-causing microbes, and can be found in approximately one third of all patients and in two thirds of all HIV patients with chronic diarrhea (Sobottka 1998). Microsporidiosis is not AIDS defining, although chronic microsporidiosis almost always occurs in severely immunocompromised patients with CD4 T cell counts of less than 50 cells/µl. Diarrhea may be very severe and is usually watery, though not bloody. It is accompanied by abdominal pain, nausea and vomiting. Fever is almost always absent. Rarely, myositis, keratoconjunctivitis and sinusitis have been described. Infections of the biliary ducts are more frequent.

Even more than in the case of cryptosporidia, it is essential that the laboratory is experienced with making the diagnosis. Microsporidia are very small, and those who have never seen them and are not explicitly asked to detect them will not find them! Culture has not generally been established. Direct detection is most successful with specialized staining methods. Special transport or preparation is not necessary. Albendazole (1-2 tbl. à 400 mg bid for 4 weeks) is quite effective, but certainly not in every case. In particular, *Enterocytozoon bieneusi* is frequently resistant to albendazole. There have been repeated positive reports in such cases, especially from France, of treatment with fumagillin (watch for thrombocytopenia!), but the case numbers remain low (Molina 2002). There have also been positive reports of symptomatic treatment with thalidomide. HAART-induced immune reconstitution, however, seems to have the greatest effect (Carr 1998+2002, Maggi 2000). The incidence of microsporidiosis has presumably been significantly decreased as a result of HAART.

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Nocardia

Nocardia are aerobic bacteria or actinomycetes that occur worldwide. Several species exist, which mainly cause pneumonia as well as systemic disease. In a collection of 30 cases of HIV patients with nocardiosis, pulmonary manifestation occurred in 21 cases (Uttamchandani 1994). Pulmonary manifestation of nocardiosis is often confused with tuberculosis. Extrapulmonary manifestation may occur in the skin, brain, nerves, muscle and bone. The immune response to Nocardia is cellular. As a result, there is generally an increased risk of pulmonary or systemic disease in immunosuppressed patients. In HIV patients, however, opportunistic infections with Nocardia are rare. Patients are usually significantly immunocompromised (Javaly 1992, Uttamchandani 1994). Nocardia respond well to sulfonamides such as sulfadiazine even in HIV patients (Pintado 2003). In cases of suspected nocardiosis, an experienced laboratory should be consulted.

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Penicillium marneffei

Most fungi belonging to the Penicillium species are not pathogenic. One exception is *Penicillium marneffei*, which seems to be a problem mainly for HIV patients in Southeast Asia, China, Hong Kong and Taiwan (Cooper 2000). In these areas, it is the most frequent fungal infection in AIDS beside cryptococcosis, and is considered AIDS-defining by many clinicians (but is not included in the CDC/WHO classification). The clinical symptoms consist of prolonged high fever, lymphadenopathy, weight loss, malaise, cough and hemoptysis, diverse cutaneous and mucocutaneous lesions (reminiscent of molluscum contagiosum) and abnormal liver enzymes.

There is often hepatosplenomegaly. Amphotericin B and itraconazole are effective treatments (Sirisanthana 1998). Primary prophylaxis is not recommended even with longer stays in endemic areas (Chariyalertsak 2002). To prevent relapses, however, patients who have had the disease should take itraconazole as a permanent prophylaxis (Supparatpinyo 1998). The only patient we have seen with *Penicillium marneffei* had spent several months on vacation in Thailand (Sobottka 1996). For HIV patients who have been to Southeast Asia, this possibility should at least be considered.

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Rhodococcus

Rhodococcus equi (previously *Corynebacterium equi*) is a sporeless, gram-positive intracellular pathogen, which is ubiquitous in air, water and soil. R. equi has been found on all continents, and was first identified as a pathogen in young horses. For half a century, only veterinarians were interested in this microorganism, but in the last two decades, it has been found more and more frequently in humans, primarily in significantly immunocompromised patients. In these patients, it causes severe granulomatous or abscess forming pneumonia, and sometimes also disseminated infection. The coryneform bacteria seen in sputum cultures are often confused with normal diphtheroid flora found in the mouth and therefore not diagnosed.

In 1986, the first case in an AIDS patient was described (Samies 1986). In a collection of 78 cases, mostly AIDS patients with less than 50 CD4 T cells/µl were affected. The main symptoms were fever, dyspnea and unproductive cough (Capdevila 1997). Cavitation, mainly in the upper lobes, was frequent. Rhodococci are best detected in sputum and blood cultures (Torres-Tortosa 2003).

Erythromycin, ciprofloxacin, rifampin and vancomycin are effective, and some of these drugs can also be combined. However, treatment is difficult and complete recovery is rare (Plum 1997), so that surgical measures may also be necessary if there is extensive cavitation.

Prognosis is rather poor. The extent to which this will change as a result of HAART remains controversial (Sanz-Moreno 2002, Torres-Tortosa 2003).

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Trypanosoma cruzi

Trypanosoma cruzi is a protozoan that is transmitted via contaminated feces of tri-atomid bugs (assassin bugs), found almost exclusively on the American continent. It causes Chagas disease, one of the most frequent causes of cardiomyopathy in South America.

HIV patients are more frequently affected and have higher levels of parasitemia (Sartori 2002), probably due to the fact that the Trypanosoma-specific immune response is mainly cellular in nature. In addition, a more frequent occurrence in HIV-infected patients is meningoencephalitis, which is usually severe and radiologically not distinguishable from cerebral toxoplasmosis or primary cerebral lymphoma. In HIV patients from South America, Trypanosoma infection should therefore be considered in the differential diagnosis (Silva 1999). However, treatment (for example benznidazole) is rarely successful.

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13. Traveling with HIV

Thomas Weitzel

HIV patients are fond of traveling. In 1995 an American study revealed that 20 % of HIV patients had traveled in the past two years, with 60 % of those having visited developing countries (Kemper 1995). In a 1996 study from the Netherlands, 20 % of the HIV patients reported traveling abroad within the past year (Simons 1999). Ever since, increasing expectancy and quality of life have caused a further rise in the travel activities of HIV patients.

Travel preparations

Depending on their immune status, HIV patients bear an increased risk of travel-associated complications. Especially if CD4 counts are below 200/µl, there is a substantial threat of severe gastrointestinal and other opportunistic infections which can be acquired while traveling. Furthermore, the effectiveness of vaccinations in this group of patients is reduced.

Therefore, HIV-infected individuals should carefully plan their traveling. According to the travel destination and style, latest travel advices should be observed. A general overview of travel recommendations can be accessed through different Internet sites (Frädrich 2000). Especially before traveling to tropical or subtropical countries it is recommended to obtain additional information from travel medicine specialists. Long-term travelers should, in advance, clarify the treatment possibilities of HIV-related problems at their destination.

A first-aid kit for HIV-infected travelers should contain, besides the usual drugs (local antihistaminics, disinfectants, sun protection, analgesics, antipyretics, antiemetics, and antidiarrheals), an antibiotic for the empirical treatment of acute diarrhea (see below).

Antiretroviral therapy (ART)

A newly started antiretroviral regimen should be proven to be effective and well tolerated for a substantial period of time (e.g. three months), before long-term traveling takes place. Depending on the destination and the activities planned, a therapy interruption can be considered. If the ART is being continued during traveling, the following aspects should be considered:

- A sufficient amount of antiretroviral drugs should be packed, preferably in the hand luggage (suitcases can get lost…).
- The availability of the ART at destination should be checked beforehand. When necessary, prescriptions and a medical letter in English should be taken along.
- For some countries it may be useful to pack antiretroviral drugs in neutral packages because of entry regulations (see below).

- Storage requirements for the drugs (refrigeration etc.) must be checked in advanced – especially when traveling over long distances.
- Steps to cope with an unplanned therapy interruption during travel should be discussed with the patient in advance.

General precautions

HIV patients' higher risk of gastrointestinal infections demands the adherence to the principles of food and water hygiene (see links below). The following food and drink are to be avoided:

- Raw fruits or vegetables that are not peeled
- Raw or undercooked meat or fish dishes
- Tap water
- Ice cubes made of tap water
- Unpasteurized milk or milk products
- Food prepared or distributed under insecure hygienic circumstances (e.g. street vendors)

Even brushing teeth or swimming carry the risk of swallowing small amounts of potentially contaminated water. In the lack of hygienic beverages, tap water should be boiled. In areas up to 2000 meters above sea level, boiling time of one minute kills all potential pathogens; at higher altitudes, the boiling time should be prolonged to three minutes. Chemical or filtration methods of water treatment are less reliable.

Certain vector-transmitted infections, e.g. leishmaniasis, pose a special risk to HIV-infected patients (see below). Repellents are helpful to avoid those threats. Products containing at least 24 % DEET are internationally recommended. Sun protection has to be applied before repellent. Sleeping area should be mosquito safe (a mosquito net is the best repellent!). Impregnation of clothes and mosquito nets with permethrine offers additional safety. Outdoors, long and bright clothes should be worn and outdoor stays during dawn or night ought to be avoided (see links).

Since condoms and lubricants abroad are not always of reliable quality, a sufficient amount of these products should be brought, to guarantee safe sex during holiday.

Because of possible *Strongyloides stercoralis* infection (see below), direct skin contact to fecally contaminated soil should be avoided. It is wise to wear closed shoes and place a towel underneath when lying on the ground.

Precautions against zoonotic infections like salmonellosis or cryptosporidiosis include proper hand washing after animal contacts.

Vaccinations

A travel medicine consultation is an opportunity to check and complete routinely recommended immunizations such as tetanus/diphtheria, pneumococcal, influenza, and hepatitis B vaccination. It has to be kept in mind that the southern hemisphere influenza season is from April to September, while in the tropics influenza can occur all year long. Additional immunizations have to be considered according to

travel style, duration, and destination. Open immunization questions usually require the consultation of a specialized institution (see links). Further details on this issue can be seen in the chapter on vaccinations in this book.

Malaria prophylaxis

The interactions between antiretroviral drugs and drugs available for malaria prophylaxis as chloroquine, mefloquine, doxycycline, and Malarone™ (atovaquone/proguanil), are inadequately evaluated.

In healthy volunteers taking mefloquine (Lariam™) together with ritonavir, a 30 % reduction of the steady-state plasma level of ritonavir was reported; however, mefloquine did not change the ritonavir level after single dose of ritonavir (Khaliq 2001). The explanation is probably a reduced bile production caused by mefloquine. No relevant interactions seem to occur if mefloquine is coadministered with nelfinavir or indinavir (Schippers 2000).

Chloroquine is metabolized by CYP2D6, but also significantly excreted by the kidneys; explicit data on interactions of chloroquine with HIV drugs are lacking. In vitro, chloroquine inhibits HIV replication and shows synergistic effects together with protease inhibitors (Savarino 2001 and 2004). If this observation or the immunosuppressive effect of chloroquine has an impact on the clinical management of HIV infection is yet uncertain.

Clinical data on the interactions of atovaquone and proguanil with HIV drugs are missing. In vitro data indicate that ritonavir causes a reduced level of atovaquone and an increased level of proguanil. Atovaquone decreases the indinavir level by 20 % and increases the aciclovir level by 30 %.

Doxycycline is not metabolized by the cytochrome P450 system. Thus, relevant interactions with HIV drugs are not anticipated.

Available data and clinical experience indicate that mefloquine as well as doxycycline and chloroquine can be safely and effectively used in patients taking antiretroviral therapy. Although clinical studies are lacking, the same applies for Malarone™. Thus, recommendations for malaria prophylaxis are not limited by concomitant HIV medication.

Common drugs for malaria stand-by treatment are chloroquine, mefloquine, Malarone™, and Riamet™ (artemether/lumefantrine). Both components of Riamet™ are substrates of CPY3A4; due to incalculable increases in drug exposure, Riamet™ is contraindicated with protease inhibitors (see Riamet™ product information). With this exception, HIV patients should follow the same recommendations as healthy travelers. However, mefloquine is often unfavorable because of frequent neurological comorbidity in HIV patients.

Entry regulations and travel insurance

Although contentious as a measure of health policy and not recommended by the WHO, more than 150 countries, among them the USA, refuse entry to HIV infected individuals. This affects especially long-term stays in connection with work or study. To avoid problems, information on entry regulations should be obtained beforehand. Peter Wiessner and Karl Lemmen's brochure "Schnellfinder" provides an

excellent and comprehensive overview on entry policies. In cooperation with David Haerry of the Swiss Aids Info Docu, a regularly updated version of this databank is available online (see links).

The American foreign ministry also publishes a list of countries with HIV-specific entry restrictions (see links). Under certain circumstances, e.g. visits of conferences or family members or business travel, journeys to the USA are possible for HIV patients if they apply for a "visa waiver". Indeed, the procedure is time consuming and the passport endorsement can complicate further travel to the USA or other countries.

Travel insurances usually exclude existing illnesses and often refuse HIV patients explicitly. For that reason, special HIV travel insurances were made available in the UK and USA (see links).

Special risks

Enteric infections

Reduced immunological defense and diminished gastric acid production increase the risk for gastrointestinal infections in HIV patients. Furthermore, bacterial enteric infections such as salmonellosis, shigellosis, and *Campylobacter* infections bear a high risk of bacteremia and relapse. Infections caused by *Cryptosporidium sp.*, *Isospora belli* and microsporidia are dangerous due to chronicity. Therefore, HIV-infected patients must strictly observe proper water and food hygiene (Hayes 2003).

Prophylactic use of antibiotics, although reducing the prevalence of travel-associated diarrhea, is not generally recommended in HIV patients. In individual situations, e.g. HIV patients with advanced immunodeficiency traveling under poor hygienic conditions, prophylaxis with ciprofloxacin (500 mg per day) could be considered. In south-east Asia an increasing rate of quinolone resistance makes azithromycin a useful alternative. Because of widespread bacterial resistance, co-trimoxazole and doxycycline are not sufficiently efficient.

Travel-associated diarrheal diseases should be empirically self-treated for five to seven days with ciprofloxacin (500 mg per day) or alternatively azithromycin (400 mg per day). In afebrile episodes of non-bloody diarrhea short-term use of loperamide is justified. Adequate oral rehydration has to be maintained.

Malaria

Malaria does not behave like an opportunistic infection. Still, the details on the interaction between HIV and malaria are widely unknown. Malaria seems to increase HIV replication through proinflammatory cytokines. HIV infected pregnant women appear to have a higher malaria risk. Malaria-HIV coinfection in pregnancy is associated with increased parasitemia and a higher incidence of prematurity as well as low birth weight (Ayisi 2003, ter Kuile 2004). Until recently, the clinical influence of HIV infection on malaria was considered to be small except for the above mentioned problems in pregnancy. However, newly published data demonstrate a negative influence of an existing HIV infection on the clinical course of malaria (Grimwade 2004).

The efficacy of antimalarial prophylaxis and therapy is not influenced by HIV. Accordingly, recommendations for malaria therapy are generally applicable in HIV patients. As described above, drug interactions of antimalarial and HIV drugs are insufficiently established. The treatment of complicated malaria is specially problematic since the indicated drugs, quinine, quinidine, or artemisinin derivates, are all CYP3A4 metabolized. The coadministration of these drugs with CYP3A4 inhibitors, especially protease inhibitors, efavirenz, and delavirdine, requires intensive care monitoring and, when possible, drug level monitoring.

Measles

Measles are, in global consideration, a common infection. In 2002, more than 200 million measles cases with about 600.000 deaths were reported worldwide (WHO, 2004). In HIV-infected patients measles often run a severe course. American studies showed a mortality rate of 40 %, mostly due to giant-cell pneumonitis (Kaplan, 1996). Non-immune HIV patients should therefore consider active or passive immunization before traveling to areas with a high prevalence of measles.

Leishmaniasis

Visceral leishmaniasis (kala azar), caused by parasites of the *Leishmania donovani* complex, is a life-threatening opportunistic infection with limited therapeutic options. An analysis of imported cases in Germany showed that most cases of visceral leishmaniasis were acquired in European Mediterranean countries, that especially long-term travelers were affected, and that HIV patients had a higher infection risk than healthy travelers (Weitzel 2004). Most frequently HIV patients with CD4 counts below 200/µl are affected (Kaplan 1996). Due to the infection's potentially extended latency period, symptoms can occur long after exposure in endemic areas. Diagnosis is challenging, mostly requiring cooperation with a specialized center. Cutaneous leishmaniasis seems not to occur more frequently in HIV patients. Severely immunocompromised HIV patients must be informed of the risk of leishmaniasis even when traveling to Mediterranean countries. Preventive measures against mosquito bites should be followed in order to avoid leishmanial infections (see above); because of the vector's small size, the use of an impregnated mosquito net of small mesh size is advisable.

Tuberculosis

Globally, tuberculosis is the most prevalent HIV-associated opportunistic infection. In many countries, risk of tuberculosis is higher than in Germany. Especially before and after long-term traveling to countries of high tuberculosis endemicity, a tuberculin skin test should be performed. Patients with a positive tuberculin skin reaction or with a known high risk exposure should receive a treatment course for latent tuberculosis (see chapter "Tuberculosis"). HIV-infected individuals should avoid risk areas as hospitals, prisons or homeless-shelters or wear adequate face masks.

Endemic mycoses

Endemic mycoses are rare infections. Nevertheless, they are able to cause life-threatening opportunistic infections in HIV patients even years after stays in en-

demic areas. Most agents of endemic mycoses are thought to enter the pulmonary tract after inhalation of infective spores. In areas endemic for *Penicillium marneffei* (South East Asia, southern China) and *Coccidioides immitis* (south-west parts of the USA, parts of Central and South America), increased exposure to dust or soil should be avoided (e.g. construction sites, agriculture, garden work, excavations, storms). *Histoplasma capsulatum* is worldwide prevalent in soil contaminated with bird and bat droppings. Exposure might happen during eco or adventure tourism and should be avoided by HIV infected persons. In individual cases, e.g. severely immunocompromised HIV patients with a foreseeable contact to agents of endemic mycoses, primary prophylaxis can be considered. Depending on the expected pathogen, either fluconazole or itraconazole should be prescribed.

Another fungus causing severe infections in HIV patients is *Sporothrix schenkii*. This worldwide occurring pathogen enters the body through cutaneous lesions. Wearing gloves while working with plants, hay, or peat moss can reduce the sporotrichosis risk.

Sexually transmitted diseases

A recent study reported the high sexual activity and frequency of risk behavior (unprotected sex) in young British tourists (Bellis 2004). In Germany, an estimated 5 to 10 % of HIV infections are acquired during holidays. HIV-positive travelers should be aware of the special risks that sexually transmitted diseases and HIV re-infection present to them.

Other parasites

Due to hygienic and climatic circumstances, the following parasitic pathogens are more frequently found in developing countries and bear risks of severe infection in HIV patients:

- *Strongyloides stercoralis* is prevalent in most tropical and subtropical areas. The parasite is transmitted by cutaneous larval invasion after skin contact with contaminated soil. In HIV patients there is the risk of a "hyperinfection syndrome" with a high fatality rate (Gompels 1991). Besides HIV infection, corticosteroid use seems to be an additional risk factor. Those drugs seem able to increase larval maturation triggering a cycle of massive autoinfection.

- *Trypanosoma cruzi* is endemic in wide parts of Latin America. This protozoan causes Chagas disease and is transmitted by triatomine bugs. Chagas disease, which often persists asymptomatically for many years, can reactivate in severely immunocompromised HIV patients. In these cases, lesions radiologically resembling cerebral toxoplasmosis are often found in the central nervous system (Rocha 1994).

- *Babesia sp.*, prevalent worldwide, are able to cause infections in a broad spectrum of vertebrates and are transmitted by ticks. Severe infections, clinically mimicking malaria or manifesting as fever of unknown origin, mainly occur in patients after splenectomy, but have also been reported in severely immunocompromised HIV patients (Falagas et Klempner 1996).

- Free-living ameba (*Acanthamoeba sp.* and *Balamuthia mandrillaris*) are ubiquitous, living in soil and water. In HIV-infected and other immunocomprom-

ised patients, these organisms are capable of causing severe infections of the central nervous system (granulomatous encephalitis) as well as local infections of the skin and cornea (Sison 1995).

Medical problems after traveling

The threat presented by the diseases discussed in this chapter makes it imperative that any symptom occurring after travel be checked. Because most tropical diseases are quite rare in temperate countries, diagnosis is often delayed. An analysis of imported visceral leishmaniasis revealed a median time span of 85 days until the diagnosis was established (Weitzel 2004). Furthermore, tropical diseases often manifest atypically in HIV patients (Karp et Neva 1999). In any event, differential diagnosis of febrile syndromes in HIV infected individuals is very broad; after traveling abroad the clinical situation can become even more complex needing close cooperation of HIV and Tropical Medicine specialists.

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Links

Travel Medicine:

http://www.cdc.gov/travel/

http://www.who.int/ith/

http://www.tropenmedicus.de/

http://www.fitfortravel.de

http://www.crm.de/

http://www.travelmed.de/

Tropical Medicine institutions in Germany:

http://www.dtg.mwn.de/institut.htm

German recommendations for malaria prophylaxis and therapy:

http://www.uni-duesseldorf.de/WWW/AWMF/ll/042-001l.htm

Entry regulations and HIV-associated restrictions:

http://www.aidsnet.ch/modules.php?name=Sections&sop=listarticles&secid=13&newlang=german

http://travel.state.gov/travel/HIVtestingreqs.html

Travel insurance and HIV infection:

http://www.nat.org.uk/

http://www.gay.com/travel/article.html?sernum=8580

Drinking water & mosquito protection:

http://www.cdc.gov/travel/food-drink-risks.htm

http://www.cdc.gov/travel/bugs.htm

14. Kaposi's Sarcoma

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Kaposi's sarcoma (KS) is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a variable clinical course. The most frequent manifestation of the disease is skin lesions, but mucous membranes, the lymphatic system and viscera – in particular the lung and gastrointestinal tract – can be involved. Four clinical forms are described: classic KS, KS secondary to immuno-suppression; endemic African KS; and the epidemic HIV-associated KS.

All types of KS are due to infection with human herpes virus-8 (HHV-8), which is transmitted sexually or via blood or saliva. Months before manifestation of the tumors, HHV-8 viremia leads to development of specific antibodies. A cutaneous eruption was described in association with HHV-8 seroconversion (Andreoni 2002).

In HIV-infected patients, KS is an AIDS-defining illness. Aggressive courses of disease, with lethal outcomes, have been observed in HIV patients with severe and untreated immunodeficiency. In such cases, the average survival time following diagnosis is less than one year. Since the introduction of HAART in 1996, the frequency of KS in HIV-infected patients has decreased sharply (by as much as 90% in the Department of Dermatovenereology at Frankfurt University Hospital), and the clinical course of disease has improved significantly. In many cases, stabilization or complete remission of tumors is possible with immune reconstitution and reduction of the HIV viral load. Of the available therapies, HAART is first line treatment. It can be used in combination with local treatments such as cryotherapy, retinoids, and radiation. Therapy with interferon-alpha, paclitaxel or chemotherapy with liposomal anthracyclines is only necessary if there is visceral progression of the disease whilst on HAART.

Signs, symptoms and diagnosis

In contrast to the classical KS found in older men, in whom the tumors usually occur on the lower legs and feet, HIV-associated KS does not have a preferential pattern of localization. It can begin on any area of the skin, but may also appear on oral, genital, or ocular mucous membranes. Typical findings are initially solitary, or a few asymptomatic purple macules or nodules, which have a predilection for distribution along relaxed skin tension lines. Disease progression is variable: the macules or tumors can remain unchanged for months to years, or grow rapidly within a few weeks and disseminate. Rapid growth can lead to localized pain and a yellow-green discoloration of the area around the tumor as a result of hemorrhage. Further progression of the tumor can lead to central necrosis and ulceration. The tumors may bleed easily. Plaque-like and nodular KS lesions, often become confluent and can be accompanied by massive edema. In the oral cavity, the hard palate is frequently affected. Lesions begin with purplish erythema and progress to plaques and nodules that ulcerate easily. KS lesions may also involve the external genitalia including the foreskin and glans penis.

The **diagnosis of KS** in the skin and mucous membranes can usually be made based on the following clinical features:

1. Purple macules or nodules
2. Distribution along skin tension lines
3. Green-yellow discoloration around the tumors corresponding to hemorrhage
4. Surrounding edema
5. Dissemination of lesions, possibly with mucocutaneous involvement

This is particularly characteristic for patients in whom HIV infection or another form of immunodeficiency is known. If there is clinical doubt, the lesions should be biopsied to confirm the diagnosis histologically. The clinical presentation may pose a challenge, especially with the telangiectatic, ecchymotic, keloidal and hyperkeratotic variants.

The important features of KS on routine histology include:

1. Epidermis is usually intact.
2. Slit-like spaces formed by new, thin-walled and partly aberrant blood vessels running alongside normal dermal vessels and adnexal structures.
3. Extravasated erythrocytes around the new vessels.
4. Hemosiderin deposits.
5. Lymphocytic inflammatory infiltrate.
6. An infiltrate of oval- or spindle-shaped cells (spindle cell KS).

When KS resolves, either spontaneously or following therapy, it often leaves gray-brown to light brown hyperpigmentation for months to years (post-inflammatory hyperpigmentation), caused by hemosiderin deposits from extravasated erythrocytes. The accompanying lymphedema can also persist for a similar length of time, particularly on the lower legs.

HHV-8, which contributes to the development of the tumor, can be detected in tumor tissue by PCR. This can be a helpful diagnostic tool in cases where the histopathological diagnosis of Kaposi's sarcoma is uncertain. HHV-8 antibodies are often detected months before the clinical manifestation of the tumor. Neutralizing antibodies seem to control the HHV-8 infection and thus protect against the clinical manifestation of Kaposi's sarcoma (Kimball 2004). In patients with Kaposi's sarcoma the titres of neutralizing antibodies are low. The HIV tat-protein is able to promote the HHV-8 transmission directly, which could be an explanation for the high rate of KS in patients coinfected with HHV-8 and HIV (Aoki 2004, Chandra 2003). Epidemiological studies have shown that a high regional incidence of KS (e.g. in Southern Italy, as well as in Central Africa) correlates with an increased regional HHV-8 seroprevalence. HHV-8 seems to mainly be transmitted sexually. The KS frequently seen in African children is presumably transmitted via saliva (Pauk et al. 2000). A saliva reservoir of HHV-8 was also found in adult HIV patients (Triantos 2004).

On initial diagnosis of KS, the following investigations help to stage the disease:

1. Complete cutaneous inspection of the patient (including oral and genital mucous membranes)
2. Lymph node ultrasound
3. Abdominal ultrasound
4. Upper GI endoscopy (optional, but always required with mucocutaneous tumors)
5. Lower GI endoscopy (optional, but always required with mucocutaneous tumors)
6. Chest radiography
7. Determination of the cellular immune status (CD4 T cells) and HIV viral load (Is initiation or optimization of antiretroviral therapy necessary?)

Prognosis and staging

HIV-associated KS ranges from indolent skin lesions to aggressive, disseminated disease with lymph node and visceral involvement. Left untreated, rapid tumor growth can lead to death of the patient within weeks. Malignant clonal tumor growth has been shown to occur in pulmonary KS. The introduction of HAART has significantly improved the prognosis for patients with KS. Patients with extensive visceral involvement often achieve complete remission.

Table 1. Staging of HIV-associated epidemic Kaposi's sarcoma (KS)
(from AIDS Clinical Trials Group/ACTG, Krown et al. 1997)

Early stage	Late stage
If **all** the following criteria are met:	If **one** of the following applies:
1. Tumor (T): 0	1.Tumor (T): 1
KS limited to skin and/or lymph nodes; minimal oral disease (non-nodular KS confined to hard palate)	Pulmonary or gastrointestinal KS; extensive oral KS; tumor-associated edema or ulceration
2. Immune system* (I): 0 CD4 T cells > 200/μl	2. Immune system* (I): 1 CD4 T cells < 200/μl
3. Systemic illness (S): 0 No history of OI or thrush, no B symptoms* of HIV infection	3. Systemic illness (S): 1 History of opportunistic infections, thrush, malignant lymphoma or HIV-associated neurological disease, B** symptoms of HIV infection

*CD4 cell count is not of any prognostic relevance in KS patients on HAART (Nasti 2003)

** unexplained fever, night sweats or diarrhea persisting for more than two weeks, involuntary weight loss of >10%

The classification system for HIV-associated KS, published in 1993 and reviewed in 1997 by the AIDS Clinical Trials Group (ACTG, Krown 1997, table 1), was adapted by an Italian working group to address KS in the HAART era. However, the changes proposed by Nasti et al (2003) have not yet been validated and accepted

on an international level. Of particular concern is the suggested omission of the CD4 cell count as a prognostic factor, which results in the classification of KS patients into those with a good (T0S0, T1S0, T0S1) and those with a bad prognosis (T1S1).

Treatment

If KS is diagnosed in HIV-infected patients who have not yet been treated, or who are no longer being treated with antiretroviral drugs, it is essential to start HAART (see HAART chapter). If the HIV viral load can be reduced (ideally below the level of detection) and immune reconstitution is achieved with an increase in the CD4 T cell count, KS stabilizes or even resolves completely in many patients. The clinical observation that KS may resolve under HAART with protease inhibitors, even in the absence of a significant improvement in the immunological status, has been confirmed with the discovery of the direct anti-proliferative effects of the PIs indinavir and saquinavir (Sgadari 2002). The PI ritonavir has also been shown to have a direct anti-tumor effect (Pati 2002) In addition, the following treatment methods are available depending on the clinical stage of KS (table 1):

- Early stage (ACTG): Local treatment (see below). With progression: primary treatment with interferon-α combined with HAART; secondary treatment with liposomal anthracyclines.

- Late stage (ACTG): Primary treatment for stage T 0, I 0, S 1 with interferon-α in combination with HAART. Otherwise liposomal anthracyclines are the first choice for treatment. Should they fail, paclitaxel or combination chemotherapy (ABV regimen) can be used.

Local therapy

Local therapy has the advantages of being (1) provided in the ambulatory care setting, (2) well-tolerated, and (3) less costly than in-patient therapy. The following methods are used depending on the size and location of tumors: cryosurgery, vinca alkaloids, intralesional bleomycin or intralesional interferons, soft x-ray radiation, electron beam therapy, cobalt radiation (fractionated), retinoids: 9-cis-retinoic acid, alitretinoin (Bodsworth 2001, Duvic 2000), and cosmetic camouflage. In addition to intralesional vinblastine, tumors of the buccal mucosa can be injected with 3 % sodium tetradecyl sulphate (which has comparable efficacy rates) (Ramirez-Amador 2002).

As Kaposi's sarcoma is a multifocal systemic disease, surgical treatment is limited to excisional biopsies for diagnosis and palliative removal of small tumors in cosmetically disturbing areas. Since tumors often extend further into the surroundings than is clinically visible and local trauma can lead to new tumors (Koebner phenomenon), local and regional recurrences can be expected. These can be prevented by radiation therapy: in order to reach the tumor cells spreading along the vascular channels, the field of radiation should be extended 0.5-1.0 cm beyond the edges of the tumor. KS is a strikingly radiosensitive tumor. Superficial macular or plaque-like KS lesions respond well to daily doses of 4-5 Gy (total dose 20-30 Gy, fractionated 3x/week) of soft x-ray radiation. To palliate fast growing tumors, a single

dose of 8 Gy is recommended (Harrison 1998). For the treatment of extensive KS with edematous swelling and/or lymph node involvement, soft x-ray radiation, originating from 50-kV beryllium-windowed units, as used in dermatology, is not sufficient. Such tumors should be treated with electron beam therapy with conventional fractionation (5x2 Gy per week) to a target volume total dose of 40 Gy.

Local chemo- and immunotherapy have the advantage of less or no systemic side effects compared to systemic treatments. Within the tumor, high concentrations of drugs with direct antiproliferative efficacy can be reached.

Chemotherapy

Chemotherapy harbors particular risks for HIV-infected patients. Bone marrow suppression, induced by chemotherapy, can lead to deterioration of existing, HIV-associated cellular immunodeficiency and occurrence of acute, life-threatening opportunistic infections. To maintain a high quality of life for the patient for as long as possible, HIV-associated KS should only be treated by chemotherapy in the presence of clinical symptoms (e.g. pain), rapid tumor progression and/or visceral involvement. In such cases, even patients with a good immune status should receive PCP and toxoplasmosis prophylaxis with cotrimoxazole (480 mg/day or 960 mg 3x/week). The myelotoxic effects of chemotherapeutic drugs on a hematopoetic system that has already been impaired by HIV infection may require further treatment with erythropoetin or blood transfusions.

The chemotherapeutics that achieve the highest remission rates for KS are liposomal anthracyclines. Treatment with intravenous pegylated liposomal doxorubicin at a dose of 20 mg/m^2 body surface area every 2-3 weeks leads to partial remission in up to 80 % of treated patients. Treatment with intravenous liposomal daunorubicin 40 mg/m^2 body surface area every 2 weeks has slightly lower remission rates (Krown 2004, Rosenthal 2002, Osoba 2001, Cheung 1999).

In comparative studies, liposomal daunorubicin showed the same and doxorubicin a higher efficiency than the previous gold standard of KS treatment, which consisted of combination therapy with adriamycin, bleomycin and vincristine (ABV regimen). In a comparative study on patients with moderate to advanced KS, the combination of pegylated liposomal doxorubicin with HAART was substantially more effective than HAART alone (response rate 76 % versus 20 %) (Martin-Carbonero 2004). The most important side effects of anthracyclines are neutropenia and anemia. This usually occurs after 8-10 cycles. The cardiotoxicity associated with anthracyclines should also be considered. However, usually it only occurs with long-term administration (cumulative doses of 450 mg doxorubicin and higher). Macular and painful erythema of the palms and soles (palmoplantar erythrodysesthesia) is another notable side effect which can limit treatment.

Paclitaxel is also a very effective drug for the treatment of KS (Tulpule 2002). The recommended dose is 100 mg/m^2 body surface area administered intravenously over 3-4 hours every 2 weeks. Partial remission is achieved in up to 60 % of all treated patients. Paclitaxel is myelotoxic and almost always leads to alopecia, often after just one dose. Whether paclitaxel has important interactions with HAART drugs (increase of paclitaxel toxicity?) is still under investigation (Bundow 2004). For this reason, patients on HAART and paclitaxel need very careful monitoring.

Paclitaxel acts by disrupting the structural reorganization of intracellular microtubuli. This leads to mitotic arrest and programmed cell death (apoptosis) (Blagosklonny 2002). Paclitaxel can also be used successfully in those patients with tumor progression under anthracycline therapy.

Docitaxel (taxotere) seems to be an interesting alternative from the taxane group. It is FDA approved for the treatment of breast cancer, but very recently a phase II clinical trial showed that taxotere is effective and safe for the treatment of KS (Lim 2005). Relapses (following anthracycline or paclitaxel therapy) may also be treated with low dose oral etoposide (Evans 2002).

Table 2: Treatment recommendations for systemic therapy of Kaposi's sarcoma (evaluation of individual drugs in text)

Therapeutic agent	Dose	Requirement	Remission rate	Side effects
IFN-α (2a,b)	1-3 mil. I.U. sc daily until remission, followed by 3 x weekly	>200 CD4 T cells/µl Endogenous IFN-α < 3 U/ml, HAART	Approx. 40%	Fever Myalgia Depression
Pegylated IFN-α 2b*	50 µg sc 1 x weekly	As for IFN-α (2a,b)	?	As for IFN-α (2a,b)
Liposomal Doxorubicin	20 mg/m^2 iv at biweekly intervals	KS stage T1, S0-1 (Explanation: see Table 1, Staging of KS)	Approx. 80%	Neutropenia Anemia Rarely: Flushing Dyspnea Back pain Palmo-plantar erythro-dysesthesia
Liposomal Daunorubicin	40 mg/m^2 iv at biweekly intervals	T1, S0-1 (Explanation: see Table 1, Staging of KS)	Approx. 60%	Neutropenia Anemia Rarely: Flushing Dyspnea Back pain Palmo-plantar erythro-dysesthesia
Paclitaxel	100 mg/m² iv at biweekly intervals	T1, S0-1 (Explanation: see Table 1, Staging of KS)	Approx.60%	Neutropenia Thrombocytopenia Anemia, alopecia Rarely: Hypotension ECG-changes

*Pegylated IFN-α 2b has only been licensed for treatment of chronic hepatitis C

Immunotherapy

Interferons (IFN-α 2a, IFN-α 2b, IFN-β) are used successfully for classic, as well as sporadic and HIV-associated, epidemic Kaposi's sarcoma. Remission rates of 45-70% can be achieved. In addition to their well-known immunomodulatory activity, interferons induce apoptosis in tumor cells and lead to reduced β-FGF expression by inhibiting angiogenesis and therefore proliferation.

There are currently no standardized treatment regimens. In principle, high and low dose therapies can be distinguished. However, due to the considerable side effects, a high dose treatment (up to 30 million IU/day) is not commonly administered. Daily doses of 3-6 million IU sc are usually given. After remission (tumor growth stopped, tumors flattened, loss of purple color, change to brownish color), interferon dosing can be reduced to 3x/week. Complete remission can, at the earliest, be expected after 6-8 weeks of treatment (often significantly later). An initial study showed that interferon doses can be reduced even further when given with HAART, thereby decreasing interferon side effects (Krown 2002). Depression with suicidal tendencies does not seem to be a dose-related side effect of interferons.

There is almost no data on the use of the new, pegylated IFN-α 2b for KS. It is de-pegylated to IFN-α 2b, the active substance, following subcutaneous application. It has been used successfully for the treatment of classical Kaposi's sarcoma (Thoma-Greber 2002) in a dose of 50µg/week subcutaneously. Whether higher doses or shorter treatment intervals are necessary for HIV-associated KS still remains to be investigated. Such studies have become more difficult to perform as a result of the significant decrease in both the incidence and prevalence of KS since the introduction of HAART. In principle, this new formulation should lead to a further improvement in the efficacy of interferon.

The efficacy of interferon treatment is dependent on the cellular immune status of the patient. In patients with more than 400 CD4 T cells/µl, remission rates are > 45%; with less than 200 CD4 cells/µl they stand at only 7 %. The endogenous interferon levels are important prognostic indicators and are significantly elevated in the advanced stages of HIV infection which leads to reduced responses to exogenous interferon. The criteria for treatment with interferon in epidemic KS therefore include an early stage of HIV disease (CD4 cells > 200/µl) and endogenous interferon levels < 3 U/ml. In the late stage of HIV disease, interferons should only be given in combination with an efficient HAART regimen. IFN-γ leads to tumor progression and is contraindicated.

Monitoring and follow-up care

In cases with isolated cutaneous and slowly progressive KS, HIV disease and HAART usually determine the necessary intervals for monitoring. However, even with a functional cellular immunity (CD4 T cells > 400/µl) and low viral load, tumor progression may be rapid with organ involvement in individual cases. Clinical examination of the skin, mucous membranes and lymph nodes is recommended at three-month intervals. The lungs and gastrointestinal tract should be monitored at 6-12 month intervals with appropriate diagnostic testing if indicated. However, evi-

dence-based data that tumor follow-up leads to improvement in the remission rates as a result of close monitoring is not yet available for Kaposi's sarcoma.

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15. Malignant Lymphomas

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Malignant lymphomas are neoplastic diseases of the lymphatic system that grow rapidly and aggressively, and lead to death within a few weeks or months if left untreated. Hodgkin's disease (HD) is distinguished from the large group of non-Hodgkin's lymphomas (NHL). In comparison to the normal population, HIV patients are affected significantly more frequently by all types of lymphoma (see Table 1). However, aggressive non-Hodgkin's lymphomas of B-cell origin are particularly frequent. The influence of HAART on the incidence of lymphomas is still the subject of controversy. In 2001, several studies indicated that a regression, if any, was by far not as impressive as with Kaposi's sarcoma or most opportunistic infections (Clarke 2001, Little 2001). In a more recent interim analysis (Kirk 2001), however, a moderate regression was demonstrated. This was shown to be particularly true for all the subtypes that mainly occur in severe immunodeficiency (see below). But, in comparison to other malignancies and opportunistic infections, the regression is much smaller, so that the relative proportion of AIDS-associated illnesses that are lymphomas is increasing. In some HIV cohorts, malignant lymphomas have already overtaken Kaposi's sarcoma as the most frequent malignancy. In the EuroSIDA study, the proportion of AIDS-defined illnesses that were malignant lymphomas increased from less than 4 % in 1994 to 16 % in 1998 (Mocroft 2000). In France, lymphomas accounted for 11 % of all deaths in HIV patients in 2000 (Bonnet 2004). In addition, in the HAART era, HIV patients are living much longer, so that the general risk of lymphoma is rising anyway (Stebbing 2004). Therefore, malignant lymphomas will be a significant morbidity and mortality factor in HIV patients in the future.

Table 1. Relative risk of different lymphomas in HIV patients in comparison to the normal population (adapted from Goedert 2000)

Malignant NHL total	165
High-grade malignancy NHL	348
Immunoblastic NHL	652
Burkitt's NHL	261
Not classifiable	580
Primary CNS lymphoma (PCNSL)	> 1,000
Low-grade malignancy NHL	14
Plasmocytoma	5
Hodgkin's disease	8

Malignant lymphomas in HIV-infected patients are also biologically very heterogenous and differ in several aspects. For example, the association with EBV and other oncogenic viruses such as HHV-8 or SV40 is very variable. The extent of immunodeficiency also varies significantly. Burkitt's lymphoma and Hodgkin's disease frequently occur even when the immune status is good. In contrast, immunoblastic and especially primary CNS lymphoma (PCNSL) are almost always associated with severe immunodeficiency. The frequency and extent of oncogenic mutations or

cytokine dysregulation differ, as does the histogenetic origin of the malignant cells (Porcu 2000).

However, HIV-associated lymphomas – both NHL and HD – have numerous common clinical features. Characteristics include the usually aggressive growth, diagnosis in the advanced stages with frequent extranodal manifestations, poorer response to treatment, high relapse rates and an overall poor prognosis (Levine 2000).

Even in the HAART era, the treatment of malignant lymphoma remains problematic. Although aggressive chemotherapy is possible in many patients with existing immunodeficiency, it is complicated and requires a close cooperation between HIV clinicians and physicians with experience in hematology/oncology.

The following discusses systemic NHL, PCNSL and Hodgkin's lymphoma separately. Multicentric Castleman's disease will also be mentioned as a distinct entity, although it is not considered a malignant lymphoma. Low-grade (indolent) NHLs are very rare in HIV patients, and will therefore not be discussed here. As there are no data or even recommendations available, the treatment of such cases in the HAART era should follow the recommendations for HIV-negative patients.

Systemic Non-Hodgkin lymphomas (NHL)

A close association between systemic NHL and AIDS has been described for a long time – the first cases were published only about a year after the first description of AIDS and even before the discovery of HIV (Ziegler 1982). High-grade B-NHLs have been AIDS-defining since 1985.

90 % of HIV-associated NHLs are of B-cell origin. They are almost always of high-grade malignancy. Two main histological types dominate: according to the WHO classification these are Burkitt's lymphomas, which comprise 30-40 % of cases, and diffuse large-cell B cell lymphomas, comprising 40-60 %. However, a relatively large proportion of HIV-associated lymphomas (up to 30 %) cannot be classified even by reference laboratories. A small proportion of NHLs (1-3 %) are primary effusion or body cavity-based lymphomas and are considered as a distinct entity (see below).

The prognosis of patients with NHL was poor in the pre-HAART era, being between 6 and 9 months (Levine 2000). Since the advent of HAART, this seems to be changing. Whether the clinical and pathological spectrum of NHL is also changing, is still unclear.

Signs and symptoms

The main symptom is lymph node enlargement. Lymphomas are firm, immobile or barely mobile and painless. A large proportion of patients have advanced-stage lymphoma at the time of diagnosis. Ann Arbor stages III-IV are almost always the rule, and B symptoms with fever, night sweats and/or weight loss are found in the majority of cases (60-80 %). General asthenia, significant malaise and rapid physical deterioration are also frequently seen. Extranodal involvement is common, and may be to a grotesque extent. In our own cohort of 203 patients, 81 % had at least one extranodal focus (Hoffmann 2003). Whether the orbital cavity, testes, heart,

breasts, bladder, kidneys, muscles, or bones – every conceivable region can be affected. However, the gastrointestinal tract, liver, and bone marrow are affected particularly frequently. Secondary CNS involvement can also occur. With extranodal disease, additional symptoms arise depending on the localization. These include, for example, abdominal pain from hepatosplenomegaly, hemorrhage or ileus symptoms due to intestinal involvement, bone pain with skeletal infiltration, or headache caused by brain disease.

Diagnosis

Rapid histological diagnosis is important. If bone marrow biopsy cannot secure the diagnosis, a lymph node (e.g. cervical, axillary or inguinal) should be extirpated. Mere puncture biopsy of a lymph node is often not sufficient to secure a representative specimen. It is important to send the material to a specialized pathology laboratory with extensive experience in lymph node morphology. All patients with suspected NHL should be staged according to the Ann-Arbor classification (Tables 2a, b).

Table 2a. Staging according to the updated Ann-Arbor classification

I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site plus its regional lymph nodes, with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph nodes regions on both sides of the diaphragm (III), can be accompanied by localized extralymphatic organ involvement (IIIE) or spleen involvement (IIIS) or both (IIIE+S)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement; or isolated involvement of an extralymphatic organ with involvement of distal (non-regional) lymph nodes.

Table 2b. Every stage is divided into categories A and B

A	Asymptomatic
B	General symptoms: a) unexplained weight loss of more than 10 % in the last six months, and/or b) unexplained persistent or recurring fever with temperatures above 38 °C, and/or c) drenching night sweats

Basic diagnostic tests for staging include chest radiography, abdominal ultrasound, bone marrow biopsy (aspiration alone is not enough!) and CT scans of the neck, thorax and abdomen. In addition to an updated immune status and viral load, the following should be determined at the very least: blood count, ESR, CRP, uric acid, LDH, liver and kidney parameters and electrolytes. ECG and echocardiography are also important beforehand. The possible cardiotoxicity of chemotherapy (anthracyclines!) during the course of treatment can only be evaluated if these tests have been performed at the start! Pulmonary function should be tested before treatment with regimens containing bleomycin is initiated.

After two cycles of chemotherapy, a restaging should be performed to evaluate treatment success. This restaging should be oriented according to the original localization of lymphoma. After completion of the protocol, a complete restaging with bone marrow biopsy (if there was initial involvement) and all CT scans is necessary. With a complete remission, restaging is recommended initially at three-monthly intervals. These intervals can be prolonged to six months after one year and to twelve months after two years. Relapses after more than three years are rare.

In advanced stages of the disease (Ann Arbor III-IV), and particularly with ENT involvement, a diagnostic lumbar puncture is necessary before initiating systemic chemotherapy to exclude meningeal involvement. In such cases, 15 mg of methotrexate should be administered intrathecally as prophylaxis.

Therapy

Due to extremely rapid generalization, even "early stages" are rarely limited. The real stage of the disease is often underestimated – every aggressive HIV-associated lymphoma should therefore be treated primarily with systemic chemotherapy with curative intent. Surgery or radiation therapy alone are not sufficient. Treatment must be started rapidly due to the aggressive nature of these lymphomas. In particular, time should not be wasted on staging. The necessary tests should be completed within a week.

In Europe, diffuse large-cell NHLs have been treated for many years with CHOP-based regimens (usually 4-6 cycles, see table). CHOP is the abbreviation used for the combination chemotherapy with the cytostatics **c**yclophosphamide, adriamycin (**h**ydroxydoxorubicin), vincristine (**O**ncovin™) and **p**rednisolone. To date, no other chemotherapy regimen has been shown to have better efficacy. CHOP can be administered in ambulatory care and is fairly well tolerated.

At least 4 cycles should be administered, and – as far as possible – 2 cycles after reaching complete remission (CR).

The standard three-week CHOP regimen ("CHOP-21") is shown in Table 3. Following the success of "CHOP-14" in older HIV-negative patients (Pfreundschuh 2004), "CHOP-21" can also be condensed: in "CHOP-14" (one cycle every two weeks) the use of the growth hormone G-CSF (e.g. Filgastrim 30-48 million units or Neupogen™ 300/480 µg s.c. daily on days 4 to 13) reduces the duration of neutropenia. This approach not only decreases the phase of increased susceptibility to infections, but also increases the dose intensity of chemotherapy. However, there is no comparative data on this yet for HIV patients. So far, we have had fairly positive experiences with this approach – in most HIV patients, it is possible to shorten the interval.

We recommend the administration of co-trimoxazole as an adjuvant therapy, up until one month after completion of the chemotherapy (960 mg three times weekly), independent of the CD4 cell count. Oral mucous membranes should be treated with mouthwashes and topical antimycotics such as amphotericin. Good compliance from the patients is an important factor. During chemotherapy, at least twice weekly monitoring of the patient's condition, blood count, liver and kidney parameters is necessary. Treatment is usually continued with the full dose according to protocol if leukocytes are above 3,000/mm^3 again after nadir and platelets more than

80,000/mm^3 on the planned day of treatment. Patients should be advised to carry out daily temperature monitoring and be told to present immediately in case of fever.

Table 3: CHOP regimen (4-6 cycles of 3 weeks each, repeat on Day 22) *

Cyclophosphamide	Endoxan®	750 mg/m^2 i.v. Day 1
Doxorubicin	Doxo-Cell®, Adriblastin®	50 mg/m^2 i.v. Day 1
Vincristine	Vincristin®	1.4 mg/m^2 (maximum 2 mg) i.v. Day 1
Prednisolone	Decortin H®	2 tbl. à 50 mg qd p.o., Day 1-5
Mesna	Uromitexan®	20 % of cyclophosphamide dose at hours 0, 4, 8 (with reference to cyclophosphamide i.v. given as a short infusion or orally)

* Standard CHOP regimen ("CHOP 21")

Rituximab in HIV infection?

The introduction of the monoclonal CD20-antibody rituximab (MabThera™) was one of the biggest advances in oncology in recent years. In numerous lymphomas, this antibody, which binds highly specifically to CD20-positive B cells (CD20 is expressed by most lymphoma cells), has markedly improved the effectiveness and length of response of conventional chemotherapy. A combination of CHOP and rituximab ("R-CHOP") is now standard in many lymphomas (overview: Kneba 2001). Rituximab is usually well tolerated, but often leads to a longer lasting B cell depletion, and occasionally to severe neutropenia (Voog 2003).

It is not clear whether rituximab has a similarly large clinical benefit for HIV patients as it has for HIV-negative patients with B cell lymphoma. The results from AMC 010, a multicenter prospective and randomized US study, have at least raised doubts (Kaplan 2003). 143 patients with CD20-positive AIDS-NHL were randomized to CHOP or R-CHOP (rituximab in the usual dose of 375 mg/m² on day 1 with a monthly maintenance therapy for 3 months following chemotherapy). In addition to the chemotherapy, all patients also received G-CSF, a co-trimoxazole prophylaxis and an AZT-free HAART. Both groups had minimal differences at baseline. In the rituximab group, the CD4 cell counts were slightly, but not significantly lower (128 vs 158 CD4 cells/µl). With regard to other parameters, such as histology, stage of disease, etc., there were no significant differences. Even the planned CHOP cycles were carried out at the same intensity in both groups, and in both groups only slight dose reductions were necessary.

Essentially, with regard to the results: neither group differed significantly in the length of response, disease-free or total survival. However, neutropenia and incidence of (especially severe) infection, were significantly higher in the rituximab group. Out of a total of 15 patients who died from an infection, 14 had received rituximab. The cause of death was usually septicemia from various bacteria – both gram-negative and gram-positive were identified. Death occurred in the majority (8/15) during the first two cycles, although 6 cases happened during the rituximab treatment at the end of the chemotherapy. Fatalities occurred in all centers and were

therefore not due to a possible lack of expertise in any one location. A further risk factor for "death from infection" was a low baseline CD4 count – 8/13 patients had less than 50 CD4 cells/µl. The cause of the high rate of severe infections is still unclear. Pathophysiologically, it is at least possible that in pre-existing T cell defects, present in HIV patients, a rituximab-induced B cell depletion has particularly negative effects.

Following these data (which have to be examined), rituximab seems at first glance to have no significant beneficial effect on HIV patients with aggressive lymphomas, and if indeed there is one, this is cancelled by the increased risk of infection. In a further study from Italy, in which rituximab was given with CDE (cyclophosphamide, doxorubicin, etoposide), fatal infectious complications occurred in 8 % of patients (Spina 2004) – in the meantime, the effect of rituximab in HIV patients is now being carefully evaluated here too.

It is our opinion that in HIV patients, rituximab should only be used within clinical trials or on patients with low or hardly any immunosuppression.

More Intensive Chemotherapy as Standard CHOP

After earlier studies showed that intensive chemotherapy led to a disproportionately high risk of infection and toxic complications (Kaplan 1997), the tendency for a long time was to withhold HIV patients from therapy and often to treat them with reduced-dose regimens. This seems to be changing in the age of HAART. Several prospective studies have shown that the tolerability of chemotherapy is improved through HAART (Powles 2002, Sparano 2004).

In the past few years, small pilot studies have been repeatedly published in which HIV patients have been treated with CHOP regimens. There are also studies in which doxorubicin has been given as liposomal Caelyx™ (Levine 2004) or where the dose of cyclophosphamide was increased (Costello 2004). In addition, CDE, a regimen which, when given for several days as infusions is supposed to overcome the potential chemotherapy resistance of lymphoma cells, is propagated again and again (Sparano 2004). The CR rates in these studies were between 50 and 75 %. In our experience, CR rates up to 70 % are also possible with HAART and standard CHOP. Whether these new attempts, which always cause a stir, are really better than CHOP, remains speculative. In our view, they are not ready for use outside of clinical trials.

Even stem cell transplantations are now possible in HIV patients – a scenario that was still unthinkable a few years ago. Very high doses of myeloablative chemotherapy in combination with HAART are well tolerated (Gabarre 2000 + 2004, Kang 2002, Re 2003, Krishnan 2004). In HIV patients with Burkitt's lymphoma, intensive protocols that were originally developed for HIV-negative patients, are also being successfully employed (see below).

Today, the decisive question regarding more intensive chemotherapy in HIV patients is, therefore, not whether it can be used, but who actually needs it or will profit from an increased dose.

HAART and classic risk factors

At first glance, the effect of HAART on the prognosis of HIV-associated NHL seems contradictory. At least four large cohort studies (Conti 2000, Levine 2000, Matthews 2000, Chow 2001) have shown sobering results. These data contradict numerous, mostly smaller, but more closely analyzed and prospective studies. These showed without exception that HAART significantly improved prognosis (Thiessard 2000, Antinori 2001, Besson 2001, Ratner 2001, Powles 2002, Vilchez 2002, Navarro 2003, Vaccher 2003, Sparano 2004). In addition to survival, some studies also showed improved disease-free survival, response rates and even improved tolerability of chemotherapy.

While the "classic" NHL risk factors for survival (including Ann Arbor stage, LDH, age, Karnofsky score) are already of lower significance in HIV patients than the HIV-relevant factors (CD4 cells, history of AIDS), then the latter presumably lose relevance too when the impact of HAART is also considered. In our own multicenter cohort with over 200 patients, the immunologic-virological success of HAART was an important and independent factor for the prognosis of patients (Hoffmann 2003). This was also true for patients who still had a relatively good immune status (> 200 CD4 cells/μl at the time of lymphoma). The only additional risk factors were extranodal disease and a history of AIDS, but had relatively weak predictive relevance.

Thus, in an ART-naïve patient, the chances of complete remission are not necessarily poor even with an otherwise poor starting condition (advanced lymphoma or HIV). Whenever there is an opportunity for immune reconstitution with HAART and the general status of the patient allows, HAART should be started as rapidly as possible. Even with moderate immunodeficiency, maximum immune reconstruction should be the main goal of every treatment. Chemotherapy with curative intent should be chosen and, if possible, doses should not be reduced.

Which HAART when?

Already existing, adequate HAART should be continued during chemotherapy if possible. In ART-naïve patients, the first one or two CHOP cycles can be completed before starting HAART. Some clinicians prefer to complete all six cycles out of concern for interactions and cumulative toxicities (Little 2003). In our opinion, this is not necessary. The right choice of antiretroviral drugs is not easy, however. D4T, ddC and ddI have a high risk of polyneuropathy (vincristine!), but are less myelotoxic than AZT. Little is known of the possible interactions between PIs and NNRTIs with CHOP, and their influence on the metabolism of cyclophosphamide and other cytostatic agents. The effect on doxorubicin seems to be limited (Toffoli 2004).

In ART-naïve patients, a combination of abacavir or tenofovir, 3TC and an NNRTI is possible. With a high viral load, however, this may rapidly lead to the development of resistance, which limits future options. Here we recommend the initial use of PI-containing combinations with regular measurements of plasma levels.

Special entities of lymphoma

Burkitt's or Burkitt-like lymphomas: the particularly high proliferative capacity and aggressiveness of Burkitt's or Burkitt-like lymphomas is a problem even in HIV-negative patients. In this case, the CHOP regimen is insufficient (Trümper 2001). Although it is still unclear whether this is also true for HIV patients with Burkitt's lymphomas, many clinicians have in recent years tended to treat such patients more intensively.

A modified dose-adapted protocol of the German multicenter study group for adult acute lymphoblastic leukemia (GMALL) has mostly been used for the treatment of HIV-negative cases of Burkitt-NHL/B-ALL, and consists of four to six short, intensive 5-day polychemotherapy cycles, alternating A and B cycles. A cytoreductive pretreatment with cyclophosphamide and prednisone, each for 5 days, was given before the first cycle. During cycle A, fractionated doses of ifosphamide for 5 days, intermediate- or high-dose methotrexate 500-3,000 mg/m^2, VM26, cytarabine (ara-C), vincristine, and dexamethasone are given. During cycle B, ara-C, VM26 and ifosphamide are replaced by doxorubicin and cyclophosphamide (Hoelzer 1996).

The preliminary data show better responses than with CHOP (Hoffmann 2004) and rates comparative to those of HIV-negative patients (Oriol 2003). However, the GMALL protocol is a very intensive chemotherapy, which cannot be administered on an outpatient basis. Strict monitoring of patients in hospital for several weeks is very important. Centers without experience in this intensive protocol should not administer it to HIV-infected patients.

As well as the GMALL protocol, a few other intensive therapies have been reported (Fieschi 2001, Cortes 2002, Lichtman 2003, Wang 2003). A significant problem with most of the currently available studies is that there is no control group. There is no randomized study. So, whether Burkitt's lymphoma in HIV patients has to actually always be treated intensively, can therefore not be definitely concluded yet.

Plasmablastic lymphomas: are a relatively new entity in HIV patients. Plasmablastic lymphomas probably belong to the diffuse large-cell NHLs, but have a completely characteristic immunophenotype – markers for the B-cell antigen CD20 are negative, whereas the plasma-cell reactive antibodies VS38c and CD138 are positive (Brown 1998, Teruya-Feldstein 2004). The oral cavity is the site of involvement (Flaitz 2002, Gaidano 2002), although extra-oral manifestations do occur (Chetty 2003). There is a close association with HHV-8 (Cioc 2004). Like Burkitt's lymphoma, plasmablastic lymphomas have a very high rate of proliferation and are extremely aggressive. More recent data shows that the earlier very poor prognosis is markedly improved by HAART (Teruya-Feldstein 2004, Lester 2004). It is our opinion that patients should receive a more intensive treatment than CHOP-21.

Primary effusion lymphoma (PEL): a further therapeutic problem is the relatively rare entity of the so-called primary effusion lymphoma which is also termed body cavity lymphoma (Carbone 1997, 2000). These lymphomas are often very difficult to diagnose histologically. A visible tumor mass is usually absent, so that malignant cells can only be found in body cavities (e.g. pleural, pericardial, peritoneal). There are histological similarities to immunoblastic and anaplastic cells with a non-B-, non-T phenotype. Every pleural or pericardial effusion occurring in an HIV patient

and containing malignant cells, is suspicious of PEL. The involved pathologist should always be informed about this suspicion.

There is a characteristic close association with the herpes virus HHV-8, which can be detected in the malignant cells. Recently, a solitary variant has been reported, which is neither morphologically nor immunophenotypically distinguishable from the classical PEL types (Chadburn 2004). The response to CHOP is usually poor and poorer than that of centroblastic NHL (Simonelli 2003). Case studies with complete remission on HAART alone have been described (Boulanger 2001, Hocqueloux 2001). We have, however, seen two PEL patients who have also died of progression despite CHOP and HAART after only a few months.

Recently, a combined chemotherapy with high dose methotrexate has been reported, with which, in at least 3/7 patients, a lasting complete remission could be achieved – a notable achievement in view of the otherwise poor prognosis, and an approach that should be followed up (Boulanger 2003). On the other hand, there are reports in which even intensive treatment regimens were unsuccessful (Waddington 2004).

Relapse Therapy, Stem Cell Transplantation

At the moment, no general recommendations for relapse therapy of NHL can be given. The prognosis of NHL relapse is poor overall, anyway. A team from the USA reported their positive experiences using the ESHAP protocol (etoposide, methylprednisolone, ara-C and cisplatin) – DHAP appears to have no effect in this case (Bi 2001). The EPOCH-regimen may also be effective. Other salvage mono-therapies with mitoguazon or liposomal daunorubicin are well tolerated, but purely palliative (Levine 1997, Tulpule 2001).

It should always be checked whether the affected patient with a relapse of lymphoma qualifies in principle for an autologous stem cell transplant (ASCT). In ASCT, the intensity of the chemotherapy can be markedly increased by the preceding gain of pluripotent stem cells (own cells: autologous; foreign cells: allogenic). Following the myeloablative chemotherapy, the patients are re-infused with the stem cells.

Over 50 cases have been described so far worldwide (Gabarre 2000 + 2004, Berenguer 2003, Ellent 2003, Krishnan 2004, Re 2003), including even a few allogenic stem cell transplants (Klang 2002). The critical problem in many hematologic centers is above all a logistical one, namely the complicated storage of stem cells, which has to conform to strict safety regulations. The storage of potentially infectious HIV material together with stem cells from non-infected patients in the normal cooling tanks is not allowed – an extra (expensive) tank is required.

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Primary CNS lymphoma

Primary CNS lymphomas (PCNSL) are a late complication of HIV infection and used to occur in up to 10 % of AIDS patients. Large autopsy series in the 1990s showed even higher prevalence rates. The incidence of PCNSL seems to have decreased significantly in the last years in comparison to systemic lymphomas.

PCNSL are EBV-associated in almost 100 % of cases (Camilleri-Broet 1997). Histologically, findings are almost always consistent with diffuse large-cell non-Hodgkin's lymphomas. In these patients, the CD4 T cells are almost always below 50/μl at the time of diagnosis. In the pre-HAART era, PCNSL had the poorest prognosis of all the AIDS-defining illnesses, with a median survival of less than three months (Fine and Maher 1993). In the last years, this bleak picture, often characterized by therapeutic nihilism, has changed significantly. In the HAART-era, survival may be several years and even complete remission has become possible (Hoffmann 2001).

Signs and symptoms

Different neurological deficits occur depending on the localization. Epileptic seizures may be the first manifestation of disease. Personality changes, changes in vigilance, headache and focal deficits such as paresis are also frequent. Fever is usually absent. As patients are almost always severely immunocompromised, constitutional symptoms may mask the actual problem.

Diagnosis

Cranial CT or (better) MRT scan should be performed rapidly. The most important differential diagnosis is cerebral toxoplasmosis. A solitary mass is usually more indicative of PCNSL. However, 2-4 lesions may be present, which are usually fairly large (more than 2 cm in diameter). More than four lesions of a PCNSL are rarely found.

In addition to an updated toxoplasmosis serology, which – if negative – makes toxoplasmosis very unlikely, a recent CD4 cell count should be available. The bet-

ter the immune status, the less likely the diagnosis of PCNSL. In our own cohort, less than 20 % of patients had more than 50 CD4 cells/µl at the time of diagnosis. At over 100 CD4 cells/µl, however, cerebral toxoplasmosis is also less likely.

In addition to the physical examination, a minimal diagnostic program (chest radiography, abdominal ultrasound) should clarify whether the CNS involvement is secondary to systemic lymphoma. This should always include fundoscopy to exclude ocular involvement (up to 20 %).

Besides cerebral toxoplasmosis, differential diagnoses include abscesses, glioblastoma and cerebral metastasis of solid tumors. In the absence of increased intracranial pressure, lumbar puncture is advised. If steroids have already been administered, however, the probability of finding malignant cells is diminished. In our experience, EBV-PCR of CSF that has been propagated by some groups has not been helpful.

In most cases, a treatment attempt for toxoplasmosis can be made initially. If this is unsuccessful, PCNSL is more likely. In such cases, stereotactic brain biopsy is essential to secure the diagnosis.

Treatment

For many years, cranial radiation therapy has been the only option for patients with PCNSL, independent of the HIV status. In HIV-negative patients, using the combination of radiation therapy and steroids, a remission of 12-18 months duration is usually achieved. In HIV patients in the pre-HAART era, radiation only improved survival from 0.9 to 3.0 months (Fine 1993). Survival of more than one year was rare.

The prognosis for HIV-negative patients has improved in the last years due to the combination of methotrexate-based (MTX) chemotherapies and radiation. Smaller studies have indicated that monotherapy with high doses of MTX could be effective, thereby reserving radiation therapy for relapses (De Angelis 2001). Whether these results will be applicable in HIV patients is not clear. In addition, the incidence of PCNSL is now diminishing to such an extent that convincing data on therapy efficacy can hardly be expected in the near future. A clear recommendation for treatment can therefore not be made at this time.

Many clinicians favor cranial radiation therapy alone in HIV-infected patients (fractionated, 40 Gy total dose). In our experience, a treatment attempt with intravenous MTX is justified (3 g/m^2 every 14 days with leucovorin rescue) – also in order to avoid possible neurological damage from radiation. A small study in HIV patients has shown that this approach is practical (Jacomet 1997).

However, the decisive factor in all cases – independent of the specific therapy chosen – is the best possible immune reconstitution. Under HAART, survival of several years has become realistic. Complete remissions have even been described after treatment with HAART alone (McGowan 1998, Corales 2000). In our own cohort of 29 patients with histologically diagnosed PCNSL, all four patients who experienced an increase in CD4 T cells survived longer than 18 months. Three out of four patients reached complete remission. One patient has now lived for over six years without evidence of relapse (Hoffmann 2001). In a multivariate analysis, HAART was shown to be the only factor associated with a prolonged survival in addition to

cranial radiation therapy. Two of these patients, however, died after about three years of a progressive neurological syndrome, which was probably a long-term sequela of radiation therapy in both cases. In view of the better prognosis for patients today, radiation toxicity should therefore be considered more than in the past. Three further studies from France, the USA and Australia have since shown a survival of several years due to HAART (Rigolet 2001, Skiest 2003, Newell 2004).

All patients with PCNSL should therefore be treated intensively with HAART, to achieve the best possible immune reconstitution. If only a moderate immune reconstitution is possible, additional immunomodulatory or antiviral therapies should be evaluated. The partially very positive reports about ganciclovir and interleukin-2 (Raez 1999, Aboulafia 2002) or hydroxyurea (Slobod 2000) should, however, be interpreted with care. "Between the lines" of these publications, in which either individual or hardly more than 2-4 patients were described, HAART was almost always a factor.

In all cases of increased intracranial pressure, rapid administration of steroids (e.g. dexamethasone 8 mg tid, decreasing the dose rapidly after resolution of edema) is indicated, even if diagnostic testing is more difficult as a result.

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Hodgkin's disease (HD)

The incidence of HD is elevated in HIV-infected patients by a factor of 5-10 compared to the HIV-negative population. For particular subtypes, such as lymphocyte-depleted and mixed-cellularity HD, the relative risk is presumably much higher (Frisch 2001). Despite this and the growing realization that these subtypes at least are clearly associated with immunodeficiency, HIV-HD is not included as an AIDS-defining illness.

An advanced stage of disease at diagnosis is typical, as is frequent extranodal involvement and a trend towards prognostically poorer subtypes (Tirelli 1995, Rapezzi 2001, Thompson 2004). Mediastinal disease is significantly less frequent than in HIV-negative patients. A further difference to HD in seronegative patients is the predominance of cases with Reed-Sternberg cells, as well as the clear association with EBV infection, which is 80-100 %, depending on the study. EBV infection is therefore seen as an important etiologic factor for development of HIV-HD.

In comparison to HIV-negative HD, which is a highly treatable tumor, the prognosis of HIV-HD is poor. In nearly all cohorts with more than 20 patients from the pre-HAART era, the median survival was only between 15-20 months, respectively (Andrieu 1993, Errante 1999, Levine 2000, Tirelli 1995). The response to chemotherapy was also moderate compared to the normal population. Complete remission rates were between 40-80 %, and hematological and infectious complications were frequent.

Even if there are initial indications that this is changing in the era of HAART, as with NHL, there is little data so far. In our own multicenter cohort of 56 patients, the median survival was 40 months. In patients with adequate HAART, the two-year survival rate was 84 %, which is encouraging (Hoffmann 2004). In the meantime, other groups have also reported better prognoses with HAART (Ribera 2002, Gérard 2003).

Signs and symptoms

B symptoms occur in the majority of cases. Extranodal and advanced stages are almost always the rule. Lymphomas are firm, immobile or hardly mobile and painless, and the distinction from HIV lymphadenopathy or tuberculous lymphadenitis is not always possible.

Diagnosis

Staging is necessary as for non-Hodgkin lymphomas (see relevant section). Diagnostic lymph node extirpation is even more important here than with NHL, as puncture only rarely allows diagnosis of Hodgkin's disease. Single accurate diagnostics are better than half-heartedly bothering the patient with repeated punctures and losing time unnecessarily! Surgical extirpation is possible as an outpatient in many centers. As with NHL, specimens should be sent to reference laboratories if possible.

Since bleomycin will be administered, a lung function test should always precede the first chemotherapy.

Treatment

Many clinicians still favor the classical ABVD regimen (four double cycles) for HIV patients. ABVD is the abbreviation for the combination chemotherapy with the cytostatics adriamycin, bleomycin, vinblastine and DTIC (dacarbazine). Ambulatory treatment is possible. It should be contemplated, however, whether this therapy is still sufficient in the HAART era, particularly for advanced stages of the disease.

Table 4: ABVD regimen (4 double cycles, repeat on Day 29)*

Adriamycin (= doxorubicin)	Doxo-Cell®, Adriblastin®	25 mg/m² i.v. Day 1 + 15
Bleomycin	Bleomycin Hexal®, Bleo-Cell®	10 mg/m² i.v. Day 1 + 15
Vinblastine	Velbe®, Vinblastin Hexal®	6 mg/m² i.v. Day 1 + 15
Dacarbazine (DTIC)	Detimedac®	375 mg/m² i.v. Day 1 + 15

* ABVD regimen. Due to strong emetogenicity of dacarbazine, 5HT3-receptor blocker anti-emetics should always be administered, e.g. granisetron, tropisetron or ondansetron.

In HIV-negative patients with advanced stages (as is almost always the case for HIV-HD) the BEACOPP regimen of the German Hodgkin Study Group has been used in the last years, mainly with escalated dosing. This has proven to be significantly more effective, both with regard to response rates and long-term survival. However, the BEACOPP regimen is more toxic. Whether these positive results can be seen in HIV-HD is still not clear. However, based on initial reports and our own experience, BEACOPP seems to be possible (Hartmann 2003). There is also growing experience to date with the Stanford V protocol, for which there have recently been promising reports (Spina 2002).

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Multicentric Castleman's Disease (MCD)

Although rare, multicentric Castleman's disease is a highly problematic illness for the affected patients – not only due to the (in HIV infection) poor prognosis, but also because many clinicians and pathologists are not very familiar with this entity. The usually severely ill patients are often subjected to diverse diagnostic and therapeutic procedures. In comparison to the benign, localized hyperplasia of lymphatic tissue, first described by Castleman in 1956, HHV-8-associated multicentric Castleman's disease, as it occurs in HIV infection, is a malignant lymphoproliferative disease (Oksenhendler 1996). Although multicentric Castleman's disease in HIV is not classified as a lymphoma or AIDS-defining illness, prognosis is poor. In a prospective study, the median survival was 14 months (Oksenhendler 1996).

The pathogenesis of the disease is not well understood. There is a close association to HHV-8, and as a result about half of the patients also have Kaposi's sarcoma. Cytokine dysregulation seems to play an important role – in particular IL-6 and IL-10 are elevated with close association to the HHV-8 viral load (Oksenhendler 2000). The extent of immunodeficiency varies significantly. We have seen an MCD patient with a normal immune status and low viral load. Progression to malignant lymphoma (often HHV-8-associated entities such as PEL) is frequent. In by far the largest prospective study to date with 60 MCD cases, 14 patients developed malignant lymphoma after a median observation period of 20 months (Oksenhendler 2002).

Signs and symptoms

The main signs are the often significant lymph node enlargements, which are almost always combined with considerable B symptoms including fever, night sweats and weight loss. Patients complain of weakness and malaise. There is always massive splenomegaly. Hepatomegaly (70 %), respiratory symptoms (65 %) and edema with hypoalbuminemia (55 %) are also seen in the majority of cases. The extent of symptoms is very variable and may fluctuate considerably. Some patients have Castleman "episodes". Lymph nodes, which may be anything from very soft (as with tuberculosis) to rock hard (as with lymphoma) on palpation, can normalize or relapse within weeks without any intervention.

Diagnosis

Ultrasound reveals hepatosplenomegaly. Laboratory tests show constantly elevated CRP, hypergammaglobulinemia and hypoalbuminemia. There is often significant anemia (may be hemolytic, often reflecting pancytopenia).

The diagnosis is made histologically after lymph node extirpation – providing that the pathologist knows what HIV-associated multicentric Castleman's disease looks

like. Clinicians should explicitly indicate their suspicion. It is possible that a significant proportion of cases are never correctly diagnosed. In the case of the symptoms described above, the pathological diagnosis of HIV-associated lymphadenopathy should not be accepted too easily. HIV alone rarely causes such severe illness! The germinal centers of affected lymph nodes have an onion skin appearance with vascular proliferation. Hyaline-vascular and plasma cell types of Castleman's disease can be distinguished.

Treatment

At present, there is no clear recommendation for a specific treatment for MCD. HAART should always be given, although it doesn't always help (Dupin 1997, Lanzafame 2000, Aaron 2002, de Jong 2003, Sprinz 2004). Some cases have even been described to occur after starting HAART, leading to the suspicion that the inflammatory component of MCD may be increased by immune reconstitution (Zietz 1999). Apart from HAART, there are numerous, very diverse forms of therapy, which unfortunately means that so far none of them is particularly convincing. The problem lies also within the countless case reports, where a probable positive "publication bias" has to be taken into account. On the other hand, something has to be done quickly in HIV patients with MCD: the course of disease can be extremely fulminant. In our experience, CRP is a useful parameter aside from symptoms and signs, for measuring the course of disease and observing the effectiveness of MCD treatment.

Immunomodulation – because of the association with HHV-8, several antiviral substances have been tried, including ganciclovir, which was successful on at least one patient (Caspar 2003). However, in other cases, antiviral therapy with foscarnet or cidofovir had no benefit (Coty 2003, Senanayake 2003, Berezne 2004). For interferon, there are positive as well as negative examples (Coty 2003, Nord 2003). In HIV-negative patients, some very optimistic data from Japan has been published, in which 7 patients were successfully treated with anti-IL-6 receptor antibodies (Nishimoto 2000). Another new approach, supported by an encouraging number of case studies, is thalidomide, which is believed to inhibit cytokine dysregulation as well as the inflammatory component of MCD (Lee 2003, Jung 2004). In contrast, steroids have no effect on MCD.

Chemotherapy – well-tolerated chemotherapies such as vincristine (2 mg i.v. as a bolus at 14-day intervals) or oral etoposide (50 mg daily) have proven effective according to several reports as well as our own experience (Scott 2001). Even CHOP chemotherapy can help, but does not seem to significantly prolong survival. Rituximab, a monoclonal antibody against CD20-expressing cells, which is also used in B cell lymphomas (see above), is being tried in several patients (Corbellino 2001, Marcelin 2003, Marrache 2003, Kofteridis 2004). In a study on 5 HIV patients with MCD, remission was achieved in 3 (Marcelin 2003).

Splenectomy – in severe cases, splenectomy may be appropriate. In a series of 40 patients, the median survival following splenectomy was 28 versus 12 months (Oksenhendler 2002). According to a US team, the symptoms were improved in 10/10 patients following splenectomy (Coty 2003). Why this should occur, is currently unclear. It is speculated that IL-6 production is reduced and that a large reservoir of HHV-8 is removed through the splenectomy.

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Part 5

Special Chapters

16. The New HIV Patient

Sven Philip Aries, Bernhard Schaaf

The initial interview

Can and should be spread over several appointments at short intervals.

What the patient should know afterwards

- In general terms, how the virus causes illness.
- The difference between being HIV-infected and suffering from AIDS.
- The importance of CD4 cells and virus burden.
- How third parties can become infected and how this can be avoided with a great degree of certainty.
- That additional venereal diseases should be avoided, as these can worsen the course of HIV infection; and that it is, at least in theory, possible to become infected with another more pathogenic or resistant strain of HIV.
- Where HIV therapy comes in and how good it can be.
- A healthy balanced diet and regular physical exercise can help improve the prognosis.
- Smoking increases the risk of a number of complications.
- Where to find further information.
- The self-help groups and facilities available in the area for the support of HIV-infected patients.
- What further tests are planned and their usefulness for future treatment.

What the doctor should know afterwards

Infection and risk

- When, where and why was the positive HIV test performed? Was there a negative test prior to this? What risks has the patient taken in the meantime? The question regarding risks can help in the assessment of potential dangers for the patient in further treatment. In the case of a patient without recognizable risk, the test result may be held in doubt until confirmation is given (see also "Laboratory").
- Where has the patient been recently? This is important because certain germs, which are dangerous for the immunodeficient patient, occur in specific regions. For example, someone who has lived in Hollywood for a lengthy period has a relevant risk of histoplasmosis (which is very rare in Europe).
- What drugs are consumed? Large amounts of alcohol are not only toxic to the liver, but also make adherence more difficult due to loss of control. For smok-

ers, the cardiovascular complications of lipodystrophy during therapy are more threatening.

- Family history of diabetes.
- Tuberculosis among contacts of the patient.

Concomitant illnesses

- What previous illnesses, what concomitant illnesses?
- Former treated or untreated infections and STDs, including syphilis and Hepatitis B/C?
- What medications are taken regularly/occasionally?

Social

- What is the social background of the patient? What does he do professionally? What duties does he have to fulfill? What are his priorities? Who knows about his infection? Who will help him when he becomes ill? Who does he talk to about his problems? Does he have any friends who are also infected? Is he interested in getting in touch with social workers or self-help groups?

The Laboratory

- The HIV test is checked in a cooperating laboratory. Western blot is only positive if gp41+120/160 or p24+120/160 react. Cross-reactive antibodies, for example in the case of collagenosis, lymphoma or recent vaccination can lead to false-positive test results.
- Complete blood count: 30-40 % of all HIV patients suffer from anemia, neutropenia or thrombopenia. Check-up at least every 3-6 months, asymptomatic patients included.
- CD4 cell count at the beginning and every 3-4 months thereafter. Allow for variations (dependent on time of day, particularly low at midday, particularly high in the evening; percentage with less fluctuation; HTLV-1 co-infection leads to higher counts despite existing immunodeficit).
- Electrolytes, creatinine, GOT, GPT, γGT, AP, LDH, lipase.
- Blood sugar determination in order to assess the probability of metabolic side-effects when undergoing antiretroviral therapy.
- Lipid profile, as a baseline determination to check the course of metabolic side-effects when undergoing antiretroviral therapy.
- Urine status (proteinuria is often a sign of HIV-associated nephropathy).
- Hepatitis serology: A and B, in order to identify vaccination candidates; C, in order to possibly administer HCV therapy prior to ART; perhaps also G, since this coinfection seems to have a positive effect on the course of HIV infection.
- TPHA test.
- Toxoplasmosis serology IgG. If negative: important for differential diagnosis, if CD4 cells <150/μl – prevention of infection (no raw meat). If positive: medical prophylaxis if necessary.

- CMV serology (IgG). For the identification of CMV-negative patients. If negative: important for differential diagnosis, then information about prevention (safe sex). In cases of severe anemia, transfusion of CMV-negative blood only. If positive: prophylaxis if necessary.
- Varicella serology (IgG). If negative: in principle, active vaccination with attenuated pathogens is contraindicated, but at > 400 CD4 cells/µl it is probably safe and perhaps useful.

The examination

- Physical diagnosis, including an exploratory neurological examination (incl. vibration sensitivity and mini-mental test).
- Tuberculin skin test according to Mendel Mantoux with 10IE (not Tine stamp test as sensitivity is too low). Positive if greater than 5 mm: give prophylaxis (3 months rifampicin and pyrazinamide is probably best); if negative: repeat examination annually.
- Chest X-ray. Contradictory recommendations, probably only makes sense in case of positive tuberculin skin test or clinical indications of disease of the thoracic organs.
- Sonographic scan of the abdomen. A harmless, informative examination as a baseline finding, but not mentioned in the standard guidelines.
- ECG and pulmonary function test. Simple tests to rule out any cardiovascular and pulmonary disease.
- For women, a PAP smear upon initial diagnosis, after 6 months and then, if negative, once a year. Important because of the approx. 1.7-fold increase in the risk of cervical carcinoma.
- For homosexually active males, an anal PAP smear is recommended every 3 years (due to approx. 80-fold increase in risk of anal carcinoma).
- Especially at low CD4 cell counts (e.g. <200/µl) funduscopy (ophthalmological consultancy!) in order to rule out active CMV retinitis or scars. Advisable in cases of good immune status also (photographic documentation as a baseline).
- Nutritional advice and/or treatment of malnutrition.
- Verifying vaccinations (see chapter on vaccinations).
- Checking the necessity of OI prophylaxis.
- Checking the indication for an antiretroviral therapy.

17. HIV and HBV/HCV Coinfections

Jan-Christian Wasmuth and Juergen Rockstroh

HIV and HCV Coinfection

Epidemiology and Transmission

Coinfection with HIV and HCV occurs frequently, due to the fact that both are transmitted via the same pathways (parenteral, sexual, vertical). 240,000 people (30 % of HIV-infected individuals) are estimated to be infected with both viruses in the USA.

Several European countries have even higher rates of coinfection. In Spain, at least 50 % of the 130,000 HIV-infected patients are also HCV-positive as a result of the high incidence of i.v. drug users. More than 90 % of coinfected individuals are positive for HCV RNA, i.e. have chronic hepatitis C.

As HCV is ten times more infectious than HIV on blood-to-blood contact, intravenous drug users and recipients of blood products are particularly susceptible to coinfection. For example, on routine testing of blood products from HIV-infected hemophiliacs treated before the discovery of HCV in the early nineties, HCV antibodies and HCV RNA were detected in the serum of over 90 % of patients. The probability of transmission from needlestick injuries after exposure to HCV-contaminated blood is 2–8 %, compared to only 0.3 % after exposure to HIV-contaminated blood.

In contrast, sexual transmission of HCV occurs significantly less frequently than HBV or HIV. As a result, HCV is rare in homosexual men and coinfection is more seldom in this group. However, recently there have been reported clusters of cases of acute hepatitis C among homosexual HIV-positive men, clearly indicating that HCV can be sexually transmitted. The risk of transmission probably depends on the number of sexual partners and the performance of sexual practices that are prone to injuries. In total, about 4–8 % of all HIV-infected homosexuals are also infected with HCV.

Perinatal transmission of hepatitis C is rare in immunocompetent individuals (<1 %). The transmission rate rises with increasing immunosuppression in HIV-positive mothers, and is estimated to be as high as 20 %. On the other hand, HIV-positive mothers treated effectively with HAART do not appear to have an increased risk for materno-fetal transmission of the hepatitis C virus (in combination with cesarean section).

Clinical course and pathogenesis

Course of hepatitis C in HIV/HCV-coinfected patients

The clinical course of hepatitis C and HIV coinfection is determined by the HIV-associated immunosuppression. Progression of immunosuppression accelerates the course of hepatitis C. This was first shown in data from the American Multicenter

Hemophilia Cohort Study (MHCS), in which 10 % of adult hemophiliacs with HCV coinfections developed hepatic failure after a latent period of 10–20 years, even before the onset of AIDS-defining opportunistic infections or neoplasms. Rapid progression of liver disease was found particularly in patients with CD4 T-cell counts below 100/µl. In the group of HIV-negative but HCV-positive patients, there was not a single case of liver failure during the same period of observation. In this group, the latent period until liver failure or hepatocellular carcinoma develop is estimated to be 30–40 years. Several studies, some of which included histological analyses, have confirmed the accelerated course of hepatitis C with concurrent HIV infection.

The improved treatment options for HIV infection have increased the likelihood of patients actually living to experience the development of liver failure. The associated decrease in mortality with HIV infection has resulted in a relative increase in hepatitis-associated mortality. In some centers, liver failure is now the most frequent cause of death in HIV-infected patients. This, together with the accelerated course of hepatitis C with HIV coinfection, has led many experts to regard hepatitis C as an opportunistic infection.

Course of HIV infection in HIV/HCV-coinfected patients

Studies, that determined the influence of hepatitis C on HIV infection, yielded contradictory results at first. The Swiss Cohort Study identified hepatitis C as an independent risk factor for the more rapid progression of HIV infection to AIDS and death. This phenomenon could not be explained by less frequent use or poorer tolerability of HAART, but was due to a diminished rise in CD4 lymphocytes in HIV patients with concurrent hepatitis C. However, long-term follow-up could not certify this difference further. In other studies (e.g. Johns Hopkins Cohort, EuroSIDA), hepatitis C did not influence the probability of progression of HIV infection, especially after correction for the use of and response to HAART. Taken together, extended follow-up of different cohorts could not show a significant influence of hepatitis C on the course of HIV infection.

Course of hepatitis C with HAART

The unfavorable course of hepatitis C in HIV infection can be improved by treatment of HIV infection with HAART. In addition, the development of liver failure can be delayed by the improved immune function under HAART. This is particularly true for patients taking protease inhibitors.

On the other hand, hepatitis C infection can aggravate the potential hepatotoxicity of several HAART regimens. Up to 10 % of patients have to discontinue HAART due to severe hepatotoxicity. This risk is associated especially with nevirapine and the so-called "d-nucleosides" (ddI, ddC, d4T). These substances should be avoided in coinfected patients.

In some coinfected patients, a temporary increase in transaminases is observed after initiation of HAART. This most likely corresponds to an increased inflammatory activity of hepatitis C as a result of the improved immune status. Nevertheless, long-term follow-up has shown that HAART improves the course of hepatitis C. Indications for HAART, according to current treatment guidelines, should be carefully checked in all coinfected patients.

Diagnosis

The diagnostic tests used in coinfected patients are no different from those used in patients with HCV monoinfection. Detection of HCV antibodies (anti-HCV) proves exposure to HCV, but does not distinguish between resolved and chronic hepatitis C. Chronic hepatitis C is diagnosed by the detection of HCV viremia (i.e. HCV RNA). It should be noted that HCV antibodies may be lost during the course of HIV infection as a result of the underlying immunosuppression. It may therefore be useful to determine HCV RNA levels, even if the anti-HCV test is negative, if there is clinical suspicion or advanced immunodeficiency. Similarly, determination of HCV RNA levels is indicated in cases of suspected acute (primary) HCV infection, as HCV antibodies usually only become detectable one to five months after infection.

Patients with HIV/HCV coinfection have significantly higher levels of HCV viremia than patients with HCV monoinfection. In parallel to an ongoing rise in viremia, the risk of perinatal or sexual transmission increases. However, the level of viremia does not have a prognostic value for the course of hepatitis C. Instead, it is possible to predict a response to treatment from the level of the HCV viremia: if the concentration of HCV RNA is below 2 million copies/ml, the probability of treatment success is significantly higher than at levels above 2 million copies/ml.

When considering the treatment of hepatitis C, genotyping is necessary before starting. Six genotypes with numerous subtypes are known to date, and are seen to have different regional distributions: genotypes 1 and 3 are predominantly found in Europe, whereas genotypes 4 and 5 are found in Africa, and genotype 6 in Asia. They are mainly of prognostic value with regard to the response to treatment. Genotypes 2 and 3 in particular are associated with significantly better responses to interferon therapy. Coinfection with several genotypes is possible.

Transaminases, the parameters of cholestasis, and markers of the synthetic capacity of the liver (CHE, albumin, total protein, and coagulation factors) should be determined. They provide the same indication and interpretation indices as in patients without HIV infection.

The importance of taking liver biopsies before the initiation of HCV therapy is controversial, and there are no consistent recommendations based on results from clinical studies. On the one hand, it is thought that HCV therapy should only be administered if there is a histologically confirmed "absolute" indication for treatment, as it may be associated with numerous side effects, possible interactions with HAART and relatively low efficacy. On the other hand, it must be assumed that HCV therapy is almost always justifiable in coinfected patients, as the course of hepatitis C is accelerated and past studies have shown that progression to fibrosis or cirrhosis occurs in approximately half of all patients. In addition, liver biopsies need to be repeated every 2 to 3 years due to the accelerated course of disease, and not all patients are prepared to go through with this. As a result, liver biopsy is currently seen as desirable, but not obligatory. It is always required if the remaining findings are inconclusive and the hepatic activity (= grading) and the degree of parenchymal liver damage (= staging) need to be determined. Fibrosis grades (F0-F4) and the Knodell score are used for histological classification. In the absence of fibrosis or significant inflammatory activity, immediate treatment is usually not required.

Before performing a liver biopsy, contraindications must be carefully considered. This is particularly important for hemophiliacs, who often cannot be biopsied (risk of hemorrhage!).

If there is clinical suspicion requiring the detection or exclusion of extrahepatic manifestations (vasculitis, glomerulonephritis, systemic cryoglobulinemia), appropriate investigations may be necessary (skin biopsy, urine tests, kidney biopsy, detection of serum cryoglobulins).

The recommendations for autoantibody testing to exclude autoimmune disease vary and test results are difficult to interpret: up to 60 % of all patients with hepatitis C have autoantibodies such as ANA, RF, anticardiolipin, SMA, and LKM1 antibodies as an accompanying autoimmune phenomenon without any clinical relevance. If the titers of these autoantibodies increase or appear for the first time during interferon therapy, treatment does not usually have to be discontinued, and so the need for routine testing of autoantibodies is arguable. In order to exclude autoimmune hepatitis, however, LKM1 antibodies should be determined before interferon therapy is initiated. Patients with positive results should be monitored closely for deterioration of liver function on interferon therapy as a sign of active autoimmune hepatitis. If liver function worsens, interferon should be discontinued. The need for immunosuppressive therapy can only be decided on a case-by-case basis.

Before treatment with interferon, TSH levels should always be determined to exclude thyroid disease. With normal thyroid function, it is sufficient to monitor TSH at 12-weekly intervals. In cases of hypothyroidism, substitution with levothyroxine is recommended, and thyreostatic treatment is similarly recommended for hyperthyroidism before initiation of interferon therapy. After adequate treatment, interferon therapy can usually be administered under close monitoring of TSH (every 4 weeks). Approximately 5 % of patients develop thyroid dysfunction on interferon therapy. This generally manifests within the first 3 months of treatment. If hypothyroidism is induced, interferon therapy can usually be continued in combination with substituted levothyroxine. The first manifestation of hyperthyroidism is enough cause for most authors to discontinue treatment, although even here it may be possible to continue interferon therapy in certain cases. In the majority of patients, thyroid dysfunction resolves after discontinuation of interferon. However, it may also persist, and therefore cases need to be considered individually.

Up to 12 % of patients with hepatitis C have thyroid autoantibodies before treatment with interferon (antibodies against thyroid peroxidase = anti-TPO, antithyroglobulin antibodies and TSH receptor antibodies). In these patients, the risk of a deterioration in thyroid function on interferon is significantly higher than in patients without these antibodies. If possible, autoantibodies should be determined in all patients before beginning treatment, but at the very least in those patients with abnormal TSH levels, in order to have a baseline value to allow subsequent monitoring.

Therapy

The goal of hepatitis C treatment is to achieve permanently negative HCV RNA levels. This is generally referred to as a sustained response. It is defined as a negative HCV RNA six months after completion of treatment.

Negative HCV RNA at the end of the treatment period is described as an end of treatment response. If transaminases have normalized, this is referred to as a bio-chemical response. However, the latter does not correlate with the further clinical course of hepatitis C and is therefore no longer used today. Failure to respond to treatment is referred to as a non-response.

In the following text, response rates always refer to sustained responses. This is because only sustained responses have been clearly associated with the resolution of liver fibrosis and extrahepatic manifestations, as well as with the prevention of further transmission.

When HCV RNA becomes detectable again after having been negative, it is re-ferred to as a relapse. The probability of a relapse is highest within the first months following completion of treatment and decreases steadily afterwards. Therefore, the success of therapy is usually determined and evaluated six months after the end of treatment. In individual cases, relapses may occur at later time points, sometimes after years. Therefore, regular monitoring is advisable even following successful treatment (monitoring of transaminases; HCV RNA if there is reason to suspect a relapse).

Hepatitis C is treated with interferons and nucleoside analogs. Interferons are gly-coproteins that protect cells from viral infection by inhibiting viral mRNA transla-tion and reducing viral penetration and release. In addition, the immune reaction is influenced via modulation of cytokine profiles. The guanosine analog ribavirin is used as a nucleoside analog. Liver transplantation may be a possible option for pa-tients who have cirrhosis and cannot be treated with interferon therapy.

The treatment of hepatitis C in HIV-infected patients differs in two main points from the treatment of hepatitis C in monoinfected patients: the response rates are lower due to the underlying immunodeficiency, and discontinuation of treatment as a result of side effects is more frequent.

Interferon monotherapy and combination treatment with standard interferon-α and ribavirin are no longer relevant. Response rates varying from 13 to 40 % and dis-continuation of treatment in approximately 30 % of cases due to side effects, were not satisfactory. Pegylated interferons henceforth have replaced standard interfer-ons. These are bound to polyethylene glycol (PEG), in contrast to conventional in-terferons (i.e. interferon-α 2a or interferon-α 2b). Pegylation shields the interferon-α protein from enzymatic degradation, and thereby considerably lengthens its half-life. As a result, absorption of interferon is slower (producing less peak concentra-tions, which are associated with side effects) and a consistently high plasma level (with less low trough levels, during which efficacy could be reduced). Pegylated interferons can therefore be administered only once instead of three times weekly.

The combination of pegylated interferon with ribavirin is regarded as standard ther-apy in coinfected patients. Best results have been found by the APRICOT study (AIDS Pegasys™ Ribavirin International Coinfection Trial), which is the largest published study in HIV/HCV-coinfected patients to date (Torriani 2004). A sus-tained response was achieved in 40 % after a treatment period of 48 weeks. Only 12 % of participants had to discontinue therapy due to adverse events. Particularly genotype 1, which is associated with a poor prognosis, showed a better response to this treatment (29 %) compared to the conventional interferon/ribavirin therapy.

The more favorable genotypes 2 and 3 reached response rates of 62 %. Overall response rates, as well as response rates according to different genotypes, were significantly better than in the other two treatment arms: standard interferon-2α plus ribavirin (total: 12 %, genotype 1: 7 %, genotypes 2+3: 20 %) or pegylated interferon with placebo (total: 20 %, genotype 1: 14%, genotypes 2+3: 36 %). All patients were treated over a period of 48 weeks regardless of the genotype. Of special interest is the finding that the relapse rate at week 72 was only 2 % for genotypes 2+3, whereas relapse-rates of up to 50 % were associated with the former treatment period of 24 weeks. Therefore, genotypes 2+3 should also be treated for 48 weeks.

Other studies such as the RIBAVIC trial or ACTG A5071 could not confirm the response rates found in the APRICOT trial. In both studies response rates of 27 % were achieved using the PEG-interferon/ribavirin combination. Direct comparison of the three trials is difficult because of methodological differences. For example, the number of patients with underlying cirrhosis was higher in the RIBAVIC trial possibly accounting for some of the treatment response differences. Indeed, the superiority of PEG-interferon/ribavirin was confirmed in these two trials.

Detailed information on interferon, PEG-interferon and ribavirin can be found in the section on Drug Profiles.

Concerns that interferon treatment could have a negative effect on HIV infection have not been confirmed in any study. In fact, there is further suppression of detectable HIV viremia in the majority of patients as a result of the antiviral effect of interferon. Absolute CD4 T-cell counts may drop slightly due to temporary leukopenia, but percentage values usually rise. No treatment study to date has shown a significant deterioration of HIV infection (Soriano 2002).

The treatment options remain inadequate for patients with a non-response or relapse. In patients treated earlier with interferon monotherapy, an attempt can be made using a combination of PEG-interferon and ribavirin. There are currently no standard recommendations for treatment of patients after failed PEG-interferon therapy. Consensus interferon could become a possible option in the future.

The management of acute hepatitis C also remains unclear. In patients with HCV monoinfection, early treatment with interferon α-2b within the first six months has shown excellent response rates (98 %!) (Jaeckel 2001). Retrospective analyses in HIV-infected patients revealed response rates of more than 80 %. These data support early treatment even in the presence of HIV coinfection. If possible, patients should be treated within prospective clinical studies.

Practical tips for management of treatment

The following treatment recommendations have been compiled for HIV coinfection:

Indications and contraindications

As HIV coinfection accelerates the course of hepatitis C and increases the risk of hepatotoxicity after initiation of HAART, the indication for treatment should be determined in **every** patient with diagnosed HIV/HCV coinfection. The algorithm in Figure 1 can be used as a guide.

In particular, treatment should be discussed for cases with a bioptically confirmed fibrosis of grade F2-F4. Extra-hepatic manifestations of hepatitis C are also an indication for treatment (vasculitis, glomerulonephritis, systemic cryoglobulinemia). The following factors are associated with a more favorable response to treatment:

- HCV RNA < 2 million copies/ml
- HCV genotype 2+3
- Age < 50 years
- Histologically, low grade of fibrosis
- Normal γ-GT
- Stable HIV infection
- Female sex (currently being discussed; possibly insufficient dose adjustment for weight in heavier men)

In addition, contraindications should be evaluated. The most important are:

- Decompensated liver cirrhosis or history of decompensation (but not compensated cirrhosis, i.e. CHILD A cirrhosis!)
- Leukopenia (<1,500/µl)
- Thrombocytopenia (< 50,000/µl)
- Anemia (< 10 g/dl)
- Severe, as yet untreated thyroid dysfunction
- CD4+ T-cell count < 200/µl (relative contraindication, see below)
- Severe psychiatric illnesses
- Symptomatic cardiac disease
- Active opportunistic infections

Methadone or polamidone substitution is **not** a contraindication if good monitoring can be ensured during the treatment phase. However, patients with active drug or alcohol abuse should first be introduced to the appropriate programs.

In addition, the immune status of the patient and current antiretroviral therapy must be considered (see below).

HCV antibodies
pos   neg
HCV RNA
pos   neg
HCV genotype and viral load
ALT
normal   elevated
Liver biopsy   PEG-IFN+RBV
FO+F1   F2-F4   HCV-RNA
at week 12
Repeat liver biopsy
after 3 years
< 2 log   > 2 log decrease
decrease   or negative
Stop   Continue
treatment   treatment
until week 48
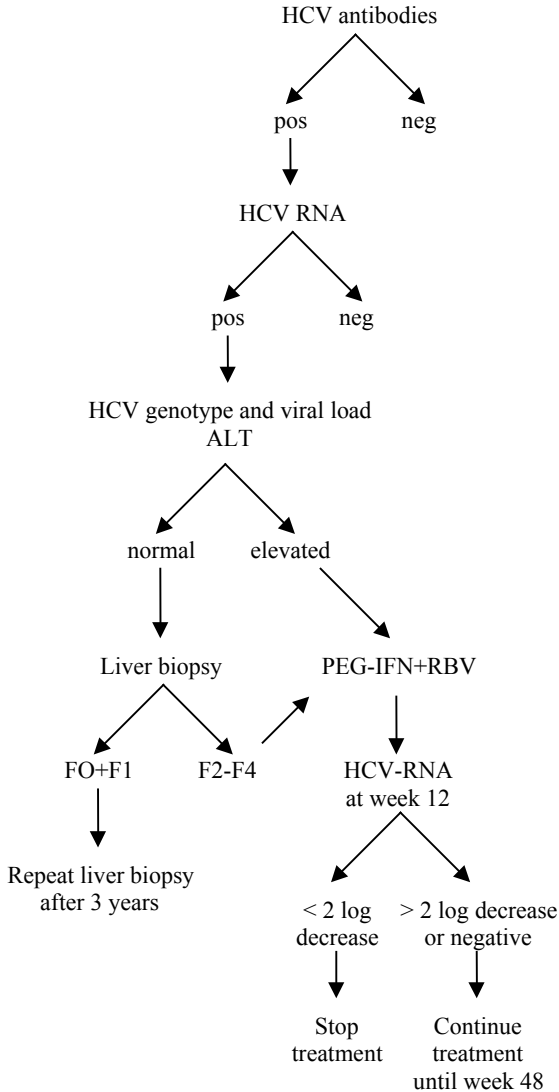
ALT, alanin aminotransf.; PEG-IFN, pegylated interferon;
RBV, ribavirin; modified after Soriano 2002 and 2004

Figure 1: Hepatitis C treatment algorithm

If possible, HCV should be treated before HIV. Reasons for this include the increased hepatotoxicity of HAART with concurrent hepatitis C; possibly, impaired immune reconstitution resulting from hepatitis C; better compliance; and finally, prevention of drug interactions. The following scheme is suggested:

Patients without HAART

If the CD4 T-cell count is above 350/µl, treatment of hepatitis C can be started. It is unclear whether a high viral load (i.e. > 50,000/ml) requires initiation of HAART.

If the CD4 T-cell count is between 200 and 350/µl, the patient might benefit from treatment of hepatitis C if HIV RNA is below 5,000 copies/ml. If it is higher, initiation of HAART should be considered.

A CD4 T-cell count below 200/µl is a relative contraindication. HAART should be initiated first. When there is an adequate increase in the CD4 count, interferon therapy can be reconsidered.

Patients on HAART

If CD4 T-cells are above 350/µl under stable HAART and the viral load is below the level of detection, treatment can be started.

If CD4 T-cells are between 200 and 350/µl and the viral load is stable below the level of detection, the decision should be dependent on the overall situation (with consideration of criteria that include severity of hepatitis, HCV genotype and status of HIV infection).

A CD4 T-cell count below 200/µl is a relative contraindication. It is a judgement call to decide whether to take the risk of a treatment attempt with interferon (with the likelihood of a poor response and the danger of a further decline in the CD4 cell count as a result of interferon treatment).

If necessary, antiretroviral treatment should ideally be modified several weeks before HCV therapy is initiated. HCV treatment should only be started if the overall clinical situation is stable, i.e. good viral suppression has been achieved and side effects have been evaluated or treated.

Didanosine is contraindicated with concurrent HCV therapy (as it can lead to pancreatitis, mitochondrial toxicity, and more cases of liver decompensation). Zidovudine should also be avoided if possible, in order to prevent additive toxicities (such as anemia and leukopenia). It is possible that a combination therapy with stavudine is also unfavorable (due to mitochondrial toxicity). Before modifying HAART, it should be insured that the treatment success of HIV therapy is not going to be compromised. If there are only limited treatment options available, the indications for the treatment of hepatitis C should be reconsidered in certain cases.

Treatment practice

The combination of PEG-interferon with ribavirin over a period of 48 weeks is recommended as the standard therapy (Soriano 2004) regardless of the genotype (Rockstroh 2004).

Two interferons are currently available as PEG-interferons: PEG-Intron™ and Pegasys™. PEG-Intron™ is administered subcutaneously and the dose is based on body weight at 1.5 µg/kg. Pegasys™ is injected subcutaneously at a fixed dose of 180 µg. Both substances are administered once a week, and must be kept refrigerated.

The dosage of ribavirin should be based on body weight and set at not lower than 10.5 mg/kg daily. The capsules can be taken once daily, or spread over the day.

Patients should be counseled extensively on the expected side effects before beginning treatment. Three main aspects should be explicitly addressed:

Almost all patients experience influenza-like symptoms or malaise when beginning treatment. As the severity of symptoms cannot be predicted beforehand, treatment should be initiated at a time when there are no important private or professional events pending (e.g. before a weekend). The administering physician should be readily available during the first days of treatment. In addition, paracetamol should be prescribed. Symptoms usually improve within the first two to four weeks. A decision to stop treatment should therefore not be made before the end of the first month if possible.

Most patients tolerate treatment quite well and can continue their daily activities normally. However, it is possible that particularly in the initial stages of treatment, they may be unable to work for several days. In rare cases, the side effects may be so grave that patients are unable to work for the entire duration of treatment. This also needs to be discussed with the patient in advance.

Patients must be made aware of the fact that both interferon and ribavirin are potentially teratogenic. A reliable method of contraception for at least six months after treatment is therefore important.

All patients require regular clinical monitoring. This should initially take place every 2 weeks; later at least every 4 weeks. Laboratory monitoring should include:

- A complete blood count and transaminases every 2-4 weeks
- Thyroid function tests every 12 weeks (more frequently with pre-existing dysfunction)
- Immune status every 12 weeks
- Lactate levels every four weeks in patients on stavudine comedication

HCV RNA is the most important parameter for measuring the treatment response and is determined after 12 weeks to decide on the duration of treatment. In practice, it is often already determined after four or eight weeks - partly because it is a motivation for further treatment if there is a treatment response.

The evaluation of psychological side effects is made at every clinic visit. Observations made by others, such as family members, may also be very helpful.

The management of possible side effects is often the decisive factor for the success of treatment. A high discontinuation rate in numerous (older) clinical studies is likely also to have been due to a lack of experience with combination therapy. Proper management of side effects probably results in significantly better treatment success rates. It is often helpful to indicate to patients that side effects are reversible after stopping therapy.

Ribavirin causes hemolytic anemia in up to 20 % of patients. This can be treated with epoetin alfa. Dose recommendations differ: usually approximately 100 IE/kg body weight are injected subcutaneously three times a week. Alternatively, halving the dose (hemoglobin below 10 g/dl) or discontinuing ribavirin altogether (hemoglobin below 8.5 g/dl) are possible options. However, dose reductions, frequently used in the past, should only be made if epoetin does not help. Newer studies have shown that the correct dosing of ribavirin is associated with a better treatment response. A daily 5 mg dose of folic acid is recommended to reduce hematoxicity.

Treatment with granulocyte colony stimulation factor (GCSF) may ameliorate an interferon-induced leukopenia. Clinical experience is very limited so far. However, so that the required dose of interferon can be maintained in case of leukopenia, this recommendation seems to be justified.

Mild depression whilst on interferon can be treated with well-tolerated antidepressants (e.g. paroxetin 20 mg daily). Therapy should be stopped immediately in cases of severe depression or on development of suicidal thoughts.

The frequent occurrence of weight loss can be lessened with dietary counseling. It is important to ensure a regular diet that is tailored to the patient's wishes (e.g. in-patients with drug addiction). It is possible that the weight loss is a form of lipoatrophy, and therefore nucleoside analogs with a lower risk for development of lipodystrophy should be used if possible.

Thyroid dysfunction may develop during treatment with interferon (see above), which might necessitate discontinuation of interferon therapy.

The duration of treatment depends on the treatment response. If HCV RNA is still positive after 12 weeks, treatment is discontinued irrespective of genotype, as a treatment response is unlikely even if therapy is continued. Earlier recommendations were to wait until week 24 because of delayed elimination kinetics in HIV patients compared to HCV-monoinfected patients. However, it is now possible to reach a decision after just 12 weeks, even in HIV patients.

If HCV RNA has dropped by at least 2 logs or is negative, treatment should be continued for another 36 weeks in patients with all genotypes. Earlier recommendations were to stop therapy after week 24 in patients with genotype 2 or 3. However, recent data from the APRICOT study showed a very low relapse rate after 48 weeks of treatment, whereas prior studies revealed relapse rates of up to 50 % if patients were treated for only 24 weeks. Therefore, patients with all genotypes should receive treatment for at least 48 weeks. Continuation of treatment beyond this time point, especially in patients with genotypes 1 and 4, could possibly reduce relapse rates further.

Recommendations for treatment of hepatitis C are constantly evolving. Therefore an experienced treatment center should always be contacted if clarifications are needed.

Due to the complexities of HIV/HCV coinfection, patients should be treated within clinical studies wherever possible.

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HIV and HBV coinfection

Introduction

The hepatitis B virus is one of the most common human pathogens worldwide. Up to 95 % of all HIV-infected patients have been infected with hepatitis B, and approximately 10-15 % have chronic hepatitis B, with considerable variation among geographical regions and risk groups. It is estimated that around 100,000 HIV-infected patients in the USA suffer from chronic hepatitis B. Sexual transmission is the most frequent route of contraction. Transmission via the bloodstream is more probable than for HIV: following a needlestick injury contaminated with HBV-infected blood, the risk of infection is around 30% (HCV approx. 2-8 %; HIV approx. 0.3 %). Primary HBV infection leads to chronic hepatitis in 2-5 % of immunocompetent adults, whereas HIV-infected patients experience chronification about five times more often. A possible reason for this is the HIV-associated T-cell defect. A polarization to a Th2-type response could result in the inhibition of specific cellular defense mechanisms (e.g. cytotoxicity, production of interferon-γ and interleukin-2, and the T-cell proliferation rate). Genetic predisposition could also play an important role in the chronification of hepatitis B. Current data indicate that virus-specific factors, such as the extent of HBV viremia, genotype (A-H), or the emergence of escape mutants do not result in differences between HIV-infected and immunocompetent patients. It should be noted, that genotype A mainly affects homosexual men who tend to be positive for the hepatitis B antigen, whereas genotype D is predominantly seen among intravenous drug users in Southern Europe and seems to be associated more often with negative hepatitis B antigen. Treatment response to interferon may be influenced by genotypes (with a possibly better response in patients with genotype A).

Hepatitis B and HIV have several common features, although hepatitis B is a double-stranded DNA virus. After entering the hepatocyte, viral DNA is integrated into the host genome. Viral RNA is translated by HBV reverse polymerase into new viral DNA and transcribed into viral proteins. Reverse transcription may be inhibited by nucleos(t)ides reverse transcriptase inhibitors. Integration of the virus into the host genome of hepatocytes and CD4+ T-cells prevents its eradication. Finally, the mechanisms for development of resistance are very similar for both viruses.

The diagnosis of HBV is established as in patients without HIV infection. Table 1 summarizes the interpretation of serological test results. Screening HIV-infected patients for HBV starts with HBsAg, anti-HBs, and anti-HBc. If a positive HBsAg is found, testing for HBeAg, anti-HBe, and HBV DNA should follow. There is debate about a so-called occult infection due to immune escape. This means patients lack HBsAg, but are positive for HBV DNA. Recent studies have not found evidence of such occult infection and the prevalence and impact in coinfection remains unclear.

Table 1: Interpretation of serological test results for HBV

Interpretation	HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV-DNA
No prior contact with HBV	–	–	–	–	–	–
Acute infection	+	–	+ (IgM)	+	–	+
Past infection with immunity	–	+	+ (IgG)	–	+	–
Chronic hepatitis B	+	–	+ (IgG)	+	–	+
Occult infection[1]	–	–	+ (IgG)	–	–	+
Pre-core mutant	+	–	+ (IgG)	–	+	+
Inactive carrier state	+	–	+ (IgG)	–	+	–
Immunity after vaccination	–	+	–	–	–	–

[1] Controversial. See text above.

In general, patients with chronic hepatitis B should be screened for hepatocellular carcinoma (HCC) every 6 to 12 months. Serum alpha fetoprotein and an ultrasound of the liver should be performed. This recommendation is independent of apparent cirrhosis, as 10 to 30 % of patients who develop HCC do not have pre-existing cirrhosis.

Course of hepatitis B with concurrent HIV infection

In HIV-infected patients, chronic hepatitis B has an unfavorable course compared with monoinfected patients, and the risk of liver-associated mortality is significantly increased.

Data from the Multicenter AIDS Cohort Study (MACS) have demonstrated the unfavorable influence of HIV infection on hepatitis B (Thio 2002). In approximately 5,000 patients observed over a period of 14 years, the risk of liver-associated mortality was 8 times higher than in HBs antigen negative HIV patients (14.2/1,000 person-years vs. 1.7/1,000) and 15 times higher than in HBs antigen negative patients without HIV infection (14.2/1,000 vs. 0.8/1,000). Liver-associated mortality due to hepatitis B has increased significantly since the introduction of HAART in this cohort.

In addition to increasing mortality, HIV coinfection accelerates the progression of hepatitis B and increases the risk of cirrhosis. Histological analysis of a series of 132 homosexual men with chronic hepatitis B, of which 65 were HIV-coinfected, showed a higher prevalence of liver cirrhosis in HBV/HIV-coinfected patients. No difference was observed in the extent of inflammatory activity. Interestingly, several patients developed severe fibrosis and cirrhosis, in the presence of only minimal inflammatory activity. This phenomenon has also been described in other immunocompromised patient populations (e.g. organ transplant recipients). HIV-positive patients possibly experience more frequent reactivation episodes of chronic hepatitis B than HIV-negative patients.

Despite the worsening described, initially the clinical course is usually more benign in HIV-positive patients, although viral replication is increased. This seems contradictory at first, but can be explained by the impairment of cellular immunity, which

may lead to an increase in viral replication, but at the same time also reduces hepatocyte damage. Therefore, transaminases in HBV/HIV-coinfected patients are frequently only mildly increased. In contrast, HBV DNA, as a marker for viral replication, is higher than in immunocompetent patients.

There is a direct correlation between the extent of immunosuppression and the control of viral replication of HBV: patients with AIDS more frequently show signs of active viral replication (HBs- and HBe antigen positive, HBV DNA detectable) than patients without AIDS. Even in cases with apparently resolved hepatitis B (anti-HBe positive, HBV DNA negative, even anti-HBs positive), increasing deterioration of the immune system may result in reactivation of the HBV infection.

Most studies on the influence of hepatitis B infection on the course of HIV disease have not been able to determine a shorter survival time. HBV infection neither leads to a more rapid decline of CD4+ cells nor to an increased frequency of AIDS-defining events. However, the reduction in HIV-associated mortality has led to an increase in mortality resulting from liver-related complications. In addition, HAART-related hepatotoxicity develops about three times more frequently in patients with chronic hepatitis B. Whether or not the prognosis of HBV/HIV-infected patients is changed by HAART and HBV-effective therapies, remains to be seen.

Prevention

All patients infected with HIV but with negative hepatitis B serology should be vaccinated! The vaccine may, however, be less effective due to immunosuppression. Approximately 30 % of HIV-infected patients have a primary non-response (only 2.5 % in immunocompetent individuals). This is particularly true for patients with CD4 cell counts less than 500/µl whose response rate is only 33 %. Therefore, a conventional dose is administered to patients with CD4 cell counts greater than 500/µl (20 µg at months 0, 1, and 12), whereas an intensive schedule is recommended for patients with CD4 cell counts less than 500/µl (20 µg at months 0, 1, 2, and the last dose between month 6 and 12). In case of non-response (checked 12 weeks after each cycle), vaccination is repeated at double the dose in four steps (40 µg at months 0, 1, 2, and 6-12). Patients with CD4 cell counts less than 200/µl, who are not on HAART, should receive HAART first and HBV immunization thereafter.

Loss of protective immunity is seen in up to 30 % during each year following seroconversion. Therefore, anti-HBs should be monitored once a year and consideration should be given to booster doses if anti-HBs-antibody levels are less than 100 IU/l. HIV patients, who are not adequately immunized against HBV, should be screened yearly to look for newly acquired infection.

HIV/HBV-coinfected patients who are seronegative for hepatitis A should be vaccinated against hepatitis A (months 0, and 6), as there is an increased rate of severe or fulminant hepatitis in case of acute hepatitis A. Patients who are susceptible to both hepatitis A and B can be vaccinated with a bivalent vaccine (months 0, 1, and 6).

Following immunization, patients should be counseled about common measures to prevent further transmission and transmission of other viruses such as hepatitis C or hepatitis D (safer-sex practices, avoidance of needle-sharing and others). They

should be educated about strategies to prevent progression of liver disease such as avoidance of alcohol consumption, tobacco use (controversial), or herbal supplements, many of which are hepatotoxic. The application of hepatotoxic drugs (e.g. anti-tuberculous agents) should be carried out cautiously.

Newborns of mothers with chronic hepatitis B should receive hepatitis B-immunoglobulin and active immunization.

Treatment

Treatment of chronic hepatitis B is problematic in coinfected patients because of the impaired immune function. As HBV persists in infected cells even after successful treatment, eradication of HBV seems not possible with current treatment strategies. Similar, development of protective anti-HBs-antibodies with subsequent loss of HBsAg is difficult to achieve because the integrated HBV pool escapes the direct antiviral effect of most anti-HBV drugs. Current treatment goals are seroconversion from HBeAg to anti-HBe, a complete suppression of HBV DNA, normalization of transaminases and improvement of liver histology. Other benefits of HBV therapy include the reduction in the risk of transmission and possibly in the risk of HAART-induced hepatotoxicity.

Drugs with HBV activity

Studies with interferon from the pre-HAART era showed almost no response (response most often 0 %). Immune reconstitution with HAART and the introduction of pegylated interferons will change and newly define the role of interferons in treatment. In general, the efficacy of IFN-α therapy is higher in HBeAg-positive than in HBeAg-negative chronic hepatitis B. Patients with high ALT levels and low HBV DNA titers show the best responses. In HBV-monoinfected patients, positive for HBeAg, the rate of seroconversion is higher with interferon than with nucleos(t)ides. This raises the question whether treatment with interferon should be offered to the particular subset of coinfected patients with several positive predictors of treatment response (HbeAg-positive, high CD4 counts, elevated ALT levels) and no need for HAART. Results on PEG-interferon are currently being awaited. However, data are limited at the moment and the inclusion of patients in prospective clinical trials is highly recommended. Treatment with interferon is limited by its toxicity. In patients with decompensated liver disease, IFN-α is contraindicated. It should be used cautiously in patients with advanced liver disease. Detailed information on the use of interferons can be found in the sections on Hepatitis C and on Drugs.

In patients with low CD4 counts, the response to IFN-α is much lower. Two drug classes are available for these patients: nucleoside and nucleotide analogs, both of which inhibit the HBV polymerase.

Lamivudine was the first nucleoside analog licensed for the treatment of chronic hepatitis B. It has excellent activity against HBV in addition to its antiretroviral efficacy. It can improve both markers of viral replication and histological activity. The rate of seroconversion in coinfected patients is about 22 to 28 % (Benhamou 1996). The optimal duration of treatment is unclear. 6 to 12 months of treatment are recommended for HBV-positive patients without HIV infection. Longer periods of treatment are associated with better response rates. In HIV-infected patients, the

treatment duration with lamivudine is usually determined by the underlying HIV infection. Long-term treatment with lamivudine is limited by the development of resistance. This is conferred by a mutation in the YMDD motif in the HBV DNA polymerase gene. Similar to a pre-core-mutant, HBeAg production may stop in case of mutations in this motif. The frequency of resistance development has been reported to be at least 20 % of patients per year. This corresponds to rates in HIV-uninfected patients, who are usually treated with 100 mg lamivudine daily. The effect of continuing lamivudine treatment on the course of hepatitis B in case of resistance is unknown. If lamivudine treatment is discontinued, the clinical picture of acute hepatitis may develop as a result of a reactivation.

Emtricitabine has added new options for the treatment of hepatitis B. Seroconversion occurs in up to 30 % of patients after 2 years. Emtricitabine, like lamivudine, is a cytosine analog licensed for the treatment of HIV infection. It should be considered interchangeable with lamivudine, as both substances share cross-resistance and are very similar in terms of characteristics and tolerability. The effective dose seems to be 200 mg once a day. The drug is well tolerated with no dose-limiting adverse events. Preliminary results suggest that resistance to emtricitabine may occur less frequently than with lamivudine.

The nucleotide analog adefovir is an alternative treatment. It has been licensed for the treatment of chronic hepatitis B since the end of 2002 in the USA and since the beginning of 2003 in Europe. The in vitro efficacy of adefovir against HBV is excellent. Loss of HBeAg occurs in about 27 % of patients treated, seroconversion in 12%. For a long time, no significant development of resistance to adefovir was observed. After 2 years of treatment, about 2.5 % of patients develop resistance (Angus 2003), although there seems to be no cross-resistance to lamivudine. Therefore, adefovir is still an option even after development of resistance to lamivudine. It is unclear whether it should be added to lamivudine therapy or given sequentially. Neither HIV resistance mutations nor an effect of adefovir on HIV have been observed to date. Nevertheless, more data are still needed to ensure adefovir does not select resistance mutations in HIV at low doses, which might compromise the future activity of tenofovir. A clinical picture of acute hepatitis may develop after discontinuation of adefovir, similar to stopping lamivudine.

The standard dose of adefovir is 10 mg once daily. Dose adjustment is necessary in cases of renal insufficiency. Several placebo-controlled studies have shown no increase in side effects when compared to placebo. In particular, the nephrotoxic effects that were observed at a dose of 120 mg have been reported with an incidence of less than 1 % after 96 weeks of observation on the lower dose.

Tenofovir is a further possibility. It is actually only licensed for treatment of HIV infection and not for treatment of hepatitis B. Several pilot studies have shown excellent effectiveness of tenofovir against hepatitis B in HIV-coinfected patients, with 70 % of patients showing undetectable HBV DNA levels after 2 years and 15 % of patients showing HBeAg seroconversion. Tenofovir is also effective in the presence of lamivudine resistance. Due to the potential (rare!) development of nephrotoxicity, creatinine and phosphate levels should be monitored regularly. Interestingly, tenofovir seems to be active if failure of adefovir therapy occurs.

In the light of the lesson learned from HIV and the high resistance rate of HBV on lamivudine therapy, combination of at least two drugs seems prudent. However,

studies on combination therapy found divergent results. The combination of IFN-α plus lamivudine or adefovir has shown no superiority so far. On the other hand, there is a clear benefit if lamivudine is combined with tenofovir. Combination of these two drugs enhances antiviral activity and delays the selection of HBV resistance. Combination therapy is being explored further in several clinical trials. At present, combination therapy with one nucleoside and one nucleotide analog should be preferred to monotherapy if feasible.

Finally, liver transplantation may be an option for selected patients who have cirrhosis and/or develop hepatocellular carcinoma.

Treatment guidelines

Several treatment guidelines have been published, although many aspects of HIV/HBV coinfection have not been looked at so far and recommendations are not uniform (Brook 2003, Murphy 2004, Soriano 2005). In principle, due to accelerated progression and increased mortality in coinfection, treatment possibilities should be examined for every patient. Treatment is recommended if:

- ALT is consistently > 2-fold above the norm (high pre-treatment ALT values correlate with better treatment responses to interferon and lamivudine);
- HBeAg is positive;
- HBV DNA > 10^5 copies/ml (the optimal threshold is unknown; lower thresholds to initiate therapy have been proposed);
- Significant inflammation or liver fibrosis has been detected bioptically.

The role of liver biopsy in coinfected patients has been discussed controversially. Currently, the indication for HBV therapy is based on serological markers alone. Indeed, liver biopsy is seen as desirable, as knowledge of the severity of liver damage may influence the choice or length of treatment, and other causes of liver disease may be excluded. Liver biopsy is recommended particularly for patients with the inactive carrier state (positive for HBsAg, but no other marker of replication). However, it is not mandatory before the initiation of HBV treatment.

The following non-binding treatment recommendations may be suggested, but need to be confirmed in further studies. An effective treatment of HIV infection must not be put at risk. Accordingly, lamivudine, emtricitabine and tenofovir, that are effective against both HIV and HBV, have to be combined with other substances effective against HIV in order to ensure an adequate HAART. On the other hand, adefovir is not effective for treatment of HIV and must not be considered as part of the HAART regimen.

The main consideration is the need for HAART (Table 2):

- If the patient is under HAART or needs HAART due to low CD4+ counts, drugs with both HIV- and HBV-activity should be included in the HAART regimen (i.e. lamivudine, emtricitabine or tenofovir).
- If there is no need for HAART, the use of drugs without HIV activity seems the best choice (i.e. adefovir or IFN-α).

The drugs currently available are summarized in Table 3.

Table 2: Treatment recommendations in HIV/HBV-coinfected patients

HAART used or needed?	Indication for treatment of Hepatitis B?	Recommendation
No	No	Monitor hepatitis B (i. e. transaminases every 3 months, INR/HBV DNA every 6 months)
		Discuss liver biopsy
Yes	Yes	Lamivudine (or emtricitabine) *plus* tenofovir: continue or add substance according to HIV regimen
		If HAART does not contain tenofovir *plus* lamivudine (or emtricitabine):
		- lamivudine (or emtricitabine) *plus* tenofovir might be added
		- adefovir might be added – but not if on tenofovir!
		- pegylated interferon might be considered
No	Yes HbeAg-positive	(Pegylated) interferon
No	Yes HbeAg-negative	Adefovir
No	Yes	If criteria for initiation of HAART have not been fulfilled, earlier administration of HAART (containing tenofovir *plus* lamivudine) might be discussed

Table 3: Current therapeutic options for chronic hepatitis B in HIV/HBV coinfection.

Drug	Dose	Length of therapy
Interferon-α	5 MU per day *or* 10 MU 3 days per week	4-6 months in HbeAg-positive patients 12 months in HbeAg-negative patients
PEG-Interferon	Pegasys™ 180 µg once a week PEG-Intron™ 1.5 µg/kg body weight once a week	Only Pegasys™ is licensed for hepatitis B in monoinfected patients. Here, length of therapy is 12 months.
Lamivudine (3TC)	300 mg QD	Minimum of 12 months in HbeAg-positive patients and 6 months after HbeAg seroconversion Indefinite in HbeAg-negative patients
Emtricitabine	200 mg QD	Undefined
Adefovir	10 mg QD	Minimum of 12 months, possibly lifelong
Tenofovir	300 mg QD	Undefined
Entecavir	0.5 mg, if 3TC naive 1.0 mg, if 3TC experienced	Undefined

Initial normalization of ALT and significant reduction of HBV DNA will be achieved in most cases by any anti-HBV agent. ALT levels do not correlate well with inflammatory activity and are influenced by many other factors such as hepatotoxicity of HAART or other drugs, alcohol consumption, and immune reconstitution. Therefore, their value for monitoring treatment is limited. HBeAg seroconver-

sion will occur in as many as 25 % of patients. The most desirable endpoint of HBsAg loss is observed in only 5-10 % of patients within one year of the start of treatment with IFN-α, but occurs less frequently with nucleos(t)ide analogs.

Data on the durability of treatment responses are heterogeneous. HBeAg loss induced by IFN-α is durable in more than 80 % of the patients for more than 5 years. Durability after lamivudine treatment is not as good, and relapses often occur when lamivudine is discontinued. Therefore, lamivudine should be continued for at least 6 months after HBeAg seroconversion.

The optimal duration of treatment is not clear at the moment. Recommendations for HBV-monoinfected patients: after seroconversion (loss of HBe antigen) or loss of HBs antigen, treatment should continue for at least another 4 to 6 months. Seroconversion should be determined on two occasions 3 months apart. For HBe-negative mutants, the parameters for treatment success are transaminases and HBV DNA (< 10^5 copies/ml) or loss of HBs antigen. Otherwise treatment should be discontinued with loss of efficacy.

Treatment of HBV may have to be continued indefinitely after seroconversion due to the persistence of HBV. This may at least be the case in patients with ongoing immunosuppression.

A transient elevation of transaminases – which is usually moderate and soon resolves – may be observed after initiation of HBV therapy. It is caused by immunoreconstitution and subsequent increased inflammatory activity. In case of marked and/or ongoing elevation of transaminases, alternative explanations have to be considered (e.g. increasing HBV replication, resistance of HBV, lactic acidosis, hepatotoxicity of antiretroviral drugs, superinfection with hepatitis viruses other than hepatitis B).

After seroconversion, treatment should be continued for at least 6 months (possibly longer) or until there is a loss of effect (elevation of transaminases and viral load). If HIV develops resistance against one of the drugs, e.g. lamivudine, it may be reasonable to switch HIV therapy, but to maintain lamivudine in order not to put the effect on HBV at risk.

As most cases of acute hepatitis B even in HIV-positive patients resolve spontaneously, only supportive treatment is recommended. In addition, data on this situation are sparse (e.g. danger of resistance in case of early therapy with no more options afterwards).

Two main issues will dominate the further development of HBV therapy in the near future. Firstly, combination therapies, including the combination with new compounds, are being investigated further and could significantly influence the development of resistance. Secondly, there are numerous new drugs with specific HBV activity that are still being developed and that will enable further progress. Entecavir is probably the next drug to be approved. It is one of the most potent anti-HBV agents examined so far and lacks anti-HIV activity. It shares no cross-resistance with adefovir or tenofovir and shows virological responses in patients with lamivudine-resistance, although not as good as in lamivudine-naive patients. It has a very good safety profile and, independent of HIV in coinfected patients, will allow management of HBV infection. The recommended dose of entecavir will probably be 1.0 mg QD for coinfected patients. Other drugs waiting in line are

clevudine and telbivudine. Both show cross-resistance to lamivudine and diminished activity in the presence of YMDD mutants.

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18. HIV-associated Skin and Mucocutaneous Diseases

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Introduction

Since 1981, when the first reports about AIDS were published in medical literature, skin and mucocutaneous diseases played an important role in the clinical diagnosis of acquired immunodeficiency. Kaposi's sarcoma in young homosexual men was the first symptom that made AIDS a visible disease (Friedman-Kien 1981, 1990). Additionally, opportunistic infections of the skin and oral cavity such as herpes simplex and candidiasis were published as being clinical markers of acquired immunodeficiency (Gottlieb 1981, Siegal 1981). In the early years of HIV infection, a broad spectrum of common cutaneous infections was noted in patients due to viruses, bacteria, fungi, protozoa, and parasites as well as many unusual manifestations of common dermatoses (Friedman-Kien 1989, Farthing 1989, Schöfer 1990, Schöfer 1991, Berger 1997).

The alterations of the cell-mediated immune system enable organisms considered to be non-pathogens to penetrate into the tissue and cause infections. Such opportunistic infections, as well as any other infections in the immunodeficient host, sometimes behave aggressively leading to a life-threatening clinical course.

The most frequent skin diseases documented in a prospective long-term study in HIV-infected patients at the Department of Dermatology and Venereology, University Hospital, Frankfurt/M, Germany, between 1983 and 2004, are summarized in Table 1.

Differences in the prevalence and incidence of mucocutaneous disease between countries may be attributable to climate, endemic diseases, hygienic standards and the availability of specialized medical facilities and drugs, as well as social, economic and cultural factors. The risk groups observed – homosexual men, IVDA, heterosexuals, and children – play an important role in the incidence and prevalence of HIV-associated mucocutaneous diseases (Tzung 2004, Geoghagen 2004, Shimizu 2000, Munoz-Perez 1998, Sivayathorn 1995, Smith 1994, Pallangyo 1992).

Among sexually transmitted diseases, chancroid is an important indicator of the spread of the HIV epidemic in tropical and subtropical regions; whereas in Europe, herpes simplex infections and a resurgence of syphilis in homosexual men are more important indicators. Recently, there has been increased reportage of lymphogranuloma venereum, an STD caused by Chlamydia trachomatis (L1-3), in homosexual men in several big cities throughout Europe. It is suspected that this is due to the changing sexual behavior of homosexual men during the past 5 to 7 years. Fear of acquiring HIV infection by unsafe sexual practices has lessened as patients live longer, healthier lives on HAART therapy. There may be a sense among patients that HIV infection no longer confers a death sentence because HAART decreases viral loads resulting in fewer diseases. In addition, many men are not aware of the risk of infection through orogenital contact with other STDs such as syphilis.

Table 1: Frequency of skin diseases in 2149 HIV-infected patients, Dept. Dermatology and Venereology University Hospital, J. W. Goethe University Frankfurt/M	No. patients	% of all HIV patients
Oral candidiasis	636	30%
Seborrheic dermatitis	619	28%
Xeroderma	600	28%
Tinea	502	23%
Folliculitis	492	23%
Syphilis (active/seropositive)	485	23%
Kaposi's sarcoma	460	21%
Pruritus	436	20%
Genital warts	368	17%
Candida infections, others	355	16%
Drug eruptions	349	16%
Herpes simplex genitoanalis	349	16%
Herpes zoster	345	16%
Gonorrhea (active/history)	340	16%
Bacterial infections	315	15%
Mollusca contagiosa	301	14%
Warts (HPV)	278	13%
Herpes simplex labialis	214	10%
Oral hairy leukoplakia	188	9%
Hair loss	135	6%
Psoriasis	117	5%
Basal cell carcinoma (BCC)	25	1.2%
Squamous cell carcinoma (SCC)	23	1.1%
Malignant melanoma	9	0.4%
Total number of patients 1982 - 2000	2149	100%

Notice: The frequency of skin diseases listed here mirrors the clinical symptoms of 2149 HIV-infected patients, who visited the Frankfurt University Hospital between 1982 and 2000 because of skin problems. Most of these patients were referred with a known HIV infection. Others were detected to be HIV-positive by their dermatological symptoms, which were interpreted as clinical markers of severe acquired immunodeficiency and led to HIV antibody testing. The major part of these patients (75%) was seen in the pre-HAART era (between 1982-1996). Since 1996, more than 80% of the patients living with HIV/AIDS in Frankfurt/M. are on HAART. This led to a significant reduction in opportunistic skin diseases (by 90%) and Kaposi's sarcoma (by 90%). The high frequency of skin disease summarized in this table is still seen in patients who are not on HAART or not yet diagnosed to be HIV-infected.

In urban areas, syphilis is now seen 4 to 10 times more frequently in homosexual men in comparison to 2000. Until today, there has been no observable increase in the incidence and prevalence of syphilis in European women, but it is very likely that the epidemic in homosexual men will be followed by a heterosexual epidemic within a few years. According to the epidemiological data, provided by the Robert Koch Institute in Berlin, the registration of new syphilis cases exceeded the number of newly registered HIV infections in 2003 by more than 1000 cases (RKI 2003).

It has become evident that a functional cell-mediated immune system plays an important role in the protection against epithelial tumors. The likelihood of developing squamous cell carcinomas, basal cell carcinomas, lymphomas, or even malignant melanoma is correlated with the length of time HIV-infected immunocompromised patients survive. Nowadays, HIV-infected patients survive longer than patients from the pre-HAART era. For this reason, these patients need to be monitored for primary cutaneous malignancies such as basal cell carcinoma, squamous cell carcinoma, melanoma, and cutaneous lymphomas.

Analogous to the long-term immunosuppressed organ transplant recipient, the HIV-infected patient has to be examined periodically for melanoma as well as non-melanoma skin cancers including actinic keratoses (Schöfer 1998). Factors such as UV-light, smoking and oncogenic viruses (especially mucocutaneous infections with HPV 16 and HPV 18) must be considered as cofactors in carcinogenesis. Skin cancer precursors such as actinic keratoses, bowenoid papulosis, Bowen's disease, and intraepithelial neoplasias of the genital or anal region must be treated early and aggressively. The incidence of anal carcinoma, an epithelial tumor typically found in old men, is now increasing in young HIV-infected homosexual men. It seems that the total duration, rather than the severity of immunodeficiency is important for the manifestation of these tumors. As in non-immunocompromised patients, risk factors such as pigmentation characteristics, sun sensitivity, sun exposure behavior patterns, and geographic location must be considered in the evaluation.

Dermatological examination and therapy in HIV-infected patients

HIV-infected patients with advanced disease often suffer from common skin diseases (Table 1), but they also present with rare dermatoses, unique to HIV infection. Careful dermatologic evaluation may lead to the diagnosis of serious systemic infections in this population such as cryptococcosis, bacillary angiomatosis, oral hairy leukoplakia, and *Penicillium marneffei* infections of the skin. Common dermatoses often present with atypical findings and may pose diagnostic dilemmas. For example, herpes simplex labialis may present as large superficial erosions or deeply ulcerating lesions rather than the classical small vesicles on an erythematous base. Eruptions of secondary syphilis may ulcerate and form rupial lesions accompanied by high fever and constitutional symptoms (malignant syphilis). It is therefore important to pursue diagnosis of all cutaneous eruptions through appropriate tests such as tissue cultures, biopsy, and swabs of lesions prior to the initiation of therapy.

Because HIV-infected patients are at high risk of contracting other STDs due to the common modes of transmission, they should be screened for them. During the past three years, 39 % of all syphilis patients who attended our Department, had HIV co-infection. Dermatologic evaluation should include complete cutaneous inspection, oral cavity examination, inspection of the anogenital region and palpation of the lymph nodes. Standard treatment regimens for skin and mucocutaneous diseases may be inadequate in HIV-infected patients due to unusual strains of organisms leading to drug resistance. In these cases, high dose regimens or second and third line therapies may have to be considered (Osborne 2003). Diagnostic and therapeu-

tic regimens of the most frequent HIV-associated skin diseases are compiled in alphabetical order in Appendix 1 of this chapter.

Table 2: Clinical Diagnostic Tools

Indication	Performance	Interpretation
Presumptive diagnosis of ulcers (mainly of syphilitic ulcers) Exudative lesions (condylomata lata, possibly secondary syphilis lesions).	**Dark-field microscopy** Secretion (mechanical pressure, if necessary use ether in local anesthesia) of serous exudate is applied to a glass slide, covered with a coverslip. Examination by dark-field microscopy (1000x). Lesions in the mouth: examination not possible due to saprophytic bacteria	Negative test does not exclude syphilis; false negative testing may be due to: prior treatment with antibiotics/ antiseptics A positive test confirms the diagnosis
Differential diagnosis of tumors, skin lesions without definite clinical diagnosis, or to confirm a clinical diagnosis	**Biopsy** Under local anesthesia: 4-mm punch-biopsy; if necessary: excisional biopsy. Fixation of the material in 10% formalin; for special investigations (immunohistology, electron-microscopy, HPV-typing) use only saline.	Dermatopathologist
Presumptive diagnosis of dermatophytosis	**Skin-scraping for KOH examination** Clean the skin with 70 % alcohol, let it dry. Use a scalpel or glass slide to scrape scales at the active edge onto a glass slide. A drop 10 - 20 % KOH is put on top of the specimen and covered with a cover slip. After ~ 20 minutes or immediately after gentle heating the specimen can be examined microscopically (10-40x magnification) for fungal elements. The specimen may be cultured as well.	Fungal elements (spores and hyphae) are not digested by KOH and can be visualized with light microscopy.
Presumptive diagnosis of herpes infections (grouped vesicles or ulcers)	**Herpes-virus detection** A smear of cells from the base of the skin lesion is taken (for culture: special swabs: Culturette™; use pressure to obtain cells). Sample can be put onto a glass slide for immediate direct fluorescent antibody testing (DFA) which will distinguish between HSV and VZV infections.	Tzanck-preparation: multinucleated giant cells (Giemsa- or Wright-stain; 400x magnification) Viral lab, positive culture proves diagno-sis; demonstration of DNA or antigen does not differentiate between living and dead viruses
Drug eruptions, presumptive allergic contact dermatitis	**Allergy testing** Serology: (RAST, lymph. transformation test); skin tests Type I reactions: Prick- and intra-cutaneous-tests. Type IV reactions: "Scratch"- and patch testing. A specialist in allergy should perform tests and interpretation.	Allergist

HAART: Influence on skin and mucocutaneous diseases

The introduction of HAART in 1996 revolutionized the dermatological management of HIV-infected patients. Opportunistic infections and the clinical manifestations of Kaposi's sarcoma abated to a level of 10 % compared to the pre-HAART era (Reinmöller 1997, Schöfer 1998, Sepkowitz 1998, Calista 2002). An Italian hospital reported that HAART had reduced the total number of HIV patients with skin problems by 40 %. The percentage of patients with cutaneous infections dropped from 66 to 53 %; the percentage of non-infectious, inflammatory diseases from 25 to 21 %; however, the percentage of patients with drug reactions increased from 8 to 23 % (Calista 2002). Appendix 2 is a compilation of antiretroviral drugs, and their cutaneous side effects. Atypical clinical courses of skin diseases and resistance to therapy, which were very common in patients with severe immunodeficiency in the pre-HAART era, are rare conditions now. They still occur, however, in patients not taking antiretroviral therapy (Mirmirani 2001). Cutaneous infections and inflammatory skin diseases have been replaced by drug eruptions caused by almost 20 currently available antiretroviral drugs. In some patients, immune system reconstitution, following 1 to 2 months after the introduction of HAART, causes clinical disease summarized as immune reconstitution inflammatory syndrome (IRIS).

Drug eruptions have many clinical patterns including macular or maculopapular exanthemas, follicular eruptions, urticaria, and toxic epidermal necrolysis (TEN), to name a few. Severe, sometimes life-threatening reactions such as Stevens-Johnson-syndrome or TEN were mainly reported in patients on combination therapy with zidovudine, didanosin, nevirapine, indinavir or amprenavir. In 86 % of these patients, the drug eruptions occurred within the first 4 weeks of treatment (Rotunda 2003). Instead of discontinuing therapy, less severe drug eruptions without mucosal involvement, blistering, or constitutional symptoms (apart from pruritis), may be treated with antihistamines and corticosteroids. This is especially important for patients, whose choice of antiretroviral combination drugs is already limited by drug resistance or severe side effects such as hematotoxicity or polyneuritis. Patients who are "treated through" drug eruptions must be monitored frequently. Corticosteroid treatment should not exceed the equivalent of 1 mg/kg/d bodyweight of prednisone.

Blister formation, involvement of the mucous membranes and constitutional symptoms (hypersensitivity syndrome) are absolute indications to stop antiretroviral therapy. TEN (e.g. induced by efavirenz, nevirapine) and hypersensitivity syndrome (e.g. induced by abacavir) may be fatal.

Drug interactions between HAART and agents used to treat cutaneous diseases are frequent and need to be carefully evaluated before being prescribed (see Chapter "Drug interactions", Mc Nicoll 2004). Azole derivatives, retinoids and drugs metabolized via the p450 pathway frequently interact with antiretrovirals.

Immunosuppressive therapies, such as ultraviolet light and cyclosporin, should be limited to a few conditions such as severe autoimmune diseases, and used only with careful clinical and laboratory monitoring. Photo(chemo)therapy is able to provoke viral infections such as herpes zoster and herpes simplex, epithelial tumors, and to

increase the HIV viral load. Despite this, we have seen the benefit of UVB 311nm phototherapy in HIV-infected patients with extreme pruritus associated with papular dermatoses or eosinophilic folliculitis, resistant to all other therapies. As long as these patients were under the protection of HAART, UV therapy caused no observable worsening of the immune status.

Eliciting the cause of a drug eruption can be challenging, especially if the patient is taking complementary medication not prescribed by a physician. It is necessary to ask explicitly whether any herbal medicines, vitamins, minerals, or food complements are being taken to improve the general health. Substances with a potential risk of sensitization or toxicity can be the cause of drug reactions (Witkowski 2003). Urticaria, angioedema, and exanthemas due to food complements are reported in the literature (Gised 1996).

The treatment of Kaposi's sarcoma (KS) varies with the clinical manifestation of the tumor, the immune status of the patient and his additional symptoms associated with the HIV infection (details see Chapter "Kaposi's sarcoma").

Conclusions

The dermatologist's role in the care of HIV-infected patients is to be familiar with HIV-associated skin and mucocutaneous diseases, their diagnoses, and management. It is also a part of the extensive interdisciplinary knowledge necessary for any physician who takes care of HIV-infected patients.

Considering the lifelong duration of antiretroviral therapy with complications such as drug intolerance, development of epithelial tumors induced by UV-light exposure or oncogenic viruses, it is recommended that patients have a dermatologic consultation before the start of antiretroviral therapy. Complete skin examination with attention to the presence of STDs should be performed. Education should include prevention of photodamage, safe sex practices, and skin care to avoid infections, especially when HIV-associated xerosis is already evident.

Despite the fact that HIV-associated opportunistic infections are less frequent in the HAART era, knowledge about these diseases and adequate treatment is still of high clinical relevance. The full spectrum of these skin diseases is still found in untreated patients around the world.

Dermatological markers of disease of severe acquired immunodeficiency (see Appendix 1) play an important role in this situation (Schöfer 1991), especially if several diseases are diagnosed in the same patient. In the absence of other immunodeficiency, HIV antibody testing must be offered to the patient as a diagnostic tool to elicit the cause of the clinical presentation.

At present, syphilis and HIV co-morbidity is of special interest. The incidence of syphilis in Western Europe has increased 4 to 10 times over the past 4 years. As HIV and *Treponema pallidum* share the same route of transmission, any patient with syphilis must be checked for HIV infection. The delayed seroconversion for HIV antibodies should be taken into account and, if initially negative, HIV testing should be repeated after 3 months.

Appendix 1:

Most frequent HIV-associated skin diseases

Acute HIV exanthema: In 40-90 % of all patients infected with the HIV-1 virus, an acute, febrile, mononucleosis-like disease with constitutional symptoms and an exanthema occurs (details see Chapter "Acute HIV-1 Infection"). This nonspecific eruption starts 1 to 3 weeks after HIV transmission, and several weeks before HIV seroconversion. The macular exanthema favors the upper trunk and is characterized as fairly non-pruritic with erythematous macules from 0.5 to 1 cm in diameter. Morbilliform or rubella-like eruptions and palmoplantar hyperkeratotic eczema occur less frequently. Histopathology reveals a nonspecific perivascular and interstitial infiltrate in the upper and mid dermis (Barnadas 1997). Oral aphthous ulcers, frequently in combination with shallow genital ulcers (bipolar aphthosis) are another important clinical symptom (Hulsebosch 1990, Porras-Luque 1998). Differential diagnosis includes viral infections (EBV, CMV), Mediterranean spotted fever (Segura 2002), secondary syphilis, drug eruptions (Hecht 2002, Daar 2001) and Behcet's disease.

Aphthous ulcers: At least three different kinds of aphthous ulcers occur in the oral cavity of HIV-infected patients. The most frequent diagnosis is recurrent aphthous stomatitis (canker sores) (1) with single or few painful lesions usually localized in the vestibule of the mouth. The ulcers occur at sites of mechanical injuries, are 3 to 10 mm in diameter and heal spontaneously after a few days. Single or multiple large aphthae (2) which are >1cm in diameter and usually persist for several weeks are less common. Both variants are of unknown origin (Rogers 1997). In a few cases, especially when multiple small lesions occur, herpes simplex viruses can be involved. Large ulcers in combination with severe immunodeficiency can be caused by cytomegaloviruses, which are usually part of a generalized CMV infection. Bipolar aphthosis (3), involving the oral and genital mucosal membranes, is an important clinical symptom of acute HIV infection or Behcet's disease. In addition to these clinical variants of aphthous ulcers, several authors have discussed the direct role of HIV retroviruses in aphthous stomatitis (Kerr 2003). The treatment of recurrent aphthosis is based upon topical anesthetics, and corticosteroids. Large persistent aphthae can require intralesional corticosteroids or systemic prednisone. Immunomodulators, such as thalidomide, are suggested for use as prophylaxis in patients with frequent and painful recurrences.

Folliculitis: pustular, papular or edematous-papular follicular lesions, involving the proximal limbs and the upper trunk**.** Possible causes include *Staphylococus, Malassezia furfur, Demodex folliculorum*, and drugs such as indinavir. Treatment depends on the etiologic agent detected by bacterial swabs and histopathology if needed. Antimicrobials against staphylococcus, and malassezia, or changing the antiretroviral drug regimen may be required. DADPS, a 10 % crotamiton or polidocanol ointment, or low-dose UV-311nm radiation are effective against severe pruritus in these patients (Holmes 2001, Simpson-Dent 1999). Today, it is well established that

HAART naive patients with pruritic eosinophilic folliculitis significantly improve after the initiation of antiretroviral therapy.

Genital warts (condylomata acuminata): Genital warts are hyperkeratotic and verrucous papules of the anogenital region, caused by human papilloma viruses (HPV 6, 11, 16, 18, etc.) which are sexually transmitted. HIV-infected patients have a high prevalence of these lesions (17 %), which depends on the number of sexual partners. Genital warts, located in the perianal or intra-anal region are characteristic of receptive anal intercourse. Patients who have anogenital warts, should be offered HIV testing, especially if they have other HIV risk factors.

In general, the clinical manifestations of common genital warts in immunodeficient patients do not differ from those in immunocompetent patients. They are diagnosed by their typical clinical features as condyloma acuminata, condyloma plana, bowenoid papulosis, Bowen's disease and giant condyloma (Buschke-Loewenstein tumor). In contrast to the findings in the immunocompetent population, HPV 16-associated lesions, such as bowenoid papulosis and Bowen's disease, which are now classified as anal intraepithelial neoplasias (AIN I-III including the erythroplasia of Queyrat), are more prevalent in immunodeficient patients. These premalignant conditions have a low rate of spontaneous remission and are very resistant to therapy (frequent relapses). It is now accepted, that genitoanal lesions due to oncogenic HPV types, especially HPV 16 and 18, are substantial risk factors for malignant cervical, penile, and anal carcinomas (Palefsky 1998). HPV 16 and 18 are able to immortalize human keratinocytes by downregulating the tumor suppressor genes p53 and pRB. The transformation rate to malignant carcinomas is low in bowenoid papulosis, but almost 30 % in Bowen's disease, which is rated as a carcinoma in situ. In contrast to the beneficial effects of HAART on the incidence and the clinical course of Kaposi's sarcoma and NHL, there is no clear impact on cervical and anal carcinoma. The incidence of these tumors is still increasing. Analogous to cervical intraepithelial neoplasia (CIN) and cervical cancer in women, regular screening (every 2 to 3 years) for AIN and anal carcinoma is advised for all HIV-infected patients on HAART (Papathanasiou 2003). Screening should include clinical inspection, aceto-white-stain, colposcopy, proctoscopy, cytology (Pap smear) and, if necessary, histopathology (Horster 2003). Clear margins should be the goal of treatment.

The typical treatment for anogenital warts is destruction by cryosurgery, electrocautery, carbon dioxide, Nd-YAG laser, trichloroacetic acid, or podophyllotoxin. CIN, PIN, and AIN are treated surgically with histological control of the excision edges to ensure complete removal of the lesion.

All of the destructive treatments have disadvantages. Since virus-harboring keratinocytes can remain in the clinically normal surrounding tissue, relapses are as frequent as 50 % in immunocompetent patients and up to 70 % in immunodeficient patients within 4 months. Alternative therapies with immunomodulatory activity, such as systemic and topical interferons, have shown some efficacy, but the outcome of the studies was closely related to the different treatment regimens and the cost of therapy was extremely high. Topical interferon (IFN-gel with 0,15 Mio IU/g) was only effective in very small warts and as an adjuvant after surgery. The relapse rate could be reduced by almost 50 %.

The immune response modifier imiquimod has been approved for the treatment of genital warts since 1998. As demonstrated in several controlled studies (Edwards 1998, Gollnik 2001, Cusini 2004), imiquimod treatment is safe and effective and has the lowest relapse rate of all treatments (6-13 % in immunocompetent patients). Imiquimod is not approved for the treatment of anogenital warts in immunodeficient patients and intraepithelial neoplasias, but results of several successful treatments of genital warts (Cusini 2004), bowenoid papulosis and Bowen's disease in HIV-infected patients have been published (Kreuter 2004, Klencke 2003, Cooley 2003). The only antiviral agent active against HPV is cidofovir, but there is little experience in HIV-infected patients (Snoeck 2001).

Tinea (dermatophytosis, ringworm infections): Infections of the skin, hair or nails with dermatophytes (in Western Europe predominantly *Trichophyton, Microsporum* and *Epidermophyton species*). Tinea has a high prevalence in the general population. There is no significant difference between HIV-negative and HIV-infected adults. The prevalence is dependent upon climate, profession, clothing, and participation in team sports. In homosexual men, the prevalence is 29 to 37 % (Torssander 1988, Schöfer see Table 1).

Typical clinical findings are superficial, scaling, round or oval erythematous plaques, that expand centrifugally with an inflammatory edge and central clearance. Deep infections, with tissue destruction and abscess formation, are rare in Europe and North America, but common in tropical regions. According to Torssander (1988), onychomycosis due to dermatophytes is frequent in HAART-naive patients and difficult to treat. Nails are discolored (white, yellow, green, black), thickened, and show growth disturbances (onychodystrophy). Subungual hyperkeratosis and onycholysis are common.

Psoriasis, yeast infections and trauma can imitate onychomycosis, so it is necessary to identify the causative organisms on KOH and fungal culture. Direct microscopic examination with addition of 10-15 % KOH solution shows translucent, septated hyphae (mycelium) and arthrospores. Culture on Sabouraud's or Kimmig's medium identifies different fungi by their growth characteristics.

Treatment of superficial fungal infections of the skin is best achieved with topical broad spectrum antifungals such as ciclopirox or azoles, applied twice daily. In severe inflammatory disease, it is helpful to start with combination therapy including topical corticosteroids for 3 or 4 days, to achieve quick relief of discomfort. Deep infections and infections involving terminal hairs (tinea capitis, tinea barbae) require systemic treatment with griseofulvin (500-1000 mg/day), terbinafine (250 mg/day), fluconazole (50 mg/day), or itraconazole (100-400 mg/day) (Elewski 2001, Millikan 2001). There are different regimens to treat onychomycosis. Itraconazole and terbinafine are typically used for two months for fingernails and three months for toenails. Griseofulvin may be used for up to 9 months or longer, until the infection clears (Aly 1996, Myskowski 1997, Torssander 1988). If only the distal part of the nail plate is infected, topical treatment with nail varnish containing antifungals, which are able to penetrate the nail plate, are advised to avoid drug interactions between systemic antifungals and antiretroviral medications (see Chapter "Drug Profiles"). If systemic therapy is necessary, fluconazole has less drug interactions in HIV-infected patients than the other antifungals mentioned.

Herpes simplex virus infections: Herpetic infections of the skin and mucous membranes are frequent opportunistic infections in HIV-infected patients. The clinical symptoms differ substantially according to the patient's immune status. As long as the cell-mediated immune functions are normal, typical localized infections with itching, erythema and grouped vesicles will appear and heal spontaneously within a few days. In contrast, very painful, deep and large ulcerations of the ano-genital region, but also of the face and other parts of the body (e.g. herpetic whitlow) will appear in patients with advanced HIV infection and severe immunodeficiency (CD4 cell count <100 cells/μl). Clinical diagnosis can be difficult in these patients because grouped vesicles might be absent and only erosions or ulcers might be visible. Along with other STDs, genital herpes plays an important role in the dynamic of the worldwide HIV pandemic. As a genital ulcer disease, herpes lesions ease HIV transmission between sexual partners by breaking the epithelial barriers (1), stimulating HIV reproduction via pro-inflammatory cytokines (2) and enhancing (3) expression of cellular HIV receptors (CD4, etc.) on the surfaces of immunocompetent cells (Jonsson 2004, Celum 2004, Steen 2004, Solomon 2003). (See also Chapter "Opportunistic Infections").

(Herpes) Zoster: Shingles is the earliest disease marker of acquired immunodeficiency, which occurs during the natural course of HIV infection. Frequently, this secondary endogenous *Varicella zoster virus* infection is diagnosed several years prior to any other opportunistic infection. HIV infection or any other kind of acquired immunodeficiency must be suspected in any zoster patient who is (1) younger than 50 years and has no other known cause of immunodeficiency, or (2) shows atypical clinical features such as multisegmental or generalized distribution of normal, hemorrhagic, or necrotic lesions. Latent VZV infections can be activated in the frame of immune reconstitution syndrome a few weeks after the initiation of effective HAART (Tangsinmankong 2004, Maurer 2004). (See also Chapter "Opportunistic Infections".

Immune reconstitution inflammatory syndrome (IRIS) related skin reactions: HAART recovers the TH-1 immune response and the tuberculin test reactivity (Girardi 2002). In association with this immune reconstitution, clinical manifestations of herpes zoster, mucocutaneous herpes simplex infections, mycobacterial infections, eosinophilic folliculitis, foreign-body granulomas and cutaneous sarcoidosis were reported recently (Handa 2001, Hirsch 2004). These infectious, as well as some non-infectious inflammatory skin diseases, occur within a few days to 3 months after the initiation of HAART. The therapy depends on the severity of clinical manifestations and consists of specific antibiotics, steroidal and non-steroidal anti-inflammatory drugs (For details, see Chapter "IRIS").

Kaposi's sarcoma: the most frequent malignant tumor of the skin and mucosal membranes associated with HIV infection (see Chapter "Kaposi's sarcoma").

Lipodystrophy and metabolic syndrome: See chapter "Lipodystrophy syndrome".

Malignant cutaneous lymphomas: Malignant B and T-cell lymphomas are rare in HIV-infected patients (Beylot-Barry 1999, Biggar 2001). Cutaneous B-cell lymphomas usually grow as red to violaceous nodules, that are easily mistaken for Kaposi's sarcoma. They can also look like persistent hematoma or nonspecific asymptomatic papules. A biopsy should be performed on any clinically unclear tumor of the skin.

Cutaneous T-cell lymphomas are rare malignancies in HIV-infected patients. The prevalence among 2149 HIV patients in Frankfurt/M. was 0.06 %. The clinical course starts with nonspecific eczematous patches (stage I), which are usually not diagnosed as cutaneous lymphoma, even after several biopsies because of the paucity of findings such as cellular atypia. These lesions are usually diagnosed as eczematous dermatitis. A linear pattern of patchy or slightly infiltrated lesions in the relaxed skin tension lines can be an early clinical indication of cutaneous T-cell lymphoma known as parapsoriasis (Munoz-Peres 1999). Histopathology becomes more evident during the plaque stage (stage II), and is striking when in stage III multiple tumors of the mycosis fungoides present. Biggar et al (2001) calculated a relative risk for cutaneous T-cell lymphomas in HIV-infected patients of 15.0 in comparison to the general population. In both HIV-infected and HIV-negative patients, the leukemic phase (Sézary syndrome) is characterized by erythroderma involving the palms and soles. In patients with erythroderma who have darker skin types and lack the histopathological signs of cutaneous T-cell lymphoma, the so-called "pseudo-Sézary syndrome" has to be considered in the differential diagnosis (Picard-Dahan 1996). Therapy with potent topical steroids (e.g. clobetasol) is effective in the patch and plaque stages. Solitary tumors can be controlled by radiotherapy (20-24 Gy) or photodynamic therapy (Paech 2002). Widespread, multiple tumors, and Sézary syndrome are treated with a combination of retinoids and interferons or chemotherapy. Recently, remission of a CD8-positive pseudolymphoma treated solely with HAART was reported (Schartz 2003).

Molluscum contagiosum: This is a benign viral infection of the skin, usually seen in children, and often in association with atopic dermatitis. The pox virus causes multiple papular skin-colored lesions with a typical central umbilication. The diagnosis is usually made on clinical grounds. After several weeks or months, an inflammatory reaction indicates the onset of spontaneous healing. In adults, mollusca are detected in the anogenital area and regarded as a sexually transmitted disease (Agromajor 2002). In HIV-infected patients, the clinical manifestations can differ significantly from those seen in the normal host. Spontaneous healing is rare; most patients have high numbers of lesions, typically occurring in the face and neck region, which is otherwise a rare location. The presence of multiple mollusca on the face, is a typical disease marker, indicating advanced cell-mediated immunodeficiency (CD4 cell count <100/µl; Schöfer 1991, Schwartz 1992). The growth of mollusca in the immunocompromised host is not always exophytic, sometimes endophytic lesions occur. Multiple mollusca have to be differentiated from hematogenous dissemination of cryptococcosis, histoplasmosis, and coccidioidomycosis, which are usually associated with fever, headache, and sometimes pulmonary infiltrates. In such cases, skin biopsies (and tissue culture) and chest x-rays are indicated. Single molluscum can exceed 1 cm in diameter and grow exophytically,

which can cause confusion with keratoacanthoma, squamous cell carcinoma, basal cell carcinoma, or common warts.

Mollusca are treated surgically with a special type of forceps, electrocautery, curettage, or with liquid nitrogen. Recently, photodynamic therapy with 5-aminolevulinic acid (Moiin 2003) and imiquimod 5 % cream were effective as well (Hengge 2000, Calista 1999, Calista 2000, Liota 2000, Smith 2002). Imiquimod is applied by the patient 3x/week (off label use). An inflammatory reaction (erythema), occurring after 3 to 4 weeks of topical treatment, indicates the beginning of the immune reaction, which leads to complete resolution of the mollusca after 6-8 weeks.

Oral hairy leukoplakia (OHL): is a clinical manifestation of Epstein-Barr virus infection, which is almost exclusively found in patients with untreated advanced HIV disease. Non-cytolytic viral replication in the glossal epithelium, especially in the lateral parts of the tongue, leads to asymptomatic white verrucous plaques that do not rub off. OHL is diagnosed on clinical findings; initially parallel white or grayish hyperkeratotic rows arranged vertically on the lateral aspects of the tongue are characteristic. Unilateral lesions are possible, but bilateral occurrence of several plaques is more typical. Important differential diagnoses include other leukoplakias, lichen planus mucosae and oral candidiasis (Patton 2002, Cherry-Peppers 2003). If the diagnosis is in doubt, a biopsy or cytology can confirm the diagnosis. As the lesions will respond to antiviral drugs such as aciclovir, ganciclovir, or foscarnet (Walling 2003), but not antifungals, treatment can be used as a diagnostic tool to distinguish OHL from candidiasis. Both diseases however, respond well on HAART, which has led to a significant decrease of these oral diseases since HAART was introduced (Triantos 1997, Ramirez-Amador 2003).

Pruritus: Chronic, often unremitting pruritus is one of the most frequent clinical symptoms of HIV infection. One in three patients is affected. Etiology remains unclear in most patients, and therefore only symptomatic treatment can be offered which may be unsatisfying (Moses 2003, Singh 2003). Pruritus in HIV-infected patients can be a complication of infectious diseases. Viral, bacterial, and fungal infections (e.g. Malassezia furfur folliculitis) and scabies can cause severe itching. Also, dry eczematous skin (xerosis), papulosquamous skin diseases, systemic lymphomas, renal insufficiency and hepatic disease are causative conditions. Finally, many antiretroviral and other drugs given to the HIV-infected patient can cause pruritus (with or without rash).

To diagnose idiopathic pruritus, it is necessary to exclude all skin and systemic diseases mentioned above. In patients on HAART, it can be useful to change the treatment regimen. Systemic antihistamines and topical corticosteroids are symptomatic treatment standards. If they are ineffective, or a prolonged systemic treatment is necessary, phototherapy (UVA-1, UVB-311nm) or photochemotherapy (PUVA) is an alternative or adjuvant therapy. (Smith 1997, Gelfand 2001, Zirwas 2001, Singh 2003) Concerning the immunosuppressive effects of ultraviolet light, it seems that patients on HAART at less risk.

Papular dermatoses: Patients can present either with monomorphic skin colored to red papules (size 2 – 5 mm) or with combined eruptions consisting of papules and

pustules (sterile eosinophilic pustulosis Ofuji). There is no special predilection for any site. The etiology of papular eruptions is heterogeneous. According to the clinical presentation and to laboratory findings (elevation of IgE, eosinophilia in peripheral blood and affected skin) they resemble the prurigo of atopic dermatitis found in adults. Autoimmune reactions against follicular antigens have also been discussed (eosinophilic folliculicits; Fearfield 1999). These papules can be due to a *hypersensitivity reaction* to drugs, microbiological agents (viruses, bacteria, fungi), parasites, or saprophytes (Sarcoptes scabiei, Demodex folliculorum, Pityrosporum ovale and others). A thorough history of drugs, microbiological and histological examinations (including special stains such as PAS) are required for a correct diagnosis.

If possible, specific infectious agents are treated. In case of sterile eosinophilic pustulosis (Ojufi), or papular dermatosis of unknown origin, therapy is symptomatic. Depending on the clinical situation, antihistamines, itraconazole (200 mg/d for 2 weeks), isotretinoin, dapsone, mild PUVA or UVB (311= narrowband UVB; most effective therapy!!) or 5 % permethrin-cream can be tried (Ellis 2004). Topical tacrolimus (0.1%) also was shown to be effective (Kawaguchi 2004).

Paronychia and ingrown nails: Ingrown toenails and inflammatory reactions of the proximal nailfold are a well known complication in diabetics, but also in patients on beta-blockers, or retinoid therapy. A few cases might be due to local pressure (wrong shoes) or occur spontaneously. Patients on HAART are the latest group of patients to regularly develop ingrown nails. These are ascribed to retinoid-like side effects of several antiretrovirals, especially indinavir, but also lamivudine. Usually, the great toenails are involved, but all other toenails and fingernails can be affected. The therapy of choice in these patients, is to replace indinavir or lamivudine as a part of the HAART regimen by other antiretrovirals. This led to complete remission in several of our patients. Surgical measures, such as Emmetplasty or its modification after Hanneke, should only be performed on patients in whom the exchange of HAART medications did not lead to a remission after 3 to 6 months (Tosti 1999, Alam 1999, Garcia-Silva 2002).

Psoriasis vulgaris: Today, psoriasis is regarded as an autoimmune disease and affects approximately 1 % of the general population. It has multifactorial inheritance with variable penetrance. Physical stimuli such as friction and UV-light, or endogenous factors such as infections, drugs, and "stress" may trigger psoriatic flares. When HIV-infected persons are exposed to such factors, psoriasis may appear for the first time or can be aggravated. The incidence of psoriasis has been reported to be between 2.5 % (Braun-Falco 1988) and 4.9 % (Schöfer 1990). The use of antiretrovirals improves psoriasis.

Typical psoriatic plaques can be eruptive, guttate, or chronic and stationary.) Atypical findings include inverse localization on the palms or soles and in the genital region and axillae, exudative, pustular, or erythrodermic manifestations. In general, the severity of psoriasis parallels the impairment of the immune system. Besides infection, drugs have to be considered as possible triggers. In the final stages of HIV infection, psoriasis can be generalized and extremely resistant to therapy. Alternatively, the disease may disappear completely.

The typical psoriatic plaque is a sharply demarcated, erythematous plaque covered with silvery scales. Clinically and histologically, it may be difficult to differentiate it from seborrheic dermatitis.

Triggering factors should be eliminated, if possible. Treatment is more difficult if the immune system is impaired. An antiretroviral therapy should be initiated or optimized. Localized lesions can be treated topically with corticosteroids, anthralins, calcium-agonists (calcipotriol or tacalcitol) or the topical retinoid, tazarotene. The scalp and nails can be treated topically with corticosteroids. Generalized or exudative eruptions are usually treated systemically: acitretin (25 – 75 mg/d) is not immunosuppressive. Methotrexate or cyclosporin are immunosuppressive and should be avoided. In some cases, however, it is necessary to use them. Recently, the successful use of hydroxyurea was reported (Kumar 2001). Zidovudine has a beneficial effect on psoriasis, probably by improving the immune status. To treat refractory psoriasis, experimental therapies such as cimetidine (400 mg, 4x/d) have been tried successfully.

The clinical relevance of immunosuppression by UV-radiation is unknown. At present, it is believed that phototherapy or photochemotherapy have no real detrimental effect for HIV patients and that they are justifiable (Akarapathanth 1999, Schoppelrey 1999). These treatments are as effective as in patients without HIV-infection. UVB311 (=narrowband UVB) is well tolerated and effective. Broadband UVB is an alternative. In case of treatment failure, photochemotherapy can be instituted (local = bath or cream PUVA, or systemic PUVA). Interactions of the mentioned antipsoriatics with antiretroviral substances are unknown. Recently, several "biologics" were introduced for the therapy of psoriasis. These compounds specifically interact with certain elements of the inflammatory cascade in psoriasis, such as TNF alpha. Up until now, only case reports can be found in the literature regarding treatment in HIV-infected patients (Bartke 2004).

Reiter's syndrome: Reiter's syndrome is regarded as a variant of psoriasis in patients who carry HLA B27. This rare chronic-relapsing disease mainly affects young men, the incidence being higher in HIV-infected men than in the general population (0.6 % to 6 %; Kaye 1989).

The classical triad consists of: urethritis (sterile yellow urethral discharge), conjunctivitis (serous or purulent) and arthritis (mainly knee-, foot- or sacroiliac joints; causing pain and leading to immobility). The triad is found in about 30 % of patients. Furthermore, constitutional symptoms (attacks of fever, malaise, leukocytosis, elevated ESR) and skin lesions can be found. The skin lesions are characterized by erythema with sterile pustules on the palms and soles, and later, hyperkeratotic, scaling, exudative lesions known as keratoderma blenorrhagicum. Psoriatic plaques can be seen as well as the typical circinate balanitis presenting as crusting, desiccated plaques in circumcised men and shallow, moist, serpiginous, painless ulcers with slightly raised borders in uncircumcised men.

The diagnosis depends on the typical pattern of arthritis plus one or more of the mentioned clinical symptoms. Gonorrhea or Chlamydia urethritis have to be excluded by microbiological methods. Psoriatic arthritis should have other clinical signs of psoriasis (nail changes) and lacks fever.

Initially, symptomatic therapy with non-steroidal anti-inflammatory agents, or possibly corticosteroids (short-term, high-dose pulse-therapy) should be given. Acitretin (25 - 75mg/d) in combination with topical fluorinated corticosteroids also proved to be effective. Alternatively, sulfasalazine has been used successfully. Arthritis is also treated with oral gold. There is one report on the successful use of infliximab in a patient with Reiter's syndrome without negative effects on the HIV viral load (Gaylis 2003).

Scabies: Scabies can be found worldwide; the prevalence varies from < 1 % to 30 % depending on the socio-economic circumstances. Scabies is characterized by extreme pruritus, especially at night. In general, the clinical presentation does not differ from that seen in HIV-negative persons. In the interdigital areas, volar sides of the joints of the hands, breasts, axillae, periumbilical region, or penile shaft, fine red burrows (S-shaped or straight lines) may be found. There may be a small papule or vesicle at one end. Excoriations and/or secondary infections make the identification of burrows difficult. Generalized eczematous eruption may be seen. Typically, in the groin or on the genitals, red-brown pruritic nodules are found. These scabies granulomas can persist for months, even after successful therapy.

In the case of severe cellular immunodeficiency, crusted scabies or Norwegian scabies can occur. Besides HIV-patients, persons with general physical or mental debilitation are affected. Over weeks to months, eczematous lesions covered with asbestos-like crusts extend over large areas and the plaques can be mistaken for psoriasis. Crusted scabies is extremely infectious and carries many more mites than regular scabies – up to 10,000 mites/g scales. The history of unremitting and intractable itching is suggestive of scabies. The diagnosis is made by the clinical picture and proven by the demonstration of the mites, their ova, or fecal droppings in the scales. On histology, the female mite can be visualized in the stratum corneum.

A single application of permethrin 5 % cream is performed (whole body application from chin to toes, usually excluding the face; leave on skin for 8 hrs, then shower off). In cases of crusted scabies, the scales have to be removed over several days (salicylic ointments) and therapy has to be repeated over 3 – 4 days. Alternative therapies are: hexachlorcyclohexane (lindane), benzoylbenzoate, pyrethrum-extracts or allethrin/piperonylbutoxid, which all have to be applied for 3 days. It is important to treat all contact persons at the same time as well!

Linen and bed-clothes have to be changed daily. Depending on the clinical presentation, another treatment one week later is sometimes recommended ("safety-day"). In cases of severe immunodeficiency, the scalp has to be treated too.

If more than 50 % of the skin is affected, or several recurrences have occurred, a combination of keratolytic/topical therapy against scabies and systemic treatment with ivermectin is recommended. Hygienic measures to prevent contact infections are extremely critical. The single therapy with 2 tablets (6 mg each; some 200μg/kg) is generally sufficient. Ivermectin is not licensed for this indication. There are no reports on complications after this therapy in HIV-infected patients (Dourmishev 1998).

Seborrheic dermatitis: The incidence in the general population is estimated to be 3 – 5 % of all young men. The liphophilic yeast Malassezia furfur (formerly named

pityrosporum ovale) is believed to be of pathogenetic relevance. Here the specific subtype appears to be more important than the density of colonization. In HIV-infection 20 – 60 % are affected depending on the immune status. Seborrheic dermatitis appearing de novo or exacerbation of mild seborrheic dermatitis in a known HIV-positive patient could indicate seroconversion from a latency state to a symptomatic state (Ippolito 2000).

Areas rich in sebaceous glands, such as the scalp, forehead, eyebrows, nasolabial folds, over the sternum, between the shoulder blades, external ear canal, and retroauricular area, develop yellowish, oily scales and crusts on mildly erythematous to very red plaques. The lesions may be pruritic.

The clinical picture is typical in most cases. Differentiation from psoriasis may be difficult both clinically and histologically. Initially, other forms of eczema such as allergic contact dermatitis and atopic dermatitis may have similar presentations.

Due to the pathogenic role of pityrosporum ovale, topical antifungals such as ketoconazole cream, other topical imidazoles or triazoles, or alternatively selendisulfide, metronidazole, and low-dose dithranol or lithiumsuccinate- and zinc-sulfate-creams are used. For the scalp, antimycotic shampoos, zinc pyrithione or tar-containing products are used. In severe cases, systemic antimycotics are given: ketoconazole (1 x 200 mg/d), itraconazole (1 x 100 mg/d) or terbinafine (250 mg/d).

Syphilis: In general, syphilis in HIV-infected patients is clinically no different from syphilis in the immunocompetent host. In some patients however, atypical findings complicate the clinical and serological diagnosis as well as the treatment. In primary syphilis, painful anal or oral chancres occur. Persistent chancres can still be found when the exanthemas of secondary syphilis and symptoms such as generalized lymphadenopathy appear. In secondary syphilis, syphilids can ulcerate and develop thick crusts (rupia syphilitica), which are accompanied by high fever and severe illness. This unusual and otherwise rare course of syphilis, which is termed "malignant" syphilis, is found in 7 % of all syphilis associated with HIV infection. In addition, early neurosyphilis and a very short latent period before the onset of tertiary symptoms of syphilis are described. Neurosyphilis is partly due to a reduced blood-brain barrier and a failure of benzathine penicillin to prevent neurosyphilis in these patients. The interpretation of syphilis serologies, especially in patients with repeated infections and severe immunodeficiency, can be complicated by false negative results and persistent antibodies. Therefore, it is advisable to verify *T. pallidum* infection in any clinical manifestation suspected to be syphilis by direct proof (dark-field microscopy, direct fluorescent antibody testing of exudates, or biopsy specimens).

The recommended treatment of syphilis, which is penicillin for all stages of the disease, has not changed over the past 60 years. *T. pallidum* has developed some resistance against macrolides (erythromycin, azithromycin), but not against penicillin. Syphilis therapy, as recommended by the CDC, WHO, and the German STD Society (DSTDG) is identical for HIV-infected and non-HIV-infected patients. It is advised however, not to use benzathine penicillin G in patients, in whom early neurosyphilis cannot be excluded. If neurosyphilis is suspected, and the patient refuses CSF puncture, high-dose penicillin G (6x5 Mega or 3x10 Mega IV should be given

for 2 (early syphilis) or 3 weeks (late syphilis). Ceftriaxone, 1g/day IM for 10 days is a widely used, but not approved alternative.

Standard regimens for early syphilis (primary and early secondary syphilis until one year after infection) are procaine penicillin G, 1.2 million units IM/day for 14 days, or benzathine penicillin G, 2.4 million units IM in a single dose, injected into different sites.

Late syphilis (any stage of disease at more than one year after infection and any syphilis of unknown duration, excluding neurosyphilis) is treated like early syphilis, but for three weeks instead of two weeks. (For more details about HIV and T. pallidum coinfection, see Chapter "HIV and Sexually Transmitted Diseases"). HIV-infected patients should be evaluated clinically and serologically for failure of treatment at 3, 6, 9, 12, and 24 months after therapy.

Xerosis/Dry skin: Dry skin is a very frequent complication of any kind of immunodeficiency. In the pre-HAART-era, we diagnosed dry skin in one in three HIV-infected patients (see Table 1). The patients complain of dry, itchy skin, which is exacerbated by any stimulus. Overall, these skin problems are very much like atopic dermatitis (Rudikoff 2002) and can culminate in acquired ichthyosis. The prevalence of dry skin in HIV-infected patients decreased after the introduction of HAART, but is sometimes seen in patients on indinavir (Garcia-Silva 2000). Some years ago, we showed that the lipid film of the skin surface has a different composition in HIV-infected patients, but is not diminished in quantity (C. Semrau: unpublished data, doctoral thesis).

Dry itchy skin is treated with the application of emollients that contain 5 to 10 % urea, or 3 to 4 % lactic acid, and dexpanthenol. If the patients take too many showers, the frequency should be reduced to one shower every (other) day, and 1 to 2 oil baths per week should be recommended. In cases with severe inflammation and fissures (eczema craquele) topical class 3 or 4 corticosteroids are very helpful in reducing the patients symptoms. They should not be used for longer than 3 to 5 days.

Appendix 2:

Skin and mucocutaneous disease related to antiretroviral drugs

1. Nucleoside analog reverse transcriptase inhibitors (NRTIs)

AZT, zidovudine, Retrovir[TM]: Drug eruptions (6 %) mostly macular, rarely severe reactions such as erythema multiforme and Stevens-Johnson syndrome, melanonychia striata medicamentosa, pigmentation and lichenoid eruptions of mucosal membranes, vasculitis, urticaria, pruritus, hyperhidrosis (5-19 %), tongue ulcers.

DDI, didanosine, Videx[TM]: Drug eruptions and itching (4 %), erythema multiforme, oral dryness (30 %), papuloerythrodermia Ofuji.

DDC, zalcitabine, HIVID™: Frequently oral ulcers; under standard regimens low rate of exanthemas, erythroderma, urticaria, angioedema. High dose treatment: dose related drug eruptions (up to 70 %), maculopapular drug eruptions, mostly starting at day 9±2 and disappearing spontaneously without discontinuation of treatment.

D4T, stavudine, Zerit™: Drug eruptions with fever.

3TC, lamivudine, Epivir™: Exanthemas, vasculitis, light sensitivity, linear nail hyperpigmentation, hair loss, paronychia, ingrown toenails.

FTC, emtricitabine, Emtriva™: Exanthemas, especially in combination with DDI and efavirenz (10 %), cause unidentified.

ABC, abacavir, Ziagen™: Maculopapular exanthemas, hypersensitivity syndrome (5 %) after 9 (3-42) days, frequently associated with respiratory problems, nausea, and vomiting, increase in liver transaminases. Any suspicion of hypersensitivity syndrome forces immediate cessation of treatment (Clay 2002). Abacavir re-exposure is contraindicated (severe, sometimes lethal reactions). For details of the management of abacavir hypersensitivity syndrome, see alphabetical drug register.

Tenofovir, Viread™: rare exanthemas.

2. Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs)

Nevirapine, Viramune™: frequent drug eruptions (33 %), severe reactions 6 % (mostly within the first 6 weeks of treatment), Stevens-Johnson syndrome 0.5 %, and few cases of toxic epidermal necrolysis. Less frequent drug reactions (22 %), when therapy is initiated with low doses. Cetirizine, as a prophylactic, is not effective (Launay 2004). Treatment must be stopped in 3-5 %. Reasons are severe skin reactions, exanthemas with fever, conjunctivitis, pain of the limbs, meningitis, eosinophilia (DRESS syndrome = Drug rash with eosinophilia and systemic symptoms; Bourezane 1998, Lanzafame 2001), occasionally diffuse loss of hair. Exanthemas are 7x more frequent, and therapy has to be stopped 3.5 x more often in women compared to men (Bersoff-Matcha 2001). According to the producer's report (Boehringer Ingelheim, February 2004), complications have to be expected mainly during the first 6 weeks of treatment (up to 18 months). During this period, hepatotoxic reactions with high transaminases and exanthemas are frequent. Patients, especially women older than forty, with residual cell mediated immune functions (CD4 cells > 250/µl), are particularly at risk.

Delavirdine, Rescriptor™: Maculopapular or erythematous rashes, with or without pruritus in up to 50 %, starting 2-3 weeks after initiation of treatment and involving especially the trunk and upper arms. Mild exanthemas without other complications can regress spontaneously without a need to discontinue treatment.

Efavirenz, Sustiva™: Frequent macular or urticarial exanthemas (11 %). Light exanthemas can regress spontaneously without discontinuation of treatment. In case of complications, it is necessary to stop treatment.

3. Protease inhibitors (PI)

Saquinavir, Invirase™, Fortovase™: Aphthous oral lesions (6 %), cheilitis, exanthemas (4 %), in rare cases Stevens-Johnson syndrome, bullous eruptions, papular pruritic folliculitis (1 %).

Ritonavir, Norvir™: exanthemas (0.9-2.6 %), papular pruritic folliculitis (8 %), perioral paresthesia (25 %).

Indinavir, Crixivan™: In many patients a sicca syndrome with very dry skin, dry mouth and eyes is observed. In addition, exanthemas are frequently papular and intensely itching, involving the lateral parts of the upper arms, the upper trunk and the lateral neck in particular, can occur. Differential diagnosis: papular pruritic eruption (folliculitis). Paronychia (pyogenic granuloma-like) and ingrown toenails, light diffuse loss of hair (12 %), severe and generalized loss of terminal and vellus hair in 1-2 %. Hematoma and hemarthrosis in hemophiliacs. Lipodystrophy ("Crixibelly", buffalo hump, facial lipotrophy, etc.), metabolic syndrome and asymptomatic hyperbilirubinemia.

Nelfinavir, Viracept™: Exanthemas (infrequent).

Amprenavir, Agenerase™: Exanthemas (3 %, mostly starting during the 2nd week of treatment, Pedneault 2000), perioral paresthesia.

Atazanavir, Reyataz™: Exanthemas (Goldsmith 2003), hyperbilirubinemia, in some cases with jaundice and scleral icterus (Orrick 2004).

Lopinavir/r, Kaletra™: Exanthemas (infrequent). Lipodystrophy.

4. Entry-Inhibitors

T-20, Enfuvirtide, Fuzeon™: Erythemas and indurations at the injection sites (96%, almost obligatory), exanthemas <1% (Ball 2003).

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19.   HIV and Sexually Transmitted Diseases

T. Lorenzen, Katrin Graefe

Syphilis

Syphilis, also called Lues, is caused by Treponema pallidum. The risk of transmission is greatest in the early stages of the disease, especially if skin or mucosal ulcers are present. For a single unprotected sexual contact, the risk of transmission is about 30 to 60 %. Like other STDs, syphilis favors the transmission of HIV due to lesions in the genital mucosa. In some European areas, the incidence of syphilis, which was relatively constant during the 1980s and early 1990s, increased to levels last seen in the mid twentieth century. In some HIV centers in Germany, the number of newly diagnosed infections doubled or tripled. The origin of this epidemic was located in Hamburg and spread to the south of Germany. In 2003, Germany had the highest incidence of syphilis in Western Europe.

Symptoms

Classic syphilis progresses in four stages, listed in Table 1:

Table 1: Course of classic syphilis

Stage	Typical clinical appearances	Time since infection
Lues I	Ulcus durum / chancre	approx. 3 weeks
Lues II	Disseminated exanthemas	approx. 6-8 weeks
Lues III	Tuberous syphilis, gumma	several years
Lues IV	Tabes dorsalis, progressive paralysis	decades

In patients coinfected with HIV, the latency period between stage II and the late stages III and IV may be significantly shorter than usual. In some cases, symptoms of the different stadiums may be present at the same time.

Furthermore, unusual manifestations with dramatic skin ulcers or necrosis, high fever and fatigue are described. Occurrence of these clinical symptoms is called *Lues maligna.*

Another unusual aspect in HIV-infected patients is a possible endogenous reactivation after prior Treponema pallidum infection.

Diagnosis

Routine screening for syphilis with TPHA, TPPA or VDRL may not be reliable in HIV-infected patients. False-negative results can be explained by inadequate production of antibodies or by suppression of IgM production due to exorbitant IgG levels. In case of doubt, specific tests such as FTA-ABS (IgG and IgM) or cardiolipin tests should be carried out.

In erosive skin or mucosal lesions, dark field microscopy should be performed to demonstrate Treponema pallidum directly.

In cases where infection has been proven serologically, a neurological examination should be performed, especially on HIV-infected patients because of the merging of clinical stages. Patients with neurological symptoms should undergo cerebrospinal fluid examination, which is particularly important for making decisions regarding the type of therapy (intramuscular or intravenous).

Therapy

Therapy of syphilis should be adapted to the stage of disease.

Recommendations for the early stages of syphilis include three intramuscular injections of benzathine penicillin 2.4 MU administered in weekly intervals (Anglo-American recommendations: only twice!). In some countries, clemizol-penicillin is still available. It should be administered intramuscularly at a dose of 1 MU daily for 2 weeks.

In cases of penicillin intolerance, tetracycline (4 x 500 mg) or erythromycin (4 x 500 mg) can be administered orally for 4 weeks, but these drugs are considered to be less effective than penicillin. Consequently, patients should be treated with the same scheme used in neurosyphilis.

Neurosyphilis is usually treated with 5 MU benzylpenicillin given intravenously every 4 hours for 21 days. Other recommendations prefer administration of benzyl-penicillin for 14 days, followed by three intramuscular doses of 2.4 MU benzathine penicillin given at weekly intervals.

In cases of penicillin intolerance, neurosyphilis can also be treated with 2 g intravenous ceftriaxone once daily for 14 days. Observational studies in small groups suggest ceftriaxone to be as effective as penicillin in the treatment of syphilis. However, cross-sensitivity may occur.

Alternative treatment options are doxycycline 2 x 100 mg per day or erythromycin 4 x 500 mg per day for at least 3 weeks. When treating with macrolides, the possible development of resistance should be considered.

On initiation of syphilis therapy, one should be aware of a possible Jarisch-Herxheimer reaction. It is caused by a massive release of bacterial toxin due to the first dose of antibiotic given. By triggering inflammation mediators, patients may experience shivering, fever, arthritis or myalgia. The symptoms of the Jarisch-Herxheimer reaction may be avoided, or at least reduced, by administering 25-50 mg of prednisolone prior to the first dose of antibiotic.

Serological controls should be performed at 3, 6 and 12 months after syphilis therapy. Because of a possible endogenous reactivation in some patients, annual controls should be considered.

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Gonorrhea

Gonorrhea, also called the clap, is caused by Neisseria gonorrhea, a diplococcal bacterium. It is typically localized in the genitourinary mucosa, but infection may also occur orally or anally. Transmission is almost exclusively through sexual activity (exception: neonatal conjunctivitis), and the incubation period is about 2 to 10 days. Co-infection with Chlamydia occurs frequently.

Symptoms

In men, primary symptoms are dysuria and urethral pain. A typical symptom is purulent secretion from the urethra, especially in the morning ("bonjour-drop"). Without treatment, the infection can ascend and cause prostatitis or epididymitis, leading to symptoms such as pain in the perineal region or scrotum or swelling of the scrotum.

In women, the course of gonorrhea is often asymptomatic, although vaginal discharge or purulent dysuria may occur. Involvement of the cervix and adnexa is rare, but if left untreated, may lead to pelvic inflammatory disease with subsequent infertility.

Extragenital manifestations of gonorrhea occasionally cause pharyngitis or proctitis. Systemic infections with symptoms such as shivering, fever, arthritis or endocarditis are rare.

Diagnosis

The diagnosis of gonorrhea is confirmed by microscopy. In a dye staining test with methylene blue or gram stain, the intracellular diplococci of Neisseria gonorrhea are traceable. This kind of diagnosis can directly be performed within several minutes at many sites. Other methods, such as serological examination, PCR or laboratory culture are also accurate, but are more complex and more expensive.

Therapy

An isolated gonorrhea is usually treated with a single dose of ciprofloxacin 500 mg orally. Other effective antibiotics are Levofloxacin 250 mg or Ofloxacin 400 mg.

Recently, the American Centers for Disease Control and Prevention reported an increasing number of fluoroquinolone-resistant bacterial isolates among men who have sex with men. Consequently, the CDC suggest a single dose of cefixime 400 mg orally or ceftriaxone 125 mg as intramuscular injection for the treatment of gonorrhea in this group of high risk patients. Intramuscular administration of spectinomycin has been an option, but it is effective only in urogenital and anorectal infection, not in pharyngeal gonorrhea. For these reasons, a pragmatic and sufficient therapy seems to be a single dose of azithromycin 1 g or doxycycline 100 mg twice daily for 7 days. These therapeutic options also treat a possible co-infection with chlamydia species (see following chapter).

In all cases of gonorrhea, the sexual partners should also be screened for infection and treated if necessary.

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Chlamydia Infection

Infections with Chlamydia trachomatis are nearly twice as prevalent as gonococcal infections. The serovars D – K cause genitourinary infections and, if vertically transmitted, conjunctivitis or pneumonia in the newborn.

The serovars L1 – L3 cause Lymphogranuloma venereum. This disease is usually considered to be a tropical disease, rarely occurring in industrialized countries. However, since 2003, Lymphogranuloma venereum has undergone a renaissance in Europe: several research groups in Germany and the Netherlands have reported an increase of cases mainly in metropolitan areas.

Symptoms

In men, a genital infection with Chlamydia is usually asymptomatic. If symptoms occur, they may be present as urethral discharge, burning or unspecific pain in the genital region. As in gonorrhea, an epididymitis, prostatitis or proctitis may occur. Reiter's syndrome with the triad reactive arthritis, conjunctivitis and urethritis is also possible.

In women, a chlamydial infection often does not cause any symptoms. But in about 20 % of female patients, unspecific symptoms such as discharge, burning or, more often, polyuria may occur as an expression of urethritis or cervicitis. Some of the patients also suffer from pelvic inflammatory disease which involves the adnexa. This disease pattern can lead to later complications such as infertility or ectopic pregnancy due to tubal occlusions.

In Lymphogranuloma venereum, a primary lesion occurs at the entry location. Some weeks later, a tender lymphadenopathy develops which is mainly unilateral. These swollen lymph nodes may grow into large bubo which tend to ulcerate, possibly leading to scars and lymphedema.

Diagnosis

A chlamydial infection may be suspected based purely on clinical symptoms. To confirm this diagnosis, microbiological procedures are necessary. Until recently, bacterial culture has been the gold standard for confirming an infection. The options in laboratory diagnostics have been expanded in the last years. But, there have been some problems due to the fact that Chlamydia trachomatis is a fastidious bacterium which requires special procedures when transported and grown in the culture medium. Disregarding this leads to decreased sensitivity. Other direct tests such as ELISA or direct immunoflorescence also lack sensitivity. Newer gene amplification methods (e.g. PCR or LCR) have shown superiority concerning sensitivity while specificity is nearly equal to results obtained by culture.

Therapy

The therapy of choice should be doxycycline, 2 x 100 mg for 7 days. International guidelines also recommend 1 g azithromycin, given as a single dose, which is an equally potent therapy, but which costs nearly twice as much as doxycycline. Alternatively, ofloxacin 2 x 200 mg or erythromycin 4 x 500 mg for 7 days can be given.

Lymphogranuloma venereum requires a longer treatment, with doxycycline being administered for a minimum of 3 weeks.

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Chancroid

Chancroid, also called *Ulcus molle*, is caused by Haemophilus ducreyi, a gram-negative bacterium. It is an endemic infection found primarily in tropical or subtropical regions of the world. In the industrialized countries, it appears to be mainly an imported disease, with only a few cases being reported by the national authorities.

Symptoms

Usually, the incubation period is about 2 – 7 days. After transmission, one or more frayed-looking ulcers may appear at the entry location, usually in genitourinary or perianal locations. These ulcers are typically not indurated, unlike the primary ulcers of syphilis (therefore the Latin name *Ulcus molle*). Characteristically, they cause massive pain. In about half of the patients the inguinal lymph nodes are swollen and painful, mostly unilaterally. Balanitis or phimosis occur less frequently.

Diagnosis

Suspected chancroid is difficult to confirm. Clinically, other ulcer-causing STDs such as syphilis or herpes simplex infections have nearly the same symptoms. Microscopy of ulcer smears may demonstrate gram-negative bacteria, but diagnosis should be confirmed from a culture of scrapings from the ulcer or pus from a bubo. Sometimes, a biopsy from the ulcer becomes necessary to differentiate it from a malignoma.

Therapy

Therapy should be conducted using a single dose of 1 g oral Azithromycin. Ceftriaxone 250 mg intramuscularly, as a single dose, is equally potent. Alternative therapies are Ciprofloxacin 2 x 500 mg for three days or Erythromycin 4 x 500 mg for 4-7 days. In fluctuant buboes, needle-aspiration of pus may be indicated.

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Condylomata acuminata

Condylomata acuminata are caused by human papillomaviruses (HPV). They are usually present as genital warts, but other locations (oral) are known to be involved. HIV-infected patients have a higher risk of acquiring genital warts.

The typical pathogens, human papillomavirus type 6 or type 11, are not normally considered to be cancerogenic. Although, in both male and female HIV-infected patients, epithelial atypia is seen more often than in uninfected persons.

Besides sexual intercourse, transmission of papillomavirus may be possible via smear infection and perhaps through contaminated objects. But the primary risk factor remains the number of sexual partners.

Symptoms

Generally, genital warts remain asymptomatic. Pruritus, burning or bleeding is rare and generally caused by mechanical stress.

Malignant degeneration of genitourinary papillomavirus infections (HPV 16, 18, etc.) is the most important complication. In contrast to HPV-associated cervical carcinoma, genital or anal carcinoma rarely develops on underlying Condylomata.

Diagnosis

Condylomata acuminata is a clinical diagnosis. Further diagnostic tests should be considered in case of persistence despite therapy or an early relapse. In addition to histological examination, direct HPV detection, including subtyping, is possible to differentiate between high and low risk types. Actually, this procedure is instrumental in gynecology in case of ambiguous histologies.

Therapy

Treatment of genital warts is performed surgically by electrosurgery, cryotherapy, curettage, or laser. Chemical interventions with podophyllin or trichloroacetic acid are also possible. Other methods have been recommended. In daily clinical practice, a surgical intervention followed by adjuvant immunotherapy with interferon beta or (possibly more effective) with imiquimod reduces the rate of relapse and seems to be the best choice for patients.

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20.   HIV and Cardiac Diseases

Till Neumann

New and effective antiretroviral drugs have decreased the mortality of HIV infection. However, antiretroviral therapy (ART) is not without side effects. It is expected that the risk of cardiac and cardiovascular diseases will rise in the following years due to the elevated cardiovascular risk profile and increased life expectancy of HIV-infected patients (Fisher 2001, Neumann 2002a). Therefore, diagnosis and therapy of HIV-associated cardiovascular diseases should become an inherent part of current therapeutic concepts of HIV infection.

Coronary heart disease (CHD)

Premature arteriosclerosis in HIV-infected patients was described shortly after the introduction of antiretroviral therapy. The observation was supported by an autopsy trial, reporting a significant increase of atherosclerotic plaques over the last two decades in HIV-infected individuals (Morgello 2002).

In contrast to case reports and autopsy trials analyzing the influence of antiretroviral therapy on myocardial infarction rate, the results of clinical observations appear to be inconsistent. At present, two major clinical trials have been published, and in one of these trials, a retrospective analysis of 36,500 patients, no rise in cardiac or cardiovascular events was detected (Bozzette 2003). Nevertheless, in the second trial, the most extensive prospective study to date, including more than 23,000 patients, a 26 % increase in the incidence of myocardial infarction was found with each year of antiretroviral therapy (Friis-Moller 2003).

However, the total incidence of myocardial infarction was small in both trials. Therefore, current treatment regimens for HIV infection might have no considerable impact on myocardial infarction rate and the concerns of cardiovascular complications have to be balanced against the marked benefits of antiretroviral treatment. Nevertheless, prevention of coronary heart disease should be integrated into current treatment procedures of HIV-infected patients.

Prevention

Prevention of cardiovascular events is based on the reduction of known risk factors. In recent years, an association between antiretroviral drugs and lipid concentrations, i.e. hypercholesterolemia and hypertriglyceridemia, has been reported (Stocker 1998, Sullivan 1997). The degree of lipid alteration differs between the types and doses of antiretroviral medication. Protease inhibitors (PIs) in particular, are able to increase lipid concentrations. In addition to hyperlipidemia, insulin resistance has also been described in association with PIs (Behrens 1999, Noor 2001).

Apart from metabolic alterations, HIV-infected patients exhibit a marked cardiovascular risk profile (Neumann 2003, 2004a, 2004b). Most notably, in some countries the cigarette consumption is two to three-fold higher than in the non-HIV-infected population.

Prevention of coronary heart disease is based on the guidelines for non-HIV-infected patients. (De Backer 2003; Table 1). Diet is the first step in the therapy of hypercholesterolemia. The second step relies on lipid lowering drugs (Dube 2003). Good results were observed using a combination of statin (Atorvastatin 10 mg/d) and fibrate (Gemfibrozil 600 mg bid) (Henry 1998). However, an increased risk of rhabdomyolysis is suspected, and thus caution is required.

Furthermore, statin therapy might also interact with the metabolism of common antiretroviral drugs. In particular, several PIs act as substrates for isoenzyme 3A4, a subgroup of the cytochrome p450 system. Inhibition of isoenzyme 3A4 by antiretroviral drugs can increase the blood concentration of statins and, therefore, induce side effects (Dube 2000). In contrast to most other statins, pravastatin and fluvastatin are not modulated by isoenzyme 3A4. Therefore, these two drugs are particularly preferred by some authors for the therapy of HIV-infected patients being treated with antiretroviral drugs.

Table 1: Prevention of coronary heart disease

1)	**Cease Smoking**
2)	Normalization of lipids
	a. LDL-Cholesterol:
	- low risk (0-1 risk factors): < 160 mg/dl (4.14 mmol/l)
	- intermediate risk (2 or more risk factors): < 130 mg/dl (3.36 mmol/l)
	- high risk (i.e. CHD or diabetes mellitus): < 100 mg/dl (2.59 mmol/l)
	b. HDL-Cholesterol: > 35 mg/dl (0.90 mmol/l) (increased risk > 40 mg/dl)
	c. Triglyceride: < 200 mg/dl (5.17 mmol/l) (increases risk < 150 mg/dl)
3)	Optimize blood glucose value (HbA1c < 6.5 %)
4)	Reduce alcohol consumption (< 15 g/d)
5)	Regular exercise training (1-2 h per week)
6)	Normalization of weight (BMI of 21-25 kg/m²)
7)	Optimize blood pressure (systolic: < 130 mmHg, diastolic < 85 mmHg)

Diagnosis

HIV-infected patients with cardiovascular risk factors or of elevated age should undergo an annual cardiac check-up, including a resting ECG. The time between two cardiac controls should be shortened in case of elevated cardiovascular risk factors. Symptomatic patients also need further detailed cardiovascular examinations (exercise ECG, stress echocardiography, in some cases scintigraphy of myocardium or coronary angiography). Clinical symptoms of coronary heart disease mostly occur due to a critical stenosis of more than 75 %. Therefore, the onset of new cardiac symptoms or increases of gravity, duration or frequency need a direct and immediate clarification (Erhardt 2002).

Therapy

In random clinical trials, low-dose aspirin (100 mg/d), or in some cases clopidogrel (75 mg/d), β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and statins, decreased the risk of mortality and re-infarction. A calcium antagonist and/or nitrate can be supplemented for symptomatic treatment.

The indication for vascular intervention (coronary angiography, including percutaneous transluminal catheter angioplasty and stent implantation) depends on the current guidelines (see Silver et al., Guidelines for Percutaneous Coronary Interventions; http://www.escardio.org/knowledge/guidelines). Clear indications are provided by a documented exercise-induced ischemia as well as typical clinical symptoms together with alterations in the ECG, increases in cardiac enzymes and/or a marked cardiovascular risk profile. It is worth emphasizing that HIV infection is not an exclusion criteria for invasive procedures. Successful cardiac interventions have been performed on HIV-infected patients, including catheter procedures and coronary artery bypass operations (Escaut 2003, Bittner 2003).

Congestive Heart Failure

Congestive heart failure includes a variety of myocardial alterations. In HIV-infected patients, the HIV-associated dilated cardiomyopathy is of major interest. It corresponds to a dilated and less contractile left ventricle.

Etiology

Myocarditis is still the most thoroughly studied cause of dilated cardiomyopathy in HIV disease. Until now, a variety of pathogens has been found in the myocardial tissue of HIV-infected patients (Patel 1996, Wu 1992). Furthermore, human immunodeficiency virus itself appears to infect myocardial cells in a patchy distribution. Although it is unclear how HIV-1 enters CD4-receptor-negative cells such as cardiomyocytes, reservoir cells may play a role in the interaction between HIV-1 and myocytes.

In addition to a direct impact of the human immunodeficiency virus or other pathogens, dilated cardiomyopathy was reported in association with an autoimmune reaction. Cardiac-specific autoantibodies (anti-α-myosin antibodies) have been reported in up to 30 % of HIV-infected patients with cardiomyopathy. However, several studies also indicate that in HIV-infected patients, dilated cardiomyopathy is associated with cardiotoxic agents (e.g. pentamidine, interleukin-2, doxorubicin) or as the sequelae of malnutrition (Nosanchuk 2002). Furthermore, it is expected that antiretroviral therapeutic drugs may induce cardiac dysfunction due to mitochondrial toxicity (Lewis 2000, Frerichs 2002).

The frequency of clinical, symptomatic dilated cardiomyopathy is estimated to be between 1 and 5 %. However, some difficulties exist in the diagnosis of heart failure. In one study, only 30 % of HIV-infected individuals with ventricular malfunction could be identified by characteristic clinical symptoms (Roy 1999).

Diagnosis

The diagnosis of chronic heart failure is based on clinical findings and symptoms. In addition to exercise intolerance, patients often exhibit dyspnea and edema. Nocturia, nightly cough (cardiac asthma), peripheral cyanosis and an increase of weight may also occur. In these cases, ECG, x-ray and echocardiography may lead to the diagnosis of heart failure.

A new parameter in the diagnosis of heart failure is the b-type natriuretic peptide (BNP) or nt-pro BNP. This peptide has the power to distinguish between lung and cardiac malfunction.

Exercise intolerance can be determined by a 6-minute walk test, exercise ECG or spiroergometry. In some cases, further diagnosis can be performed with magnetic resonance tomography (MRT) or computer tomography (CT). Invasive diagnosis including myocardial biopsies is often recommended in unknown cases of chronic heart failure. Stable chronic heart failure patients in a low stage should be controlled annually. In a higher stage, the controls should include ECG, echocardiography and occasional BNP measurements every 6 months.

Therapy

The therapy of congestive heart failure depends on current guidelines (Remme 2001 or   guidelines   for   chronic   heart   failure; www.escardio.org/knowledge/guidelines)http:/// and begins with moderate and regular exercise in combination with a healthy diet, including a reduced fluid and salt intake. Non-steroidal anti-rheumatics (NSAR), antiarrhythmics and calcium antagonists should be limited.

Medication of congestive heart failure includes:

- from NYHA I (no limitation):

  ACE inhibitor (control blood pressure and renal function) and beta-blocker (beginning with low dose therapy under regular control of blood pressure and heart rate. If a low-dose therapy is tolerated, the beta-blocker medication should be increased slowly).

- from NYHA II (slight limitation of physical activity):

  digitalis glycosides and diuretics.

- from NYHA III (marked limitation of physical activity):

  spironolactone (low dose with controlled potassium).

NYHA III and NYHA IV require cooperation with a cardiologist. In the presence of ventricular arrhythmia, the indications for an implantable cardioverter defibrillator (ICD) have to be considered.

Therapeutic options that could eliminate the causes of heart failure (such as operative valve replacement in the case of a primary vitium or intensive antibiotic therapy for bacterial myocarditis) have priority. In these cases, cooperation with a specialized center is recommended.

Prognosis

Chronic heart failure is associated with a reduced life expectancy. In cases of NYHA III-IV, the annual mortality rate rises by up to 30 %. While in some cases, a total recovery was described (Fingerhood 2001, Tayal 2001), the majority of patients with HIV-associated dilated cardiomyopathy still have a progression of left ventricular dysfunction (Felker 2000). It is still unclear whether antiretroviral medication has an influence on the recovery of ventricular function. Early diagnosis and conventional therapy seem to be the most promising ways to reduce the progression of disease.

Pericardial Effusion

Before effective antiretroviral drugs were available, pericardial effusion was the most frequent cardiac manifestation. In clinical trials, the incidence of pericardial effusions was recognized to be as high as 11 % per year (Heidenreich 1995). However, the majority of HIV-associated pericardial manifestations are described as asymptomatic. Nevertheless, the spectrum ranges from acute or chronic pericarditis to an acute pericardial tamponade (Silva-Cardoso 1999). Pericardial diseases could be caused by HIV itself, further pathogens, or neoplasms (Stotka 1989). However, non-HIV-associated causes of pericardial effusion, such as uremia, trauma, irradiation, and drugs, have to be considered. In some cases of lipodystrophy an increase in the cardiac lipid tissue could simulate an extensive pericardial effusion (Neumann 2002c).

Echocardiography is referred to as the standard method for diagnosis and control of pericardial diseases. Nevertheless, further diagnosis should be performed by computer tomography and/or magnetic resonance tomography when a neoplasm or an increase in the cardiac lipid tissue is suspected. Pericardial puncture has to be considered for symptomatic patients.

Cardiac Arrhythmias

Cardiac arrhythmias can depend on medication. Antiretroviral drugs, e.g. efavirenz, or co-therapy with methadone, are expected to prolong the QT interval, an alteration in ECG which might cause "Torsade de pointes" tachycardia (Castillo 2002). Further drug combinations such as a macrolide and a chinolone may have the same effect on the QT interval.

Initiation or change of medication, which might influence the QT interval, should be controlled daily by ECG. In case of arrhythmias, electrolyte and glucose concentrations have to be determined repeatedly.

Valvular Heart Disease

Valvular heart disease of HIV-infected patients occurs as a bacterial or mycotic endocarditis. The most frequent germ is staphylococcus aureus, being detected in more than 40 % of HIV-infected patients with bacterial endocarditis. Further pathogens include streptococcus pneumoniae and hemophilus influenzae (Currie 1995). Mycotic forms of endocarditis, which may also occur in patients who are not intra-

venous drug abusers, mostly belong to aspergillus fumigatus, candida species or cryptococcus neoformans.

Signs of infective endocarditis include fever (90 %), fatigue, and lack of appetite. An additional heart murmur may also be present (30 %). In these cases, repeated blood samples should be taken and transesophageal echocardiography performed (Bayer 1998). Due to the fact that the detection of the infectious agent is often difficult, an antibiotic therapy has to be started early, even without the microbiology results.

In most cases, previously damaged valves are affected. Therefore, antibiotic prophylaxis is recommended in all persons with a previously damaged endocardium and planned interventional procedure, e.g. dental work or operations on the respiratory or gastrointestinal tract.

Further Cardiac Manifestations

Heart neoplasms are rarely found in HIV-infected patients. These manifestations occur predominantly in the advanced stages of the disease. On autopsy, the rate of cardiac localized Kaposi's sarcoma is less than one percent.

As well as neoplasms, vascular alterations including vasculitis and perivasculitis have been described as further cardiovascular manifestations in HIV-infected patients. In particular, the function of the pulmonary vessels can deteriorate, resulting in pulmonary arterial hypertension and, consequently, right heart dilatation (Mehta 2000). For further information on pulmonary arterial hypertension see the chapter "HIV-associated pulmonary hypertension (PAH)".

Table 2. Cardiac diseases in HIV-infected patients

Pericardial diseases
- Pericardial effusion
- Pericarditis (viral, bacterial, mycotic)
- Neoplasm (Kaposi's sarcoma, lymphoma)

Myocardial diseases
- HIV-associated dilated cardiomyopathy
- Myocarditis (acute or chronic)
- Neoplasm (Kaposi's sarcoma, lymphoma)
- Drug side-effects (especially by antiretroviral therapy)

Endocardial diseases
- Infective endocarditis (bacterial, mycotic)
- Nonbacterial thrombotic endocarditis

Vascular diseases
- Arteriosclerosis
- Vasculitis, perivasculitis
- Pulmonary artery hypertension

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21. HIV-associated Pulmonary Hypertension

Georg Friese, Mirko Steinmüller and Ardeschir Ghofrani

Pulmonary hypertension is a severe life-limiting disease often affecting younger patients. The connection between HIV infection and the development of pulmonary hypertension is well documented (Mette 1992, Simonneau 2004). The underlying pathobiology still remains unclear. Given that the prognosis of HIV infection has been improved by HAART, severe pulmonary hypertension is becoming a life-limiting factor (Nunes 2002).

Etiology, pathogenesis, classification

Pulmonary hypertension is caused by vasoconstriction, reduction of arterial elasticity by structural remodeling of the vessel walls, obstruction of vessels, as well as vessel rarification. All forms show the development of functional alterations (reversible vasoconstriction) and structural changes (vascular remodeling), often occurring in combination with intravascular thrombosis. The increase of right ventricular afterload induces right ventricular hypertrophy and/or dilatation.

Chronic pulmonary hypertension is divided into five groups according to the classification developed at the 1998 *World Symposium on Primary Pulmonary Hypertension* in Evian (modified in Venice, 2003). HIV-associated pulmonary hypertension belongs to group number one (PAH):

Pulmonary arterial hypertension (PAH)

1.1 Primary pulmonary hypertension

    a) Sporadic disorder

    b) Familial disorder

1.2 Associated with

    a) Collagen vascular disease

    b) Congenital systemic-to-pulmonary shunt

    c) Portal hypertension

    d) **HIV-associated pulmonary hypertension**

    e) Drugs

    f) Persisting PAH of the newborn

Pulmonary hypertension is classified into three clinical stages:

1. Latent pulmonary hypertension is characterized by mean pulmonary arterial pressures (PAP) below 21 mmHg with an exercise-induced increase to values above 30 mmHg. The patients suffer from dyspnea upon exercise.

2. At the stage of manifested pulmonary hypertension, mean PAP exceeds 25 mmHg at rest. Patients already suffer from dyspnea during light exercise.

3. Severe pulmonary hypertension is characterized by a severely reduced cardiac output at rest, which cannot be increased upon exercise due to the increase in right ventricular afterload. Thus, patients are unable to perform any physical activity without distress.

Diagnosis

Right heart catheterization

For the diagnosis of chronic pulmonary hypertension, right heart catheterization is still considered to be the gold standard. Essential parameters of pulmonary hemo-dynamics can be evaluated. The main parameter is pulmonary resistance, which can be abnormal even without affecting pulmonary arterial pressure. A test for reversi-bility of vasoconstriction should be performed at the stage of manifested pulmonary hypertension in order to identify patients responding to vasodilatory therapy. These "responders" are identified using oxygen insufflation or vasodilators during right heart catheterization. For example, during nitric oxide inhalation these patients show a decrease in pulmonary arterial pressure of 30 % and a simultaneous nor-malization of cardiac output.

ECG

ECG alterations induced by pulmonary hypertension are present after a two-fold increase in the musculature of the right heart. Typical signs are:

- right axis deviation (mean QRS-axis $> + 110°$)
- RS-ratio in lead V6 < 1
- S wave in lead I and Q wave in lead III
- S waves in lead I, II and III
- increased P-wave amplitude (not obligatory).

Chest radiography

Pulmonary hypertension can be inferred by chest radiography observations:

- enlarged right descending pulmonary artery (diameter greater than 20 mm)
- central pulmonary arterial dilatation in contrast to narrowed segmental arteries
- pruning of peripheral pulmonary blood vessels
- enlargement of transversal diameter of the heart and increase of retrosternal contact area of the right ventricle.

Echocardiography

Echocardiography allows recognition of right ventricular dilatation and estimation of systolic pulmonary arterial pressure. Typical signs are:

- right ventricular myocardial hypertrophy
- abnormal septum movements
- abnormal systolic intervals
- abnormal movement patterns of the pulmonary valve
- altered ejection flow profile of the right ventricle (transthoracic Doppler echocardiography).

Ventilation-perfusion scan, pulmonary angiography and CT scan

These radiological techniques are used to identify or exclude chronic thromboembolic pulmonary hypertension (CTEPH) and may guide operative treatment. CTEPH is an important differential diagnosis in intravenous drug abusing HIV patients who suffer from recurring thromboembolisms (Figure 1).

Therapy

General treatment

Various modalities of general treatment have been established for the therapy of pulmonary hypertension on the basis of empirical data. These are:

1. Diuretics

In the later stages of pulmonary hypertension, volume retention may cause an enormous increase in right ventricular preload followed by congestive hepatomegaly, edema and ascites formation. Volume retention is not only caused by chronic right heart failure but also by stimulation of the renin-angiotensin system followed by elevated aldosterone levels. For this reason, a combination of loop diuretics (e.g. furosemide 20-80 mg per day) and aldosterone antagonists (e.g. aldactone 50 - 200 mg per day) has proved to be successful. The usual contraindications, as well as the risk of dehydration followed by a critical decrease of right ventricular preload, have to be considered. A preload of about 6-10 mmHg is needed for optimal right ventricular performance.

2. Digitalis

The use of digitalis is still much debated. According to a randomized placebo-controlled double-blind trial, only patients suffering simultaneously from cor pulmonale and decreased left ventricular function benefit from digitalis medication. However, digitalis medication is always justified in the case of tachycardic atrial arrhythmias. It has to be considered that digitalis has a high arrhythmogenic potential in combination with hypoxemia, which might lead to severe complications.
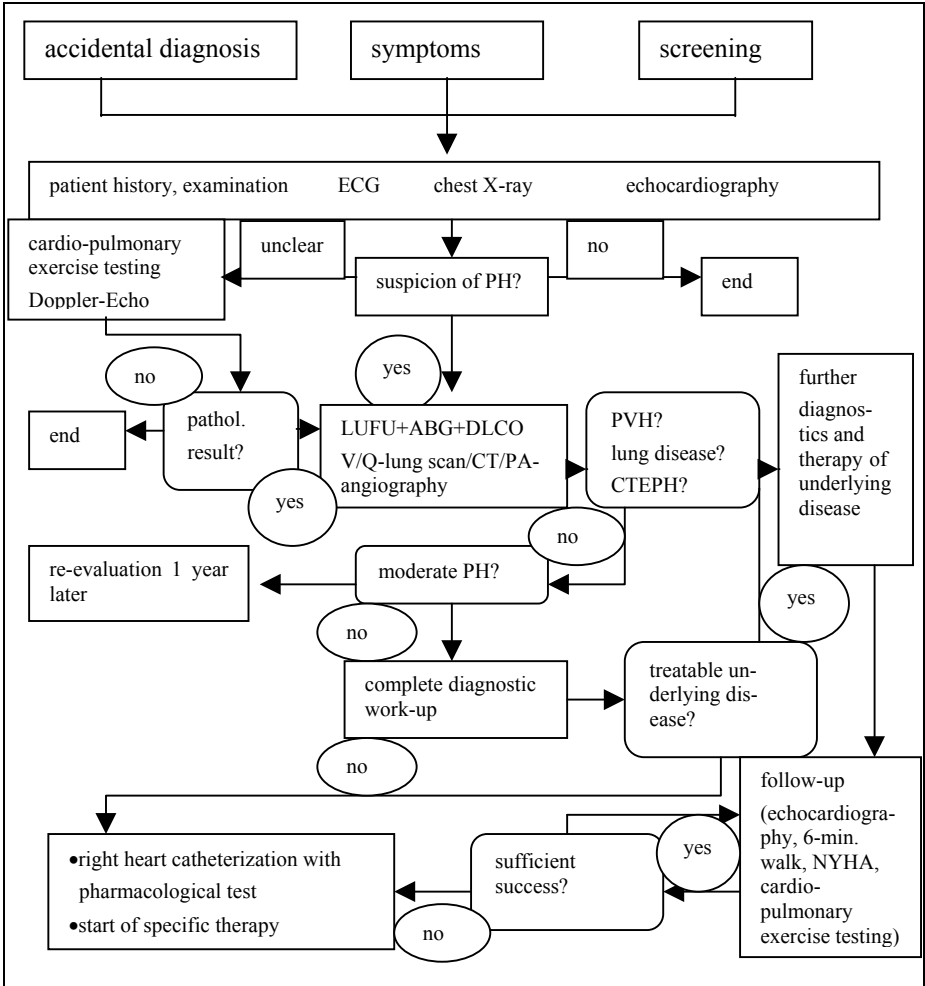
Figure 1. Diagnostic and therapeutic algorithm: suggestion for diagnostic procedures on suspicion of pulmonary hypertension. LUFU: lung function test; ABG: arterial blood gases; DLCO: CO diffusion capacity.

3. Anticoagulation

After considering the contraindications, the application of heparin or oral anticoagulants such as phenprocoumon and warfarin, are established treatments for chronic pulmonary hypertension. Long-term anticoagulation therapy addresses the following aspects about the pathophysiology of PAH:

- increased risk of in-situ thrombosis caused by altered blood flow in narrowed and deformed pulmonary vessels

- increased risk of thrombosis caused by peripheral venous stasis, right ventricular dilatation and reduced physical exercise

- decreased levels of circulating thrombin and fibrinogen degradation products, which are supposed to act as growth factors in vascular remodeling processes.

The dose of anticoagulants should be adjusted to maintain the prothrombin time at an international normalized ratio (INR) of 2.5.

4. HAART

HAART is considered to be a general treatment for HIV-associated pulmonary hypertension. According to the CDC classification, pulmonary hypertension is a symptomatic complication and therefore classified as category B. This is independent of CD4 cell numbers and virus load, indicating an obligation to administer antiretroviral treatment. Evidence shows that prognosis of HIV-associated pulmonary hypertension is improved upon effective antiretroviral therapy (Zuber 2004). Additionally, the immune status of this high-risk group has to be stabilized to prevent systemic infection, and above all pneumonia.

Specific treatment

The aim of specific therapy is to decrease pulmonary arterial pressure, thereby reducing right ventricular afterload. Substances currently used for treating pulmonary hypertension or tested in clinical studies are:

- calcium channel blockers
- prostanoids (intravenous, inhaled, oral, subcutaneous)
- endothelin receptor antagonists (selective, non-selective)
- phosphodiesterase-5 inhibitors.

In addition to the immediate effect of muscle relaxation, some vasodilators (especially prostanoids and phosphodiesterase-5 inhibitors) seem to have a sustained antiproliferative effect.

1. Calcium channel blockers

Currently, nifedipine and diltiazem are the most commonly used calcium channel blockers. Around 5-10 % of primary pulmonary hypertension patients are so-called responders. The response to calcium channel blockers should be evaluated during right heart catheterization.

The effects on the systemic circulation are major disadvantages of oral calcium channel blocker therapy. Peripheral vasorelaxation causes hypotension and the negative inotropic effect of calcium channel blockers leads to a reduction in the cardiac output. Furthermore, unselective vasodilation in the pulmonary circulation may have adverse effects on gas exchange by increasing ventilation-perfusion mismatches. For long-term therapy, up to 250 mg nifedipine or 720 mg diltiazem is used. The dose must be slowly increased over weeks to the correct treatment dosage.

2. Intravenous prostacyclin

Reduction of endothelial prostacyclin synthesis in lung tissue has been described in patients suffering from pulmonary hypertension (Christman 1992, Tuder 1999). Therefore, substitution of exogenous synthetic prostacyclin was an obvious therapeutic option. Due to its short half-life, iloprost is continuously infused intravenously using a portable pump via a catheter or an implanted port. The intravenous

dosage of iloprost is slowly increased to the usual dose of between 0.5 and 2.0 ng per kg bodyweight per minute.

The treatment of outpatients with intravenous prostacyclin is today an established method for the long-term therapy of severe pulmonary hypertension (Barst 1996, Sitbon 2002). Long-term therapy with intravenous prostacyclin induces a sustained hemodynamic benefit in the treatment of primary pulmonary hypertension (e.g. HIV-associated pulmonary hypertension).

The disadvantages of intravenous prostacyclin are:

- systemic side effects of unselective vasodilators, e.g. arterial hypotension, orthostasis, skin hyperemia, diarrhea, jaw- and headache
- risk of acute right heart decompensation due to application failures
- possible catheter infection
- tachyphylaxis

Tachyphylaxis is observed in the long-term application of intravenous prostacyclin and requires increased doses.

Conclusion: experiences with prostacyclin in HIV-associated pulmonary hypertension are based on smaller, uncontrolled trials. However, these studies suggest an improvement in the prognosis of affected patients (Aguilar 2000, Cea-Calvo 2003).

3. Inhaled Prostanoids

Many disadvantages of the intravenous route of application can be avoided by using aerosolized prostanoids (e.g. the recently approved prostanoid Ventavis™). Alveolar deposition of prostanoids stimulates a selective intrapulmonary effect. In a recent multi-centric, randomized, placebo-controlled trial, repeated inhalation of iloprost was proven to be effective and safe in HIV-negative patients (Olschewski 2002). Patients treated with iloprost showed a significant improvement in exercise capacity as measured by the six-minute walk test, as well as in NYHA classification.

The effect of this treatment on HIV-associated pulmonary hypertension was demonstrated in a further clinical trial at our center (Ghofrani 2004). Disadvantages of this form of therapy are the sophisticated aerosolization technology, short duration of action after a single application (60-90 min) requiring frequent inhalations (6-9 per day) and the treatment-free interval during the night. Per day 25 to 75 µg iloprost are given in 6-9 inhalations.

4. Endothelin-receptor antagonists

Selective and non-selective endothelin antagonists proved effective in several experimental trials. An improvement in the capacity for physical exercise and an increase in the complication-free survival time of PPH-patients has been demonstrated in a phase III trial for the orally administered endothelin antagonist bosentan (Rubin 2002). The doses applied vary between 62.5 and 125 mg, twice daily. Elevated liver enzymes are major side effects of this therapy. Therefore, stringent controls of liver enzymes are necessary. The use of bosentan in patients suffering from HCV/HIV coinfection has to be considered carefully.

Based on these data, bosentan was approved for the treatment of pulmonary arterial hypertension in Europe. Due to the potential increase in liver enzymes, frequent

controls of liver enzymes are required. Bosentan can only be prescribed by physicians who are registered by the company Actelion and admitted to the prescription list.

An uncontrolled study reports first experiences with the treatment of HIV-associated pulmonary hypertension with bosentan (Sitbon 2004).

5. Phosphodiesterase-5 (PDE5) inhibitors

Recent data suggest a strong pulmonary vasodilative potential of sildenafil, a selective phosphodiesterase-5 inhibitor. High effectivity and tolerability of this orally administered substance are demonstrated in clinical trials with low patient numbers for several forms of pulmonary hypertension (Ghofrani 2002, Schumacher 2001, Carlsen 2002). A recently completed phase III trial may allow sildenafil to be approved for the treatment of pulmonary arterial hypertension.

Today there are no definite and generally accepted recommendations for the treatment of HIV-associated pulmonary hypertension. However, considering the associations within group one of pulmonary arterial hypertension (Venice 2003), a similar therapeutic regime as for idiopathic pulmonary hypertension can be applied depending on the clinical severity of the disease (Figure 2). 25 to 150 mg sildenafil are usually given per day in two or three single applications.

Conclusion for clinicians

HIV patients suffering from exercise-induced dyspnea should be tested for pulmonary hypertension when other pulmonary or cardiac diseases (e.g. restrictive or obstructive ventilation disorders, pneumonia, coronary heart disease) have been excluded. The incidence of pulmonary hypertension is elevated by a factor of 1,000 in HIV patients compared to the general population. Estimated numbers of unreported cases are not included.

A suspected diagnosis of pulmonary hypertension can be substantiated by non-invasive diagnostic methods (e.g. echocardiography). Since new therapeutic options have recently become available, correct diagnosis is essential.

Further diagnosis and treatment of patients suffering from every kind of pulmonary hypertension should be performed in specialized centers with experience in the treatment of pulmonary hypertension and HIV infection.
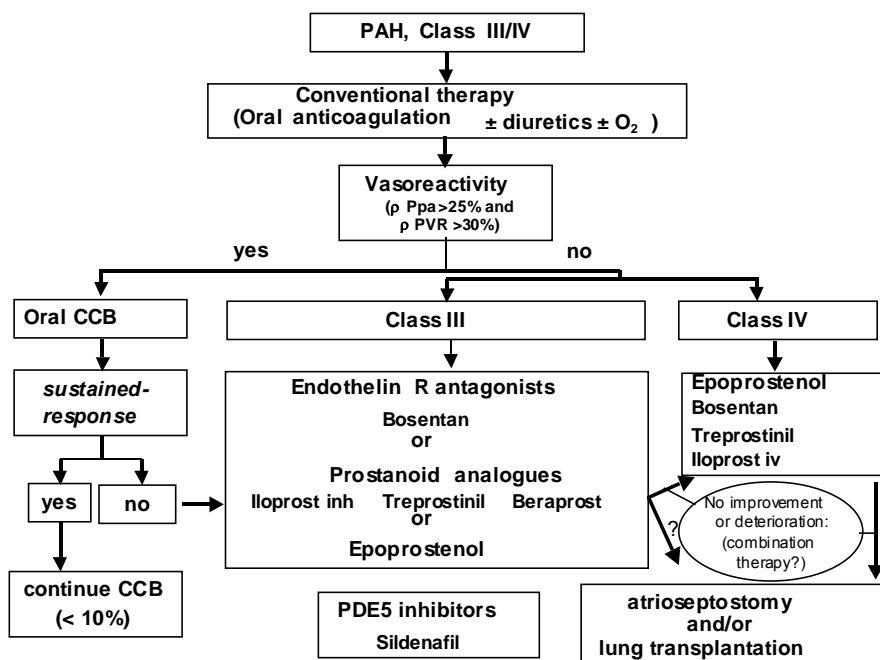
Figure 2. Therapeutic algorithm of pulmonary arterial hypertension depending on severity and vasoreactivity (adapted from World symposium on pulmonary hypertension, Venice 2003). Class: NYHA classification; Ppa: pulmonary arterial pressure; PVR: pulmonary vascular resistance; CCB: calcium channel blocker; PDE5: phosphodiesterase 5.

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22. HIV and Pulmonary Diseases

Sven Philip Aries, Bernhard Schaaf

The spectrum of lung diseases in HIV-infected patients encompasses complications typical for HIV such as tuberculosis, bacterial pneumonia, lymphomas and HIV-associated pulmonary hypertension, but also includes typical everyday pulmonary problems such as acute bronchitis, asthma, COPD and bronchial carcinomas (Table 1). Classical diseases such as PCP have become rarer as a result of HAART and chemoprophylaxis, so that other complications are on the increase. None other than acute bronchitis is the most common cause of pulmonary problems in HIV patients (Wallace 1997). However, particularly in patients with advanced immunodeficiency, it is vital to take all differential diagnoses into consideration. Anamnestic and clinical appearance are often essential clues when it comes to distinguishing between the banal and the dangerous.

Table 1: Pulmonary complications in patients with HIV infection

Infections	Neoplasia	Other
Pneumocystis jiroveci	Kaposi's sarcoma	Lymphocytic interstitial pneumonia
Bacterial pneumonia	Non-Hodgkin's lymphoma	
S. pneumoniae	Hodgkin's lymphoma	Non-specific interstitial pneumonia
S. aureus		
H. influenzae	Bronchial carcinoma	Pulmonary hypertension
B. catarrhalis		
P.aeruginosa		COPD
Rhodococcus equi		
Nocardia asteroides		Bronchial hyperreactivity
Mycobacteria		
M. tuberculosis		
Atypical mycobacteria		
Other		
Cytomegalovirus		
Aspergillus spp.		
Crytococcus neoformans		
Histoplasma capsulatum		
Toxoplasma gondii		

This chapter presents an outline of differential diagnoses in patients with respiratory complaints. PCP, mycobacterioses and pulmonary hypertension are covered in detail in chapters elsewhere.

Anamnesis

What previous illnesses has the patient had?

Someone who has suffered from PCP once has a higher risk of subsequent infection.

A patient with hyperlipidemia and carotid stenosis might have coronary heart disease.

What medication does the patient take?

Taking cotrimoxazole usually prevents PCP, and the risk of bacterial pneumonia may also be reduced (Beck 2001). In the case of PCP prophylaxis with pentamidine inhalation, however, atypical, often apically pronounced manifestations of PCP are to be expected. When treatment with abacivir is started, asthma could also be due to hypersensitivity. T-20 seems to increase the risk of bacterial pneumonia, at least among smokers.

Does the patient smoke?

Although smoking is more harmful to HIV-positive than to HIV-negative persons, it is still more common among HIV-positives (Royce 1990). All HIV-associated and HIV-independent pulmonary diseases are more common in smokers than in non-smokers. This is true for bacterial pneumonia and PCP, but also applies to asthma, COPD and pulmonary carcinomas (Hirschtick 1996). Smoking promotes the formation of a local immune deficit in the pulmonary compartment: it reduces the number of alveolar CD4 cells and the production of important pro-inflammatory cytokines such as IL-1 and TNF-α (Wewers 1998). Furthermore, smoking suppresses the phagocytosis capacity of alveolar macrophages. This effect is more pronounced in HIV patients than in HIV-negative patients. HIV infection itself, however, does not seem to have any direct influence on the ability to kill bacteria (Elssner 2004).

Motivating the patient to restrict nicotine intake is thus an important medical task, particularly in HIV consultations. Strategies which promise success and are supported by the evidence of clinical studies include participation in motivational groups, nicotine substitutes and taking buproprion. In the latter situation, interactions, particularly with ritonavir, should be taken into consideration.

Where does the patient come from?

Another important question is that of the travel history and/or the origin of the patient. There are places where diseases such as histoplasmosis and coccidioidomycosis occur endemically. Histoplasmosis, for example, is more widespread in certain parts of the USA and in Puerto Rico than PCP, while it is rare in Europe.

How did the patient become infected with HIV?

Intravenous drug users suffer more often from bacterial pneumonia or tuberculosis (Hirschtick 1995). Pulmonary Kaposi's sarcomas are almost exclusively found in MSM (men who have sex with men).

What are the symptoms ?

Coughing or shortness of breath alone are not always useful in differentiating between PCP and bacterial pneumonia, and further information is needed. Thus, for

example, it is typical for the onset of bacterial pneumonia to be more acute. Patients usually go to the doctor after only 3-5 days of discomfort, whereas patients with PCP suffer from symptoms for an average of 28 days (Kovasc 1984). PCP patients typically have dyspnea and a non-productive cough. A large quantity of discolored sputum is more likely to indicate a bacterial cause or a combination of infections.

What does the chest x-ray look like ?

Table 2: What does the chest x-ray look like ?

Chest x-ray	Typical differential diagnosis
Without pathological findings	PCP, Asthma, KS of the trachea
Focal infiltrates	Bacterial pneumonia, mycobacteriosis, lymphoma, fungi
Multifocal infiltrates	Bacterial pneumonia, mycobacteriosis, PCP, KS
Diffuse infiltrates	PCP (centrally pronounced), CMV, KS, LIP, cardiac insufficiency, fungi
Miliary image	Mycobacteriosis, fungi
Pneumothorax	PCP
Cavernous lesions	Mycobacteriosis (CD4 > 200/µl), bacterial abscess (Staph., Pseudomonas)
Cystic lesions	PCP, fungi
Pleural effusion	Bacterial pneumonia, mycobacteriosis, KS, lymphoma, cardiac insufficiency
Bihilar lymphadenopathy	Mycobacteriosis, KS, sarcoidosis

The most important question of all: What is the immune status?

The number of CD4 cells provides an excellent indication of the individual risk of a patient of suffering from specific opportunistic infections. In patients with a CD4 cell count of more than 200/µl, infection with typical opportunistic HIV-associated diseases is very unlikely. Here, as with HIV-negative patients, one generally tends to expect more "normal" problems such as acute bronchitis and bacterial pneumonia. However, tuberculosis should always be considered as a possibility. Although the risk of becoming infected with tuberculosis grows along with increasing immunodeficiency, more than half of all tuberculosis infections in HIV-positive patients occur at a CD4 cell count of above 200/µl (Lange 2004, Wood R 2000).

At less than 200 CD4 cells/µl, PCP occurs and, more rarely, pneumonia/pneumonitis with cryptococci; however, bacterial pneumonia is the most common pulmonary disease at this stage, too.

Below 100 CD4 cells/µl, there is an increase in the number of pulmonary Kaposi's sarcomas and Toxoplasma gondii infections. At less than 50/µl CD4 cells, infections with endemic fungi (Histoplasma capsulatum, Coccidioides immitis), non-endemic fungi (Aspergillus, Candida species), atypical mycobacteria and different viruses (mostly CMV) may occur. Especially in patients with advanced immunodeficiency, pulmonary disease may represent an organ manifestation of a systemic infection. Rapid, invasive diagnostic procedure is thus advisable in such patients.

Pulmonary Complications

Bacterial pneumonia

Bacterial pneumonia occurs more often in HIV-positive than in HIV-negative patients, and, like PCP, leaves scars in the lung. This often results in a restriction of pulmonary function which persists for years (Alison 2000). Although bacterial pneumonia occurs in the early stages of HIV infection, the risk grows along with increasing immunosuppression. A case of bacterial pneumonia significantly worsens the long-term prognosis of the patient (Osmond 1999). Thus, contracting bacterial pneumonia more than once a year is regarded as AIDS-defining. The introduction of HAART went hand in hand with a significant reduction in the occurrence of bacterial pneumonia (Jeffrey 2000).

Clinically and prognostically speaking, there is no great difference between bacterial pneumonia in HIV-infected patients and pneumonia in an immunocompetent host. However, the HIV-patient is more likely to present with less symptoms and a normal leucocyte count (Feldman 1999). Etiologically, pneumococci and haemophilus infections are most common. In comparison with immunocompetent patients, infections with *Staphylococcus aureus*, *Branhamella catarrhalis,* and in the later stages (less than 100 CD4 cells/µl) *Pseudomonas spp*. occur more often. The possibility of rare pathogens such as *Rhodococcus equi* and nocardiosis should also be considered in the presence of slow-growing, cavitating infiltrates. Polymicrobial infections and co-infections with *Pneumocystis jiroveci* are common (10-30 %), which makes clinical assessment difficult (Miller 1994).

Also important for the risk stratification of the patient, in addition to the usual criteria (pO2, extent of infiltrate, effusion, circulatory condition, extrapulmonary involvement and confusion of the patient), is the CD4 cell count. The mortality of patients with less than 100 CD4 cells/µl is increased more than sixfold. Therefore, it probably makes sense when dealing with patients with a pronounced immune defect, not to rely on the risk scores validated for immunocompetent patients and to admit apparently less severely ill patients to hospital (Cordero 2000).

If mycobacteriosis is not suspected, treatment of patients with a CD4 cell count of more than 200/µl should include drugs effective against *S. pneumoniae, H. influenzae* and *S. aureus*. However, there are no controlled studies available to support this. In accordance with recommended therapies for patients with community-acquired pneumonia and co-morbidities, a group 2 cephalosporin such as cefuroxime, or group 3a such as cefotaxime/ceftriaxone, or an aminopenicillin with beta-lactamase inhibitor (ampicillin/sulbactam or amoxycillin/clavulanic acid, e.g. Augmentan™ 875/125 mg, twice daily) should be prescribed. In the case of regionally increased incidence of legionella infection, combination with a macrolide is advisable (e.g. Klacid™ 500 mg twice daily). Once positive culture results have been obtained, the patient should receive further specific treatment. With advanced immunodeficiency (CD4 cells less than 200/µl), primary consideration should be given to bronchoscopic diagnostics, due to the broader spectrum of pathogens (Dalhoff 2002).

Pneumococcus vaccination is recommended. However, there is no proof that it is of benefit at CD4 cell counts lower than 200/µl. Due to the frequency of secondary bacterial infections, an annual influenza vaccination is also advisable.

Which diagnostic strategy makes sense in the presence of pulmonary infiltrates?

The intensity of the diagnostic workup in a patient with pulmonary infiltrates is based on the HIV stage and the expected spectrum of pathogens. With a CD4 cell count of more than 200/µl, non-invasive basic diagnostics and calculated antibiotic therapy are justified. This basic diagnostic investigation includes taking two blood cultures and a microscopic and cultural sputum examination. In 25-60 % of cases, the bacteremia rate is higher than in immunocompetent patients (Miller 1994). The main value of sputum culture is the demarcation of mycobacterial and aspergillus infections.

Antigen detection in the urine should be considered in individual cases (e.g. pneumococcus, legionella, cryptococcus, histoplasma). The determination of the cryptococcus antigen in serum has a high predictive value for the detection of invasive cyptococcosis (Saag 2000). A chest CT is sometimes helpful in the diagnostic workup (high resolution CT, HRCT): PCP, for example, might be depicted on an HRCT, but missed on conventional chest x-ray.

In advanced stages (below 200 CD4 cells/µl), bronchoscopic investigation is recommended (Dalhoff 2002). The diagnostic success rate of a bronchoscopy in HIV-infected patients with pulmonary infiltrates is 55-70 % and rises to 89-90 % when all techniques are combined, including transbronchial biopsy (Cadranel 1995). The sensitivity of bronchoalveolar lavage (BAL) amounts to 60-70 % in bacterial pneumonia (patients without previous antibiotic treatment), and 85-100 % in PCP (Baughman RP 1994). Due to the high sensitivity of BAL, transbronchial biopsy is only recommended if PCP is suspected, if the initial diagnostic workup is negative, or if patients are taking chemoprophylaxis (Dalhoff 2002). If invasive pulmonary aspergillosis or CMV is considered, transbronchial biopsy should be the preferred method in order to differentiate between colonization and tissue invasion. Open surgical biopsies and CT-controlled trans-thoracic pulmonary biopsies are rarely necessary.

Asthma bronchiale

It could be supposed that an immunosuppressing disease such as HIV infection would at least protect patients from manifestations of exaggerated immune reaction such as allergies and asthma. However, the opposite is the case: in a study from Canada concerning HIV-infected men, more than half of the interviewees had suffered an episode of wheezing within the previous 12 months, and nearly half of those showed evidence of bronchial hyperreactivity. These findings were particularly distinct among smokers (Poirer 2001). With progression of the disease, it is likely to lead to an imbalance between too few "good" TH1 cells, producing interferon and interleukin-2, and too many "allergy-mediating" TH2 cells with an increased total IgE. In cases of unspecific coughing, dyspnea or recurrent bronchitis, the possibility of bronchial hyperreactivity, asthma or emphysema should be kept in mind.

Emphysema

Smokers with HIV develop pulmonary emphysema more often than smokers without HIV. It is possible that a pathogenic synergy arises from smoking and the pulmonary infiltration with cytotoxic T cells due to HIV infection (Diaz 2000). Smoking crack increases the risk of pulmonary emphysema even more. Here, it seems that superficial epithelial and mucosal structures are destroyed (Fliegil 1997). Furthermore, cocaine can lead to unusual manifestations with pneumothorax or alveolar infiltrates.

Lymphoid interstitial pneumonia (LIP):

LIP is a form of pneumonia which takes a chronic or subacute course and is extremely rare in adults. Radiologically, its reticulonodular pattern makes it similar to PCP. This illness is paraneoplastic, rarely idiopathic and, in HIV and EBV disease, parainfectious. In contrast to PCP, patients with LIP usually have a CD4 cell count of more than 200/µl and normal LDH values. A CD8-dominated lymphocytic alveolitis with no pathogen detection is characteristic. Definite diagnosis often calls for an open pulmonary biopsy. LIP is considered sensitive to steroids. The role played by HAART is unclear, especially as LIP has occasionally been observed in the context of immune reconstitution during HAART.

Bronchial carcinoma

HIV patients are at considerably higher risk of bronchial carcinoma. A retrospective analysis covering 8,400 patients from the years 1986-2001 showed an eightfold increased incidence of bronchial carcinoma in the period after 1996 than that for the normal smoking population. Interestingly, the majority of bronchial carcinomas are histologically adenocarcinomas, which leads to the discussion of whether HIV infection itself causes a genetic instability (Bower 2003). In comparison to HIV-negative patients, HIV-positive patients with bronchial carcinoma are younger, the disease is often more advanced at presentation and takes a more aggressive course (White 1996, Karp 1993). The decision to treat with chemotherapy, and if so, what kind, has to be made for each case individually. A small cohort study (Powles 2003) showed that HIV-infected patients with advanced bronchial carcinoma have a similarly bad prognosis to that of HIV-negative patients, regardless of immune status during HAART and chemotherapy.

Less common opportunistic infections

The detection of CMV in BAL repeatedly gives rise to discussion regarding clinical relevance. At over 90 %, seroprevalence is high, and colonization of the respiratory tract is common. CMV pneumonia is the primary reason for 3.5 % of pulmonary infiltrates in AIDS patients. The significance of the pathogen in the later stages may well be underestimated, since histological examination of autopsy material showed pulmonary CMV infections in up to 17 %. (Afessa 1998, Waxman 1997) Invasive pulmonary aspergillosis (IPA), which only occurs in the late stages and usually in conjunction with additional risk factors such as neutropenia or steroid therapy (Mylonakis 1998), is discussed in the Chapter on OIs.

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23. HIV-1 associated Encephalopathy and Myelopathy

Christian Eggers and Thorsten Rosenkranz

HIV Encephalopathy

The primary cause of HIV encephalopathy (HIVE) is the infection of the CNS caused by HIV. If untreated, 15-20 % of patients will eventually develop HIVE. Since the introduction of highly active antiretroviral therapy (HAART) the incidence of the disorder has decreased. Other terms used for this condition with largely the same significance are AIDS dementia complex, AIDS dementia, and HIV-associated cognitive motor complex. HIVE only occurs in the later stages of HIV infection when there is a profound immune suppression (CD4 count below 200/µl). The incidence of HIVE will likely increase in developed countries as a consequence of increasing life expectancy (Valcour 2004).

In HIVE, there is a high level of replication of HIV in macrophages and microglial cells of the brain. Neuronal cells have not been shown to be infected. However, different immunopathological mechanisms lead to functional and structural damage of these cells. With respect to viral replication and viral quasispecies, the CNS is partially independent from the hematolymphatic compartment (Eggers 2003). The viral load in the brain parenchyma and the cerebrospinal fluid has been shown to be high in HIVE, and loosely correlates with the extent of the disease.

Clinical manifestation

HIVE is considered to be a subcortical dementia, typically emerging over the course of weeks and months. Acutely developing symptoms point to another etiology. Fever, exhaustion, the effects of tranquilizers and reduced physical condition, e.g. with opportunistic infection, may all mimic dementia. In these cases, diagnosis of HIVE can only be made after repeated examinations when the condition mimicking dementia has improved.

Symptoms are occasionally noted by relatives earlier than by the patient himself. This is why a history given by these persons is of utmost importance. Typical complaints are slowing of reasoning, forgetfulness, difficulties concentrating, lack of energy drive, mild depressive symptoms and emotional blunting. For symptoms and signs see Tables 1 and 2.

Table 1: Symptoms of HIV encephalopathy including history given by close relatives or companions	
Cognition	Forgetfulness, difficulties concentrating, mental slowing (apprehension, processing).
Emotional	Loss of drive and initiative, withdrawal from social activities, failure to manage the financial and administrative aspects of one's life, depressive mood, emotional blunting.
Motor	Slowing and impairment of fine movements (e.g. typing, buttoning up), and disturbance of gait.
Autonomous	Impaired micturition (urgency), loss of sexual libido, erectile dysfunction.

Table 2: Signs of HIV Encephalopathy	
Neurological findings	Early stages: impaired gait, slowing of rapidly alternating movements, hypomimia, occasionally tremor and short stepped gait.
	Later: brisk tendon reflexes, positive Babinski sign, slowing of gaze saccades, sphincter impairment including incontinence. Palmomental, grasp and glabella reflexes. Occasionally accompanying polyneuropathy.
	In the terminal stages spastic tetraplegia and dual incontinence.
Neuropsychological findings	Slowing of psychomotor speed (e.g. naming the months in reverse), impairment of short term memory (recall of verbally presented items, digit span), and mental flexibility (spelling simple words backwards).
Psychological findings	Early stages: emotional blunting, disappearance of strong personality traits, distractability, loss of initiative.
	Later: problems with recalling events in the correct time order, disorientation in time, space and situation. Finally mutism.

Impairment of alertness, neck stiffness and focal or lateralizing neurological signs (e.g. hemiparesis, aphasia) are not typical of HIVE. Psychotic symptoms without cognitive or motor disturbance do not warrant a diagnosis of HIVE. The coincidence of psychosis with HIVE is rare. Focal and generalized epileptic seizures are rare manifestations of HIVE.

The severity of HIVE may functionally be categorized according to the Memorial Sloan Kettering scale (Price 1988).

Severity of HIVE

Stage 0:	(normal) normal mental and motor function.
Stage 0.5:	(equivocal/subclinical) no impairment of work or capacity to perform activities of daily living (ADL); normal gait; slowing of ocular movements and movements of extremities may be present.
Stage 1:	(mild) able to perform all but the more demanding aspects of work or ADL, but with unequivocal signs or symptoms of functional, intellectual or motor impairment; can walk without assistance.
Stage 2:	(moderate) able to perform basic activities of self-care, but cannot work or maintain the more demanding aspects of daily life; able to walk, but may require a single prop.
Stage 3:	(severe) major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable psycho-motor slowing); motor disability (cannot walk without assistance, usually manual slowing and clumsiness.
Stage 4:	(end stage) almost mutistic. Intellectual and social comprehension and output are at a rudimentary level; almost or completely mute; parapa-retic or paraplegic with urinary and fecal incontinence.

Diagnostic work-up

Making a diagnosis of HIVE requires a synopsis of clinical information and the results of laboratory tests. No laboratory test result on its own warrants the diagnosis of HIVE. Rather, the diagnosis requires the exclusion of other conditions (Table 3).

Clinically, the cognitive and psychological signs and symptoms are invariably accompanied by motor signs, although these may be subtle (Table 2). The HIV dementia scale (Power 1995) is an easy-to-use bedside instrument for the detection and quantification of the cognitive impairment of HIVE.

Laboratory tests are mainly employed to exclude differential diagnoses. MRI should be performed in preference to CT, and often shows patchy, diffuse, hyperintense and relatively symmetrical lesions in the white matter. These changes indicate leukoencephalopathy. In addition, atrophy with enlargement of the ventricles and the extraventricular CSF spaces may be seen. However, none of these findings are specific for HIVE, and the disease may be present with a normal MRI. Unlike progressive multifocal leukoencephalopathy (PML), the white matter lesions do not affect the cortical U-fibers, i.e. they don't reach the cortical ribbon. Edema, space occupying lesions and contrast enhancement are not typical of HIVE and should raise suspicion of other conditions.

TABLE 3: Differential diagnoses of HIV encephalopathy and diagnostic work-up

Condition	Adequate diagnostic step (commentary)
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >45/3) (serological findings may be atypical for active neurosyphilis)
CMV encephalitis	CSF (pleocytosis, potentially granulocytic; decreased glucose, elevated total protein)
	PCR for CMV in CSF, CMV antigen (pp65) in blood
	Antibody testing in blood and CSF (IgG and antibody index may be increased)
	MRI (potentially sub-ependymal hyperintensity and contrast enhancement)
	Occurs mostly in association with manifestation of other organs (retinitis, colitis, pneumonitis, esophagitis)
Toxoplasmosis	CT / MRI (single or multiple lesions found most frequently in basal ganglia or thalamus, space occupying effect, edema, frequently with contrast enhancement (patchy or ring-shaped))
	Presence of toxoplasma-specific IgG in blood and CSF (rarely total seronegativity)
	(may rarely pass as diffuse microglial nodule encephalitis)
Primary CNS lymphoma	CT / MRI (single or multiple lesions most frequently adjacent to ventricles, space occupying effect, edema, almost invariably intense contrast enhancement (patchy more than ring-shaped))
	CSF cytology
	EBV PCR in CSF (HIV-associated CNS lymphomas EBV-induced)
	PET or SPECT (tracer enhancement in lesion)
VZV encephalitis	CSF (marked inflammatory signs)
	VZV specific IgG in blood and CSF (IgM may be absent)
	VZV PCR in CSF
	Mostly antecedent or accompanying cutaneous zoster lesions
Cryptococcal meningitis	CSF (opening pressure frequently elevated, cell count and protein may be normal), India ink stain
	Cryptococcal antigen in blood and CSF, fungal culture
Tuberculous meningitis and other bacterial infections	CSF, culture, PCR for mycobacteria
	appropriate tests
Progressive multifocal leukoencephalopathy (PML)	MRI (single or multiple lesions of white matter, no space occupying effect, no edema, no contrast enhancement)
	PCR for JC virus in CSF
Intoxication	Determination of drug levels / screening for illicit drugs
Metabolic encephalopathy and impaired general physical condition	Determination of electrolytes, renal and hepatic markers, hormones (thyroid, cortisol), blood count
	Hypoxemia? (blood gas analysis)
	Reduced physical state? (bed ridden, wasting, pyrexia)
Depression with "pseudo dementia"	Psychiatric examination
Other "subcortical" dementia forms	Normal pressure hydrocephalus, Parkinsonian syndromes, other neurodegenerative conditions, subcortical arteriosclerotic encephalopathy

CSF analysis shows a normal or even decreased white cell count. In contrast, total protein and albumin concentrations may be slightly elevated (blood-brain-barrier disruption). Oligoclonal bands and an increased IgG index indicate autochthonous immunoglobulin production within the CNS. However, these findings are unspecific and are frequently present in the asymptomatic stages of HIV infection. Although there is a statistically significant correlation of a higher CSF viral load with HIVE, this association is of little value in the context of an individual patient. The electroencephalogram (EEG) shows no or only mild signs of generalized slowing. Moderate or severe slowing or focal arrhythmic delta activity are atypical for HIVE.

Treatment

According to the pathogenesis of HIVE, treatment should aim at suppressing viral replication in the CNS. It is an unresolved issue whether the antiviral compounds need to penetrate into the CSF. A variety of clinical (Letendre 2004), virological (de Luca 2002), pathological and electrophysiological studies suggest that substances reaching higher CSF concentrations are more effective. In contrast, we found no association of the number of CNS-penetrating substances and their CSF levels with the magnitude of CSF viral load suppression (Eggers 2003). HAART-induced neurocognitive improvement correlates more closely with viral load suppression in the CSF than in the plasma (Marra 2003).

In the absence of prospective, controlled studies with clinical end points, we consider it important that any antiretroviral regimen in patients with HIVE includes as many as possible CNS-penetrating substances. We suggest any of the following: zidovudine, lamivudine (high concentrations in *ventricular* CSF; unpublished observations), nevirapine and indinavir.

A number of small studies have investigated the effect of selegeline, nimodipine, lexipafant and the antioxidant agent CPI-1189 in the treatment of HIVE. These drugs act on the molecular pathogenesis of HIVE and are used in conjunction with antiretroviral treatment. Although a trend for clinical and neuropsychological improvement was seen with some substances, none of them can be recommended for routine clinical use.

Prognosis

An optimal HAART may lead to significant clinical improvement of HIVE. The extent of improvement includes restoration of working ability in patients previously dependent on caregivers. We observed this effect to last for the entire observation time of up to four years, in parallel with sufficiently suppressed plasma viremia. During the first months of treatment, the radiological signs of leukoencephalopathy may become more prominent, but eventually regress over the following one to two years.

Autopsy studies and clinical case series show, however, that some patients develop a clinically apparent CNS disease despite effective HAART-induced suppression of plasma viral load (Brew 2002; own unpublished observations). Even with rapid decrease of plasma viremia during HAART, many HIVE patients show a significantly protracted decrease of the CSF viral load (Eggers 2003). On these grounds,

we recommend that, in patients with HIVE, the CSF viral load should be determined during the first one or two years of HAART. Modification of the antiviral regimen should be considered when clinical and virological studies suggest ongoing CNS viral replication with complete suppression of plasma viremia.

HIV-associated myelopathy

Clinical characteristics

HIV-infected patients may develop a myelopathy without the neuropsychological signs and symptoms of HIVE, labeled HIV-associated myelopathy (HIVM). The histopathological hallmark are vacuoles, most prominent in the cervical and thoracic parts of the spinal cord, and lipid-laden macrophages, hence the term "vacuolar myelopathy" (Petito 1985). These changes are reminiscent of severe combined degeneration and may occur in HIV-negative patients. As HIV viral products have only inconsistently been shown to be part of the lesions, the role of the virus in the disease process is uncertain. Pathogenetically, a disturbance of cobalamin-dependent trans-methylation has been discussed. Like HIVE, HIVM occurs mainly with advanced immunosuppression. Only a proportion of patients with the autoptic finding of vacuolar myelopathy show clinically apparent myelopathy during life (dal Pan 1994).

Diagnostic work-up

A patient may be suspected of having HIVM if he has a spastic-atactic gait, hyperreflexia with positive Babinski sign, disturbance of sphincter control, erectile dysfunction, and slight signs of sensory dysfunction in a glove and stocking distribution. The diagnosis of an independent HIVM should only be made when concomitant cognitive impairment is significantly less prominent than myelopathy. Electrophysiological tests, which show increased latencies of somatosensory evoked potentials (SEP) and motor evoked potentials on transcranial magnetic stimulation, are compatible with the diagnosis. CSF, microbiological and spinal imaging studies are inconspicuous or unspecific, and they have their importance in the exclusion of differential diagnoses, as listed in Table 4. Spinal imaging should include MRI of the cervical and, possibly, the thoracic cord.

Treatment

Early observations of significant improvement with zidovudine monotherapy (Oksenhendler 1990) were later confirmed with HAART. This is why any patient with HIVM should be offered effective HAART. A controlled trial showed L-methionine to bring about improvement of electrophysiological but not clinical parameters.

Table 4: Differential diagnoses of HIV myelopathy and diagnostic work-up

Condition	Adequate diagnostic step (commentary)
Mechanical compression of the bone marrow (cervical myelopathy, disk herniation)	Degenerative changes of the cervical spine
	MRI shows reduced CSF spaces around the spinal cord with hyperintense lesions of the cord parenchyma
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >45/3) (serological findings may be atypical for active neurosyphilis)
CMV myelopathy	CSF (signs of inflammation)
	PCR for CMV in CSF
	Antibody testing in blood and CSF (IgG and antibody index may be increased)
Toxoplasmosis	Contrast enhancing cord lesion on MRI
VZV myelitis	CSF (marked inflammatory signs)
	VZV-specific IgG in blood and CSF (IgM may be absent)
	VZV PCR in CSF
	Mostly antecedent or accompanying cutaneous zoster lesions
HSV myelitis	CSF (inflammatory signs may be absent), HSV PCR in CSF
HTLV-1 (tropical spastic paraparesis)	Travel to the Caribbean, West Africa or East Asia
	Slow evolution of symptoms, bladder dysfunction characteristic, CSF inflammation, HTLV-1 specific antibodies
Severe combined degeneration	Vitamin B12 levels, increased erythrocyte volume
Heredo-degenerative diseases (hereditary spastic paraparesis, adrenoleukodystrophy, Friedreich's ataxia, etc.)	Appropriate tests

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24. Neuromuscular Diseases

Thorsten Rosenkranz and Christian Eggers

Polyneuropathy and Polyradiculopathy

Peripheral neuropathies may complicate all stages of HIV infection. During the early asymptomatic stages peripheral neuropathies are uncommon, but electrodiagnostic testing reveals subclinical evidence of peripheral nerve involvement in about 10 % of cases. In later stages, symptomatic neuropathies occur in some 30-50 % of patients. Neuropathological studies have shown pathological changes with a prevalence approaching 100 % in patients with AIDS.

The neuropathies can be classified as primary HIV-associated or as secondary diseases caused by neurotoxic substances or opportunistic infections. Although neuropathies related to HIV infection have been on the decline since the introduction of HAART, there has been an increase in the prevalence of toxic neuropathies (Authier 2003). Different types of peripheral neuropathies can be distinguished on the basis of when they occur with respect to the stage of HIV disease, and by the clinical course, major symptoms and electrophysiological and neuropathological features.

Clinical features

Acute, inflammatory, demyelinating polyneuropathy (AIDP), Guillain-Barré syndrome (GBS)

AIDP usually occurs at seroconversion or at asymptomatic stages of HIV infection. The typical clinical presentation is that of areflexia, symmetrical ascending weakness and relative sparing of sensory nerve fibers. Involvement of cranial nerves and cervical and thoracic spinal nerves leads to respiratory insufficiency, dysarthria and dysphagia. Parasympathetic and sympathetic nerve involvement may cause life threatening cardiac arrhythmias and severe arterial hypo- or hypertension.

Cerebrospinal fluid (CSF) typically shows a raised concentration of protein caused by the dysfunction of the blood-brain-barrier. In contrast to HIV-negative patients with AIDP, a moderate pleocytosis of up to 50 leucocytes/µl CSF is found in most HIV-positive patients.

The progressive stage is followed by a few days or weeks of stable disease until recovery begins. If secondary axonal damage has occurred, recovery can last up to two years. A persistent disability of varying degrees develops in about 30 %.

Table 1: Polyneuropathies and polyradiculopathies in HIV infection

Type	HIV infection	Clinical features	Findings
Primary HIV-associated polyneuropathies			
Acute, inflammatory, demyelinating poly-neuropathy (Guillain-Barré syndrome, GBS)	Seroconversion, asymptomatic, no or beginning immunosup-pression	Symmetrical weak-ness > sensory loss, areflexia	ENG with demyelinat-ing features, elevated CSF protein and mod-erate CSF-pleocytosis (< 50 c/µl)
Chronic demyelinat-ing inflammatory polyneuropathy (CIDP)	Asymptomatic beginning im-munosuppres-sion, rarely AIDS	Distal and proximal weakness > sensory loss, areflexia	ENG with demyelinat-ing features, elevated CSF protein and mod-erate CSF-pleocytosis (< 50 c/µl)
Vasculitic neuropathy	Asymptomatic no or beginning immunosup-pression, rarely AIDS	Mostly asymmetric, acute loss of function of single nerves, rarely distal symmetrical sensory and motor disturbances	Elevation of ANA, cryo-globulinemia, hepatitis C virus coinfection; vasculitis in nerve bi-opsy but also in mus-cle, kidney and other organs
Neuropathy in diffuse, infiltrative leukocyto-sis syndrome (DILS)	Beginning im-munosuppres-sion	Mostly asymmetrical weakness and sen-sory loss, rarely distal symmetrical distur-bances	Disease resembling Sjögren's syndrome; CD 8 cells > 1200/µl
Distal symmetrical sensory polyneu-ropathy (DSSP)	AIDS or ad-vanced immuno-suppression	Distal symmetrical sensory loss, pares-thesia and pain of the legs	ENG with axonal fea-tures predominantly involving sensory nerves of the legs
Secondary polyneuropathies			
Medication–related toxic neuropathy	Beginning or advanced im-munosuppres-sion	Distal symmetrical sensory loss, pares-thesia and pain of the lower legs	Treatment with DDI, DDC, D4T, vincristine, dapsone
Acute neuromuscular weakness syndrome	Beginning or advanced im-munosuppres-sion	Acute progressive tetraparesis	Lactic acidosis during NRTI treatment, axonal nerve damage, addi-tional myopathy
Mononeuritis multi-plex in CMV-infection or non-Hodgkin lym-phoma	AIDS	Asymmetric, acute loss of function of single nerves	CMV infection of other organs, CMV DNA detection in plasma; non-Hodgkin lymphoma
Polyradiculitis in CMV or M. tuberculosis infection or due to meningeal lymphoma	AIDS	Flaccid paraparesis, sensory loss, bladder dysfunction	CMV or mycobacterial infection at other sites, detection of mycobacte-ria in CSF, malignant cells in CSF

Chronic, inflammatory, demyelinating polyneuropathy (CIDP)

Whereas AIDP is a monophasic, self-limiting disease, the course of CIDP is chronic progressive or relapsing-remitting. Weakness and sensory disturbances commonly develop over several months. In some cases, relapses, incomplete remissions and periods of stable disease alternate with each other.

In CIDP, as in AIDP, the CSF is abnormal with an elevated protein level. A moderate pleocytosis is often found instead of the classical acellularity. The underlying pathological mechanisms of both AIDP and CIDP seem to be macrophage and complement-mediated demyelination. The reason why a chronic persistence of the autoimmune process occurs in CIDP is unknown.

CIDP is a rare complication of seroconversion or the early stages of infection before AIDS.

Vasculitic neuropathy

Necrotizing vasculitis with involvement of peripheral nerves is a rare cause of neuropathy in HIV infection. Most patients develop a mononeuritis multiplex characterized by acute, relapsing dysfunction of individual peripheral nerves. The prognosis of the disease is determined by the involvement of other organs such as heart, kidneys or muscles in the vasculitic process. An immune complex attack associated with Hepatitis C virus infection or cryoglobulins appears to play an essential role in the pathological mechanism.

Diffuse infiltrative lymphocytosis syndrome (DILS)

DILS is a rare cause of distal symmetrical and often painful neuropathy. It resembles Sjögren's syndrome, but has multivisceral infiltration characterized by CD8 hyperlymphocytosis (CD8 cell count >1000/µl). Sicca syndrome with parotidomegaly, lymphadenopathy, splenomegaly, pneumonitis and renal dysfunction may occur in association with axonal neuropathy (Gherardi 1998).

Distal symmetrical sensory polyneuropathy (DSSP)

DSSP is the most common neuropathy in HIV-positive patients and becomes symptomatic in the later stages of infection when the CD4 cell count is at or below 200/µl. The clinical course is predominated by slowly progressive sensory symptoms such as numbness, dys- and paresthesia of feet and lower legs (Table 2). Approximately 30-50 % of patients complain of burning, lacerating or stabbing pain. It mainly involves toes and soles and sometimes makes walking difficult. Leading clinical findings are depressed or absent ankle reflexes, an elevated vibration threshold at toes and ankles and decreased sensitivity to pain and temperature in a stocking distribution, whereas proprioception is usually normal. Weakness and atrophy of intrinsic foot muscles are mild and are not features of the disease. The fingers and hands are rarely involved.

Involvement of the upper legs and trunk, significant weakness of leg muscles or decreasing proprioception are not typical for DSSP and should raise suspicion of other disorders, for instance a conjoined myelopathy. Loss and dysfunction of small sympathetic and parasympathetic nerve fibers may cause postural hypotension, erectile dysfunction, gastroparesis and alterations of skin or nails in many DSSP patients.

Table 2: Clinical features of distal symmetrical sensory polyneuropathy

Numbness, pain, dys- and paresthesia of the feet and lower legs
Decreased or absent deep ankle tendon reflexes
Decreased or absent vibratory sense of the toes and ankles
No or only minimal motor dysfunction
No or only minimal involvement of the hands and arms
Slowly progressive course
Electrodiagnostic studies with features of axonal nerve damage
Autonomic dysfunction: orthostatic hypotension, erectile dysfunction

Medication-related toxic neuropathy

A distal symmetrical sensory peripheral neuropathy occurs in about 10-30 % of patients treated with DDI, D4T or DDC. It is indistinguishable from HIV-induced DSSP on clinical examination or in electrodiagnostic studies. The only difference is in the exposure to neurotoxic nucleoside antiretroviral medication. Brew et al. (Brew 2003) found an elevation of serum lactate in over 90 % of patients with D4T-related neuropathies.

Nucleoside neuropathy develops after a mean of 12–24 weeks of treatment. After withdrawal, there can be a temporary worsening for 2–4 weeks and improvement usually begins after 6–12 weeks. In several cases the restitution remains incomplete. In these cases there may have been an additional pre-existent damage to the peripheral nerves due to the HIV infection.

Subclinical disturbance of peripheral nerve function confirmed by pathological findings in electrodiagnostic studies elevates the risk of developing NRTI-related neuropathy. In the American TORO-1 study, 11 % of patients treated with T-20 (enfurvitide) developed neuropathy versus 5 % in the control group (Lalezari 2003), but the European TORO-2 study did not confirm these results (Lazzarin 2003).

Table 3: Neurotoxic drugs frequently used in HIV medicine

NRTI	ddI, ddC, d4T
Antibiotic	dapsone, metronidazole, isoniazid
Cytotoxic	vincristine

Acute neuromuscular weakness syndrome

In the course of a NRTI-induced lactic acidosis a life threatening tetraparesis resembling AIDP may occur. In most cases axonal peripheral nerve damage was found, but in a few patients demyelination was also detected. In addition, muscle biopsy revealed myositis or mitochondrial myopathy in some cases (Simpson 2004).

Table 4: Diagnostic work-up

Procedure	Findings	Condition
Basic examinations (recommended for all cases)		
Medical history	Drugs	Medication-related toxic PNP
	Opportunistic diseases	Neuropathy associated with CMV infection or lymphoma
	Alcohol abuse	Alcoholic PNP
Neurological examination	Clinical type of PNP (distal symmetrical, mononeuritis multiplex, etc.)	Symptoms not due to myelopathy or myopathy
Electromyography Electroneurography	Confirmation of neuropathy	Symptoms not due to myelopathy or myopathy
	Demyelinating features	AIDP, CIDP
	Axonal features	DSSP, Multiplex Neuropathy, DILS
Blood tests	HbA1c, glucose	Diabetic polyneuropathy
	Vit B12, B1, B6, Fe, ferritin	PNP due to malnutrition or malassimilation
	ANA, cryoglobulins, HCV-serology, circulating immune complexes, ANCA	Vasculitic neuropathy
	TPHA	Neurosyphilis
	CD8 cells > 1200/µl lactate	Neuropathy associated with DILS NRTI-induced toxic neuropathy
	CMV DNA (if CD4 cells < 100/µl)	Mononeuritis multiplex due to CMV-infection
Additional tests (necessary only in particular cases)		
CSF	Elevated total protein	AIDP, CIDP
	Pleocytosis (granulocytes), CMV DNA	Polyradiculitis due to CMV infection
	Lymphoma cells, EBV DNA	Lymphomatous meningitis
	Elevated IgA, acid fast bacilli, mycobacterial DNA	Tuberculous polyradiculitis
Autonomic tests (sympathetic skin reaction, heart rate variability)	Involvement of sympathetic or parasympathetic nerves	Additional autonomic neuropathy
MRI (lumbar spine)	Compression of the cauda equina	Spinal lymphoma Spinal toxoplasmosis
Nerve and muscle biopsy	Necrotizing vasculitis	Vasculitic neuropathy
	Perivascular CD8 infiltration without necrosis	DILS-associated neuropathy

Polyneuropathy and polyradiculopathy due to other diseases

In patients with advanced HIV disease, mononeuritis multiplex may be caused by CMV infection or non-Hodgkin lymphoma. Acute or subacute polyradiculopathies of the cauda equina with rapidly progressive flaccid paraparesis of the legs, bowel dysfunction and sensory disturbances occur in the course of opportunistic infections (CMV, M. tuberculosis) or meningeal non-Hodgkin lymphoma. Other important causes of a polyneuropathy are alcohol abuse, diabetes mellitus, malnutrition in patients with long lasting gastrointestinal diseases, neoplastic diseases or cachexia.

Diagnosis

A diagnosis of neuropathy can usually be made based on medical history and clinical examination. Electrodiagnostic studies may be performed for confirmation and for differentiation from other diseases such as myelopathy. Cerebrospinal fluid analysis may be necessary if there is a suspicion of infection with, for example, CMV or syphilis. Sural nerve and muscle biopsy may only be necessary in atypical cases – for instance painful DSSP with a high CD4 cell count and low viral load and without neurotoxic medication or other risk factors. Table 4 gives some recommendations for practical purposes in clinical practice.

Treatment

Causative treatment options only exist for some of the rare neuropathies or polyradiculopathies. Intravenous immunoglobulins and plasmapheresis have been proved effective in the therapy of AIDP. Corticosteroids are also effective in CIPD. In clinical trials on the treatment of CIDP, no difference in the efficacy of immunoglobulins, plasmapheresis or corticosteroids has been shown. However, an individual patient may just respond to one out of the three procedures. In patients who only respond to higher dosages of corticosteroids, other immunosuppressive agents such as azathioprine, low dose weekly methotrexate or cyclosporin may replace long term steroid therapy. We have seen CIDP patients who were in partial remission after temporary steroid therapy and who have remained stable for years with ART alone.

In medication-related neuropathy the offending agent should be withdrawn. However, replacement of DDI or D4T might be difficult in some cases of multiple drug-resistant HIV infection. In this situation, the reduction in the quality of life by neuropathic symptoms must be balanced against the risk of deterioration of immunological and viral parameters. A small open-label study with 2 x 3500 mg L-acetyl-carnitine resulted in peripheral nerve regeneration, demonstrated in skin biopsies, and in improvement of neuropathic symptoms induced by neurotoxic NRTI (Hart 2004).

A causative treatment for DSSP does not exist. ART might improve the function of sensory nerves in a few cases, and therefore starting ART or optimizing a current ART should be considered in newly diagnosed DSSP. In most cases the neuropathic symptoms still persist.

Symptomatic treatment is directed at irritative symptoms such as pain and paresthesia. It is not effective against deficits of nerve function including sensory loss or weakness.

Table 5: Causative treatment of polyneuropathies and polyradiculopathies

Condition	Treatment
AIDP	Intravenous immunoglobulins 0.4 g/kg daily for 5 days *or:* plasmapheresis (5 x in 7-10 days)
CIDP	Intravenous immunoglobulins 0.4 g/kg daily for 5 days *or:* plasmapheresis (5 x in 7-10 days) *or:* prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12–16 weeks
Vasculitic neuropathy	Prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12–16 weeks
Neuropathy due to DILS	Start or improvement of ART plus prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12–16 weeks
Distal symmetrical sensory polyneuropathy	A causative treatment is not known, ART may improve nerve function, for symptomatic treatment. See table 6
Medication–related toxic neuropathy	Withdrawal of the neurotoxic substances, if possible.
Mononeuritis multiplex or polyradiculitis due to CMV-infection	Intravenous foscarnet 2 x 90 mg/kg daily plus intravenous ganciclovir 2 x 5 mg/kg daily.
Lymphomatous meningitis	Start or improvement of ART plus intrathecal methotrexate (intraventricular shunt or lumbar puncture) 12-15 mg 2 x/weekly until CSF is free of malignant cells, subsequently 1 x/week for 4 weeks and subsequently 1 x/month plus 15 mg oral folinate after each injection plus systemic treatment of lymphoma (see chapter "Malignant Lymphoma")
Polyradiculitis due to infection with M. tuberculosis	Treat tuberculosis (see chapter "OIs")

The agents listed in table 6 are recommended because they have proved useful in daily practice and because they interfere only slightly and in a predictable way with ART. A controlled study showed that lamotrigine was effective in reducing the symptoms of neurotoxic neuropathy (Simpson 2003). The drug is well tolerated if one adheres to the slow dose escalation regimen and stops treatment or reduces the dose when a skin reaction occurs. In a small study, gabapentin was shown to be effective in reducing DSSP-induced pain (Hahn 2004). The advantages of this substance are good tolerability and lack of interference with ART.

The tricyclic antidepressants amitriptyline and nortriptyline both have significant anticholinergic side effects. The dose necessary for reducing neuropathic pain is in the same range as for treating depression and many patients do not tolerate these dosages. However, lower dosages have proved ineffective in DSSP. Nortriptyline has no sedative side effects. We use this substance with good success rates, although clinical trials for its use in HIV-associated neuropathy are lacking. The anticonvulsant carbamazepine is widely used for the treatment of neuropathic pain. However, it induces some enzymes of the CYP450 system and interferes significantly with ART. Thus its use in HIV medicine is very limited. Pregabalin, an anticonvulsant drug similar to gabapentin, has recently been approved for the treatment of painful neuropathy. It effectively relieves pain in studies of patients with painful

diabetic peripheral neuropathy. Like gabapentin, it does not interfere with ART and is well tolerated. We are successfully treating an increasing number of patients with DSSP and neurotoxic neuropathy with this new substance.

Table 6: Symptomatic treatment of painful neuropathy

	Treatment	Adverse effects
Step 1:	Physical therapy, supporting measures (wide shoes, etc.),	Rarely allergy
	lidocaine 5 % gel several times a day	
Step 2:	Temporary trial of 3-4 x 1000 mg paracetamol *or* 2-3 x 50 mg diclofenac *or* 4 x 40 drops novaminsulfone for 10-14 days	Nausea, vomiting, allergy (rarely)
Step 3:	Gabapentin 300 mg at night, dose escalation of 300 mg a day every third day up to a maximum dose of 3x1200 mg *or*	Sedation, nausea, dizziness, rarely pancreatitis
	Pregabalin 2x75 mg for 1 week, dose escalation to 2x150 in the 2nd week, possible escalation up to 2x300 mg *or*	Nausea, vomiting, diarrhea, allergic drug rash
	Lamotrigine 25 mg at night, dose escalation of 25 mg every 5 days up to 300 mg *or*	Allergy, sedation, cephalgia, nausea
	Amitriptyline 25 mg at night, dose escalation of 10-25 mg every 2-3 days up to 3 x 50 mg *or*	Sedation, orthostatic hypotension, constipation, dizziness, dry mouth, dysrhythmia, retention of urine, caveat: glaucoma
	Nortriptyline 25 mg in the mornings, dose escalation of 25 mg every 2-3 days up to 2-3 x 50 mg	Orthostatic hypotension, constipation, dizziness, dry mouth, dysrhythmia, retention of urine, caveat: glaucoma
Step 4:	Flupirtine 3 x 100, dose escalation up to 3 x 600 mg *or*	Sedation, constipation, nausea
	Retarded morphine 2 x 10 mg gradual escalation up to 2 x 200 mg	Sedation, constipation, nausea
General practice	Proceed one step if symptoms persist.	
	Substances within step 3 may be combined (for instance an anticonvulsant and an antidepressant), substances of step 3 and step 4 may also be combined (for instance flupirtine and an anticonvulsant).	
	If a rapid relief of symptoms is necessary, treatment should be started with step 4 substances and a low dose step 3 drug should simultaneously be started with slow escalation.	
	The slower the escalation the greater the possibility of reaching an effective dosage.	

Potent opioids may be used to manage moderate or severe pain if a slow dose escalation of an antidepressant or anticonvulsant is not possible and an immediate analgesic effect is desired (Sindrup 1999). Even in cases of substituted or non-substituted drug abuse, opioids should be used (Breitbart 1997). Sometimes, the dosage of methadone must only be moderately increased for a sufficient analgesic effect.

Myopathy

Myopathies occur in 1-2 % of all HIV patients. They may appear at any stage of the disease. Table 7 gives a synopsis of the most important types of myopathy in HIV infection.

Polymyositis mediated by cytotoxic T cells is the most common HIV-associated myopathy. AZT-induced myopathy occurs very infrequently with the AZT dosages used today. Some substances commonly used in HIV medicine (DDI, co-trimoxazole, pentamidine, sulfadiazine, lipid lowering drugs) may rarely cause acute rhabdomyolysis with tetraparesis and marked elevation of serum CK levels. Notably, PIs raise the serum concentration of statins increasing the risk of statin-induced myopathy and rhabdomyolysis (Hare 2002).

Clinical features

Myopathy in HIV infection usually presents with exercise-induced myalgia of proximal muscles followed by slowly progressive, symmetrical weakness and atrophy of proximal muscles. Limb girdle muscles are most commonly involved, but distal muscles and muscles of trunk, neck, face or throat may also be affected.

Diagnosis

Myalgia, fatigue and elevated serum CK levels are frequently found in HIV infection. But these unspecific symptoms and signs on their own do not warrant the diagnosis of myopathy. The diagnosis of probable myopathy requires weakness, muscle atrophy or myopathic features demonstrated by electromyography. A muscle biopsy confirms the diagnosis and may give some additional clues to the classification and pathogenesis of the muscle disease.

Table 7: Myopathies in HIV infection

Primary HIV-associated	Secondary
Polymyositis	AZT myopathy
Nemaline (rod body) myopathy	Vasculitic myopathy
Vacuolar myopathy	Lymphomatous muscle infiltration
Inclusion body myositis	Infectious myositis
	Medication-related toxic rhabdomyolysis

Treatment

Moderate myalgia may respond to non-steroidal anti-inflammatory drugs.

Prednisone (100 mg daily for 3-4 weeks, subsequent tapering) or intravenous immunoglobulin (0.4 g/kg for 5 days) have been shown to be effective in treatment of polymyositis (Espinoza 1991, Viard 1992).

The treatment of AZT myopathy is cessation of the drug. Myalgia usually resolves within 1-2 weeks. If symptoms persist for 4-6 weeks, prednisone as described above may be effective.

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25. HIV and Psychiatric Disorders

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Psychiatric disorders occur frequently in HIV-infected patients but the reported prevalence rates differ considerably, depending on the stage of infection and study population. Fact is, though, that there are multiple factors that can have an impact on comorbid psychiatric illness: psychiatric disorders, e.g. substance abuse, can be an independent risk factor for HIV infection. Furthermore, there are the neuropathological effects of the virus itself, and there is evidence that the infection of microglia leads to neuronal damage due to the excretion of neurotoxins. Additionally, opportunistic infections and some of the antiretroviral drugs may cause psychiatric symptoms.

Apart from the affection of the patient's well-being, psychiatric disorders may lead to problems in antiretroviral therapy: adherence to antiretroviral medication becomes poorer. Therefore, early diagnosis and therapy of psychiatric disorders are of vital importance for HIV-positive individuals (Angelino 2001).

Major depression

Major depression is the most frequently occurring psychiatric disorder in HIV patients. Reports on prevalence rates differ substantially and reach up to 40 % (Angelino 2001). Major depression is a severe illness with serious complications: up to 15-20 % of all patients with recurrent depressive episodes commit suicide. Further common complications are physical, social or role model function impairment (Low-Beer 2000).

Major depression interferes with all aspects of being and may have a severe impact on quality of life. It is characterized by depressed mood, decreased energy and loss of interest. Patients tend to be unable to experience joy or satisfaction in activities that would usually generate these feelings; they may feel ill, lack energy and experience a sense of doom. Also feelings of guilt, a lack of self-esteem and self-reproach are frequent (Angelino 2001). Additionally, neurovegetative symptoms such as loss of appetite and sleep disturbances with so-called early morning wakening or fatigue are common. Furthermore, depressed patients describe somatic symptoms such as pain or vertigo. Often the severity of symptoms changes during the day with greater severity in the morning and relief in the evening. Poor concentration and cognitive impairment, the so-called pseudodementia in depression may also occur. The individual presentation of these symptoms varies notably and may therefore make diagnosis difficult.

Two simple questions, though, may provide valuable hints:

1. During the past month have you often been bothered by feeling down, depressed or hopeless?

2. During the past month have you often been bothered by little interest or pleasure in doing things?

These two questions are being recommended by the U.S. Preventive Services Task Force for screening for depression in primary care. If at least one of the two questions is confirmed by the patient, further diagnostic testing is recommended (Pignone 2002). The following criteria of ICD-10 should be explored when making a diagnosis of depression:

a) *Pervasive low mood (see above)*

b) *Loss of interest and enjoyment (see above)*

c) *Reduced energy, diminished activity*

d) Disturbed or increased sleep

e) Diminished or increased appetite

f) Poor concentration and attention

g) Poor self-esteem and self-confidence

h) Ideas of guilt and unworthiness

i) Psychomotor retardation or agitation

j) Ideas or acts of self-harm or suicide

Therapy is indicated if symptoms last for more than two weeks and when at least two of the first three symptoms in addition to at least one of the other symptoms are reported by the patient.

All of these symptoms might occur as a reaction to a stressful life event or sad circumstances. In these cases treatment is not immediately necessary. If the symptoms persist for an unreasonable period of time – more than a couple weeks – a depressive episode might have been triggered. This should then be treated accordingly (Ebert 2001). Aggressive treatment is also obviously necessary in suicidality. HIV-positive patients are more at risk than the general population. The highest rate of suicidal thoughts and attempts occur approximately one to two years after diagnosis of HIV infection. Altogether, though, the rate of suicide among HIV patients has dropped recently – probably due to the improvement of therapy since the beginning of the HAART era (Einsiedel 2001).

Treatment

Treatment of depression is based on two principles: medication and psychotherapy. Since we cannot discuss different aspects of psychotherapy in this article, we will focus on pharmacological treatment. In general, treatment of depressed HIV-infected patients does not differ from that of other patients. Medication must always be part of a therapeutic regimen. It should consist of acute phase therapy, maintenance therapy and prophylaxis of a relapse of depression. The goal of treatment should be the complete remission of depressive symptoms. After alleviation, treatment should be continued for at least six months. At the end of treatment, medication should be reduced slowly over a period of weeks.

Once antidepressant medication has been initiated, it may take two weeks for patients to experience a benefit. Side effects, however, might occur earlier, and patients should be informed about this. A non-response to treatment is considered when – given a standard dose of medication or therapeutic serum levels have been

attained – there is no relevant benefit for the patient after four to six weeks (Benkert 2003).

At such time, a switch to an antidepressant of another class should be considered. Another period of two to four weeks latency for the therapeutic effect has to be taken into account. Alternatively, an augmentation strategy – added medication with e.g. lithium or thyroid preparations – could be started, since effects might be seen earlier. Sometimes the combination of two antidepressants might bring relief. These strategies should only be provided by experienced therapists. Without thorough experience in treating psychiatric disorders, one should concentrate on three to four antidepressant drugs. In this way, side effects and therapeutic benefits can be more easily observed.

The choice of the appropriate antidepressant can be based on the side effect profile, e.g. sedating vs. activating. Previous therapies are important too: a drug that previously had beneficial results in a patient will be effective in this patient again (Ebert 2001).

Selective Serotonin (5-HT) Re-uptake Inhibitors

So-called serotonin (5-HT) re-uptake inhibitors (SSRI) are considered to be first-line medication in depressed HIV-positive patients since they are effective and well tolerated. Starting with low doses reduces the probability of adverse effects.

Recently, there have been reports on SSRI medication precipitating suicide, especially in children and adolescents. When looking at available data though, these findings are not consistent and are not easily transferable to adults. In most countries, population suicide rates have fallen in the last years even though significantly more antidepressants – and especially SSRIs – have been prescribed. Furthermore, it is difficult to show effects of medication on suicide since suicide is rare, even among depressed patients, and it is therefore difficult, especially in short clinical trials, to assess the risks of medication-related suicides statistically.

Overall, the risk of suicide for adults does not seem to be increased by medication with SSRIs. However, long-term studies are required to gain further information on benefits and risks (Gunnel 2004). Nonetheless, doctors should closely monitor patients with psychiatric disorders, regardless of their medication, for suicide risk, and, if indicated, ask for suicidal thoughts or self-harm in order to react promptly.

Table 1: Selective Serotonin (5-HT) Re-uptake Inhibitors (SSRI) *

Drug (Trade name™)	Dosage / day (generally once daily administration)	a) Interactions with HAART b) Evaluation / comments c) Selected side effects
Citalopram (Cipramil™, Se-pram™)	20 mg in the morning, therapeutic dose is 20-60 mg	a) Lopinavir/r, ritonavir increase citalopram levels b) effective, well tolerated, non-sedating antidepressant c) Initially diarrhea, nausea, decreased sexual arousal / erection
Fluoxetine (e. g. Fluctin™, Pro-zac™)	10 mg in the morning for 2-3 days, then 20 mg	a) Increased levels of amprenavir, de-lavirdine, efavirenz, indinavir, lopinavir/r, nelfinavir, ritonavir and saquinavir. Nevirapine decreases fluoxetine levels b) Activating; most clinical trials conducted with fluoxetine c) see above
Fluvoxamine (Fevarin™, Fluvox-amin-neuraxpharm™)	50 mg in the morning, after 3-4 days increase dose to 100-200 mg	a) Increased levels of amprenavir, de-lavirdine, efavirenz, indinavir, lopinavir/r, nelfinavir, ritonavir and saquinavir. Nevirapine decreases fluoxetine levels b) Potent inhibitor of CYP1A2 c) see above
Paroxetine (Seroxat™, Tagonis™)	10 mg in the morning for 2-3 days, therapeutic dose is 20 mg	a) Lopinavir/r, ritonavir increase paroxetine levels b) Somewhat sedating, administration at bedtime if possible c) see above
Sertraline (Gladem™, Zoloft™)	25-50 mg in the morning, lowest effective dose 50 mg, maximum 150 mg	a) Lopinavir/r, ritonavir increase sertraline levels b) Non-sedating. In agitation, akathisia, or insomnia, combination with benzodiazepine possible – applicable for all SSRIs c) see above

* Note: SSRIs should not be combined with monoamine oxidase inhibitors (MAOI) e.g. Moclobemid (Aurorix™). Adjustment of dosage is required in renal or hepatic disorder. (Angelino 2001, Benkert 2001, Einsiedel 2001)

Tricyclic antidepressants

Tricyclic antidepressants (TCAs) – named after their chemical structure which contains three rings – are effective and, in HIV patients, well studied agents. However, side effects are more frequent in this class of antidepressants. Their anticholinergic effects need to be pointed out: they are contraindicated in patients with urinary retention and closed-angle glaucoma and they should be avoided in patients with bundle branch blocks. Furthermore, TCAs are easier to under- or overdose than SSRIs. Serum levels should therefore be obtained if possible.

Table 2: Tricyclic antidepressants

Drug (Trade name™)	Dosage/day	a) Interactions with HAART b) Evaluation/comments c) Selected side effects
Amitriptyline (e. g. Saroten™, Laroxyl™, Novo-protect™, Amineu-rin™)	Initially 2-3 x 25 mg usual therapeutic dose 3 x 50 mg or 2 x 75 mg	a) Lopinavir/r, ritonavir increase amitriptyline levels b) Promotes sleep. Weight gain, constipation – might be desired side effects c) Delirious syndrome when fast dose increase
Clomipramine (Anafranil™, Hydi-phen™)	2-3 x 25 mg for three days usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase clomipramine levels b) Initially possible agitation, combination with benzodiazepine possible, also see above c) Effective in chronic pain
Doxepin (Aponal™, Sin-quan™)	Initially 3 x 25 mg usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase doxepin levels b) see above c) Often orthostasis
Imipramine (Tofranil™, Pryleugan™)	2-3 x 25 mg for three days usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase imipramine levels b) see above c) Especially at the start of therapy anticholinergic adverse effects

For further reading see Angelino 2001, Benkert 2001, Einsiedel 2001

Other drugs / therapies

There are numerous other antidepressants but at the time being there is not much data on their use in HIV-infected patients. These include the noradrenergic and serotonergic drug mirtazapine (unlike SSRIs and tricyclic agents, there are so far no reports on sexual dysfunction with this drug) and the combined serotonin-noradrenaline re-uptake inhibitor venlafaxine. The selective noradrenaline re-uptake inhibitor reboxetine seems to be interesting in the therapy of HIV-infected patients since it is not metabolized via cytochrome P450 (CYP450) (Carvalhal 2003).

Table 3: Other antidepressants

Drug (Trade name)	Dosage / day	a) Interactions with HAART b) Evaluation / comments c) Selected side effects
Mirtazapine (Remeron™)	Initially 15 mg at bedtime usual therapeutic dose 30-45 mg	a) not known b) Sedating, promotes sleep, weight gain no sexual dysfunction c) Cave!: not in leukopenia!
Reboxetine (Edronax™)	Initially 2 to 4 mg maintenance therapy 8 mg to 12 mg	a) not known b) not sedating c) Dry mouth, insomnia, sweating, tremor and urinary retention. Cave!: Dose reduction (2 x 2 mg) in renal or hepatic insufficiency
Venlafaxine (Trevilor™)	Initially 37.5 mg in the morning administer twice daily maintenance therapy 75 to 375 mg/day	a) Lopinavir-ritonavir, ritonavir increase venlafaxine levels b) Extended release formulation with lesser side effects. Effective in anxiety c) Initially high rates of gastrointestinal side effects. RR ↑, allergic skin reactions, delayed ejaculation

For further reading see Angelino 2001, Benkert 2003

New formulations of existing antidepressants are being developed: intravenous formulations with a faster onset of antidepressant action or a once-weekly administered SSRI. (Norman 2004). Furthermore, single enantiomers have been introduced in several countries, e.g. the S-enantiomer of the SSRI citalopram, escitalopram. It is more than twice as potent at inhibiting serotonin uptake and is supposed to maintain therapeutic efficacy at a lower effective dosage. Pharmacokinetic interaction with ritonavir – a CYP3A4 substrate and prototype CYP3A4 inhibitor – which may potentially affect plasma concentrations of escitalopram, was not clinically significant (Gutierrez 2003). None of these agents, however, will be a sovereign remedy, and one should, especially when experience in psychiatric care is limited, only use a few drugs and know them well instead of trying all available substances.

In addition to the above, herbal medicines are also in use, even though there is an ongoing discussion about their effectiveness. There were great expectations especially about St. John's wort – a herbal substance without serious adverse effects – when clinical trials demonstrated an antidepressant effect in mild to moderate depression (Linde 1996). Unfortunately hopes have fallen somewhat since St. John's wort did not show an advantage above placebo in further clinical trials (Hypericum Depression Trial Study Group 2002). Remarkably enough, though, the SSRI in this trial was not very effective either and merely showed a positive trend above placebo in effectiveness.

In addition to the above, there are more therapeutic options aside from medication, e.g. controlled sleep withdrawal, where the patient has to stay awake throughout the night. Following this procedure, there is a significant reduction of symptoms the next day in about one half of treated patients– but only until the next night's sleep. Repeated sleep withdrawal, though, might reduce the duration of a depressive episode. Phototherapy, especially in seasonal depression, and electroconvulsive therapy carried out in specialized centers for non-responding patients, are therapeutic options too. There are no data on these therapies in HIV patients. Evidence does exist, however, from small clinical trials for a therapeutic effect of exercise in HIV patients (Neidig 2003). Three times a week jogging for half an hour is a good antidepressant and a therapeutic chance that is possibly not tried often enough.

Psychotic disorders

Psychotic means the occurrence of delusions or prominent hallucinations, and typically the patient has no insight into their pathologic character. The prevalence of psychotic disorders in individuals with HIV or AIDS is rather unclear: rates vary between 0.2 and 15 % (Sewell 1996). Basically, psychotic disorders can be classified into two different forms:

Primary psychotic disorders

Psychosis that occurs independently of infection with HIV is to be seen as a comorbid condition. Diseases such as schizophrenia, schizophreniform disorder and brief psychotic disorder can be classified into this group. Typical symptoms are delusions, hallucinations, disorganized speech (e.g. frequent derailment or incoherence) or grossly disorganized or catatonic behavior. Etiopathogenetically, a biopsychosocial concept, the vulnerability-stress-coping model, is assumed. It is thought that genetic and psychosocial factors determine a predisposition or an increased vulnerability for psychotic decompensation.

Therefore, an infection with a neuropathological virus such as HIV could trigger a pre-existing psychosis (Einsiedel 2001).

Secondary psychotic disorders

Characteristic symptoms of a secondary psychotic disorder are prominent hallucinations or delusions. They are caused by an organic disorder of the central nervous system (CNS) as a consequence of a general medical condition. In HIV patients this could, for example, be an opportunistic infection, cerebral lymphoma or HIV en-

cephalopathy. In addition to that, psychotic symptoms can be caused by medications or drug-drug interactions. The occurring delusional themes are numerous, including somatic delusions, delusions of grandeur, religious delusions, and, most frequently, paranoia or persecutory delusions. Diseases that affect subcortical structures or the temporal lobes are more frequently associated with delusions than others. In hallucinations, every sensory quality (auditory, visual, olfactory, gustatory or tactile) might be affected.

Patients with a previously undiagnosed general medical condition, such as HIV infection, might develop an acute psychiatric condition due, for example, to HIV encephalopathy, brain damage from an opportunistic CNS infection such as toxoplasmosis, neoplasms involving the CNS, or metabolic dysfunction. In all acute psychotic disorders, a magnetic resonance image of the brain (more sensitive than computed tomography) and examination of cerebral spinal fluid should therefore be carried out as soon as possible. HIV infection does not show any specific psychopathological findings (Röttgers 2000).

Treatment

While in organic psychosis, the causative general medical condition must be treated first, in primary psychosis, according to its multifactorial etiology, therapy should consist of a combination of pharmacological, psychotherapeutic, psychoeducational and sociopsychiatric intervention.

Symptomatic treatment with neuroleptics is initially the most important line of treatment in the acute phase of primary psychotic disorders. In principle, the pharmacological treatment of HIV patients does not differ much from that of other populations, but it should be started at low doses and titrated cautiously (Farber 2002), since a dysfunction of the blood brain barrier and consequently a higher rate of medication side effects is to be expected: start low, go slow!

In acute psychotic disorder, regardless of the etiology, the use of a conventional antipsychotic agent, e.g. haloperidol 5 mg PO or IM, is usually successful. For additional sedation in cases with more severe agitation, comedication with a benzodiazepine is possible. When aggressive behavior is present, diazepam 5 to 10 mg PO or IM is a good choice; if fear or anxiety is the leading symptom, lorazepam up to 2.5 mg is indicated. In the further course of treatment, change to an atypical antipsychotic agent (see below) is recommended.

In less acute symptomatic psychotic disorders and in primary comorbid psychosis the use of atypical antipsychotic agents is again the treatment of choice, due to various reasons: atypical antipsychotic agents cause significantly less extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) than typical antipsychotic drugs. Furthermore, they might provide an advantage in non-responding patients and in the treatment of negative symptoms: *asociality*, the withdrawal from relationships; *avolition*, the loss of initiative and drive; *affective flattening* or inappropriateness; *alogia*, a poverty of speech production and content; *anhedonia*, difficulty experiencing pleasure. These are often the most debilitating symptoms in psychotic disorders. Because of the lower risk of developing EPS and TD – for which HIV-infected patients are more susceptible than others – treatment with atypical antipsychotic agents might improve adherence to psychopharmacological treatment

too. In case of insufficient effectiveness, a different atypical antipsychotic agent should be selected after approximately four weeks.

Table 4: Atypical antipsychotic agents

Drug (Trade name)	Dosage/day	a) Interactions with HAART b) Evaluation/comments c) Selected side effects
Amisulpirid (Solian™)	twice daily positive symptoms: 400-800 mg negative symptoms: 50-300 mg maintenance therapy: 200-400 mg	a) No interaction to be expected b) Nearly complete renal elimination, poses advantage in patients with liver damage c) EPS in doses > 400 mg/d possible, usually not severe
Clozapine (Leponex™)	prescribing doctor needs to register at manufacturers start with 6.25-12.5 mg, increase every 1-2 days by 25 mg to max. 600 mg. maintenance therapy: 100-400 mg	a) Because of risk of agranulocytosis (1-2 %) in HIV patients not recommended b) Atypical antipsychotic agent with significance for non-responding schizophrenia and in patients with non-tolerable EPS c) Agranulocytosis; seizures; sedation; weight gain and hyperglycemia
Olanzapine (Zyprexa™)	starting dose 5 mg h.s. maintenance 5-20 mg when sedation during daytime is wanted: two to three doses/day	a) No interaction with PIs b) Good antipsychotic effect. Few EPS when < 20 mg. Trials with HIV patients available. Side effects, weight gain (depending on dosage) and/or sedation might be favorable. c) In 1-10 %: EPS (e.g. akathisia), drowsiness, orthostasis, liver enzymes↑. Cave!: hyperglycemia possible
Quetiapine (Seroquel™)	start with 25 mg slow titration to 300 to 450 mg divided into two doses/day	a) Cave!: Contraindication in combination with ritonavir, macrolide antibiotics and ketoconazole. b) No trials with HIV patients published. c) Common (>10 %) sedation, drowsiness. Occasionally orthostasis, liver enzymes↑, weight gain. Cave!: Leukopenia
Risperidone (Risperdal™)	slow titration over one week start with 0.5-2 mg maintenance dose: 4-6 mg divided into two doses/day in renal or hepatic insufficiency do not exceed 4 mg/day !	a) NRTIs increase risperidone plasma level. b) Good antipsychotic effectiveness. Dose dependent EPS: seldom when ≤ 6 mg. Trials with HIV patients published. No influence on blood count, no increase in seizures. First atypical antipsychotic agent available in long acting formulation (twice weekly). c) Orthostasis, especially in the beginning and at high doses – titrate slowly!

Table 4: Atypical antipsychotic agents

Drug (Trade name)	Dosage/day	a) Interactions with HAART b) Evaluation/comments c) Selected side effects
Ziprasidone (Zeldox™)	start with 2 x 20 mg Maximum dose is 2 x 80 mg IM administration possible.	a) Not examined b) So far no trials with HIV population. Contraindicated in patients with long QT interval, cardiac arrhythmias, myocardial infarction. EPS rates not higher than in placebo. Only minimal weight gain. c) Cave: QTc prolongation! > 1 %: drowsiness, hypotension, sedation

Acute treatment in psychiatric emergency

Most important: de-escalation by "talking down" – this includes measures such as staying in contact with the patient, taking him seriously and adopting a non-confrontational position. Should the use of restraints be necessary, stay calm but act firmly. Always leave the patient the chance to correct inappropriate behavior and always use the least possible restrictive method of restraint.

Table 5: Psychiatric emergency (Benkert 2003; Currier 2004)

Diagnosis	Psychopharmacological treatment
Agitation in acute psychosis Agitation and aggression in mania Acute intoxication with psychoactive drug	Haloperidol 5-10 mg PO or IM, may be repeated after 30 min, maximal 50 mg in the first 24 hrs. Cave: EPS – then 2.5-5 mg (1/2-1 Amp.) biperidene (Akinethon™) IV or IM. **plus** oral or IV application of 2 mg lorazepam, when panic is predominant; maximum dose 10 mg / day (inpatient) **or** diazepam, when stronger sedation is needed; in aggressive patients: 10 mg PO, IM or slowly IV. Repetition after 30 min possible. Maximum dose 40-60 mg parenteral or 60-80 mg oral (inpatient). Cave: hypotension, respiratory depression **alternatively** oral treatment with 2 mg of risperidone plus 2 mg of lorazepam (Currier 2004)
Delirium due to general medical condition (e.g. infection, exsiccosis, electrolyte metabolism disorder)	treatment of general medical condition if necessary antipsychotic agent e.g. melperone 50-100 mg for sedation or haloperidol (especially in psychotic symptoms) 2-5 mg PO or IM.
Drug-induced delirium (e.g. antidepressants, antibiotics, rarely efavirenz or others)	change or reduce causative substance in accordance to severity of symptoms, if necessary antipsychotic agent e.g. melperone 50-100 mg for sedation or haloperidol 2-5 mg PO or IM in hospitalized patients if necessary clomethiazole 2 capsules every 2 hours, maximum dose 20 capsules/day. Cave: respiratory depression, hypersecretion; strictly for inpatients only!

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26.   HIV and Wish for Parenthood

Ulrike Sonnenberg-Schwan, Carole Gilling-Smith, Michael Weigel

Introduction

Since 1996, the optimization of antiretroviral therapy has led to great improvements in both the quality of life and life expectancy of people living with HIV/AIDS, at least in countries where HAART is widely available. Nowadays, HIV infection can be seen as a chronic, but treatable disease. This "normalization" has encouraged many patients, male and female, to include perspectives in the planning of their lives that had previously been seen as being impossible to fulfil. Planning a family is often among these perspectives. Procreation without risk, or at a very low risk level of infection for the uninfected partner or prospective child, is now an option for couples in whom one or both partners are HIV-infected. The low materno-fetal transmission rate that can be achieved today has added to the acceptance of planned motherhood in seropositive women. Ethical and legal controversies have also been overcome in many European countries.

Options for HIV-affected couples to realize the wish for parenthood theoretically vary from unprotected intercourse to several techniques of assisted reproduction, donor insemination or adoption. Usually, couples are advised against unprotected intercourse, as the priority is to prevent infection in the uninfected partner or child.

Transmission rates for unprotected heterosexual intercourse range from 1/1000 per contact (male to female) to <1/1000 (female to male). These numbers are hardly useful in individual counseling situations. They can be much higher in patients with high viral load or in the presence of other sexually transmittable diseases. Viral load in semen or genital secretions does not always correlate with that in plasma, and HIV can be detected in semen even when viral load in blood plasma is below the limit of detection. In other words, couples should not risk unprotected intercourse on the basis of the infected partner having an undetectable load. Consistent use of condoms can decrease the transmission risk in heterosexual relationships by 85% (Davis 1999) and abstention from condom use, restricted to the time of ovulation, has been proposed as an option for discordant couples. Mandelbrot et al. (1997) reported a transmission rate of 4 % in 92 couples using carefully timed, but unprotected intercourse to conceive. Although infections were restricted to couples who also reported inconsistent use of condoms outside the fertile period, available data cannot support this as a safe option for couples.

Donor insemination is an alternative safe option for a small number of couples, but due to legal restrictions it is only offered in a minority of centers. In the UK, for example, there are no restrictions on donor insemination, whereas in Germany the access is limited. In addition, most couples wish for a child that is the biological offspring of both parents. Adoption in many countries is merely a theoretical option: HIV infection of one partner usually renders this procedure very difficult, or even impossible in most countries (e.g. in Germany).

To minimize the risk of HIV transmission, the following options are recommended:

- Self-insemination or assisted reproduction in case of infection in the female partner
- Assisted reproduction with processed sperm in case of infection in the male partner

In several – mostly European – countries, reproductive assistance for couples affected by HIV has been set up in the past few years, and access for these couples has now been established by law in France. Equal access for HIV-positive women and men is granted in most, but not all of these countries.

The safety of sperm washing

The technique of processing sperm from HIV-positive men prior to the insemination of their HIV-negative partners was first published by Semprini et al. in 1992. The first inseminations with sperm, washed free of HIV, were carried out in Italy and Germany as early as 1989 and 1991, respectively. Up to mid 2003, more than 1,800 couples had been treated in about 4,500 cycles, applying various techniques of assisted reproduction. More than 500 children have been born with no single seroconversion reported in the centers closely following the protocol of washing and testing the sperm prior to assisted reproductive techniques.

Native ejaculate mainly consists of three fractions: spermatozoa, seminal plasma and nuclear concomitant cells. HIV progenome and virus has so far been detected in the seminal plasma, the concomitant cells, and occasionally in immobile spermatozoa. Several studies have indicated that viable, motile spermatozoa are not likely to be a target for HIV infection (Weigel 1999, Pena 2003, Gilling-Smith 2003).

Motile spermatozoa can be isolated by standardized preparation techniques. After separation of the spermatozoa from plasma fractions and NSC (non-spermatozoa cells), the spermatozoa are washed twice with culture medium and resuspended in fresh culture medium. Incubation for 20 – 60 minutes allows motile sperm to "swim-up" to the supernatant. To be more certain that it is not contaminated with viral particles, an aliquot of the sample should be tested for HIV nucleic acid using highly sensitive detection methods (Weigel 2001; Gilling-Smith 2003). Depending on the method, the lowest limit of detection is 10 cp/ml. Since HIV could, theoretically, remain undetected, sperm washing is currently regarded as a very effective risk reduction, but not a risk-free method.

Most of the European centers that offer assisted reproduction to HIV-discordant couples, are part of the CREATHE-network, which aims to optimize treatment and safety of the methods as well as to compile an extensive database. There are high hopes that soon sufficient clinical cases can be reported to demonstrate the safety and reliability of sperm washing.

Pre-conceptual counseling

The initial counseling of the couple should not only consider extensive information on all reproductive options available, diagnostics and prerequisites for reproductive treatment, but also the psychosocial situation of the couple. Important issues to discuss are the financial situation, current psychosocial problems, the importance of a network of social support from family or friends, and planning and perspectives

about the future as a family, including possible disability or death of one of the partners. A supporting, empathic and accepting mode of counseling is advisable, as many couples feel distress if their motives for, or entitlement to, parenthood are questioned. In many cases, it is necessary to discuss the risks of unprotected intercourse, not only during reproductive treatment but at all times. In cases where professional psychosocial services are not integrated, co-operation with organizations in the AIDS counseling system or self-help groups is advisable.

Possible stress occurring during the work-up and treatment of the couple should be discussed as well as doubts or fears of the couple. Many couples for example are afraid that their test results might indicate that parenthood is impossible.

If the male partner is HIV-infected, the couple need to know that the risk of HIV infection can be minimized, but not excluded. HIV-positive women have to be informed about the risks of vertical transmission and the necessary steps to avoid it. In any case, couples should know that even using state-of-the-art reproductive techniques, achieving a pregnancy cannot be guaranteed.

Table 1: Pre-treatment investigations

General	Comprehensive medical and psycho-social history
Female examination	Gynecological examination, sonography, tubal patency test, basal temperature
	if necessary, endocrine profile, cervical smear (cytology, microbiology)
	(UK: 2-5 FSH/LH and mid-luteal progesterone to evaluate female fertility)
	Serology (rubella, toxoplasmosis, syphilis, CMV, HBV, HCV)
HIV-specific assessments	HIV-associated and accompanying symptoms
	Blood glucose, GOT, GPT, GGT, complete blood count
	Ultra-sensitive HIV-PCR, CD4, CD8 cell counts
	HIV antibody test of the partner
Male examination	Spermiogram, semen culture
	Serology (HBV, HCV)

Male HIV infection

Following the decision to conceive with reproductive assistance, the couple should undergo a thorough sexual health and infection screen. The referring physician should also provide information on the male partner's HIV status. The possibility of HIV infection in the female partner also has to be excluded. In some cases, it might be necessary to treat genital infections before transmission.

Table 1 shows the investigations as provided in the *German recommendations for assisted reproduction in HIV-discordant couples* (Weigel 2001). There are small differences between the European centers. For the UK recommendations see Gilling-Smith et al. 2003.

After sperm washing and testing for HIV, spermatozoa can be utilized in three different reproductive techniques depending on whether the couples have any additional fertility issues: intra-uterine insemination (IUI), extracorporal fertilization by

conventional in-vitro fertilization (IVF) and intracytoplasmic sperm injection followed by embryonic transfer. According to the German recommendations, the choice of method depends on the results of gynecological and andrological investigations and the couple's preference. The success rate using IUI has been shown to be reduced if the sperm is washed and then cryopreserved before use. This is necessary in some centers where PCR testing of the washed sample for HIV cannot be done on the day of insemination. This, together with the fact that semen quality can be impaired in some HIV-infected men (Dulioust 2002; Müller 2003; Nicopoullos 2004), results in a number of couples being advised to have IVF or ICSI.

Couples should be informed about three further important aspects:

- Sperm-washing and testing can greatly reduce the risk of infection, but cannot exclude it completely. Following recent study results, this risk seems to be only theoretical and cannot be expressed in percentages.
- During treatment, consistent condom use is of utmost importance. HIV infection of the woman in the early stages of pregnancy can increase the risk of transmission to the child.
- Most couples attending European centers have to pay for treatment costs themselves. These are dependent on the type of technique applied, and range from about € 500 to € 5,000 per cycle. An exception is France, where couples have cost-free access to treatment. In Germany, health insurances sometimes cover a part of the costs, but they are not obliged to.
- Even the most sophisticated techniques cannot guarantee successful treatment.

Following successful treatment, couples are usually monitored for HIV status for 6 months to one year after childbirth, depending on the center.

Female HIV infection

HIV-positive women with unimpaired fertility can conceive by self-insemination. Similar to cases in which the male partner is infected, the German guidelines recommend a fertility screen and further investigations, as listed in Table 1. In some cases, ovarian stimulation may be advisable. Ovarian stimulation, however, requires highly qualified supervision to avoid multiple gestations.

It is important to time ovulation accurately (i.e., by use of computer-based ovulation kits or urine sticks). A simple inexpensive way of determining whether the cycles are ovulatory, which can be helpful in women who have regular cycles, is a basal temperature chart beginning about three months before the first self-insemination.

At the time of ovulation, couples can either have protected intercourse with a spermicide-free condom and introduce the ejaculate into the vaginal cavity afterwards, or the ejaculate can be vaginally injected using a syringe or applied with a portio cap after masturbation. Thus, the conception remains in the private sphere of the couple.

More than two inseminations per cycle are not advisable, as the fraction of motile sperm in the ejaculate can decrease with any additional tries. Furthermore, the couple might experience psychological strain through extensive planning.

After one year of unsuccessful self-insemination, the couple should have further fertility investigations with a view to assisted conception.

Fertility disorders

Following recent preliminary data and reports from some centers, fertility disorders in HIV-positive women seem to have a higher prevalence than in an age-matched HIV-negative population. In some cases, women will only be able to conceive by assisted reproduction. Dependent on the fertility status of both partners, IVF and ICSI can be considered as methods of choice.

Although many centers throughout Europe offer assisted reproduction if the male partner is infected, access to treatment for HIV-positive women is not guaranteed everywhere.

Recent data reported from Strasbourg indicated that over a period of 30 months, 48 HIV-positive women were enrolled in their program, 22 of them with fertility disorders. 9 of them conceived following assisted reproduction during that time, resulting in the birth of 6 children (Ohl 2004). The treatment of HIV-positive women is possible in Belgium, France, Germany, Great Britain, and Spain.

HIV infection of both partners

A growing number of HIV-concordant couples now seek reproductive counseling. In some centers, these couples are also accepted for reproductive treatment. One option might also be timed unprotected intercourse, but the discussion, pertaining to the transmission of mutated drug-resistant virus between partners, is still ongoing. Couples should be offered the same range of fertility counseling and screening as HIV-discordant couples. The current health of each partner should be carefully evaluated with a full report from their HIV physician.

Psychosocial aspects

- Experiences, from more than a decade of counseling, show the importance of offering professional psychosocial support to couples before, as well as during, and after reproductive treatment.

- Up to one third of the couples decide against the realization of their wish for parenthood after in-depth counseling. Accepting the desire to become parents and dealing with the underlying motives as well as the psychosocial situation in an empathic way enables couples to see obstacles as well as to develop alternative perspectives if this wish cannot be realized for various reasons.

- Frustration and disappointment may accompany failures or strains during treatment (i.e., unsuccessful treatment cycles, premature termination of pregnancy). Left alone with these strains, couples sometimes decide to conceive using unprotected intercourse, to avoid further stress. Depending on the risk perception of the partners, this decision may sometimes be well planned, but other times be born out of despair.

- Psychiatric co-morbidities in one or both partners (i.e., substance abuse, psychoses) can be reasons to at least postpone treatment. Professional diagnosis and support will be necessary in these cases.

- Often, the central importance of the wish for parenthood of many migrant couples is overlooked in parts of the medical and psychosocial counseling system. Language or communication difficulties on both sides, ignorance of different cultural backgrounds and lack of acceptance of "strange" life-styles can lead to feelings of discrimination, isolation, helplessness or despair in couples.

Summary

For many heterosexual couples, having a child is the expression of a fulfilled partnership and an important perspective on life. This is no less true in couples afflicted with HIV/AIDS.

Couples where the male partner is seropositive while the female is not, do not need to either risk an infection of the woman or abandon the wish for a child. Scientific results from the last decade and experiences from all European programs have shown that it is possible to use specialized techniques to separate sperm cells from the infectious parts of the ejaculate and to transfer the processed sperm using different methods of assisted reproduction, with almost no risk of infection.

Given the possibilities of decreasing the mother-to-child transmission rate to less than 2%, the desire for motherhood has now become a widely accepted option for HIV-positive women. Using either self-insemination or assisted reproduction, depending on the fertility status of the couple, they can conceive without risking infection of the HIV-negative partner.

Nevertheless, equal access for HIV-positive men and women is not granted throughout the European programs. HIV-positive women or HIV-concordant couples are still excluded from reproductive support in some centers.

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27. Post-Exposure Prophylaxis (PEP)

Thore Lorenzen, Katrin Graefe

Transmission

According to the current state of knowledge, there is a risk of HIV transmission if an HIV-negative person comes into contact with the blood, semen or vaginal fluids of an HIV-positive source person. In the opinion of leading experts, exposure of intact skin to HIV-contaminated body fluids (e.g. blood) is not sufficient to transfer the virus.

Transmission is possible if HIV-containing material enters the body by:

– accidental needlestick injury or incision by surgical instruments

– exposure of damaged skin or mucosal membranes

– unprotected sexual intercourse with an HIV-infected person

– IDU sharing needle or equipment

– transfusion of HIV-contaminated blood or blood products

Transmission risk

HIV is not a very contagious pathogen. The transmission rate after a high-risk contact is about 1:1000 to 1:100. Compared with HIV, the transmission rate for hepatitis C virus is 10 times higher, and 100 times higher for hepatitis B virus. Factors for the probability of transmission are the amount of incorporated virus and the exposure time. Contact with body fluids of a patient with a high viral load probably holds a higher risk of contagion than a similar contact with body fluids of a patient under HAART with a suppressed viral load. Additionally, quick removal of infectious material e.g. from damaged skin or mucosal membrane by washing or disinfection supposedly decreases the risk of an HIV infection. For percutaneous contact with HIV-containing blood, experts assume an infectiousness of 0.3 % in total. According to retrospective data, calculations have been established to assess the transmission risks of accidental exposure more precisely (see Table 1).

Table 1: Calculations to assess estimated individual transmission risk after HIV exposure *

Type of Exposure	Relative Risk
Deep needlestick injury or cut	16 : 1
Fresh blood on the penetrating instrument	5 : 1
Penetrating needle previously placed in blood vessel	5 : 1
Source person with high viral load (acute HIV infection, AIDS without ART)	6 : 1
Exposition of mucosal membrane	1 : 10
Exposition of inflammatory damaged skin	1 : 10

* Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2002

Table 2 provides information about the assumed transmission risk of other types of exposure to HIV, for example unsafe sexual contact. Since only few data exist these risk estimates should be judged with caution.

Table 2: HIV transmission risk for unprotected sexual contacts *

Type of contact	Transmission risk per contact
Unprotected receptive anal sex with HIV-infected person	0.82 % (0.24–2.76)
Unprotected receptive anal sex with person of unknown HIV status	0.27 % (0.06–0.49)
Unprotected insertive anal sex with person of unknown HIV status	0.06 % (0.02–0.19)
Unprotected receptive vaginal sex	0.05 – 0.15 %
Unprotected insertive vaginal sex	0.03 – 5.6 %
Oral sex	Probability not known, single cases have been reported, particularly with incorporation of semen in the mouth.

* Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2002

Evaluation of primary HIV infection indicates that the establishment of the virus in various tissue reservoirs does not occur immediately after incorporation of the virus. Within a small time frame the establishment of the virus might be prevented by post-expositional intervention.

Simian models show that in mucosal membranes HIV primarily infects the local immunocompetent cells such as Langhans' cells. These cells or their siblings migrate to regional lymph nodes: detection of HIV in the blood occurs days later. The process of local infection and migration of the cells to the lymph nodes takes approximately 24 to 48 hours. Theoretically, treatment with appropriate substances can reduce the transmission of an initially local infection to a systemic infection.

Effectiveness and limitations of PEP

Early reports on the use of AZT after occupational needlestick injuries date from 1989. An analysis of retrospective case-control studies shows that even prophylaxis with a single substance after exposure reduces the probability of an infection by approximately 80 %. The combination of multiple drugs is supposedly even more potent. Unfortunately there have been transmissions despite the use of PEP. Transmission of HIV infection cannot always be prevented. Many of the described cases of PEP failure following accidental exposure were treated with AZT mono-prophylaxis. But there are also reports about failures of antiretroviral combination therapies.

With increasing prevalence of resistance under antiretroviral therapy future problems might arise with transmission of resistant virus strains.

When is PEP indicated?

The risk of possible HIV transmission should be considered by a physician experienced in HIV treatment. It is important to establish whether the source person has a supposed or confirmed HIV infection. Unclear HIV status should be clarified: the source person should be asked for consent to perform HIV testing. Denial of consent has to be respected as per actual jurisdiction. If the source person agrees to be tested, this should be performed immediately. For source persons with confirmed HIV infection, the actual HIV viral load, stage of disease, former and current HAART have to be taken into consideration. The affected person should be asked about the first aid procedures that have already been performed.

After clarification of these queries, the exposed person has to be informed about possible adverse effects and risks of pharmaceutical PEP. It should be emphasized that none of the administered substances is approved for use in this special setting. This is also important with regard to the coverage of cost, especially for sexual exposure. The medication cannot be prescribed at the expense of the health insurance. PEP for occupational exposure is usually covered by statutory accident insurance (in Germany).

Table 3 gives an overview of situations in which PEP is recommended according to current guidelines. This serves as an orientation, although deviations may be necessary in individual cases.

Potential risks of PEP

The risks of PEP mainly concern the adverse effects of the antiretroviral substances. Most frequently this refers to gastrointestinal symptoms such as nausea, vomiting or diarrhea. Also possible are changes of hematology, transaminases or creatinine. There have been reports about elevated triglyceride and cholesterol levels and insulin resistance even in short term use of protease inhibitors.

It is unknown whether the temporary use of antiretroviral substances may lead to long term side effects, but this seems secondary since the main emphasis is to prevent a chronic and potentially life-threatening disease. For pregnant women particular caution is required since data concerning teratogenicity are lacking.

Table 3: Overview of recommendations for usage of PEP

Occupational Exposure	
• Percutaneous needlestick injury with hollow needle (body fluids with high viral load: blood, liquor, material from biopsies, cultured virus)	Recommended
Deep injury (e.g. cuts), apparently blood stained	Recommended
Needle used before for intravenous injection	Recommended
• Superficial injury (e.g. with surgical needle)	Considered
Where required, exemption, if source person has AIDS or high viral load	Recommended
• Contact of mucosal membrane or damaged skin with fluids with high viral load	Considered
• Percutaneous contact with body fluids other than blood (e.g. urine, saliva)	Not Recommended
• Contact of intact skin with blood (including high viral load)	Not Recommended
• Contact of skin or mucosal membranes with body fluids such as urine or saliva	Not Recommended
Non-occupational Exposure	
• Transfusion of HIV containing blood products (or if HIV contamination is highly probable)	Recommended
• Unprotected receptive sex with an HIV-infected person	Recommended
• IDU sharing needle or equipment	Recommended
• Unprotected receptive oral sex with ejaculation with an HIV-infected person	Considered
• Kissing and other sexual contacts without semen-/blood-mucosal membrane contact	Not Recommended
• Accidental needlestick injury	Not Recommended

Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2002, Eur J Med Res 2002; 7:509-27.

Initial Interventions

According to actual guidelines, depending on the type of exposure, different procedures are recommended following HIV-exposure. Following needlestick or cut injuries with HIV-contaminated instruments, fluid should be expressed by squeezing the tissue surrounding the wound and striking out proximal blood vessels towards the wound. Too intense massage or contusions have to be avoided. The wound should be flushed with an alcoholic, virucidal antiseptic for a minimum of 10 minutes. For skin that has been in contact with blood or body fluids removal of the infectious material and subsequent extensive disinfection with a skin antiseptic appears sufficient. After contamination of an eye, immediate flush with PVP iodine solution 2.5 % is recommended. If such a solution is not available the eye should be washed with water. The oral cavity should be washed several times (about 10-

15 seconds each) with an aqueous solution or preferably 80 % alcohol after contact with potentially infectious material.

Needlestick or cut injury		Contamination of damaged skin, eye or oral cavity
Expressing fluid by squeezing the tissue surrounding the wound (≥ 1 minute)		Intensive washing with easily accessible liquid: high proof alcohol (undenaturated for the oral cavity), water or isotonic saline solution, possibly PVP iodine solution

Intensive antiseptic washing or application of an antiseptic depot of antiviral agent

Figure 1: Recommended initial interventions after HIV exposure (Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2002)

Persons, who through sexual exposure, have contact of anal or genital mucosae to infectious material should wash the penis with soap and water; genital mucosae should be flushed with water after urination which might wash contaminated material from the urethra. Intense washing of the vagina or intestines is not recommended due to an elevated risk of injuries.

After implementation of the initial interventions, an expert in HIV treatment and antiretroviral therapy should be consulted for the decision whether pharmaceutical PEP needs to be started or continued.

Accurate evaluation and documentation of the course of the accident is very important, especially for occupational exposure. The process of informing the patient about the risks of PEP needs to be documented carefully and an informed consent should be signed by the patient.

Initiation of PEP

Time is the most important factor for initiation of PEP. Because of the above mentioned mechanism, it has to be assumed that the best chance of preventing transmission is within the first 24 hours after exposure. After that time period, the risk of systemic spread of the virus increases. Initiating PEP after more than 72 hours following exposure does not seem reasonable.

PEP should be initiated as soon as possible, preferably within 2 hours of exposure.

If, in this short time frame, consultation with a physician experienced in HIV treatment is not possible, it might be advantageous to just initiate PEP. Interrupting a regimen that isn't indicated is always an option.

Actual recommendations prefer a regimen with a combination of antiretroviral substances given over 4 weeks, preferably consisting of two NRTIs and one PI (see Table 5). NNRTIs, especially nevirapine, should not be used for PEP because of the risk of severe adverse effects (hepatotoxicity). For efavirenz such severe adverse effects have not been reported but the impact on the CNS, particularly in the first weeks of intake, limits its use for PEP.

As far as possible, known resistance against antiretroviral substances of the source person should be taken into account; in many cases, this information will not be available. Therefore use of standard regimens for PEP has proven practical. Recommended combinations are shown in Table 5.

Tenofovir is not listed in the table of standard prophylaxis. This substance needs one phosphorylization step less for activation compared to the other NRTIs which might be beneficial concerning time. Until now, no evidence exists confirming this hypothesis, but current trials are ongoing.

In addition, since 2003, a substance with a completely new approach is available, namely the fusion inhibitor enfuvirtide or T20 (Fuzeon™). The inhibition of viral cell entry might be interesting with regard to increasing efficiency of PEP. The subcutaneous route of application and high costs currently prevent its routine use.

Furthermore, difficulties in monitoring a possible seroconversion might occur as development of antibodies against enfuvirtide may lead to cross reaction with gp41 and a positive result in the HIV-Elisa test.

During pregnancy, PEP should only be used after careful consideration of the benefits since there are only limited data on teratogenic effects. In any case, advice of a physician experienced in HIV treatment and pregnancies should be obtained.

After contact with potentially infectious material, not only HIV, but also other diseases might be transmitted. Apart from HIV, testing should be performed for Hepatitis B and Hepatitis C. Persons exposed to Hepatitis B should receive hepatitis B immunoglobulin and a vaccine series simultaneously if they have no sufficient vaccination status.

Table 4: Recommended antiretroviral combinations for HIV Post-exposure Prophylaxis *

NRTI		PI / NNRTI
AZT + 3TC		Nelfinavir (Viracept™, 2 x 1,250 mg)
1. Combivir™ (2 x 300/150 mg) or	plus	or Lopinavir/r (Kaletra™, 2 x 400/100 mg) or
2. Retrovir™ (2 x 250 mg) plus Epivir™ (2 x 150 mg or 1 x 300 mg)		Indinavir (Crixivan™, 3 x 800 mg) or Efavirenz (Sustiva™, 1 x 600 mg)

* Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2002. Comment: routine use of efavirenz is not recommended by the editors of HIV medicine due to high incidence of CNS events.

After unprotected sexual contacts, transmissions of other STDs such as syphilis or gonorrhea should be taken into consideration. Testing is recommended at 2 and 4 weeks after exposure.

Management of PEP

After initiation of PEP, the patient should not be discharged without a follow-up consultation. The consecutive intake of antiretrovirals demands a high amount of discipline and potential adverse effects should be diagnosed early. Persons exposed

to HIV are under high psychological pressure. It is important not to dramatize the situation but emphasize the generally low risk of transmission.

Adverse effects generally include gastrointestinal symptoms. Less frequent are changes in hematology, liver enzymes or creatinine. These should be tested after 14 days and again after 4 weeks - at the end of the PEP. Despite close monitoring, different studies report discontinuation rates of 40 and 50 %. At the end of a completed course or discontinued PEP, HIV testing should be performed after 6 weeks, 3 and 6 months. An HIV PCR only needs to be performed if there is reasonable suspicion of a primary HIV infection.

In any case, the patient has to be advised to practice safer sex until a reliable negative test result is achieved.

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Part 5

Drugs

28. Drug Profiles

Bernd Sebastian Kamps, Christian Hoffmann

3TC - Lamivudine

3TC is a well-tolerated cytidine analog. Resistance develops rapidly: only a single point mutation (M184V) is required. However, this mutation can increase the sensitivity of AZT-resistant viruses and reduce viral fitness.

3TC is also effective against hepatitis B virus.

Trade name: Epivir™; component of Combivir™ and Trizivir™, Kivexa™

Epivir™ tablets: 150 mg or 300 mg 3TC; oral solution 10 mg/ml

Combivir™ tablets: 150 mg 3TC + 300 mg AZT

Trizivir™ tablets: 150 mg 3TC + 300 mg AZT + 300 mg abacavir

Zeffix™ tablets: 100 mg 3TC. These should not be used in HIV patients (the dose is sufficient for HBV, but too low for HIV!).

Class: Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Manufacturer: GlaxoSmithKline

Indication: HIV infection (also chronic hepatitis B)

Oral dose Epivir™: 300 mg qd or 150 mg bid. Dose adjustment is required with reduced creatinine clearance:

CrCl (ml/min)	Dose
30–49	150 mg qd
15–29	150 mg first dose, then 100 mg qd
5–14	150 mg first dose, then 50 mg qd
<5	50 mg first dose, then 25 mg qd

Children receive 4 mg/kg, with a maximum of 150 mg bid.

Oral dose Combivir™: 1 tablet bid, containing 150 mg 3TC and 300 mg AZT.

Oral dose Trizivir™: 1 tablet bid, containing 150 mg 3TC and 300 mg AZT and 300 mg abacavir.

Patients with a creatinine clearance below 50 ml/min or with impaired liver function should not receive Combivir™ or Trizivir™, but rather the individual formulations of AZT and 3TC.

Side effects: rare when using the individual drug. Fatigue, nausea, vomiting, diarrhea, headache, insomnia, myalgia and arthralgia may occur, but are usually due to other drugs in the combination (see AZT and abacavir). Peripheral polyneuropathy, pancreatitis and lactic acidosis are rare.

Comments/Warnings: 3TC requires dose adjustment based on renal function.

Internet sources:

USA: Epivir™: http://hiv.net/link.php?id=49

Combivir™: http://hiv.net/link.php?id=50

Trizivir™: http://hiv.net/link.php?id=51

References:

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Abacavir (ABC)

Abacavir is a guanosine analog with good CNS penetration. Abacavir is now licensed for once-daily dosing, both as the individual drug and as a component of the fixed-dose combination Kivexa™.

The main problem with abacavir is the hypersensitivity reaction (HSR). Abacavir should therefore be prescribed by HIV clinicians! The drug is otherwise well-tolerated, possibly causing less mitochondrial toxicity than other drugs. Cross-resistance occurs with numerous other NRTIs. Resistance develops rapidly with triple nuke regimens containing 3TC and tenofovir.

Trade name: Ziagen™; component of Kivexa™/ Epzicom™ and Trizivir™

Ziagen™ tablets: 300 mg abacavir; oral solution 20 mg/ml in 240 ml bottles

Kivexa™ tablets: 600 mg abacavir + 300 mg 3TC

Trizivir™ tablets: 300 mg abacavir + 150 mg 3TC + 300 mg AZT

Drug class: NRTI

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Oral dose: 300 mg bid or 600 mg qd. Abacavir can be taken with or without food.

Side effects: abacavir causes a hypersensitivity syndrome (HSR) in about 2 to 8 % of patients. This usually occurs within the first six weeks after initiation of treatment. Pruritus and rash are common, but may also be absent. The HSR may present as just fever and slowly developing malaise. Gastrointestinal complaints (nausea, vomiting, diarrhea, abdominal pain) and fatigue are also possible, but not necessarily linked to the HSR. Elevated liver function tests, insomnia and dizziness are rare. There is probably a genetic predisposition for the HSR.

Comments/Warnings: abacavir is contraindicated in cases with previously diagnosed abacavir hypersensitivity and after interruption of therapy, if a prior HSR cannot be definitively ruled out in retrospect. Patients should be well advised about the HSR, but not frightened. With only mild symptoms (see below), abacavir should not be stopped too quickly, as an intercurrent infection may simulate the HSR. Therapy may be continued for one or two days under close observation.

Rechallenge after suspected HSR is contraindicated, as a repeated allergic reaction can be fatal.

Patients should be told to consult a doctor **immediately** if at least two of the following symptoms occur:

- fever
- shortness of breath, sore throat or cough
- rash (erythema and/or pruritus)
- nausea or vomiting or diarrhea or abdominal pain
- extreme fatigue or diffuse pain or general malaise

Abacavir should not be used in a triple nuke combination with 3TC and tenofovir due to rapid development of resistance.

Interactions: 0.7 g/kg ethanol (e.g. 0.5 l wine) increases the AUC of abacavir by 41 % and increases half-life by 26 %.

Internet sources:

USA: http://hiv.net/link.php?id=53

References:

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Acyclovir

Trade name: Zovirax™ (among many others)

Drug class: virostatic

Manufacturer: acyclovir is manufactured by several companies. Generics are sometimes significantly cheaper than the originally introduced formulation (Zovirax™).

Indications: treatment and prophylaxis of HSV and VZV infections.

Dose: for genital HSV infection: 400 mg 5x/day. In severe cases (ulcerating genital herpes) intravenous treatment with 5-10 mg/kg iv tid. For HSV encephalitis or HSV esophagitis 10 mg/kg iv tid.

For dermatomal herpes zoster 800 mg po 5x/day for one week. In cases of disseminated or complicated herpes zoster 10 mg/kg iv tid.

Side effects: rare. Headache, nausea and elevation of creatinine may occur. Phlebitis can occur with intravenous dosing.

Comments/Warnings: contraindicated in cases of hypersensitivity to acyclovir or valacyclovir. Initiation of treatment for HSV infections should be within the first 24 hours after appearance of symptoms if possible, for VZV infection within the first 4 days. Adequate fluid intake is important.

Internet sources:

USA: http://hiv.net/link.php?id=55

References:

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Agenerase™ see Amprenavir

Ambisome™ see Amphotericin B

Amphotericin B

Trade names: Amphotericin B™, Ambisome™

Amphotericin B™: 50 mg amphotericin B powder/bottle

Liposomal amphotericin B: 50 mg vials of Ambisome™

Drug class: antimycotic

Manufacturer: Amphotericin B™: Bristol-Myers Squibb; Ambisome™: Gilead

Indications: aspergillosis, cryptococcosis, treatment-resistant candidiasis, histoplasmosis, coccidioidomycosis.

Indications for Ambisome™: life-threatening situations with the mycoses listed above. Mainly in cases of pre-existing impaired renal function, elevations in creatinine on amphotericin B (creatinine > 2.0 mg/dl) or poor tolerability of amphotericin B infusions.

Ambisome™ is expensive!

Dose (per day) of amphotericin B™:

Aspergillosis: 1.0 to 1.5 mg/kg

Candidiasis: 0.2 to 0.8 mg/kg

Coccidioidomycosis: 0.5 to 1.0 mg/kg

Cryptococcosis: 0.7 to 1.0 mg/kg

Histoplasmosis: 0.5 to 1.0 mg/kg

Dose of Ambisome™: initial daily dose of 1 mg/kg, if necessary this may be gradually increased to 3 mg/kg.

Side effects: nephrotoxicity! Hypokalemia! Gastrointestinal complaints. Frequent: fever, chills, and hypotension approx. 10-20 min after starting infusions. Thrombophlebitis (central venous line always necessary for non-liposomal amphotericin B!). Side effects are generally less severe with Ambisome™.

Comments/Warnings: daily monitoring of electrolytes (a central venous line is always necessary due to hypokalemia and the usually required potassium substitution! Sodium should be kept at normal levels), creatinine, BUN, ALT, blood count. If possible, do not combine with other nephrotoxic drugs.

Always prehydrate with 1000 ml 0.9 % NaCl. First test dose always with 5 mg in 250 ml 5 % glucose over 30–60 min under strict monitoring of blood pressure and pulse for the first hour. If the test dose is tolerated, half of the planned maintenance dose may subsequently be given on the same day. In cases of fever/chills (can be very impressive!): 50 mg pethidine iv plus 1 ampule clemastine, may be repeated after 30 min; steroids only if complaints persist (prednisolone 1 mg/kg).

If side effects are severe, switch to Ambisome™, which is probably not more effective (apyrexia, survival) than conventional amphotericin B, but significantly better tolerated and less nephrotoxic (no test dose, no prehydration, no central line necessary). Never mix amphotericin infusions, and always protect from light. Infuse slowly! The longer the infusion time (>3 hours), the better the tolerability! Always use 5 % glucose as a diluent!

Internet sources:

USA: Ambisome™: http://hiv.net/link.php?id=58

References:

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Amprenavir

Due to the high pill burden, unboosted dosing of amprenavir (8 pills bid) is hardly acceptable today. When boosted with ritonavir, the drug undoubtedly has better

efficacy, but was nevertheless inferior to efavirenz in one study. In the USA, the improved formulation, fosamprenavir, has been licensed since 2003 (see corresponding chapter). It is possible that Agenerase™ will be withdrawn from the market as soon as fosamprenavir becomes available worldwide.

Trade name: Agenerase™

50 mg and 150 mg capsule, 15 mg/ml oral solution

Drug class: protease inhibitor

Manufacturer: GlaxoSmithKline

Indications: HIV infection with previous PI-treatment

Oral dose: 8 capsules amprenavir bid of 150 mg each (1200 mg bid)

Important note: The bioavailability of amprenavir oral solution is 14 % lower than the capsulated formulation; amprenavir solution therefore requires higher dosing: 17 mg/kg tid (=1.1 ml/kg tid), with a maximum total dose of 2800 mg daily.

Boosted (= in combination with ritonavir) 4 capsules APV bid of 150 mg each **plus** 100 mg ritonavir bid. Also possible: 8 capsules APV qd **plus** 200 mg ritonavir qd. Dose for amprenavir solution: 1.5 ml/kg bid.

Side effects: mostly gastrointestinal with nausea, vomiting, diarrhea, flatulence, tenesmus, perioral paresthesia. Occasionally headache, fatigue; rash in 5-10 % of patients, usually in the second week of treatment. Stevens-Johnson syndrome is rare (<1 %).

In combination with ritonavir, elevations of cholesterol, triglycerides and transaminases occur more frequently. Lowered glucose tolerance, rarely diabetes mellitus. Lipodystrophy.

Comments/Warnings: amprenavir is contraindicated in pregnancy and in children under 4 years; and as concurrent treatment with rifampin, ergotamines, cisapride, bepridil, pimozide, midazolam and triazolam. Concurrent treatment with amiodarone, warfarin, lidocaine, tricyclic anti-depressants, quinidine, cyclosporine and tacrolimus should be avoided. Measurement of plasma levels is recommended. Amprenavir is not recommended for concurrent treatment with lovastatin, simvastatin, carbamazepine, phenobarbital, phenytoin or sildenafil (Viagra™: increased incidence of hypotension, priapism!)

Use with caution in patients with a history of sulfonamide allergy.

Concurrent treatment with rifabutin: Reduce rifabutin dose by 50 %.

Amprenavir should be taken at least one hour before or after antacids or ddI. Dose adjustment (measure plasma levels!) is usually necessary in combination with lopinavir.

Amprenavir solution contains 50 % propylene glycol. It is therefore contraindicated for concurrent administration with disulfiram or metronidazole.

Internet sources:

USA: Capsules: http://hiv.net/link.php?id=61
Solution: http://hiv.net/link.php?id=62
Combination with ritonavir: http://hiv.net/link.php?id=63

References:

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       2004 Jul 26. http://amedeo.com/lit.php?id=15356829

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       associated with virus load response to treatment in vivo. Clin Infect Dis 2001, 33: 2075-7.
       http://amedeo.com/lit.php?id=11700580

Atazanavir

Atazanavir is a new protease inhibitor that was licensed in 2004 for treatment-experienced patients. Compared to other PIs, atazanavir has a favorable lipid profile. Whether this will have implications for lipodystrophy remains to be seen. Another advantage is the possibility of once-daily dosing.

Boosting with ritonavir is recommended (100 mg ritonavir, 300 mg atazanavir), particularly in combination with tenofovir and efavirenz.

The most important side effects of atazanavir are elevated bilirubin levels, which may even be associated with jaundice.

Trade name: Reyataz™

100, 150 and 200 mg capsules

Drug class: protease inhibitor (PI)

Manufacturer: Bristol-Myers Squibb

Indications: atazanavir is indicated in combination with other antiretroviral drugs for treatment of HIV-1-infected, treatment-experienced adults experiencing treatment failure. Licensing for treatment-naïve patients is expected in 2005.

Oral dose: 300 mg atazanavir qd combined with 100 mg ritonavir qd, and taken with a meal.

Side effects: hepatotoxicity, hyperbilirubinemia (up to 50 %), elevated transaminases; jaundice is not unusual. Diarrhea in approx. 30 %. In addition: nausea, vomiting, headache, insomnia, abdominal pain, rash, and asthenia. In contrast to other PIs: No dyslipidemia. The effect on lipodystrophy remains unknown.

Comments/Warnings: capsules should be swallowed without chewing.

The following are contraindicated: cisapride, pimozide, midazolam, triazolam, simvastatin, lovastatin, ergotamines, calcium antagonists and proton pump inhibitors. Life-threatening interactions may occur with concomitant administration of amiodarone, lidocaine (systemic dosing), tricyclic anti-depressants and quinidine (measure plasma levels!).

It should not be given with rifampin (reduces plasma levels of atazanavir by 90 %), St. John's wort, and antacids; caution with sildenafil, vardenafil.

When combined with efavirenz, efavirenz should be given once-daily (600 mg) and the atazanavir dose should be increased to 400 mg.

Do not combine with indinavir.

Atazanavir should not be taken simultaneously with ddI. Combination of these drugs is only possible if ddI is taken at least two hours after atazanavir/ritonavir and food. The reason: the buffer in ddI chewable tablets prevents absorption of atazanavir.

Rifabutin: reduce rifabutin dose by 75 % (instead of 300 mg daily, give only 150 mg every other day or three times per week).

Clarithromycin: do not combine boosted atazanavir with clarithromycin.

Caution with impaired liver function. Atazanavir is contraindicated in patients with moderate to severely impaired liver function (Child Pugh B and C).

Contraception: an alternative to the pill is recommended.

Internet sources:

USA: http://hiv.net/link.php?id=224

References:

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Atovaquone

Trade name: Wellvone™

Suspension with 750 mg/5 ml

Drug class: antibiotic

Manufacturer: GlaxoSmithKline

Indications: PCP prophylaxis in cases of hypersensitivity to cotrimoxazole; also reserve drug for treatment of mild to moderate cases of PCP and for cerebral toxoplasmosis.

Dose: for treatment 750-1500 mg bid (i.e. 1-2 measuring spoons of 5 ml bid) for 21 days. For prophylaxis 750 mg bid (i.e. 1 measuring spoon of 5 ml bid) or 1500 mg qd.

Side effects: gastrointestinal complaints such as nausea, vomiting and diarrhea are frequent (but often mild), as are rashes, which occur in approx. 20 %. More rarely headache, insomnia. Elevated liver enzymes, amylase. Anemia (rare).

Comments/Warnings: atovaquone should be taken with meals, ideally with fatty dishes, as this improves absorption. Atovaquone is considerably more expensive than other drugs for PCP prophylaxis (costs approx. 1,000 Euro/month)!!

Rifampin and possibly also rifabutin lower plasma levels of atovaquone by approx. 50 %. The combination with these two drugs is therefore not recommended. Fluconazole probably increases levels.

Lopinavir seems to lower the plasma concentration of atovaquone. Dose adjustment may be necessary.

Internet sources:

UK: http://hiv.net/link.php?id=174

References:

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Azithromycin

Trade names: Ultreon™, Zithromax™

Ultreon™ tablets with 600 mg

Zithromax™ tablets with 250 mg

Zithromax™ powder for suspension with 200 mg per 5 ml

Drug class: macrolide antibiotic

Manufacturer: Pfizer, Mack-Illert

Indications: treatment and prophylaxis of MAC infection. Infections of the upper and lower respiratory tract, otitis media. Uncomplicated gonorrhea, uncomplicated genital infections with Chlamydia trachomatis, chancroid.

Dose: primary prophylaxis of disseminated MAC infection: 1200 mg azithromycin weekly (2 tablets Ultreon™ 600 mg per week). MAC treatment: 1 tablet Ultreon™ 600 mg qd, only in combination with ethambutol and rifabutin.

Uncomplicated gonorrhea: 1000 mg azithromycin as a single dose.

Uncomplicated genital infections with Chlamydia trachomatis: if an alternative to doxycycline is needed, 1000 mg azithromycin may be given as a single dose.

Chancroid: 1000 mg azithromycin as a single dose.

Side effects: mainly gastrointestinal with stomach cramps, loss of appetite, nausea, vomiting, diarrhea. Rarely, elevations of transaminases, cholestatic jaundice. Reversible ototoxicity with high doses. Rarely taste disturbances.

Comments/Warnings: caution in cases of known macrolide allergy! Reduced absorption of azithromycin with concurrent dosing of Mg- and Al-containing antacids. These drugs should be taken one hour before or two hours after azithromycin.

Internet sources:

USA: http://hiv.net/link.php?id=176

References:

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http://amedeo.com/lit.php?id=9827282

AZT - Zidovudine

AZT remains an important component of many HAART regimens due to its good CNS penetration and relatively low mitochondrial toxicity (good long-term tolerability!).

Patent protection for AZT expires in September in the United States (http://hiv.net/link.php?id=243).

Trade name: Retrovir™; component of Combivir™ and Trizivir™

Retrovir™ capsules: 100 mg or 250 mg, tablets: 300 mg; 200 ml bottles for infusion (10 mg/ml), 10 mg/ml syrup

Combivir™ tablets: 300 mg AZT + 150 mg 3TC

Trizivir™ tablets: 300 mg AZT + 150 mg 3TC + 300 mg abacavir

Manufacturer: GlaxoSmithKline

Indications: HIV infection. Prevention of maternal-fetal HIV transmission.

Dose: 250 mg bid. In Combivir™ and Trizivir™ 300 mg bid.

Creatinine clearance below 20 ml/min: 300 to 400 mg daily.

Hemodialysis: 300 mg daily. Hepatic failure: 100 mg tid.

Side effects: nausea, vomiting, abdominal discomfort, headache, myalgia, and dizziness. Macrocytic anemia (MCV almost always elevated), rarely neutropenia. Elevations in LDH, CPK and transaminases may occur. Episodes of lactic acidosis are rare.

Comments/Warnings: do not combine with d4T! There is increased myelotoxicity if used with other myelosuppressive drugs, especially ganciclovir, but also co-trimoxazole, dapsone, pyrimethamine, interferon, sulfadiazine, amphotericin B, ribavirin and various other chemotherapeutic agents.

Ribavirin antagonizes the antiviral activity of AZT in vitro. Concurrent use of AZT and ribavirin should therefore be avoided.

Initially monthly monitoring of blood count, transaminases, CPK and bilirubin. Gastrointestinal complaints can be treated symptomatically and usually subside after a few weeks. Anemia can develop even after months.

AZT should always be a component of transmission prophylaxis!

Internet sources:

USA: Retrovir™ tablets: http://hiv.net/link.php?id=66

Retrovir™ IV infusion: http://hiv.net/link.php?id=67

Combivir™: http://hiv.net/link.php?id=68

Trizivir™: http://hiv.net/link.php?id=69

References:

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Caelyx™ see Doxorubicin, liposomal

Cidofovir

Trade name: Vistide™

Vials with 375 mg in 5 ml

Drug class: virostatic

Manufacturer: Gilead

Indications: CMV retinitis in HIV-infected patients without renal dysfunction, mainly in cases of resistance/contraindications to ganciclovir or foscavir. As a curative measure for PML, although efficacy is uncertain.

Dose: induction dose 5 mg/kg iv weekly, by day 21 maintenance therapy with 5 mg/kg iv every two weeks. A precise treatment plan (comedication, hydration, etc.) is necessary!

Side effects: renal failure is dose limiting! Proteinuria, elevated creatinine. Cases of acute renal failure have been reported after 1 or 2 doses of cidofovir. Less frequent: neutropenia, dyspnea, alopecia, decreased intraocular pressure, iritis, uveitis.

Fever, chills, headache, rash, nausea and vomiting are usually caused by probenecid and should subside within 12 hours. Complaints may be lessened with food intake, antipyretics, or anti-emetics.

Comments/Warnings: with normal renal function, cidofovir should be given according to the following scheme (draw up protocol):

–3 h	2 g probenecid (4 tbl. of 500 mg)
–3 to –1 h	1000-2000 ml 0.9 % NaCl
0 to + 2 h	Cidofovir in 500 ml 0.9 % NaCl over 1-2 h. 1000 ml 0.9 % NaCl in parallel.
+4 h	1 g probenecid (2 tbl. of 500 mg)
+10 h	1 g probenecid (2 tbl. of 500 mg)

If serum creatinine increases by more than 0.3 mg/dl: reduce dose to 3 mg/kg. If serum creatinine increases by more than 0.5 mg/dl above levels prior to treatment: **discontinue** cidofovir. Cidofovir is always contraindicated at serum creatinine levels > 1.5 mg/dl or creatinine clearance below 55 ml/min or proteinuria > 100 mg/dl.

Potentially, nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, iv pentamidine or vancomycin must be avoided or discontinued at least 7 days prior to treatment with cidofovir.

Always ensure sufficient hydration! Probenecid is always necessary to reduce nephrotoxicity! Cidofovir should only be used if other drugs are unsuitable.

Renal function (serum creatinine, electrolytes, proteinuria) and blood count should be checked before **each** dose of cidofovir.

Probenecid has drug interactions with acetaminophen, acyclovir, angiotensin converting enzyme inhibitors, aminosalicylic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, non-steroidal anti-inflammatory drugs and theophylline.

Internet sources:

USA: http://hiv.net/link.php?id=71

References:

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Clarithromycin

Trade names: Klacid™, Mavid™

Mavid™ tablets with 500 mg

Klacid™ tablets with 250 mg

Drug class: antibiotic

Manufacturer: Abbott

Indications: prophylaxis and treatment of MAC disease.

Dose: 500 mg bid, both for primary prophylaxis and for maintenance therapy. 50 % dose reduction and good hydration if creatinine clearance is below 30 ml/min.

Side effects: mainly gastrointestinal complaints such as nausea, vomiting, abdominal discomfort (rarely tenesmus), and diarrhea. In addition, allergic skin reactions, headache, elevated transaminases, alkaline phosphatase and bilirubin.

Comments/Warnings: no concurrent treatment with rifampin, carbamazepine, cisapride, terfenadine, pimozide and other macrolide antibiotics such as erythromycin or azithromycin.

Lopinavir and ritonavir increase clarithromycin levels.

If administered concurrently, oral treatments with clarithromycin and AZT should be taken 1-2 hours apart.

Internet sources:

USA: http://hiv.net/link.php?id=73 (trade name: Biaxin)

References:

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Clindamycin

Drug class: antibiotic

Manufacturer: Clindamycin is manufactured by several different companies.

Indications: for HIV patients: mainly cerebral toxoplasmosis.

Dose: 600 mg iv q 6 h or 600 mg po q 6 h (always with pyrimethamine and leukovorin). Half dose for (oral) maintenance therapy. In renal failure, reduce dose to a quarter or a third of the normal dose.

Side effects: diarrhea in 10-30 % of patients. Allergies are also frequent and often require discontinuation.

In cases of infection with Clostridium difficile: fever, leukocytosis and risk of toxic megacolon.

Pseudomembranous colitis: the clinical spectrum ranges from mild watery to severe persistent diarrhea, leukocytosis, fever and severe abdominal cramps, which may be accompanied by stools with blood and mucus and may progress to peritonitis, shock and toxic megacolon.

Comments/Warnings: clindamycin is contraindicated in inflammatory bowel disease or history of antibiotic-induced colitis. Caution with reduced hepatic or renal function and in asthma. No concurrent administration of antiperistaltics.

In cases of persistent diarrhea during treatment with clindamycin, discontinue clindamycin and initiate therapy with vancomycin, as this may be due to pseudomembranous colitis.

Internet sources:

USA: http://hiv.net/link.php?id=76 (trade name Cleocin™).

References:

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Combivir™

Tablets containing 150 mg 3TC + 300 mg AZT

Drug class: NRTI

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Oral dose: 1 tablet bid

In cases of reduced renal function (creatinine clearance below 50 ml/min) and anemia, Combivir™ should be replaced with the individual drugs to allow for adjustment of 3TC and AZT doses.

Warnings and side effects: see chapters on 3TC and AZT.

Internet sources:

USA: http://hiv.net/link.php?id=68

Co-trimoxazole (Trimethoprim-sulfamethoxazole)

Drug class: antibiotic

Manufacturer: co-trimoxazole is manufactured by several different companies.

Indications: prophylaxis and treatment of Pneumocystis pneumonia (PCP). Prophylaxis and treatment (reserve drug) of cerebral toxoplasmosis.

Dose: PCP *prophylaxis*: 80/400 mg qd or 160/800 mg trimethoprim/sulfamethoxazole 3 x/week. PCP *therapy*: 5 mg/kg (based on trimethoprim) po or iv q 8 h x 21 days, therefore usually 5 to 6 ampules à 80/400 mg q 8 h. Toxoplasmosis prophylaxis: 1 tablet (160/800 mg) qd.

Reduced renal function: halve dose with creatinine clearance of 15 to 50 ml/min. Co-trimoxazole is contraindicated below 15 ml/min.

Side effects: allergies. High intravenous doses cause myelotoxicity (anemia, neutropenia!), but also nausea, vomiting, headache, elevated transaminases.

Treatment can often be continued in cases of slight allergic skin rash. In other cases desensitization is usually possible.

Comments/Warnings: caution with sulfonamide allergy! Co-trimoxazole oral suspension for children can be used for desensitization: increase the dose slowly over

six days from 12.5, 25, 37.5, 50 and 75 to 100 % of the 480 mg tablet dose (for details see Leoung 2001, see below).

Co-trimoxazole can increase levels of anticoagulants and phenytoin and reduce the efficacy of oral contraceptives.

References:

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Crixivan™ see Indinavir

d4T - Stavudine

Stavudine is a thymidine analog similar to AZT. Subjective tolerability is good; the drug was long considered an important alternative to AZT. Newer guidelines are more cautious, due to unfavorable data on mitochondrial toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy), particularly in combination with ddI.

New extended release capsules that allow once-daily dosing have been approved since 2002, but were still not available by the end of 2004 due to production difficulties.

Trade name: Zerit™

Capsules: 15 mg, 20 mg, 30 mg, 40 mg. Solution 1 mg/ml.

Drug class: NRTI

Manufacturer: Bristol-Myers Squibb

Indications: HIV infection

Oral dose: 40 mg bid for body weight > 60 kg, but 30 mg bid for body weight < 60 kg.

In renal failure:

Weight	CrCl 26-50 ml/min	CrCl below 26 ml/min (incl. dialysis patients)*
<60 kg	15 mg bid	15 mg qd
>60 kg	20 mg bid	20 mg qd

*Hemodialysis: patients should take d4T after dialysis, and at the same time on non-dialysis days.

Side effects: peripheral neuropathy, especially in combination with ddI (up to 24 %). d4T has been linked to lipoatrophy more than other NRTIs. However, the following are less frequent than with AZT: diarrhea, nausea, vomiting, headache. Very rare, but potentially fatal: lactic acidosis, which occurs mostly in combination with ddI (especially in pregnancy!). Further side effects: hepatic steatosis, pancreatitis.

Comments/Warnings: d4T should not be combined with AZT.

Contraindicated with existing peripheral neuropathy.

If possible, no concurrent treatment with other neurotoxic drugs (ddC, ethambutol, cisplatin, INH, vincristine, etc.)

d4T can be taken on an empty stomach or with a light meal. If symptoms of peripheral neuropathy occur, treatment with d4T should be discontinued.

References:

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Dapsone

50 mg tablets

Drug class: antibiotic

Manufacturer: Fatol

Indications: reserve drug for prophylaxis of Pneumocystis pneumonia and cerebral toxoplasmosis.

Dose: 100 mg daily. Alternative: 50 mg qd **plus** pyrimethamine 50 mg bid/week **plus** folinic acid 30 mg/week.

Side effects: allergies (pruritus, rash), fever. Frequently hemolytic anemia (with almost obligatory elevation of LDH!), hepatitis.

Discontinue if severe rash, muscle weakness or severe myelosuppression develop.

Comments/Warnings: dapsone is contraindicated in severe anemia and must be used with caution in patients with G-6-PD deficiency. It is contraindicated in Mediterranean G-6-PD deficiency. Not to be taken simultaneously with ddI, antacids and H2 blockers (to be taken at least two hours apart). Development of LDH on dapsone can not usually be used for diagnostic purposes.

Drug interactions: rifabutin and rifampin lower dapsone levels.

References:

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Daraprim™ see pyrimethamine

Daunorubicin, liposomal

Trade name: DaunoXome™

50 mg vials of liposomal daunorubicin

Drug class: cytostatic

Manufacturer: Gilead

Indications: AIDS-associated Kaposi's sarcoma in patients with CD4 cells < 200/µl and severe mucocutaneous or visceral KS.

Dose: initial treatment with 40 mg/m^2 q 2 wks; continued as long as KS remains clinically stabile.

DaunoXome is administered intravenously over 30-60 minutes.

Side effects: during infusion: back pain, flushing, chest tightness. Symptoms usually resolve with a lower rate of infusion or if infusion is stopped. Fatigue, headache, chills. Pancytopenia, elevated transaminases and alkaline phosphatase.

In myelosuppression (absolute neutrophil count below 1,000/mm^3): either treat with G-CSF or delay the next dose until neutrophil count has improved.

Decompensated cardiac failure can occur suddenly and even several weeks after discontinuation of therapy.

Comments/Warnings: contraindicated if there is hypersensitivity to daunorubicin or other anthracyclines; in patients who can be effectively treated with local therapy. Caution with pre-existing cardiovascular disease and patients previously treated with anthracyclines.

LVEF should be evaluated before initiation of treatment, and monitored when the cumulative dose is 240 mg/m^2 (watch out for development of cardiomyopathy!).

Regular ECG monitoring. Temporary changes such as T-wave flattening, ST-segment depression and mild arrhythmia do not necessarily require discontinuation of DaunoXome™ treatment.

Internet sources:

USA: http://hiv.net/link.php?id=82 (2.3 MB)

References:

1.   Gill PS, Wernz J, Scadden DT, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol 1996; 14: 2353-64. http://amedeo.com/lit.php?id=8708728

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DaunoXome™ see Daunorubicin, liposomal

ddC - Zalcitabine

ddC is an NRTI and was one of the first antiretroviral drugs. It is now used very rarely due to complicated dosing, risk of polyneuropathy and cross-resistance with ddI. It is presumably less potent than ddI and d4T.

Trade name: Hivid™

0.375 mg tablets

0.75 mg tablets

Drug class: NRTI

Manufacturer: Hoffmann-La Roche

Indications: HIV infection

Oral dose: 0.75 mg tid. Dose adjustment for renal failure: creatinine clearance of 40 to 10 ml/min: 0.75 mg bid, CrCl < 10 ml/min: 0.75 mg qd.

Side effects: peripheral neuropathy (up to 30 %), stomatitis with oral ulcers (up to 4 %), pancreatitis (<1 %). Rarely: rash, lactic acidosis, hepatic steatosis.

Comments/Warnings: ddC is contraindicated in patients with pre-existing poly-neuropathy. Use with caution in patients with a history of pancreatitis.

ddC should not be administered with neurotoxic drugs, e.g. ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine. Combination with ddI and d4T is not recommended, as there is little available data and a risk of cross-resistance. Combination with AZT is best.

Internet sources:

USA: http://hiv.net/link.php?id=84

References:

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ddI - Didanosine

ddI is an NRTI that was introduced in the early nineties. The main side effects of ddI are gastrointestinal complaints. Pancreatitis is a specific, though rare, side effect, which is presumably dose-dependent. It may occur in up to 10 % of patients, and can be fatal in individual cases.

ddI has a long intracellular half-life. As a result, convenient once-daily dosing is possible; however, the drug must be taken on an empty stomach.

The ddI dose should be reduced in combination with tenofovir (see below); some authors advise against this combination altogether (Clotet 2004, Negredo 2004). Combination with d4T is also problematic as there are cumulative toxicities.

Patent protection for ddI expires in August 2006 in the USA (http://hiv.net/link.php?id=243).

Trade name: Videx™

Enteric coated capsules: 125 mg, 200 mg, 250 mg, 400 mg. Powder: 4 g per bottle.

Drug class: NRTI

Manufacturer: Bristol-Myers Squibb

Indications: HIV infection

Oral dose: 400 mg qd (body weight > 60 kg) or 250 mg qd (body weight < 60 kg). ddI must be taken on an empty stomach, at least 2 hours after or at the latest 1 hour before meals.

Side effects: diarrhea, nausea, headache, rash. Pancreatitis, even after longer periods on treatment! Peripheral polyneuropathy. Rarely: episodes of lactic acidosis, especially in combination with d4T.

Comments/Warnings: acute and chronic pancreatitis are contraindications – caution in patients with alcoholism! If possible, concurrent treatment with drugs that can cause pancreatitis (e.g. intravenous pentamidine) should be avoided. The following drugs should be used with caution: ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine, etc. (peripheral neuropathy).

Concurrent dosing with tenofovir increases the C_{max} and AUC of ddI by 28 % and 44 %, respectively. The ddI dose should therefore be reduced to 250 mg. Tenofovir should be taken two hours before or one hour after ddI.

Treatment with indinavir, ddC, dapsone, ketoconazole, itraconazole, or tetracyclines should be given 2 hours before or after ddI.

Initially, monthly monitoring of amylase, blood count, transaminases and bilirubin. Patients should be informed about the risk of pancreatitis. ddI should be discontinued if there is clinical suspicion for pancreatitis, with no rechallenge.

Internet sources:

USA: http://hiv.net/link.php?id=86

References:

1. Butt AA. Fatal lactic acidosis and pancreatitis associated with ribavirin and didanosine therapy. AIDS Read 2003; 13: 344-8. http://amedeo.com/lit.php?id=12889452

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Diflucan™ see Fluconazole

Delavirdine

Delavirdine is rarely used, due to impractical dosing and drug interactions. However, the drug has theoretical potential. It is fairly well tolerated (no hepatotoxicity, no CNS problems), and increases levels of indinavir and saquinavir. Disadvantage: It has the usual NNRTI cross-resistance, and high pill burden.

Trade name: Rescriptor™

100 mg tablets

200 mg tablets

Drug class: non-nucleoside reverse transcriptase inhibitor (NNRTI)

Manufacturer: Pfizer

Indications: HIV infection

Oral dose: 400 mg tid

Side effects: rash, usually occurring within the first six weeks of treatment. In uncomplicated cases, symptomatic treatment with antihistamines. If systemic effects

such as fever, conjunctivitis, myalgia and arthralgia occur, delavirdine should be discontinued. Nausea, elevated transaminases.

Comments/Warnings: delavirdine is contraindicated for concurrent treatment with rifabutin, rifampin, carbamazepine, phenytoin, alprazolam, astemizole, phenobarbital, cisapride, midazolam, terfenadine and triazolam.

There is little data on combination with nelfinavir, lopinavir and ritonavir. Amprenavir levels seem to be reduced by delavirdine.

Delavirdine interacts with numerous drugs via reduction of CYP3A-activity. It increases the AUC of sildenafil, dapsone, clarithromycin, quinidine and warfarin. Delavirdine levels are lowered by ddI, H_2 blockers, carbamazepine, phenytoin and antacids.

Patients should know that they may also dissolve delavirdine in water: stir tablets in a glass for a few minutes and drink. Rinse the glass with a small amount of water and drink the rest.

Internet sources:

USA: http://hiv.net/link.php?id=178

References:

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Doxorubicin (liposomal)

Trade name: Caelyx™

10 ml (20 mg) and 25 ml (50 mg) vials

Drug class: anthracycline

Manufacturer: Essex

Indications: AIDS-associated Kaposi's sarcoma with < 200 CD4 cells/µl and severe mucocutaneous or visceral KS in patients not tolerating chemotherapy with other drugs or with progressive disease despite treatment.

Dose: in adults 20 mg/m^2 in 250 ml 5 % glucose solution intravenously over 30 minutes. Repeat after 3 weeks.

Side effects: myelosuppression (only 10-15 % neutropenia grade III-IV), cardiomyopathy, stomatitis (rarely severe), palmar-plantar erythrodysesthesia (PPE or hand-foot syndrome - erythematous rash which may be very painful. Treatment: cool affected areas). Rare: nausea (mild), diarrhea, alopecia.

Comments/Warnings: liposomal doxorubicin is contraindicated in decompensated cardiomyopathy, severe myelosuppression (neutrophils < 1,000/µl, platelets < 50,000/µl) and in patients who have previously received maximum cumulative doses of anthracyclines.

Cardiological examination is important (ECG, echocardiography: left ventricular ejection fraction, LVEF) before initiation of treatment and at periodic intervals during treatment. If the cumulative dose of 450 mg/m^2 is exceeded, echocardiography is necessary before each further cycle.

It is important to inform patients of PPE (may be induced by sweating, pressure, friction – therefore no tight gloves, no sun, no long warm showers, cool drinks).

Do not administer intramuscularly or subcutaneously. This drug is expensive: in Germany, two 20 mg vials cost approximately 1,343 Euro!

References:

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Efavirenz

Efavirenz is a frequently used NNRTI. However, it has multiple CNS side effects (disturbances of sleep architecture, morning dizziness, somnolence). Further disadvantages include drug interactions and cross-resistance, as with the other members of this drug class.

Trade name: Sustiva™, Stocrin™

Capsules: 50 mg, 100 mg, 200 mg, 600 mg

Drug class: NNRTI

Manufacturer: Bristol-Myers Squibb, MSD

Indications: HIV infection

Oral dose: 600 mg daily (1 capsule of 600 mg qd or 3 capsules of 200 mg qd), preferably before going to bed.

Side effects: nightmares, confusion, dizziness, somnolence, abnormal thinking, impaired concentration, insomnia, and depersonalization. These CNS symptoms usually resolve after a few weeks. A rash (15 %) may also occur in the first weeks, but severe cases of blistering, desquamation and ulceration are rare.

Elevation of liver function tests and biliary enzymes, especially γGT; hypercholesterolemia, hypertriglyceridemia.

Comments/Warnings: contraindicated in pregnancy!

Contraindicated for concurrent treatment with ergotamines, astemizole, cisapride, midazolam, terfenadine and triazolam. Should not be combined with contraceptive pills.

Should not be given in combination with saquinavir or amprenavir without ritonavir boost (insufficient plasma levels of saquinavir and amprenavir).

Dose adjustments in combination with:

- Lopinavir: increase lopinavir dose to 4 capsules bid.
- Atazanavir: increase ritonavir boost to 400 mg (ATV/RTV: 400/100); take with meals
- Indinavir: increase indinavir dose to 1,000 mg tid.
- Rifabutin: increase rifabutin dose to 450 to 600 mg/day.
- Methadone: possibly increase methadone dose by 20 to 40 %.

When switching therapy from a PI to efavirenz, overlapping therapy is recommended for one week.

Efavirenz should not be taken with fatty meals, as this reduces absorption.

Internet sources:

USA: http://hiv.net/link.php?id=88

References:

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Emtricitabine (FTC)

Emtricitabine is a well-tolerated cytidine analog, comparable to 3TC both biochemically and in its resistance profile, but has a significantly longer half-life. It can be taken once a day.

Trade name: Emtriva™

Previously: Coviracil™; also in Truvada™ in combination with tenofovir.

Hard capsules with 200 mg; solution: 170 ml with 10 mg/ml.

Drug class: NRTI

Manufacturer: Gilead

Indications: HIV infection

Dose: 200 mg qd (solution: recommended dose 240 mg = 24 ml)

Dose adjustment is required with reduced creatinine clearance:

CrCl (ml/min)	Dose
30–49	200 mg every 2 days
15–29	200 mg every 3 days
Below 14 or ialysis	200 mg every 4 days

Side effects: probably rare. Most commonly headache, nausea, diarrhea, rash. Possibly hyperpigmentation.

Internet sources:

USA: http://hiv.net/link.php?id=223

References:

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Emtriva™ see Emtricitabine

Enfuvirtide see T-20

Epivir™ see 3TC

Epzicom™ see Kivexa

Erypo™ see Erythropoetin

Erythropoietin

Trade name: Erypo™

Vials with 2,000, 4,000 or 10,000 I.U./ml

Drug class: anti-anemic

Manufacturer: Janssen-Cilag

Indications: anemia in renal failure, induced by drugs such as AZT, ribavirin or chemotherapy (symptomatic anemia; asymptomatic anemia only occurs when hemoglobin values are below 10-11 g/dl or hematocrit is below 33 %, and endogenous erythropoietin levels are below 500 mU/ml). Note: Always exclude other, more frequent causes of anemia (iron deficiency?)!

Dose: 100 I.U./kg body weight once weekly subcutaneously until a hematocrit of 30 to 35 % is reached. If there is no response after 6 weeks of treatment, increase dose to 200 I.U./kg/week. If there is no response after a further 6 weeks: discontinue. If response is achieved, a weekly maintenance dose of 100-200 I.U./kg body weight is usually sufficient. At hematocrit values > 40 % or hemoglobin > 13 g/dl: discontinue.

Side effects: flu-like symptoms especially at the start of treatment, such as headache, arthralgia, asthenia, dizziness and fatigue.

Comments/Warnings: erythropoietin is contraindicated with uncontrolled hypertension. It is expensive and should be used very sparingly. Before initiating treatment, other causes of anemia should be excluded, as mentioned above. These include:

- Vitamin B12 or folic acid deficiency, iron deficiency, occult blood loss, hematological disorders such as thalassemia and myelodysplasia.
- AIDS-defining illnesses with bone marrow involvement such as MAC infection, tuberculosis, CMV infection, malignant lymphoma, Kaposi's sarcoma.

Strict monitoring of blood pressure initially!

Subcutaneous administration of Erypo™ is **contraindicated** in patients with chronic renal insufficiency or terminal renal failure due to the risk of antibody-induced erythroblastopenia (PRCA, Pure Red Cell Aplasia).

Erypo™ must be stored at 2° to 8° Celsius in the original package. Do not freeze!

Drug interactions: erythropoietin can diminish the efficacy of concurrently administered antihypertensives. Concurrent treatment with anticonvulsive drugs may increase seizure susceptibility.

As cyclosporine A binds to erythrocytes, blood concentrations of cyclosporine A should be monitored if administered together with erythropoietin.

Ethambutol

Drug class: tuberculostatic

Manufacturer: Ethambutol is manufactured by several different companies.

Indications: tuberculosis, MAC infection

Dose: 15 to 25 mg/kg (maximum 2 g) daily, usually 3 tablets à 400 mg qd. Ethambutol should only be given as combination therapy.

Dose reduction in renal failure:

CrCl	Dose
Above 75 ml/min	25 mg/kg
40-75 ml/min	15 mg/kg
30-40 ml/min	15 mg/kg every second day
<30 ml/min	Measurement of serum levels required *

*Serum levels should be within the range of the minimal inhibitory concentration 2-5 µg/ml after 2-4 hours.

Side effects: ethambutol can lead to optical neuritis with impaired vision (decreased acuity, restricted fields, loss of red-green color discrimination). It is usually reversible if ethambutol is discontinued immediately.

Other side effects: nausea, vomiting, abdominal pain, headache, dizziness, pruritus, arthralgia, elevated serum uric acid (acute gout attacks possible!), abnormal liver function tests.

Comments/Warnings: ethambutol is contraindicated with pre-existing optical nerve damage.

Ophthalmologic examination before initiation of treatment and subsequently at 4-week intervals (color discrimination, field of vision, acuity). Immediate discontinuation to prevent optical atrophy if drug-related impairment of vision occurs.

Patients should be informed that impairment of vision may occur and to immediately report this to the treating physician.

Aluminum hydroxide reduces absorption of ethambutol; ethambutol should therefore be taken at least one hour before antacids.

Monitor liver values and uric acid levels at monthly intervals.

References:

1.   Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. N Engl J Med 1996, 335:377-83. http://amedeo.com/lit.php?id=8676931

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Filgrastim see G-CSF

Fluconazole

Fluconazole is the drug of choice for treatment of candidiasis in HIV infection and for secondary prophylaxis of cryptococcosis. It is also a component of acute therapy for cryptococcosis.

Trade name: Diflucan™

50 mg, 100 mg and 200 mg capsules

Oral solution with 50 mg per 10 ml

Powder for suspension with 50 mg per 5 ml

Bottles for infusion with 100 mg, 200 mg and 400 mg

Diflucan Derm: 50 mg capsules; oral solution with 50 mg in 10 ml

Drug class: antimycotic

Manufacturer: Pfizer

Indications: Candida infection and cryptococcal meningitis. Also certain rare mycoses.

Dose: for oral candidiasis: 100 mg qd po; for Candida esophagitis 200 mg qd for 7-10 days. Double the dose on the first day in each case. An attempt may be made with a higher dose if there is persistent candidiasis after 10 days (up to 800 mg daily).

Cryptococcal meningitis: Initially, 400 mg daily (up to 800 mg in life-threatening cases), combined with flucytosine and amphotericin B if possible. After completion of acute therapy – usually after 6 weeks – maintenance therapy with 200 mg fluconazole daily.

Renal insufficiency: halve dose with creatinine clearance of 50 to 10 ml/min; reduce to 25 % below 10 ml/min.

Side effects: overall good tolerability, rarely gastrointestinal complaints and elevated transaminases. Reversible alopecia in approximately 10 % of cases with more than 400 mg daily.

Comments/warnings: long-term treatment may lead to development of Candida-resistant strains. Fluconazole is not effective against C. krusei or Aspergillus. In cases of C. glabrata infection, higher doses are required (sensitivity is dose-dependent). Fluconazole levels are reduced with concurrent administration of rifabutin or rifampin. Fluconazole increases the serum concentrations of rifabutin (nausea, neutropenia, uveitis), atovaquone, clarithromycin, theophylline, opiates, cumarine derivatives, benzodiazepines, cyclosporine, tacrolimus, phenytoin and anti-convulsive drugs as well as AZT.

The tablets have good absorption, and infusions (2-3 times more expensive) are only required in cases of non-adherence, severe mucositis or problems with absorption.

Internet sources:

USA: http://hiv.net/link.php?id=94

References:

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Fosamprenavir

Fosamprenavir (previously GW433908) is a calcium phosphate ester of amprenavir. It has improved solubility and is better absorbed than amprenavir. This significantly reduces the number of pills compared to amprenavir. Overall tolerability is fairly good, and Fosamprenavir has an interesting resistance profile and a variety of possibilities for dosing (see below).

Trade name: USA: Lexiva™, Europe: Telzir™

700 mg capsules

Drug class: protease inhibitor

Manufacturer: GlaxoSmithKline

Indications: HIV infection, both treatment-naïve and -experienced patients

Dose: the recommended daily doses for **treatment-naïve** patients vary:

- 1,400 mg bid (without ritonavir) = 2 pills bid
- 1,400 mg qd + 200 mg ritonavir qd = 4 pills qd
- 700 mg bid + 100 mg ritonavir bid = 2 pills bid.

The once-daily version is not recommended for PI-experienced patients. **PI-experienced** patients should therefore only receive the following dose:

- 700 mg bid + 100 mg ritonavir bid (2 pills bid).

There are no restrictions with respect to fasting conditions – fosamprenavir may be taken with or without food.

Side effects: diarrhea, nausea, vomiting, headache, rash (up to 20 %). Rarely Stevens-Johnson syndrome (< 1 %).

Comments/warnings: contraindicated: cisapride, pimozide, midazolam, triazolam, ergotamines. Flecainide and propafenone are also contraindicated when fosamprenavir is boosted with ritonavir. There may be life-threatening interactions upon concurrent administration of amiodarone, lidocaine (systemic), tricyclic antidepressants and quinidine (measure levels!).

Do not use together with rifampin (this reduces amprenavir plasma levels by 90 %), delavirdine or St. John's wort; use cautiously with simvastatin, lovastatin, sildenafil, vardenafil.

Carbamazepine, phenobarbital, phenytoin and dexamethasone can lower plasma levels of amprenavir.

Efavirenz seems to lower plasma levels significantly (probably to an extent that is clinically relevant). However, this is not the case if fosamprenavir is boosted with ritonavir. But: if fosamprenavir + ritonavir are administered once-daily, the ritonavir dose should be increased by 100 mg: efavirenz + 1,400 mg fosamprenavir qd + **300** mg ritonavir qd. Twice-daily dosing does not require a dose adjustment of ritonavir.

Rifabutin: dose reduction of rifabutin by at least 50 %. If fosamprenavir is boosted with ritonavir, a 75% reduction of the rifabutin dose is required (instead of 300 mg daily, only 150 mg every other day, or 150 mg three times per week).

Ketoconazole, itraconazole: if dosed > 400 mg daily, possibly dose reduction of ketoconazole/itraconazole. If fosamprenavir is boosted with ritonavir, ketoconazole and itraconazole doses above 200 mg daily are not recommended.

Caution in patients with sulfonamide allergy.

Caution with reduced liver function (possibly dose reduction). There is no data on the combination with ritonavir for such cases.

Methadone: an increased methadone dose might be required.

Contraception: an alternative to the pill is recommended.

Caution in combination with lopinavir – plasma levels of both drugs are reduced!

Internet sources:

USA: http://hiv.net/link.php?id=222

References:

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Fortovase™ see Saquinavir

Foscarnet

Trade name: Foscavir™

250 ml and 500 ml bottles with 24 mg/ml

Drug class: virostatic

Manufacturer: AstraZeneca

Indications: reserve drug for induction and maintenance therapy of CMV retinitis. Severe acyclovir-resistant herpes or varicella zoster infections.

Dose: 90 mg/kg iv over at least 2 hours twice daily for induction therapy (2-3 weeks) of CMV retinitis. 90-120 mg/kg over 2 hours once daily for maintenance therapy.

HSV and VZV infections: 60 mg/kg iv bid for 2 weeks.

Side effects: nephrotoxicity! Usually reversible after discontinuation of foscarnet. Electrolyte changes (hypocalcemia, hypokalemia) are also common. More rarely: anemia, neutropenia, fever, rash, headache, nausea, vomiting, diarrhea. Often painful penile ulcerations (wash after every urination!!!).

Comments/Warnings: good hydration! At least 2.5 l fluids daily! To prevent hypocalcemia give one ampule of 10 % calcium solution in 100 ml 5 % glucose immediately prior to infusion of foscarnet. Give 500-1,000 ml 5 % glucose before or after foscarnet dose. Do not mix infusions.

Initial monitoring of Na, K, Ca, creatinine, blood count at least 3x/week.

No concurrent treatment with other nephrotoxic drugs.

Dose reduction is necessary in renal insufficiency.

References:

1.   Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in HIV-infected patients: results of foscarnet therapy. Clin Infect Dis 1998, 27: 1525-7. http://amedeo.com/lit.php?id=9868672

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Foscavir™ see Foscarnet

Fuzeon™ see T-20

Ganciclovir

Trade name: Cymeven™

Bottles for injection with 500 mg

Capsules (500 mg) should no longer be used. Valganciclovir is better.

Drug class: virostatic

Manufacturer: Hoffmann-La Roche

Indications: CMV retinitis. Since the approval of valganciclovir: only for use in patients for whom oral treatment is not possible.

Dose: initial treatment with normal renal function: 5 mg/kg bid as an iv infusion over one hour. Treatment duration: 14 to 21 days.

Maintenance therapy: 6 mg/kg iv qd, 5 x/week.

Side effects: leukopenia, anemia and thrombocytopenia are dose limiting. Nausea, vomiting, diarrhea or CNS symptoms such as confusion or headache are rare.

Comments/Warnings: monitor blood count at least every two days. Reduce dose by 30 % to 50 % for neutrophil counts between 500 and 800/μl; discontinue drug when neutrophil count is below 500/μl (G-CSF if necessary!).

Contraindicated in neutropenia < 500/µl, thrombocytopenia < 25,000/μl and concurrent chemotherapy (KS, NHL).

Caution if administering with ddI (increased toxicity!), as ganciclovir doubles ddI levels. Avoid combination with AZT (anemia).

Ganciclovir is a potential teratogen and carcinogen. Reliable contraception is required.

Dose adjustment is necessary in renal insufficiency.

Internet sources:

USA: http://hiv.net/link.php?id=97

References:

1.   Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multi-centric Castleman's disease with ganciclovir treatment. Blood 2003; : Blood 2003 Nov 13 http://amedeo.com/lit.php?id=14615380

2.   Czock D, Scholle C, Rasche FM, Schaarschmidt D, Keller F. Pharmacokinetics of valganciclovir and ganciclovir in renal impairment. Clin Pharmacol Ther 2002, 72: 142-50. http://amedeo.com/lit.php?id=12189361

3.   Imai Y, Shum C, Martin DF, Kuppermann BD, Drew WL, Margolis TP. Emergence of drug-resistant cytomegalovirus retinitis in the contralateral eyes of patients with AIDS treated with ganciclovir. J Infect Dis 2004; 189: 611-5. Epub 2004 Jan 28. http://amedeo.com/lit.php?id=14767813

G-CSF

Trade names: Neupogen™ (Filgrastim), Granocyte™ (Lenograstim)

Granocyte™: Vials with 13.4 mil I.U. and 33.6 mil I.U.

Neupogen™: prefilled syringes with 300 μg and 480 μg

Neupogen™: vials with 300 μg in 1 ml and 480 μg in 1.6 ml

Drug class: cytokine

Manufacturer: Amgen, Chugai Pharma

Indications: neutropenia, especially drug-induced (AZT, ganciclovir, interferon, myelosuppressive chemotherapy), rarely HIV-related.

Dose: according to protocol for chemotherapy, usually approx. 5 μg/kg Neupogen™ daily on fixed days. Outside of chemotherapy protocols, 1-5 μg/kg Neupogen™ 1-3x/week, titrate dose down. The goal is usually at least 1,000 neutrophil granulocytes/μl. For Granocyte™ doses see product information.

Side effects: bone, back or muscle pain in 10 to 20 % of patients, sometimes severe (requiring generous analgesia). Irritation at the injection site.

Comments/Warnings: G-CSF is expensive. Long-term treatment should be avoided (change the drug causing neutropenia if possible). Remainders of individual ampules should be kept refrigerated in a syringe.

Monitoring: blood count twice weekly.

Internet sources:

USA, Neupogen™: http://hiv.net/link.php?id=100

References:

1.   Campbell TB, Rapaport E, Schooley RT, Kuritzkes DR. Increased replication of HIV-1 minor variants during hematopoietic stem-cell mobilization with filgrastim. J Infect Dis 2004; 190: 257-66. Epub 2004 Jun 22. http://amedeo.com/lit.php?id=15216459

2.   Davidson M, Min YI, Holbrook JT, et al. Use of filgrastim as adjuvant therapy in patients with AIDS-related cytomegalovirus retinitis. AIDS 2002, 16:757-65. http://amedeo.com/lit.php?id=11964532

3.   Davidson M, Min YI, Holbrook JT, et al. Influence of filgrastim (granulocyte colony-stimulating factor) on HIV type 1 RNA in patients with cytomegalovirus retinitis. J Infect Dis 2002, 186: 1013-8. http://amedeo.com/lit.php?id=12232843

Hivid™ see ddC

Indinavir

Indinavir was one of the first protease inhibitors to be licensed in 1996. Problems with side effects are limiting its use today. There is manifold cross-resistance with other PIs. Indinavir requires three times daily dosing on an empty stomach in its unboosted form – an unacceptable form of administration for many patients today. Therefore, indinavir is now used almost exclusively with ritonavir boosting.

Trade name: Crixivan™

Capsules of 100 mg, 200 mg, 333 mg and 400 mg

Drug class: protease inhibitor

Manufacturer: Merck

Indications: HIV infection

Dose: in combination with ritonavir: 800 mg bid (two 400 mg capsules bid) plus 100 mg ritonavir bid (one 100 mg capsule bid). Or, 400 mg bid (one 400 mg capsule bid) plus 400 mg ritonavir bid (four 100 mg capsules bid).

Dose without ritonavir boost (uncommon): 800 mg tid (two 400 mg capsules tid) one hour before or two hours after meals.

Impaired liver function: 600 mg tid (three 200 mg capsules tid).

Side effects: nephrolithiasis (in up to 25 %). Less frequently: nephrotoxicity with elevated serum creatinine. Diarrhea, nausea, vomiting.

A sicca syndrome occurs relatively frequently (dry skin, mouth, eyes); ingrown toenails and paronychia; rarely alopecia. Asymptomatic hyperbilirubinemia.

Lipodystrophy ("Crixbelly"), dyslipidemia, disorders of glucose metabolism.

Comments/Warnings: the concurrent use of rifampin, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, or St. John's wort is contraindicated.

The following dose adjustments are necessary:

- Rifabutin: 1000 mg indinavir tid + 150 mg rifampin.
- Ketoconazole and itraconazole: 600 mg indinavir tid.
- Sildenafil: maximum 25 mg sildenafil/48h.

If unboosted, indinavir must be taken on an empty stomach. At least 1.5 l of fluid should be consumed daily to prevent nephrolithiasis. Symptoms (hematuria, flank pain) must be explained to patient. The occurrence of nephrolithiasis and skin problems correlates with plasma levels. No concurrent administration of ddI.

In combination with ritonavir, indinavir can be taken twice daily and with meals. Sufficient fluid intake is still necessary.

Internet sources:

USA: http://hiv.net/link.php?id=102

References:

1. Aarnoutse RE, Brinkman K, Benetucci J, Begovac J, Stek M Jr, Burger DM. Pharmacokinetics of indinavir/ritonavir (800/100 mg twice a day) combined with efavirenz in HIV-infected patients. AIDS 2004; 18: 565-7. http://amedeo.com/lit.php?id=15090812

2. Acosta EP, Wu H, Hammer SM, et al. comparison of two indinavir/ritonavir regimens in the treatment of HIV-infected individuals. J Acquir Immune Defic Syndr 2004; 37: 1358-1366. http://amedeo.com/lit.php?id=15483465

3. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. Antimicrob Agents Chemother 2004; 48: 1904-7. http://amedeo.com/lit.php?id=15105157

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7. Ghosn J, Lamotte C, Ait-Mohand H, et al. Efficacy of a twice-daily antiretroviral regimen containing 100 mg ritonavir/400 mg indinavir in HIV-infected patients. AIDS 2003; 17: 209-14. http://amedeo.com/lit.php?id=12545081

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9. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997, 337:725-33. http://amedeo.com/lit.php?id=9287227

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11. Schwarz JM, Lee GA, Park S, et al. Indinavir increases glucose production in healthy HIV-negative men. AIDS 2004; 18: 1852-4. http://amedeo.com/lit.php?id=15316349

12. Voigt E, Wickesberg A, Wasmuth JC, et al. First-line ritonavir/indinavir 100/800 mg twice daily plus nucleoside reverse transcriptase inhibitors in a German multicentre study: 48-week results. HIV Med 2002, 3:277-282. http://amedeo.com/lit.php?id=12444946

13. Wasmuth JC, la Porte CJ, Schneider K, Burger DM, Rockstroh JK. Comparison of two reduced-dose regimens of indinavir (600 mg vs 400 mg twice daily) and ritonavir (100 mg twice daily) in healthy volunteers (COREDIR). Antivir Ther 2004; 9: 213-20. http://amedeo.com/lit.php?id=15134183

Interferon alfa 2a/2b

Trade names: 2a: Roferon™, pegylated: Pegasys™; 2b: Intron A™, pegylated: PegIntron™

Pegasys™ (pegylated interferon alfa-2a): vials with 135 and 180 μg

PegIntron™ (pegylated interferon alfa-2b): vials with 50, 80, 100, 120 and 150 μg

Roferon-A™: prefilled syringes with 3, 4.5, 6 or 9 mil I.U. Alternatively, vials with 3 or 18 mil I.U. or cartridges with 18 mil I.U.

Intron A™ (Interferon alfa-2b): either in pen devices with 18, 30 or 60 mil I.U. or in vials with corresponding syringes and cannulas with 18 or 25 mil I.U.

Drug class: cytokine

Manufacturer: Hoffmann-La Roche (Roferon™, Pegasys™); Essex Pharma (Intron A™, PEG-Intron™)

Indications: severe Kaposi's sarcoma with good immune status (> 300 CD4 cells/μl); in such cases also always try HAART first. Chronic hepatitis C, possibly also for hepatitis B.

Dose: Pegasys™: 180 μg 1 x/week

PEG-Intron™: 1.5 μg/kg body weight 1 x/week

Standard interferons: 6 mil I.U. 3 x/week

Duration is dependent on success of treatment of KS, on HCV genotype and success of treatment for hepatitis C. Interferon is injected subcutaneously.

Side effects: influenza-like symptoms such as fever, chills, headache and myalgia are frequent. CNS side effects such as depression (even suicidality), irritability, fatigue, sleeping disorders, personality changes.

Anemia, thrombocytopenia and leukopenia. Disorders of thyroid function as in autoimmune thyroiditis. Reversible hair loss. Possibly also impaired vision.

Comments/Warnings: influenza-like symptoms usually occur a few hours after dosing and can be reduced with acetaminophen. Administration of interferon is recommended in the evenings before going to bed, and one to two 500 mg tablets acetaminophen may be taken one hour earlier.

All side effects are usually reversible after discontinuation of interferon.

Contraindications are severe liver or renal dysfunction (decompensated liver cirrhosis), severe heart disease, bone marrow disorders, CNS disorders (e.g. epilepsy, severe depression), uncompensated thyroid disorders.

Monitor blood count every two weeks initially, later monthly with standard laboratory tests. TSH every three months.

Interferons must be kept refrigerated.

References:

1. Ballesteros AL, Franco S, Fuster D, et al. Early HCV dynamics on Peg-interferon and ribavirin in HIV/HCV co-infection: indications for the investigation of new treatment approaches. AIDS 2004; 18: 59-66. http://amedeo.com/lit.php?id=15090830

2. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. N Engl J Med 2004; 351: 451-9. http://amedeo.com/lit.php?id=15282352

3. De Luca A, Di Giambenedetto S, Cingolani A, et al. Liver fibrosis stage predicts early treatment outcomes with peginterferon plus ribavirin in HIV/hepatitis C virus co-infected patients. AIDS 2004; 18: 1602-4. http://amedeo.com/lit.php?id=15238782

4. Farel C, Suzman DL, McLaughlin M, et al. Serious ophthalmic pathology compromising vision in HCV/HIV co-infected patients treated with peginterferon alpha-2b and ribavirin. AIDS 2004; 18: 1805-9. http://amedeo.com/lit.php?id=15316341

5. Keating G, Curran M. Peginterferon-alpha-2a (40kD) plus Ribavirin: A review of its use in the management of chronic hepatitis C. Drugs 2003; 63: 701-730. http://amedeo.com/lit.php?id=12656650

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7. Moreno L, Quereda C, Moreno A, et al. Pegylated interferon alpha2b plus ribavirin for the treatment of chronic hepatitis C in HIV-infected patients. AIDS 2004; 18: 67-73. http://amedeo.com/lit.php?id=15090831

8. Myers RP, Benhamou Y, Bochet M, Thibault V, Mehri D, Poynard T. Pegylated interferon alpha 2b and ribavirin in HIV/hepatitis C virus-co-infected non-responders and relapsers to IFN-based therapy. AIDS 2004; 18: 75-9. http://amedeo.com/lit.php?id=15090832

9. Neau D, Trimoulet P, Winnock M, et al. Comparison of 2 regimens that include interferon-alpha-2a plus ribavirin for treatment of chronic hepatitis C in HIV-coinfected patients. Clin Infect Dis 2003; 36: 1564-71. http://amedeo.com/lit.php?id=12802757

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11. Soriano V, Nunez M, Camino N, et al. Hepatitis C virus-RNA clearance in HIV-coinfected patients with chronic hepatitis C treated with pegylated interferon plus ribavirin. Antivir Ther 2004; 9: 505-9. http://amedeo.com/lit.php?id=15456081

12. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. N Engl J Med 2004; 351: 438-50. http://amedeo.com/lit.php?id=15282351

Interleukin-2

Interleukin-2 is not licensed for HIV therapy; it may be justified in individual cases in the absence of CD4 cell reconstitution – less than 100 CD4 cells despite several months of complete viral suppression. It should otherwise only be used within clinical studies (ESPRIT, SILCAAT).

Trade name: Proleukin™ (Aldesleukin)

Bottles for injection with 18×10^6 I.E.

Drug class: cytokine

Manufacturer: Chiron

Dose: in cycles: 4.5-9 Mio I.E. sc bid for 5 days, repeat after 6-8 weeks.

Side effects: almost obligatory fever, very often also chills. In addition fatigue, malaise, nausea/vomiting, myalgia, rarely hypotension (caution with antihypertensive drugs), dyspnea.

Comments/warnings: extensive counseling of patient! The clinician must have experience with this drug! Generous administration of paracetamol to reduce fever and influenza-like symptoms. Side effects usually subside 1-2 days after the last dose. IL-2 is contraindicated in individuals with severe coronary disease, severe infections or pO2 < 60 mm; it is also contraindicated in pregnancy.

Antihypertensive drugs may potentiate further any hypotension induced by IL-2.

IL-2 toxicity increases if hepatotoxic, nephrotoxic, myelotoxic or cardiotoxic drugs are administered at the same time.

Internet sources:

USA: http://hiv.net/link.php?id=112

References:

1. Bonnet F, Saves M, Morlat PH, et al. Correlations of soluble interleukin-2 and tumor necrosis factor type II receptors with immunologic and virologic responses under HAART. J Clin Immunol 2002, 22: 75-82. http://amedeo.com/lit.php?id=11998896

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5. Stellbrink HJ, Van Lunzen J, Westby M, et al. Effects of interleukin-2 plus highly active antiretroviral therapy on HIV-1 replication and proviral DNA (COSMIC trial). AIDS 2002, 16: 1479-1487. http://amedeo.com/lit.php?id=12131185

Intron A™ see Interferon

Invirase™ see Saquinavir

Isoniazid (INH)

Drug class: tuberculostatic

Manufacturer: isoniazid is offered by different manufacturers

Indications: combination therapy of tuberculosis.

Prophylactic treatment after tuberculin conversion.

Dose: 200 to 300 mg qd (4 to 5 mg/kg, maximum 300 mg) po, iv only in severe cases during the first two weeks of therapy. For prophylaxis of neuropathy 100 mg pyridoxine po qd.

Pediatric dose: 6 (to 10) mg/kg qd, maximum 300 mg.

Side effects: toxic hepatitis, more frequent in older patients, with chronic liver disease and alcohol abuse. Peripheral neuropathy. Discontinue isoniazid in severe cases and treat for several weeks with pyridoxine and vitamin B12. Psychosis, CNS symptoms. Fever, rash, nausea, vomiting, anemia, leukopenia, thrombocytopenia.

Comments/Warnings: contraindications are acute hepatitis and history of INH-associated hepatopathy or severe febrile reactions, peripheral neuropathy, macrohematuria.

Patients with epilepsy on treatment with carbamazepine or an hydantoin derivative might require dose adjustment of these drugs if given concurrently.

Interactions with barbiturates, cycloserine, theophylline, phenytoin and rifampin; doses of these drugs should be reduced due to CNS disorders.

Reduced absorption if taken concurrently with aluminum-based antacids.

No alcohol during treatment. Caution with ddI, d4T and ddC due to peripheral neuropathy.

Initially, biweekly monitoring of blood count, transaminases, bilirubin, and renal function. Discontinue isoniazid with elevation of transaminases to more than 3-fold initial levels and symptoms; or with a 5-fold elevation even in the absence of symptoms.

References:

1.   Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifam-picin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. Lancet 2002, 360: 528.
http://amedeo.com/lit.php?id=12241657

2.   Casado JL, Moreno S, Fortun J, et al. Risk factors for development of tuberculosis after isoniazid chemoprophylaxis in HIV-infected patients. Clin Infect Dis 2002, 34:386-389.
http://amedeo.com/lit.php?id=11753825

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5.   Scholten JN, Driver CR, Munsiff SS, Kaye K, Rubino MA, Gourevitch MN et al. Effectiveness of isoniazid treatment for latent tuberculosis infection among human immunodeficiency virus (HIV)-infected and HIV-uninfected injection drug users in methadone programs. Clin Infect Dis 2003; 37: 1686-92. Epub 2003 Nov 17. http://amedeo.com/lit.php?id=14689352

Itraconazole

Trade name: Sempera™

100 mg capsules

Oral solution (Sempera Liquid™) with 10 mg/ml (150 ml)

Drug class: antimycotic

Manufacturer: Janssen-Cilag / GlaxoSmithKline

Indications: histoplasmosis, aspergillosis, treatment-resistant Candida infections (second choice).

Dose: histoplasmosis, aspergillosis 200 mg bid.

Fluconazole-resistant Candida infections: 100 mg qd to 100 mg bid (up to 200 mg bid), ideally as itraconazole oral solution.

Side effects: nausea, vomiting, rash, dizziness. Toxic hepatitis.

Comments/Warnings: due to numerous interactions and unreliable plasma levels, oral dosing of itraconazole is problematic. However, in contrast to fluconazole, it is effective for many non-albicans strains, aspergillosis, and histoplasmosis.

No concurrent administration of itraconazole capsules with ddI, H2 blockers, omeprazole, antacids. No concurrent administration (of capsules or oral solution) with rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital, simvastatin, lovastatin and isoniazid (these lower the bioavailability of itraconazole).

Itraconazole increases serum levels of cyclosporine, calcium antagonists, digoxin, lovastatin, simvastatin and indinavir. Dose adjustment of indinavir: 600 mg tid.

Itraconazole has a negative inotropic effect and should not be given to patients with heart failure unless the benefit clearly outweighs the risk.

To achieve maximum absorption of the drug:

- the capsules should be taken immediately after a full meal. Acidic drinks such as coke and orange juice may increase absorption;
- the oral solution should be taken between meals, and not together with grapefruit juice.

Internet sources:

USA: http://hiv.net/link.php?id=114

References:

1. Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. Clin Infect Dis 2001, 33: e83-90. http://amedeo.com/lit.php?id=11550120

2. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced HIV infection in thailand. Clin Infect Dis 2002, 34: 277-284. http://amedeo.com/lit.php?id=11740718

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Kaletra™ see Lopinavir

Kivexa™

Combination pill with 3TC (300 mg) and abacavir (600 mg).

As with Ziagen™, watch for hypersensitivity syndrome.

Trade name in the USA: Epzicom™

Drug class: nucleoside reverse transcriptase inhibitors (NRTI)

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Dose: 1 tablet daily. Replace Kivexa™ with the individual drugs if kidney function is impaired (creatinine clearance below 50 ml/min), in order to adjust the 3TC dose.

Side effects: hypersensitivity syndrome with abacavir (see abacavir section!).

Comments/Warnings: abacavir hypersensitivity syndrome, which occurs in about 8 % of patients, can be life-threatening. Refer to detailed description in abacavir chapter.

Kivexa™ is contraindicated with impaired liver function.

For further information, see chapters on 3TC and abacavir.

Internet sources:

 http://hiv.net/link.php?id=240

Reference:

1.   DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin Infect Dis 2004; 39 :1038-46. http://amedeo.com/lit.php?id=15472858

Klacid™ see Clarithromycin

Lamivudine see 3TC

Lexiva™ see Fosamprenavir

Lopinavir

Lopinavir is a relatively well-tolerated PI and an effective drug for salvage therapy, particularly in PI-experienced patients with multiple resistance mutations. It remains to be proven whether or not Kaletra™ is superior to other boosted PIs for first-line therapy. Disadvantages include the often significant dyslipidemia, probably more extreme than with some other PIs. As with all PIs, lipodystrophy and various drug interactions should be considered.

Trade name: Kaletra™

Capsules with 133.3 mg lopinavir (LPV) + 33.3 mg ritonavir (RTV); bottles of 180 capsules.

Solutions with 80 mg lopinavir + 20 mg ritonavir per ml; bottles of 160 ml.

Keep refrigerated!

Drug class: protease inhibitor

Manufacturer: Abbott

Indications: HIV infection

Oral dose: 3 capsules bid or 5 ml solution bid with meals.

In combination with efavirenz or nevirapine, the dose should be increased to 4 capsules bid or 6.5 ml solution bid. Measure plasma levels!

Side effects: mainly diarrhea, nausea, dyslipidemia, and lipodystrophy. Also: headaches, and elevated transaminases.

Comments/Warnings: drug interactions are numerous. All drugs metabolized by the CYP3A or CYP2D6 enzyme systems are contraindicated: flecainide, propafenone, astemizole, terfenadine, ergotamines, cisapride, pimozide, midazolam, triazolam.

Rifampin and St. John's wort reduce the efficacy of lopinavir.

Caution with: lovastatin, simvastatin (myopathy, rhabdomyolysis), carbamazepine, phenobarbital, phenytoin or sildenafil (hypotension), amiodarone, warfarin, lidocaine, tricyclic antidepressants, quinidine, cyclosporine, tacrolimus. Measure plasma levels in patients with reduced liver function tests, especially in cases with hepatitis B or C coinfection or significantly elevated transaminases.

If lopinavir is combined with ddI, the latter must be taken one hour before or two hours after lopinavir. Lopinavir solution contains alcohol, therefore no comedication with disulfiram or metronidazole. Caution with the pill (contraception not safe).

When used with rifabutin, the rifabutin dose should be reduced by 75 %, i.e. to 150 mg qd every two days.

Increasing the methadone dose may be necessary.

Internet sources:

USA: http://hiv.net/link.php?id=116

References:

1.   Clarke S, Mulcahy F, Bergin C, et al. Absence of opioid withdrawal symptoms in patients receiving methadone and the protease inhibitor lopinavir-ritonavir. Clin Infect Dis 2002, 34: 1143-5. http://amedeo.com/lit.php?id=11915005

2.   Cvetkovic R, Goa K. Lopinavir/Ritonavir: A review of its use in the management of HIV infection. Drugs 2003; 63: 769-802. http://amedeo.com/lit.php?id=12662125

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Mavid™ see Clarithromycin

Mycobutin™ see Rifabutin

Nelfinavir

Nelfinavir is a relatively well-tolerated PI, but is slightly less potent than boosted PIs. A nelfinavir-based PI regimen is less potent than NNRTI regimens. Main problems include high pill burden and frequent diarrhea.

The 625 mg capsule allows a pill reduction to 2 capsules bid, but is not yet available everywhere.

Trade name: Viracept™

250 mg tablets; 50 mg/g oral powder, 144 g

Drug class: protease inhibitor

Manufacturer: Hoffmann-La Roche, Pfizer

Indications: HIV infection

Oral dose: 1250 mg bid or 750 mg tid with meals.

Side effects: diarrhea! Meteorism, and nausea also occur. Lipodystrophy, dyslipidemia, reduced glucose tolerance.

Comments/Warnings: contraindicated for comedication with rifampin, the pill, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, and St. John's wort.

In combination with rifabutin: 150 mg rifabutin qd and increase nelfinavir dose to 1000 mg tid.

Methadone: if withdrawal symptoms occur, dose may be increased.

Sildenafil: maximum 25 mg/48 h.

Nelfinavir should be taken with meals. Diarrhea can usually be controlled with loperamide (2 mg with each fluid bowel movement, up to a maximum of 16 mg/day).

Boosting with ritonavir is not advisable, as levels are not significantly changed.

Internet sources:

USA: http://hiv.net/link.php?id=118

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Neupogen™ see G-CSF

Nevirapine

Nevirapine is a frequently prescribed NNRTI, which is also used successfully for the prevention of mother-to-child transmission. As with all NNRTIs, a single point mutation is sufficient to develop high-level resistance. Nevirapine is very useful for simplification of successful HAART regimens. In order to prevent allergic reactions, lead-in dosing is always required.

Nevirapine has good long-term tolerability with a favorable lipid profile. The main problem, besides development of resistance, is hepatotoxicity within the first months of treatment (see below).

Trade name: Viramune™

200 mg tablets

50 mg/5 ml suspension

Drug class: NNRTI

Manufacturer: Boehringer Ingelheim

Indications: HIV infection

Oral dose: 1 tablet bid. Always start with lead-in dosing! The initial lead-in dose (1 tablet/day over two weeks) reduces the frequency of rash. For resumption of treatment after treatment interruption, lead-in dosing is generally not necessary if the drug was well tolerated. Due to its long half-life, nevirapine should be discontinued at least three days before other backbone drugs, in order to prevent the development of resistance. Nevirapine may be taken on an empty stomach or with meals.

Side effects: mainly hepatotoxicity, rash. Less frequently: fever, nausea, drowsiness, headache, myalgia. These side effects may occur with or without hepatotoxicity and/or rash. γGT elevation on nevirapine is almost the rule.

To detect **hepatotoxicity** (occurring in 15 %; defined as an increase in transaminases to at least three times the upper limit of normal), liver function tests should be monitored biweekly for the first two months. Thereafter, monthly tests are necessary, as more than half of the hepatotoxic episodes occur after the first quarter of treatment. In such cases, treatment must be interrupted until liver function tests have returned to initial levels. Treatment is restarted with 200 mg qd. The dose may be increased to 200 mg bid only after a prolonged period of observation. If liver

enzymes increase again, nevirapine should be permanently discontinued. The website of the EMEA provides detailed guidelines: http://hiv.net/link.php?id=120.

A **rash**, often pruritic and usually occurring within the first six weeks of treatment, can be treated with antihistamines if mucous membranes are not involved and if transaminases are normal. Topical formulations are effective against pruritus. Nevirapine must be discontinued if a severe rash occurs; in these cases, steroids may be used (e.g. prednisolone 1 mg/kg for 3-5 days). Nevirapine should also be discontinued if other systemic symptoms occur (fever, conjunctivitis, myalgia, arthralgia, malaise). If the rash occurs during the first two weeks of treatment, the dose should not be increased until the rash has resolved completely. Prophylactic treatment with steroids or antihistamines is not advised.

Comments/Warnings: cautious use in hepatic dysfunction (measure plasma levels).

Contraindicated for comedication with rifampin, ketoconazole, St. John's wort and the pill.

Azole derivatives: fluconazole should be used for antimycotic treatment.

Dose adjustment in combination with

- Lopinavir: possibly increase Kaletra™ dose to 4 capsules bid (measure plasma levels!)
- Indinavir: increase indinavir dose to 1000 mg tid.
- Methadone: if withdrawal symptoms occur, dose may need to be increased.

Nevirapine has a favorable long-term profile. In particular, lipid levels are usually positively influenced. γGT is almost always increased during long-term treatment. Values of up to 150 U/l can be tolerated. Nevirapine should not be given for post-exposure prophylaxis.

Internet sources:

USA: http://hiv.net/link.php?id=121

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Norvir™ see Ritonavir

Pegasys™ see Interferon

PegIntron™ see Interferon

Pentacarinat™ see Pentamidine

Pentamidine

Trade name: Pentacarinat™

300 mg vials

Drug class: antibiotic

Manufacturer: Aventis, GlaxoSmithKline

Indications: treatment and secondary prophylaxis of Pneumocystis pneumonia if co-trimoxazole is contraindicated (hypersensitivity, resistance to treatment).

Dose: treatment: 200-300 mg Pentacarinat™ iv for five days (4 mg/kg), then halve the dose. In very mild cases, daily inhalations with 300 mg. In renal failure and creatinine clearance of 50 to 10 ml/min: 4 mg/kg q 24-36 h; below 10 ml/min: 4 mg/kg q 48 h.

Prophylaxis: inhalation of 300 mg 1-2 x/month.

Side effects: frequent with intravenous dosing! Nausea, vomiting, metallic taste; nephrotoxicity (increased creatinine in the second week of treatment) up to renal failure. Hypo- or hyperglycemia (may start even months after end of treatment), acute hypotension, arrhythmia, pancreatitis. Leukopenia and thrombocytopenia.

Inhalation may induce cough, rarely asthma.

Comments/Warnings:

Inhalation: pentamidine as an aerosol is contraindicated in asthma and treatment with beta-blockers. Inhalation may be ineffective with pulmonary disease. Prior inhalation of a ß-mimetic may be desirable.

Infusions: caution in liver or renal failure, hyper- or hypotension, hyperglycemia, cytopenia. Always ensure sufficient intake of electrolytes and fluids. No concurrent administration of other nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, foscarnet). Patient should remain in supine position before, during and after infusions of pentamidine (caution: hypotension!). Pentamidine should be infused slowly over at least 2 hours! Daily monitoring of BUN, serum creatinine, blood count, fasting blood glucose, urinalysis and serum electrolytes, weekly monitoring of bilirubin, alkaline phosphatase, transaminases.

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Proleukin™ see Interleukin-2

Pyrimethamine

Trade name: Daraprim™

25 mg tablets

Manufacturer: GlaxoSmithKline

Indications: prophylaxis and treatment of cerebral toxoplasmosis. Prophylaxis of Pneumocystis pneumonia.

Dose: treatment of toxoplasmosis: Daraprim™ 2 tbl. à 25 mg bid (for 3 days, then halve the dose) **plus** Leucovorin™ 1 tbl. à 15 mg every other day **plus either** sulfadiazine, clindamycin or atovaquone (second choice).

PCP prophylaxis in combination with dapsone: Daraprim™ 2 tbl. à 25 mg per week **plus** Dapsone™ 1 tbl. à 50 mg qd **plus** Leucovorin™ 2 tbl. à 15 mg per week.

Side effects: nausea, colics, vomiting, diarrhea, leukopenia, anemia or thrombocytopenia. Rarely seizures, tremor or ataxia.

Comments/Warnings: pyrimethamine is contraindicated in megaloblastic anemia resulting from folic acid deficiency. Caution in patients with seizures, renal failure, asthma or G6PD deficiency. All patients taking pyrimethamine should receive folinic acid to decrease risk of myelosuppression. Initial monitoring of blood count at weekly intervals.

Product information UK: http://hiv.net/link.php?id=124

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Rebetol™ see Ribavirin

Ribavirin

Trade name: Copegus™ (Roche), 200 mg tablets

Rebetol™ (Essex), 200 mg capsules

Drug class: virostatic

Indications: chronic Hepatitis C, only in combination with interferon

Dose: total daily dose 800 mg for body weight < 65 kg, 1000 mg for 65-85 kg, 1200 mg for > 85 kg. Capsules are divided into two daily doses and taken with food. The duration of treatment depends on the genotype and success of treatment.

Side effects: the most frequent side effect is hemolytic anemia; gastrointestinal complaints, headache and fatigue may also occur. Rarely lactic acidosis, pancreatitis in combination with NRTIs.

Comments/Warnings: ribavirin is contraindicated in severe coronary disease, renal failure, decompensated liver cirrhosis, and hemoglobinopathy. It is also contraindicated in pregnancy and reliable contraception is required due to ribavirin's potential teratogenicity.

Dose reduction for hemoglobin < 10 g/dl or for a decrease in hemoglobin of more than 2 g/dl. Reduce dose to 600-800 mg/day; consider erythropoetin.

Discontinue ribavirin at hemoglobin values < 8.5 g/dl.

Avoid concurrent treatment with other myelosuppressive medications.

Ribavirin can lead to lactic acidosis in combination with other nucleoside analogs! The risk seems increased particularly for concurrent dosing with ddI. But care should be taken with all other NRTIs!

Efavirenz-induced depression may worsen on ribavirin.

Monitoring of laboratory values (blood count, AST, ALT, amylase, lipase) initially at biweekly intervals, later monthly. Lactate measurement if unspecific symptoms occur!

Internet sources:

USA: Copegus™:   http://hiv.net/link.php?id=197,   Rebetol™: http://hiv.net/link.php?id=126

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Rescriptor™ see Delavirdine

Retrovir™ see AZT

Reyataz™ see Atazanavir

Rifabutin

Trade name: Mycobutin™

150 mg capsules

Drug class: antibiotic

Manufacturer: Pharmacia

Indications: infections with Mycobacterium avium complex (MAC) in combination with two other drugs (usually ethambutol and azithromycin).

Dose: 300 mg rifabutin daily (+ azithromycin + ethambutol).

Renal failure: dose reduction by 50 % for creatinine clearance < 30 ml/min.

Dose adjustments for concurrent dosing with antiretroviral drugs:

Drug	Recommendation
Atazanavir/r*	Rifabutin: 150 mg every other day or three times per week
Fosamprenavir/r	Rifabutin: 150 mg every other day or three times per week
Indinavir/r*	Rifabutin: 150 mg every other day or three times per week
Lopinavir/r*	Rifabutin: 150 mg every other day or three times per week
Saquinavir/r*	Rifabutin: 150 mg every other day or three times per week
Tipranavir/r*	Consider rifabutin 150 mg every other day or 3 times per week. Further dosage reduction may be necessary.
Nelfinavir	Nelfinavir 1000 mg tid or 1250 mg bid + Rifabutin: 150 mg qd
Delavirdine	Rifabutin is contraindicated
Efavirenz	Rifabutin: Increase to 450 QD or 600 mg twice or three times weekly
Nevirapine	Standard dose

* /r = boosted with ritonavir

Side effects: Nausea, vomiting, elevation of liver enzymes, jaundice. Uveitis usually only with a daily dose > 300 mg and concurrent treatment with clarithromycin or fluconazole. Red discoloration of urine, skin and body secretions (patients should be informed about this!).

Comments/Warnings: Rifabutin is contraindicated in cases of known hypersensitivity to rifabutin and rifampin; also in thrombocytopenia and severe hepatic dysfunction.

Rifabutin can decrease the efficacy of the following drugs:

analgesics, anticoagulants, corticosteroids, cyclosporine, digitalis (except digoxin), dapsone, oral antidiabetics, oral contraceptives, narcotic analgesics, phenytoin and quinidine.

Erythromycin, ketoconazole, itraconazole, fluconazole and clarithromycin can increase plasma levels of rifabutin.

Antacids should be taken at least three hours after rifabutin.

Monitor blood count and liver enzymes initially biweekly, later monthly.

Internet sources:

USA: http://hiv.net/link.php?id=129

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Rifampin

Drug class: tuberculostatic

Manufacturer: rifampin is manufactured by several companies

Indications: tuberculosis.

Dose: 600 mg daily (body weight > 50 kg) or 450 mg (body weight < 50 kg).
Ideally taken in the morning on an empty stomach!

Side effects: toxic hepatitis (up to 20 %), cholestatic changes. Red discoloration of
urine and other body fluids (inform patients of this!). Soft contact lenses may per-
manently stain red. Allergies are frequent. Gastrointestinal complaints such as nau-
sea, vomiting, diarrhea.

Comments/Warnings: caution in patients with chronic liver disease. Discontinue
rifampin if ALT > 100 U/l or with elevated bilirubin (careful re-exposure with
gradually increasing doses is possible after normalization of values), and in patients
with severe and persistent diarrhea (pseudomembranous colitis!).

Rifampin should be avoided if concurrent ART with NNRTIs or PIs is necessary.

Rifampin increases metabolism of numerous drugs, reducing their efficacy if administered concurrently. These drugs include atovaquone, warfarin, barbiturates, benzodiazepines, beta-blockers, clarithromycin, contraceptives, steroids, oral anti-diabetics, cyclosporine, dapsone, digitalis, doxycycline, erythromycin, haloperidol, ketoconazole, methadone, phenytoin, theophylline, trimethoprim, verapamil.

Combination with ketoconazole or voriconazole is contraindicated.

Antacids, opiates and anticholinergics reduce the bioavailability of orally administered rifampin if given simultaneously. To avoid this interaction, rifampin should be given several hours before these drugs.

Not for use in pregnancy.

Blood count and liver values should be monitored fortnightly.

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Ritonavir

Due to its gastrointestinal side effects, the therapeutic dose of ritonavir is hardly acceptable and rarely prescribed. However, ritonavir has become an important drug for boosting other protease inhibitors. In these combinations, when lower doses are used, side effects of ritonavir are tolerable. Numerous drug interactions must be considered.

Trade name: Norvir™

100 mg soft gel capsules

80 mg/ml oral solution

Drug class: protease inhibitor

Manufacturer: Abbott

Indications: HIV infection

Oral dose: in rare cases, in which ritonavir is used as a single PI, the dose is 600 mg bid (increase dose over two weeks: 300 mg bid on day 1-2, 400 mg bid on day 3-5, 500 mg bid on day 6-13).

The optimal use of ritonavir, however, is for boosting of other PIs! Daily doses in combination with

- Saquinavir (Fortovase™ or Invirase™):

    100 mg ritonavir bid + 1000 mg saquinavir bid

    or

    400 mg ritonavir bid + 400 mg saquinavir bid

- Indinavir (Crixivan™):

    100 mg ritonavir bid + 800 mg indinavir bid

    or

    400 mg ritonavir bid + 400 mg indinavir bid

- Amprenavir (Agenerase™):

    100 mg ritonavir bid + 600 mg amprenavir bid

    or

    200 mg ritonavir qd + 1200 mg amprenavir qd

- Lopinavir (Kaletra™): Fixed combination, see lopinavir.

- Atazanavir (Reyataz™): 100 mg ritonavir qd + 300 mg atazanavir qd.

- Fosamprenavir: 200 mg ritonavir qd + 1400 mg fosamprenavir qd (once-daily is not suitable for treatment-experienced patients!)

    or

- 100 mg ritonavir bid + 700 mg fosamprenavir bid

Side effects: very frequent when used as single PI (600 mg bid): nausea, vomiting, diarrhea, headache, perioral paresthesia and electric sensations on arms and legs. Elevated transaminases and γGT, often significant dyslipidemia, reduced glucose tolerance and, rarely, diabetes mellitus. Lipodystrophy.

Comments/Warnings: even the low boosting doses used in combination with other PIs have multiple drug interactions! The following are contraindicated: rifampin, amiodarone, astemizole, bepridil, terfenadine, encainide, flecainide, cisapride, triazolam, ergotamine, simvastatin, lovastatin, quinidine, and St. John's wort. Sildenafil should be avoided!

Caution should be taken and plasma levels measured for both ritonavir and (if possible) the following comedications: methadone, immunosuppressants (cyclosporine, tacrolimus), macrolide antibiotics (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclic antidepressants, other antidepressants (fluoxetine, paroxetine,

sertraline), neuroleptics (haloperidol, risperidone, thioridazine), antimycotic drugs (ketoconazole, itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline, and warfarin.

Internet sources:

USA: http://hiv.net/link.php?id=31

References:

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Roferon see Interferon

Saquinavir

Saquinavir was the first PI to be licensed for HIV therapy in 1995. It is well tolerated except for gastrointestinal problems, and with no serious short-term problems. It is almost exclusively used together with a ritonavir boost. Recently, film-coated tablets (Invirase 500™) have been approved in both the US and the EU. Invirase 500™ is now the preferred formulation of saquinavir.

Trade name: Invirase™, Fortovase™

500 mg film-coated tablets (Invirase 500™) = preferred formulation of saquinavir !

200 mg soft gel capsules (Fortovase™)

200 mg hard gel capsules (Invirase™) = should no longer be used

Drug class: protease inhibitor

Manufacturer: Hoffmann-La Roche

Indications: HIV infection

Oral dose: Combination with ritonavir is generally preferred: Invirase™ or Fortovase™: 1000 mg bid plus 100 mg ritonavir bid.

Treatment without boosting (only in exceptional cases): 1200 mg (Fortovase™) tid (6 capsules tid).

Side effects: mainly gastrointestinal: diarrhea, nausea, abdominal discomfort, meteorism. Rarely elevation of transaminases or γGT, headache. As with other PIs, lipodystrophy, dyslipidemia and reduced glucose tolerance may occur with long-term treatment.

Comments/Warnings: contraindicated for comedication with rifampin, astemizole, terfenadine, cisapride, triazolam, ergotamine, simvastatin, lovastatin, and St. John's wort.

If saquinavir is not combined with other protease inhibitors it must be taken with meals.

Internet sources:

USA: http://hiv.net/link.php?id=132

References:

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Sempera™ see Itraconazole

Sobelin™ see Clindamycin

Stavudine see d4T

Sulfadiazine

Drug class: sulfonamide antibiotic

Indications: treatment and prophylaxis of cerebral toxoplasmosis, only in combination with pyrimethamine.

Dose: For treatment 2-3 500 mg tablets qid (daily dose 4-6 g). For prophylaxis halve the dose (500 mg qid)!

Renal insufficiency: creatinine clearance 50-10 ml/min: halve dose. At values below 10 ml/min: administer one third of the dose.

Side effects: very frequently allergies with pruritus, fever and urticaria, often treatment-limiting. Rare: Stevens-Johnson syndrome. Gastrointestinal complaints such as nausea, vomiting, diarrhea. Renal problems with renal failure, crystalluria, nephrolithiasis in up to 7 %. Anemia, leukopenia, thrombocytopenia. Elevated liver enzymes.

Comments/Warnings: sulfadiazine   is   contraindicated   in   sulfonamide hypersensitivity and allergies to sulfonyl urea antidiabetics, acetazolamide or thiazide diuretics; also in G6PD deficiency, renal failure and severe hepatic disease or dysfunction (e.g. acute hepatitis); and during pregnancy and breastfeeding.

Sulfadiazine can increase levels of sulfonyl ureas (oral antidiabetics), anticoagulants, diphenylhydantoin.

Concurrent dosing with antacids reduces absorption of sulfadiazine (separate administration 1-2 hours apart).

Ensure sufficient intake of fluids (at least 2 l daily).

Monitor blood count, ALT, creatinine, and BUN at least weekly initially.

Monitor urine! In case of crystalluria: alkalize urine.

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Stocrin™ see Efavirenz

Sustiva™ see Efavirenz

T-20 (Enfuvirtide)

T-20 is the prototype of a new drug class – the entry inhibitors. It has been licensed in the USA and Europe since 2003 for the treatment of HIV-1 infection in treatment-experienced adults and children above 6 years who have received at least one drug out of each of the antiretroviral drug classes (PI, NNRTI and NRTI) and developed treatment failure or intolerance.

T-20 is well tolerated, but can only be administered subcutaneously as an injection. However, this drug is important in salvage therapy.

Not unimportant: treatment costs are more than 2,000 Euro per month. T-20 doubles the cost of HAART.

Trade name: Fuzeon™

Drug class: fusion inhibitor (or entry inhibitor)

Manufacturer: Hoffmann-La Roche

Indications: treatment of HIV-1 infection in patients with evidence of HIV-1 replication despite ongoing HAART.

Dose: 90 mg subcutaneously bid.

Side effects: generally well tolerated. However, almost all patients have local injection site reactions: erythema, inflammation, induration, rash (change injection sites!). There may be inflammation at more than one site. In the licensing studies, approximately 10 % of patients required intermittent use of analgesics or were tem-

porarily affected in their daily activities. However, only 3 % of patients had to stop therapy.

Patients on T-20 possibly have an increased risk of contracting bacterial pneumonia. Therefore, it is important to be particularly vigilant in patients with risk factors for pneumonia (low baseline CD4+ count, high viral load, iv drug users, smokers, history of pulmonary disease).

Hypersensitivity reactions with rash, fever, nausea, chills, hypotension or elevated transaminases are rare (< 1 %).

Comments/warnings: interactions with other drugs are not known.

Injection sites: upper arm, ventral hip, and abdomen. Change injection sites! Do not inject at sites with inflammatory signs from previous injections. Do not inject at sites with naevi, scars or disrupted skin integrity.

Internet sources:

USA: http://hiv.net/link.php?id=225

References:

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Tenofovir

Tenofovir DF is the prodrug of the acyclic **nucleotide** analog tenofovir, and has good oral bioavailability. It also has efficacy against hepatitis B virus. Tenofovir has a good tolerability profile and probably only low mitochondrial toxicity. However, several interactions must be considered (particularly with once-daily drugs such as ddI and atazanavir!), as well as weak efficacy in triple nuke regimens. Cautious use in patients with renal disease.

Some authors now warn of combination with ddI.

Trade name: Viread™, Truvada™

300 mg tablets

Drug class: nucleotide reverse transcriptase inhibitor

Manufacturer: Gilead

Indications: HIV infection

Oral dose: 300 mg qd, to be taken with a meal.

Dose adjustments for renal insufficiency:

CrCl (ml/min)	Dose
30–49	300 mg every two days
15–29	300 mg twice per week
Patients on dialysis	300 mg once weekly or after a total of 12 hours of dialysis

Side effects: generally well tolerated. Rarely: elevation of liver enzymes. Rare cases of renal failure have been reported, partly in the form of Fanconi's syndrome, a defect of proximal tubular transport. Patients with existing renal disease should therefore either not receive tenofovir or otherwise always require dose reduction.

It is not currently known whether long-term treatment with tenofovir can lead to bone density changes. Animal studies showed changes in bone density at doses 30 times higher than the therapeutic dose.

Comments/Warnings: concurrent treatment with tenofovir and other drugs that are eliminated via active tubular secretion can lead to increased serum concentrations of both drugs: cidofovir, acyclovir, valacyclovir, ganciclovir, valganciclovir.

Use with caution in combination with ddI: co-medication with tenofovir increases the Cmax and AUC of ddI by 28 % and 44 %, respectively. Pancreatitis may occur, and therefore the dose of ddI should be reduced to 250 mg. Tenofovir should be taken two hours before or one hour after ddI.

Atazanavir and lopinavir increase tenofovir levels.

Larger controlled studies on the use of tenofovir in pregnancy are yet to come. In monkey studies, tenofovir was effective in the prophylaxis of SIV transmission, but also resulted in growth disorders.

Internet sources:

USA: http://hiv.net/link.php?id=134

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Tipranavir

Tipranavir is the first nonpeptidic PI. It has good efficacy against many strains of HIV that are resistant to other commercially available protease inhibitors.

Trade name: Aptivus™

250 mg capsules

Drug class: non-peptide protease inhibitor (NPPI)

Manufacturer: Boehringer Ingelheim

Indications: Combination treatment of HIV-infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV strains resistant to multiple protease inhibitors.

Oral dose: Tipranavir has shown greater effectiveness when taken in combination with 200 mg ritonavir. The approved dose of ritonavir-boosted tipranavir regimens is 500 mg tipranavir plus 200 mg ritonavir, both taken twice daily and used in combination other anti-HIV drugs.

Contraindication: Moderate and severe hepatic impairment (Child-Pugh Class B and C).

Combination with rifampin and delavirdine.

Side effects: diarrhea, nausea, vomiting, headache, abdominal pain. Rash. Elevated transaminases, amylase, cholesterol, triglycerides. Rarely: dizziness, fatigue, depression, insomnia.

Comments/Warnings: antacids reduce tipranavir levels by 30 %; rifampin reduces levels by 80 %.

Tipranavir lowers the levels of lopinavir, saquinavir and amprenavir. As a result, double PI regimens with these drugs should currently not be considered.

Tipranavir contains a sulfonamide component. Use cautiously in persons with sulfonamide allergy.

Patients with hepatitis B or C co-infection have a higher risk of hepatotoxicity and monitoring is advised. Obtain liver function tests at baseline and during treatment.

Tipranavir should not be taken with moderate or severe hepatic impairment; hepatitis, hepatic decompensation, and fatalities have been reported with tipranavir-ritonavir.

ddI should be taken at an interval of several hours to tipranavir.

Refrigerate before opening bottle; may store at room temperature and use within 60 days after opening.

References:

1.   Hicks C. RESIST-1: a phase 3, randomized, controlled, open-label, multicenter trial comparing tipranavir/ritonavir to an optimized comparator protease inhibitor/r regimen in antiretroviral experienced patients: 24 week data. Abstract H-1137a, 44th ICAAC 2004, Washington.

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Trizivir™

Trizivir is a fixed combination of AZT+3TC+abacavir. It is frequently used to simplify HAART regimens.

A disadvantage of Trizivir is that is does not seem to be as effective as "divergent" combinations comprised of several drug classes. It is an interesting option for patients with compliance problems, and also for patients with a long list of

comedications with potential drug interactions (tuberculostatic drugs, cumarine derivatives).

Trade name: Trizivir

Tablets containing 150 mg 3TC **and** 300 mg AZT **and** 300 mg abacavir.

Drug class: NRTI

Manufacturer: GlaxoSmithKline

Indications: HIV infection

Oral dose: 1 tablet bid. In cases of impaired renal function (creatinine clearance less than 50 ml/min), the individual drugs should be given separately to allow for dose adjustment of 3TC and AZT.

Side effects: mostly gastrointestinal, see the individual drugs. Hypersensitivity reaction with abacavir (see under abacavir!). There are possibly additive effects with regard to mitochondrial toxicity.

Comments/Warnings: watch closely for hypersensitivity reactions (see abacavir). See individual drugs.

Internet sources:

USA: http://hiv.net/link.php?id=51

References:

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Truvada™

Truvada™ is a fixed-dose combination pill containing tenofovir (300 mg) and emtricitabine (200 mg). It was licensed by the EMEA in November 2004, and reached the market in early 2005. Overall tolerability is good. Truvada is a component of many once-daily HAART regimens.

Drug class: nucleoside and nucleotide reverse transcriptase inhibitor (NRTI).

Manufacturer: Gilead

Indications: HIV infection

Oral dose: 1 tablet daily

With reduced creatinine clearance of 30-49 ml/min, it is recommended to reduce the dose to 1 tablet every two days. Truvada should not be prescribed at values lower than this.

Side effects: see chapter on tenofovir

Comments/Warnings: refer to information in the tenofovir chapter.

In HIV/HCB-coinfected patients with chronic hepatitis, exacerbation of hepatitis may occur after discontinuing Truvada. In such cases, clinical and laboratory monitoring is recommended for several months.

Absorption of Truvada is not affected by food intake.

Internet sources:

USA: http://hiv.net/link.php?id=241

References:

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      418. Abstract WePeB5701, XV Int AIDS Conf 2004, Bangkok.

Valcyte™ see Valganciclovir

Valganciclovir

Valganciclovir is the first CMV drug with good efficacy that can be administered orally. Valganciclovir is a prodrug of ganciclovir and therefore has a similar toxicity profile: neutropenia, anemia and thrombocytopenia. Due to the improved bioavailability, valganciclovir has largely replaced the earlier form of ganciclovir.

Trade name: Valcyte™

450 mg tablets

Drug class: virostatic

Manufacturer: Hoffmann-La Roche

Indications: oral induction and maintenance therapy of CMV retinitis.

Dose: for induction therapy 900 mg bid for 3 weeks (or until scar formation of CMV lesions), then suppressive therapy with 900 mg qd.

The following doses should be used for renal failure:

CrCl (mL/min)	Induction therapy	Suppressive therapy
> 60	900 mg bid	900 mg qd
40 – 59	450 mg bid	450 mg qd
25 – 39	450 mg qd	450 mg q 48 h
10 – 24	450 mg q 48 h	450 mg 2 x/week

Side effects: frequently leukopenia, but also thrombocytopenia, anemia. Gastrointestinal complaints such as nausea, vomiting and diarrhea are more frequent than with intravenously-administered ganciclovir.

Comments/Warnings: monitoring of blood count at least 2-3 x/week during induction. Discontinuation if neutrophils below 500/µl (G-CSF if needed!). Contraindicated in neutropenia < 500/µl, thrombocytopenia < 25,000/µl and concurrent chemotherapy (Kaposi's sarcoma, NHL).

Caution when concurrent dosing with ddI, as valganciclovir can double levels of ddI (increased toxicity!).

Valganciclovir is potentially teratogenic and carcinogenic; reliable contraception is required.

Valganciclovir must be taken with meals.

The drug is extremely expensive! It should be discontinued when sufficient immune reconstitution has been reached (see OI chapter).

Internet sources:

USA: http://hiv.net/link.php?id=135

References:

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Vfend™ see Voriconazole

Videx™ see ddI

Viracept™ see Nelfinavir

Viramune™ see Nevirapine

Viread™ see Tenofovir

Vistide™ see Cidofovir

Voriconazole

Voriconazole is a very promising oral broad spectrum antimycotic. A comparative study of voriconazole and amphotericin B for the treatment of invasive aspergillosis showed significantly better treatment results with voriconazole after 12 weeks (53 % versus 32 %).

Trade name: Vfend™

50 mg and 200 mg tablets

Bottles for injection with 200 mg

Drug class: antimycotic

Manufacturer: Pfizer

Indications: treatment of invasive aspergillosis; treatment of fluconazole-resistant, severe Candida infections (including C. krusei); treatment of severe fungal infections caused by Scedosporium spp and Fusarium spp.

Dose: 200 mg bid po

For intravenous dosing: 3 to 6 mg/kg every 12 hours.

Side effects: elevated transaminases, rash and impairment of vision most commonly led to discontinuation of treatment in clinical studies.

Visual impairments (overly bright images, blurred vision, light sensitivity or altered color vision) occurred in approximately 30 %, usually appearing within 30 minutes of taking voriconazole, and lasting approximately 30 minutes.

More rarely fever, nausea, vomiting, diarrhea, headache, abdominal pain.

Comments/warnings: voriconazole is metabolized via the cytochrome 450 enzymatic pathway. Serum levels of voriconazole may be significantly reduced by several drugs, which are therefore contraindicated for co-administration: rifampin, carbamazepine, barbiturates.

Serum levels of several drugs are significantly elevated by voriconazole, and therefore comedication is contraindicated: sirolimus, ergotamine derivatives, terfenadine, astemizole, cisapride, pimozide, quinidine.

Concurrent administration of rifabutin is also contraindicated.

Administration together with NNRTIs or protease inhibitors (exception: indinavir) may require dose modifications, as is the case with a number of other drugs: cyclosporine, tacrolimus, anticoagulants, digoxin, statins, calcium antagonists, vincristine, vinblastine, phenytoin, omeprazole (see product information).

Voriconazole tablets should be taken one hour before or two hours after a meal.

Avoid strong sun exposure, and driving at night (due to potential visual impairment).

References:

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Zerit™ see d4T

Ziagen™ see Abacavir

Zidovudine see AZT

Zovirax™ see Acyclovir

29. Drug-Drug Interactions

Leonie Meemken and Laura Dickinson

Drug-drug interactions are divided into pharmacodynamic (PD) and pharmacokinetic (PK) interactions.

PD drug-drug interactions can change the pharmacological effect of drugs. Furthermore, the pharmacological effect and, indeed, side effects of two or more drugs can act additively or antagonistically.

PK drug-drug interactions are associated with inappropriate plasma concentrations of drugs. Changes in plasma concentrations can be the result of inadequate absorption, transport, metabolism or elimination. In HIV therapy, a considerable number of drug-drug interactions occur during transport via p-glycoprotein or metabolism by isoenzymes of the cytochrome P450 enzyme system (Piscitelli 2001).

Mechanism of drug-drug interactions during metabolism

The cytochrome P450 enzyme system consists of an array of isoenzymes. Approximately 50 % of all drugs are substrates of CYP3A4, including HIV protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). CYP3A4 resides in the liver and enterocytes of the gastrointestinal tract; therefore partial metabolism begins in the intestine.

The rate of metabolism can depend on the genetic polymorphism of the enzymes involved. Therefore, absence of enzymes or reduced enzyme activity leads to a prolonged storage period of drug in the body.

Drugs metabolized by P450 enzymes can have an effect by way of three processes: by metabolism as a substrate, by inhibition or induction of enzymes, or a combination of these three, for example ritonavir (RTV), efavirenz (EFV) and nelfinavir (NFV). The specific drug combination determines which function is dominant.

Substrate

Substrates are metabolized by P450 enzymes and their plasma concentrations are influenced by drugs that inhibit or induce their metabolic pathway.

Inhibitors

Many inhibitors inhibit specific P450 enzymes in an **irreversible** way. Metabolism will return to normal once the inhibitor has been removed and new enzymes have been produced.

> Example: PIs are CYP3A4 inhibitors and inhibit the metabolism of calcium-channel blockers metabolized via CYP3A4.

Clinically relevant CYP3A4 inhibitors include PIs, imidazole antifungals, macrolides, nefazodone and selective serotonin re-uptake inhibitors (SSRI).

They can all inhibit the metabolism of CYP3A4 substrates (e.g. imidazole antifungals, calcium-channel blockers, immunosuppressants, lipid lowering agents, oral contraceptives, PIs). Inhibition of enzymes can cause a dose-related increase of plasma concentrations within minutes or hours, thus potentially causing toxicity. So drugs with a long half-life and a narrow therapeutic index can cause serious side effects.

Furthermore, two substrates can **competitively** inhibit each other **reversibly** if both are substrates of the same enzyme.

> Example: Cyclosporin and PIs are both competitively metabolized by CYP3A4.

Inducers

Inducers increase the production of enzymes and thus accelerate metabolism. Consequently, the plasma levels of substrates are lowered, producing subtherapeutic concentrations. This has particular relevance for HIV therapy as this can lead to loss of virological control and development of resistance. CYP3A4 inducers include carbamazepine, phenytoin, rifabutin, rifampicin and St John's Wort. The maximal inducing effect is usually achieved after one to two weeks of intake. After stopping therapy with an inducer, the effect of this drug interaction will continue for a few days or weeks until the enzyme quantity returns to the baseline level (Haefeli 2000).
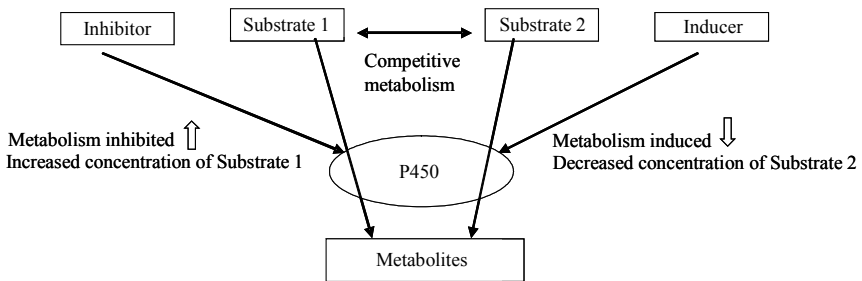
Figure.1: Metabolism of substrates via CYP450.

Important drug-drug interactions in HIV therapy

NRTIs

Elimination

Tenofovir (TDF) is primarily eliminated by a combination of glomerular filtration and active renal tubular secretion. There may be competition for elimination with drugs that are also excreted by this pathway, such as cidofovir, valganciclovir and ganciclovir. Patients receiving concomitant nephrotoxic agents should be carefully monitored for changes in serum creatinine and phosphate levels. Toxic reactions can appear to be dose related.

Added virological failure has been observed in patients with high viral load and low CD4 cell count when didanosine (DDI) is administered in combination with TDF. However, further studies are warranted to confirm this effect. Increased DDI plasma concentrations in the presence of TDF have been well investigated, and a DDI dose reduction to 250 mg once daily is recommended. Patients should be closely monitored for DDI-associated side effects such as pancreatitis and neuropathy (Piscitelli 2001).

> Advice: the combination of TDF 300 mg and DDI 250 mg can be administered with food (Kearney 2001).

Moreover, increased DDI concentrations have been demonstrated in patients with renal failure taking allopurinol (Liang 2001).

Intracellular Phosphorylation

Drug-drug interactions during intracellular phosphorylation have been shown to occur *in vitro* when ribavirin is co-administered with zidovudine (AZT), stavudine (D4T) or DDI. Whereas plasma concentrations of AZT and active D4T metabolites decrease in the presence of ribavirin, plasma concentrations of active DDI metabolites increase. The *FDA Adverse Event Reporting System* describes 24 patients who developed toxic symptoms (pancreatitis, peripheral neuropathy and symptomatic hyperlactatemia/lactic acidosis), on average one month after initiation of therapy containing these drugs (FDA Announcement). These symptoms also occur when AZT and DDI are combined (Piscitelli 2001).

Pharmacodynamic drug-drug interactions

PD drug-drug interactions play an important role within the NRTI class because of the potential for additive side effects. A summary of additive toxic effects within the NRTI class and in combination with comedications is described in table 1.

NNRTIs

EFV and nevirapine (NVP) are inducers of CYP3A4, therefore drugs metabolized via this enzyme are eliminated more rapidly when combined with them. Additionally, *in vitro* data describes an inhibitory effect of EFV.

Dose adjustments of a number of PIs are recommended in the presence of NNRTIs. A dose increase of lopinavir (LPV) and atazanavir (ATV) is suggested due to decreased concentrations (lopinavir/r from 400/100 mg BID to 533/133 mg BID and atazanavir/r from 300/100 mg QD to 400/100 mg QD). No dosage adjustment is necessary in combination with other **boosted** PIs or unboosted nelfinavir (NFV) (Clinical Pharmacology Database 2004).

Table 1: Additive toxic effects (DHHS Guidelines 2005)

Hematotoxicity	Peripheral neuropathy	Pancreatitis	Nephrotoxicity	Liver toxicity
Amphotericin B	DDC	Co-trimoxazole	Acyclovir (iv)	Azithromycin
AZT	DDI	DDI	Adefovir	Clarithromycin
Cidofovir	D4T	D4T	Aminoglycosides	Delavirdine
Co-trimoxazole	Isoniazid	Pentamidine	Amphotericin	Efavirenz
Cytotoxic drugs	Linezolid	RTV	Cidofovir	Fluconazole
Dapsone		3TC (children)	Foscarnet	Isoniazid
Flucytosine			Indinavir	Itraconazole
Ganciclovir			Pentamidine	Ketoconazole
Hydroxyurea			RTV	Nevirapine
Interferon			Tenofovir	NRTIs
Linezolid				Protease inhibitors
Peginterferon				Rifabutin
Primaquine				Rifampin
Pyrimethamine				Voriconazole
Ribavirin				
Rifabutin				
Sulfadiazine				
Valganciclovir				

Protease inhibitors

PIs are inhibitors of CYP3A4. RTV and LPV/r are strong inhibitors; other PIs have a weaker inhibitory effect (Tseng 1999). The strong inhibitory effect of RTV has been exploited to an advantage. A low dose of RTV is sufficient to enhance otherwise unfavorable PK of other PIs, therefore allowing twice-daily and, in some cases, once-daily dosing. Two boosting effects have been observed: inhibition of elimination (resulting in prolonged half-life: indinavir; IDV, amprenavir; APV and ATV) and inhibition of metabolism (increasing maximum plasma concentrations: saquinavir; SQV and LPV).

Combination of two PIs in the presence of low dose RTV may provide added potency and prove to be useful salvage regimens. However, complex and difficult to predict interactions can result. PK studies are required to ensure that therapeutic plasma concentrations are achieved and unfavorable interactions avoided. It is important to use therapeutic drug monitoring (TDM) to monitor plasma concentrations of PIs in double PI regimes in an attempt to optimize therapy (see chapter on Salvage-therapy).

Drug-drug interactions between comedications and PIs can generally result in increased plasma concentrations of the comedications in the presence of boosted PI regimens.

Comedication

PIs are well known to increase plasma concentrations of comedications, resulting in an increased number and strength of side effects due to inhibition of CYP3A4. Common adverse events attributable to these interactions are illustrated in table 2. To avoid such side effects, the dosage of comedications should be adapted in specific combinations; otherwise drugs with a low affinity for the cytochrome P450 system should be used in preference.

Table 2: Common side effects caused by drug-drug interactions between comedications and protease inhibitors (Dresser 2000)

Comedication	Side effects
Terfenadine, cisapride, pimozide	QT-prolongation
Simvastatin, lovastatin	rhabdomyolysis, myalgia
Calcium-channel blockers, anti-arrhythmic drugs, phosphodiesterase inhibitors	hypotension
Benzodiazepines, antidepressants	sedation
Carbamazepine	ataxia
Ergot alkaloids	ergotism

Antituberculosis drugs

Rifampicin should be avoided because of its strong inducing effect resulting in an increased risk of virological failure and development of resistance. In addition, serious side effects can occur in combination with PIs. As an alternative, rifabutin is used at a reduced dosage of 3 x 150 mg/week with **boosted** PIs (*e.g.* LPV, SQV, APV, IDV) or unboosted PIs (ATV, NFV). An increased rifabutin dose of 450 QD or 600 mg two or three times per week is recommended in combination with EFV (CDC Guidelines 2004). Further information is available in the Tuberculosis chapter.

Antifungal drugs and Macrolides

Antifungal drugs (ketoconazole, itraconazole, fluconazole) and macrolides (erythromycin, clarithromycin) are CYP3A4 inhibitors and increase plasma concentrations of NNRTIs and PIs. However, fluconazole has only a weak inhibitory effect. Increased plasma concentrations are shown for drugs combined with fluconazole at a dose of more than 200 mg QD. Due to this weak interaction compared with other imidazole antifungals, fluconazole is a more favorable choice in HIV therapy. Additionally, ketoconazole and itraconazole are associated with hepatotoxicity and require an acidic environment for optimal absorption. An alternative antifungal drug for specific fungal infections is the more expensive caspofungin, which can also be easily combined with antituberculosis drugs because of its low affinity for P450 enzymes.

Azithromycin is a macrolide, which possesses a low potential for drug-drug interactions with antiretroviral drugs, with the exception of NFV (Piscitelli 2001).

Methadone

NNRTIs reduce methadone plasma concentrations within the first 14 days of intake, therefore opiate withdrawal can occur in these patients. In these cases, doses of methadone should be increased in 10 mg steps. Drug-drug interactions between methadone and PIs are not particularly predictable. Reduced methadone concentrations are described with RTV, NFV and LPV/r. However, reduced methadone concentrations are not always associated with opiate withdrawal. When co-administered, reduced concentrations of APV and methadone have been reported; therefore APV TDM is recommended (Antoniou 2002).

Herbals

St John's Wort is an herbal preparation used to treat depression. Its active constituent, hypercillin has strong induction properties. St. John's wort has been reported to induce both CYP3A4 and p-glycoprotein. IDV plasma concentrations were decreased by up to 50 % (Piscitelli 2000) and NVP by up to 35 % (de Maat 2001). For this reason, St. John's wort is contraindicated in combination with PIs and NNRTIs and patients should be advised about this.

Subtherapeutic plasma concentrations of SQV (administered 1200 mg TID) were also observed in combination with garlic supplements. Allicin, one active agent of garlic capsules, decreases trough concentrations of unboosted SQV by up to 49 % and AUC by 51 %. After discontinuing garlic intake, 60-70 % of SQV plasma concentrations returned to baseline levels (Piscitelli 2002).

In a PK study using 7 patients, reduced plasma concentrations of IDV were measured in combination with unboosted IDV and 1000 mg vitamin C. Minimum concentrations of IDV decreased by about 32 % (Slain 2003).

Potential inducing effects of ginseng have been shown *in vitro* (Henderson 1999); studies are warranted to establish these effects in patients.

Drugs of abuse/recreational drugs

Drug interactions involving drugs of abuse are of particular concern due to an increased risk of life threatening side effects. However, not surprisingly, data in this area are sparse. Several fatal cases with regard to the simultaneous intake of RTV and ecstasy (MDMA) or gammahydroxybutyrate (GHB) have been reported in the literature (Hales 2000, Harrington 1999). Metabolic inhibition of amphetamines, MDMA and phencyclidine (PCP), can result in hypothermia, hypertension, arrhythmias, tachycardias and cramps. Reduced metabolism of ketamine can result in respiratory depression, hallucinations and unconsciousness. Increased LSD plasma concentrations are associated with hallucinations, psychosis, agitation and flashbacks, and GHB with cramps, bradycardia, unconsciousness or respiratory depression. Cocaine, in the presence of NNRTIs, is metabolized more rapidly so that the liver toxic metabolite norcocaine can accumulate (Antoniou 2002). Marijuana (tetrahydrocannibinol, THC) probably has a lower interaction potential (Kosel 2002). Moreover, the effects of recreational drugs on the metabolism of antiretrovirals (ARVs) are not well known and require careful consideration. When patients insist on using recreational drugs, the doses of some should be reduced by up to a quarter of the original dose. Alcohol should be avoided, breaks should be taken during

dancing and continuous water intake is necessary to avoid dehydration. It is important to monitor for symptoms of recreational drug-associated adverse events.

Summary

In an attempt to predict or avoid drug-drug interactions, a complete medication history, including herbal remedies and recreational drug use is necessary. In particular, combinations involving inducers (*e.g.* rifampicin) and inhibitors (*e.g.* ketoconazole) can result in unfavorable plasma concentrations of ARVs. For example, inhibitors can increase concentrations of ARVs to such an extent that toxicity develops and inducers can reduce concentrations to a point where resistance can occur. If there are no clear clinical data about a specific drug-drug interaction, theoretical consideration can help to exclude severe drug-drug interactions. It is important to look at the bilateral effect of HIV therapy: *ARVs can influence comedications and vice versa.* Dose adjustments of ARVs and/or comedications may need to be considered. For detailed information on drug interactions refer to www.hiv-druginteractions.org

Drug plasma concentrations can also be influenced by many different factors such as age, gender, liver disease and genetic polymorphism. Individualized dosing with the use of TDM is, in many cases, very important.

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Individual Drugs

Comment: plasma concentrations of drugs are affected by many factors: such as ethnicity, kidney and liver failure, age or sex. Therefore predictions of possible interactions can be challenging and in a number of cases therapeutic drug monitoring (TDM) can prove useful. Abbreviations used in this table: AUC = area under the curve, QD = once daily, BID = twice daily, ↓↑ = AUC decrease or increase, TDM = therapeutic drug-monitoring, TID = three times daily

3TC

Lamivudin, Epivir™ ; component of Combivir™ and Trizivir™, Kivexa™

Approved dose: 150 mg BID or 300 mg QD

Elimination: renal

Drugs	Interactions	Comments
NRTIs		
DDC, FTC [1-3]	Antagonism	**Avoid combination.**
NNRTIs [1-3]	No significant interaction	
PIs [1-3]	No significant interaction	

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Abacavir

ABC, Ziagen™; component of Trizivir™, Kivexa™

Approved dose: 300 mg BID or 600 mg QD

Metabolism via alcohol dehydrogenase and glucuronidation pathway

Drugs	Interactions	Comments
Alcohol [1-3]	ABC ↑ 41 %.	Not clinically significant.
NRTIs [1-2]	Not clinically significant.	
NNRTIs [1-2]	Not clinically significant.	Caution when starting concomitant therapy: (NNRTI-allergy/ABC-HSR*).
PIs TPV/r [4]	ABC: 40% ↓	Clinical relevance is unknown. No dose adjustment at the moment.

* HSR = hypersensitivity reaction

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Amprenavir

see Fosamprenavir

Atazanavir

ATV, Reyataz™

Approved dose: ATV/RTV: 300/100 mg

Metabolism: Atazanavir (ATV) is primarily metabolised by CYP3A4 and inhibits CYP3A4, CYP2C9, CYP1A2 and UDP-glucuronosyltransferase (UGT)-1A1 [1].

Drugs	Interactions	Comments
NRTIs		
TDF [2,31]	ATV 400 + TDF 300 QD [2]: ATV ↓ 25 % (Cmin 40 % ↓)	ATV/RTV 300/100 QD. [2,3] Taken with a light meal.
	ATV/r 300/100 +TDF 300 QD: ATV ↓ 11% (Cmin 20 % ↓) TDF ↑ 37% (Cmin 29 % ↑)	Boosted ATV plasma concentration are 2-4-fold higher than unboosted ATV without TDF.
NNRTIs		
EFV [3-5]	ATV 400 + EFV 600 QD: ATV ↓ up to 74 % [4,5]	ATV/RTV 400/100 QD [3]. Taken with a light meal.
NVP [24]	Theoretically: NVP ↓	No data.
PIs		
IDV/r [3,6]	Risk of additive hyperbilirubinemia	**Avoid combination.**
SQV/r [8,9]	ATV 300 + SQV/r 1600/100 QD: SQV ↑ 60 %, RTV ↑ 41 % [8]	Synergistic effect [9].
NLF [26]	NLF 1250 BID + ATV 400 QD: Cmin NLF: 57,4%↑, M8: 124%↑, No effect on AUC, Cmax, Tmax	
FPV/r [27]	ATV 150 or 200 + FPV/r 700/100 BID: all levels > 0,27 mcg/ml for ATV and > 0,28 mcg/ml for APV	Adaequate plasma levels of both drugs in the combination.
LPV/r [28,30]	LPV/r 400/100BID + ATV400QD: if necessary: + NRTI o.NNRTI ATV-level above 150 ng/ml, LPV- level above 1400 ng/ml	Case reports.

Drugs	Interactions	Comments
Antiarrhythmic drugs Amiodarone, bepridil, quinidine, flecainide, lidocaine [3,11]	Theoretically: antiarrhythmic drugs ↑	**Avoid combination:** bepridil, quinidine [3]. Possible: dose adjustment of the antiarrhythmic drugs.
Antibiotics Clarithromycin [12]	Clarithromycin ↑ 1,9-fold (Caution: QT-prolongation) Active Clarithromycin metabolite ↓ 70 %, ATV ↑ 30 %	**Avoid combination** or 50 % dose reduction of Clarithromycin. Theoretical alternative: azithromycin.
Erythromycin [13]	Theoretically: ATV ↑	
Anticoagulants Warfarin	Theoretically: warfarin ↑	Check INR
Antidepressants Tricyclic antidepressants [14]	Theoretically: tricyclic antidepressants ↑	Monitor anticholinergic effects.
St. John's wort [3]	Theoretically: ATV ↓	**Avoid combination.**
Antiepileptics Carbamazepine, phenytoin, primidon [3]	Theoretically: ATV ↓	Theoretical alternative: gabapentin, lamotrigine, valproic acid.
Antifungal drugs Itraconazole, ketoconazole, voriconazole [18]	Theoretically: ATV ↑	Theoretical alternative: fluconazole.
Antihistamines Loratadine (> 20 mg), terfenadine [3,15,16]	Theoretically: antihistamines ↑ risk of QT-prolongation ↑	**Avoid combination:** terfenadine, loratadine (> 20 mg) [3]. Theoretical alternative: cetirizine, fexofenadine [15,16].
Antihypertensives Calcium-channel blockers [17] such as bepridil, diltiazem, nifedipine, verapamil	Bepridil, diltiazem ↑ 2-fold Theoretically: calcium-channel blockers ↑	Theoretically: dose reduction of calcium-channel blockers. 50 % dose reduction of diltiazem.
Bosentan [11,23]	Theoretically: ATV ↓	**Avoid combination** or TDM. Off label use: sildenafil for pulmonary hypertension.

Drugs	Interactions	Comments
Antipsychotic drugs Bromperidol, chlorprothixen, clozapine, flupendixol, haloperidol, pimozide, risperidone, sertindole	Theoretically: antipsychotics ↑	**Avoid combination** with pimozide**.** Monitor for side-effects of antipsychotics. Prefer: atypical antipsychotics (less anticholinergic effects).
Antituberculosis drugs Rifampicin [21]	90 % AUC-reduction of the protease-inhibitors	**Avoid combination.**
Rifabutin [21]	ATV 400 + Rifabutin 150 QD: Rifabutin ↑ 2-fold	ATV 400 QD + rifabutin 150 mg 3 times a week.
Cytotoxic drugs Paclitaxel, vinca-alkaloids [22], irinotecan [3]	Theoretically: cytotoxic drugs ↑	Monitor side-effects.
Gastritis-/ Ulcer healing drugs Proton pump inhibitor (PPI)	Omeprazole 40 + ATV/r 300/100: ATV ↓ 76 % (Cmin 78 % ↓)	**Avoid combination:** PPI not recommended.
H2-receptor antagonists, antacids [25,29]	Famotidin + 1./2./3. 1. ATV 400 QD = ATV-level 40-50% ↓ 2. ATV/r 300/100 QD = ATV-level of ATV/TDF 3. ATV/r 400/100 QD = ATV-level = ATV 300/100 QD	**At least 12h time-lag:** H2-receptor antagonists, antacids. ATV/r + H2-receptor antagonists: concurrent intake could be possible.
Hypnotics Barbexaclone, phenobarbital	Theoretically: ATV ↓	**Avoid combination** or TDM.
Benzodiazepine (such as alprazolam, triazolam, diazepam, midazolam, zolpidem) [10]	Theoretically: benzodiazepine ↑	**Avoid combination:** midazolam, triazolam. Theoretical alternative: oxazepam, lorazepam, temazepam.
Immunosuppressants Cylosporine, sirolimus, tacrolimus [11]	Theoretically: immunosuppressants ↑	Dose adjustment of immunosuppressants with TDM.
Lipid-lowering drugs Atorvastatin, lovastatin, simvastatin [19]	Theoretically: statins ↑	**Avoid combination:** lovastatin, simvastatin. Theoretical alternative: pravastatin, fluvastatin, rosuvastatin.
Oral contraceptives [11]	ATV: ethinylestradiol ↑ 48 %, norethindrone ↑ 110 % RTV: ethinylestradiol ↓	Monitor for side-effects, when necessary reduce dose.
Phosphordiester-		

Drugs	Interactions	Comments
ase-type 5 Inhibitors (PPH)		
Sildenafil, tadalafil vardenafil [11]	Theoretically: PPH ↑	Start with lowest dose.
Substitution		
Methadone	No data	
Others		
Ergot alkaloids [11]	Theoretically: ergotamine ↑	**Avoid combination:** Theoretical alternative: triptane.

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32. Aptivus™, Boehringer Ingelheim.

AZT

Zidovudin, Retrovir™; component of Trizivir™, Combivir™

Approved dose: 250 or 300 mg BID

Metabolism: Glucuronidation pathway, Elimination: renal

Drugs	Interactions	Comments
NRTIs		
D4T [1-3]	Antagonism	**Avoid combination.**
NNRTIs	No significant interaction	
Antibiotics		
Atovaquone	AZT ↑ 35 % ± 23 %	Monitor for AZT side-effects.
Clarithromycin [4]	AZT ↓ 10-25 %	Take 2 - 4 h apart, monitor for AZT efficacy.
Cotrimoxazol [2]	Haematotoxicity ↑	
Dapsone [5]	Haematotoxicity ↑	
Antiepileptics		
Fosphenytoin, pheny-toin [2]	Clearance of AZT ↓ 30 % and phenytoin ↑↓	Monitor for AZT side-effects, TDM of phenytoin.
Valproic acid [2]	AZT ↑ 79 %	Monitor for AZT side-effects.
Antifungal drugs		
Fluconazole [2]	AZT ↑ 74 %	Monitor for AZT side-effects.
Antimalarials		
Pyrimethamine [2]	Increased hematotoxicity ↑	
Antiviral Drugs		
Acyclovir [7]	Case report: profound lethargy	
Cidofovir [8]	Increased hematotoxicity ↑	See: Probenecid.
Foscarnet [6]	Increased risk of anaemia ↑ (less risky than with ganciclovir)	
Ganciclovir [9-10], Valganciclovir	Increased hematotoxicity ↑	**Avoid combination.** Theoretical alternative: Foscarnet + AZT. Ganciclovir +DDI.
Interferon [11]	Increased hematotoxicity ↑	If necessary, reduce AZT dose.
Ribavirin [12]	In vitro AZT-antagonism, in vivo case reports of increased viral load, increased risk of mitochondrial toxicity (e.g. lactic acidosis)	**Avoid combination.**
Cytotoxic drugs		
Doxorubicin [2] and a lot of other cytotoxic drugs.	Increased hematotoxicity ↑	**Avoid combination** or control haemogram closely. Monitor kidney function.
Substitution		
Methadone [14]	AZT ↑ 41 %	Monitor for AZT side-effects.

Drugs	Interactions	Comments
Uricosuric drug		
Probenecid [13]	AZT ↑ 80 %	Monitor for AZT side-effects. Take 50% of AZT dose when combined with cidofovir and probenecid.

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D4T

Stavudin, Zerit™

Approved dose: > 60 kg: 20 mg BID, < 60 kg: 15 mg BID

Elimination: 34-43 % renal

Drugs	Interactions	Comments
NRTIs		
AZT	Antagonism	
DDI [1]	Risk of lactic acidosis, pancreatitis, neuropathy ↑	Not recommended for first line therapy, but for patients with a specific resistance profile.
DDC [1]	Risk of neuropathy ↑	**Avoid combination.**
Co-Medication		
Dapsone [1]	Risk of neuropathy ↑	**Avoid combination.**
Isoniazid	Risk of neuropathy ↑	**Avoid combination.**
Pentamidine [3]	Additive pancreas toxicity when given i.v.	**Avoid combination.** Start D4T after one week.
Ribavirin [4-6]	Case reports about an increased viral load in combination with D4T, further an increased risk of mitochondrial toxicity (e.g. lactic acidosis, pankreatitis)	Closely monitor amylase, lipase, lactate.
Vinca Alkaloid [1]	Risk of neuropathy ↑	**Avoid combination.**

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DDC

Zalcitabin, Hivid™

Approved dose: 0,75 mg TID

Elimination: 62-75% renal

Drugs	Interactions	Comments
NRTIs		
DDI [1-2]	Toxicity ↑	**Avoid combination.**
3TC [1-2]	Antagonism	**Avoid combination.**
D4T [1-2]	Risk of neuropathy ↑	**Avoid combination.**
FTC	Antagonism	**Avoid combination.**
NNRTIs	No significant interaction	
PIs	No significant interaction	
Co-Medication		
Aminoglycosides [2]	DDC-toxicity ↑ (reduced clearance)	**Avoid combination.**
Amphotericin [2]	DDC-toxicity ↑ (reduced clearance)	**Avoid combination.**
Antacids [3]	DDC ↓ 25 %	**Avoid combination.**
Cimetidine [1]	DDC ↑ 36 %	**Avoid combination.**
Dapsone [4]	Dapsone clearance ↓ 20 % (concentrations ↑), risk of neuropathy ↑	**Avoid combination.**
Foscarnet [2]	DDC-toxicity ↑ (reduced clearance)	**Avoid combination.**
Isoniazid	Risk of neuropathy ↑	**Avoid combination.**
Pentamidine [5]	Additive pancreas toxicity when given i.v.	**Avoid combination.**
Probenecid [3]	DDC ↑ 50 %	**Avoid combination.**
Vinca Alkaloid	Risk of neuropathy ↑	**Avoid combination.**

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DDI

Didanosine, Videx™

Approved dose: < 60 kg: 250 mg QD, > 60 kg: 400 mg QD

Metabolism: Hypoxanthine-oxidase; elimination: 30-50 % renal

Drugs	Interactions	Comments
NRTIs		
D4T [1-3]	Risk of lactic acidosis, pancreatitis, neuropathy ↑	Not recommended for first line therapy, but for patients with a specific resistance profile.
TDF [3-5]	DDI EC 250 QD + 300 TDF QD has equivalent DDI AUC compared to DDI 400 mg alone. Dose recommendation: Patients ≥ 60 kg: DDI 250 mg Patients < 60 kg: DDI 200 mg	**Probably unfavourable combination.** Virological failure in patients with high viral load and low CD4 cells [4]. Closely monitor amylase, lipase, lactate.
	Despite dose reduction there is probably an increased risk of lactic acidosis and pancreatitis	Take DDI and TDF together with food.
DDC [1-3]	Toxicity ↑	**Avoid combination.**
PIs		
ATV [1,3]	DDI tablets: ATV ↓ 87 %, DDI-EC: no data	Take DDI 2h apart from ATV.
Co-Medication		
Allopurinol [6]	DDI ↑ 122 % (Cmax ↑ 116 %)	**Avoid combination,** especially in renal failure.
Cimetidine [1]	Theoretically: DDI ↑	Monitor side-effects.
Dapsone [7]	Increased risk of neuropathy ↑	**Avoid combination.**
Ganciclovir (GCV), Valganciclovir (VGCV) [8-10]	Risk of lactic acidosis and pancreatitis ↑ GCV i.v.: DDI ↑ 70 % (VGCV is metabolised to GCV)	Closely monitor amylase, lipase, lactate.
Isoniazid	Risk of neuropathy ↑	**Avoid combination.**
Methadone [11]	DDI 41 % ↓	Not clinically significant.
Pentamidine [12]	Additive pancreas toxicity when given i.v.	**Avoid combination or stop** DDI and start after 1 week again.
Ribavirin RBV [13]	In vitro: DDI + active metabolite ↑ risk of lactic acidosis, pancreatitis, neuropathy ↑	**Avoid combination.** Do not combine DDI and RBV !
Vinca Alkaloids [1]	Risk of neuropathy ↑	Vinblastine less neurotoxic than vincristine.

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Efavirenz

EFV, Sustiva™, Stocrin™

Approved dose: 600 mg QD

Metabolism: Efavirenz is mainly metabolised by CYP2B6 and minor by CYP3A4 and CYP1A2. In vitro EFV is an inducer of CYP3A4 and a poor inhibitor of CYP3A4,-2C9,-2C19 [1].

Note: wrong positive Cannabinoid test in urine with CEDIA DAU multilevel THC assay [2].

Drugs	Interactions	Comments
NRTIs	not clinically significant interactions [1]	
NNRTIs Nevirapine NVP [3,33]	NVP 400 QD + EFV [3]: EFV ↓ 22 % (Cmin 36 % ↓)	**Unfavourable combination.** Less efficacy and increased toxicity [33].
PIs APV/r [4-6,32]	APV/r 600/100 BID + EFV: APV ↓ 77 % (Cmin ↓, Cmax 80% ↓) [4]	APV/r: 450/200 BID [4]. APV/r: 600/200 BID [5,6.].
FPV/r	FPV/r 700/100 BID+ EFV 600 QD: => No clinically significant interaction	Off label use: when use FPV/r QD, increase RTV up to 300 mg /d [32].
ATV [7,8]	ATV 400 QD + EFV: ATV ↓ up to 74 %	ATV/r: 300/100 QD.
IDV/r [2,9,10]	1. IDV 800 TID + EFV [2] : IDV ↓ 31 % (Cmin 40 % ↓)	1. IDV 1000 TID.
	2. IDV/r 800/100 BID + EFV : IDV ↓ 19 % (Cmin 48 % ↓) [9]	2. IDV/r 800/100, probably higher doses for pre-treated patients are necessary [10].
LPV/r [11]	LPV/r 400/100 + EFV: LPV ↓ 25 % (Cmin 44 % ↓)	LPV/r: 533/133 BID. Caution: increase LPV/r dose may not be adequate, monitor with TDM.
SQV/r [12-15]	SQV 1200 TID + EFV: SQV ↓ 62 % [12,13]	SQV/r 400/400 BID or SQV/r 1200/100 QD [14,15].
NFV [2,16]	1. NFV 750 TID + EFV [2] : NFV ↑ 20 %, M8 ↓ 40 %	1. In this study no dose adjustment necessary.
	2. NFV 1250 BID + EFV: NFV ↓ 38 % [16]	2. Not clinically significant, possibly monitor with TDM.

Drugs	Interactions	Comments
Antiarrythmic drugs Amiodarone, bepridil, quinidine, flecainide, lidocaine	Theoretically: antiarrythmic ↓ ↑	**Avoid combination.**
Antibiotics Clarithromycin [2,17,18]	Clarithromycin 500 BID + EFV 400 QD: active Clarithromycin metabolite ↑ 34 % (Cmax 49 % ↑) 46 % developed exanthema [2,18]	Theoretical alternative: azithromycin [17].
Erythromycin [17]	Theoretically: EFV ↑	Monitor for EFV side-effects. Theoretical alternative: azithromycin.
Antiepileptics Carbamazepine, phenytoin, primidone [2]	Theoretically: EFV ↓	**Avoid combination** or TDM. Theoretical alternative: gabapentin, valproic acid, lamotrigine.
Antifungal drugs Itraconazole, ketoco-nazole, voriconazole [2,21]	Theoretically**:** EFV ↑, Azole ↓ Voriconazole + EFV: voriconazole 77 % ↓ (Cmax 61 % ↓) EFV ↑ 44 % (Cmax 38 % ↑)	**Avoid combination:** vorico-nazole. Itra-/ ketoconazole: not stud-ied. Theoretical alternative: fluconazole [1].
Antihistamines Astemizole, loratadine (> 20 mg), terfenadine [1,2,19,21]	Theoretically: antihistamines ↓↑ Risk of QT-prolongation [1,21]	**Avoid combination:** Ter-fenadine. Theoretical alterna-tive: cetirizine, fexofenadine [2,19].
Antihypertensives Calcium-channel blockers such as Felo-dipine, nifedipine, verapamil [23]	Theoretically: calcium-channel blockers ↓ ↑	Perhaps reduce dose of cal-cium-channel blockers.
Bosentan [18,31]	Theoretically: EFV ↓ [18]	**Avoid combination** or TDM. Off label use: sildenafil is used for pulmonary hyperten-sion [31].
Antipsychotic drugs Bromperidol, chloropro-thixen, clozapine, flupendixol, haloperi-dol, pimozide, risperi-done, quetiapine, sertindole [2,18,28]	1. Theoretically: antipsychotics ↓↑ 2. Clozapine (active metabolite ↑) 3. QT-prolongation of pimozide	**Avoid combination** with pimozide. Prefer: atypical antipsychotics (less anticholinergic effects).

Drugs	Interactions	Comments
Antituberculosis drugs		
Rifabutin [2,16,29]	Rifabutin ↓ 38 % (Cmax 32 % ↓)	Rifabutin 450 mg QD or 600 mg two or three times per week.
Rifampicin [2,29, 36,37]	EFV ↓ 26 % (Cmax 20 % ↓)	EFV 800 QD; probably EFV 600 for patients < 50 kg only with TDM.
Cytotoxic drugs		
Cyclophosphamide [18,30]	Theoretically: neurotoxic metabolite ↑	Avoid additional neurotoxic drugs.
Hypnotics		
Barbexaclone, phenobarbital	Theoretically: EFV ↓	**Avoid combination** or TDM.
Benzodiazepine (e.g. Diazepam, midazolam triazolam), zolpidem [2,22]	Theoretically: benzodiazepine ↓	**Avoid combination:** midazolam, triazolam [2]. Theoretical alternative: lorazepam, oxazepam, temazepam [22].
Immunosuppressants		
Cylosporine, sirolimus, tacrolimus	Report about dose reduction of cylosporine when combined with EFV [35].	Dose adjustment of immunosuppressants via TDM.
Herbals		
St. John's Wort [2]	Theoretically: EFV ↓	**Avoid combination.**
Lipid-lowering drugs		
Atorvastatin, lovastatin, simvastatin [24-26]	Atorvastatin and simvastatin 48 % and 58 % ↓, respectively	Theoretical alternative: Pravastatin, fluvastatin, rosuvastatin.
Oral contraceptives [2]	Oestrogen ↑, ethinylestradiol ↑ 37 %	Use additional contraception method. Not enough data.
Phosphordiesterase-Inhibitors (PPH)		
Sildenafil, tadalafil, vardenafil	Theoretically: PPH ↓ ↑	Caution: low starting dose.
Recreational drugs		
Cocaine [27]	Theoretically: norcocaine ↑	Caution: liver toxicity.
Substitution		
Methadone [27]	Methadone: 60 % ↓	Opiate withdrawal within 2 weeks. If necessary increase methadone dose up to 100 %. Dose reduction of methadone when stopping EFV therapy.

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Emtricitabine

FTC, Emtriva™; component of Truvada™

Approved dose: 200 mg QD

Elimination: renal

Drugs	Interactions	Comments
NRTIs DDC, 3TC	Antagonism	**Avoid combination.**
NNRTIs	No significant interaction	
PIs	No significant interaction	

Fosamprenavir

FPV, Lexiva™, Telzir™

Approved dose: APV/r: 600/100 mg BID, FPV/r: 700/100 mg BID (where APV/r alternatively FPV/r are stated in the tables administered at their approved dose)

Metabolism: Fosamprenavir (FPV) is a prodrug of Amprenavir (APV) and is hydrolysed in the gut epithelium by cellular phosphatases during absorption to the active compound. APV is metabolised by CYP3A4 and is an inhibitor of CYP3A4 (as potent as Indinavir and Nelfinavir). Additionally, there are reports suggesting that APV is also an inducer of CYP3A4 (35). Except the drug interaction between APV and LPV/r, the inducing effect may not be seen with the dose commonly used for boosting.

In boosted APV regimes, ritonavir (RTV) could contribute to the reported drug interactions. RTV is a strong inhibitor of CYP3A4 and a poor inhibitor of CYP2D6 and an inducer of CYP3A4, CYP1A2, CYP2C9 and the glucuronidation pathway [1].

Drugs	Interactions	Comments
NRTIs [3,30,31]	No interactions with AZT, 3TC, ABC, DDI, TDF	
NNRTIs EFV [4-6]	FPV/r + EFV 600 QD: => Interactions not clinically significant	Off label use: when use FPV/r QD, increase RTV dose up to 300/d [6].
NVP [7,8]	FPV/r + NVP 200 BID: => Interactions not clinically significant	In this study no dose adjustment was necessary.
PIs ATV [17,18]	ATV 150 or 200 + FPV/r 700/100 BID: all levels > 0,27 mcg/ml for ATV and > 0,28 mcg/ml for APV	Adaequate plasma levels of both drugs.

Drugs	Interactions	Comments
IDV [19]	APV 800 + IDV 800 TID: APV ↑ 33 % IDV ↓ 38 % (Cmin 27 % ↓)	In this study no dose adjust-ment was necessary.
LPV/r [9-16]	FPV/r 700/100 + LPV/r 400/100 BID: APV ↓ 63 % (Cmin 65 % ↓) LPV ↑ 37 % (Cmax 30 % ↑, Cmin 52 % ↑) [10]	**Unfavourable combination** [5]. **Avoid combination** or TDM.
	FPV 700 + LPV/r 400/100 BID: APV ↓ 64 % (Cmin 69 % ↓) LPV ↓ 48 % (Cmin 61 % ↓) [9]	
	FPV 700 + LPV/r 533/133 BID: APV ↓ 26 % (Cmin 42 % ↓) LPV: Adequate concentrations [10]	
	Dose separation corrected LPV-concentrations, but not APV plasma concentrations [11]	
NFV [2,19]	APV 800 + NFV 750 TID: APV: Cmin 3-fold ↑ NFV ↑ 15 % [19]	In this study no dose adjust-ment was necessary [2].
SQV/r [20,21]	FPV 700 + SQV/r 1000/100 BID: FPV not affected RTV 100: SQV ↓ 14 % (Ctrough SQV 24 % ↓)	FPV + SQV + RTV **100**: unsafe. => TDM of SQV.
	FPV 700 + SQV/r 1000/200 BID: FPV not affected, RTV 200: SQV ↑ 12 %	FPV + SQV + RTV **200**: safe.
Antiarrythmic drugs		
Amiodarone, bepridil, quinidine, flecainide, lidocaine [3]	Theoretically: antiarrythmic drugs↑	**Not recommended.**
Antibiotics		
Clarithromycin, erythromycin [2,3]	Theoretically: APV ↑ Theoretically: erythromycin, clarithromycin ↑	Dose reduction of clarithro-mycin in patients with kidney failure.
Anticoagulants		
Warfarin [3]	Theoretically: Warfarin ↑↓	Control INR.
Antidepressants		
Tricyclic antidepressants [2,3]	Theoretically: APV and tricyclic antidepressants ↑	Monitor for side-effects of both drugs.
Paroxetin [33]	FPV 700/100 BID + Paroxetin 20 QD: paroxetin ↓ 60% ↓	Dose adjustment if necessary.
St. John's wort [2,3]	Theoretically: APV ↓	**Avoid combination.**

Drugs	Interactions	Comments
Antiepileptics Carbamazepine, phenytoin, primidone [2,3,27]	Theoretically: APV ↓, antiepileptics ↑	Theoretical alternative: gabapentin, lamotrigine, val-proic acid.
Antifungal drugs Itraconazole, ketoconazole, voriconazole [1,2]	Theoretically: APV ↑, azole ↑ [2]. Caution, dose-related toxicity of both drugs [1]	Theoretical alternative: fluco-nazole [1].
Antihistamines Astemizole, loratadine (> 20 mg), terfenadine [3,28,29]	Theoretically: antihistamines ↑ and risk of QT-prolongation ↑	**Avoid combination:** ter-fenadine [2,3]. Cave: loratadine > 20 mg. Theoretical alternative: ceti-rizine, fexofenadine [28,29].
Antihypertensives Calcium-channel blockers Felodipine, nifedipine, verapamil [2]	Theoretically: calcium-channel blockers ↑	**Avoid combination** or reduce dose of calcium-channel blockers if necessary.
Bosentan [26]	Theoretically: APV ↓	**Avoid combination** or TDM. Theoretical alternative: off label use of sildenafil for pulmonary hypertension.
Antipsychotic drugs such as bromperidol, chlorprothixen, cloza-pine, flupendixol, haloperidol, pimozide, quetiapin, risperidone, sertindol [2]	Theoretically: antipsychotic drugs ↑	**Avoid combination:** pim-ozide, clozapine. Prefer: atypical antipsychotics (less anticholinergic effects).
Antituberculosis drugs Rifampicin [2,25]	APV + Rifampicin 600 QD APV ↓ 82 % (Cmin 92 % ↓)	**Avoid combination**.
Rifabutin [6,25]	Rifabutin ↑ 200 %	Rifabutin: 150 mg 3x/week. Monitor for side-effects.
Gastritis-/ Ulcer healing drugs PPIs [32]	Esomeprazol + FPV/+r: adequate steady-steady APV-levels	
Antacids [22]	FPV/r: adequate absorption	
H2-Blocker Cimetidine [3,22]	theoretically: Cimetidine ↑ FPV/r: weak interaction with rani-tidine APV ↓ 18-30 % (Cmin unchanged, Cmax 35-51 % ↓)	Higher potential for drug-interaction with cimetidine. Prefer: ranitidine.

Drugs	Interactions	Comments
Hypnotics		
Barbexaclone, phenobarbital	Theoretically: APV ↓	**Avoid combination** or TDM.
Benzodiazepine (such as diazepam, fluraze-pam, midazolam, tri-azolam), zolpidem [1-3]	Theoretically: benzodiazepine ↑ prolonged sedation	Caution: benzodiazepine. Theoretical alternative: lo-razepam, oxazepam, temaze-pam.
Immunosuppressants		
Cylosporine, sirolimus, tacrolimus	Theoretically: immunosuppressants ↑	Dose adjustment of immuno-suppressants via TDM.
Lipid-regulating drug		
Atorvastatin, lova-statin, simvastatin [1,2,23]	FPV/r 700/100 BID or FPV/r 1400/200 QD + 10 mg Atorvas-tatin QD [23] FPV/r ↑ 230 % (Cmax: 404 % ↑) FPV ↑ 253 % (Cmax: 284 % ↑)	**Avoid combination:** simvastatin, lovastatin [1,2], atorvastatin ≥ 20 mg. Theoretical alternative: pravastatin, fluvastatin, rosu-vastatin.
Oral contraceptives [2]	APV ↓ 22 % (Cmin 20 % ↓) Ethinylestradiol (Cmin 32 % ↑) Norethindrone ↑ 18 % (Cmin 45 % ↑)	**Avoid combination** or TDM of APV concentrations and use additional contraceptive methods.
Phosphordiester-ase-Inhibitors (PPH)		
Sildenafil, tadalafil, vardenafil [6,26]	Theoretically: PPH ↑ [26] Sildenafil + FPV/r: Sildenafil ↑ 210 % [6]	**Not recommended:** silde-nafil, valdenafil, tadalafil: low starting dose.
Substitution		
Methadone [2,24]	Active methadone enantiomers: 13 % ↓ (Cmax 25 % ↓) Comparison with historical studies: APV ↓ 30 % (Cmax 27 %, Cmin 25% ↓)	TDM of APV, if necessary adjust dose of both drugs.
Others		
Dexamethasone	Theoretically: APV ↓	
Ergotamine	Theoretically: APV ↑	**Avoid combination.** Theo-retical alternative: triptane.
Theophylline	Theoretically: Theophylline ↓	TDM of Theophylline.

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Indinavir

IDV, Crixivan™

Approved dose: IDV: 800 mg TID, IDV/r: 800/100 mg BID (an increased number
of side-effects possibly suggests elevated IDV plasma-concentrations. Monitor for
IDV toxicity by TDM)

Metabolism: Indinavir (IDV) is primarily metabolised by CYP3A4 and is an in-
hibitor of CYP3A4. For optimal adsorption an acidic gut ph is necessary, therefore
IDV should be taken with a light meal [1].

Drugs	Interactions	Comments
NRTIs		
DDI [2-4]	DDI EC + IDV: no interaction [4]	Take DDI 1h apart from IDV [2,3].
NNRTIs		
EFV [2,5-7]	IDV/r 800/100 BID + EFV 600 QD: IDV ↓ 19 % (Cmin 48 % ↓) [6]	IDV/r 800/100, probably higher doses for pre-treated patients are necessary [6]. No QD-IDV in combination with EFV [7].
NVP [5,8-9]	IDV/r 800/100 BID + NVP: IDV: Cmin 57 % RTV: Cmin 59 % but IDV > 100 ng/ml [8]	1. IDV: 1000 TID [2] 2. IDV/r: 800/100 BID [8] Probably pre-treated patients need an increased dose of IDV [8]. Assumption: NVP QD decreases IDV/r more than NVP BID [9].

Drugs	Interactions	Comments
Pis		
ATV [10]	Both IDV and ATV increase bili-rubin levels	**Avoid combination.**
APV [11]	IDV 800 + APV 800 TID APV ↑ 33 %, IDV ↓ 38 % (Cmin 27 % ↓)	In this study no dose adjust-ment was necessary.
LPV/r [16-21]	IDV 800 BID + LPV/r 400/100 BID: PK-value of LPV insignificant lower [16]	TDM of both drugs.
NFV [12]	IDV 1200 + NFV 1250 BID	In this study no dose adjust-ment was necessary.
Antiarrythmic Drugs		
Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone	Theoretically: antiarrythmic drugs ↑	**Avoid combination,** if neces-sary reduce dose of antiar-rythmic drugs.
Antibiotics		
Clarithromycin [5]		Dose adjustment for patients with renal failure.
Antidepressants		
St. John's wort [2]	Theoretically: IDV ↓	**Avoid combination.**
Trazodone [5]	Theoretically: trazodone ↑	Avoid combination or possi-bly reduce trazodone dose.
Antiepileptics		
Carbamazepine, phenytoin, primidone [2,23]	Theoretically: IDV ↓, antiepileptics ↑	Theoretical alternative: gabapentin, lamotrigine, val-proic acid.
Antifungals		
Itraconazol, ketoco-nazole, voriconazole [5,26]	Theoretically: IDV and azole ↑ IDV 400 + Ketoconazole 400: IDV ↑ 68 % [5]	IDV: 600 TID [5]. Theoretical alternative: fluconazole [26].
Antihistamines		
Astemizole, loratadine (> 20 mg), terfenadine [2,24,25]	Theoretically: Antihistamines and risk of QT-prolongation ↑	**Avoid combination:** ter-fenadine [2]. Theoretical alternative: ceti-rizine, fexofenadine [24,25].
Antihypertensives		
Calcium-channel blockers such as felo-dipine, nifedipine, verapamil	Theoretically: calcium-channel blockers ↑ [2]	Reduce dose of calcium-channel blockers if necessary.
Bosentan [5,32]	Theoretically: IDV ↓ [5]	**Avoid combination** or TDM. Off label use: sildenafil for pulmonary hypertension [32].

Drugs	Interactions	Comments
Antipsychotic drugs		
Bromperidol, chlor-prothixen, clozapine, flupendixol, haloperidol, pimozide, quetiapine, risperidone, sertindole [2]	Theoretically: IDV and antipsychotic drugs ↑	**Avoid combination** with pimozide. Monitor for side-effects. Prefer: atypical antipsychotics (less anticholinergic effects).
Antituberculosis drugs		
Rifabutin [2,3,30]	Rifabutin ↑ 173 % IDV ↓ 33 % [30]	IDV: 1000 TID + Rifabutin: 150mg/d [2]. IDV/r: 800/100 BID + Rifabutin: 150 mg 3x/week.
Rifampicin [2]	IDV ↓ 89 %	**Avoid combination** [2].
Cytotoxic drugs		
e.g. docetaxel, paclitaxel, vinca alkaloid [5]	Theoretically: cytotoxic drugs ↑	
Gastritis-/ Ulcer healing drugs		
Antacids [2],	IDV requires acidic pH for adequate absorption, possible: IDV ↓	Antacids 1h apart from IDV.
H2-Blocker	Theoretically: IDV ↓	TDM of IDV.
Proton pump inhibitor (PPI): e.g. Omeprazole [5,22]		TDM of IDV.
Hypnotics		
Barbexaclone, phenobarbital	Theoretically: IDV ↓	**Avoid combination** or TDM.
Benzodiazepine e.g. Alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem [2,5]	Prolonged sedation	**Avoid combination:** Alprazolam, midazolam, triazolam [2]. **Cave:** clorazepate, diazepam, estazolam, flurazepam [5]. Theoretical alternative: lorazepam, oxazepam, temazepam [5].
Immunosuppressants		
Cylosporine, siroli - mus, tacrolimus [27]	Theoretically: immunosuppressants ↑	Dose adjustment of immuno-suppressants by TDM.
Lipid-lowering drugs		
Atorvastatin, lovastatin, simvastatin [2,5]	Theoretically: Atorvastatin, lovastatin ↑	**Avoid combination:** simvastatin, lovastatin [2]. Cave: atorvastatin [5]. Theoretical alternative: pravastatin [5], fluvastatin, rosuvastatin.

Drugs	Interactions	Comments
Oral contraceptives [5]	Estradiol ↑ 24 % Norethindrone ↑ 26 %	No dose adjustment necessary.
Phosphordiesterase-Inhibitors (PPH)		
Sildenafil, tadalafil, vardenafil [5,31]	Theoretically: PPH ↑ IDV 800 TID+ Sildenafil 25: Sildenafil ↑ 304 % [31] IDV + Vardenafil: Vardenafil ↑ 16-fold IDV ↓ 30% (Cmax 40 % ↓) [5]	Sildenafil: 12,5 mg every 48h [5]. Avoid combination or TDM.
Others		
Dexamethasone [2] Ergotamine [2]	Theoretically: IDV ↓ Theoretically: IDV ↑	TDM of IDV. **Avoid combination.** Theoretical alternative: triptane.
Grapefruit juice [1]	AUC of IDV: 26 % ↓	**Avoid combination** [1].
Interleukin [5,28]	IL-2 + IDV: IDV ↑ 88 %	If necessary adjust dose of both drugs. TDM of IDV.
L-Tyroxin [5,29]	Thyroxin ↑ because IDV inhibits UDP-GT [29]	Perhaps l-tyroxin dose could be reduced.
Vitamine C [32]	IDV 800 TID+ 1g vitamine C: Cmin IDV 32 % ↓(not significant)	Avoid high doses of vitamine C.

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Lopinavir/r

LPV/r, Kaletra™

Approved dose: LPV/r 400/100 mg BID

Metabolism: LPV is co-formulated with Ritonavir and primarily metabolised by CYP3A4. LPV/r is a strong inhibitor of CYP3A4 and induces the glucuronidation pathway as well as CYP 2C9 and CYP 2C19 [1].

Drugs	Interactions	Comments
NRTI		
TDF [41,42]	TDF ↑ 32 % (Cmax 15 % ↑), LPV/r: Adequate plasma concentration 18 heavily pre-treated patients: Cmin LPV 34 % ↓, Cmin RTV 44 % ↓ [41]	In the expanded access program of Viread and ABT-418 no increase in side-effects observed. LPV/r: TDM.
NNRTI		
EFV [2,3]	EFV 600 QD + LPV/r BID [3]: LPV ↓ 25 % (Cmin 44 % ↓)	LPV/r: 533/133 BID [2].
NVP [2,4,45]	1. LPV/r 400/100 + NVP 200 BID: Extensively pre-treated patients [4]: LPV/r ↓ 27 % (Cmin 51 % ↓) 2. LPV/r 400/100 + NVP200 BID (patients with viral load < 80 c/ml, n= 31): Adequate plasma concentrations of both drugs [45]	Clinical experiences: LPV/r: 533/133 BID [2].
Protease-Inhibitors		
ATV [14,46]	LPV/r 400/100 BID + ATV400 QD: ATV-level above 150 ng/ml, LPV- level above 1400 ng/ml	Case reports. Adequate concentrations of both drugs.
FPV/r [5-8] APV/r [9-13]	1. FPV/r 700/100 BID + LPV/r BID: APV ↓ 63 % (Cmin 65 % ↓) LPV ↓ 37 % (Cmax 30 % ↓, Cmin 52 % ↓) [6] 2. FPV/r 700/100 + LPV/r 533/133 BID [7]: APV ↓ 26 % (Cmin 42 % ↓) LPV: Adequate plasma concentration 3. Dose separation corrects LPV-concentration, but not APV plasma concentrations [8]	**Unfavourable combination,** wide variability of concentrations => TDM.
IDV/r [15-19]	IDV 800 BID + LPV/r BID	TDM. If high concentrations are observed consider a dose reduction.

Drugs	Interactions	Comments
NFV [24]	NFV 1000 BID + LPV/r: LPV/r ↓ 27 % (Cmax 21 % ↓, Cmin 33 % ↓)	TDM.
SQV/r [20-23]	SQV 1000 BID + LPV/r: Adequate SQV- and LPV-plasma level	Synergic effect, favourable combination: TDM.
Antiarrythmic drugs		
Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone	Theoretically: antiarrythmic drugs ↑	**Avoid combination:** amiodarone [2]. Monitor for side-effects, perhaps dose reduction.
Antibiotics		
Clarithromycin [25-27]	Clarithromycin ↑ Dose reduction with patients of liver and renal failure Creatinine clearance: 60-30 ml/min: 50 % reduction. < 30 ml/min: 75 % reduction [25]	Dose reduction in patients with liver and renal failure. Theoretical alternative: azithromycin [26,27].
Anticoagulants		
Warfarin [25]	Warfarin ↓	Monitor INR.
Antidepressants		
Nefazodone [28]	Theoretically: LPV/r ↑	Monitor for side-effects. Theoretical alternative: SSRIs.
St. John's wort [2]	Theoretically: LPV/r ↓	**Avoid combination.**
Antiepileptics		
Carbamazepine, phenytoin, primidone, [2,25,40]	Theoretically: LPV/r ↓ antiepileptics ↑	Theoretical alternative: gabapentin.
Lamotrigine[47]	Lamotrigine 100 + LPV/r 400/100 BID: lamotrigine Cmin: 56% ↓	Dose adjustment of 200 % for lamotrigine, not for LPV/r.
Antifungal drugs		
Itraconazole, ketoconazole, voriconazole [1,2,25]	LPV/r and azole ↑ Caution: possible dose-related toxicity of both drugs.	**Avoid combination:** Itraconazole, ketoconazole, no dose > 200 mg. Theoretical alternative: fluconazole [1].
Antihistamines		
Astemizole, loratadine (> 20 mg), terfenadine [2,29,30]	Theoretically: Antihistamines ↑ and increased risk of QT-prolongation	**Avoid combination:** terfenadine. Theoretical alternative: cetirizine, fexofenadine [29,30].

Drugs	Interactions	Comments
Antihypertensives		
Calcium-channel blockers [2,31] such as Amlodipine, felodipine, nifedipine, verapamil	Theoretically: calcium-channel blockers ↑	Theoretically dose reduction of calcium-channel blockers.
Bosentan [25,39]	Theoretically: LPV/r ↓	**Avoid combination** or TDM. Off label use: sildenafil for pulmonary hypertension [39].
Antipsychotic drugs		
Bromperidol, chlorprothixen, clozapine, flupendixol, haloperidol, pimozide, quetiapine, risperidone, sertindole [25,28]	Theoretically: LPV/r and antipsychotic drugs ↑	**Avoid combination** with pimozide. Monitor side effects. Prefer: atypical antipsychotics (less anticholinergic effects).
Antituberculosis drugs		
Rifabutin [2,37]	Rifabutin: 303 % ↑ Rifabutin-metabolite ↑ 47,5 fold No effect of LPV/r	Rifabutin: 150 mg 3x/week. Monitor for side-effects.
Rifampicin [2,37]	LPV/r + Rifampicin 600/QD: LPV/r ↓ 75 % (Cmin 99 % ↓)	**Avoid combination.**
Cytotoxic drugs		
Docetaxel, etoposide, paclitaxel, tamoxifen, vinca alkaloid [38]	Theoretically: cytotoxic drugs ↑	Monitor for side-effects of the cytotoxic drugs.
Gastritis-/ Ulcer healing drugs		
Antacids, H2-Blocker, proton pump inhibitors (PPI) [44]	No significant interaction after 48 week therapy	
Hypnotics		
Barbexaclone, phenobarbital	Theoretically: LPV ↓	**Avoid combination** or TDM.
Benzodiazepine such as alprazolam, diazepam, midazolam, triazolam, zolpidem [25]	Theoretically: Benzodiazepine ↑ Prolonged sedation	**Avoid combination:** midazolam, triazolam. Theoretical alternative: lorazepam, oxazepam, temazepam.
Immunosuppressants		
Cylosporine, sirolimus tacrolimus [2,25,43,48]	Theoretically: immunosuppressants ↑ Tacrolimus + LPV/r: (3 patients) Tacrolimus 10-20-fold ↑ [43]	Dose adjustment of immunosuppressants with TDM.

Drugs	Interactions	Comments
Lipid lowering drugs		
Atorvastatin, lovastatin, simvastatin [32-35]	Atorvastatin, pravastatin + LPV/r: Atorvastatin ↑ 5,9 fold Pravastatin ↑ 30 %	Low starting dose: atorvastatin. Theoretical alternative: pravastatin, fluvastatin.
Oral contraceptives [2,25]	Ethinylestradiol ↓ 42 % Norethindrone ↓ 17 %	Use additional contraceptive method.
Phosphordiesterase Inhibitors (PPH)		
Sildenafil, tadalafil, vardenafil [2,25]	Theoretically: PPH ↑ Sildenafil 100 + RTV 500 BID Sildenafil ↑ 1000 %	Sildenafil 25 mg every 48h.
Substitution		
Methadone [36]	Methadone ↓ 36 % (Cmax 44 % ↓)	Monitor for opiate withdrawal; if necessary increase methadone dose.
Others		
Atovaquone	Theoretically: atovaquone ↓	If necessary increase dose.
Disulfiram [2]	Kaletra liquid contains alcohol and can cause sickness when combined with disulfiram	**Avoid combination.**
Dexamethasone [2]	Theoretically: LPV/r ↓	
Metronidazole [2]	Kaletra liquid contains alcohol and can cause sickness when combined with metronidazole	**Avoid combination.**
Theophylline [2]	Theoretically: theophylline ↓	TDM of theophylline.

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Nelfinavir

NFV, Viracept™

Approved dose: 1250 mg BID

Metabolism: Nelfinavir (NFV) is primarily metabolised by CYP2C19 more than CYP3A4 and CYP2D6. NFV is an inhibitor of CYP3A4. It is metabolised to an active metabolite M8 (approx. 30% of parent compound), with equal antiretroviral potency to NLF. M8 is metabolised by CYP3A4 [1,2].

Drugs	Interactions	Comments
NRTI		
DDI [1,2]	DDI: fasting, NFV: with a light meal	Take DDI 2h apart from NFV.
TDF [3]	No clinically significant interaction	
NNRTI		
EFV [2,4,5]	NFV 750 TID + EFV 600 QD: NFV ↑ 20 %, M8 ↓ 40 % NFV 1250 BID + EFV 600 QD: NFV ↓ 38 % (Cmin 65 % ↓)	No clinically significant interaction, possibly monitor NLF by TDM.
NVP [6]	NFV 750 TID + NVP 200 BID	In this study no dose adjustment was necessary.
Protease-Inhibitors		
ATV [8,28]	NLF 1250 BID + ATV 400 QD: Cmin NLF: 57,4%↑, M8: 124%↑, No effect on AUC, Cmax, Tmax	
APV [9]	NFV 750 + APV 800 TID: APV: (Cmin 2,9-fold ↑) NFV ↑ 15 %	TDM.
IDV [10]	NFV 1250 + IDV 1200 BID	In this study no dose adjustment was necessary.
LPV/r [7]	NFV 1000 + LPV/r 400/100 BID: (healthy volunteers) LPV/r ↓ 27 % (Cmax 21 % ↓, Cmin 33 % ↓)	Possible dose adjustment of LPV/r using TDM.
SQV [11-13,14]	NFV 1250 + SQV 1000-1200 BID NFV 1250 + SQV/r 1000/100 BID M8↑ 2,7-fold	In this study no dose adjustment was necessary. Low potential for interaction.
TPV/r	Theoretically: NLF ↓	**Avoid combination.**
Antiarrythmic drugs		
Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone [2]	Theoretically: antiarrythmic drugs ↑	**Avoid combination** or monitor for toxic effects.

Drugs	Interactions	Comments
Antibiotics Azithromycin, clarithromycin, erythromycin [1,15]	NFV 750 TID + Azithromycin 1200 QD: NFV ↓ 28 %, M8 ↓ 23 % Azithromycin ↑ >100 %	Caution: azithromycin side effects. No dose adjustment with clarithromycin and erythromycin.
Antidepressants Nefazodone	Theoretically: NFV ↑	**Avoid combination** or monitor for toxic effects. Theoretical alternative: SSRIs.
St. John's wort [2]	Theoretically: NFV ↓	**Avoid combination.**
Antiepileptics Carbamazepine, phenytoin, primidone [2,18]	NFV + Phenytoin: NFV: adequate plasma concentration, phenyotin ↓	Caution: TDM of antiepileptics and NFV.
Antifungal drugs Caspofungin [1,19]	Caspofungin: Approved dose 50 mg, theoretically increase dose up to 70 mg/QD	Azole: no dose adjustment is necessary.
Antihistamines Astemizole, loratadine (> 20 mg), terfenadine [2,16,17]	Theoretically: antihistamines ↑ Increased risk of QT-prolongation	**Avoid combination:** terfenadine. Theoretical alternative: cetirizine, fexofenadine.
Antihypertensives Calcium-channel blockers [20] such as Amlodipine, nifedipine, verapamil	Theoretically: calcium-channel blockers ↑	Theoretically: dose reduction of calcium-channel blockers.
Bosentan [20,26]	Theoretically: NFV ↓	**Avoid combination** or TDM. Off label use: sildenafil for pulmonary hypertension.
Antimalarials Mefloquine [18]	No clinically significant interaction	
Antipsychotic drugs e.g. bromperidol, chlorprothixen, clozapine, flupendixol, haloperidol, pimozide, quetiapine, risperidone, sertindole [16]	Theoretically: NFV and antipsychotic drugs ↑	**Avoid combination** with pimozide. Monitor for side-effects. Prefer: atypical antipsychotics (less anticholinergic effects).

Drugs	Interactions	Comments
Antituberculosis drugs		
Rifabutin [23]	NFV 750 TID + Rifabutin 300 QD: NFV ↓ 32 % Rifabutin ↑ 207 %	Rifabutin: 150 mg/QD. NFV: 1000 TID. NFV: 1250 BID.
Rifampicin [2,23]	NFV ↓ 82%	**Avoid combination.**
Hypnotics		
Barbexaclone, phenobarbital	Theoretically: NFV ↓	**Avoid combination** or TDM.
Benzodiazepine [2] e.g. alprazolam, diazepam, midazolam triazolam, zolpidem	Benzodiazepine ↑, prolonged sedation	**Avoid combination:** midazolam, triazolam.
Immunosuppressants		
Cylosporine, sirolimus, tacrolimus [20,27]	Theoretically: immunosuppressants ↑ NFV + Tacrolimus: (5 liver transplant patients) tacrolimus concentration 16-fold lower than in the HIV-negative control group [27]	Dose adjustment of immunosuppressants with TDM.
Lipid-lowering drugs		
Atorvastatin, lovastatin, simvastatin [21,2]	NFV 1250 BID + Atorvastatin 10 or simvastatin 20 Atorvastatin ↑ 74 % Simvastatin ↑ 506 %	**Avoid combination:** simvastatin. Low dose atorvastatin Theoretical alternative: pravastatin, fluvastatin.
Phosphordiesterase Hemmer (PPH)		
Sildenafil, tadalafil, vardenafil [18,24,25]	Theoretically: PPH ↑	Sildenafil 25 mg every 48h.
Oral contraceptives [2]	NFV 750 TID + 0,4 Norethisteron + 35 µg Ethinyl estradiol: Ethinyl estradiol ↓ 47 % Norethisteron ↓ 18 %	Use additional contraceptive method.
Substitution Methadone [2,22]	NFV 1250 BID + Methadone: Methadone ↓ 47 %; in this study no opiate withdrawal [22]	But monitor for opiate withdrawal.
Others Dexamethasone Ergot alkaloids [2,20]	Theoretically: NFV ↓ Theoretically: NFV ↑	TDM. **Avoid combination.** Theoretical alternative: triptane.

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Nevirapine

NVP, Viramune™

Approved dose: NVP 200 mg BID (lead-in period: 200 mg QD in the first 14 days)
NVP stands for the approved dose of NVP in the table.

Metabolism: Nevirapine (NVP) is primarily metabolised by CYP3A4 and is an inducer of CYP3A4 and 2B6 [1,2].

Drugs	Interactions	Comments
NRTI	No clinically significant interaction [1]	
NNRTI EFV [2,4,32]	EFV 600 QD + NVP 400 QD [4]: EFV ↓ 22 % (Cmin 36 % ↓)	Unfavourable combination: less efficacy and increased toxicity [32].
Protease-Inhibitors ATV/r [2,30]	Possibly: ATV ↓	Currently no recommendation of dose adjustment of ATV.
APV [6,7]	APV/r 600/100 BID + NVP: APV ↓ 35 % (Cmin 20 % ↓, Cmax 35 % ↓) [6]	TDM. APV/r 450/200 BID [7].
FPV [31]	FPV/r 700/100 BID + NVP: Interaction not clinically significant	In this study no dose adjustment was necessary.
IDV and IDV/r [8,9,10]	IDV/r 800/100 BID + NVP: IDV: Cmin 57 % RTV: Cmin 59 % but IDV > 100 ng/ml [8]	1. IDV: 1000 TID [9] 2. IDV/r: 800/100 BID [8] Probably pre-treated patients need an increased dose of IDV [8]. Assumption: NVP QD decreases IDV/r more than NVP BID [10].
LPV/r [2,5,33,34]	1. LPV/r 400/100 + NVP200 BID: Pre-treated patients of clinical trial LPV/r ↓ 27 % (Cmin 51 % ↓)	LPV/r: 533/133 BID [2].
	2. LPV/r 400/100 + NVP200 BID: (VL < 80 c/ml, n=31) Adequate concentrations of both drugs [33]	
NFV [11,12]	NFV 750 TID + NVP: NFV ↑ 4%, Cmax 14% ↑	In this study no dose adjustment was necessary.
Antiarrythmic drugs Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone	Theoretically: antiarrythmic drugs ↓	If necessary increase dose of antiarrythmic drugs.

Drugs	Interactions	Comments
Antibiotics Clarithromycin, erythromycin [1,15]	Clarithromycin 500 BID + NVP: Clarithromycin ↓ 35 %, Clarithromycin active metabolite ↑ 58 %, NVP ↑ 26 %	No dose adjustment. Monitor liver function tests. Theoretical alternative: azithromycin.
Antidepressants Nefazodone	Theoretically: NVP ↑	**Avoid combination:** liver toxicity.
St. John's wort [2]	Theoretically: NVP ↓	**Avoid combination.**
Antiepileptics Carbamazepine, phenytoin	Theoretically: NVP ↓	**Avoid combination:** Theoretical alternative: gabapentin, lamotrigine, valproic acid.
Antifungal drugs Itraconazole, ketoconazole, fluconazole, voriconazole [2,16]	Theoretically: NVP ↑, Azole ↓	TDM of NVP.
	Ketoconazole 400 QD + NVP [16]: Ketoconazole ↓ 63 % (Cmax 40 % ↓), NVP ↑ 15-28 %	
	Fluconazole + NVP [2]: Fluconazole: NVP ↑ 100 %	
	Voriconazole: no data	
Antihypertensives Calcium-channel blockers such as amlodipine, felodipine, nifedipine, verapamil	Theoretically: calcium-channel blockers ↓	If necessary increase dose of calcium-channel blockers.
Bosentan [3,26]	Theoretically: NVP ↓	Theoretical alternative: off label use of sildenafil for pulmonary hypertension.
Antituberculosis drug Rifabutin [21,22]		No dose adjustment.
Rifampicin [22-25]	NVP (Cmin 68 % ↓)	**Avoid combination.**
Cytotoxic drugs Cyclophospamide [3]	Theoretically: neurotoxic metabolite ↑	Avoid combination with 2 or more neurotoxic drugs.
Drugs of abuse/recreational drugs Cocaine [18]	Theoretically: norcocaine ↑ (liver toxicity)	**Avoid combination.**
Gastritis-/ Ulcer healing drugs Cimetidin	Theoretically: NVP ↑	Theoretical alternative: famotidin, nizatidin, ranitidin.

Drugs	Interactions	Comments
Hypnotics		
Barbexaclone, phenobarbital	Theoretically: NVP ↓	
Benzodiazepine e.g. diazepam, midazolam, triazolam, zolpidem	Theoretically: benzodiazepine ↓	Theoretical alternative: lorazepam, oxazepam, temazepam.
Immunosuppressants		
Cylosporine, sirolimus, tacrolimus	Theoretically: immunosuppressants ↓	Dose adjustment of immunosuppressants with TDM.
Lipid-lowering drugs		
Atorvastatin, Lovastatin, Simvastatin [1,15,16]	Theoretically: statins ↓	Theoretical alternative: Pravastatin.
Oral contraceptives [17]	Ethinylestradiol 0.035 + Norethindrone 1.0: Ethinylestradiol ↓ 29 %, Norethindrone ↓ 18 %	Use additional contraceptive method.
Phosphordiesterase Inhibitors PPH		
Sildenafil, tadalafil, vardenafil	Theoretically: PPH ↓	Caution: For each patient adapt dose individually.
Substitution		
Methadone [2,19,20]	Methadone ↓ after 4-10 days: opiate withdrawal	Increase methadone dose in 10 mg steps.
Others		
Dexamethasone	Theoretically: NVP ↓	
Sulfametoxazol	Exanthema ↑	
Warfarin [27]	Warfarin ↓ ↑	Control INR.

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Saquinavir

SQV, Invirase 500, Fortovase™ sgc, Invirase™ hgc

Approved dose SQV: SQV/r: 1000/100 mg BID [3]

Metabolism: 90% of Saquinavir (SQV) is metabolised by the isoenzyme CYP3A4. SQV is a weak inhibitor of CYP3A4. In vitro studies have shown that SQV is also a substrate of p-glykoprotein (P-gp) [1,2].

Drugs	Interactions	Comments
NRTI		
DDI [1]		Take DDI 1 h before or 2 h after SQV.
TDF [4,5]	No significant interaction known	
NNRTI		
EFV [6-9]	SQV 1200 TID + EFV 600 QD: SQV ↓ 62 % [6]	1.SQV/r 400/400 BID [7]. 2.SQV/r 1200/100 QD [8]. 3.SQV/r 1000/100 BID[9].
Protease-Inhibitors		
ATV [16-19]	SQV 1600 QD + ATV/r 300/100 QD: SQV ↑ 60 %, RTV ↑ 41 % [16]	Synergistic effect.
	SQV 1000 BID + ATV/r 300/100 QD: SQV, ATV, RTV ↑ [19]	No dose adjustment necessary.
APV [20]	SQV/r 1000/100 + APV 600 BID: => Adequate plasma concentration	Insufficient data. => TDM.
FPV/r [21]	SQV 1000 + FPV/r 700/100 or 700/200 BID: no effect on FPV, but on 1. RTV 100: SQV ↓ 14% 2. RTV 200: SQV ↑ 12%	SQV + FPV + RTV **100**: TDM. SQV + FPV + RTV **200**: Safe.
IDV [22-24]	IDV 800 TID + single dose SQV: SQV ↑ 5-8 fold [22,24]	Insufficient data.
LPV/r [3,12-15]	SQV 1000 + LPV/r 400/100 BID: Adequate plasma concentration of SQV and LPV	Synergistic effect.
NFV [25-29]	SQV/r 1000/100 + NFV 1250 BID: NFV-M8 ↑ 2,7 fold	In this study no dose adjustment was necessary.
TPV/r [48]	TPV/r 500/200 + SQV 1000 BID: SQV: AUC 70%, Cmax 66%, Cmin 81% ↓	**Avoid combination.**

Drugs	Interactions	Comments
Antiarrythmic drugs Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone [3]	Theoretically: antiarrythmic drugs ↑	**Avoid combination.**
Antibiotics		
Clarithromycin	SQV 1200 TID + Clarithromycin 500 BID: SQV ↑ 177 % Clarithromycin ↑ 45 %	Unboosted SQV: no dose adjustment was necessary.
Erythromycin [2,3]	SQV 1200 TID + Erythromycin 250 QD: SQV ↑ 99 % (Cmax 106 % ↑)	
Antidepressants Nefazodone [2]	Theoretically: SQV ↑	Monitor for side-effects. Theoretical alternative: SSRIs.
St. John's wort [2]	Theoretically: SQV ↓	**Avoid combination** or TDM.
Antiepileptics Carbamazepine [3,30], phenytoin, primidone	Theoretically: SQV ↓, antiepileptics ↑	Theoretical alternative: gabapentin, lamotrigine, valproic acid [30].
Antifungal drugs Itraconazole, ketoconazole, voriconazole [2,33]	Theoretically: SQV ↑ Invirase 600 TID + 200 ketoconazole QD SQV ↑ 160 % Fortovase 800 or 1200 BID + itraconazole 100 QD => SQV concentrations are equivalent to SQV 1400 BID	No dose adjustment. Monitor for toxic effects.
Antihistamines Astemizole, loratadine (> 20 mg), terfenadine [2,31,32]	Risk of QT-prolongation ↑ (Terfenadine ↑ 368 %)	**Avoid combination:** terfenadine. Theoretical alternative: cetirizine, fexofenadine.
Antihypertensives Calcium-channel blockers [2] such as amlodipine, felodipine, nifedipine, verapamil	Theoretically: calcium-channel blockers ↑	Theoretical dose reduction of calcium-channel blockers.
Bosentan [3,43]	Theoretically: SQV ↓	**Avoid combination** or TDM. Off label use: sildenafil for pulmonary hypertension.

Drugs	Interactions	Comments
Antipsychotic drugs e.g., Bromperidol, chlorprothixen, clozapine, flupendixol, haloperidol, pimozide, quetiapine, risperidone, sertindole [2,40]	Theoretically: SQV and antipsychotic drugs ↑	**Avoid combination** with pimozide. Monitor for side-effects. Prefer: atypical antipsychotics (less anticholinergic effects).
Antituberculosis drugs Rifabutin [41]	Fortovase 1200 TID + Rifabutin QD: SQV ↓ 40%	SQV/r + Rifabutin: 150 mg 3x/week.
Rifampicin [2,41,47]	SQV/r 1000/100 BID + Rifampicin 600 QD: 11 patients with symptoms of cell damage	**Avoid combination.**
Gastritis-/ Ulcer healing drugs Antacids, proton pump inhibitor (PPI)	No data	Interactions unlikely.
H2-Blocker Cimetidine [3,35]	SQV 1200 TID vs SQV 1200 BID + Cimetidine 400 BID: SQV ↑ 120 % (Cmax ↑ 179 %, Cmin ↑ stabile)	Theoretical alternative: famotidine, nizatidine, ranitidine.
Hypnotics Barbexaclone, phenobarbital	Theoretically: SQV ↓	**Avoid combination** or TDM.
Benzodiazepine such as midazolam, triazolam, diazepam, zolpidem [2,3]	Prolonged sedation	**Avoid combination:** midazolam. Caution: alprazolam, triazolam. Theoretical alternative: lorazepam, oxazepam, temazepam [3].
Immunosuppressants Cylosporine, sirolimus tacrolimus [3,46]	Theoretically: immunosuppressants ↑, Cylosporine-concentration 3-fold higher after starting the combination with SQV	Dose adjustment of immunosuppressants with TDM.

Drugs	Interactions	Comments
Lipid-lowering drugs		
Atorvastatin, Lova- statin, simvastatin [2,34]	SQV/r: 400/400 BID + 40 mg Ator- vastatin QD, pravastatin, simvastatin: Atorvastatin ↑ 5,9-fold Pravastatin: ↓ 35 % Simvastatin ↑ 34,6-fold	**Avoid combination:** sim- vastatin, lovastatin. Theoretical alternative: pravastatin, fluvastatin, rosuvastatin, low dose of atorvastatin.
Phosphordiester- ase-Inhibitors (PPH)		
Sildenafil, tadalafil, vardenafil [2,3,42]	Theoretically: PPH ↑ Fortovase: 1200 TID + Sildenafil 100 Sildenafil ↑ 210 % (Cmax ↑ 140 %)	Sildenafil 25 mg every 48h. Other PPH: starting with a low dose.
Substitution		
Methadone [36-39]	SQV/r + R- and S-Methadone: No significant change of the pk- values of SQV. R-Methadone ↓ 20 %	Interactions unlikely.
Others		
Dexamethasone Ergot alkaloids [3]	Theoretically: SQV ↓ Theoretically: SQV ↑	TDM. **Avoid combination.** Theo- retical alternative: triptane.
Garlic capsules [44] ingredients: Allicin	SQV 1200 TID + Allicin 300: SQV ↓ 51 %	**Avoid combination.**
Warfarin [3,45]	Report of hypoprothrombinaemia: 20 % lower warfarin concentration with SQV	If necessary increase warfa- rin dose.

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T-20

Enfuvirtid, Fuzeon™

No clinically significant interaction.

Tenofovir

TDF, Viread™; component of Truvada™

Elimination: TDF is eliminated by a combination of glomerular filtration and active renal tubular secretion.

Approved dose: TDF 300 mg QD

Drugs	Interactions	Comments
NRTI		
DDI [1-5]	DDI EC 250 QD + TDF 300 QD DDI AUC equivalent to DDI 400 alone Dose recommendation: Patients ≥ 60 kg: DDI 250 mg Patients < 60 kg: DDI 200 mg Despite dose reduction of DDI there is probably an increased risk of lactic acidosis and pancreatitis.	**Probably unfavourable combination.** Virological failure in patients with high viral load and low CD4 cell count [4]. Closely monitor amylase, lipase and lactate. DDI and TDF can be taken with meals.
ABC [6], FTC [7], D4T [8], 3TC [9]	No clinically significant interaction	
NNRTI		
EFV [9]	No clinically significant interaction	
Protease-Inhibitors		
ATV [11]	ATV 400 QD + TDF 300 QD: ATV ↓ 25 % (Cmin 40 % ↓) TDF ↑ 24 % [11]	ATV/r 300/100 QD: Administer with food.
ATV/r [10,12,13,27]	ATV/r 300/100 + TDF QD [10] ATV ↓ 25 % (Cmin ATV: 23 % ↓, not significant) [12] , no change in Cmin	Boosted ATV-plasma-concentration are 2-4-fold higher than unboosted ATV without TDF [13].
IDV [9]	No clinically significant interaction	

Drugs	Interactions	Comments
LPV/r [14,15,23,28]	Healthy volunteers: TDF: 32 % ↑ (Cmax 15% ↑) LPV/r: unchanged	In clinical studies no increased appearance of renal side-effects.
	18 heavily pre-treated patients: Cmin LPV 34 % ↓, Cmin RTV 44% ↓	TDM of LPV/r.
NFV [18]	No clinically significant interaction	
RTV [14]	No clinically significant interaction	
SQV [16,17]	No clinically significant interaction	
FPV [25,26]	No clinically significant interaction	
Co-Medication		
Methadone [20]	No clinically significant interaction	
Oral contraceptives [19]	No clinically significant interaction	
Ribavirin [21]	No clinically significant interaction	
Rifampicin [22]	No clinically significant interaction	
Nephrotoxic drugs		
e.g. amphotericin B, aminoglycoside, cidofovir, foscarnet, pentamidine (i.v.), vancomycin [2]	No data, but perhaps additive nephrotoxicity.	**Avoid combination.**
e.g. acyclovir, cylosporine, cisplatin, probenecid, salicylate, tacrolimus, valaciclovir, valganciclovir	No data, but these drugs are renally eliminated as is Tenofovir	**Avoid combination** in patients with risk of renal failure; or monitor kidney function weekly.

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